UNIVERSIDADE DE SÃO PAULO
FACULDADE DE MEDICINA DE RIBEIRÃO PRETO
PROGRAMA DE PÓS GRADUAÇÃO EM NUTRIÇÃO E METABOLISMO
DEPARTAMENTO CIÊNCIAS DA SAÚDE

BRUNA RAMOS DA SILVA

Avaliação do perfil metabólico, oxidativo e antropométrico em mulheres com câncer de mama.

Ribeirão Preto
2022

BRUNA RAMOS DA SILVA

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Tese apresentada à Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo para obtenção do título de Doutor em Ciências da Saúde

Área de Concentração: Nutrição e Metabolismo.

Orientador: Prof. Dr. Alceu Afonso Jordão Junior

Ribeirão Preto
2022

FICHA CATALOGRÁFICA

Silva, Bruna Ramos

Avaliação do perfil metabólico, oxidativo e antropométrico em mulheres com câncer de mama/ Bruna Ramos da Silva ; orientador Alceu Afonso Jordão Junior – Ribeirão Preto, 2022.

147 f. : il.

Tese de Doutorado apresentada à Faculdade de Medicina de Ribeirão Preto/USP. Área de Concentração: Nutrição e Metabolismo

Orientador: Jordão Junior, Alceu Afonso.

1. Composição Corporal. 2. Estresse oxidativo
3. Alterações Metabólicas. 4. Cancêr de Mama

Bruna Ramos da Silva

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Aprovado em:

Banca Examinadora

Prof. Dr. Alceu Afonso Jordão Junior

Instituição: Faculdade de Medicina de Ribeirão Preto - USP

Julgamento: _____ Assinatura: _____

Prof.

Instituição:

Julgamento: _____ Assinatura: _____

Prof.

Instituição:

Julgamento: _____ Assinatura: _____

Prof.

Instituição:

Julgamento: _____ Assinatura: _____

Dedicatória

Aos meus pais, ***Anatanael e Maria José*** *por todo amor, suporte e carinho, por estarem sempre ao meu lado acreditando no meu potencial. Obrigada por serem a minha base para cada conquista alcançada.*

Em especial, a minha mãe, ***Maria José****, que com muito amor, também contribuiu efetivamente durante a coleta de dados do trabalho e tornou possível a realização do mesmo.*

Ao meu esposo, ***Renê****, pelo seu apoio constante e incentivo em todas as atividades e novos projetos. Meu amigo e parceiro, me acompanhando até mesmo em outro país.*

Aos meu queridos mentores e Orientadores, ***Alceu e Mirele,*** *por todo os ensinamentos e opotunidades dadas ao longo de 10 anos. Sempre terei gratidão por toda parceria ao longo desses anos.*

Agradecimentos

A ***Deus****, por sempre estar guiando meus passos, por todas as bençõe colocadas na minha trajetória, sempre zelando por mim. Obrigada por permitir a concretização desta etapa.*

A toda a minha ***Família*** *por ser a minha rede de suporte incondicional. A minhas irmãs e minha sobrinha, pelo forte elo que ultrapassa os oceanos. Em especial, ao meu cunhado* ***Lucas*** *que juntamente com a minha irmã* ***Letícia*** *contribuíram com o desenvolvimento gráfico de imagens utilizadas em artigo científico publicado.*

Ao meu esposo ***Renê****, por toda atenção, auxílio e suporte nas análises estatísticas do trabalho. Pelo crescimento pessoal e profissional partilhado.*

Aos meus mentores, orientadores e amigos ***Prof. Dr. Alceu Afonso Jordão Junior e Profa. Dra. Mirele Savegnago Mialich*** *a quem gostaria de reforçar o meu imenso agradecimento por todo carinho, suporte e amizade que construímos ao longo do tempo. Obrigada por acreditarem no meu potencial.*

A todos que fazem parte do ambulatório de oncologia nutricional ANONCO e ao Laboratório de Estudos em Nutrição e Oncologia LENOn, por todos os ensinamentos, discussões e oportunidades. Em especial gostaria de agradecer a ***Drª. Juliana Schieri*** *por me acolher no ambulatório de nutrição e por ter contribuído ativamente nos saberes construídos ao longo da pós graduação, obrigada por ser uma inspiração.*

A todos do ambulatório de mastologia clínica, em especial aos profissionais de enfermagem que durante toda a coleta de dados me auxiliaram nesta etapa e foram

peça fundamental para a execução do trabalho, além da amizade construída nesse período. Obrigada ***Alaíde,*** *sem você este trabalho não seria possível.*

A todo ***Prado's Lab*** *e a* ***Profa. Dra. Carla Prado****, por ter me recebido em seu laboratório (Human Nutrition Reserach Unit - HNRU) e ter me proporcionado ensinamentos, oportunidades, experiências e por terem sido minha família e rede de suporte no Canadá. Jamais esquecerei esse período da minha vida.*

As amigas ***Izabella Schiavoni, Camila Manca e Ana Paula Pagano*** *por todo acolhimento e amizade nestes anos de Pós-Graduação.*

Aos ***docentes e funcionários do Curso de Nutrição e Metabolismo da FMRP –USP****, pela presença constante e essencial em minha vida profissional e pessoal.*

A todos Professores membros da banca de defesa*, por contribuírem para o aperfeiçoamento desse trabalho.*

Á Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) *- Código de Financiamento 001 - pela bolsa de estudo no período inícial do doutorado.*

A Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) *pelo fornecimento da bolsa de Doutorado, processo FAPESP Nº 2017/07963-0 e pela bolsa de Doutorado sanduíche no Exterior (BEPE) processo FAPESP Nº 2019/09877-9.*

Saber viver

A vida é o dever que nós trouxemos para fazer em casa.
Não sei…
se a vida é curta
ou longa demais para nós.
Mas sei que nada do que vivemos
tem sentido,
se não tocarmos o coração das pessoas.

Muitas vezes basta ser:
colo que acolhe,
braço que envolve,
palavra que conforta,
silêncio que respeita,
alegria que contagia,
lágrima que corre,
olhar que sacia,
amor que promove.

E isso não é coisa de outro mundo:
é o que dá sentido à vida.

É o que faz com que ela
não seja nem curta,
nem longa demais,
mas que seja intensa,
verdadeira e pura…
enquanto durar.

Cora Coralina

RESUMO

Silva, B. R. **Avaliação do perfil metabólico, oxidativo e antropométrico em mulheres com câncer de mama.** 2022. 147 p. Tese (Doutorado) – Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, 2022.

Objetivo: Avaliar o papel da quimioterapia no perfil nutricional, metabólico e oxidativo e comparar os resultados a um grupo controle. **Métodos:** Foi realizado um estudo prospectivo. Mulheres que estavam começando a quimioterapia sem nenhum tratamento de quimioterápico prévio foram recrutadas e seguidas por 7 meses em média. O grupo controle consistiu em um grupo de mulheres sem histórico de câncer ou tratamento quimioterápico. Qualidade de vida (QV) por meio do questionário EORTC QLQ-BR23, Ingestão dietética pelo recordatório de 24h, nível de fadiga por meio do pictograma da fadiga, impedância bioelétrica, testes de desempenho físico, e amostra de sangue para análises bioquímicas e oxidativas foram coletados em 2 períodos: diagnóstico (T0) e após 1 mês da conclusão da terapia (T1), para as pacientes com câncer de mama (CM) e uma única avaliação para o grupo controle. Média, desvio padrão, regressão linear e ANOVA em SAS Studio foram usados para explorar os resultados. **Resultados**: foram incluídas 61 mulheres com CM e 59 controles. Não foram encontradas alterações de composição corporal e ingestão dietética, porém em T1 as pacientes com CM apresentaram piora da fadiga, qualidade de vida, estado nutricional, ângulo de fase (AF), lipídios séricos, níveis de inflamação, albumina, adiposidade visceral (visceral adiposity index) e cerca de 70% da amostra desenvolveu síndrome metabólica. Quando comparados ao controle, embora tenham apresentado similaridades com relação ao índice de massa corporal (IMC), composição corporal e idade, as mulheres com CM apresentaram piores resultados em todos os marcadores de saúde e pior ingestão dietética. O AF foi significativamente correlacionado com o índice de risco nutricional (NRI), teste de velocidade de marcha, dinamometria, 2,2-Diphenyl-1-picrylhydrazyl (DPPH), retinol sérico e glutationa peroxidase. **Conclusão:** Encontramos evidências de que o tratamento quimioterápico resultou na piora dos fatores prognósticos, como AF e risco nutricional e alterações metabólicas, mesmo sem alterações no peso corporal, massa gorda e ingestão alimentar. Apesar da alta prevalência de obesidade na amostra, também foi verificado risco nutricional presente, o que reforça a necessidade do acompanhamento nutricional independente de perda de peso. Em comparação ao controle, as pacientes com CM

também apresentaram características metabólicas, nutricionais e dietéticas piores. Nossos resultados mostram que o AF é uma ferramenta fácil e acessível e pode ser correlacionada com o NRI, marcadores de funcionalidade física e antioxidantes sérico em pacientes com câncer de mama, independentemente da idade ou IMC

Palavras-chave: Composição Corporal; Ângulo de Fase; Alterações Metabólicas; Estresse Oxidativo; Câncer de Mama.

ABSTRACT

Silva, B. R. **Assessment of metabolic, oxidative, and anthropometric profiles in women with breast cancer.** 2022. 147 p. Tese (Doutorado) – Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto, 2021.

Objective: To evaluate the impact of chemotherapy in the nutritional, metabolic and oxidative profile and compare the results to a control group. **Methods**: A prospective study with women starting chemotherapy with no prior chemotherapy treatment. The control group consisted of women with no history of cancer or chemotherapy treatment. Quality of life (QL) through the EORTC QLQ-BR23 questionnaire, dietary intake by the 24-hour recall, level of fatigue, bioelectrical impedance, physical performance tests, and blood sample for biochemical and oxidative analysis were collected in two-time points: diagnosis (T0) and one month after completion of therapy (T1), for patients with breast cancer (BC) and a single assessment for the control group. Mean, standard deviation, linear regression and ANOVA in SAS Studio were used. **Results**: 61 women with BC and 59 controls were included. No changes in body composition and dietary intake were found. Still, at T1, patients with BC had worsening fatigue, quality of life, nutritional status, PhA, serum lipids, inflammation, albumin, visceral adiposity (VAI), and around 70% of the sample developed metabolic syndrome. Compared to the control, although they showed similarities in body mass index (BMI), body composition and age, women with BC had worse results in all health markers and worse dietary intake. PhA was significantly correlated with NRI, gait speed test, handgrip test, DPPH, serum retinol and glutathione peroxidase. **Conclusion**: We found evidence that chemotherapy treatment worsened prognostic factors, such as PhA and nutritional risk and metabolic alterations, without body weight, fat mass, and food intake changes. Despite the high prevalence of obesity in the sample, a significant level of nutritional risk was also observed, reinforcing the need for nutritional counselling independent of weight loss. Compared to controls, patients with BC also have worse metabolic, nutritional, and dietary characteristics. Our results show that PhA is an easy, affordable, and accessible tool correlated with NRI, markers of physical functionality and serum antioxidants in BC patients, regardless of age or BMI.

Keywords: Body composition; Phase Angle; Metabolic Changes; Oxidative Stress; Breast cancer.

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APRESENTAÇÃO

Atualmente o câncer de mama é o câncer mais prevalente na população em geral. Embora esta condição tenha altas taxas de cura, as estatísticas mostram um aumento exponencial de mortes por doenças cardiovasculares, sendo estas responsáveis por 35% das mortes não relacionadas ao câncer.

Globocan, 2021; Coughlin et al., 2020.

Doença cardiovascular (DCV) é a principal causa de morte em todo o mundo, sendo esta também uma condição crescente dentre os sobreviventes do câncer de mama (CM). Pesquisas mostram que as complicações cardiovasculares estão relacionadas a mais de 1/3 da mortalidade não relacionada ao câncer e dentre as possíveis causas deste aumento, estão as alterações metabólicas. A Síndrome Metabólica (SM) frequentemente tem sido associada como possível desfecho da terapia antineoplásica. Os possíveis efeitos colaterais do tratamento clínico, associados a características próprias tumorais, tornam os indivíduos susceptíveis a um conjunto de alterações metabólicas e cardíacas. Em adição, características antropométricas e de composição corporal (obesidade) e inadequações alimentares podem contribuir para o desenvolvimento da SM.

Como um campo recente de estudo, alterações inflamatórias e a inflamação subclínica crônica, bem como o aumento do estresse oxidativo, podem estar interligados como características de base e atuarem como um gatilho para as alterações metabólicas. Considerando o exposto, optei por realizar um estudo longitudinal, que pudesse investigar o impacto da quimioterapia no aparecimento de alterações metabólicas, oxidativas e no estado nutricional e as suas associações com composição corporal e consumo alimentar em mulheres antes e após o tratamento quimioterápico. Além disso, também foi investigado o papel desempenhado exclusivamente pela obesidade em relação ao câncer, por meio de comparações com um grupo controle pareado.

Esta tese buscou, portanto, estudar os impactos da quimioterapia na sobrevida, qualidade de vida e em desfechos secundários como alteração do estado nutricional, ingestão dietética, marcadores prognósticos, metabólicos e oxidativos, antes, durante e após a quimioterapia de mulheres recém diagnosticadas com câncer de mama inicial. Esta tese é composta por 8 capítulos.

O primeiro capítulo apresenta o referencial teórico que fundamentou este trabalho, em especial um panorama geral da problemática do estudo e sua justificativa. O segundo capítulo explicita os objetivos da tese, a linha do tempo do trabalho e sua concretização está apresentada em quatro manuscritos elaborados a partir da pesquisa realizadas na Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo e no Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo.

No capítulo 3 constam os resultados e discussão sobre o impacto da quimioterapia na qualidade de vida, marcadores de funcionalidade física e estado nutricional das mulheres com câncer de mama. Consiste no manuscrito "Performance of functionality measures and phase angle in women exposed to chemotherapy for early breast cancer" publicado na revista Clinical Nutrition Espen.

O capítulo 4 contém os resultados e discussão sobre o impacto da quimioterapia nas características metabólicas e a prevalência de síndrome metabólica na amostra estudada. Consiste no manuscrito "Metabolic syndrome and unfavorable outcomes on body composition and in visceral adiposities indexes among early breast cancer women post-chemotherapy" publicado na revista Clinical Nutrition Espen.

O capítulo 5 consta o manuscrito intitulado "An evaluation of metabolic, dietetic, and nutritional status reveals impaired outcomes in breast cancer patients undergoing chemotherapy compared with a matched control group", o qual avaliou e comparou as variáveis de composição corporal, metabólicas e dietéticas das mulheres com câncer de mama pós quimioterapia em comparação a um grupo controle pareado e a um controle em eutrofia, a fim de elucidar o papel de idade e composição corporal nos desfechos encontrados.

O capítulo 6 apresenta o manuscrito “Phase angle is related with oxidative stress and antioxidant biomarkers in Breast Cancer patients undergoing chemotherapy”, submetido para publicação na Clinical Breast Cancer. Este trabalho explorou o estresse oxidativo e sua relação com o ângulo de fase, bem como os seus determinantes. Além disso, os resultados também foram comparados a um grupo controle sem câncer de mama.

No sétimo e último capítulo da tese, apresento as considerações finais, incluindo as principais implicações dos achados dos estudos para as pesquisas que possam embasar e apoiar o tratamento nutricional, e o cuidado clínico de pacientes com câncer de mama, a fim de promover melhorias no serviço prestado bem como os resultados em saúde e qualidade de vida.

Por fim, destaca-se que esta tese foi desenvolvida no Programa de Pós-Graduação em Nutrição e Metabolismo da Faculdade de Medicina de Ribeirão Preto (FMRP) da USP, instituição que contribuiu fortemente durante a minha trajetória e busca constante de conhecimentos durante esses 5 anos. Em 2017 – 2019 participei do Ambulatório de Nutrição Oncológica (ANONCO) da Profª. Drª. Paula Chiarelo, no qual colaborei em discussões e análise de composição corporal de casos clínicos. Em 2017, participei do Programa de Aperfeiçoamento de Ensino, estágio realizado junto à disciplina RNM4205, Práticas de Nutrição e Saúde III coordenado pela Profª Drª Paula Chiarelo.

Em janeiro de 2020 fui contemplada pela Fundação de Amparo à Pesquisa (FAPESP) com a bolsa de estágio no exterior (BEPE), onde realizei o doutorado sanduíche na Universidade de Alberta, Canadá, sob supervisão da Profª. Drª. Carla Prado. Essa oportunidade permitiu a investigação mais aprofundada em composição corporal por meio de técnicas mais sofisticadas como ressonância magnética, tomografia computadorizada, DEXA, novos modelos de impedância bioelétrica, ultrassom e pletismografia. Também foi realizado treinamento de análise de gasto energético por meio de calorimetria indireta e pela total body calorimetry unit, além da atuação em diferentes ensaios clínicos explorando abordagens dietéticas no estado nutricional em mulheres com câncer de mama.

1 INTRODUCÃO

Atualmente, devido a sua alta incidência, o câncer está entre as patologias com maior significância no campo de saúde pública. Os dados epidemiológicos publicados pelo GLOBOCAN em 2021, apontam que o câncer de mama atualmente é o tipo de câncer mais prevalente na população em geral em termos globais [1,2]. Segundo dados da Organização Mundial da Saúde (OMS) 626.679 mortes ocorreram em 2018 em todo o mundo [3]. Dentre os diversos tipos de neoplasias, o câncer de mama é o que mais acomete mulheres todos os anos, sendo responsável por 23% (1.380.000) de todos os casos novos de câncer e 14% (458.400) de todas as mortes por câncer [4,5]. No Brasil, para os anos de 2016-2017, foram esperados aproximadamente 66 mil casos novos [5].

Em paralelo ao câncer de mama, a obesidade apresenta-se como importante fator para alteração da homeostase e, portanto, está associada ao risco de desenvolvimento de doenças crônicas, uma vez que o tecido adiposo possui papel chave para a indução de inflamação de baixo grau [6–8]. Por meio de produção de citocinas pró inflamatórias através da ativação do sistema imune, ocorre uma cascata inflamatória que promove um estado inflamatório subclínico [9].

Cronicamente, este processo está envolvido na fisiopatologia de inúmeras condições clínicas como diabetes, doenças cardiovasculares e neurodegenerativas, diversos tipos de câncer (dentre eles o de mama), doenças hepáticas e alteração de composição coporal como a sarcopênia e caquexia [8–12]. Além disso, estas alterações, bem como o risco de desenvolvimentos de tais alterações, é principalmente agravado para mulheres na pós-menopausa [13]. Estes eventos pró-inflamatórios em indivíduos com obesidade podem ser mediados por meio da regulação de citocinas nos adipócitos e ativação do sistema imune, os quais favorecem a progressão de células neoplásicas [14].

Assim a gordura corporal, principalmente a central (visceral), é tida como agente desencadeador de alterações metabólicas como resistência a insulina, aumento dos níveis séricos de glicose, triglicérides (TG), colesterol total (CT) e lipoproteínas de baixa densidade (LDL) e redução das lipoproteínas de alta densidade (HDL), isto é a dislipidemia, que aumentam significativamente a morbidade e mortalidade cardiovascular como demonstra os dados do estudo de Framingham de forma indiscutível a relação das dislipidemias, diabetes, hipertensão arterial para o desfecho de eventos cardiovasculares [15–17].

Desta forma desarranjos metabólicos ligados ao ganho de peso também representam um risco para o desenvolvimento ou progressão do câncer e também estão correlacionados à terapêutica da doença e ao avanço da idade [18]. A patogênese do câncer de mama e a obesidade não está tão bem delimitada, porém, sabe-se que existe uma relação com o aumento de estrógeno livre no tecido adiposo [19]. O excesso de secreção de insulina também pode ser correlacionado, por meio do aumento dos níveis de fatores de crescimento celular, induzindo, portanto, à proliferação celular, a partir do controle do anabolismo e apoptose celular [20].

Em um estudo realizado por Nahas e colaboradores, foi verificado que as mulheres após o tratamento tiveram um elevado risco de desenvolver síndrome metabólica,obesidade central [21] e, também, doenças cardiovasculares [22,23]. Em outro estudo com 91 mulheres na pós-menopausa que estavam em seguimento do tratamento quimioterápico, também foi observado alto índice de comorbidades associadas, onde 50% do casos eram obesas, 36% hipertensas e 13% diabéticas [24]. Wulaningsih investigou a relação entre os marcadores inflamatórios séricos e a mortalidade por câncer de mama em mulheres com obesidade, encontrando associação significativa entre todos os marcadores e a obesidade, bem como com o risco de morte por causas cardiovasculares [25]. Além disso, as mulheres submetidas à quimioterapia também podem estar mais vulneráveis as alterações metabólicas no tecido muscular, sugerindo que o tratamento oncológico pode promover mudanças metabólicas no músculo esquelético, que resultam em obesidade sarcopênica, onde existe a associação do excesso de gordura corporal conjuntamente com a perda de massa magra [26]. Ao mesmo tempo este estresse causado pelo diagnóstico e tratamento do câncer de mama também se relaciona com ganho de peso por meio da promoção de mudança no estilo de vida, o qual é caracterizado por inatividade física e hábitos alimentares inadequados [27–29]. Em um estudo cujo objetivo era avaliar a alteração de peso durante a quimioterapia, encontrou-se uma elevação ponderal em 66,3% na amostra após o término da terapia [30].

Com relação à ingestão alimentar, o tratamento pode repercutir de diferentes maneiras; por meio da alteração de paladar, e toxicidade que ocasiona náuseas e ulcerações em todo trato gastrointestinal (mucosite) devido à quimioterapia [31]. Os efeitos decorrentes da toxicidade gastrointestinal podem ser classificados em agudos, tardios e antecipatórios, e costumam ocorrer após a infusão da quimioterapia, sendo comum a utilização de medicamentos antineoplásicos com alto potencial emético, como a ciclofosfamida, epirrubicina e a doxorrubicina, tais quais compõem alguns dos esquemas utilizados para

o tratamento do câncer de mama no Brasil [32]. Assim, a terapêutica, de forma geral contribui significativamente para as alterações do padrão alimentar que podem impactar diretamente na ingestão dietética.

Dois estudos que buscaram explorar o consumo alimentar de mulheres com câncer de mama durante o tratamento quimioterápico, encontraram alteração de apetite, peso corporal e inadequações na ingestão de nutrientes [33,34].

Outro ponto de destaque na patogênese do câncer e que contribui para aumento do estado inflamatório, é a perda da homeostase dos processos oxidativos. O aumento da produção de radicais livres somados à diminuição da atividade do sistema antioxidante, podem promover a ativação de fatores transcricionais de citocinas que iniciam ou perpetuam o processo inflamatório por meio da ativação do sistema imune [35,36]. Desta forma, o estresse oxidativo é tido como fator de risco para o aparecimento de inúmeras condições crônicas, incluindo o câncer, agravamento do tumor [37] e alterações metabólicas também associadas a inflamação [38]. Portanto, é provável a existência de uma relação entre a resposta ao tratamento e desfecho clínico ao estresse oxidativo [39].

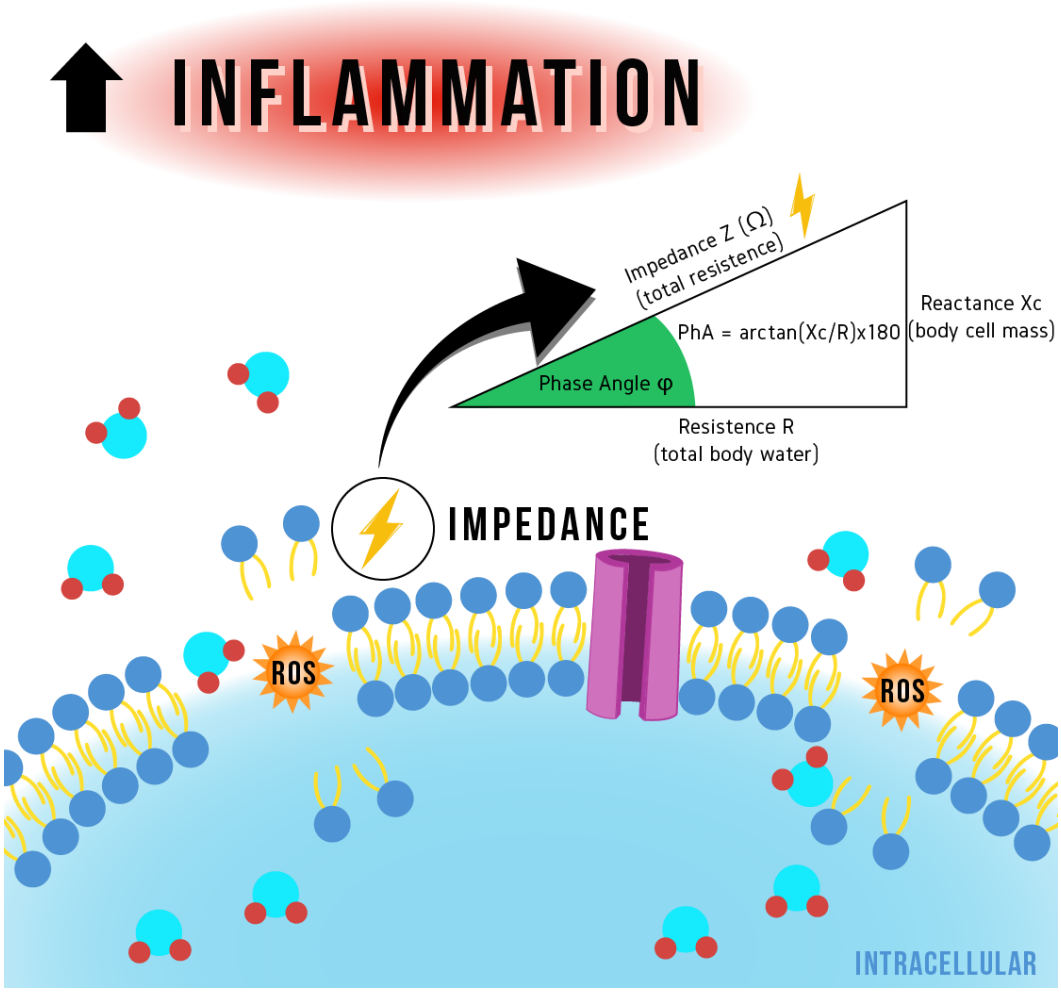
Essa alteração do perfil oxidativo difere entre os diferentes tumores, porém já esta estabelecido que tumores sólidos, dentre eles o câncer de mama, apresenta altos níveis de espécies oxidativas [40]. Em um estudo de revisão, que buscou correlacionar estresse oxidativo, câncer de mama e sua progressão, foram encontradas evidencias de que este estresse é causado pelo tratamento quimioterápico somado ao estresse gerado pelo tumor, o qual contribui para o crescimento do tumor através da angiogenese e capacidade metastática [37].

Um agravante para o desbalanço redox é a quantidade de gordura corporal, o tecido adiposo apresenta-se como mais um fator promotor do estresse oxidativo, no qual é influenciado tanto por características clinicas da doença como também pela adiposidade corporal. Desta forma, é provável que a relação estabelecida entre o câncer e a oxidação podem mudar frente à obesidade, devido aos mecanismos inflamatórios relacionados ao excesso de gordura corporal [41]. Além disso, novas evidências sugerem que o processo oxidativo também pode afetar a composição corporal e portanto o estado nutricional.

O ângulo de fase (AF) que é uma medida obtida pela impedância bioelétrica (BIA), considerado um indicador de saúde e integridade celular [42], associado a sobrevida e prognóstico em inúmeras condições clínicas, inclusive o câncer de mama [43–46], pode também estar relacionado ao processo inflamatório e oxidativo [47–52]. Em uma revisão conduzida por Silva et al em 2021, foi elucidado o potencial do AF como um marcador

de estresse oxidativo (Figura 1), principalmente considerando sua acessibilidade, custo e complexidade de execução, porém, os autores destacam que poucos trabalhos foram conduzidos para confirmar a associação [53].

Figura 1: Possível associação do ângulo de fase e estresse oxidativo.



Extraído de: Silva BR, et al., 2021[53].

Legenda: Danos celulares por espécies reativas de oxigênio (EROS) podem levar à ruptura da membrana celular, promovendo ruptura da célula e alteração no equilíbrio de água / fluido. Isso pode impactar a condutividade na célula, o que será refletido no ângulo de fase (AF). O AF também está relacionado ao conteúdo massa celular do corpo (massa celular corporal), que pode estar diminuido como resultado de lesões celulares causadas por EROS.

Dentre as medidas de intervenção, tanto para prevenção no desenvolvimento do câncer, como possivelmente no prognóstico e reincidência da doença, está o consumo de alimentos fontes de antioxidantes que podem atuar na recuperação da homeostase oxidativa [54], bem como a manutenção do peso corporal. Em um estudo realizado por Carioca e colaboradores em 2015, que buscou avaliar a associação de estresse o oxidativo e sua associação com antioxidantes, adiposidade corporal e estadiamento clínico do câncer de mama, encontrou que o aumento da ingestão de antioxidantes possui potencial de suavizar os radicais livres [55].

Portanto, a avaliação tanto de marcadores oxidativos e antioxidantes bem como sua relação com a obesidade e a composição coporal são pontos importantes na prática clínica, principalmente considerando a sobrevida e qualidade de vida da população, porém esta relação ainda não está muito clara, devido a poucos trabalhos que objetivaram elucidar esta questão inerente ao estresse oxidativo e composição corporal.

Logo, é importante a realização de trabalhos que exploram a repercursão da adiposidade e alimentação associados ao tratamento quimioterápico, visando predizer o risco de alterações metabólicas, nutricionais e o aumento do estresse oxidativo de forma precoce, bem como a abordagem de novas técnicas diagnósticas, a fim de possibilitar a adoção de intervenções dietéticas e ações direcionadas para a otimização do manejo clínico.

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2. OBJETIVOS

2.1 Objetivo Geral

Avaliar o impacto da quimioterapia no perfil oxidativo e sua relação com os marcadores prognósticos e metabólicos em mulheres portadoras de câncer de mama inicial em quimioterapia.

2.2 Objetivos Específicos

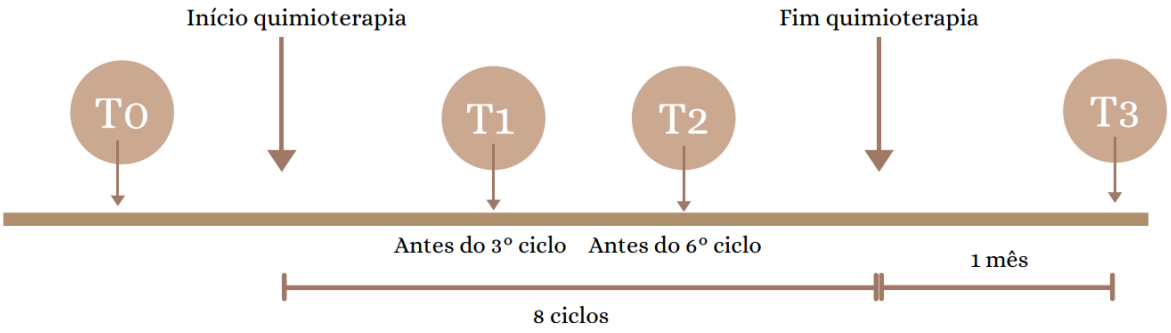
- Identificar a prevalência e incidência de obesidade em mulheres acometidas pelo câncer de mama durante a quimioterapia.
- Descrever as características metabólicas, de estado nutricional e de estresse oxidativo durante o tratamento quimioterápico.
- Comparar características nutricionais, dietéticas e metabólicas ao grupo de mulheres controle sem histórico de câncer.
- Avaliar marcadores de prognóstico clínico na amostra estudada.
- Avaliar o impacto da quimioterapia na qualidade de vida, efeitos colaterais e medidas de funcionalidade física.
- Avaliar e descrever as alterações de ingestão alimentar antes, durante e após a quimioterapia.

3. LINHA DO TEMPO

Para o desenvolvimento desta tese e cumprimento dos seus objetivos, a coleta de dados foi estruturada de forma que permitisse avaliações prévias, durante e após o tratamento quimioterápico.

Durante todo o trabalho, foraram realizadas quatro coletas de dados nos períodos: de diagnóstico (T0), durante a quimioterapia (T1, T2) e 1 mês após término do tratamento quimioterápico (T3), quando foram 8 ciclos de quimioterapia recebidos. Para as pacientes que receberam apenas 4 ciclos (n=2), foram realizadas 1 avalição durante o tratamento quimiotérapico. A figura 1 apresenta um fluxograma ilustrativo do período de coleta de dados.

Figura 1 – Fluxograma do período de avaliação das participantes.



4. PERFORMANCE OF FUNCTIONALITY MEASURES AND PHASE ANGLE IN WOMEN EXPOSED TO CHEMOTHERAPY FOR EARLY BREAST CANCER

Este capítulo apresenta o artigo intitulado “Performance of functionality measures and phase angle in women exposed to chemotherapy for early breast cancer” de autoria de Bruna Ramos da Silva, Sarah Rufato, Mirele Mialich, Loris Cruz, Thais Gozo e Alceu Afonso Jordão Junior. O artigo foi públicado na revista *Clinical Nutrition Espen* em abril de 2021 (autorização do uso do artigo na seção 9. Anexos). A seguir é apresentado a referência completa bem como o número DOI da publicação.

Ramos da Silva B, Mialich MS, Cruz LP, Rufato S, Gozzo T, Jordao AA. Performance of functionality measures and phase angle in women exposed to chemotherapy for early breast cancer. Clin Nutr ESPEN 2021. Volume 42, April 2021, Pages 105-116. **https://doi.org/https://doi.org/10.1016/j.clnesp.2021.02.007**.

Performance of functionality measures and phase angle in women exposed to chemotherapy for early breast cancer

Bruna R. Silva[1], Mirele S. Mialich[1], Loris P. Cruz[2], Sarah Rufato[1], Thais Gozzo[2], Alceu A. Jordao[1]
[1]Department of Health Sciences, Ribeirão Preto Medical School. University of Sao Paulo (USP), Bandeirantes avenue 3900, 14049-900, Ribeirão Preto, São Paulo, Brazil.
[2] Nursing School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Abstract

Purpose: The study aimed to analyze the influence of chemotherapy on nutritional status and the phase angle (PhA) as nutritional indicator for breast cancer women undergoing chemotherapy. **Methods**: A prospective study was performed. Women who were starting chemotherapy with no previous chemotherapy treatment were recruited. Quality of life (QoL) was collected using the EORTC QLQ-BR23 questionnaire. Bioelectrical impedance analysis, performance tests, and blood sample to albumin analyzes were collected at 2-time points: diagnosis (T0) and after 1 month of completion of therapy (T1). Mean, standard deviation, linear regression, and ANOVA in R were used to explore the results. **Results:** 61 women were included. We did not find any changes in body composition. However, PhA, nutritional risk index (NRI), gait speed (GS), and handgrip strength (HGS) had expressive changes ($p<0.001$). 75.4% of women had PhA values below the cut-off point of 5.6º, and the group that had a lower average of PhA also expressed low NRI. PhA was a nutritional status marker and its values were influenced by changes in NRI. ($p<0.05$). **Conclusion:** We have found supporting evidence for chemotherapy treatment resulting in worsening of prognostic factors such as PhA, and yet PhA was related to no nutritional risk. Besides a higher prevalence of obesity, 80% of the sample showed some nutritional risk level, implying the possibility of a sub-notification candidate who might benefit, for instance, from nutritional intervention in obesity groups. Further investigation about this theme may improve health measures for the prevention and screening of disease among breast cancer.

Keywords: Early breast cancer; Fatigue; Quality of life; Body Composition; Phase angle

Background

Breast cancer is the most common cancer type in women and the second one most held overall across the world [1]. Its high incidence turns the condition into a very important public health problem. In Brazil, 66,280 new cases are expected for the year 2020 [2], and, regarding mortality, the numbers remain alarming: according the report of the World Health Organization (WHO), the breast cancer is one of the principal causes of cancer-related deaths in the female population with 626,679 deaths in 2018 around the world [3]. Moreover, there is an elevated risk of appearing distant metastases, around one third of them, which can increase the severity of the disease, leading to different prognoses [4,5]. As there are many factors associated to the disease, there is a genetic component as well. Family history is considered as a risk factor for some specific genes types and, due to this, breast cancer is one of the heritable cancers, with rates of 15% of total incidence [6,7]. Besides genetic, there are other factors that cannot be changed as age, which it is more common in women in postmenopausal, occurring more frequently after 55 years old and ethnicity. Generally speaking, white women are more inclined to develop breast cancer [7,8].On another aspect, lifestyle habits are considered potentially modifiable behavioral factors, such as the overweight, which is strongly correlated to breast cancer [9]. Regarding obesity, it is not only associated to cancer but also to several chronic diseases due to metabolic alterations in which fat tissue plays a central role in inflammation prompting, especially in menopausal women [10]. The obesity systemic inflammation occurs through cytokines and chemokines pathways that have been suggested being involved in breast cancer development and neoplasia progression [9–11]. This modification in metabolic profiles, likewise, can favor the increment of growth factors such as leptin and insulin/IGF pathways, feeding the evolution and survival of tumors [12]. Considering obesity endocrine modulation, it is multifaceted and might be related to increase of estrogen levels and of insulin in the adipose mass though, controlling the anabolism and cancer cell apoptosis [13,14].Contributing to this field, adiposity-and tumor-resulted metabolic alterations can be enhanced by the chemotherapy treatment and all these factors increase the incidence of metabolic syndrome (MS) in breast cancer survivors [15,16]. In research, the authors predicted the MS prevalence of 10 – 40,5% among breast cancer women [17]. Additionally, in a previous study, our research group found an MS prevalence of approximately 54% of breast cancer survivors [18]. Also, nutritional outcomes may contribute to MS occurrence. Several studies have investigated the influences of body composition, and obesity with SM may contribute to the

development and progression of tumor affecting quality of life and survival in breast cancer [19–21].

The necessity in understanding the influence of this highlighted association between survival and nutritional alterations that breast cancer patients may be subjected, the accurate assessment of body composition, especially of body fat, lean mass, and phase angle (PhA), is fundamental given the epidemic of chronic illness [22,23]. In special it is important to underlying the potential of PhA in this area of expertise, which is acquired by bioelectrical impedance analysis (BIA), and it has been as an effective method as an indicator of cellular integrity and of cell death that contributes to cancer prognoses [24–26]. BIA is an excellent health screening tool because it is a portable, easy, practical, non-invasive and non-expensive method when compared with other health markers as blood analysis. Although, the estimation of body composition by BIA has been criticized by several authors its limited accuracy (i.e. body fat, fat-free mass), especially in a population with obesity [27–29], however, PhA has been shown as a useful tool in several clinical conditions as it is not depends on prediction equations.

The PhA is claimed to be a good malnutrition maker, especially for hospitalized patients [30], and also an indicator of sarcopenia and caquexia [31]. Besides, the researches in humans have shown evidences to support the relation of PhA an prognosis to differences conditions, such as, in head neck cancer [25], colorectal patients [32], gastrointestinal and hepatobiliary-pancreatic cancer patients [33], liver disease [34] and elderly people as well [35].

Considerer mortality, a systematic review conducted with 48 articles, found a correlation between phase angle and mortality in 42 of them [36], this same relationship between PhA and prognoses was reported in another systematic review with advanced cancer patients [37]. Specify PhA cut off values already has already proposed, a study synthesized data from 249,844 health individuals provided mean values of phase angle for males and females [38] and also specific values for breast cancer patients [24]. Additionally, in some studies the PhA has been shown as a possible marker not only for prognoses but also for inflammatory and oxidative stress in elderly women [35] and renal illness [39]. However, considering PhA as a nutritional indicator, the results are still controversial, a example is a study by Rinaldi showed that the PhA is not an independent indicator of malnutrition [40].

Nevertheless, considering the association among PhA nutritional status is still unclear, particularly for specifics populations such as breast cancer patients, research in this field

need to be conducted to fill this gap. Moreover, cancer patients can present malnutrition or fast nutritional status loss, especially patients undergoing chemotherapy, in this regard, it is essential to develop studies that explore techniques to track these changes. We hypothesized that both chemotherapy treatment may promote changes in PhA, nutritional, functional status and, PhA is an independent index also able to predict alterations in prognostics markers. In order to contribute to this field of knowledge, this study aims to investigate the association among body composition, PhA, nutritional status markers, and metabolic characteristics of women with stages I-III breast cancer before, and after chemotherapy. This may help us to identify any shortcomings in the current evidence base, allowing us to focus our public health efforts to improve and target the nutritional health care provided and ameliorate the quality of life.

Methods

Study Population

A prospective exploratory observational study was performed with female newly diagnosed with early breast cancer, patients were recruited through clinical oncology practices at Mastology ambulatory of General Hospital of School of Medicine of Ribeirao Preto, Sao Paulo, Brazil. This study received the approval from the Mastology committee of the hospital to contact all the patients followed in the breast cancer clinic, who meet the study inclusion criteria. We adopted a prospective quantitative approach in which all females with newly diagnosed breast cancer care between August 2017 to August 2019 were tracked and screened during their cancer care.

During the clinical orientation of chemotherapy, a responsible nurse informed the patient about the study, those who were interested know more about the study were forwarded to talk with the study researcher. All women treated in the hospital during the follow-up, who met the following inclusion criteria were enrolled in the study: age ≥18 years and <65 years; a histologically confirmed diagnosis of early breast cancer (range of stage I – III); and very first chemotherapy treatment course. Patients with metabolic syndrome (MS), with worse blood pressure control, which means the use of two or more antihypertensive drugs, lipid disorders, which means values above the normal range for triglycerides, total cholesterol and low dense cholesterol according to the criteria of the National Cholesterol Education Program'sAdult Treatment Panel III (NCEP-ATP III) [41] and, the Brazilian nation recommendations [42], with any type of diabetes (type I, type II, gestational) or with a more recent glucose test above 125 mg/dl according to the results available on the electronic clinical records; who previously has already received

or started chemotherapy in any other moment of life; those fitted with a defibrillator, cardiac pacemaker, metal implants or those with a local infection/wound preventing the use of bioelectric impedance analysis pads, those unable to use a handheld dynamometer due to a neuromuscular disorder were all excluded. The Institutional Review Board at the University of São Paulo, General Hospital, approved the current study.

Data Collection

We prospectively collected data at baseline, it means, before starting chemotherapy (Time 0 or T0) and, until 1 month after completing the treatment (T1), totalizing 8 cycles of chemotherapy. The average of the follow up was 7 months for each woman. Quality of life using the EORTC QLQ-BR23 questionnaire, anthropometric assessments, bioelectrical impedance analysis, muscle function measured with use of handgrip strength and of Gait speed test (4 meters), and a blood test to chemical albumin analyzes were assessed in all evaluation times (T0 and T1). Also, a written informed consent was obtained at the baseline visit.

EORTC QLQ-BR23

The European Organization for Research and Treatment of Cancer developed a measuring system for quality of life questionnaire (EORTC QLQ-C30). It is a quality of life questionnaire for cancer, and its scale has been validated in patients with multiples types of cancer, including solid tumors [43]. It is from this document that another supplementary module specific for breast cancer was developed and validated, the EORTC QLQ-BR 23 [43]. These instruments have been translated into different languages world-wide, including in Portuguese – Brazil [44]. The EORTC QLQ-BR23 is comprised of 23 questions to measure body image, sexual functioning, fatigue, future perspective, side effects, breast and arm symptoms, and psychology effects by hair loss. The average was transformed into a 0–100 scale, in which a higher score corresponds to a higher level of symptom in the symptoms scale and a higher level of functionality, in the functional scale. For the global health status, a higher score means a better quality of life.

Anthropometric Assessments

Anthropometric characteristics that were measured include body weight and body height, as proposed by Lohman [45]. Body mass index (BMI) was calculated as the ratio between the body weight and the height squared (kg/m^2). Interpretation of these results followed the international classification proposed by the World Health Organization [46].

Bioelectrical impedance analysis

Body composition was assessed by using the bioelectrical impedance multiple-frequency (BIS) analysis (Body Composition Monitor – Fresenius Medical Care®), with different frequencies (5 to 1,000 kHz). The BIS analysis provided data regarding fat mass (FM), fat-free mass (FFM) and phase angle (PhA). Moreover, the Fat Mass Index (FMI) was calculated considering fat mass (kg) / height square (m^2) [47], which was considered as cutoff for obesity value $\geq$ 9.5 kg/m^2 [48], and the skeletal muscle mass (ASM) was calculated following the equation suggested by Kyle [49], considering as cutoff values < 5.7kg/m^2. For the PhA was considered as worse prognosis values < 5.6º [24].

Physical Function:

Handgrip Strength

Handgrip strength (HGS) was assessed by the CharderMG4800 dynamometer. Patients were asked to sit comfortably with their shoulder adducted and forearm neutrally rotated, elbow flexed to 90°, and forearm and wrist in a neutral position using the dominant hand [50]. The highest value of the three tests was used for the analysis [51]. The interpretation of muscle weakness followed the classification proposed by Yang [52], where values below < 20kg where considered as weakness. Were considered as "yes" for weakness group, participants whose HGS values were below the cutoff.

Gait Speed Test 4 meters

The Gait speed (GS) test assesses physical performance and can be useful to evaluate different categories of health issue risk [53]. Each participant was timed walking 4 meters' distance without verbal encouragement, then the speed was calculated considering distance (m) / time in seconds [54]. It was used as a cutoff point for slowness <0.8m/s [55], were considered as "yes" for slowness group, participants whose GS values were below the cutoff.

Sarcopenia:

For sarcopenia diagnose, it was followed the European Working Group on Sarcopenia in Older People (EWGSOP) guideline, published in 2010, with definition and criteria for identification [56]. For sarcopenia classification, the guideline uses the evaluation of criteria as muscle mass, muscle strength, and performance, which the low muscle mass is considered as the first indicative. The value of ASM was used as muscle mass.

Fatigue assessment:

Fatigue was evaluated through a pictographic instrument created especially for cancer patients [57] and validated to be used in Brazil [58]. The Fatigue Pictogram is an illustrated tool that has two questions about fatigue (the intensity of fatigue and impact of

fatigue) and each question has 5 pictures representing the response options, that it can be from no fatigue up to extreme fatigue.

Blood biochemical analysis

For the biochemical analysis, the parameters assessed were albumin (AL) and total protein (TP) levels. The AL and TP tests require between 3 and 8 fasting hours, however, the blood sample for those tests was collected with other regular hospital blood tests during a hospital visit, and for those orders, 12 hours of fasting were required. A nurse during the hospital blood collection collected a 9ml tube of peripheral blood in T0 and T1. This sample was processed in the laboratory of the nutrition and metabolism department of the Ribeirão Preto medical school. AL was used for nutritional risk index (NRI) calculation.

Nutritional Risk Index (NRI)

The nutritional risk index was proposed in 1988 [59] in order to assess the nutritional status of patients through albumin levels. In 2005, this index was modified [60], introducing the ideal body weight into the formula. The NRI was calculated following the equation:

NRI = (1.519 × serum albumin, g/dL) + {41.7 × present weight (kg)/ideal body weight(kg)}

The ideal body weight was calculated using the Lorentz formula, for females [61]:

Ideal weight = (height − 100) − ((height − 150)/2). In those cases that body weight was bigger than ideal weight, the fraction present weight (kg)/ideal body weight(kg) was adopted as 1 [60].

Risk stratification the NRI for malnutrition was classified as:

normal risk (≥100); mild risk (97.5 ≤ NRI<100); moderate risk (83.5≤ NRI <97.5); severe risk (NRI <83.5) [60,62]. were considered as “no” for patients with nutritional risk group, participants whose NRI values were below the cutoff (<100).

Statistical Analysis

This study was a post hoc analysis of data from an ongoing study which aim to explore possible changes in body composition, metabolic and oxidative stress parameters. All women included in this study, consistently maintained all data collection appointments and, nobody left the study, therefore, we had no missing data within participants for static analysis. Characteristics were summarized with the use of descriptive statistics such as mean, standard deviation (SD), median, interquartile range, frequency, and percentage. The associations between the variables were analyzed by the Pearson correlation

coefficient or Spearman correlation coefficient for the ordinal variable. It was applied the analysis of variance (ANOVA) to analyze whether there was a statistically significant difference between the mean values of the variables of interest and to compare the differences in the mean cross the time. The Cohen's effect size was calculated for the comparison between the means. For verification of the crude relationship between PhA (independent variable) and body composition, fatigue and measures physical functionality linear regression was performed. Multiple regression analysis was conducted to further test whether PhA was predicted by the independent variables.

The categorical variable (fatigue pictogram) was used as a Dummy variable. To assess the ability of regressions models making predictions, it was used the verification by the least square methods. A level of significance was set at 0.05, and language R on Rstudio was used for all data analysis.

Results

During the follow-up, was identified 180 new diagnostics of early breast cancer patients, in which 82 patients met the inclusion criteria. Of this total, 4 women denied participation in the study for personal reasons and 14 were excluded due to technical reasons such as no availability of bioelectrical impedance device at the baseline collect, absence at the scheduled collection visit, no fasting at the data collection visit or started chemotherapy before at baseline data collection schedule. 64 women were enrolled in the study, however due to cancer progression or changes in the treatment protocol before the baseline visit, 3 women were excluded, fig 1 present the flow chart of patient eligibility.

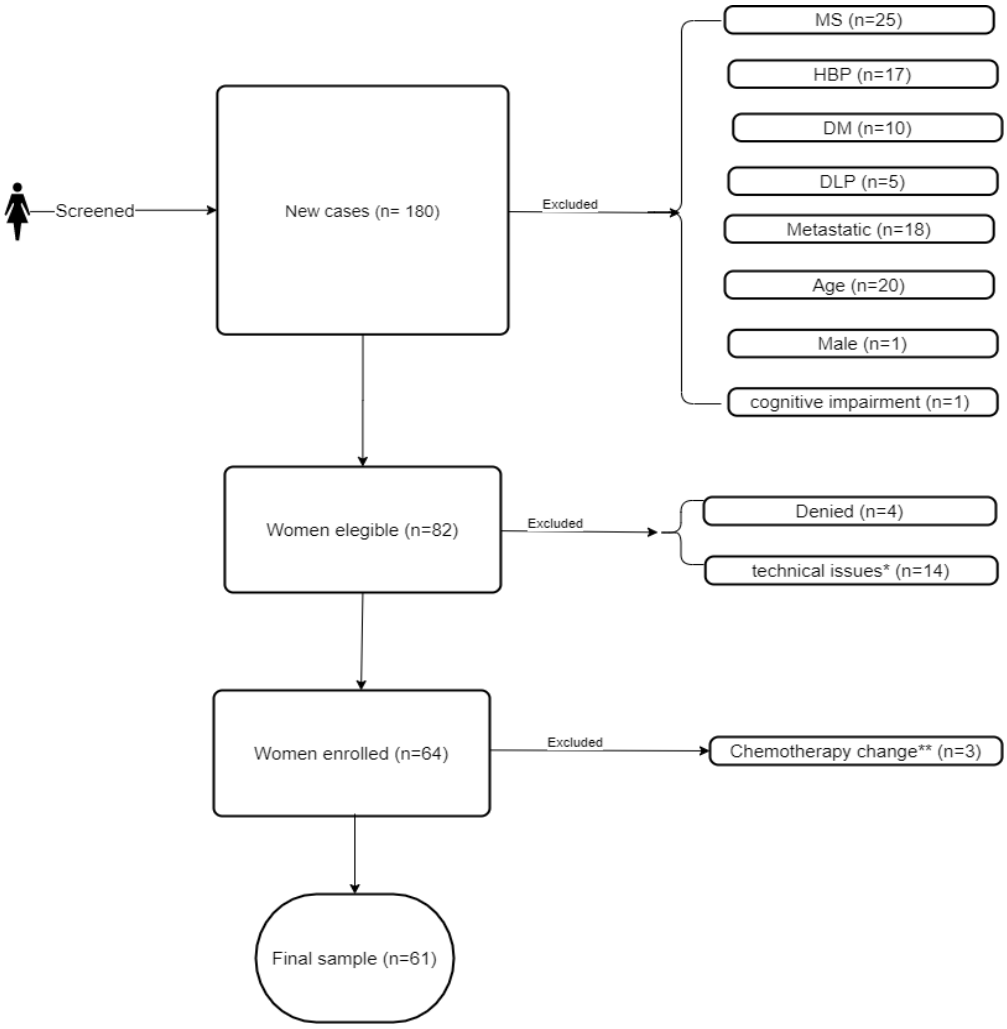


Fig. 1 Screening flowchart. Captions, MS: metabolic syndrome; HBP: high blood pressure; DM: diabetes mellitus; DLP: dyslipidemia. * technical issues include no availability of impedance bioelectrical device, absence at the scheduled collection visit, or no fasting at the data collection visit. ** change of chemotherapy protocol previously proposed before the baseline visit.

The final sample of this study included 61 women with early breast cancer (59% Stage II, 35%Stage III and 6.7% Stage I), of which 18.7% (N =12) of the participants were from the same city as the hospital and the total sample included came from 28 different cities. The mean age was 46.4 years old (range, 26 – 64 years old) and the majority of women were younger than 50 years (63.3%), all participants completed all data collection points. The principal prescribed protocol of treatment was the combination between Doxorubicin, Cyclophosphamide, and Docetaxel (AC-T), and the mean of follow-up since the first evaluation until the last evaluation was 7 months. Table 1 present the complete clinics data.

Table 1: *Sample clinic characteristics*

Variables	N	%
Age		
26 – 39	15	25%
40 – 49	23	38.30 %
50 – 59	17	27.80 %
60 – 64	6	10%
Cancer stage		
I	4	6,6%
II	36	59%
III	21	35%
Chemotherapy		
Neoadjuvant	44	72%
Adjuvant	17	28%
Expected cycle numbers		
4*	1	2%
8	60	98%
Cycles performed		
4	1	2%
5	2	3%
6	2	3%
7	5	8%
8	51	83%
Treatment Protocol		
AC	1	2%
AC-T	60	98%

* one participant received a shorter protocol of chemotherapy, for this case, the follow-up time was 4 months. Caption: AC – Cyclophosphamide and Doxorubicin; ACT – Cyclophosphamide, Doxorubicin and Docetaxel

The average of total gained of weight during the study was 1.8 kg and, according to BMI classification, it was observed a high prevalence of overweight and obesity at T0 (78.3%) with a slight worsening at T1 (81.6%) (table 2). However, the classification by NRI showed an expressive alteration with increase of nutritional moderate and severe risk on which more than half of the sample was classified as moderate (table 3).

Concerning the HGS results, it was observed a slight gradual alteration among the time whereby there was a decrease of 1.4 kg of the strength in T1 in comparison to T0. Regarding body composition results, it was detected an increase in FM (+0.23 kg) and a

decrease in FFM (-1.58 kg) when compared to the first evaluation with the last one. About mean of the values for FM in the sample, it was high since the baseline evaluation and none of the women in this study had values of ASM lower than the cut-off point, consequently, none of them were classified with any level of sarcopenia. Additionally, phase angle decreased (-0.88º, SD=0.77), with 75.4% of women at values below the cut-off point of 5.6º (table 1). Tables 2 and 3 present the complete data of the anthropometric, body composition, and nutritional status.

Table 2: *Sample characteristics*

Variable	T0	T1	P-value
Weight (kg)	71.7 (SD=12.6)	73.5 (SD=12.6)	0.843
IMC	28.54 (SD=5.46)	28.95 (SD=4.37)	0.844
NRI	101.96 (SD=9.97)	93.98 (SD=8.31)	<0.001*
FFM (KG)	34 (SD=7.1)	32.5 (SD=5.6)	0.979
FM (KG)	28.82 (SD=9.09)	28.78 (SD=8.94)	0.849
PhA	6.05 (SD=0.75)	5.16 (SD=0.77)	<0.001*
HAND GRIP (KG)	24 (SD=5.1)	22.6 (SD=5.6)	0.436
GS (M/S)	0.78 (SD=0.14)	0.78 (SD=0.16)	0.928
Fatigue Pictogram	1.57 (SD= 0.88)	2.38 (SD= 1.11)	<0.001*
Impact of Fatigue Pictogram	1.47 (SD= 0.95)	2.09 (SD= 1.11)	<0.001*
Albumin	3.97(SD+0.66)	3.45(SD+0.54)	<0.001*
Total protein	7.52(SD+0.66)	7.40(SD+0.96)	0.435

GS: gait speed; FFM: fat-free mass, FM: fat mass, PhA: phase angle; * the mean difference is significant at a level of 0.05

Table 3: *Nutritional status classification.*

Variable	Time	Classification			
NRI		**Normal risk**	**Mild risk**	**Moderate risk**	**Severe risk**
	T0	29.51% (30)	19.67% (12)	29.51% (18)	1.64% (1)

	T1	19.67% (12)	14.75% (9)	55.74% (34)	9.84% (6)
BMI (kg/m²)		**Normal weight**	**Overweight**	**Obesity**	
	T0	19.97% (12)	49.18% (30)	31.14% (19)	
	T1	16.39% (10)	50.81% (31)	32,78% (20)	
FMI (kg/m²)		**Normal value**	**Obesity**		
	T0	8.19% (5)	91.80% (56)		
	T1	4.91% (3)	95.08% (58)		

NRI: nutrition risk index, BMI: body fat index, FMI: fat mass index.

The chemotherapy impact in the QoL. A worsening in QoL was reported for both scales assessed, by the EORTC23 symptoms scale as also the global health status. As expected, the better score for the global health status was in T0, which means, before starting chemotherapy. Regarding the scale of the function, the scores increased, starting with a mean of 71.97 (SD=19.48) in T0 and going up to the higher value in the last evaluation, with a mean of 73.03 (SD=18.83). For the scale of symptoms, women started with a worsening cross the assessment – the mean in T0 was 18.28 (SD=13.96) and the mean in T1 was 31.81 (SD=11.90). Table 4 presents the description of the complete results.

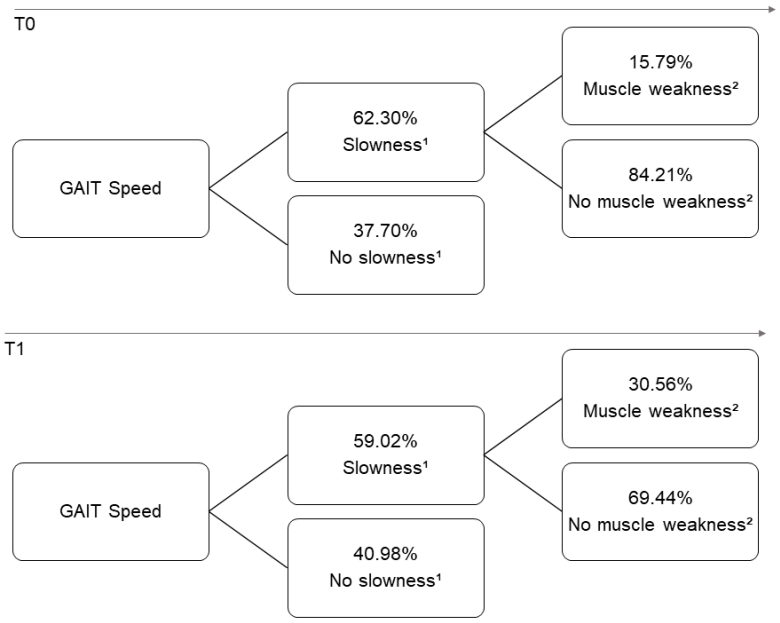
Table 4: Comparison of EORTC during the assessments

Scales	**T0**			**T1**		**P-value**
	Mean	*SD*	*SD*	*Mean*	*SD*	
Function scale	71.97	19.48	19.16	73.06	18.83	0.79
Symptoms scale	18.28	13.96	14.85	31.81	11.90	P<0.001*
Global health status	80.57	13.31	12.87	69.88	11.68	P<0.001*

* The mean difference is significant at a level of 0.05

Regarding the physical function covariates, the results indicated a higher prevalence of slowness even before starting the chemotherapy, in T0, and still higher at the end of the study, as expected. The HGS had a minimum alteration for total of the sample, however, when it was assessed the weakness together with slowness, the number of women with both conditions was the double in T1: approximately 6% of the total sample was classified as slowness and weakness in T0 and, at the end of study, it was 12% in T3 (Fig 2). Figure 2 presents the complete data.

Fig 2: Simple Diagram with the evolution of the sample physical function during the assessments



[1]for classification as slowness was used the gait speed < 0.8m/s. [2]for classification, as muscle weakness was used the grip straight < 20kg.

The PhA had a positive significant correlation for both times T0 and T1, with variables related to physical function, body composition, and nutritional status. In T0, the main correlations were with FFM, HGS and NRI, especially with FFM which the correlation was high (r=0.60). In this same period, handgrip and NRI showed a middle correlation (r=0.42; r=0.33) respectively. For T1, the significant correlations were with FFM, GS and NRI, in which the highest correlations were for GS (r=0.39) and NRI (r=0.31). Table 5 has a complete description of all correlations.

Table 5: Pearson correlation of phase angle and other studies variable

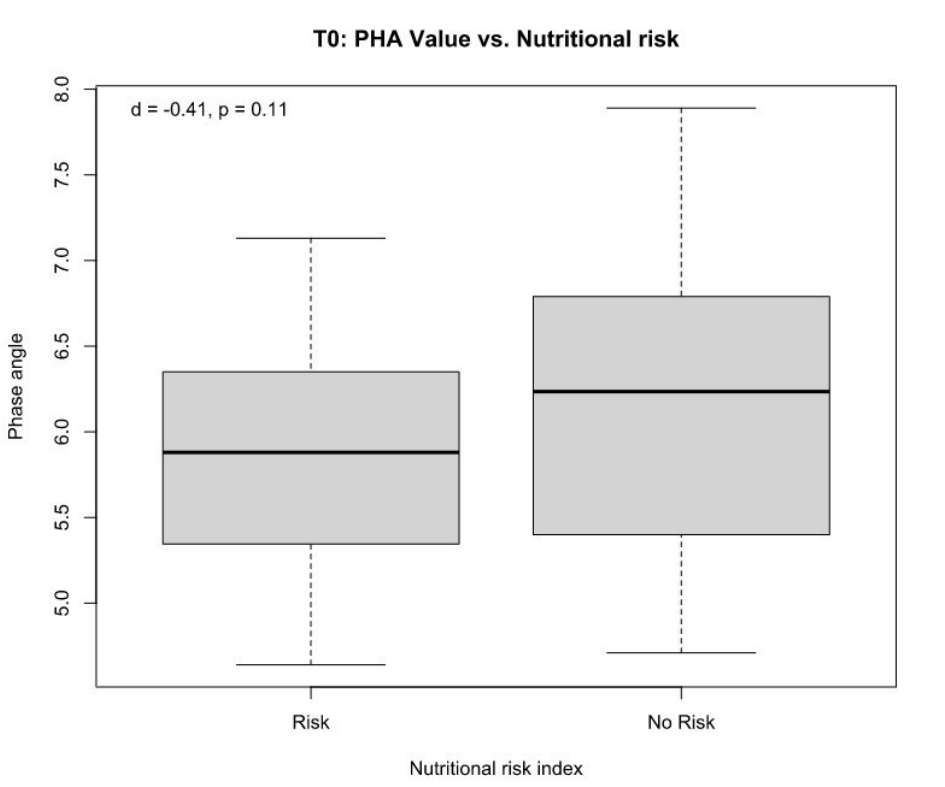
	T0		**T1**	
pairs	**r**	**p**	**r**	**p**
Weight	0.153	0.241	0.186	0.151
FM	-0.110	0.399	0.089	0.498
FFM	0.602	<0.001***	0.278	0.030*
BMI	0.150	0.248	0.215	0.097
Hand Grip	0.429	0.001**	0.083	0.526
Gait Speed	0.097	0.456	0.394	0.002**
Fatigue[1]	0.197	0.129	-0.014	0.916
Impact of	0.071	0.588	0.138	0.287

Fatigue[1]				
NRI	0.335	0.008**	0.317	0.013*

[1] spearman correlation to assess the correlation between categorical variable; *p<0.05; ** p<0.01; ***p<0.001

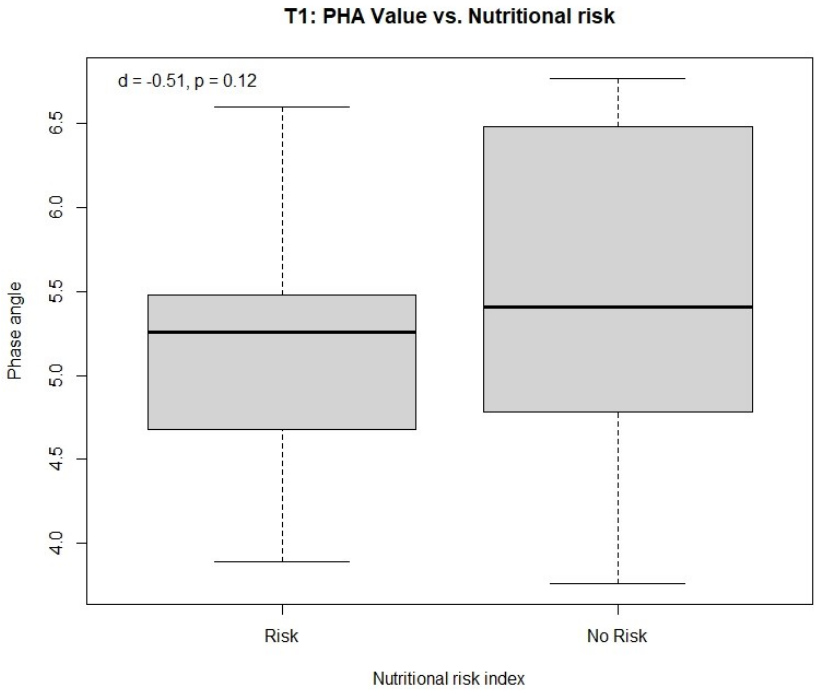
Another highlight in this sample was the distribution of the participants with lowers values of PhA among nutrition risk assessed by NRI. Women who were classified with nutritional risk by NRI also had lower mean values of PhA in both times (T0 and T1), with a worsening in T1 when compared to whom were considered as normal risk (Fig 3 and Fig 4). The Cohen' results suggest a medium effect size. Fig 3 shows the distribution of the PhA angle among the participants classified with nutritional risk and no nutritional risk at the first assessment and Fig 4 at the last assessment.

Fig 3: Distribution of phase angle results for among the participants classified with nutritional risk and no nutritional risk at the baseline evaluation.



For classification as no nutritional risk was adopted values of NRI equal or higher than 100 and nutritional risk values of NRI lower than 100 as proposed by creator author.; The mean difference is significant at a level of 0.05. d: Cohen's d.

Fig 4: Distribution of phase angle results for among the participants classified with nutritional risk and no nutritional risk at the last evaluation.



For classification as no nutritional risk was adopted values of NRI equal or higher than 100 and nutritional risk values of NRI lower than 100 as proposed by creator author. The mean difference is significant at a level of 0.05. d: Cohen's d.

It was performed a regression model to determine how much the PhA variation may be explained by NRI and then, the relation was examined for both times, first and last evaluation. The results of NRI explained 11.2% of variance in PhA (P=0.008) in T0, and 10% (P=0.01) in T1. However, when multiple regression model for parameters significantly associated with PhA was performed, considering age, handgrip, fatigue results, FFM, IMC, TP, and NRI as the independent variable, the model explained 57% in T0 (table 5) and 50% in T1 (Table 6). In the multiple model, the PhA was significantly predicted by handgrip (Beta=0.04, P<0.05) and age (Beta= -0.02, P<0.05) in T0 and by GS (Beta=2.07, P<0.05), fatigue level 2 (Beta= -0.59, P<0.05) fatigue level 4 (Beta= -1.32 P<0.01) and FFM (Beta=0.02, P<0.01). The complete data are presented in Table 6.

Table 6: Multiple linear regression analysis of variables influencing the phase angle in T0 and T1.

Coefficients	Beta	Standard error	P-value	Coefficients	Beta	Standard error	P-value
T0				T1			
Intercept	2.646843	1.131797		Intercept	0.823419	1.559511	0.60009

			0.0238 *				
HAND	0.040236	0.018066	0.0309 *	HAND	-0.009566	0.016137	0.5563
GS	-0.023629	0.495439	0.9622	GS	2.07132	0.679121	0.00383**
FatPic2	0.058879	0.211289	0.7818	FatPic2	-0.598247	0.252661	0.02225*
FatPic3	0.665263	0.339735	0.0563	FatPic3	-0.80452	0.409404	0.05559
FatPic4	-0.096424	0.556421	0.8632	FatPic4	-1.322991	0.419398	0.00286**
Impact2	-0.161447	0.26149	0.54	Impact2	0.346446	0.269648	0.20543
Impact3	-0.871951	0.486878	0.0799	Impact3	1.13287	0.35117	0.00234**
Impact4	0.295699	0.472919	0.5349	Impact4	1.508202	0.450158	0.00164**
Impact5	NA	NA	NA	Impact5	1.763421	0.817306	0.03633*
FFM	0.030737	0.015861	0.0588	FFM	0.02983	0.010995	0.00942**
NRI	0.008863	0.009895	0.375	NRI	0.023386	0.014697	0.11856
TP	0.164146	0.135912	0.2333	TP	-0.039052	0.106076	0.71449
Age	-0.02042	0.008314	0.0179 *	Age	-0.009371	0.010539	0.37863
BMI	0.009854	0.015396	0.5253	IMC	0.020474	0.016521	0.22166
Multiple R squared	0.5763			Multiple R squared	0.5065		
Adjusted R square	0.4473			Adjusted R square	0.342		
P-value	**P<0.001*** **			P-value	**P=0.001** **		

*p<0.05; ** p<0.01; ***p<0.001; HAND: handgrip; GS: gait speed; Fat Pic1: fatigue pictogram level 1; Fat Pic2: fatigue pictogram level 2; fat Pic3: Fatigue pictogram level 3; Fat Pic4: fatigue pictogram level 4; FFM: Fat-free mass; NRI: nutritional risk index; TP: total protein; BMI: Body mass index.

Discussion

In this study, breast cancer incidence was more common in younger women, before the menopausal age, and the majority presented together with obesity condition, reinforce the role of adiposity as a risk factor for breast cancer even among women with less age. Several studies have been showing the association of breast cancer and adiposity with risk as well as with progression and recurrence of the tumor [9,63,64]. The chemotherapy was a change promoter cross the time as during the 7 months of follow up it was observed significant alterations, with a pouring in QoL, side effects, anthropometric measures, body composition, physical function, and nutritional risk. The effects of adjuvant

chemotherapy on QoL of breast cancer women could be observed over-time (P<0.001). Women with post-chemotherapy were reported to show less scores for global health status when compared to the first assessment. Paraskevi (2012) in a review conducted founded similar results, that women in chemotherapy may be exposed by several side effects and negative outcomes in their QoL [65]. Interestingly, the symptoms scale was still higher during all assessments; even after 1 month of completion of treatment the score kept higher than the first evaluation, signalizing the extended side effects. Nurgali et al (2018) addressed the possibility of long-term sequelae after treatment which it is not frequently covered by the approach of symptoms management [66].

Regarding the anthropometric outcomes, the average of total weight gained was 1.8 kg, after completion of the study, which was lower than expected as the literature reports higher values. In the systematic review conducted with women who had received chemotherapy, Vence et al (2011) reported an expected common weight gains between 2.5–6.2 kg [67]. The alterations in fat and lean mass were not clinical and statistical significant during the follow-up time. For lean mass, the alteration after 7 months was 1.5 kg, and the fat mass remained almost unchanged, despite high levels for all assessments time.

Sarcopenia is a condition usually associated with cancer patients and with prognosis and progression of tumor [68,69]. It is also connected to chemotherapy outcomes [70] as well as to increase of therapeutic toxicity [71], even in obese individuals, [72] and it might be correlated with MS [73]. Although some studies have already described this disorder present in breast cancer patients [74,75], our results are contrasting due to none of the patients in this study developed sarcopenia, nonetheless it was identified a significant worsening in physical function markers.

The HGS is an indicator of an individual's muscle functionality and it could be considered as a marker for poor health status [76], and the GS is an assessment of individual's performance status and it is related to prognosis as well. Pamoukdjian et al (2017) in a cohort study showed the GS as an independent predictor of early death [77]. In weakness patients assessed by HGS, approximately 15% had conjunctly slowness at the baseline evaluation, and at T1, after chemotherapy completion, the value was the double, approximately 30%. Despite the absence of sarcopenia in the sample, the chemotherapy promoted loss of muscle quality and functionality. Bashin et al (2020) published a position statement of the Sarcopenia Definitions and Outcomes Consortium (SDOC), claiming that weakness and slowness are generally predictive of poor health

consequences and the expert collaborators were agreeable about both conditions together being included as a definition of sarcopenia [78].

Notwithstanding those contrasting findings, we also observed a deterioration in the nutritional status. During the assessments, the nutritional risk measured by NRI had an expressive increase ($P<0.005$), showing some level of risk in more than 80% of the sample. Agreeable to our findings, Gioubasanis et al (2014) appointed the nutritional risk in a sample with overweight [79]. This result represents one more factor of worsening in the survival rates, once malnutrition is considered as a prognostic indicator of bad consequences in cancer patients [80]. Even though the management of malnutrition is recognized as an important therapy, the identification of nutritional risk remains deficient, especially for obesity patient. Spiro et al (2006), in a study with oncological trainees, founded a lack of identification of malnutrition, considering BMI as a useful tool in the screenings of malnutrition [81]. In regard of obesity cancer patients, the correct nutritional assessment is not addressed due to wrong conclusion of well-nourished [79].

For the correct diagnoses of malnutrition, some techniques and tools have already been proposed, and the NRI showed to be useful for this proposal, even when compared with isolated use of albumin or BMI [82–84]. Cho et al (2018) presented NRI as a strong independent predictor of mortality even after to adjust by other variables and superior predictability then only albumin levels[85]. Albumin reductions can be associated with inflammatory conditions, in which proinflammatory mediators increase albumin losses, and consequently my not reflect nutritional status [60]. Decreases in Albumin levels also might suggest several other alterations to which hospitalized patients can be exposed as infection, renal and hepatic dysfunction, protein loss and dehydration [62]. In this context, the association of albumin another steady parameter, like body weight, as NRI is, reduces confounding variables and enhance the tracking of nutritional risk and poor clinical outcome [60,62]. Similarly with our results, the NRI showed to be useful to predicted chemotherapy side effects as well [86].

However, it is suggested that this tool used alone has a low sensitivity and specificity in the nutrition evaluation, therefore it has been recommended its use combined with others tools [87]. In this perspective, an important complement of nutritional status can be the PhA. Firstly, because several studies with patients with different chronic conditions such as HIV, cirrhosis and numerous types of cancer including breast cancer, have already established PhA as an independent marker of prognosis and survival [24,26,34,88–92]. In a review conducted in 2015 with 27 studies, the authors indicated that the use of PhA

could enhance the clinical care in prevention, diagnosis, prognosis and outcomes related to treatments that affect nutritional and overall health status [88]. PhA can be used to monitor nutritional status as well [93–95], in a study published in 2020 was found that malnutrition risk was not significantly correlated with age and serum albumin, but was correlated with lower PhA [96]. Also PhA showed be useful to identify the risk of disability [97], as a potential indicator of disease-related functionality in breast cancer patients survivors [98].

Secondly, it is useful for breast cancer patients and a cutoff of prognosis has already been proposed as values below 5.6 [24]. In our results, it was found an important decrease of PhA which the values were below 5.6, and it had a positive correlation between PhA angle and NRI whereby the greater the severity of NRI the lower the values of PhA the patients had, according to what has been shown by literature.

On top of that, PhA was also positively correlated with other prognoses markers used in this study, such as HGS, fatigue results, and GS, highlighting its importance as a tool that could be related to several health status markers, and be able to identify fluctuations in the nutritional status that only body composition results (FM and FFM) were able to. In our model of linear regression analyses, the NRI accounted for 11% of PhA angle, and conjunctly the measures of strength, physical performance, body composition, NRI and fatigue accounted for 57% of the variance in the PhA in T0 and 50% in T1. Indeed, the PhA is a promising parameter in cancer care as screening tool, this only measurement could monitor nutritional status, functionality, and fatigue without body composition alteration, as we showed in our results and besides, PhA is a prognoses indicator as other studies have already shown. Furthermore, PhA could be easily incorporated into routine patient care as it is a simple, fast, non-invasive, low-cost procedure, performed at the bedside and thus, it can help to identify the patient who needs a target nutritional intervention. An appropriate nutritional therapy remains as a fundamental goal to improve and achieve healthy values of PhA, an example can be high protein diet [99], Mediterranean diet [100] and resistance training [101].

We hypothesized that the changes in nutritional status, developing of MS, and alterations in prognostic markers as the PhA in this population can be promoted by modification of stress oxidative and the PhA is a tool able to predict them. In a study Tomereli et al (2018) showed the relation of PhA and inflammatory and oxidative marks in elderly women independently of body composition [35] and also Choi et al (2020) showed that PhA can be an independent correlated with glycemic parameters [102].

Notably, as a limitation of our study, the sample size was relatively small. For furthers studies, the comparison of different groups, including patients with metastasis, and biochemical parameters results can elucidate better both the changes promoted by chemotherapy and the relationship with PhA in breast cancer women.

Conclusion

PhA changes accompanies nutritional deterioration, and, although these patients have not developed sarcopenia, other prognostic parameters have worsened, especially in a sample of overweight women, who may mask this assessment. PhA was also positively correlated with GS and HGS. Supported by the easy applicability, low cost and the good correlation with nutritional risk, the use of parameters such as GS, HGS, and PhA have shown to be useful tools in the nutritional screening to track the individuals who will be benefit from target intervention. Future studies conducted by our group should correlate the findings of the phase angle with biochemical parameters, particularly oxidative stress evaluating the applicability of the PhA in measuring nutritional alterations in different populations and stages of breast cancer.

Declarations

Funding
São Paulo Research Foundation (FAPESP). Grant number: 2017/07963-0 and FAPESP fellowship Grant number: 2019/09877-9

Conflicts of interest/ Competing interests:
The authors declare that they have no conflict of interest.

Ethical standard
All human studies have been approved by the appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.
All persons gave their informed consent prior to their inclusion in the study.

Availability of data and material
All relevant data are within the paper

Code availability
Not aplicable

Corresponding author
Email address: bruna.ramos.silva@usp.br (Bruna Ramos da Silva)

Authors' contributions: The authors' responsibilities were as follows – AAJJ: conceptualized the study; BRS, LAPC, TOG, and AAJJ: were responsible for the research design; BRS and LAPC: conducted the research and analyzed the data; BRS, MM, and AAJJ: wrote the paper and had primary responsibility for final content; and all authors: contributed to data interpretation and read and approved the final manuscript.

Acknowledgments
We thank to Rene Augusto Avalloni de Morais for his support in the statistical analysis.

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5. METABOLIC SYNDROME AND UNFAVORABLE OUTCOMES ON BODY COMPOSITION AND IN VISCERAL ADIPOSITIES INDEXES AMONG EARLY BREAST CANCER WOMEN POST-CHEMOTHERAPY.

Este capítulo apresenta o artigo intitulado “Metabolic syndrome and unfavorable outcomes on body composition and in visceral adiposities indexes among early breast cancer women post-chemotherapy” de autoria de Bruna Ramos da Silva, Sarah Rufato, Mirele Mialich, Loris Cruz, Thais Gozo e Alceu Afonso Jordão Junior. O artigo foi publicado na revista *Clinical Nutrition Espen* em junho de 2021. A seguir é apresentado a referência completa bem como o número DOI da publicação.

Ramos da Silva B, Rufato S, Mialich MS, Cruz LP, Gozzo T, Jordao AA. Metabolic Syndrome and unfavorable outcomes on body composition and in visceral adiposities indexes among early breast cancer women post-chemotherapy. Clin Nutr ESPEN 2021. **https://doi.org/https://doi.org/10.1016/j.clnesp.2021.06.001**.

Metabolic Syndrome and unfavorable outcomes on body composition and in visceral adiposities indexes among early breast cancer women post-chemotherapy.

Bruna Ramos da Silva[1*], Sarah Rufato[1], Mirele S. Mialich[1], Loris P. Cruz[2], Thais Gozzo[2], Alceu A. Jordao[1],

*Corresponding author: Bruna Ramos da Silva (), tel: 55 16 3315 4564

[1]Department of Health Sciences, Ribeirão Preto Medical School. University of Sao Paulo, 3900, Bandeirantes Avenue, Ribeirão Preto, São Paulo, Brazil.

[2] Nursing School of Ribeirão Preto, University of Sao Paulo, 3900, Bandeirantes Avenue, Ribeirão Preto, São Paulo, Brazil.

Abstract

Purpose: The study objected to investigate potential changes in metabolic, dietary, and nutritional status in women with stages I-III breast cancer exposed to chemotherapy. **Methods**: Women who were starting chemotherapy with no previous treatment were recruited. Anthropometrics, bioelectrical impedance analysis, handgrip strength, blood pressure and blood sample were collected. Visceral adiposity index and lipid accumulation product were calculated. Dietary intake was evaluated, and the multiple source methods program was applied. Metabolic syndrome (MetS) was assessed following the NCEP-ATP III criteria (defined as 3 of 5 components of MetS). All data were collected at 2-time points: diagnosis (T0) and after 1 month of completion of therapy (T1). Mean, standard deviation, percentage, and ANOVA in SAS Studio® were used to explore the results. **Results:** 61 women were included. We did not find any changes in anthropometrics and body composition. However, phase angle, extracellular water (EX) and EX/TBW had expressive changes ($p<0.001$). The results showed changes in lipid profile ($p<0.001$), and greater unfavorable outcomes on adiposities index ($P<0.001$). At the end of the study, 68,8% (N=42) of the women developed MetS post-chemotherapy. **Conclusion:** We have found supporting evidence for chemotherapy treatment resulting in worsening of nutritional markers, lipid profile and adiposity markers. After chemotherapy part of the sample developed MetS, even without changes in body weight, fat mass, and food intake. Breast cancer patients may benefit from targeted interventions before starting chemotherapy to prevent MetS post-treatment, and therefore reduce the risk of cardiovascular disease. Further investigation into this theme is needed.

Keywords: Early breast cancer; Metabolic syndrome; Multiple Source Method program; VAI index; LAP index

Background

As a global epidemic, metabolic syndrome (MetS) is highly observed worldwide. Results from the National Health and Nutrition Examination Survey (NHANES) showed an increase of over 35% in the prevalence of MetS among adults in the United States between the reports from 1988 to 2012 [1]. In Brazil, data from the National Health Survey in 2013 found a MetS prevalence of 8.9%, which is significantly higher among women compared to men, [2,3]. MetS can be described as a set of metabolic and cardiovascular alterations, including, obesity, diabetes, hypertension, and dyslipidemia, whereby all those disorders are connected through similar metabolic pathways [4].

Related, breast cancer can be linked to MetS as a risk factor [5] and also as a result of cancer treatment [6], once breast cancer survivors can exhibit health disorders such as metabolic alterations and cardiovascular diseases [7]. Nahas et al suggested a prevalence of MetsS among women with breast cancer starting in 10% and up to 40% [8]. This association can be intensified for older women in which some insights suggest a higher risk of MetS among postmenopausal breast cancer exposed to chemotherapy [9–12]. Besides the association with treatment, frequently, the anomalous values of, fasting blood lipid levels, lipoproteins, fasting glucose, and blood pressure can be associated with nutritional imbalance [13]. Particularly, obesity role play as a trigger for these conditions. Several studies have already described the relationship between overweight and metabolic alterations where widespread obesity is related to the increasing MetS cases [14] and breast cancer incidence as well [15]. The link between obesity and metabolic issues is complex however the central key is low-grade inflammation. The fat tissue can induce a systemic inflammation through the immune activation and production of cytokines and chemokines [16] in which promotes metabolic alterations intricate with several diseases [17] and also is involved in breast cancer risk and progression [18–20]. The adipocyte cells have their endocrine modulation related to serum levels of leptin, insulin/IGF, and estrogen whereby can contribute to tumor growth [21,22]. In this context, obesity can be considered as a modifiable factor to prevent MetS and as a part of the clinical treatment to achieve better health results as well. Related to obesity the food intake and diet are important ways to manage this condition. In research were found differences in the food intake between a MetS group and a non-MetS group among patients with cancer whereby the MetS group had a higher consumption of energy and fat [23]. Was also has already suggested that MetS can be linked to the consumption of western dietary pattern, meat, and fried food while dairy could offer some level of

protection [24]. In a review the authors proposed strategies to enhance clinic outcomes among people with MetS the implementation of the Mediterranean diet, low-carbohydrate, and low-fat diet for instance [25]. Besides nutritional imbalance of energy, fat, and carbohydrate, others inadequacy also can be correlated with MetS results as low intake of fiber in the diet [26] and although controversial, might protein can be associated as well. Lim et al founded a higher consumption of protein among MetS patients [23] however, have already proposed that intakes of protein lower than the recommendation by the guidelines were associated with a higher risk of metabolic disorders, especially among women [27]. Regarding the food intake among women with breast cancer, it is possible to say that it is similar to MetS through which both diseases share the same characteristic, analogous dietary patterns with obesity [28]. Another common factor between breast cancer patients and individuals with MetS is the treatment, as in the MetS, for breast cancer greater intake of vegetables, fruit, whole cereals, and monounsaturated fat might enhance the prognoses and overall rates of survival [29]. Thus, for both conditions balanced nutritional consumption can prevent and improve the results for these patients, however more than only weight management, to enhance body composition results should be emphasized, particularly for breast cancer women. Some insights have been suggested about the impact of the treatment on nutritional and physical performance outcomes [30]. There is also an association of survival and nutritional outcomes, though just shallow measurement weight monitoring is not able to detect the alterations that breast cancer patients may be subjected [31] and for this reason to explore and to evaluate body composition and an accurate assessment of body fat, lean mass, and phase angle (PhA) is fundamental, with a special highlight for PhA, that is considered as an indicator of prognosis for breast cancer patients [32,33] and as an inflammatory marker [34,35]. Besides, not only for weight, fat mass, muscle mass, and health outcomes for breast cancer and metabolic cancer the proper diet approach might plays to improve PhA as well. Some evidence has suggested that this measurement may be modulated by the protein amount in the diet [36,37] however further investigations are needed. Nevertheless, considering the association among MetS, metabolic disorders, obesity, and dietary inadequacies and their association with poor outcomes among breast cancer patients, research in this field is needed, principally among women undergoing chemotherapy. We hypothesized that breast cancer, chemotherapy treatment, and obesity may promote changes, in nutritional and metabolic profile, and also diet might be associated with poor outcomes. In order to contribute to this field of knowledge, this study

aims to investigate potential changes in metabolic, dietary, and nutritional status in women with stages I-III breast cancer exposed to chemotherapy.

Methods

Study Population

A prospective cohort study was performed with females newly diagnosed with early breast cancer, patients were recruited through clinical oncology practices at Mastology ambulatory of General Hospital of School of Medicine of Ribeirao Preto, Sao Paulo, Brazil. This study received approval from the Mastology committee of the hospital and the Institutional Review Board at the University of São Paulo, protocol number: HCRP 14608/2017 to contact all the patients followed in the breast cancer clinic, who meet the study inclusion criteria. We adopted a prospective quantitative approach in which all females with newly diagnosed breast cancer care between August 2017 to August 2019 were tracked and screened during their cancer care.

During the clinical orientation of chemotherapy, a responsible nurse informed the patient about the study, those who were interested know more about the study were forwarded to talk with the study researcher. All women treated in the hospital during the follow-up, who met the following inclusion criteria were enrolled in the study: age ≥18 years and <65 years; a histologically confirmed diagnosis of early breast cancer (range of stage I – III); and very first chemotherapy treatment course. Patients with MetS, with worse blood pressure control, which means the use of two or more antihypertensive drugs, lipid disorders, which means values above the normal range for triglycerides, total cholesterol and low dense cholesterol according to the criteria of the National Cholesterol Education Program'sAdult Treatment Panel III (NCEP-ATP III) [38] and, the Brazilian nation recommendations [39], with any type of diabetes (type I, type II, gestational) or with a more recent glucose test above 125 mg/dl according to the results available on the electronic clinical records; who previously has already received or started chemotherapy in any other moment of life; those fitted with a defibrillator, cardiac pacemaker, metal implants or those with a local infection/wound preventing the use of bioelectric impedance analysis pads, those unable to use a handheld dynamometer due to a neuromuscular disorder were all excluded.

Data Collection

We prospectively collected data at baseline, before starting chemotherapy (Time 0 or T0), until 1 month after completing the treatment (T1), totalizing 8 cycles of chemotherapy. The last evaluation was made 1month after finalized the chemotherapy due to the possible

association between hormone therapy and the increase of MetS risk [40]. Thus, to study only the effect of chemotherapy on the sample, the last evaluation was collected before the hormone therapy starting to avoid possible bias. Anthropometric assessments, bioelectrical impedance analysis, food intake, and blood chemical analyzes were assessed at the first and last evaluations (T0 – T1). Socioeconomic, demographic, behavior, clinical, and therapeutic data were collected directly from patients using questionnaires or obtained from medical records. Also, written informed consent was obtained at the baseline visit.

Anthropometric Assessments

Anthropometric characteristics that were measured include body weight, body height, and waist (WC) and hip circumference (HC) as proposed by Lohman [41]. Body mass index (BMI) was calculated as the ratio between the body weight and the height squared (kg/m^2). Interpretation of these results followed the international classification proposed by the World Health Organization [42].

Bioelectrical impedance analysis

Body composition was assessed by using the bioelectrical impedance multiple-frequency (BIS) analysis (Body Composition Monitor – Fresenius Medical Care®), with different frequencies (5 to 1,000 kHz). The BIS analysis provided data regarding fat mass (FM), fat-free mass (FFM), phase angle (PhA), total body water (TBW), extracellular water (EW) and intracellular water (IW). It is also calculated the ratio between EI and TBW.

Handgrip Strength

Handgrip strength (HGS) was assessed by the CharderMG4800 dynamometer. Patients were asked to sit comfortably with their shoulder adducted and forearm neutrally rotated, elbow flexed to 90°, and forearm and wrist in a neutral position using the dominant hand [43]. The highest value of the three tests was used for the analysis [44]. The interpretation of muscle weakness followed the classification proposed by a Brazilian cohort [45], where values below < 16kg were considered as weakness. Were considered as “yes” for the weakness group, participants whose HGS values were below the cutoff.

Adductor Pollicis Muscle Thickness

Adductor Pollicis Muscle Thickness (APMT) was measured by using a Lange skinfold calliper. Patients sat in a chair with both arms relaxed and the elbows at a 90-degree angle with the hands over the legs. APMT was measured by skinfold calliper with continuous pressure of 10 g/mm2 to the dominant hand, in the vertex of an imaginary triangle formed by extension of the thumb and index finger [46]. 3 measurements were done and the mean

between the measurements was considered. Low APMT value for females was considered less than 19.8mm [47].

Dietary data collection

Dietary data collection occurred using a 4-dietary recall of 24 hours for study, the specific time frame was from the time the participant awoke in the morning to the time they slept at night. For this method was used the methodology of the triple-pass 24-hour recall according to Nightingale et al [48] to improve the accuracy for quantification of the recall. The results obtained by the recall were inserted in the nutritional software Diet Box® to calculate the total of amount of energy and macronutrients ingested. This software uses the Brazilian table of food composition in the assessment.

Reported values were analyzed by the Multiple Source Method program (MSM) to estimate the usual intake distribution for daily-consumed nutrients. The MSM is a statistical method proposed for use in Europe by a German team [43] and is accessible through an online platform open source in which by the probability of consumption and the amount consumed and regressions models correct the within-person variance of the food intake results obtained by the record and generate the usual intake for each participant [43]. Prior studies have shown that the MSM is a useful tool that provides usual nutrient and food intake estimates [44,45], thus in order to improve the accuracy of the food consumption collected data, the MSM was applied. For the protein requirements and adequacy was used for patients with breast cancer the recommendation of 1.2g/kg as proposed by ESPEN guidelines [49]. For the fiber requirements and adequacy, it was used for adult female recommendations being 25 g/d, according to a review with definitions and regulations for dietary fiber based on official recommendations by dietary reference intakes (DRIs) [50].

Blood biochemical analysis

For the blood biochemical analysis was asked fasting for 12 hours previously. A nurse during the hospital blood collection collected a 9ml tube of peripheral blood in T0 and T1. This sample was processed in the nutrition and metabolism laboratory. The peripheral blood was collected, and serum was used for the following analysis: Albumin (AL); Total protein (TP); C-reactive Protein (CRP), fasting glucose (FG); Triglycerides (TG); High-density lipoprotein (HDL) and total cholesterol levels (CT). For the low-density lipoprotein (LDL) was used the Friedwald equation [51].

Visceral Adiposity Index and Lipid Accumulation Product Index

Visceral fat dysfunction and lipid over accumulation were used to assess cardiovascular risk using the visceral adiposity index (VAI) and, The lipid accumulation product index (LAP). VAI was calculated according to the formula for women: VAI = (WC(cm)/(36,58+(BMI *1.89) *(TG/0.81) *(1.52/HDL) [52], and LAP was calculated according to the formula for women LAP= [waist (cm)−58] × TG concentration (mmol/l) [53]. For VAI index classification was considered being “metabolically healthy” was defined as VAI <1.59, and “metabolically unhealthy” as VAI ≥1.59 [54]. For LAP index classification was considered LAP >30.40 as metabolically unhealthy [55]

Metabolic Syndrome (MetS)

For diagnosing of MetS were followed the criteria of the National Cholesterol Education Program’s Adult Treatment Panel III (NCEP-ATP III) [38] and the Brazilian nation recommendations of MetS [39]. For both the MetS is characterized by three or more of these components: Waist circumference (WC) greater than 88cm; fasting glucose (FG) ≥100 mg / dL or previous diagnosis of diabetes mellitus; High dense cholesterol (HDL)<50 mg / dL; Triglycerides (TG) ≥150 mg / dL; blood pressure ≥ 130 mmHg or ≥ 85 mmHg or diagnosis of arterial hypertension.

Statistical Analysis

The sample size calculation was performed using G*Power software version 3.1.9.4, taking into consideration the effect of chemotherapy on lipids status [56]. The effect size of 0.575 showed that with a significance level of 95% and statistical power of 80%, the minimum number of participants required was 33. This study is a post hoc analysis. All women included in this study, consistently maintained all data collection appointments and, nobody left the study, therefore, we had no missing data within participants for static analysis. Characteristics were summarized with the use of descriptive statistics such as mean, standard deviation (SD), median, and percentage. Shapiro-Wilk test was used to verify the distribution of continuous variables, and the homogeneity of variances was assessed by the Bartlett test. It was applied the analysis of variance (ANOVA) to analyze whether there was a statistically significant difference between the mean values of the variables of interest and to compare the differences in the mean across the time. ANOVA was used twice, the first test was considered the entire data, and the second the outliers were removed. The results were the same for both, thus the outliers did not influence the results reported.

A level of significance was set at 0.05, and SAS Studio on SAS Institute Inc. 2015. SAS/IML® 14.1 User's Guide, was used for all data analysis.

Results

During the recruitment was identified 180 new diagnostics of breast cancer patients, in which 57 were excluded due to previous metabolic alteration (diabetes, dyslipidemia, MetS or high blood pressure), 18 were excluded due to diagnoses of metastatic breast cancer, and 2 due to cognitive issues. 4 women denied participation in the study for personal reasons, and 14 were excluded due to technical reasons such as no availability of bioelectrical impedance device at the baseline collect, absence at the scheduled collection visit, no fasting at the data collection visit or started chemotherapy before at baseline data collection schedule. The final sample included in this study was 61 women with early breast cancer (58.3% Stage II, 35% Stage III and 6.7% Stage I), and the average or mean time from T0 to T1 was 7 months. The mean age was 46.4 years old (range, 26 – 64 years old), the majority of women were younger than 50 years (63.3%) and 65.6% were premenopausal at recruitment (N=40). The prescribed protocol of treatment was the combination between Doxorubicin, Cyclophosphamide, and Docetaxel (AC-T) according to the Brazilian Society of Clinical Oncology guidance, which recommends the combination of 4 cycles Doxorubicin 60 mg / m2 IV + cyclophosphamide 600 mg / m2 IV every 21 days, followed by 4 cycles of docetaxel 100 mg / m2 IV every 21 days [57,58]. Demographic and clinic characteristics are shown in Table 1.

Table 1**:** Sample demographics and clinic characteristics**.**

Variables	**N**	**%**
Age		
26 – 39	15	25%
40 – 49	23	38.3%
50 – 59	17	27.8%
60 – 64	6	10%
Marital status		
single	22	36%
married	39	64%
Education		
Primary incomplete	10	16.4%
Primary	24	39.4%
Secondary	23	37.7%
College / University	4	6.5%
Menopausal status		
Premenopausal	40	65.6%
Postmenopausal	21	34.4%
Cancer stage		

I	4	6,6%
II	36	59%
III	21	35%
Chemotherapy		
Neoadjuvant	44	72%
Adjuvant	17	28%
Expected cycle numbers		
4*	1	2%
8	60	98%
Cycles performed		
4	1	2%
5	2	3%
6	2	3%
7	5	8%
8	51	83%
Treatment Protocol		
AC	1	2%
AC-T	60	98%

* One participant received a shorter protocol of chemotherapy, for this case, the follow-up time was 4 months. Caption: AC – Cyclophosphamide and Doxorubicin; ACT – Cyclophosphamide, Doxorubicin and Docetaxel

The average total gain of weight during the study was 1.8 kg (table 2), and regarding body composition results, it was detected a slight alteration, with an increase in FM (+0.23 kg) and a decrease in FFM (-1.58 kg) when compared to the first evaluation with the last one. It was verified that 19.86% (N=12) of the sample had low values of HGS at the baseline, and 24,5% at T1. Concerning APMT, 57,4 % (N=35) were below the cut-off value at baseline, and 65.5% (N=40) at the last evaluation. Additionally, EX increased almost 2L. The changes in the EW and the ratio of EW, TW and PhA had an expressive reduction ($P<0.001$). It was also not found significant alterations in blood pressure results. Table 2 present the complete data of the anthropometric, body composition, and blood pressure.

Table 2: Sample characteristics.

Variable	T0	T1	P-value
Height (cm)	159.62 SD=7.01)	159.62 SD=7.01)	-
Weight (kg)	71.7 (SD=12.6)	72.1 (SD=12.40)	0.84
BMI	28.53 (SD=5.45)	29.23 (SD=5.47)	0.47
WC (cm)	94.69 (SD=11.43)	95.69 (SD=11.02)	0.62
HC (cm)	105.99 (SD=9.86)	106.09 (SD=9.86)	0.94
WHR	0.89 (SD=0.07)	0.90 (SD=0.07)	0.81

FFM (KG)	34 (SD=7.10)	33.8 (SD=8.40)	0.97
FM (KG)	28.82 (SD=9.09)	28.86 (SD=10.04)	0.84
PhA	6.04 (SD=0.76)	5.18 (SD=0.76)	**<0.0001**
TBW (L)	31.9 (SD=5.12)	33.22 (SD=6.10)	0.19
EW (L)	14.35 (SD=2.20)	16.00 (SD=3.09)	**0.001**
IW (L)	17.54 (SD=3.25)	17.22 (SD=3.33)	0.58
EW/TW	0.45 (SD=0.02)	0.48 (SD=0.02)	**<0.0001**
BP sys [mmHg]	126.62 (SD=19.73)	129.78 (SD=18.12)	0.32
BP dia [mmHg]	80.70 (SD=12.27)	81.76 (SD=12.27)	0.78

WC: Waist Circumference, HC: Hip Circumference, WHR: Waist-hip ratio, BMI: Body mass index, APMT: Adductor Pollicis Muscle Thickness, HGS: Handgrip Strength, FFM: Fat-free mass, FM: Fat Mass, PhA: Phase angle. TBW: Total body water. EW: Extracellular water. IW: Intracellular water. EX/TW: the ratio between extracellular water and total water BP sys: Systolic blood pressure. BP dia: Diastolic blood pressure. * The mean difference is significant at a level of 0.05

Concerning food intake, during the time followed up, we have not found any significant statistical alterations in the consumption of macronutrients, fiber, cholesterol, and adequacy of protein in the diet (Table 3). However, when was assessed the percentage of women who did not achieve the daily protein recommendation for patient with cancer, was found that 56% (N=35) of the sample had protein intake lower than 90% of the recommendation by the ESPEN guidelines [49]. Although there was no difference regarding fiber intake during the assessments, the values of both times were lower than the DRIs recommendation, with a worsening in the last evaluation. We have found significant statistic alterations only regarding vitamin C levels, where was found a decrease after chemotherapy in its levels. Table 3 presents the complete results of food intake during the assessments.

Table 3: Food intake of the sample cross time.

Variable	T0	T1	P-value
Energy (kcal)	1776.23 (SD=725.75)	1700.83 (SD=494.86)	0.50
CHO (g)	235.48 (SD=103.55)	233.92 (SD=81.12)	0.92
Protein (g)	80.41 (SD=39.68)	76.40 (SD=23.14)	0.49
Protein g/kg	1.15 (SD=0.60)	1.06 (SD=0.35)	0.32
Lipids (g)	56.81 (SD=31.08)	53.09 (SD=19.30)	0.42

Col (g)	264.87 (SD=207.67)	277.01 (SD=129.27)	0.70
Fiber (g)	17.49 (SD=11.17)	15.35 (SD=6.50)	0.19
Calcium (mg)	396.95 (SD=270.71)	464.23 (SD=252.19)	0.15
Vitamin C (mg)*	150.46 (SD=115.06)	15.35 (SD=7.05)	**0.001**

Captions: CHO: Carbohydrate; Protein g/kg: it was considered the ratio between the total amount of protein and body weight for each participant. Col: Cholesterol. * The mean difference is significant at a level of 0.05.

The treatment impacted the biochemical bloody results, overall, all tests poorer after chemotherapy ($p<0.05$), especially for triglycerides, total cholesterol, and albumin ($P<0.001$), the only exceptions were for FG and TP results that remains almost the same before and after the treatment, the mean of FG and TP were in T0 92.57 (SD=14.41), 7.52 (SD=0.66) and T3 were 92.40 (SD=14.60), 7.40 (SD= 0.96) respectively. Table 4 presents the complete data of the biochemical test and their variance between the assessments.

Table 4: Biochemical blood analyses before and after chemotherapy treatment.

Variable	T0	T1	P-value
Fasting glucose	92.57 (SD=14.41)	92.40 (SD=14.60)	0.949
Triglycerides*	114.86(SD=51.80)	180.63(SD=80.83)	**<0.001**
High-density lipoprotein (HDL)*	38.19(SD=12.04)	32.13(SD=8.20)	**0.001**
Low-density lipoprotein (LDL)*	79.06(SD=12.04)	92.02(SD=23.38)	**0.001**
Total cholesterol*	140.20(SD=23.50)	160.27(SD=26.57)	**<0.001**
Total protein	7.52(SD=0.66)	7.40(SD=0.96)	0.435
CRP	7.35(SD=13.73)	15.94(SD=31.38)	**0.05**
Albumin*	3.97(SD=0.66)	3.45(SD=0.54)	**<0.001**

Captions: CRP: C reactive protein. * The mean difference is significant at a level of 0.05.

As expected, following the changes of the lipid, after treatment, patients increased all adiposity markers, for both adiposity index (VAI and LAP), and its changes were statistically significant ($P<0.001$). Fig 1 and 2 present the distribution of VAI and LAP respectively before and after the chemotherapy.

Fig 1: Distribution for the visceral adiposity index results among the participants at the baseline and last evaluation.

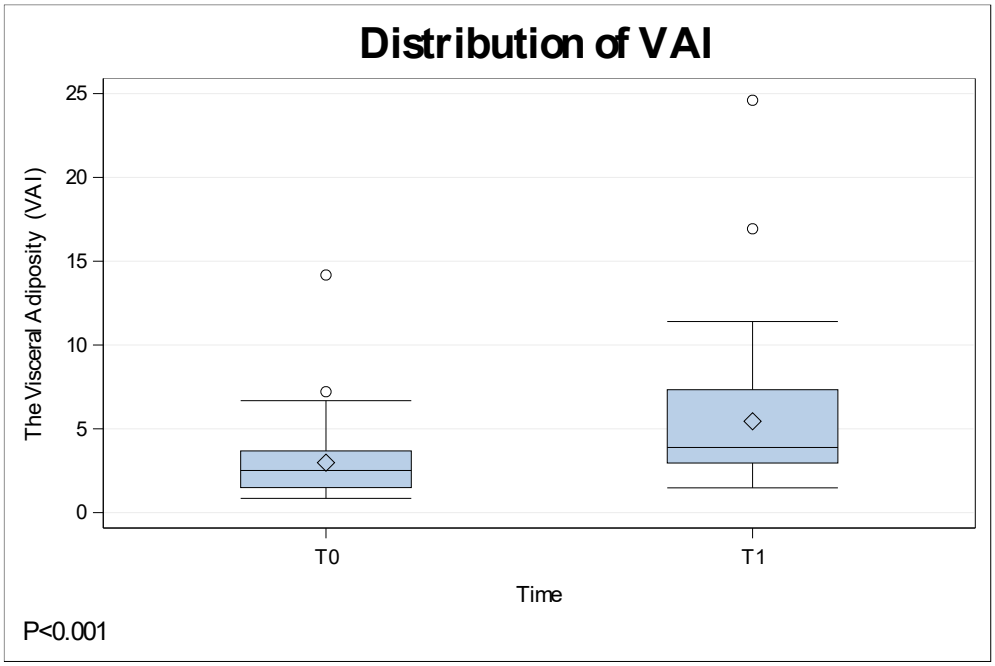
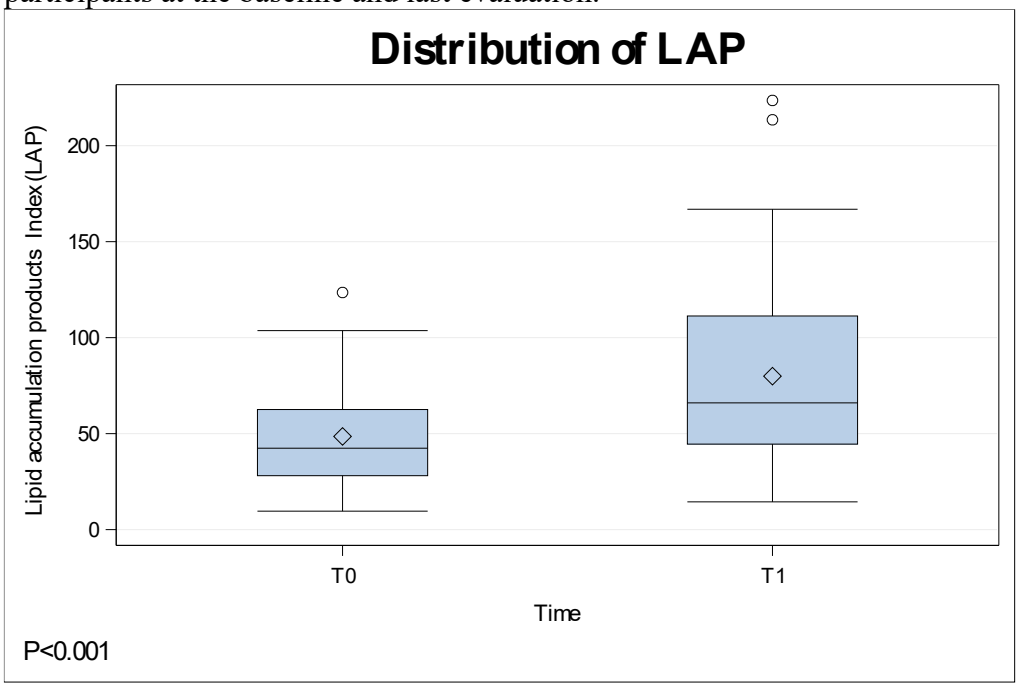


Fig 2: Distribution for the lipid accumulation products index results among the participants at the baseline and last evaluation.



At the baseline assessment, approximately 70% of the sample were classified as metabolic unhealthy by VAI and 72% by LAP. At the last evaluation, 95% were classified as metabolic unhealthy by VAI and 87% by LAP. According to BMI classification, it was observed a high prevalence of overweight and obesity at T0 (78.3%) with a slight worsening at T1 (81. 6 %), considering the classification by FMI more than 90% of the

women were classified with obesity since the first evaluation. At the end of the study, an expressive number of the women developed MetS post-chemotherapy, 68,8% (N=42) of the total of the sample, being the most participants, almost 58% (N=24) were younger than 50 years of age (Table 5). Table 5 presents the complete description of metabolic and nutritional status description.

Table 5: Description of anthropometrics and body composition results among the groups.

Variable	Time	Classification			
BMI (kg/m²)		**Normal weight**	**Overweight**	**Obesity**	
	T0	19.97% (12)	49.18% (30)	31.14% (19)	
	T1	16.39% (10)	50.81% (31)	32,78% (20)	
FMI (kg/m²)		**Normal value**	**Obesity**		
	T0	8.19% (5)	91.80% (56)		
	T1	4.91% (3)	95.08% (58)		
MetS		**No**		**Yes**	
		32 - 49 years	**50 - 64 years**	**32 - 49 years**	**50 - 64 years**
	T0	62.30% (38)	37.70% (23)	0% (0)	0% (0)
	T1	23% (14)	8.20% (5)	39.30% (24)	29.50% (18)
VAI index		**Met healthy**	**Met unhealthy**		
	T0	29.50%	70.50%		
	T1	5%	95%		
LAP index		**Met healthy**	**Met unhealthy**		
	T0	27.90%	72.10%		
	T1	13.10%	86.90%		

Caption: BMI: Body mass index; FMI: Fat mass index; MetS: Metabolic syndrome; VAI: The visceral adiposity index; Lipid accumulation product index; Met healthy: Metabolic healthy; Met unhealthy: metabolic unhealthy.

Discussion

The breast cancer incidence was less common in older women in this sample, it means after the menopausal age, and the majority presented together with an excess of weight condition, emphasized the function of adiposity as a risk factor for breast cancer, even among younger women. The most common cancer stage was II and III, due to this study was done in a high complexity hospital, which means the predominance of more advanced to complicated clinical cases. In this sample, chemotherapy promoted worsening in prognostic markers for breast cancer and nutritional status, visceral adiposity markers as well as metabolic profile ($P<0.001$). Physical markers have been showing to be an important screening tool for nutritional status and prognosis, especially for patients with cancer [59]. In this context, APMT could be an accessible and cheap method to evaluate

the adductor pollicis muscle that is responsible for hand strength and function. Research has already reported APMT as a good marker for sarcopenia [60], length of hospitalization [61], nutritional status [62] and malnutrition [63]. Although in this study was not found significant alteration after chemotherapy in APMT values, it was verified high prevalence of low values of APMT for both times.

Even though the values of FM and FFM did not have a significant variation, others prognostic markers as PhA, and parameters of body water distribution also deferred after therapy ($P<0.001$). Regarding EW, it has already been related to nutritional parameters, in which malnutrition promoted an increase in EW values [64]. Similarly, EW/TBW is also a health marker, Tanaka et al (2020) reported the association between locomotive syndrome risk and frailty and EW/TBW results [65]. Alterations in hydration status also were already associated with an increase of mucositis in cancer patients and predictors of therapeutic durability in advanced lung cancer [66,67]. In our sample, important changes in EW, and EW/TBW could be observed over time, reinforcing loss of nutritional status already punctuated by low APMT values, and PhA alterations.

Was not found an alteration in the food intake in the time followed, the only exception was vitamin C, which has significantly decreased at the last assessment. One of the reasons for this may be the decrease in the intake of fresh foods and citrus fruits in response to the side effects of chemotherapy, mucositis is a possible consequence, and it becomes painful to consume these foods in the presence of this condition, however further investigations about this theme are necessary to confirm that. Regardless changes in macronutrient levels were not verified, we observed an inadequacy of the diet, especially of protein and fiber amounts. 56% of the participants had a protein intake below the recommendation for patients with cancer, in which approximately 50% of the women consumed <1.0 g/kg/day for both times. The management of protein inadequacy is essential during cancer care. Some insights have already reported the association between low protein intake, and risk of low muscle mass and sarcopenia [68,69]. Also, sarcopenia is a well-recognized condition associated with cancer patients and it is related to poor clinical outcomes, prognosis and progression of tumor [70,71]. Concerning fiber consumption, its values were below the recommendation since the baseline assessment as well. Two reviews conducted to explore the risk of breast cancer and fiber intake pointed that fiber consumption was significantly associated with a reduced risk of breast cancer for both publications [72,73], highlight the importance of the adequation of this nutrient.

Chemotherapy had a negative impact on lipid markers and adiposity index. In the current study, there were not found changes in body weight, body fat mass and food intake, especially among fat and sugar levels and yet the participants had a worsening on blood chemical analyzes. The effects of adjuvant chemotherapy on TG, CT, LDL and HDL could be observed over time ($P<0.001$). Agreeable with our results, Li et al (2018) reported levels of TC, TG, LDL were significantly higher among post chemotherapeutic patients [56]. Madssen et al (2018) also described a worsening of the lipid profile in breast cancer patients after received the treatment [74]. As a consequence of the lipids levels alterations, the adiposity markers and visceral fat dysfunction, measured by LAP and VAI index increased significantly after chemotherapy in this study.

Developed by Amato et al (2010), VAI is an adiposity index and a marker for visceral dysfunction [52], in which several studies have already been related its relationship with coronary atherosclerosis disease [75], cardiometabolic risk [76], and visceral adipose tissue measured with magnetic resonance [52]. Concordant with our results, Cardoso-Penã et al (2020) also described high VAI values in breast cancer survivors [77]. Considering LAP, this is an analogous adiposity index, developed by Kahn in 2005 [53] and it is another important complementary tool to screen visceral fat dysfunction. This index was already strongly associated with atherogenic profile [78], with of severity of non-alcoholic fatty liver disease [79], and predicted MetS [80]. Similarly, with our results, Godinho-Mota et al (2020) in a cohort of breast cancer patients found after chemotherapy a worsening in lipid profile, VAI and LAP index without alteration in food consumption [81].

A significant number of women in the study had at least 3 of the 5 criteria for MetS at the last evaluation, of which, 57% of those women were lower than 50 years old. In fact, research has been showing MetS as a possible chemotherapy outcome [8,82–85], and this condition is recognized as an adverse outcome that affects the prognoses and overall survival in patients with breast cancer [86–88]. Our results confirm these findings already reported, however, we were the first study also evaluated food intake together. The crucial point in the study is how lipids and adiposity markers can change fast, without important body composition and food consumption variation, in patients exposed to chemotherapy and were free from any serious comorbidities before starting the treatment. In addition to the clinic consequences of MetS, it also contributes to increasing the risk of various conditions such as atherosclerosis, cardiac dysfunction and other cardiovascular diseases, especially with the combination of more MetS components [89], reflecting directly to the

survival rates and clinical evolution of those women who developed MetS after chemotherapy. An appropriate target nutritional therapy remains as a fundamental goal to prevent MetS and its bad outcomes. Thus, our findings highlight the necessity to implement targeted behavioral approaches and dietetic counselling jointly at clinical cancer care to prevent unfavorable metabolic results. To further illustrate how nutrition has tremendous potential in MetS management, research has been showing the effectiveness of the dietary approach to control, treat or prevent MetS such as vegetarian diet patterns, Mediterranean diet, calorie restriction, Dietary approaches to stop hypertension (DASH diet) and the Index of Healthy Eating (HEI-2010) [90–93].

Dexamethasone was administered intravenously in low dosage (10-20mg) before each chemotherapy cycle, and also it was taken orally (4mg) twice per day, for 3 days of each Docetaxel cycle. Corticosteroids may impact body composition, insulin resistance and glucose levels, mainly when used in high doses and/or for a prolonged period [94], but in this study, we did not find significant differences between T0 and T1 regarding macronutrients intake, weight, lean mass, fat mass and blood glucose level.

Notably, as a limitation of our study, the sample size was relatively small, and we did not evaluate the physical activity level. Although we used a dietary recall to investigate food consumption which is not a gold standard, we collected multiple food records and, also, we applied the methodology of the triple-pass, and the reported values were analyzed by the Multiple Source Method, both techniques are known to increase the accuracy of the data [48,95–97]. The strengths of this study include the prospective evaluation before and after chemotherapy treatment, the strict inclusion criteria (all patients with previous metabolic disorders were excluded), the inclusion of several adiposity indexes, the use of promising prognostic markers as PhA, as well as food intake evaluation. For further studies, the comparison of different groups, including patients with metastasis, and other biochemical parameters results as inflammation and oxidative stress markers can elucidate better the mechanism involved in the metabolic changes promoted by chemotherapy and the development of MetS.

Conclusion

This prospective study has found that women undergoing breast cancer chemotherapy, after completion of the treatment had a worsening in prognostic factors and nutritional parameters, such as PhA, albumin levels, EW, EW/TBW and APMT. Also, chemotherapy promoted an increase of blood lipids, adiposity markers, visceral fat dysfunction, and

these women had at least 3 of 5 MetS parameters, without alterations in food intake, body weight or body composition, including body fat mass and fat-free mass.

In order to prevent those alterations, target nutritional therapy is needed at the begging of clinical treatment. Future studies conducted by our group should explore these findings with inflammatory and oxidative stress parameters to better understand how chemotherapy can promote alterations in adiposity markers, visceral fat dysfunction and the development of MetS.

Declarations

Funding

São Paulo Research Foundation (FAPESP). Grant number: 2017/07963-0 and FAPESP fellowship Grant number: 2019/09877-9. Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – CAPES Brasil (Coordination for the Improvement of Higher Education Personnel, in free translation) – Financing Code 001 Doctoral scholarship granted.

Conflicts of interest/ Competing interests:

The authors declare that they have no conflict of interest.

Ethical standard

All human studies have been approved by the appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

All persons gave their informed consent prior to their inclusion in the study.

Availability of data and material

All relevant data are within the paper

Code availability

Not aplicable

Corresponding author

Email address: bruna.ramos.silva@usp.br (Bruna Ramos da Silva)

Authors' contributions: The authors' responsibilities were as follows – AAJJ: conceptualized the study; BRS, LAPC, TOG, and AAJJ: were responsible for the research design; BRS and LAPC: conducted the research and analyzed the data; BRS, MM, and AAJJ: wrote the paper and had primary responsibility for final content; and all authors: contributed to data interpretation and read and approved the final manuscript.

Acknowledgments

We thank all of the research group on Nutrition and Breast Cancer of the University of São Paulo, especially the students who assisted in all phases of the study.

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6. AN EVALUATION OF METABOLIC, DIETETIC, AND NUTRITIONAL STATUS REVEALS IMPAIRED OUTCOMES IN BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY COMPARED WITH A MATCHED CONTROL GROUP.

Este capítulo apresenta o artigo intitulado “An evaluation of metabolic, dietetic, and nutritional status reveals impaired outcomes in breast cancer patients undergoing chemotherapy compared with a matched control group”. De autoria de Bruna Ramos da Silva, Sarah Rufato, Mirele Mialich, Loris Cruz, Thais Gozo e Alceu Afonso Jordão Junior. O artigo foi submetido para publicação na revista *Journal of the Academy of Nutrition and Dietetics* em 10 de janeiro de 2022 (prova de submissão na seção 9. Anexos). A seguir é apresentado o artigo submetido.

An evaluation of metabolic, dietetic, and nutritional status reveals impaired outcomes in breast cancer patients undergoing chemotherapy compared with a matched control group.

Abstract

Purpose: Nutritional status changes in breast cancer patients during treatment are prevalent. However, the metabolic implications of those alterations are poorly understood. We firstly aimed to characterize body composition, lipids, glucose levels, as well as indexes that express cardiovascular risk in breast cancer patients after completion of chemotherapy and then to compare those results with a matched control group. **Methods**: A cross-sectional nested case-control study was performed. Women who completed their chemotherapy were recruited (BC group) and compared with a group of age- and body mass index-matched (MC group), as well as a group of healthy, non-malignant women (HC group). Body composition by bioelectrical impedance analysis, handgrip strength, and blood sample were collected. Visceral adiposity, triglyceride glucose and lipid accumulation product indexes were calculated. Food consumption was assessed. **Results:** BC patients demonstrated worse values of phase angle, nutritional risk index, extracellular body water to total body water ratio and lower handgrip straight. Additionally, those women had impairments in lipids, worst glucose levels, visceral fat dysfunction and consequently higher cardiovascular risk, presenting important unhealthy dietary patterns with higher carbohydrate and caloric intake and insufficient protein and fiber ingestion. No differences were observed between MC and HC. **Conclusion:** Breast cancer patients present unhealthy metabolic, nutritional, and dietetic features when compared to a group of age- and BMI-matched non-malignant females. Also, breast cancer patients had higher levels of cardiovascular risk. Further investigations are required to examine the underlying mechanisms and the potential longitudinal changes during surveillance time.

Keywords: Early breast cancer; Nutritional status; Cardiovascular risk; Metabolic changes.

Background

Breast cancer is the most diagnosed cancer across the world, with more than 2.2 million cases in 2020 [1]. Likewise, in Brazil breast cancer was one of the most diagnosed cancers in 2020 with 66.280 new cases [2]. Although breast cancer is the main prevalent form of cancer, it has one of the best survival rates as well. In Brazil, the relative survival rate of 5 years between 2005 to 2009 was 87% [3], whereas high-income countries presented 85% to 90% during 2010 through 2014 [1]. Considering the risk factors, this tumour is strongly associated with obesity and unhealthy body composition at the diagnosis [4], however, weight gain and fat mass increase can be enhanced after treatment [5].

Not only adiposity factors are subject to alterations by cancer treatment, but several other nutritional indicators, as lean mass and sarcopenia [6], and functional capacity measured by Hand Grip Strength (HGS) [7] can also be affected. Phase angle (PhA), obtained by bioelectrical impedances, is considered both a prognosis and survival marker [8–10]. Its alteration has already been demonstrated as linked to an increased nutritional risk measured by the Nutritional risk index (NRI) after cancer treatment in breast cancer patients [11].

Similarly, metabolic changes are another possible consequence for those patients, such as lipids and glucose levels increases [12,13]. Moreover, Godinho-Mota et al (2020) reported a visceral fat dysfunction among breast cancer patients after chemotherapy [14]. Considering visceral fat accumulation, the adiposity indices as the visceral adiposity index (VAI), lipid accumulation product index (LAP), and triglyceride glucose index (TyG), could be important metabolic alterations tracking tools [15–19]. Furthermore, in a previous study, our research group found a metabolic syndrome prevalence of more than 50% of breast cancer survivors [20], and the combination of those alterations with unhealthy body composition and improperly food intake might lead to the development of secondary illness, for instance, the cardiovascular diseases in breast cancer survivors [21–23], reflecting directly to the survival rates and clinical evolution after the cancer care. However, worsening in blood pressure and metabolism components are commonly identified in the association with other conditions besides cancer and the treatment, such as age, body mass index (BMI), dietetics imbalance [24]. In particular, obesity role plays as a trigger for these alterations, in which widespread obesity is related to the increasing metabolic syndrome (MetS) cases [25].

Accordingly, a comparison group is important in order to identify whether the bad outcomes are associated with breast cancer and the treatment or it is associated with age,

BMI, and body fat mass amount, once those characteristics are also associated with breast cancer incidence [26]. We hypothesized that breast cancer patients would demonstrate impairments in lipids, glucose, and body composition, which would be worse in patients compared to a matched control group of non-malignancy history females. We further hypothesized that these impairments may be explained by the presence of unhealthy body composition and dietetic inadequacy. In order to contribute to this field of knowledge, this study aims comprehensively characterize metabolism components in breast cancer patients post-chemotherapy, and to compare body composition, metabolic profile, and food intake results to non-malignant females of similar age and BMI. We also aimed to compare breast cancer patients and matched control females to a reference group of nonmalignant, healthy normal BMIs females.

Methods

Study Population

A cross-sectional nested case-control study was performed. This study involved 88 participants: 36 patients diagnosed with early breast cancer after 1 month of chemotherapy completion (BC females), 36 non-malignant females of similar age and BMI (MC females) and 16 as a reference group of nonmalignant, healthy females (HC females) with normal BMIs (normal range). Breast cancer patients were recruited through clinical oncology practices at Mastology ambulatory of General Hospital of School of Medicine of Ribeirão Preto, São Paulo, Brazil. During the clinical consultation, a responsible nurse informed the patient about the study. Those who were interested in knowing more about it were forwarded to talk to the study researcher. Women who met the following inclusion criteria were enrolled in the study: age ≥18 years and <65 years; a histological confirmed diagnosis of early breast cancer (range of stage I – III); completion of the breast cancer chemotherapy treatment course. Patients who previously have already received or started chemotherapy in any other moment of life; with any type of diabetes (type 1, type II or had diabetes gestational); those fitted with a defibrillator, cardiac pacemaker, metal implants or those with a local infection/wound preventing the use of bioelectric impedance analysis pads, those unable to use a handheld dynamometer due to a neuromuscular disorder were all excluded. It was adopted the breast cancer patient data collection with 1 month after finalized the chemotherapy due to the possible association between hormone therapy and the increase of MetS risk [27]. Thus, to study only the effect of chemotherapy on the sample, the evaluation was made before the hormone therapy starting to avoid possible bias.

Women in both control groups (MC and HC) were recruited at the same hospital, the participants were employees or graduate student from the School of Medicine of Ribeirão Preto, São Paulo, Brazil. For both groups (BC and CG) potential participants were weighed and measured to determine BMI and completed a Health Status Screening Form to determine if they had any prior cancer or were under hormone or any other medication which could modify the metabolism that would have excluded them from participating in the study. Table 1 shows all the inclusion and exclusion criteria among the groups. After screening, the participants eligible for the study were scheduled for the data collection visit. The Institutional Review Board at the University of São Paulo, General Hospital, approved the current study, protocol number: HCRP 14608/2017.

Table 1: Eligibility criteria for all participant groups.

Criteria	Breast Cancer Patients	Matched Control	Health Control
Inclusion Criteria			
Age	> 18 years old	Within ± 3 years of matched patient	> 18 years old <60 years old
BMI		Within ± 2kg/m2 of matched patient	18.5 - 24.9
Sex	female	female	female
Clinical characteristics:			
Cancer diagnosis	Recent diagnosis of breast cancer without previous chemotherapy	No history of cancer	No history of cancer
cancer stage	Clinical stages I- III		
Treatment	After completion of chemotherapy OR finished chemotherapy course		
exclusion criteria			
metastasis			
Previous diagnosis of cancer			
Diabetes any type			
HIV			
thyroid disease that is not currently managed with medication			
Pregnancy			
BIA exclusion factors			
Uncontrolled BP			

Captions: BMI: Body mass index; BP: Blood Pressure.

Data Collection

All participants underwent anthropometric assessments, bioelectrical impedance analysis, handgrip straight test, food intake; and blood chemical analyzes were collected. Socioeconomic, demographic, behavioral, clinical, and therapeutic data were collected

directly from participants using questionnaires or obtained from medical records in the BC group. In addition, written informed consent was obtained at the begging of the visit. After 3 weeks of the data collection, a dietary food record was collected by phone call.

Anthropometric Assessments

Measured anthropometric characteristics include body weight, body height, waist (WC), and hip circumference (HC) as proposed by Lohman [28]. Body mass index (BMI) was calculated as the ratio between the body weight and the height squared (kg/m^2). Interpretation of these results followed the international classification proposed by the World Health Organization [29].

Bioelectrical impedance analysis

Body composition was assessed by using the bioelectrical impedance multiple-frequency (BIS) analysis (Body Composition Monitor – Fresenius Medical Care®), with different frequencies (5 to 1,000 kHz). The BIS analysis provided data regarding fat mass (FM), fat-free mass (FFM), phase angle (PhA), total body water (TBW), extracellular water (EW) and intracellular water (IW). It was calculated the ratio between EW and TBW as well. For the PhA, it was considered as worse values < 5.6º [8], and for the ratio between EW and TBW the overhydrated was considered as ECW/TBW ≥0.4 [30].

Handgrip Strength

Handgrip strength (HGS) was assessed by the CharderMG4800 dynamometer. Participants were asked to sit comfortably with their shoulder adducted and forearm neutrally rotated, elbow flexed to 90°, and forearm and wrist in a neutral position using the dominant hand [31] or contralateral side to mastectomy, in the adjuvant cases, and lymphedema (BC group). The highest value of the three tests was used for the analysis [32]. The interpretation of muscle weakness followed the classification proposed by a Brazilian cohort [33], in which values below < 16kg were classified as weakness. It was considered as “yes” for the weakness group participants whose HGS values were below the cutoff.

Dietary data collection

The collection of dietary data occurred through a 24-hour food record for the study. It was collected 2 dietary records: the first one was collected on the day of the study visit and the second was collected after 3 weeks. The specific time frame was from the time the participant awoke in the morning until the time they slept at night. For this method it was used the methodology of the triple-pass 24-hour recall according to Nightingale et al [36], to improve the accuracy for quantification of the recall. The results obtained by the

recall were inserted in the nutritional software Diet Box® to calculate the total amount of ingested energy and macronutrients. This software uses the Brazilian table of food composition in the assessment.

Reported values were analyzed by the Multiple Source Method (MSM) to estimate the usual intake distribution for daily-consumed nutrients. The MSM is a statistical method proposed in Europe by a German team [43] which accessible is through an open source online platform. By the probability of consumption and the amount consumed and regressions models, it corrects the within-person variance of the food intake results obtained by the record and yet it generates the usual intake for each participant [43]. Prior studies have shown that the MSM is an useful tool that provides usual nutrient and food intake estimates [44,45], thus, in order to improve the accuracy of the food consumption collected data, the MSM was applied. For the protein requirements and adequacy it was used for breast cancer patients the recommendation of 1.2g/kg, as proposed by ESPEN guidelines [37]. For the fiber requirements and adequacy, it was used for adult female recommendations being 25 g/d, according to a review with definitions and regulations for dietary fiber based on official recommendations by dietary reference intakes (DRIs) [38].

Blood biochemical analysis

For the blood biochemical analysis it was asked to all groups, to fast for 12 hours previously. During the study visit at the hospital a nurse collected a 9ml tube of peripheral blood for the BC group and a researcher nurse collected it for MC and HC groups. This sample was processed in the nutrition and metabolism laboratory. The peripheral blood was collected, and serum was used for the following analysis: Albumin (AL); Total protein (TP); C-reactive Protein (CRP); fasting glucose (FG); Triglycerides (TG); High-density lipoprotein (HDL); total cholesterol levels (CT). For the low-density lipoprotein (LDL) it was used the Friedwald equation [39].

Nutritional Risk Index (NRI)

The nutritional risk index was proposed in 1988 [40] in order to assess the nutritional status of participants through albumin levels. In 2005, this index was modified [41], introducing the ideal body weight into the formula. The NRI was calculated following the equation:

NRI = (1.519 × serum albumin, g/dL) + {41.7 × present weight (kg)/ideal body weight(kg)}

The ideal body weight was calculated using the Lorentz formula for females [42]:

Ideal weight = (height − 100) − ((height − 150)/2). In those cases that body weight was over than ideal weight, the fraction present weight (kg)/ideal body weight(kg) was adopted as 1 [41].

Risk stratification the NRI for malnutrition was classified as:

normal risk (≥100); mild risk (97.5 ≤ NRI<100); moderate risk (83.5≤ NRI <97.5); severe risk (NRI <83.5) [41,43]. It was considered as "no" for patients with nutritional risk group, participants whose NRI values were below the cutoff (<100).

Visceral Adiposity Index, Lipid Accumulation Product Index and Triglyceride Glucose Index.

Metabolic disorders, insulin resistance, visceral fat dysfunction and lipid over accumulation were used to assess cardiovascular risk by using the triglyceride glucose index (TyG), visceral adiposity index (VAI), and lipid accumulation product index (LAP). TyG was calculated as described by Simental-Mendia et al (2008), according to the formula: TyG index = Ln (Natural logarithm) [(TG(mg/dL) × FG(mg/dL)/2] [44]. VAI was calculated according to the formula for women: VAI = (WC(cm)/(36,58+(BMI *1.89) *(TG/0.81) *(1.52/HDL) [45], and LAP was calculated according to the formula for women LAP= [waist (cm)−58] × TG concentration (mmol/l) [46]. For TyG index was considered as cutoff for metabolic syndrome and insulin resistance values >8.45 for females [47]. VAI index classification considered as being "metabolically healthy" was defined as VAI <1.59, and "metabolically unhealthy" as VAI ≥1.59 [48]. For LAP index classification it was considered LAP >30.40 as metabolically unhealthy [49].

Blood pressure.

The blood pressure (BP) was evaluated using automated cuff, the Omron device (HEM-7200) from the Omron 7000 line. Two measures were taken 60 seconds apart and repeat until both measures are within 6 mmHg for both systolic and diastolic.

Statistical Analysis

The sample size calculation was performed using G*Power software version 3.1.9.4, taking into consideration the effect of chemotherapy on lipids status [50]. The effect size of 0.575 showed that with a significance level of 95% and statistical power of 80%, using a Student t-test for paired data with a 2-sided significance level of .05. The minimum number of participants required was 29. Characteristics were summarized with the use of descriptive statistics such as mean, standard deviation (SD), median, and percentage. Shapiro-Wilk test was used to verify the distribution of continuous variables. It was applied paired t-tests to compare the BC group to matched MC group, and two-tailed two-

sample t-tests were used to compare BC group to HC group as well as MC females to HC females to analyze whether there was a statistically significant difference among the mean values of the variables of interest and to compare the differences among the groups. The analysis was run twice: the first test was considered the entire data, and in the second the outliers were removed. The results were the same for both, therefore the outliers did not influence the results reported. A level of significance was set at 0.05, and SAS Studio on SAS Institute Inc. 2015. SAS/IML® 14.1 User's Guide was used for all data analysis.

Results

Regarding the BC group, during the recruitment 4 women denied participation in the study for personal reasons, and 14 were excluded due to other reasons such as absence at the scheduled collection visit or no fasting at the data collection visit. Along of 36 BC females included, 67% were Stage II, 28% were Stage III, and there were 5.5% at Stage I. The mean age was 45 years old (range, 26 – 64 years old), and the majority of women was younger than 50 years (69.5%). The prescribed protocol of treatment was the combination among Doxorubicin, Cyclophosphamide, and Docetaxel (AC-T). Demographic and clinic characteristics of the BC group are shown in table 2.

Table 2: Sample clinic characteristics.

Variables	N	%
Cancer stage		
I	2	5.50%
II	24	67%
III	10	28%
Chemotherapy		
Neoadjuvant	25	69%
Adjuvant	11	31%
Expected cycle numbers		
4*	1	3%
8	35	97%
Treatment Protocol		
AC-T	36	100%

* One participant received a shorter protocol of chemotherapy. Caption: ACT – Cyclophosphamide, Doxorubicin and Docetaxel

There were no differences between the breast cancer patients and matched and health control in terms of age (45.3 years, 44.8 years, and 41.4 years respectively, $P>0.05$), and FFM (34.2 kg, 36.1 kg and 35.2 kg years respectively, $P>0.05$). Regarding of weight, BMI, WC and FM, there were also no differences between BC and MC ($P>0.05$). According to BMI classification and FM results, it was observed a high prevalence of

overweight and obesity in the BC group as well as in the MC, and for both measurements (BMI and FM) there were significant differences when both BC and MC were compared to CH ($P<0.05$). BC females also differed from the MC and HC in terms of PhA and EX/TBW results, in which BC had the lowest values for PhA (5.3). The non-malignancy groups (MC and HC) presented better values of HGS, NRI and BP as well. Table 3 present the complete data of the anthropometric, body composition, nutritional risk, HGS, and blood pressure among the groups.

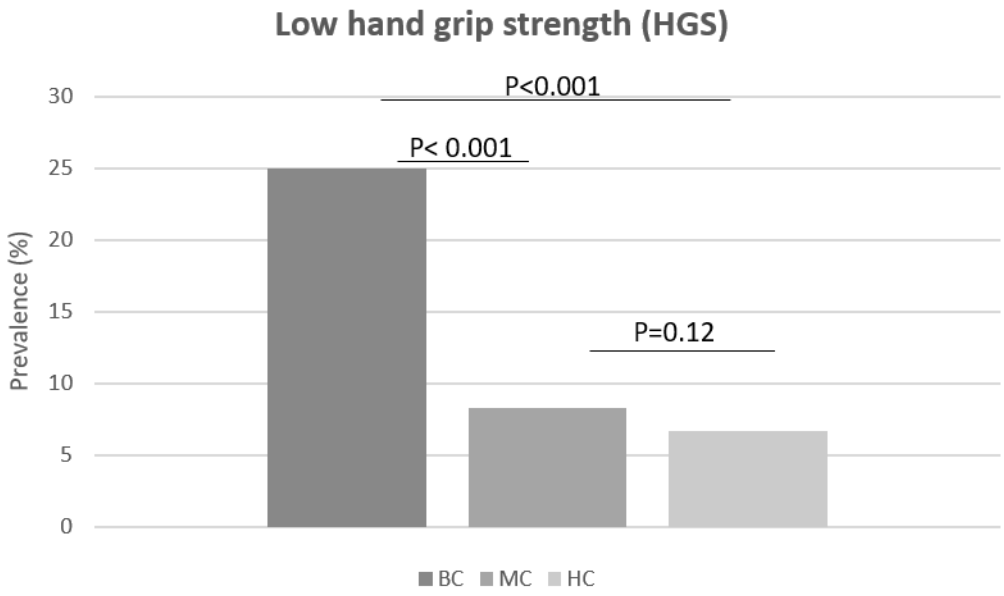
Table 3: Sample characteristics.

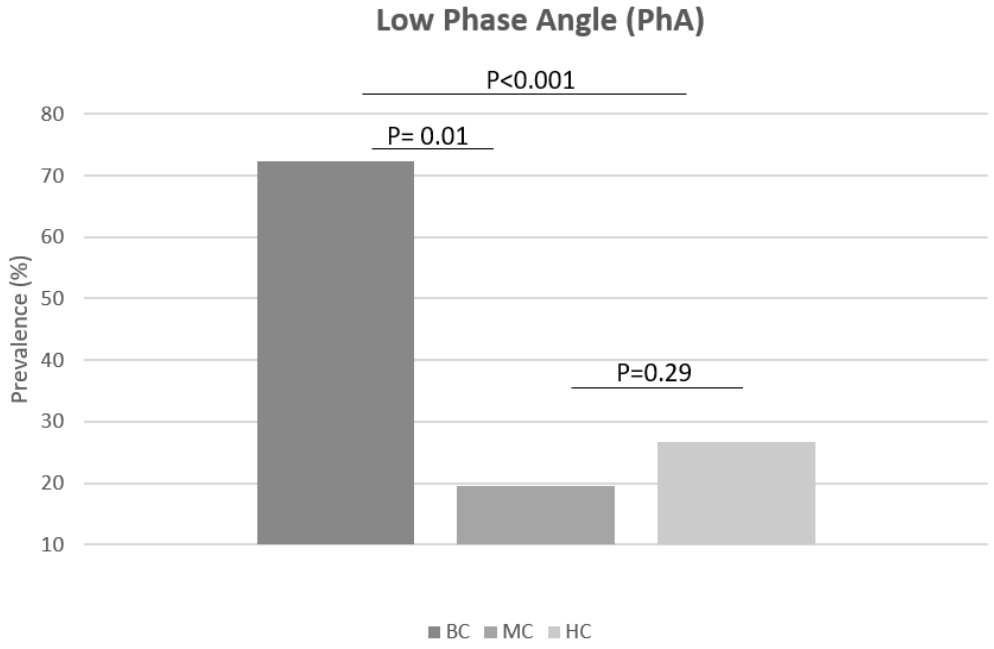
Variable	BC	MC	HC	*Significance*		
	Average and SD			BC vs MC	BC vs HC	MC vs HC
Age (y)	45.3 (SD=8.9)	44.8 (SD=9.0)	41.4 (SD=9.9)	0.23	0.18	0.23
Height (cm)	159.3 (SD=7.7)	162.9 (SD=5.8)	161.5 (SD=7.8)	**0.03**	0.37	0.47
Weight (kg)	74.0 (SD=13.8)	76.6 (SD=15.3)	59.8 (SD=8.2)	0.1	**0.03**	**0.01**
BMI	29.0 (SD=4.9)	28.6 (SD=4.7)	22.2 (SD=2.7)	0.11	**0.001**	**0.001**
WC (cm)	95.4 (SD=10.5)	94.4 (SD=11.8)	82.6 (SD=8.1)	0.56	**0.001**	**0.007**
FFM (KG)	34.2 (SD=9.5)	36.1 (SD=6.2)	35.2 (7.3)	0.28	0.7	0.65
FM (KG)	28.1 (SD=9.6)	30.1 (SD=11.3)	18.9 SD=4.4)	0.25	**0.02**	**<0.001**
PhA	5.3 (SD=0.8)	6.4 (SD=0.8)	6.3 (SD=0.9)	**<0.001**	**<0.001**	0.69
TBW	33.3 (SD=7.1)	33.5 (SD=4.8)	30.3 (SD=7.5)	0.83	0.18	0.06
EW	15.8 (SD=3.5)	14.7 (SD=2.3)	13.3 (SD=3.4)	**0.03**	**0.02**	0.08
IW	17.5 (SD=3.9)	18.5 (SD=2.7)	17.0 (SD=3.7)	0.17	0.7	0.12
EW/TBW	0.5 (SD=0)	0.4 (SD=0)	0.4 (SD=0)	**<0.001**	**<0.001**	**0.04**
BPsys [mmHg]	122.1 (SD=16.1)	115.5 (SD=13.8)	111.3 (SD=10.3)	0.06	**0.02**	0.29
BPdia [mmHg]	80.7 (SD=11.6)	74.3 (SD=9.0)	71.1 (SD=10.5)	**0.02**	**0.008**	0.28
HGS (kg)	22.5 (SD=5.7)	27.1 (SD=6.3)	24.4 (SD5.1)	**<0.001**	0.19	0.39
NRI	93.4 (SD=9.5)	101.4 (SD=7.0)	98.0 (SD=7.4)	**<0.001**	0.14	0.11

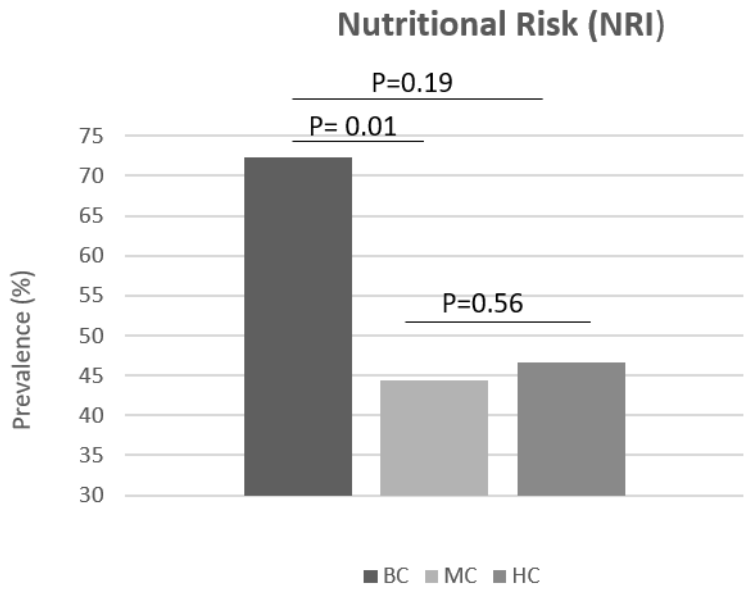
WC: Breast cancer group; MC: Matched control group; HC: healthy control group; Waist circumference, BMI: Body mass index, APMT: Adductor pollicis muscle thickness, HGS: Handgrip strength, FFM: Fat-free mass, FM: Fat mass, PhA: Phase angle. TBW: Total body water. EW: Extracellular water. IW: Intracellular water. EX/TW: The ratio between extracellular water and total water BP sys: Systolic blood pressure. BP dia: Diastolic blood pressure. NRI: Nutritional risk index * The mean difference is significant at a level of 0.05.

Considering the nutritional markers tools, BC females had the highest prevalence of inadequacy and critical values for all measurements (PhA; HGS and NRI) when compared with matched and healthy control. MC and HC had no difference in any of those markers. Figure 1 shows those comparisons.

Fig 1: Prevalence of low handgrip straight, low phase angle and nutritional risk among the groups.







CAPTIONS: BC: Breast cancer patients; MC: Matched control group; HC: Healthy control group. The mean difference is significant at a level of 0.05

Daily caloric and carbohydrate intake were higher in the BC group (1744kcal and 245.2 g respectively) and differ in statistically significance from MC for both values. The range of protein intake/kg for BC group was 0.3g/kg – 1.9g/kg, and only 41.6% of the patient (N=15) achieved the minimal recommendation from Espen guidelines. Interesting, BC females also were the group with the highest intake of fiber, being statically significant when compared to the matched group (P=0.005). Additionally, the other macronutrient distribution did not differ between any participant groups. Table 4 shows the complete food intake results and their comparisons among the groups.

Table 4: Food intake results among the groups.

Variable	**BC**	**MC**	**HC**	***Significance***		
	Average and SD			**BC vs MC**	**BC vs HC**	**MC vs HC**
Energy (kcal)	1744.3 (SD=559.1)	1363.8 (SD=572.6)	1590.2 (SD=498.0)	**0.004**	0.35	0.19
CHO (g)	245.2 (SD=93.0)	177.9 (SD=729.2)	177.8 (SD=93.2)	**0.001**	**0.02**	0.99
Protein (g)	77.9 (SD=24.0)	72.7 (SD=39.1)	78.5 (SD=25.9)	0.5	0.93	0.59
Protein g/kg	1.1 (SD=0.4)	1.0 (SD=0.6)	1.3 (SD=0.3)	0.37	0.1	0.08
Lipids (g)	50.7 (SD=21.0)	47.3 (SD=22.3)	48.5 (SD=23.1)	0.51	0.74	0.86
Col (g)	281.5 (SD=141.7)	255.3 (SD=220)	262.1 (SD=184.9)	0.99	0.69	0.83
Fiber (g)	15.9 (SD=7.5)	10.4 (SD=6.9)	13.3 (SD=7.5)	**0.005**	0.26	0.19

Captions: Breast cancer group; MC: Matched control group; HC: healthy control group; CHO: Carbohydrate; Protein g/kg: it was considered the ratio between the total amount of protein and body weight for each participant. Col: Cholesterol. * The mean difference is significant at a level of 0.05.

Concerning about biochemical results, and overall, BC group had the worst value among all analyses, and it was significantly different from the matched group in regarding of FG, TG, HDL, TC, TP, and albumin results (P<0.05). MC and HC did not differ in any biochemical parameters. Table 5 presents the complete data of biochemical test and their variance among the group results.

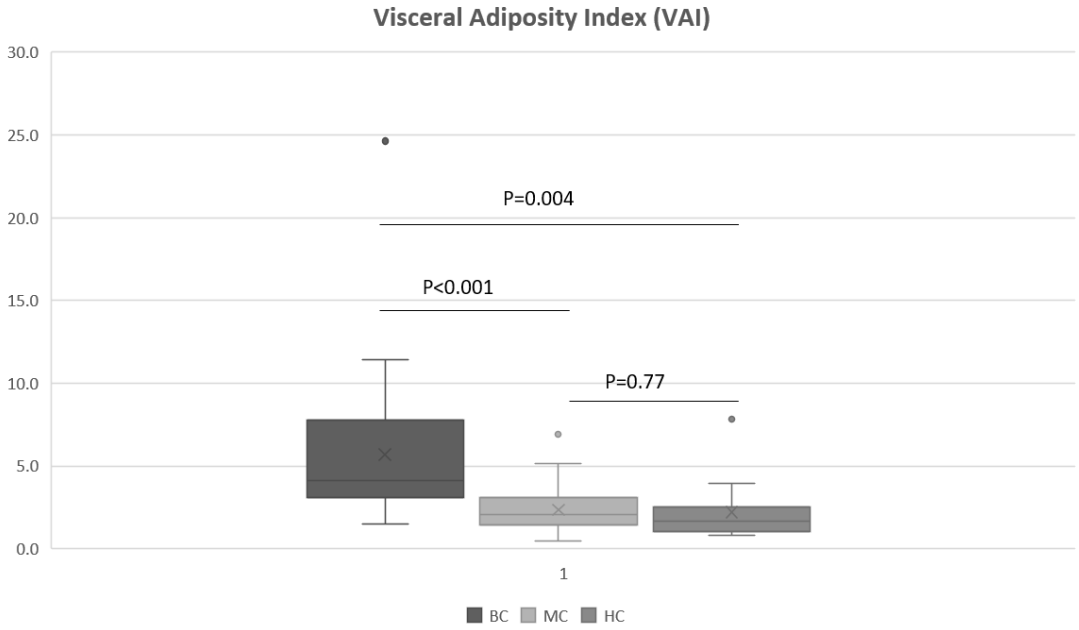
Table 5: **Biochemical test and their variance between the groups.**

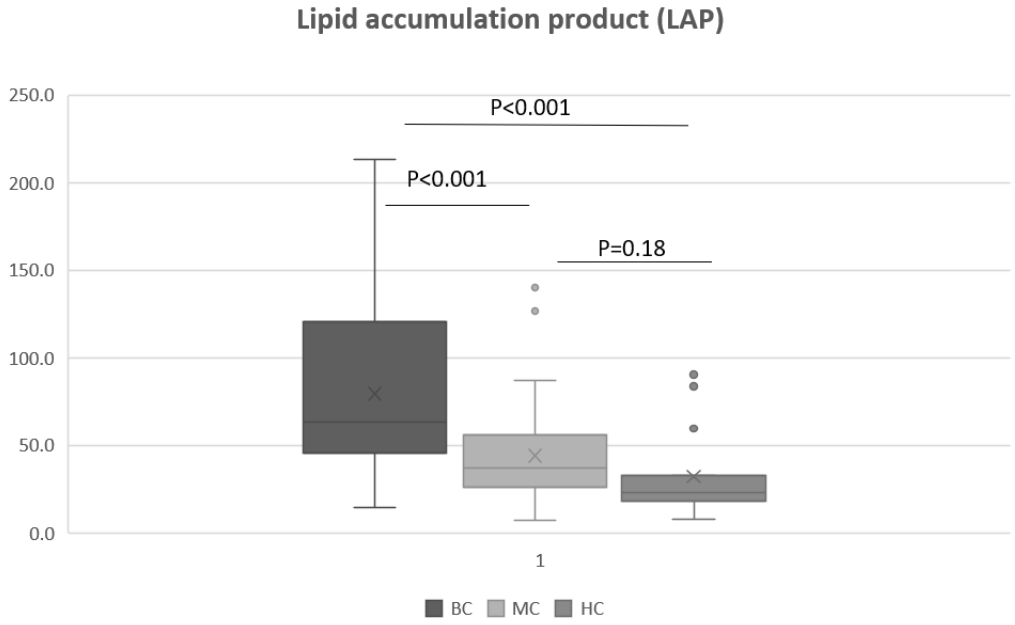
Variable	BC	MC	HC	*Significance*		
	Average and SD			BC vs MC	BC vs HC	MC vs HC
FG	96.6 (SD=13.4)	86.2 (SD=10.6)	86.7 (SD=10.2)	**0.02**	0.11	0.88
TG	178.3 (SD=85.7)	103.4 (SD=47.3)	101.6 (SD=46.9)	**<0.001**	**0.001**	0.9
HDL	30.6 (SD=7.4)	40.4 (SD=9.6)	44.8 (SD=9.5)	**<0.001**	**<0.001**	0.14
LDL	94.6 (SD=21.1)	86.1 (SD=19.0)	80.9 (SD=21.6)	0.09	**0.04**	0.4
TC	160.9 (SD=27.3)	147.1 (SD=23.1)	146 (SD=26.0)	**0.02**	0.07	0.88
TP	7.5 (SD=0.9)	8.2 (SD=0.8)	8.5 (SD=0.7)	**0.001**	**<0.001**	0.22
CRP	17.8 (SD=31.8)	12.1 (SD=12.9)	10.6 (SD=10.3)	0.4	0.46	0.67
Albumin *	3.4 (SD=0.6)	3.9 (SD=0.5)	3.7 (SD=0.5)	**<0.001**	0.12	0.15

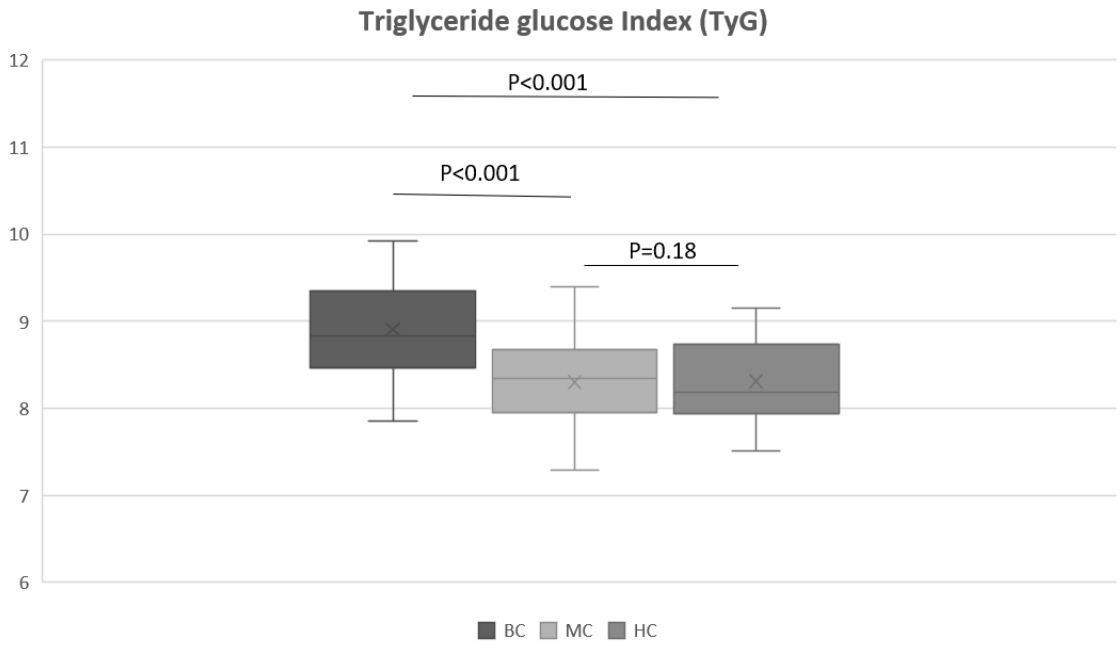
Captions: BC: Breast cancer group; MC: Matched control group; HC: healthy control group; FG: Fasting glucose; TG: Triglycerides; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; TC: Total cholesterol; TP: Total protein. CRP: C reactive protein. The mean difference is significant at a level of 0.05.

As expected, following the metabolic differences observed in table 5, BC group patients had worse values of all adiposity markers, for both adiposity index (VAI and LAP), and metabolic and cardiovascular risks measured by TyG index. For the three indices, the mean value of BC group was statistically higher (P<0.05). Furthermore, it was not found difference regarding MC and HC groups for those evaluations. Figure 2 present the distribution of VAI, LAP and TyG among the groups.

Fig 2: **Distribution of visceral fat, lipid accumulation and triglyceride glucose index among the groups.**


Visceral Adiposity Index (VAI)
30.0
25.0
20.0
15.0
10.0
5.0
0.0
P=0.004
P<0.001
P=0.77
1
BC
MC
HC


Lipid accumulation product (LAP)
250.0
200.0
150.0
100.0
50.0
0.0
P<0.001
P<0.001
P=0.18
1
BC
MC
HC



CAPTIONS: BC: Breast cancer patients; MC: Matched control group; HC: Healthy control group. The mean difference is significant at a level of 0.05

Discussion

To our knowledge, only a few articles aimed to make similar comparisons. A meta-analysis conducted by Hernandez et al (2014) identified 22 studies in which compared breast cancer patients with a control group [51]. However, only 2 studies included dietetic data besides the metabolic factors comparisons [52,53], and we were the only study conducted with Brazilian population in which included both body composition and nutrition status parameters. Breast cancer patients on average are presented with a high prevalence of abdominal obesity, high body weight, BMI and fat mass, and consequently the matched control as well. Both groups differed from the healthy control group in all of those obesity indicators.

The results of our study indicate that, despite similar age, BMI, waist and hip circumferences fat-free mass and fat mass (not statically significant), it was possible to verify impairments in aspects of nutritional status markers among BC and matched control group, but not between the MC and HC groups. BC group presented the lowest values of PhA, and the highest prevalence of low HGS, nutritional risk by NRI and overhydration by EW/TBW. All those parameters are considered indicators of poor nutritional status [8,54–56]. Regarding PhA, the BC group had values lower than the cutoff proposed by Gupta et al (2008) in which values below 5.6 are considered a sign of poor prognosis for breast cancer patients [8]. PhA values for both healthy controls did not

differ as well as NRI and HGS values. Besides nutritional status, breast cancer patients on average presented poor indicators of metabolic health, with the highest levels of BP, FG, all lipids' markers, CRP, and the lowest level of albumin. Despite significant differences in body weight, WC, and fat mass levels, MC and HC did not differ in any biochemical parameters. This result is concordant with previous research that has already reported differences in glucose metabolism and metabolic syndrome prevalence among breast cancer patients [52], as well as alterations in insulin homeostasis when compared to the control group [57].

Obesity is a condition that is frequently associated with abnormalities in lipid metabolism [58], however, in this study, we did not find lipids impairments in the MC group, only among the cancer patients. In addition to body composition, other components can contribute to lipids alterations, as the own tumor, in which lipid metabolism changes influence proliferation and dissemination of cancer cells [59], and chemotherapy itself has the potential to promotes modifications in serum lipids [60]. Thus, those components may explain the reason of presence of lipids alterations only in BC group. Moreover, poor metabolic indicators contribute to increasing the risk of various conditions such as atherosclerosis, and other cardiovascular diseases [23], and according to Bell et al (2014) metabolic syndrome components can increase risk of death by 3 times [52].

In order to verify and compare cardiovascular risk, we included in this study adiposity and lipid accumulation indices. Several studies have already shown the VAI, LAP and TyG indices as simple and good markers of cardiovascular outcomes and as screen tools for cardiovascular disease risk [61–66]. Kouli et al (2017), during a 10-year follow-up of a cohort of 3,042 adults, found that VAI was independently associated with an elevated risk of CVD in 10 years [61]. Furthermore, considering the TyG index, a study with a Brazilian population found superior performance compared to the HOMA method for estimation of insulin resistance [67]. In this study, as expected according to the discrepancies of biochemical blood results among the groups, the BC had the worst value of VAI, LAP and TyG, indicating a visceral fat dysfunction, therefore, high cardiovascular disease risk. Additionally, despite the difference in body composition, it was not found any difference of those indices among the MC and HC.

We attempted to identify possible reasons for the difference in the metabolic and nutritional markers between patients and MC females by measuring food intake as body composition did not influence those results (MC group presented healthier results than BC). There have been many studies performed outlining the role of diet and disturb on

glucose and lipids metabolism. A review conducted by Siôn A.P & Hodson L (2017) concluded that energy intake, independent of nutrient content, is a crucial regulator of hepatic lipid accumulation [68]. Furthermore, CHO levels in diet are also responsible for metabolic profile alterations where high ingestion is associated with an increase in serum lipids [69,70]. Concordantly, in this study, we confirmed breast cancer patients had the highest level of energy and carbohydrate intake, and it was statistically different from the matched group intakes and from HC regarding CHO consumption, however, considering caloric intakes, it did not differ from the healthy females. We hypothesized that along the reasons we did not find discrepancies in caloric ingestion among patients and the healthy control. There could be differences in the energy expenditure and level of physical activity, notably, and, as a limitation of our study, we did not evaluate those components. Curiously, BC presented the highest level of fiber ingestion, despite being far from the 25g/day recommendation, evidencing the diet inadequacies among the population overall. In addition to the dietary shortcomings observed, the patients had low protein intake/kg as well. Although it was not statistically significant when compared to the other groups (MC and HC), it is still clinically relevant, especially considering that changes in nutritional status markers have already been identified in this sample (PhA, NRI and EW/TBW) and low HGS. Besides, there is a potential for the development of sarcopenic obesity in those patients with an intake below 1.2g / kg [71].

Contrary to our hypotheses, we observed no differences in body composition (FM and FFM) between breast cancer patients and matched females, and also no differences in FFM among the 3 groups, though BC still had a higher nutritional risk. However, as we hypothesized, cancer patients demonstrated impairments in lipids, worst glucose levels, visceral fat dysfunction and consequently higher cardiovascular risk in which those females presented important unhealthy dietary patterns with higher carbohydrate and caloric intake and insufficient protein and fiber ingestion. Accordingly, our findings highlight the need for the implementation of a targeted dietetic approach to treat and mostly to prevent unfavorable metabolic and nutritional outcomes. Successfully, dietetic management has already shown to be an effective method to control and prevent metabolic impairments [72–75]; it is particularly important in the breast cancer patient population where the metabolic risks are increased by the tumor and chemotherapy besides the diet and body composition unfavorable.

Remarkably our study has already mentioned-limitations as not inclusion of energy expenditure and physical activity investigation and the sample size was relatively small.

For further studies, the inclusion of those components and expanding the follow-up of these patients could better elucidate the mechanism involved in metabolic changes and whether these results are maintained in the long term or enhanced by hormone therapy.

Conclusion

This study has found that women undergoing breast cancer chemotherapy, after completion of the treatment, presented poor indicators of nutritional and metabolic health, such as PhA, NRI, EW/TBW HGS, dyslipidemia, and visceral fat dysfunction by adiposity indices when compared to a group of age- and BMI-matched non-malignant females. Body composition and age do not explain these differences. Furthermore, the dietetic investigation revealed a higher energy intake and carbohydrate and insufficient consumption of protein and fiber.

Considering the possibility of poor prognosis related to the nutritional markers, sarcopenic obesity or the subsequent threat of developing cardiovascular disease in survivorship, this study highlights the necessity for more effective lifestyle intervention as exercise and nutrition counseling during breast cancer treatment.

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7. PHASE ANGLE IS RELATED WITH OXIDATIVE STRESS AND ANTIOXIDANT BIOMARKERS IN BREAST CANCER PATIENTS UNDERGOING CHEMOTHERAPY

Este capítulo apresenta o artigo intitulado “Phase angle is related with oxidative stress and antioxidant biomarkers in Breast Cancer patients undergoing chemotherapy.” de autoria de Bruna Ramos da Silva, Sarah Rufato, Mirele Mialich, Loris Cruz, Thais Gozo e Alceu Afonso Jordão Junior. O artigo foi enviado para a revista *European Journal of Nutrition*, para publicação em 17 Janeiro de 2022 (prova de submissão na seção 9. Anexos). A seguir é apresentado o artigo submetido.

Phase angle is related with oxidative stress and antioxidant biomarkers in Breast Cancer patients undergoing chemotherapy.

Bruna Ramos da Silva[1], Mirele S. Mialich[1], Loris P. Cruz[2], Sarah Rufato[1], Thais Gozzo[2], Alceu A. Jordao[1]

[1]Department of Health Sciences, Ribeirão Preto Medical School. University of Sao Paulo (USP), Bandeirantes avenue 3900, 14049-900, Ribeirão Preto, São Paulo, Brazil.

[2] Nursing School of Ribeirão Preto, University of São Paulo, Ribeirão Preto, São Paulo, Brazil

Corresponding author: Bruna Ramos da Silva, ORCID iD: 0000-0002-8674-5753 (bruna.ramos.silva@.usp.br)

Abstract

Purpose: The study aimed to analyze the influence of chemotherapy on health biomarkers, and to examine the relation among phase angle (PhA), oxidative stress and metabolic profile**. Methods**: A prospective study was performed. Women who were starting were recruited. Also, this study included a control group. Bioelectrical impedance analysis (BIA), 24h food recall, and blood sample were collected at 2-time points: diagnosis (T0) and after 1 month of completion of therapy (T1) for main study group and 1 time point for control group. ANOVA or Mann-Whitney Wilcoxon Test were used to compare variables. Linear regression analysis was conducted to further test if PhA is related with the dependent variables, after adjusting for age**. Results**: 61 women with breast cancer and 58 healthy were included. There was no difference after treatment and between the groups concerning anthropometrics, fat mass and fat-free mass. Breast cancer patients had a worsening in PhA and visceral adiposity index ($P<0.001$). In T1 PhA was statically correlated with extracellular water, albumin, hemoglobin, and the antioxidant marker (2,2 Diphenyl 1 picrylhydrazyl). The linear model showed PhA was significantly predicted by C reactive protein, DPPH (Beta= 0.00022, $p=0.02$), MDA, total body water/extracellular water, body mass index and fat mass. This model explained 58% of PhA variability ($p<0.001$). **Conclusion**: Our findings show that PhA is an easy and affordable tool which is correlated stress oxidative markers in breast cancer patients, regardless of age or BMI.

Keywords: body composition, phase angle, inflammatory markers, oxidative stress

Introduction

Breast cancer is the most common cancer in women (2.3 million new cases in 2020) and the second among all population across the world [1]. Nearly 30% of all new diagnosis will progress and become metastatic disease [2]. Oxidative stress is a condition promoted by an imbalance between oxidants and antioxidants, with increased reactive oxygen species (ROS) levels [3]. This condition has been shown to play an important role in the pathogenic of cancer, which can be related to development, proliferation, and progression of metastatic cancer cells [4].

Besides, ROS can be linked to inflammation through immune cell recruitment and cytokine production that trig inflammatory pathways, promoting chronic inflammation. [5,6]. Moreover, chronic inflammation also is key to the development of several diseases such as diabetes, cardiovascular disease, metabolic syndrome, neurodegeneration, ageing, cancer, and its progression [5–10].

In addition, oxidative stress can lead to body composition alteration as losses of muscle mass and strength, promoting sarcopenia [11,12]. This is particular important once sarcopenia is a prognosis factor among cancer patients [13,14], and in breast cancer, patients can be especially critical when combined with obesity, resulting in an increase in mortality [15,16].

Adding to the promotion of oxidative environment, antineoplastic agents potentially increase the oxidative stress, by the elevation of peroxidation and reduction of antioxidant nutrients as well as antioxidant enzymes

[17,18], which may explain the bad outcomes related to the after of treatment, especially regarding metabolic alterations [19–23]. Previous research conducted by our group showed a deterioration in nutritional status, physical function, visceral adiposity markers and development of metabolic syndrome post chemotherapy in early breast cancer patient [24,25].

Thus, tracking oxidative stress and inflammation markers are important to identify individuals with greater risk for further complications. However, there are several limitations regarding monitoring ROS, which involve expensive and complex techniques and the need for qualified staff and facilities to perform laboratory analyses, limiting its use in clinical practice.

To overcome these limitations, phase angle (PhA) obtained from bioelectrical impedance analysis (BIA), a simple, fast, non-invasive, and affordable technique that has been

explored as a potential measurement to screen for oxidative stress and inflammation impairments [26–31].

PhA is considered as an indicator of cellular health [32], related to health issues as malnutrition [33,34], loss of physical function [25], poor prognoses, and mortality [35–40], also reflects the hydration status [41], and is associated with the extracellular and intracellular water ratio (ECW/ICW) [42].

In a narrative review conducted in 2021, the authors discussed the potential role of PhA as a marker of oxidative stress, which might be justified due to its capacity to identify cellular integrity, which may occur as an ROS outcome [43]. Also, the cellular injuries promoted by ROS, might lead to water/fluid disbalance, and decrease of body cell mass, impacting cell membrane conductivity and therefore, PhA results [43].

Although this result seems promising, only a few studies have explored this field, and therefore there is a lack of evidence to confirm it. Since inflammation and oxidative stress might be intimately linked to cancer evolution, prognosis, and post-chemotherapy bad outcomes, and PhA might be a potential screen tool for these biomarkers the study aimed to examine the relation between PhA and inflammatory and oxidative stress biomarkers in women with breast cancer, before and 1 month after chemotherapy treatment. We also further explored any possible alterations in the markers promoted by chemotherapy.

Methods

Study Population

A prospective study was performed with women newly diagnosed with early stages breast cancer. Patients were recruited through clinical oncology practices at Mastology ambulatory of General Hospital of School of Medicine of Ribeirão Preto, São Paulo, Brazil. This study received approval from the Mastology committee of the hospital and the Institutional Review Board at the University of São Paulo, protocol number: HCRP 14608/2017 to contact all the women followed in the breast cancer clinic.

During the clinical orientation of chemotherapy, a responsible nurse informed the patient about the study, those who were interested know more about it were forwarded to talk with the study researcher. All women who met the following inclusion criteria were enrolled in the study: age ≥18 years and <65 years; a histologically confirmed diagnosis of early breast cancer (range of stage I – III); and very first chemotherapy treatment course. Smokers, metabolic syndrome; worse blood pressure control, which means the use of two or more antihypertensive drugs; lipid disorders, which means values above the normal range for triglycerides, total cholesterol and low dense cholesterol, according

to the criteria of the National Cholesterol Education Program's Adult Treatment Panel III (NCEP-ATP III) [44] and, the Brazilian nation recommendations [45]; diabetes type I or II or with a more recent glucose test above 125 mg/dl according to the results available on the electronic clinical records. Were excluded: pregnant women; who previously has already received or started chemotherapy in any other moment of life; those fitted with a defibrillator, cardiac pacemaker, metal implants or those with a local infection/wound preventing the use BIA pads, those unable to use a handheld dynamometer due to a neuromuscular disorder.

Besides, once no cut-off for oxidative paraments has been proposed, we also include a control group of women with no history of cancer or chemotherapy treatment in this study. For this group, the same exclusion criteria were applied. Women in the control group were recruited at the same hospital, the participants were employees or graduate student from the School of Medicine of Ribeirão Preto, São Paulo, Brazil.

Data Collection

We collected data at baseline, before starting chemotherapy (T0), until one month after completing the treatment (T1), totalizing eight cycles of chemotherapy. The last evaluation was made 1 month after finalizing the chemotherapy and before the hormone therapy started, due to the possible association between hormone therapy and the increase of metabolic alterations [46]. We recruited participants from July 1st, 2017, to December 30th, 2018, and the data collection was completed in July 2019. BIA and blood chemical analyzes were assessed at the T0 and T1. Also, food records were collected 4 different times. Socioeconomic, demographic, and therapeutic, were collected directly from patients using questionnaires or obtained from medical records. Written informed consent was obtained at the baseline visit.

A single evaluation was conducted for the control group, and the participants underwent the same assessment as the breast cancer participants group. A second food record was collected by a phone call a month later.

Anthropometric Assessments

Anthropometric characteristics that were measured include body weight and body height, as proposed by Lohman [47]. Body mass index (BMI) was calculated as the ratio between the body weight and the height squared (kg/m^2). Interpretation of these results followed the international classification proposed by the World Health Organization [48].

Bioelectrical impedance analysis

Body composition was assessed by using the bioelectrical impedance multiple-frequency (BIS) analysis (Body Composition Monitor – Fresenius Medical Care®), with different frequencies (5 to 1,000 kHz). The BIS analysis provided data regarding fat mass (FM), fat-free mass (FFM), phase angle (PhA), total body water (TBW), extracellular water (ECW) and intracellular water (IW).

Dietary data collection

Dietary data collection occurred using a 4-dietary recall of 24 hours for study, for the breast cancer group and 2 for the control group. The specific time frame was from the time the participant awoke in the morning to the time they slept at night. For this method was used the methodology of the triple pass 24-hour recall according with Nightingale et al [49] to improve the accuracy for quantification of the recall. The results obtained by the recall was inserted in the nutritional software Diet Box® to calculate the total of amount of energy and macronutrients ingested. This software uses the Brazilian table of food composition in the assessment. Reported values were analyzed by the Multiple Source Method program (MSM) to estimate the usual intake distribution for daily consumed nutrients. The MSM is a statistical method proposed for use in Europe by a German team [50] and is accessible through an online platform open source in which by the probability of consumption and the amount consumed and regressions models correct the within-person variance of the food intake results obtained by the record and generate the usual intake for each participant [50]. Prior studies have shown that the MSM is a useful tool that provides usual nutrient and food intake estimates [51,52], thus in order to improve the accuracy of the food consumption collected data, the MSM was applied.

Blood biochemical analysis

Venous blood samples were collected for the blood biochemical analysis after fasting for 12 hours previously. A nurse during the hospital blood collection collected a 9ml tube of peripheral blood in T0 and T1. This sample was processed in the nutrition and metabolism laboratory. The peripheral blood was collected, and serum was used for the following analysis: Albumin (AL); C-reactive Protein (CRP); For the oxidative stress biomarkers evaluation, were analyzed: Malondialdehyde (MDA), for lipoperoxidation, and 8-hydroxydeoxyguanosine (8-HDG) for DNA oxidative damage assessment. For the antioxidant biomarkers evaluation, were analyzed: 2,2-diphenyl-1-picrylhydrazyl (DPPH); Glutathione (GSH); Seric tocopherol, retinol, and vitamin C.

Visceral Adiposity Index (VAI).

Visceral fat dysfunction was used to assess cardiovascular risk by using the visceral adiposity index (VAI). VAI was calculated according to the formula for women: VAI = (WC (cm)/ (36,58+(BMI *1.89) *(TG/0.81) *(1.52/HDL) [53].

VAI index classification considered as being "metabolically healthy" was defined as VAI <1.59, and "metabolically unhealthy" as VAI ≥1.59 [54].

Statistical analysis

The sample size calculation was performed using G*Power software version 3.1.9.4, taking into consideration the effect of independent variables on PhA. For a linear regression model, considering a large effect size of 0.35 showed that with a significance level of 95% and statistical power of 80%, the minimum number of participants required was 43. This study was a post hoc analysis of data from an ongoing study which aim to explore possible changes in body composition, metabolic and oxidative stress parameters. All women included in this study, consistently maintained all data collection appointments and, nobody left the study, therefore, we had no missing data within participants for static analysis.

Data are described as mean ± standard deviation. The normality (Shapiro-Wilk) and homogeneity of variances (Levene) of all variables were tested ($p > 0.05$). The variables were compared using ANOVA or Mann-Whitney Wilcoxon Test depending on the distribution of the data. The correlations of oxidative damage with the biochemical and BIA parameters and body compartments were evaluated using Pearson's or Spearman correlation coefficient depending on the distribution of the data. The strength of the correlation was classified as very weak for $r < 0.19$, weak for $0.20 \leq r < 0.39$, moderate for $0.4 \leq r < 0.59$, strong for $0.6 \leq r < 0.79$, and very strong for $r \geq 0.80$. Multiple regression analysis was conducted to further test whether PhA was predicted by the independent variables. To assess the ability of regressions models making predictions, it was used the verification by the least square methods. A p value < 0.05 was considered statistically significant for all tests. SAS studio was used for all statistical analyzes.

Results

During the recruitment, we identified 180 new diagnostics of breast cancer patients. Fifty-seven were excluded due to diabetes, dyslipidemia, metabolic syndrome, or high blood pressure. Eighteen were excluded for metastatic breast cancer, and two were due to cognitive impairments. Four women did not want to join the study, and 14 were excluded due to absence at the scheduled collection visit, no fasting at the data collection visit, or starting chemotherapy before at baseline data collection schedule. The final sample

included in this study was 61 women with early stages breast cancer, which more than half were stage II, younger than 50 years (63.3%) and 65.6% premenopausal at recruitment (65.6%).

The prescribed protocol of treatment was the combination between Doxorubicin, Cyclophosphamide, and Docetaxel (AC-T) according to the Brazilian Society of Clinical Oncology guidance, which recommends the combination of 4 cycles Doxorubicin 60 mg / m2 IV + cyclophosphamide 600 mg / m2 IV every 21 days, followed by 4 cycles of docetaxel 100 mg / m2 IV every 21 days [55,56]. Table 1 summarizes the clinic and demographic characteristics of breast cancer participants.

For the control group, 61 women were recruited. However, three did not attend the data collection visit. Therefore, the final sample included was 58 women.

Table 1: Clinic characteristics of breast cancer patients.

	N=61	%
Menopausal status		
Premenopausal	40	65.60 %
Postmenopausal	21	34.40 %
Cancer stage		
I	4	6,6%
II	36	59%
III	21	35%
Chemotherapy		
Neoadjuvant	44	72%
Adjuvant	17	28%
Cycles		
4*	1	2%
8	60	98%
Treatment		

Protocol		
AC	1	2%
AC-T	60	98%

* One participant received a shorter protocol of chemotherapy, for this case, the follow-up time was 4 months. Caption: AC – Cyclophosphamide and Doxorubicin; ACT – Cyclophosphamide, Doxorubicin and Docetaxel

Both groups, control, and breast cancer patients, presented overweight according to BMI. We did not find any statistically significant alteration in body weight, BMI, most of the body composition parameters (FM, FFM and TBW), and GSH levels during the follow-up period. Still, chemotherapy impacted PhA, EW, EW ratio, AL, CRP, HB, and VAI ($p<0.05$). MDA and DPPH improved, and alpha tocopherol increased after one month of chemotherapy treatment ($p<0.05$) (Table 2).

Regarding the comparison between breast cancer patients and the control group, there is no difference between age, weight, height, BMI, FM, FFM or TBW (Table 2). The control group presented healthier values for PhA, EX, EX ratio, AL, CRP, MDA, DPPH, GSH and VAI when compared to both times (T0 and T1) and all were statistically significant ($p<0.05$). The non-breast cancer participants also presented lower values of serum alpha tocopherol and retinol and better food ingestion, with lower calories, carbohydrate, total and saturated fat and higher protein, fiber, and vitamin E intake ($p<0.05$). Table 2 shows the complete data.

Table 2: Sample characteristics and comparison among time and groups

Variable	T0	T1	CG	T0 x T1	T0 x CG	T1 x CG
Age (years)	46.50 (SD=9.85)	-	43.37 (SD=9.74)	-	0.08	0.08
Weight (kg)	71.7 (SD=12.6)	73.5 (SD=12.6)	76.35 (SD=19.75)	0.843	0.24	0.61
BMI (kg/m2)	28.54 (SD=5.46)	28.95 (SD=4.37)	28.57 (SD=6.90)	0.844	0.22	0.55
FFM (KG)	34 (SD=7.1)	32.5 (SD=5.6)	35.62 (SD=6.38)	0.979	0.46	0.06
FM (KG)	28.82 (SD=9.09)	28.78 (SD=8.94)	30.23 (SD=13.82)	0.849	0.51	0.64
PhA	6.05 (SD=0.75)	5.16 (SD=0.77)	6.35 (SD=0.81)	**<0.001**	**0.03**	**<0.001**
TBW (L)	31.90 (SD=5.12)	33.22 (SD=6.22)	33.37 (SD=5.91)	0.19	0.38	0.89
EX (L)	14.35 (SD=2.20)	16.00 (SD=3.09)	14.77 (SD=3.00)	**0.001**	0.38	**0.03**

TBW/EX	0.45(SD=0.02)	0.48 (SD=0.02)	0.44 (SD=0.02)	**<0.001**	0.06	**<0.001**
Energy (kcal)	1775 (SD=725)	1700 (SD=490)	1240 (SD=250)	0.5	**<0.001**	**<0.001**
Carb (g)	235.48 (SD=103.55)	233.92 (SD=81.12)	67.59 (SD=18.80)	0.92	**<0.001**	**<0.001**
Protein (g)	80.41 (SD=39.68)	76.40 (SD=23.14)	147.25 (SD=41.7)	0.49	**<0.001**	**<0.001**
Fat (g)	56.81 (SD=31.08)	53.09 (SD=19.30)	42.13 (SD=6.09)	0.42	0.01	**<0.001**
Sat fat (g)	18.08 (SD=12.05)	17.41 (SD=5.83)	14.06 (SD=13.45)	0.37	0.44	**<0.001**
Col (mg)	264.87 (SD=207.67)	277.01 (SD=129.27)	251.71 (SD=112.56)	0.7	0.97	0.12
Fiber (g)	17.49 (SD=11.17)	15.35 (SD=6.50)	37.87 (SD=14.31)	0.19	**<0.001**	**<0.001**
Vit A (mcg)	405.11 (SD=1115)	424.41 (SD=200.13	128.77 (SD=58.12)	**<0.001**	0.18	**<0.001**
Vit E (mg)	6.73 (SD=5.25)	8.31 (SD=0.85)	434.53 (SD=397.78)	0.0013	**<0.001**	**<0.001**
Vit C (mg)	150.46 (SD=115.06)	15.35 (SD=7.05)	11.06 (SD=4.95)	**0.001**	**<0.001**	0.75
Sel (mcg)	42.12 (SD=37.55)	44.35 (SD=5.97)	5.85 (SD=2.82)	0.03	**<0.001**	**<0.001**
AL (g/dL)	3.97 (SD=0.65)	3.44 (SD=0.64)	3.87 (SD=0.46)	**<0.001**	0.35	**<0.001**
HB (g/dL)	12.84 (SD=1.30)	11.40 (SD=1.19)	-	**<0.001**	-	-
CRP (mg/dL)	7.35 (SD=13.73)	15.94 (SD=31.47)	10.13 (SD=8.97)	**0.05**	**0.02**	0.17
VAI	2.97 (SD=2.14)	5.45 SD=3.42)	2.73 (SD=1.37)	**<0.001**	0.46	**<0.001**
MDA	7.89 (SD=1.99)	5.27 (SD=2.66)	4.05 (SD=1.30)	**<0.001**	**<0.001**	**0.002**
GSH	0.18 (SD=0.04)	0.20 (SD=0.09)	0.21 (SD=0.05)	0.42	**0.03**	0.3
DPPH	36.71 (SD=17.02)	45.08 (SD=16.28)	73.80 (SD=16.13)	**0.01**	**<0.001**	**<0.001**
8HDG	7.88 (SD=4.43)	6.88 (SD=2.50)	7.52 (SD=2.20)	0.82	0.44	0.17
retinol (µM)	1.55 (SD=4.34)	1.59 (SD=3.93)	1.40 (SD=4.35)	0.56	**0.05**	**0.01**
alpha tocopherol (µM)	22.46 (SD=7.37)	28.91 (SD=9.24)	17.82 (11.36)	**<.0001**	**0.01**	**<.0001**
vitamin C (mg/dL)	2.46 (SD=2.02)	1.35 (SD=1.08)	1.14 (SD=1.47)	**0.05**	**<.0001**	**<.0001**

BMI: Body mass index, FFM: Fat-free mass, FM: Fat Mass, PhA: Phase angle. TBW: Total body water. ECW: Extracellular water. ECW/TBW: the ratio between extracellular water and total body water. Carb: Carbohydrate, Sat fat: Saturated fat, Vit A: Vitamin A, Vit E: Vitamin E; Vit C: Vitamin C, AL: Albumin, CRP: C reactive protein, HB: Hemoglobin, VAI: Visceral adiposity index, MDA: Malondialdehyde, GSH: Glutathione, DPPH: α-diphenyl-β-picrylhydrazyl * The mean difference is significant at a level of 0.05

The PhA had a statistical significance correlation for both times, T0 and T1, with variables related to body composition, nutritional status, and oxidative stress. For the control group, PhA a statistical significance correlation only with body composition parameters. In T0, PhA was positive correlated with FFM, TBW, IW, AL and GSH, and negative correlated to FM ($p<0.05$). For T1, the significant correlations were with EW, AL, HB and DPPH. For the control group, PhA was correlated to FFM, FM TBW and IW ($p<0.05$). Table 3 has a complete description of all correlations.

Table 3. Pearson correlation of phase angle and other studies variable

	T0		**T1**		**CG**	
Pears	r	p	r	p	r	p
Weight	0.02	0.82	0.23	0.06	-0.10	0.42
FFM	0.6	**<0.001**	0.21	0.1	0.67	**<0.001**
FM	-0.49	**<0.001**	-0.12	0.35	-0.51	**<0.001**
TBW	0.37	**0.003**	-0.01	0.89	0.35	**0.007**
EW	-0.01	0.9	-0.25	**0.05**	-0.12	0.36
IW	0.55	**<0.001**	0.19	0.14	0.61	**<0.001**
AL	0.29	**0.02**	0.25	**0.05**	-0.02	0.37
HB	0.03	0.77	0.27	**0.03**	-	-
CRP	0.17	0.19	0.23	0.07	0.01	0.91
MDA	-0.008	0.94	-0.17	0.19	0.03	0.78
DPPH	0.01	0.91	0.3	**0.01**	0.04	0.75
GSH	0.25	**0.05**	-0.02	0.83	0.04	0.73
8HDG	0.04	0.86	0.36	0.13	0.17	0.48
retinol	0.44	**0.0008**	0.16	0.22	0.34	0.36
alfa tocopherol	0.17	0.19	-0.14	0.29	0.1	0.67
vitamin C	-0.11	0.4	-0.27	**0.03**	-0.04	0.85

FFM: Fat-free mass, FM: Fat Mass, TBW: Total body water. ECW: Extracellular water. ICW: Intracellular water. AL: Albumin, CRP: C reactive protein, HB: Hemoglobin, MDA: Malondialdehyde, GSH: Glutathione, DPPH: α, α-diphenyl-β-picrylhydrazyl. Model adjusted for age and BMI.

It was performed a multiple regression model to determine how much the PhA variation may be explained by body composition, nutritional, biochemical and stress oxidative parameters for both times. In T0, the model showed that AL (Beta= 0.004, p=0.03), TBW/ECW (Beta= 0.16, p<0.001), BMI (Beta= 0.001, p= 0.0002), and FM (Beta= 0.0009, p=0.00078) explained 49% of PhA variability (p<0.001). In T1, PhA was significantly predicted by CRP (Beta= 0.00005, p=0.05), AL (Beta=0.00302, p<0.001), MDA (Beta= -0.00111, p=0.05), DPPH (Beta= 0.00022, p=0.02), TBW/ECW (Beta= -0.19577, p<0.001), BMI (Beta=0.00177, p<0.001), and FM (Beta= -0.00049, p=0.00025) and this model explained 58% of PhA variability (p<0.001). The complete data are presented in Table 4.

Table 4. Multiple linear regression analysis of variables influencing the phase angle in T0 and T1.

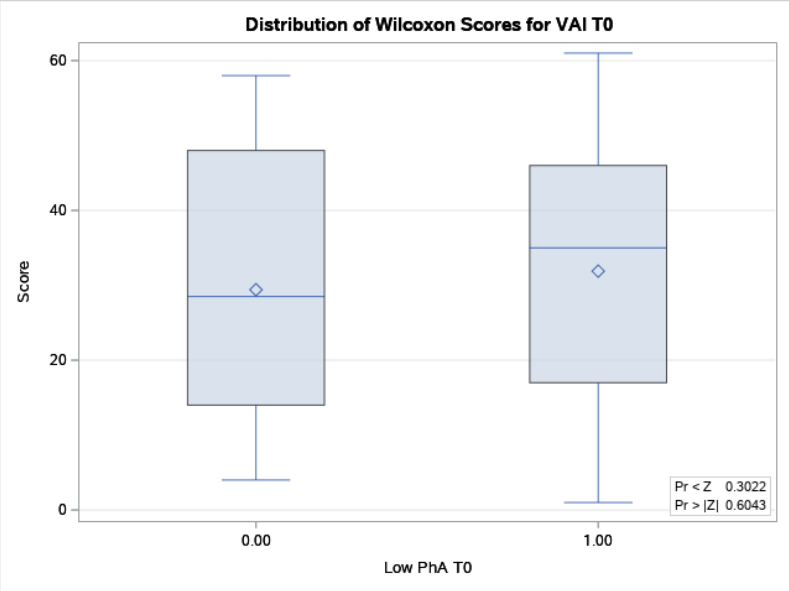
	T0			**T1**		
Coefficients	**Beta**	**Standard error**	**P-value**	**Beta**	**Standard error**	**P-value**
Intercept	7.31012	0.34821	<.0001	5.48285	0.35212	<.0001
CRP	*	*	*	0.00010	0.00005	0.05
ALB	0.004971	0.002314	0.03	0.01331	0.00302	<.0001
MDA	*	*	*	-0.00111	0.00057	0.05
DPPH	*	*	*	0.00022	0.00010	0.02
ECW/TBW	0.168136	0.02563	<.0001	-0.19577	0.02548	<.0001
BMI	0.001926	0.000492	0.0002	0.00177	0.00042	<.0001
FM	0.000904	0.000328	0.0078	-0.00049	0.00025	0.05
R²	0.49			**R²**	0.58	

Adjusted R²	0.45	**Adjusted R²**	0.53
P-value	**<.0001**	**P-value**	**<.0001**

***** FFM, CRP, MDA and DPPH were removed from the model in T0 by backward elimination selection. BMI: Body mass index, FFM: Fat-free mass, FM: Fat Mass, TBW: Total body water. EW: Extracellular water. IW: Intracellular water. ECW/TBW: the ratio between extracellular water and total body water. AL: Albumin, CRP: C reactive protein, MDA: Malondialdehyde, GSH: Glutathione, DPPH: α-diphenyl-β-picrylhydrazyl. Model adjusted for age.

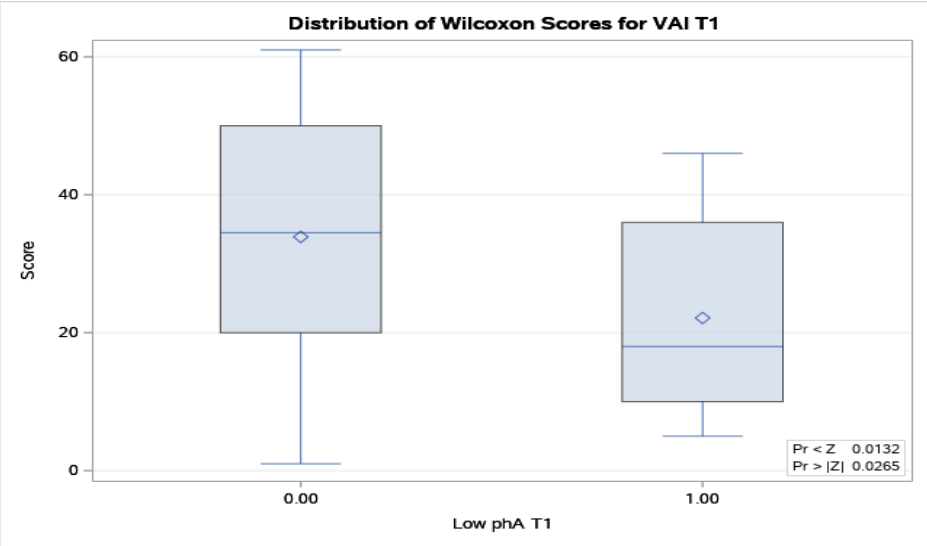
Another highlight in the breast cancer patients' group was the distribution of the participants with lowers values of PhA among visceral adiposity results assessed by VAI. Women who were classified as metabolic unhealthy (i.e., high values of VAI) also had low PhA values (p=0.02), only after the chemotherapy (in T1) (Figure 2). As shown in Table 2, both measurements also changed significantly in T1 (p<0.001). Fig 1 shows the distribution of low PhA angle among VAI results at the first assessment and Fig 2 at the last assessment.

Fig 1: Distribution of low phase angle among visceral adiposity index results at the baseline evaluation.



Captions: PhA: Phase angle, VAI: Visceral adiposity index, 0.00: low phase angle, 1.00: Normal values of phase angle. For classification as low phase angle was adopted values equal or lower than 5.6 as proposed by Gupta et al 2008. The mean difference is significant at a level of 0.05

Fig 2: Distribution of low phase angle among visceral adiposity index results at the follow-up evaluation.



Captions: PhA: Phase angle, VAI: Visceral adiposity index, 0.00: low phase angle, 1.00: Normal values of phase angle. For classification as low phase angle was adopted values equal or lower than 5.6 as proposed by Gupta et al 2008. The mean difference is significant at a level of 0.05

Discussion

In this study, we did not find any differences among anthropometrics results and the main body composition variables (i.e., FM, FFM and TBW). However, we still observed an important deterioration in healthy markers like ECW/TBW, PhA and AL.

ECW/TBW ratio is consider a useful tool to detect water variation, thus is regard an index of edema and its change can be related to malnutrition, electrolytes irregularities and might modify in an obesity scenario [57,58]. In addition, water fluctuations impact PhA results [42] and, therefore it can be related to nutritional status, both parameters play an important role in cancer care [59]. After chemotherapy PhA dropped to below the cutoff value associated with lower breast cancer survival (≤5.6º) proposed by Gupta et al [60]. In association, a worsening in other nutrition markers as AL was observed, in inflammation status represented by CRP levels and in visceral dysfunction according to VAI levels.

Regarding oxidative stress markers, it was observed an improvement in T1. The MDA levels, which is a product of lipidic oxidation, decreased at the same time that total oxidant capacity (DPPH) and glutathione (GSH) increased. Also, this alteration could be explained due to modification in serum alpha-tocopherol levels, which increased simultaneously. Alpha-tocopherol is a fat-soluble vitamin and can be considered one of the most potent antioxidants, which protect from ROS damage, especially the lipid

peroxyl radicals [61,62]. We hypothesized that the organism responded to the oxidant's growth, which was characterized by the increase of alpha-tocopherol levels. In this scenario, the liver mobilized its fat-soluble vitamin stores to regulate oxidative stress to a physiological level. These serum antioxidant changes are not observed for vitamin C, a water-soluble vitamin and therefore is not stored in the body. Evidently, this oxidative liver regulation may change in a long-term response when the liver stores are consumed. Despite hepatic vitamin E mobilization to restore oxidative balance, the inflammatory process continues in this sample, evidenced by the higher levels of PCR and lower levels of AL.

Concerning the comparisons to the control group, the results of our study indicate that, regardless of similarity in age, weight, BMI, and body compositions features as FFM, FM and TBW (all were not statically significant), it was possible to verify important differences in health markers. Breast cancer patients presented worse PhA, AL, VAI, food consumption and higher oxidative markers (i.e., fewer antioxidants and more oxidants species) which were more discrepant after chemotherapy treatment. These results are confirmed by other studies which have already reported an oxidative impairment among cancer patients when compared a control group [63–65].

In spite of lower oxidative stress, the control group had a higher level of CRP when compared to T0 and no differences when compared to T1. We believe between the reasons is the body composition profile of the control group. The control group presented higher body weight and higher FM, which might increase inflammation levels, especially for FM [66]. Although is known the relationship between inflammation and oxidative stress [67], it did not promote higher ROS in control group, and it might be related to higher levels of oxidants (which this group had), a healthier diet as shown in Table 2 and the level of physical active, which unfortunately was not explored in this study. Additionally, food intake was assessed only twice to the control group and for both group it was used a 24h food recall which may not capture the actual daily eating habits of participants.

Our main goal was to verify which of our variables might be related to PhA, especially with regards to oxidative stress markers, which is involved in physiopathology in a variety of diseases [6,67].

To our knowledge, only a few articles aimed to make similar analyzes, and we are the first study exploring the relationship of PhA and oxidative stress parameters among breast cancer patients. In this sense, after adjusting for age and BMI, we found a significant positive correlation between PhA and antioxidants agents (DPPH, retinol and GSH). In

our model of linear regression analyses, conjunctly the measures of body composition as FM and ECW/TBW, BMI and health markers as AL, CRP, MDA and DPPH accounted for 49% of the variance in the PhA in T0 and 58% in T1. Indeed, the PhA is a promising health parameter. Our research group's review identified 16 studies that reported an association between PhA and direct and indirect inflammatory biomarkers [43]. Also, a cutoff to predict an increase in CRP levels has already been proposed [31].

Although the results for oxidative stress are still less expressive, our results agree with previous studies that evaluated this relationship with PhA. Zouridakis et al. in 2016 reported a positive correlation between PhA and total antioxidant capacity (TAC) [68] and Venâncio et al. in 2021 found a negative correlation with advanced oxidation protein products [29]. In addition, another Brazilian group described a positive correlation among PhA and catalase, and total radical-trapping antioxidant potential and a negative correlation with ferrous oxidation-xylenol orange (FOX) and AOPP [26,27]. In our results, the association among PhA and oxidant, antioxidant, CRP, and AL were found only in the breast cancer group. For healthy populations, body composition parameters are the main determinants of PhA (Table 3). The same pattern is observed in the linear model, where after PhA deterioration in T1, post chemotherapy, the biomarkers contributed to the model (Table 4).

In fact, according to Norman et al. (2012), in a healthy population, PhA is mainly determined by age, sex, and BMI [69], which concords with our results. In sick conditions, additional parameters can impact PhA. Compared to a healthy population, PhA in disease states is usually lower and might be affected by infection, inflammation, or other parameters related to disease [69,70]. Moreover, considering the body composition determinants on PhA, FFM together with extracellular and intracellular water might exert a more substantial effect [42]. It can be explained by the fact PhA is a cellular integrity marker, consequently, cell membrane rupture can affect the equilibrium of water in the cell [71], which can elucidate the relation between PhA and ECW/ ICW. Our results also found a correlation between PhA and BIA's fluids components.

Interestingly, after chemotherapy, we found that women with lower PhA values (i.e., PhA below 5.6) also presented as metabolic unhealthy (i.e., high VAI values). Similarly, other studies also found a VAI worsening in breast cancer patients after chemotherapy [19,72]. VAI is an index for visceral adiposity proposed by Amato et al [54], which has been related to cardiometabolic risk, metabolic syndrome, and cardiovascular diseases [53,73,74]. In addition, the link between poor PhA values and metabolic alterations involves obesity,

inflammatory pathways, and oxidative stress [75]. The adiposity tissue can induce inflammation and oxidative imbalances, which leads to glucose and lipid metabolism alteration. It can cause damage to and loss of cell function [75,76]. Since PhA is an identifier of the dysfunction in cell membrane integrity [32], it can also be associated with metabolic impairments. According to Longo et al. low PhA might be a risk indicator for changes in the cardiometabolic profile [77].

Our interest in exploring PhA as a screening tool for oxidative stress and, consequently, for metabolic risk is justified because the metabolic syndrome is known as an expected outcome in breast cancer survivors [21,24,78–82], which reflects in poor prognoses and overall survival in patients with breast cancer [83–85]. Due to the relation between metabolic dysfunction and cardiovascular disease (CVD), it is known that, among mortality causes of non-cancer-related, breast cancer survivors present a higher risk for CVD mortality [86,87]. This scenario highlights the necessity to explore screening tools to detect individuals at metabolic risk. In this context, potentially, PhA could be a tool that would be easily integrated into routine patient care as it is an affordable, non-invasive, simple method but effective in identifying those who would take advantage of a targeted behavioral approach. The present study is not without limitations. The sample size was relatively small and did not explore energy metabolism or physical activity level. We used a dietary recall to examine food intake, which is not a gold standard but applied the Multiple Source Method to increase the accuracy of the data. Still, the dietary records may not capture participants' actual daily eating habits, especially concerning micronutrients. The strengths of this study include the originality, only a few groups have studied this subject so far, the prospective approach, and the inclusion of a control group strict inclusion criteria.

Further studies are needed to investigate the association among PhA, oxidative stress and metabolic impairments and extrapolate these findings to other populations, ages, and sex. Additionally, there are no cutoff values for oxidative stress disorders and a PhA's cutoff to screen oxidative stress has not been proposed yet. Finally, it is necessary to note that there is a lack of generalizability of these finds once there is a large variability in PhA values obtained from different BIA devices [88,89].

Conclusion

Our results suggest that breast cancer patients have worse nutritional status, food consumption, biochemical blood markers and oxidative stress biomarkers than a control group with similar age and body composition. Chemotherapy promoted a deterioration in

PhA, increased visceral adiposity by VAI index and inflammation by PCR and a higher mobilization of regulatory antioxidant mechanisms. Participants who presented low PhA also had an unhealthy metabolic profile. PhA was statically correlated to oxidative stress parameters regardless of age and BMI. Thus, PhA might be a potential inexpensive alternative to monitor oxidative stress and metabolic disorders in breast cancer patients with obesity. In-depth studies are needed to confirm these findings.

Declarations

Funding

BRS was founded by São Paulo Research Foundation (FAPESP). Grant number: 2017/07963-0 and FAPESP Grant number: 2019/09877-9

Conflicts of interest/ Competing interests:

The authors declare that they have no conflict of interest.

Ethical standard

All human studies have been approved by the appropriate ethics committee and have, therefore, been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

All persons gave their informed consent prior to their inclusion in the study.

Availability of data and material

All relevant data are within the paper

Code availability

Not aplicable

Corresponding author

Email address: bruna.ramos.silva@usp.br (Bruna Ramos da Silva)

Authors' contributions: The authors' responsibilities were as follows – AAJJ: conceptualized the study; BRS, LAPC, TOG, and AAJJ: were responsible for the research design; BRS and LAPC: conducted the research and analyzed the data; BRS, MM, and AAJJ: wrote the paper and had primary responsibility for final content; and all authors: contributed to data interpretation and read and approved the final manuscript.

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8. CONSIDERAÇÕES FINAIS

Este estudo destaca lacunas específicas quanto aos conhecimentos relacionados aos impactos negativos da quimioterapia nas características metabólicas e de estado nutricional pós-tratamento. Embora esta terapêutica seja fundamental e cientificamente comprovada como eficaz para o tratamento do câncer de mama, estes resultados reforçam a necessidade do acompanhamento nutricional a fim de manejar e prevenir as alterações decorrentes.

Destaca-se ainda que, apesar da obesidade e inadequações alimentares conhecidamente serem importantes fatores promotores de alterações metabólicas, principalmente as relacionadas a SM, este estudo identificou que as mulheres com câncer de mama quando comparadas as mulheres sem câncer de mama e com obesidade apresentaram piores resultados em relação aos exames bioquímicos e de estado nutricional. Durante o período de estudo, as pacientes acompanhadas apresentaram rápida perda de estado nutricional evidenciados pelo AF e índice de risco nutricional (NRI), sem alteração de peso corporal, o que demonstra que a desnutrição pode ser uma condição camuflada e muitas vezes subdiagnosticada. Além disso, estas alterações também foram seguidas por uma perda significativa da qualidade de vida.

No final do estudo foi identificado que a maior parte da amostra desenvolveu SM, no qual, além de ser um fator de risco para reincidência tumoral e metástases, também implica no risco aumentado para o desenvolvimento de outras condições clínicas como as doenças cardiovasculares. A despeito das similaridades com o grupo controle, este estudo também identificou que as pacientes com câncer de mama também apresentaram maiores níveis de marcadores de estresse oxidativo quando comparadas com mulheres sem câncer de mama. Além disso, foi demonstrado que o AF foi positivamente correlacionado a agentes marcadores antioxidantes e inflamação (proteína C reativa) independentemente do Índice de Massa Corporal (IMC).

Adicionalmente, foi identificado uma piora da adiposidade corporal por meio do Visceral Adiposty Index (VAI) em associação com a deterioração do AF. As participantes que apresentaram baixo valores de AF também apresentaram valores de VAI acima do ponto de corte, indicando uma piora do perfil metabólico, uma vez que o VAI pode ser relacionado a SM e DCV.

Resumidamente, nesse estudo foi demonstrado a associação do AF com marcadores de risco nutricional, marcadores metabólicos, inflamatório e agentes antioxidantes. Por fim, é importante salientar a necessidade de implementação de ações associadas a esta temática, para que implementações de medidas profiláticas sejam estimuladas e adotadas concomitantemente com o tratamento e manejo clínico do câncer de mama a fim de promover melhores resultados em saúde, melhor prognóstico e qualidade de vida das mulheres com câncer de mama.

8.1 Implicações para abordagens nutricionais futuras em nutrição e câncer de mama

Embora seja consenso que a desnutrição é um importante fator prognóstico para varias condições clínicas, esta muitas vezes pode se apresentar como uma condição oculta concomitantemente a diferentes faixas de peso corporal, inclusive obesidade. Spiro et al. (2006), constatou uma deficiência na identificação da desnutrição entre pacientes com IMC elevado [1], dentre os possíveis fatores está a falsa conclusão de "bem nutridos" e o uso somente do IMC como ferramenta de triagem [2]. Deste modo, é necessário o uso de outras ferramentas de triagem além do peso corporal para o diagnóstico preciso do estado nutricional, especialmente para pacientes com câncer de mama onde o risco nutricional decorrente da doença e o tratamento frequentemente está associado a obesidade e até mesmo ganho de peso [3].

Nesse sentindo, ferramentas de avaliação física como a dinamometria e teste de velocidade de marcha (TVM), bem como o AF apresentam um grande potencial para triagem da desnutrição, risco nutricional, sarcopenia, baixa qualidade de vida e mortalidade [4–11]. Além disso, novas evidências também sugerem o AF como possível ferramenta de triagem para a inflamação e estresse oxidativo [12–16]. É importante destacar que além do potencial clínico da adoção destas medidas de triagem na prática nutricional, o AF, TVM e a dinamometria também apresentam outras vantagens em comum que justificam o seu uso como a facilidade de execução, portabilidade, baixo custo e pontos de cortes já estabelecidos na literatura para diferentes populações.

Ressalta-se ainda que, além da implementação destas medidas de triagem de uma avaliação do estado nutricional acurada, os dados do projeto também destacam a necessidade da implementação do aconselhamento nutricional em associação ao atendimento clínico das mulheres com câncer de mama, principalmente devido às

alterações metabólicas e do metabolismo lipídico no qual as pacientes podem estar sujeitas após a quimioterapia. A nutrição como medida de intervenção terapêutica é uma importante aliada dos tratamentos clínicos, por exemplo; no manejo da desnutrição, sarcopenia e baixa massa muscular; recuperação do AF e manejo; e prevenção da síndrome metabólica [17–22].

Exemplos de intervenções dietéticas e orientações nutricionais de acordo aos desfechos aqui relatados, incluem: dieta com alto teor de proteínas [23], suplementação com creatina e coenzima Q-10 [21], Dieta Mediterrânea [20] e suplementação nutricional parenteral [22], as quais já demonstraram aumentar e melhorar o estado nutricional e o AF. No que diz respeito ao manejo das alterações metabólicas, principalmente relacionados ao metabolismo lipídico e a SM, de acordo com a literatura, as intervenções dietéticas podem incluir: Dieta Mediterrânea, restrição calórica, abordagens dietéticas para controle da hipertensão (dieta DASH) e o Índice de Alimentação Saudável (HEI-2010) [19,24–26]. Porém, mesmo para pacientes com câncer que sabidamente necessitam de acompanhamento dietético, muitas vezes a terapia nutricional ainda é uma medida pouco abordada em conjunto dos cuidados de sáude usuais [27].

A presente tese descreve os impactos negativos da quimioterapia no estado nutricional e a promoção de alterações metabólicas, disfunção de marcadores de gordura visceral e desenvolvimento de síndrome metabólica e enaltece a importância de adoção de ações preventivas por meio da implementação do aconselhamento nutricional como parte do tratamento clínico oncológico. Em adição, apresenta ainda diferentes técnicas para uma análise fidedigna do estado nutricional da população em estudo, como as medidas de funcionalidade física e o AF.

Dados do projeto poderão fomentar e instigar outras pesquisas que possam dar continuidade e ampliação de evidências científicas para os impactos e efeitos colaterais da quimioterapia, o papel do estresse oxidativo como base para as alterações inflamatórias, metabólicas e nutricionais, bem como alternativas e novas estratégias dietéticas para a prevenção e manejo das alterações clínicas aqui apresentadas.

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10. ANEXOS

10.1 APROVAÇÃO COMITE DE ÉTICA

HOSPITAL DAS CLÍNICAS DA FACULDADE DE MEDICINA DE RIBEIRÃO PRETO DA UNIVERSIDADE DE SÃO PAULO

FMRP-USP
RIBEIRÃO PRETO

Ofício nº 908/2018
CEP/MGV

Ribeirão Preto, 05 de abril de 2018.

Processo HCRP nº 14608/2017

Prezados Pesquisadores,

O trabalho intitulado **"AVALIAÇÃO DO PERFIL METABÓLICO, OXIDATIVO E ANTROPOMÉTRICO EM MULHERES COM CÂNCER DE MAMA" – Projeto de Pesquisa Versão 3, de 19 de março de 2018**, foi analisado "AID REFERENDUM" pelo Comitê de Ética em Pesquisa e enquadrado na categoria: **APROVADO,** bem como os Termos de Consentimento Livre e Esclarecido Versão 3, de 22 de março de 2018.

De acordo com Carta Circular nº 003/2011/CONEP/CNS, datada de 21/03/2011, o sujeito de pesquisa ou seu representante, quando for o caso, deverá rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última do referido Termo; o pesquisador responsável deverá da mesma forma, rubricar todas as folhas do Termo de Consentimento Livre e Esclarecido – TCLE – apondo sua assinatura na última página do referido Termo.

Este Comitê segue integralmente a Conferência Internacional de Harmonização de Boas Práticas Clínicas (IGH-GCP), bem como a Resolução nº 466/2012 CNS/MS.

Lembramos que devem ser apresentados a este CEP, o Relatório Parcial e o Relatório Final da pesquisa.

Atenciosamente,

DRA MARCIA GUIMARÃES VILLANOVA
COORDENADORA DO COMITÊ DE ÉTICA EM PESQUISA DO HCRP E DA FMRP-USP

Ilustríssimos Senhores
BRUNA RAMOS DA SILVA
PROF. DR. ALCEU AFONSO JORDÃO JUNIOR (ORIENTADOR)
Depto. de Clínica Médica

10.2 TERMO DE CONSENTIMENTO

1) Grupo de estudo principal: Pacientes com câncer de mama

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO

Título do estudo: "Avaliação do perfil metabólico, oxidativo e antropométrico em mulheres com câncer de mama."
Pesquisador Responsável: Bruna Ramos da Silva (16)33154564 / bruna.ramos.silva@usp.br
Pesquisadores Participantes:
Dra Mirele Savegnago Mialich Grecco (16)33154564 / mirele.mialich@usp.br
Prof. Dr. Alceu Afonso Jordão Junior (16)33154564 / alceu@fmrp.usp.br
Instituição/Departamento: Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto / Departamento de Clínica Médica.
Local da coleta de dados: Hospital das Clínicas de Ribeirão Preto

Prezada Senhora

Você está sendo convidada para participar, como voluntária, em uma pesquisa. Após ser esclarecida sobre as informações a seguir, no caso de aceitar fazer parte do estudo, assine ao final deste documento, que está em duas vias. Uma delas é sua e a outra é do pesquisador responsável. Em caso de recusa você não será penalizado de forma alguma. Em caso de dúvida você pode procurar o Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo ou pelo telefone (16) 3602-2228.

O objetivo deste projeto é avaliar a composição corporal, ou seja, serão analisadas as diferenças entre a quantidade de gordura e de músculo distribuídos pelo corpo, além de investigar sobre a quantidade de algumas vitaminas e agentes oxidantes e alguns sintomas decorrentes do seu tratamento. A sua participação é voluntária e este estudo não irá interferir no seu tratamento.

Todos os participantes desta pesquisa serão recrutados nas dependências do Hospital das Clínicas de Ribeirão Preto (FMRP-USP), mais especificamente, no Ambulatório de Mastologia e ao término da pesquisa todos os participantes receberão os resultados obtidos. A sua participação na pesquisa terá duração de aproximadamente dois anos e consistirá das seguintes avaliações e procedimentos:

ENTREVISTA - Serão feitas perguntas sobre seus dados pessoais, como idade, escolaridade e presença de doenças crônicas como hipertensão arterial e diabetes mellitus. Será o nosso 1° encontro, no qual agendaremos um dia para a próxima avaliação.

AVALIACÃO COMPOSICÃO CORPORAL - Serão verificados os valores de pressão arterial, seu peso e sua altura e serão medidos seu braço, sua cintura e quadril com uma fita métrica. Para a medida da musculatura e a quantidade de gordura do corpo utilizaremos um aparelho chamado bioimpedância, neste exame são colocados dois adesivos na mão e dois adesivos nos pés e ligados por meio de fios num aparelho eletrônico. Este exame não causa dor, demora mais ou menos 2 minutos estará

terminado. Esta avaliação será realizada antes da primeira quimioterapia; na metade do ciclo de quimioterapia; após 1 mes do final da quimioterapia.

AVALIACÃO DOS SINTOMAS DA QUIMIOTERAPIA- Por meio de perguntas sobre alguns efeitos que o tratamento pode causar, como desconforto no estômago (enjoos ou vômitos), machucados na sua boca e mudança do gosto dos alimentos. Esta avaliação será realizada entre cada ciclo de quimioterapia proposto no seu tratamento.

COLETA DE SANGUE - Nesse dia você terá que vir em jejum de 12 horas (não comer ou beber, exceto os medicamentos que você faz uso), será feita uma coleta de sangue para ver as taxas de glicemia de jejum (teste para ver a dosagem de açúcar no sangue), triglicerídeos e colesterol (teste para ver a dosagem de gordura no sangue) e algumas vitaminas (A, C e E, que agem combatendo os radicais livres produzidos) e estresse oxidativo (teste para ver os antioxidante e radicais livres que geram inflamação no corpo), serão coletados 10ml de sangue, aproximadamente 1 colher de sopa. Se você tiver outros exames pedidos pelo seu médico, faremos a coleta para você. A coleta de sangue será realizada no seu braço oposto ao lado da cirurgia, e ocorrerá antes da primeira quimioterapia; após 1 mes do final da quimioterapia.
As amostras de sangue, num total de 10ml de sangue, aproximadamente 1 colher de sopa, serão analisadas e armazenadas no Laboratório de Nutrição e Metabolismo (Multiusuário) da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo. Pedimos a sua autorização para armazenar a sua amostra durante o período de desenvolvimento da pesquisa, caso haja necessidade de repetição dos exames e, após as análises, elas serão destruídas e você pode, a qualquer momento, pedir por escrito o material biológico (sangue) armazenado.

Você e seu médico do Hospital das Clínicas receberão uma cópia informando os resultados dos exames realizados e se identificarmos alterações em seus exames, você será comunicada e seu médico irá decidir o melhor para seu tratamento.

Todas as avaliações e coleta de sangue ocorrerão em dias agendados, de acordo com a sua disponibilidade, serão feitas nas dependências do Hospital das Clínicas no ambulatório da Ginecologia e a pesquisa não lhe acarretará custos adicionais, já que as avaliações e a entrevista serão feitas em dias de atendimento no hospital.

Também pedimos sua autorização para a coleta de alguns dados relacionados ao seu tratamento no prontuário médico do Hospital das Clínicas da FMRP/USP, como, o tipo do tumor e esquema quimioterápico.

Os riscos da sua participação na pesquisa estão relacionados aos desconfortos em relação a punção para coleta de sangue, que pode causar dor local, mancha roxa na pele, tontura, e raramente, infecção; você também pode sentir algum desconforto com a medida da pressão arterial, e constrangida na hora das medidas do corpo, e na avaliação com o aparelho de bioimpedância. Nesse sentido, serão tomados todos os cuidados em relação à punção; quanto às medidas, estas serão feitas em local reservado, minimizando, assim, os desconfortos.

Sua participação neste estudo é voluntária, ou seja, não é obrigatória. Você pode aceitar participar do estudo e depois desistir a qualquer momento. Isto não prejudicará seu atendimento no hospital. Você também poderá pedir a qualquer momento que as

suas informações sejam excluídas completamente deste estudo e ter acesso aos resultados da pesquisa.

Eu, _____,
concordo em participar do estudo "Avaliação do perfil metabólico, oxidativo e antropométrico em mulheres com câncer de mama", como participante. Fui devidamente informado em detalhes pelo(s) pesquisador(es) responsável(is) no que diz respeito ao objetivo da pesquisa, aos procedimentos, aos riscos e benefícios, à forma de ressarcimento no caso de eventuais despesas, bem como à indenização se houver danos decorrentes da pesquisa. Declaro que tenho pleno conhecimento dos direitos e das condições que são asseguradas e que posso retirar meu consentimento a qualquer momento, sem que isto leve a qualquer penalidade ou interrupção de meu acompanhamento/ assistência/ tratamento.

Entendo que as informações obtidas neste trabalho são confidenciais, e que os resultados desta pesquisa poderão ser publicados em revistas com sigilo da identidade dos participantes. E que irei receber a resposta a qualquer pergunta ou esclarecimento de qualquer dúvida a respeito dos procedimentos, riscos, benefícios e de outras situações relacionadas com a pesquisa e o tratamento. Tenho a liberdade de retirar meu consentimento e deixar de participar do estudo, a qualquer momento, sem que isso traga prejuízo à continuidade do meu tratamento. Declaro que, concordo inteiramente em participar da pesquisa.

A participação neste estudo não acarretará custos e não será disponível nenhuma compensação financeira adicional, uma vez que as avaliações foram programadas para ocorrer durante a própria rotina dentro do hospital, ou seja, no próprio período de internação ou consulta médica. No caso de algum dano decorrente dessa pesquisa poderá ser acionada uma compensação por danos, sendo garantido este direito a indenização em casos de danos, comprovadamente, decorrentes da participação na pesquisa, por meio de decisão judicial ou extrajudicial, conforme as leis vigentes no país.

Ribeirão Preto, _____ de _____ de _____.

Nome do participante:_____ Assinatura _____

2) Grupo controle:

TERMO DE CONSENTIMENTO LIVRE E ESCLARECIDO – GRUPO CONTROLE

Título do estudo: "Avaliação do perfil metabólico, oxidativo e antropométrico em mulheres com câncer de mama."
Pesquisador Responsável: Bruna Ramos da Silva (16)33154564 / bruna.ramos.silva@usp.br
Pesquisadores Participantes:
Dra Mirele Savegnago Mialich Grecco (16)33154564 / mirele.mialich@usp.br
Prof. Dr. Alceu Afonso Jordão Junior (16)33154564 / alceu@fmrp.usp.br
Instituição/Departamento: Universidade de São Paulo, Faculdade de Medicina de Ribeirão Preto / Departamento de Clínica Médica.
Local da coleta de dados: Hospital das Clínicas de Ribeirão Preto

Prezada Senhora

Você está sendo convidada para participar, como voluntária, em uma pesquisa, sua participação se dará por ser uma pessoa saudável, sem nenhuma doença oncológica. Todos os dados que obtivermos com sua participação é meramente para compararmos com os dados de outros participantes que possuem a doença que estamos estudando. Após ser esclarecida sobre as informações a seguir, no caso de aceitar fazer parte do estudo, assine ao final deste documento, que está em duas vias. Uma delas é sua e a outra é do pesquisador responsável. Em caso de recusa você não será penalizado de forma alguma. Em caso de dúvida você pode procurar o Comitê de Ética em Pesquisa do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo ou pelo telefone (16) 3602-2228.

O objetivo deste projeto é avaliar a composição corporal, ou seja, serão analisadas as diferenças entre a quantidade de gordura e de músculo distribuídos pelo corpo, além de investigar sobre a quantidade de algumas vitaminas e agentes oxidantes. A sua participação é voluntária e este estudo não irá interferir em nada de sua rotina ou atividades desenvolvidas no hospital.

Todas as participantes desta pesquisa serão recrutadas nas dependências do Hospital das Clínicas de Ribeirão Preto (FMRP-USP), sendo que a sua participação na pesquisa será realizada em um único momento e consistirá das seguintes avaliações e procedimentos:

ENTREVISTA - Serão feitas perguntas sobre seus dados pessoais, como idade, escolaridade, ingestão alimentar e presença de doenças crônicas como hipertensão arterial e diabetes mellitus. Será o nosso 1° encontro, no qual agendaremos um dia para a avaliação.

AVALIAÇÃO COMPOSIÇÃO CORPORAL - Serão verificados os valores de pressão arterial, seu peso e sua altura e serão medidos seu braço, sua cintura e quadril com uma fita métrica. Para a medida da musculatura e a quantidade de gordura do corpo

utilizaremos um aparelho chamado bioimpedância, neste exame são colocados dois adesivos na mão e dois adesivos nos pés e ligados por meio de fios num aparelho eletrônico. Este exame não causa dor, demora mais ou menos 2 minutos e estará terminado.

COLETA DE SANGUE - Nesse dia você terá que vir em jejum de 12 horas (não comer ou beber, exceto os medicamentos que você faz uso), será feita uma coleta de sangue para ver as taxas de glicemia de jejum (teste para ver a dosagem de açúcar no sangue), triglicerídeos e colesterol (teste para ver a dosagem de gordura no sangue) e algumas vitaminas (A, C e E, que agem combatendo os radicais livres produzidos) e estresse oxidativo (teste para ver os antioxidante e radicais livres que geram inflamação no corpo), serão coletados 10ml de sangue, aproximadamente 1 colher de sopa.

As amostras de sangue serão analisadas e armazenadas no Laboratório de Nutrição e Metabolismo (Multiusuário) da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo. Pedimos a sua autorização para armazenar a sua amostra durante o período de desenvolvimento da pesquisa, caso haja necessidade de repetição dos exames e, após as análises, elas serão destruídas e você pode, a qualquer momento, pedir por escrito o material biológico (sangue) armazenado.

Você receberá uma cópia informando os resultados dos exames realizados e se identificarmos alterações em seus exames, você será comunicada.

Todas as avaliações e coleta de sangue ocorrerão em dias agendados, de acordo com a sua disponibilidade e serão feitas nas dependências do Hospital das Clínicas no ambulatório da Ginecologia. A pesquisa não acarretará custos. Os riscos da sua participação na pesquisa estão relacionados aos desconfortos em relação a punção para coleta de sangue, que pode causar dor local, mancha roxa na pele, tontura, e raramente, infecção; você também pode sentir algum desconforto com a medida da pressão arterial, e constrangida na hora das medidas do corpo, e na avaliação com o aparelho de bioimpedância. Nesse sentido, serão tomados todos os cuidados em relação à punção; quanto às medidas, estas serão feitas em local reservado, minimizando assim, os desconfortos.

Sua participação neste estudo é voluntária, ou seja, não é obrigatória. Você também poderá pedir a qualquer momento que as suas informações sejam excluídas completamente deste estudo. Você não terá nenhum benefício em participar desta pesquisa, pois como já explicamos, seus dados serão meramente para comparar com os dados de uma pessoa em tratamento de doença.

Eu, _____,
concordo em participar do estudo "Avaliação do perfil metabólico, oxidativo e antropométrico em mulheres com câncer de mama", como participante. Fui devidamente informado em detalhes pelo(s) pesquisador(es) responsável(is) no que diz respeito ao objetivo da pesquisa, aos procedimentos, aos riscos e benefícios, à forma de ressarcimento no caso de eventuais despesas, bem como à indenização se houver danos decorrentes da pesquisa. Declaro que tenho pleno conhecimento dos direitos e das condições que são asseguradas e que posso retirar meu consentimento a qualquer

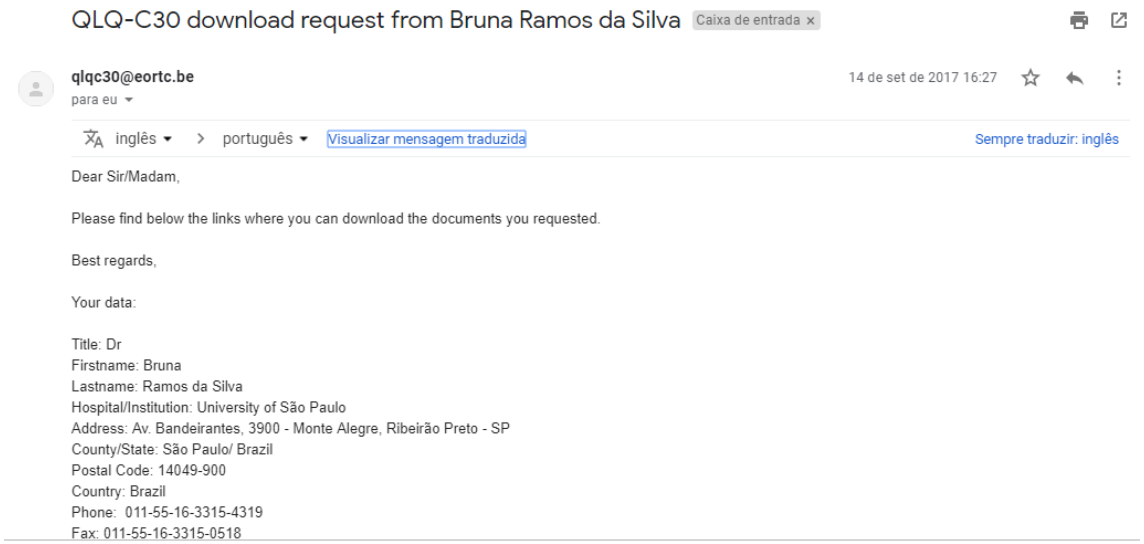
momento, sem que isto leve a qualquer penalidade. Entendo que as informações obtidas neste trabalho são confidenciais, e que os resultados desta pesquisa poderão ser publicados em revistas com sigilo da identidade dos participantes. E que irei receber a resposta a qualquer pergunta ou esclarecimento de qualquer dúvida a respeito dos procedimentos, riscos, benefícios e de outras situações relacionadas com a pesquisa. Tenho a liberdade de retirar meu consentimento e deixar de participar do estudo, a qualquer momento, sem que isso traga prejuízo. Declaro que, concordo inteiramente em participar da pesquisa.

A participação neste estudo não acarretará custos e não será disponível nenhuma compensação financeira adicional, uma vez que as avaliações foram programadas para ocorrer durante a própria rotina dentro do hospital. No caso de algum dano decorrente dessa pesquisa poderá ser acionada uma compensação por danos, sendo garantido este direito a indenização em casos de danos, comprovadamente, decorrentes da participação na pesquisa, por meio de decisão judicial ou extrajudicial, conforme as leis vigentes no país.

Ribeirão Preto, _____ de _____ de _____.

Nome do participante:_____ Assinatura _____

10.3 APROVAÇÃO VIA EMAIL DO USO DO EORTC



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Your data:

Title: Dr
Firstname: Bruna
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County/State: São Paulo/ Brazil
Postal Code: 14049-900
Country: Brazil
Phone: 011-55-16-3315-4319
Fax: 011-55-16-3315-0518

Email: bruna.ramos.silva@usp.br
Protocol: "EVALUATION OF THE METABOLIC, OXIDATIVE AND ANTHROPOMETRIC PROFILE IN WOMEN WITH BREAST CANCER.

Documents requested:

Breast Module (BR23) in Portuguese
QLQ-C30 Scoring Manual
Scoring Instructions: Breast BR23

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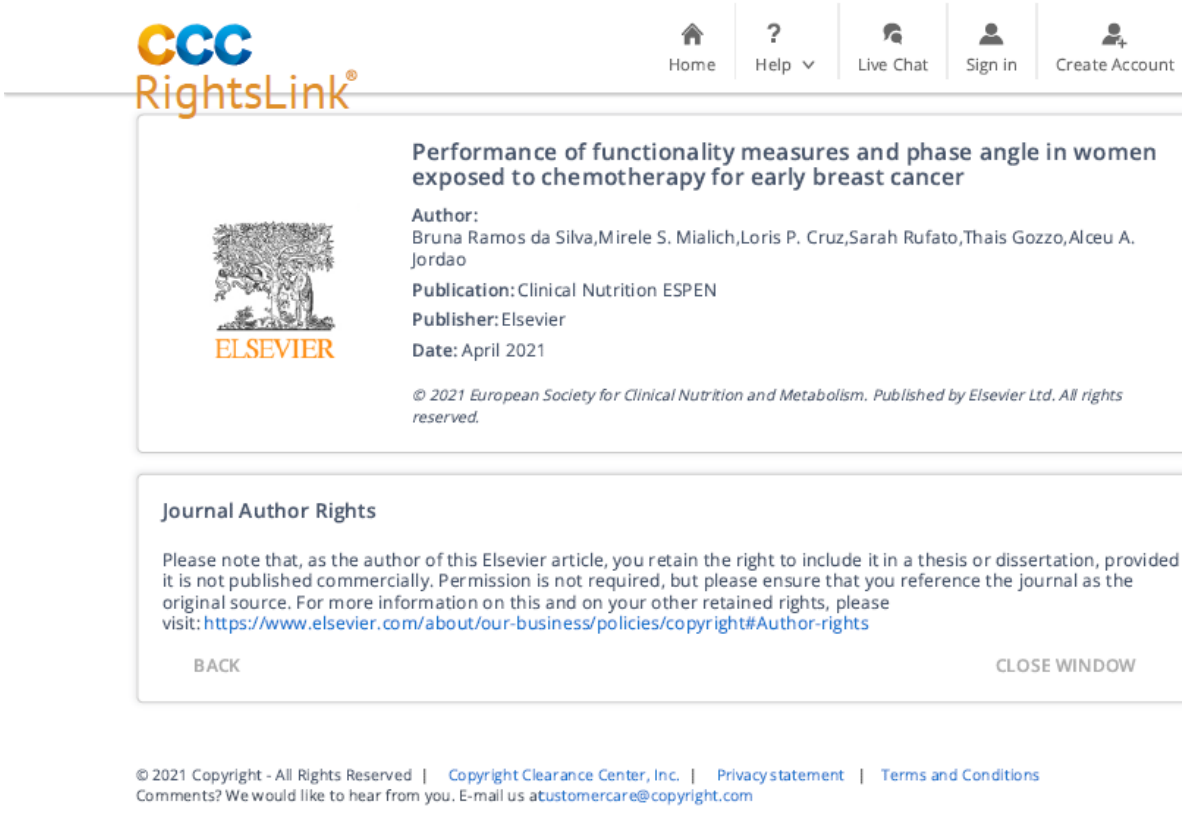

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Performance of functionality measures and phase angle in women exposed to chemotherapy for early breast cancer

Author:
Bruna Ramos da Silva,Mirele S. Mialich,Loris P. Cruz,Sarah Rufato,Thais Gozzo,Alceu A. Jordao

Publication: Clinical Nutrition ESPEN

Publisher: Elsevier

Date: April 2021

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10.5 PROVA DE SUBMISSÃO DE ARTIGO EM REVISTA CIENTÍFICA

Journal of the Academy of Nutrition and Dietetics

An evaluation of metabolic, dietetic, and nutritional status reveals impaired outcomes in breast cancer patients undergoing chemotherapy compared with a matched control group.

--Manuscript Draft--

Manuscript Number:	
Article Type:	Research Paper
Keywords:	Early breast cancer; cardiovascular risk; nutritional status; metabolic changes.
Corresponding Author:	Bruna Ramos da Silva Universidade de São Paulo Ribeirão Preto, SP BRAZIL
First Author:	Bruna Ramos da Silva
Order of Authors:	Bruna Ramos da Silva
	Sarah Ruffato
	Mirele Mialich
	Loris Cruz
	Thais Gozzo
	Alceu Jordão
Abstract:	Purpose : Nutritional status changes in breast cancer patients during treatment are prevalent. However, the metabolic implications of those alterations are poorly understood. We firstly aimed to characterize body composition, lipids, glucose levels, as well as indices that express cardiovascular risk in breast cancer patients after completion of chemotherapy and then to compare those results with a matched control group. Methods : A cross-sectional nested case-control study was performed. Women who completed their chemotherapy were recruited (BC group) and compared with a group of non-malignant age- and body mass index-matched (MC group), as well as a group of healthy, non-malignant women (healthy group). Body composition by bioelectrical impedance analysis, handgrip strength, and blood sample were collected. Visceral adiposity, triglyceride glucose and lipid accumulation product indices were calculated. Food consumption was assessed. Results: BC patients demonstrated worse values of phase angle, nutritional risk index, extracellular body water to total body water ratio and lower handgrip strength. Additionally, those women had impairments in lipids, worst glucose levels, visceral fat dysfunction and consequently higher cardiovascular risk, presenting important unhealthy dietary patterns with higher carbohydrate and caloric intake and insufficient protein and fiber ingestion. No differences were observed between MC and HG. Conclusion: Breast cancer patients present unhealthy metabolic, nutritional, and dietetic features when compared to a group of age- and BMI-matched non-malignant females. Also, breast cancer patients had higher levels of cardiovascular risk. Further investigations are required to examine the underlying mechanisms and the potential longitudinal changes during surveillance time.

10.6 PROVA DE SUBMISSÃO DE ARTIGO EM REVISTA CIENTÍFICA

European Journal of Nutrition

Phase angle is related with oxidative stress and antioxidant biomarkers in Breast Cancer patients undergoing chemotherapy.

--Manuscript Draft--

Manuscript Number:		
Full Title:	Phase angle is related with oxidative stress and antioxidant biomarkers in Breast Cancer patients undergoing chemotherapy.	
Article Type:	Original Contribution	
Keywords:	Body composition; Phase angle; Inflammatory markers; Oxidative stress	
Corresponding Author:	Bruna Ramos da Silva, Bacharel of science University of Sao Paulo: Universidade de Sao Paulo BRAZIL	
Corresponding Author Secondary Information:		
Corresponding Author's Institution:	University of Sao Paulo: Universidade de Sao Paulo	
Corresponding Author's Secondary Institution:		
First Author:	Bruna Ramos da Silva, Bacharel of science	
First Author Secondary Information:		
Order of Authors:	Bruna Ramos da Silva, Bacharel of science	
	Mirele Mialich	
	Sarah Ruffato	
	Loris Cruz	
	Thais Gozzo	
	Alceu Jordão	
Order of Authors Secondary Information:		
Funding Information:	Fundação de Amparo à Pesquisa do Estado de São Paulo (2017/07963-0; 2019/09877-9)	B.Sc. Bruna Ramos da Silva
Abstract:	Purpose : The study aimed to analyze the influence of chemotherapy on health biomarkers, and to examine the relation among phase angle (PhA), oxidative stress and metabolic profile . Methods : A prospective study was performed. Women who were starting were recruited. Also, this study included a control group. Bioelectrical impedance analysis (BIA), 24h food recall, and blood sample were collected at 2-time points: diagnosis (T0) and after 1 month of completion of therapy (T1) for main study group and 1 time point for control group. ANOVA or Mann-Whitney Wilcoxon Test were used to compare variables. Linear regression analysis was conducted to further test if PhA is related with the dependent variables, after adjusting for age . Results : 61 women with breast cancer and 58 healthy were included. There was no difference after treatment and between the groups concerning anthropometrics, fat mass and fat-free mass. Breast cancer patients had a worsening in PhA and visceral adiposity index (P<0.001). In T1 PhA was statically correlated with extracellular water, albumin, hemoglobin, and the antioxidant marker 2,2-Diphenyl-1-picrylhydrazyl (DPPH). The linear model showed PhA was significantly predicted by C reactive protein, DPPH (Beta= 0.00022, p=0.02), Malondialdehyde (MDA), total body water/extracellular water, body mass index and fat mass. This model explained 68% of PhA variability (p<0.001). Conclusion : Our findings show that PhA is an easy and affordable tool which is correlated stress oxidative markers in breast cancer patients, regardless of age or body mass index.	