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Pamela Carvalho da Rosa

TREINAMENTO FUNCIONAL ALTERA O PERFIL METABÓLICO, MITOCONDRIAL E REDOX DE CÉLULAS MONONUCLEARES DE MULHERES COM SÍNDROME METABÓLICA

Santa Maria, RS
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Dissertação apresentada ao Curso de Pós-Graduação em Ciências Biológicas: Bioquímica Toxicológica, da Universidade Federal de Santa Maria (UFSM, RS), como requisito parcial para obtenção do título de **Mestre em Ciências Biológicas: Bioquímica Toxicológica.**

Orientador: Prof. Dr. Rômulo Pillon Barcelos
Co-orientador: Prof. Dr. Félix Alexandre Antunes Soares

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Santa Maria, RS
2019

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Com amor, gratidão e profunda admiração, à minha querida mãe Eneida, sua dedicação e persistência foram fundamentais nesta caminhada.

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A educação é a arma mais poderosa que você pode usar para mudar o mundo.

(Nelson Mandela)

RESUMO

TREINAMENTO FUNCIONAL ALTERA O PERFIL METABÓLICO, MITOCONDRIAL E REDOX DE CÉLULAS MONONUCLEARES DE MULHERES COM SÍNDROME METABÓLICA

AUTORA: Pamela Carvalho da Rosa
ORIENTADOR: Rômulo Pillon Barcelos
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A síndrome metabólica (SM) é uma combinação de anormalidades metabólicas, como hipertensão, hiperglicemia, obesidade abdominal e dislipidemia. Essas condições ocorrem simultaneamente e aumentam o risco para o desenvolvimento de diabetes tipo 2 e doenças cardiovasculares, e ainda podem estar relacionadas com o comprometimento das funções mitocondriais e do sistema de defesa antioxidante, uma vez que ocorre maior produção de espécies reativas de oxigênio (EROs), redução da fosforilação oxidativa e, consequentemente, menor síntese de adenosina trifosfato. Neste sentido, o desenvolvimento de estratégias terapêuticas, incluindo intervenções no estilo de vida, como dieta e exercícios físicos regulares voltados ao metabolismo mitocondrial, podem ser importantes e relevantes para o tratamento e prevenção da SM. Além disso, já está descrito na literatura os efeitos benéficos do exercício físico no metabolismo mitocondrial e status redox, porém, o seu impacto sobre células mononucleares do sangue periférico (PBMCs) de pacientes com SM permanece desconhecido. Portanto, este estudo pretende determinar se o exercício físico altera o metabolismo energético, capacidade dos complexos mitocondriais e o estresse oxidativo de PBMCs a partir de mulheres com SM, e associá-los aos parâmetros de exercício físico. Para realização deste estudo, foram recrutadas mulheres de meia-idade sedentárias com mais de 45 anos, e com pelo menos 3 fatores de risco relacionados à SM. As participantes realizaram um programa de treinamento funcional de 12 semanas (3d/semana). As células (PBMCs) foram obtidas a partir da coleta de sangue das participantes com SM; realizada antes do treinamento (baseline) e 72 horas após o término do protocolo de treinamento para evitar efeitos agudo do exercício (após o treinamento). Após o isolamentos, as PBMCs foram utilizadas para mensurar os seguintes parâmetros: atividades da lactato desidrogenase (LDH) e citrato sintase (CS) relacionadas ao metabolismo energético, e a capacidade respiratória dos complexos mitocondriais (I-IV). A produção de EROs foi realizada a partir da oxidação da diclorofluoresceína e produção de peróxido de hidrogênio (H_2O_2), bem como a atividade da catalase (CAT) associada ao sistema antioxidante endógeno. O protocolo de treinamento produziu um aumento nos níveis de LDH das PBMCs, enquanto a atividade da CS permaneceu inalterada. Além disso, houve um aumento na produção de EROs induzida pelo exercício, bem como melhora no sistema antioxidante, indicando um mecanismo de adaptação. As PBMCs também demonstraram um aumento na atividade das desidrogenases e na capacidade de transferência de elétrons mitocondriais. Além disso, houve um aumento na capacidade aeróbica das participantes, enquanto que a massa corporal pernameceu inalterada após o treinamento. Em conclusão, nossos resultados fornecem novas evidências de que um programa de treinamento funcional de 12 semanas altera o estado redox das PBMCs e a capacidade de transferência de elétrons mitocondriais em resposta ao estímulo do metabolismo, além de melhorar a capacidade aeróbica de mulheres com SM. Portanto, nossos dados sugerem que as PBMCs podem ser eficazes para detectar e avaliar mudanças nos perfis celulares de pacientes não saudáveis, e dessa forma, podem vir a ser utilizadas como fonte de biomarcadores para a controle e qualidade do exercício físico.

Palavras-chaves: Exercício Físico. Metabolismo Energético. Respiração Mitocondrial. Estado Redox e PBMCs.

ABSTRACT

FUNCTIONAL TRAINING MODIFIES THE METABOLIC PROFILE, MITOCHONDRIAL AND REDOX OF THE MONONUCLEAR CELLS IN WOMEN WITH METABOLIC SYNDROME

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Metabolic syndrome (MS) is a combination of metabolic abnormalities, such as hypertension, hyperglycemia, abdominal obesityand dyslipidemia. These conditions occur simultaneously and increase the risk for type 2 diabetes and cardiovascular diseases development, and may be related to mitochondrial and antioxidant defense system dysfunction, once those conditions increase reactive oxygen species (ROS) generation, reduction of oxidative phosphorylation and, consequently, lower ATP synthesis. In this sense, the development of therapeutic strategies, including lifestyle interventions, such as diet and regular physical exercises directed to mitochondria metabolism, might be relevant and important for MS treatment and prevention. Moreover, it is well-known the beneficial effects of exercise at mitochondrial metabolism and redox states, but its impact on peripheral blood mononuclear cells (PBMCs) from patients with MS remains unclear. Therefore, this study intends to determine whether exercise training changes the energy metabolism, mitochondrial complexes capability and oxidative stress of women's PBMCs with MS, and associate them to the exercise parameters. To this, untrained middle-age women over 45 years old, and with three risk factors related to MS were recruited. Participants performed a functional training protocol during the 12-weeks (3d/wk). Cells (PBMCs) were obtained from subject's blood collection with MS before training (baseline) and 72 hours after the end of the training protocol (to avoid acute exercise effects - after training). After isolation, PBMCs were used to measure the following parameters: lactate dehydrogenase (LDH) and citrate synthase (CS) activity related for energy metabolism, and the mitochondrial complexes respiratory capability (I-IV). ROS production was performed for dichlorofluorescein oxidation and hydrogen peroxide (H_2O_2**)** production, as well as catalase (CAT) activity associated endogenous antioxidant system. The training protocol produced an increase in PBMCs LDH levels, while CS activity remained unaltered. Moreover, PBMCs demonstrated an increase in exercise-induced ROS formation, as well as antioxidant system improvement, indicating an adaptation mechanism. The PBMCs depicted an increase in dehydrogenases activity and mitochondrial electron transfer capacity. Moreover, had an increase aerobic capacity in participants, while body weight remained unaltered after training. In conclusion, we provided novel evidence that a 12-week functional exercise-training program modifies PBMCs redox state and mitochondrial electron transfer capacity in response to metabolism stimulation, in addition to improved aerobic capacity in women with MS. Therefore, our data suggests that PBMCs could be effective to detect and assess changes cellular profiles from unhealthy patients, as well as biomarkers source for physical exercise control and quality.

Key-words: Physical Exercise. Energy Metabolism. Mitochondrial Respiratory. Redox state. PBMCs.

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LISTA DE ABREVIATURAS E SÍMBOLOS

ATP	Adenosina trifosfato
CAT	Catalase
CS	Citrato sintase
CuZnSOD	Cobre zinco superóxido dismutase
DCF	Diclorofluoresceína
EROs	Espécies reativas de oxigênio
GPx	Glutationa peroxidase
GR	Glutationa redutase
GSH	Glutationa reduzida
GSSG	Glutationa oxidada
H_2O_2	Peróxido de hidrogênio
HDL	Lipoproteína de alta densidade
LDH	Lactato desidrogenase
MnSOD	Manganês superóxido dismutase
NADPH	Nicotinamida adenina dinucleotídeo fosfato reduzida
NCEP/ATP III	*National Cholesterol Education Program's Adult Treatment Panel III*
$O_2^{\bullet-}$	Ânion superóxido
$^{\bullet}OH$	Radical hidroxila
$ONOO^-$	Radical peroxinitrito
OXPHOS	Fosforilação oxidativa
PBMCs	Células mononucleares de sangue periférico
SM	Síndrome metabólica
$VO_{2máx}$	Capacidade aeróbica máxima

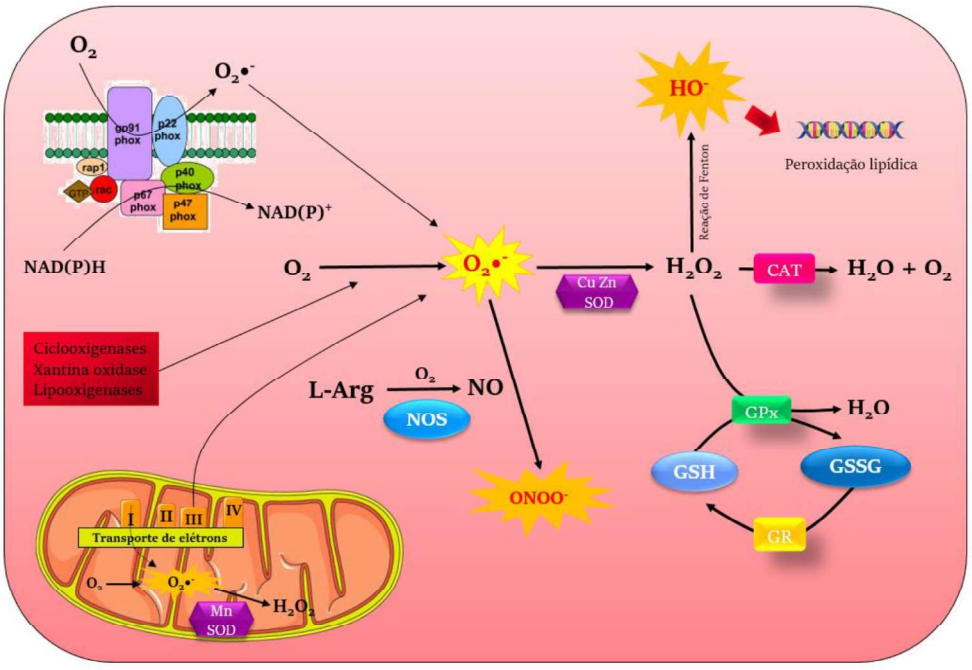
SUMÁRIO

1 INTRODUÇÃO

1.1 ESTRESSE OXIDATIVO E A DISFUNÇÃO MITOCONDRIAL EM DISTÚRBIOS CARDIOMETABÓLICOS

O estresse oxidativo é uma situação metabólica que corresponde a um excesso de espécies reativas de oxigênio (EROs), resultante de um desequilíbrio entre a produção exagerada e uma capacidade biológica limitada para neutralizar esses radicais livres. As principais EROs resultantes da redução química de oxigênio molecular (O_2) incluem o ânion superóxido ($O_2^{\bullet-}$), o radical hidroxila ($^{\bullet}OH$), o peróxido de hidrogênio (H_2O_2), o ácido hipocloroso (HClO), o radical peroxinitrito ($ONOO^-$) e o óxido nítrico (NO) (RAY; HUANG; TSUJI, 2012). Além disso, as fontes primárias de EROs são o sistema de transporte de elétrons mitocondrial e várias enzimas oxidases, incluindo a nicotinamida adenina dinucleotídeo fosfato reduzida (NADPH oxidase), as ciclooxigenases, a xantina oxidase, as lipooxigenases e a óxido nítrico sintase (NOS) (MÜNZEL et al., 2010). Na figura 1, pode-se observar as principais moléculas pró-oxidantes e as enzimas do sistema antioxidante.

Figura 1 - Representação esquemática das principais fontes de EROs e do sistema antioxidante



Notas: A ativação da NAD(P)H oxidase efetua a transferência de equivalentes redutores do NADPH para o oxigênio, gerando o radical $O_2^{\bullet-}$. Além disso, o H_2O_2 pode ser gerado como produto secundário, através da dismutação do $O_2^{\bullet-}$ pela ação da SOD (BABIOR, 2004; VIGNAIS, 2002). A enzima CuZnSOD (citosólica) por dismutação gera o H_2O_2, o qual pode ser convertido em $^{\bullet}OH$, catalisada pelas reações de Fenton e Haber–Weiss (MIQUEL et al., 1980). Ambas enzimas, CAT e GPx, são responsáveis pela conversão do H_2O_2 em H_2O e oxigênio. A GPx, remove o H_2O_2 com a oxidação da glutationa (GSSG), a qual volta a sua forma reduzida (GSH) novamente pela enzima GR, podendo assim ser reutilizada em um outro processo antioxidante da GPx (PENG et al., 2014).

Fonte: A autora (2019).

Resumidamente, as EROs são formados a partir de processos de oxidação e redução (FRIDOVICH, 1997). A redução do oxigênio na presença de um elétron livre gera ânion $O_2\bullet^-$, o qual é um radical instável e pode agir como um agente oxidante, sendo reduzido a H_2O_2, ou como agente redutor, formando o $ONOO^-$ (DARLEY-USMAR; WISEMAN; HALLIWELL, 1995). O H_2O_2 é uma espécie não radicalar e lipossolúvel, pode ser formado espontaneamente pela dismutação do $O_2\bullet^-$, esta reação pode ser catalisada pela enzima superóxido dismutase (SOD) (CHANNON; GUZIK, 2002; FRIDOVICH, 1997). Além disso, as enzimas catalase (CAT), glutationa peroxidase (GPx), glutationa redutase (GR), e as SODs, tais como cobre zinco (CuZnSOD) e a manganês (MnSOD), bem como os componentes exógenos como vitaminas A, C, E e flavonóides participam do mecanismo de defesa antioxidante (KALININA; CHERNOV; SAPRIN, 2008; VALKO et al., 2007).

Como mencionado anteriormente, a mitocôndria é considerada uma importante fonte de EROs, uma vez que elétrons escapam durante o processo de transdução de energia e, assim, o radical $O_2\bullet^-$ é formado (LOPEZ-FABUEL et al., 2016; MURPHY, 2009), mais especificamente, nos complexos I e III da cadeia transportadora de elétrons (BRATIC; LARSSON, 2013). A produção excessiva desses radicais pode levar a um extenso dano oxidativo às mitocôndrias (FINKEL, 2005), no entanto, as defesas antioxidantes mitocondriais, como à MnSOD, podem neutralizar as EROs e minimizar os efeitos oxidativos nessas organelas (MURPHY; SMITH, 2000).

As mitocôndrias são formadas por uma membrana interna e a outra externa, na membrana interna são encontrados diferentes complexos proteicos responsáveis pela oxidação de equivalentes redutores produzidos no ciclo de Krebs. Esses complexos proteicos compreendem: complexo I (NADH-desidrogenase), complexo II (succinato desidrogenase), complexo III (citocromo c-redutase), complexo IV (citocromo c-oxidase) e complexo V (ATP-sintase) (LAMPL et al., 2015). Os elétrons resultantes dessas oxidações são utilizados para formar um gradiente de prótons, que serão aproveitados como força motriz para a produção de adenosina trifosfato (ATP). As mitocôndrias também são indispensáveis para o metabolismo e

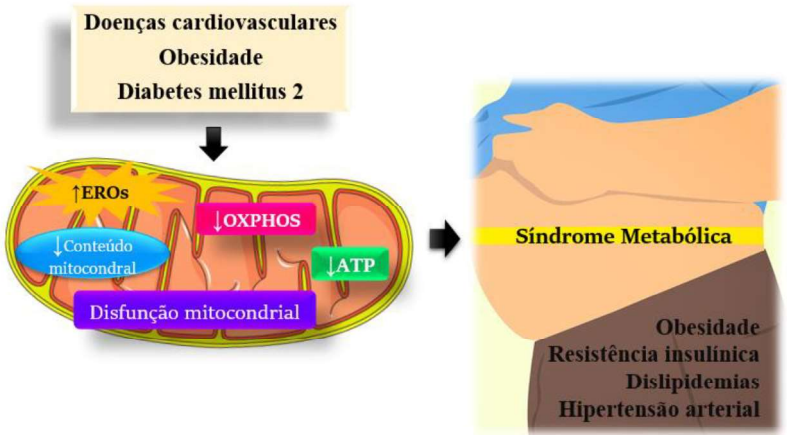
sobrevivência celular, além de produzir ATP, essas organelas estão envolvidas no metabolismo de produção de uréia, homeostase de cálcio e regulação do estado redox celular (MURPHY; SMITH, 2007), bem como são cruciais nos processos de morte celular, via apoptótica e autofágica (GOZUACIK; KIMCHI, 2004; ORRENIUS; ZHIVOTOVSKY; NICOTERA, 2003).

Muitos estudos têm revelado que as EROs são importantentes moléculas sinalizadoras, uma vez que participam da ativação/inativação de várias moléculas, que desencadeam mecanismos de defesa e ativação de enzimas antioxidantes. Essas moléculas também controlam vários processos biológicos como, por exemplo, crescimento celular, migração celular, expressão de genes pró-inflamatórios e biogênese mitocondrial (SCHIEBER; CHANDEL, 2014; ZHANG et al., 2016). As EROs estão amplamente envolvidas em adaptações celulares relacionadas às mitocondrias (VYAS; ZAGANJOR; HAIGIS, 2016), incluindo mudanças na morfologia e dinâmica mitocondrial (COGLIATI et al., 2013; NEVES et al., 2008). Entretanto, em excesso, são a principal causa de disfunção mitocondrial (BALABAN; NEMOTO; FINKEL, 2005; RAHA; ROBINSON, 2000) e causam danos as estruturas celulares, culminando, finalmente, em uma ampla gama de doenças (VALKO et al., 2007). Já está descrito na literatura que as EROs mitocondriais causam danos a proteína mitocondrial, lipídios e ácido desoxirribonucleico mitocondrial (DNAmt), resultando em modificações na função mitocondrial, assim como podem extravazar para o citosol (FRIDOVICH, 1997; SAWYER; VALENTINE, 1981; VÁSQUEZ-VIVAR; KALYANARAMAN; KENNEDY, 2000). Além disso, alterações nas funções mitocondriais podem ser observadas no desenvolvimento e progressão de diversas doenças crônicas (LIAO; DONG; CHENG, 2017; MISHRA; KUMAR, 2014; REQUEJO-AGUILAR; BOLAÑOS, 2016).

Corroborando com essa hipótese, acredita-se que os efeitos deletérios estruturais e funcionais no sistema cardiovascular é gerado pela superprodução de EROs mitocondriais (MARZETTI et al., 2013), os quais podem causar disfunção mitocondrial durante a isquemia/reperfusão (TOMPKINS et al., 2006). Além disso, estudos demonstram que há uma redução na fosforilação oxidativa (OXPHOS) e produção de ATP mitocondrial em tecidos afetados pela diabetes (SHARMA, 2015), resultante de uma contínua redução da função mitocondrial ligada à superprodução de oxidantes e liberação de citocinas pró-inflamatórias (DUGAN et al., 2013). Em indivíduos com resistência à insulina e obesos, também ocorre prejuízos à mitocondria como, por exemplo, redução na OXPHOS e conteúdo mitocondrial (CIVITARESE; RAVUSSIN, 2008) acompanhada de múltiplas anormalidades na função e morfologia mitocondrial (KOLIAKI; RODEN, 2016) (figura 2).

Portanto, os efeitos nocivos do estresse oxidativo acarretam em disfunção mitocondrial, e são fatores comuns para o desenvolvimento e a progressão de uma variedade de distúrbios cardiometabólicos, incluindo à obesidade, resistência insulínica, diabetes mellitus 2 e doenças cardiovasculares, conforme mostrado na figura 2 abaixo:

Figura 2 – Disfunções associadas aos distúrbios cardiometabólicos



Fonte: A autora (2019).

Considerando os eventos acima citados, verifica-se que tanto o estresse oxidativo quanto a disfunção mitocondrial possuem papéis fundamentais na síndrome metabólica (SM). A SM, é também chamada de síndrome X, plurimetabólica, quarteto mortal, ou ainda, síndrome de resistência à insulina, descrições que podem diferir em componentes ou critérios, porém, todos apontam para um fenótipo dismetabólico similar (SAMSON; GARBER, 2014). Nesse sentido, a SM é caracterizada pela presença concomitante de diversos fatores de risco, incluindo à obesidade, resistência insulínica, dislipidemia e hipertensão arterial (ALBERTI; ZIMMET; SHAW, 2006; LAAKSONEN et al., 2004). Tais alterações são consequências de um estilo de vida sedentário acrescida de maus hábitos alimentares (BRUUNSGAARD, 2005) e, consequentemente, estão fortemente relacionadas ao desenvolvimento de doenças cardiovasculares e da diabetes mellitus 2 (ALBERTI et al., 2009).

Tendo em vista as várias definições propostas para a SM, a definição mais utilizada é a do *National Cholesterol Education Program's Adult Treatment Panel III* (NCEP/ATP III). De acordo com este critério, a SM representa a combinação de pelo menos três componentes, dos cinco parâmetros citados: obesidade abdominal, níveis elevados de triglicerídeos, níveis diminuídos de colesterol ligado a lipoproteína de alta densidade (HDL), pressão arterial e a

glicemia de jejum alterada (tabela 1) (NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP) EXPERT PANEL ON DETECTION EVALUATION AND TREATMENT OF HIGH BLOOD CHOLESTEROL IN ADULTS (ADULT TREATMENT PANEL III), 2002).

Tabela 1- Critérios de diagnóstico da SM pela NCEP/ATP III

Parâmetros ATP III	Valores
Circunferência da cintura	> 102 cm para homens ou > 88 cm para mulheres
Níveis de triglicerídeos	≥ 150 mg/dL
Níveis de HDL	< 40 mg/dL para homens ou < 50 mg/dL para mulheres
Pressão arterial	≥ 130 mmHg sistólica; ≥ 85 mmHg diastólica
Glicemia de jejum	≥ 100 mg/dL

Fonte: Adaptado de (PRASAD, 2014).

Pode-se observar que todas essas complicações seguidamente acometem obesos e isso demonstra uma forte correlação entre SM e a obesidade (DUPUY et al., 2008). Sucintamente, com uma ingestão calórica extra e um estilo de vida sedentário, o excesso de energia é armazenado na forma de gordura e, essa gordura visceral está diretamente associada com a resistência à insulina e dislipidemias (FOX et al., 2007; NEELAND et al., 2013; ODA, 2008). De fato, a produção de EROs aumenta paralelamente ao acúmulo de gordura nos adipócitos, provavelmente ativa a NADPH oxidase e diminui a expressão de enzimas antioxidantes (FURUKAWA et al., 2004), ressaltando o papel crítico das EROs no desenvolvimento de disfunção vascular e hipertensão arterial (MONTEZANO et al., 2015). Além disso, o estresse oxidativo no tecido adiposo sob condições de SM, resulta em diminuição da adiponectina antiinflamatória e em aumento de citocinas inflamatórias (OTANI, 2011; SOARES et al., 2005), culminando no comprometimento da sinalização da insulina através da deterioração da translocação do transportador de glicose 4 (ASNAT BLOCH-DAMTI, 2005).

Da mesma maneira, as mitocôndrias estão claramente implicadas no desenvolvimento de componentes e complicações da SM. O desbalanço entre o sistema antioxidante e a superprodução de EROs mitocondriais, promovem o estresse oxidativo (DAIBER, 2010), afetando severamente as funções mitocondriais (KELLEY et al., 2002) como, por exemplo, defeitos no transporte de elétrons, atividades enzimáticas e diminuição na produção de ATP

(MONTGOMERY; TURNER, 2014; PORTO et al., 2015). Portanto, tal disfunção metabólica tem forte correlação com o estresse oxidativo (ROLO; PALMEIRA, 2006), levando ao comprometimento da cadeia respiratória mitocondrial (MOGENSEN et al., 2007; WELLS et al., 2008) (figura 2).

O processo inflamatório também é um dos precursores de várias complicações envolvendo os componentes da SM (YAO et al., 2014). A inflamação ocorre por consequência do estresse oxidativo causado pelo excesso de gordura acumulada nos adipócitos (KLÖTING; BLÜHER, 2014; RASK-MADSEN; KAHN, 2012) e, como resultado, ocorre a liberação de citocinas pró-inflamatórias, como a interleucina-1, a interleucina-6 e o fator de necrose tumoral alfa, o que resulta no desenvolvimento de um estado sistêmico inflamatório crônico de baixo grau (NAKAMURA; FUSTER; WALSH, 2014; WISSE, 2004). Portanto, os pacientes que sofrem de SM exibem um desequilíbrio evidente no estado redox e inflamatório que afeta as respostas celulares e, consequentemente, as subclasses de células imunes (CARRIER, 2017; DEVARAJ; GOYAL; JIALAL, 2008; HOLVOET, 2008).

1.2 AS CÉLULAS DO SISTEMA IMUNOLÓGICO: CÉLULAS MONONUCLEARES DE SANGUE PERIFÉRICO

As PBMCs (do inglês Peripheral Blood Mononuclear Cells), uma vez isoladas do sangue periférico, são constituídas de diferentes tipos de células como, por exemplo, monócitos, linfócitos B, T e natural Killer (AROSA; CARDOSO; PACHECO, 2012). As PBMCs, além de integrarem a linha de frente do sistema imunológico humano (POURAHMAD; SALIMI, 2015), são mediadores essenciais de estresse oxidativo e inflamação uma vez que produzem citocinas, quimiocinas e fatores de crescimento que podem levar a efeitos patológicos ou até mesmo benéficos nos tecido (SPANIDIS et al., 2018). Nas subclasses de leucócitos de pacientes com SM observa-se um fenótipo metabólico diferente, o que demonstra o seu papel de biomarcador clínico que reflete amplamente em comorbidades já manifestada (PECHT et al., 2014). Da mesma maneira, os monocitos/macrófagos estão envolvidos na inflamação no tecido adiposo (POWELL et al., 2012).

Dessa forma, as PBMCs surgem como modelo para o estudo da inflamação e sistema imune, considerando suas várias funções anti-patógeno, entre outros, em um ambiente de exposição à inflamação (LEE et al., 2007). Tal conjunto de células, são ativadas, proliferam-se e diferenciam-se em consequência de diferentes situações/estímulos (BROERE et al., 2011;

LUCKHEERAM et al., 2012). Além disso, é importante ressaltar que estes processos são coordenados pela produção de EROs, e também, ocorrem sob necessidades de reprogramação metabólica (MOTWANI; GILROY, 2015; PALMER et al., 2012).

Estudos demonstram que as EROs têm forte influências sobre as células do sistema imune. Especificamente o H_2O_2 é importante na detecção, modulação e sinalização de processos do metabolismo redox nessas células (DI MARZO; CHISCI; GIOVANNONI, 2018). O H_2O_2 exibe também a capacidade de oxidar proteínas (BURDO; RICE-EVANS, 1989; HALLIWELL; CLEMENT; LONG, 2000; HUANG; SIKES, 2014) que podem ativar vias de regulação metabólicas (ALDOSARI et al., 2018; DI MEO et al., 2018; SIES, 2017), incluindo patológicas e / ou protetoras, de forma concentração-dependentes (MARINHO et al., 2014). Portanto, as EROs fornecem um mecanismo pelo qual as células imunes podem "detectar" alterações no equilíbrio redox, e assim, exercer as respostas adaptativas, uma vez que vários estados patológicos, incluindo à SM, são caracterizadas por estado redox alterado (HUANG; SIKES, 2014).

O importante papel das mitocôndrias nas atividades das células imunes é sabido. Evidências demonstram que a morfologia e o metabolismo mitocondrial regulam fortemente essas células durante a resposta imune (BUCK et al., 2016). Entretanto, disfunções mitocondriais em PBMCs já foram investigadas em outras doenças crônicas, incluindo obesidade (CALTON et al., 2016), diabetes mellitus 2 (HARTMAN et al., 2014) e doenças cardiovasculares (CHEN; ZHOU; MIN, 2018). Especialmente, em pacientes que sofrem de SM exibem um desequilíbrio redox evidente aliado a um estado inflamatório crônico, afetando as respostas celulares e, consequentemente, as subclasses de células imunes (PICARD et al., 2015). Todavia, é importante salientar que estudos relatando as possíveis consequências da SM em mitocôndrias de PBMCs não são bem documentados.

Portanto, a avaliação da função metabólica em células isoladas de sangue humano para o tratamento e diagnóstico de doenças é importante para pesquisa. Neste sentido, estudos demonstram que essas células circulantes detectam o estresse metabólico em pacientes e, são utilizados como biomarcadores (CIFRE et al., 2017; REYNÉS et al., 2015) de disfunções mitocondriais em patologias humanas, incluindo diabetes e doença cardiovascular (KRAMER et al., 2014). Além disso, dados anteriores sustentam a hipótese de que as PBMCs não são apenas participantes em mecanismos de inflamação e respostas imunes, mas também são considerados indicadoras de longo prazo das respostas do corpo a diferentes condições/estímulos como, por exemplo, o exercício físico (LEE et al., 2007, MARIGGIÒ et al., 2010, TURNER et al., 2011).

Sabendo que as PBMCs podem ser acessadas de forma relativamente fácil por meio de coletas de sangue devido à sua exposição sistêmica, tais células surgem como ferramenta para detectar o estado funcional da célula e, posteriormente, desenvolver estratégias para o tratamento da SM. Portanto, modelos que consigam detectar e avaliar as alterações na função mitocondrial e no estado oxidativo de pacientes com SM, poderiam diminuir lacunas encontradas na literatura.

1.3 EXERCÍCIO FÍSICO COMO ESTRATÉGIA DE TRATAMENTO DA SM

Tradicionalmente, o exercício físico é conhecido como a intervenção mais eficaz para prevenir e tratar os fatores de risco agrupados na SM (PEDERSEN; SALTIN, 2015). Corroborando com esses achados, sabe-se que a prática regular de exercícios físicos exercem efeitos benéficos sobre as respostas imunes e antiinflamatórias (DE ARAÚJO et al., 2013; KRÜGER; MOOREN, 2014), assim como regulam o metabolismo energético e a defesa antioxidante (ALLEN; TRESINI, 2000; COLLINS et al., 2012).

Quando praticado dentro dos limites fisiológicos, o exercício físico leva à reorganização da resposta de diversos sistemas, entre eles, o sistema imunológico e assim, atua modulando a resposta imune inata e/ou inflamatória através de várias funções (ORTEGA et al., 2010). Além disso, sabe-se que os moduladores bioquímicos liberados durante o exercício atuam em situações de desequilíbrio homeostático, estimulando as respostas imunes, alertando o organismo e ajudando a afastar o ataque de patógenos (FLESHNER; CAMPISI; JOHNSON, 2003; ORTEGA, 2003; ORTEGA et al., 2007). Consequentemente, os componentes da resposta imune, modificam-se de acordo com o estímulo recebido (COSTA ROSA; VAISBERG, 2002). Como exemplo disso, a atividade quimiostática em neutrófilos, é aumentada em resposta à sessões de exercício crônico e, isto é depende da intensidade do treinamento físico (NIEMAN; NEHLSEN-CANNARELLA, 1994). Além disso, o exercício promove alterações no metabolismo e na função de macrófagos e linfócitos de ratos portadores de tumor (BACURAU et al., 2007). Da mesma forma, foi encontrada uma supressão da infiltração de macrófagos M1 e/ou alteração fenotípica do macrófagos M1 (pró-inflamatório) para o macrófagos M2 (anti-inflamatórios) em resposta ao exercício aeróbico de 16 semanas (60 min/dia, 5 vezes/semana) (KAWANISHI et al., 2010, 2013).

De acordo com observações no modelo de PBMCs, os resultados encontrados demonstram que 8 semanas de exercício regular induz alterações mitocondriais em termos de

quantidade mitocondrial (biogênese mitocondrial) e a qualidade (equilíbrio entre biogênese e dinâmica), além de promover a melhora na defesa antioxidante. Portanto, esses achados poderiam ser uma ligação entre eventos mitocondriais em células do sistema imunológico e células musculares esqueléticas (BUSQUETS-CORTÉS et al., 2017). Outros estudos confirmam que a redução da função mitocondrial de PBMCs está associada a redução da força e qualidade muscular, além da função física global e, isto é devido ao declínio físico e bioenergético (TYRRELL et al., 2015). Por outro lado, existem evidências de que o exercício aeróbico aumenta não só a capacidade aeróbica máxima ($VO_{2máx}$) mas também a respiração mitocondrial das PBMCs em indivíduos infectados pelo vírus da imunodeficiência humana (HIV) (KOCHER et al., 2017a).

O exercício físico também influencia diretamente a produção de EROs, que podem variar de acordo com o tipo de exercício, volume, intensidade e a população utilizada (DE SOUSA et al., 2017). Nesse sentido, sabe-se que uma única, aguda e extenuante sessão de exercício físico gera elevada produção de EROs, causando danos ao organismo (FISHER-WELLMAN; BLOOMER, 2009), enquanto que sessões regulares de exercício físico resultam em adaptações corporais que levam à resistência ao dano oxidativo por modulação de vias antioxidantes (VIÑA et al., 2012). Durante o treinamento de resistência ou ainda, chamado *endurance*, pode-se aumentar as atividades de enzimas antioxidantes como, por exemplo, SOD e GPx no músculos e no plasma (AZIZBEIGI et al., 2014; BROOKS et al., 2008; LAMBERTUCCI et al., 2007; VIEIRA JUNIOR et al., 2013). Além disso, há evidências de que o exercício físico seria o único método capaz de reduzir o estresse oxidativo, quando comparada à outras intervenções, como restrição calórica, farmacoterapia ou suplementação antioxidante (VINCENT; INNES; VINCENT, 2007).

Importantes vias de sinalização foram propostas como mediadores das respostas adaptativas ao exercício físico (CSALA et al., 2015; MORRIS et al., 2008; SAMJOO et al., 2013). De fato, durante a pratica de exercícios físicos as EROs mitocondriais geradas são necessárias para a ativação de vias de sinalização associadas à adaptação muscular (YAVARI et al., 2015). As sessões de exercício provocaram aumentos na produção de EROs, que ativam o fator de transcrição nuclear eritróide 2 (Nrf2), o qual entra no núcleo e liga-se ao elemento responsivo antioxidante, levando ao aumento da expressão de uma série de genes antioxidantes (DONE; TRAUSTADÓTTIR, 2016). O exercício físico regular também é considerado um poderoso estímulo para promover melhorias às mitocôndrias (GRANATA; JAMNICK; BISHOP, 2018a), incluindo alterações na bioenergética e no conteúdo mitocondrial, assim como mudanças na função respiratória mitocondrial (DAUSSIN et al., 2008; MONTERO;

LUNDBY, 2017; TREWIN; BERRY; WOJTOVICH, 2018). O treinamento físico aumenta a biogênese mitocondrial (GRANATA; JAMNICK; BISHOP, 2018a); via regulação do co-ativador 1α do receptor ativado por proliferador de peroxissoma gama (PGC-1α) (STEINBACHER; ECKL, 2015). Estudos também relatam que alterações no conteúdo mitocondrial muscular estão relacionadas principalmente ao volume de treinamento (JACOBS; LUNDBY, 2013a; LUNDBY; JACOBS, 2016), enquanto que a capacidade respiratória mitocondrial depende da intensidade (BURGOMASTER et al., 2008; GILLEN et al., 2016; HARMER et al., 2008). Neste sentido, pode-se observar que o exercício físico tem influências diretas em uma ampla gama de adaptações mitocondriais, desde a morfologia até mesmo na dinâmica mitocondrial (COGLIATI et al., 2013; NEVES et al., 2008). Portanto, é evidente que o exercício físico desempenha um importante papel na melhora de disfunções metabólicas em indivíduos sedentários.

Neste contexto, vários protocolos de treinamento são desenhados para minimizar os efeitos deletérios da SM, incluindo inflamação crônica, estresse oxidativo e disfunções mitocondriais. Além disso, a utilização do treinamento físico enquanto estratégia de prevenção e tratamento tem sido largamente empregada. Diante deste quadro, apresentamos o método de treinamento funcional, que combina a sustentação da própria massa corporal e pesos livres para o treinamento de força (CAYRES et al., 2014). Este método, tem como foco a melhoria de movimentos fundamentais; utilizando exercícios semelhantes às atividades de vida diária para melhorar à aptidão física (WEISS et al., 2010).

Nos últimos anos, o treinamento funcional se tornou um dos métodos mais utilizados de treinamento tanto para melhorar a saúde quanto o desempenho esportivo. A prática deste treinamento leva à prevenção e / ou tratamento de lessões, melhora o equilíbrio, além de aumentar a potência muscular. Além disso, o treinamento funcional tem como príncipio preparar o organismo de maneira íntegra, segura e eficiente através do centro corporal, chamado *core*, que tem como significado “núcleo”, que abrange um grande número de grupos musculares desde a coluna lombar, região do abdômen até o quadril (MONTEIRO; EVANGELISTA, 2010). Vários dos objetivos deste método de exercício representam são voltados à utilização dos padrões fundamentais do movimento humano, como, por exemplo, empurrar, puxar, agachar, girar, lançar, dentre outros, envolvendo a integração de todo o corpo (MONTEIRO; CARNEIRO, 2010).

A vantagem deste modelo de treinamento comparado a outros métodos tradicionais é a integração global dos movimentos (GAMBETTA, 2007), baseado em uma prescrição coerente e segura capaz de melhorar todas as qualidades do sistema musculoesquelético, como força,

velocidade, equilíbrio, coordenação, flexibilidade, lateralidade e resistência cardiorespiratória e neuromuscular (CAMPOS; NETO, 2004). Além disso, tem-se como pressuposto que o treinamento funcional pode influenciar na melhora da postura; diminuir a incidência de lesões; melhorar a estabilidade articular, principalmente da coluna vertebral; aumentar a eficiência dos movimentos; melhorar o equilíbrio estático e dinâmico; melhorar a força, coordenação motora, resistência cardiovascular e periférica-muscular; e ainda, melhorar a lateralidade, flexibilidade e propriocepção (MONTEIRO; CARNEIRO, 2010).

Adicionalmente, estudos destacam que o objetivo deste treinamento é resgatar a capacidade funcional do indivíduo, através de um programa individualizado, utilizando exercícios que se relacionam com atividades específicas do indivíduo, os quais transferem seus ganhos de forma efetiva para o seu cotidiano (DELIA, 2013). Entretanto, a literatura existente sobre os efeitos deste modelo de treinamento em doenças crônicas, especialmente na SM, e ainda, em PBMCs permanecem desconhecidos.

Neste contexto, tendo em vista a necessidade de verificar os efeitos do modelo de treinamento funcional em mulheres com SM. Então, essas células podem ser uma boa estratégia para detectar as disfuncões metabólicas e, posteriormente, tratar doenças cardiometabólicas. Sabendo que a modulação via exercício pode influenciar na reprogramação metabólica das PBMCs, este estudo visa avaliar a influência do treinamento funcional sobre o metabolismo, mitocôndria e estresse oxidativo das PBMCs de mulheres com SM.

2 OBJETIVOS

2.1 OBJETIVO GERAL

O objetivo geral deste trabalho é investigar se o exercício físico modifica o metabolismo energético, a eficiência dos complexos mitocondriais e o status redox em PBMCs de mulheres com SM, e associá-los aos parâmetros de exercício físico.

2.2 OBJETIVOS ESPECÍFICOS

Avaliar em PBMCs de mulheres com SM:

- Atividade das enzimas relacionadas com o metabolismo energético como: lactato desidrogenase (LDH) e citrato sintase (CS);
- Capacidade respiratória dos complexos mitocondriais I, II, III e IV da cadeia transportadora de elétrons;
- Níveis de EROs como: oxidação da diclorofluoresceína (DCF) e produção de H_2O_2;
- Atividade da enzima CAT relacionada com o sistema antioxidante;

- Determinar nas participantes os parâmetros de exercício físico como: massa corporal e o $VO_{2máx}$;
- Verificar o efeito do modelo de PBMCs como ferramenta para avaliar as adaptações induzidas pelo treinamento funcional no perfil de células com SM.

3 MANUSCRITO

Effects of training on electron transfer capability and redox state in peripheral blood mononuclear cells from women with metabolic syndrome

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Effects of training on electron transfer capability and redox state in peripheral blood mononuclear cells from women with metabolic syndrome

3.1 ABSTRACT:

Sedentary lifestyle is highly related to a metabolic syndrome (MetS), which is defined as the combination of interrelated risk factors. Evidence demonstrated a close link between MetS, mitochondrial dysfunction and oxidative stress, which may contribute to increase the risk for type 2 diabetes and cardiovascular diseases development. Despite knowledge of the beneficial effects of exercise on remodelling in mitochondrial metabolism and redox states, the impact of functional training on peripheral blood mononuclear cells (PBMCs) from patients with MetS remains unclear. This study intends to determine how functional training influences the electron transfer capability and redox state of women's PBMCs with MetS. Untrained women with MetS over 45 years old were recruited to functional training. Exercise training was carried out three times per week for 12 weeks. The biochemical analyses were performed in PBMCs, which were obtained before training (baseline) and 72 hours after the end of the functional training protocol to avoid acute exercise effects. Training produced an increase in lactate dehydrogenase activity of PBMCs, while citrate synthase activity remained unaltered. In PBMCs was also observed an increase in reactive oxygen species (ROS) exercise-induced formation, as well as antioxidant system adaptation. The PBMCs depicted an increase in electron transfer capacity and dehydrogenases activity. Our data suggests that functional training induces ROS production/scavenging and changes in energy metabolism in PBMCs. In addition, we confirmed that functional training improves mitochondrial function and antioxidant system, consequently leading the organism to positive adaptations.

KEY WORDS: Exercise, metabolism, mitochondria, electron transfer, ROS, antioxidant

3.2 INTRODUCTION

Sedentary lifestyle is highly related to a metabolic syndrome (MetS), which is defined as the combination of interrelated risk factors including abdominal obesity, insulin resistance, dyslipidemia and high blood pressure (ALBERTI; ZIMMET; SHAW, 2006). Moreover, evidence demonstrated a close link between MetS, a state of chronic inflammation and oxidative stress, which is also implicated in development of cardiovascular diseases (WELLEN; HOTAMISLIGIL, 2005).

Considered this clusters of several risk factors, recent evidence showed that the MetS is associated with mitochondrial dysfunction caused by reactive oxygen species (ROS) overproduction (MABALIRAJAN; GHOSH, 2013) lead to oxidative phosphorylation and adenosine triphosphate reduction (SHARMA, 2015), and reduces mitochondrial content (CIVITARESE; RAVUSSIN, 2008), compromising in mitochondrial functions and morphology (KOLIAKI; RODEN, 2016). Moreover, research has been made in understanding mitochondrial structure, function and their physiology in MetS such as diabetes, obesity, hypertension and heart disease (BHATTI; BHATTI; REDDY, 2017).

Recent work has demonstrated increased mitochondrial ROS, oxidative stress, and altered mitochondrial morphology and dynamics in peripheral blood mononuclear cells (PBMCs) from patients with diabetes mellitus (KIZHAKEKUTTU et al., 2012; WIDLANSKY et al., 2010). PBMCs can undergo activation, proliferation, and differentiation pathways under different situations (BROERE et al., 2011; LUCKHEERAM et al., 2012). It is interesting to note that these processes are coordinated by ROS production, which occurs under metabolic reprogramming needs (MOTWANI; GILROY, 2015; PALMER et al., 2012). In this sense, it is biomarkers source utilized to detect and treat several diseases (GARCÍA-RAMÍREZ et al., 2008; HARTMAN et al., 2014; TYRRELL et al., 2015). However, previous data has supported the hypothesis that PBMCs are not only participants in inflammation mechanisms and immune

responses, but are also long-term biomarkers of whole-body responses to different conditions/stimuli, such as physical exercise (LEE et al., 2007; MARIGGIÒ et al., 2010; TURNER; BOSCH; ALDRED, 2011).

Traditionally physical exercise is considered a powerful tool for preventing and treating chronic diseases, such as cardiovascular disease, obesity, type-2 diabetes and MetS (PEDERSEN; SALTIN, 2015). Moreover, many studies have shown that regular exercise exerts beneficial effects on immune responses and anti-inflammatory systems (DE ARAÚJO et al., 2013; KRÜGER; MOOREN, 2014), and reduce oxidative stress markers (VINCENT; INNES; VINCENT, 2007). Briefly, ROS exert a dual role, damaging or cellular signaling, depending on the production rate, ROS produced during exercise act as signalling molecules to regulate several body functions, such as energy metabolism and antioxidant defence (ALLEN; TRESINI, 2000; COLLINS et al., 2012). These ROS can be generated at higher rates from different sources depending on the exercise intensity and type (POWERS; JACKSON, 2008). Notably, signalling pathways work collectively and interact with each other to process and transfer signals, which involves multiple organelles and cellular compartments (TRACHOOTHAM et al., 2008). One of them, the mitochondria, plays a role that goes beyond energy maintenance balance, it are involved in essential functions of the cell, for example, cell signalling and apoptosis regulation.

Considering these conditions, mitochondrial ROS are important cellular stress sensor, and inductors of cellular adaptation (VYAS; ZAGANJOR; HAIGIS, 2016), leading to important changes in mitochondrial morphology and dynamics (COGLIATI et al., 2013; NEVES et al., 2008). One of the most recognized inducers of mitochondria adaptation is physical exercise, which is a potent stressor to mitochondrial bioenergetics, redox homeostasis, and total content, structure, and function (MILLER; HAMILTON, 2012; TREWIN; BERRY; WOJTOVICH, 2018; YOULE; VAN DER BLIEK, 2012).

However, the effectiveness of training models, as such functional training, on mitochondrial dysfunction and ROS overproduction in PBMCs from patients with MetS remains unclear in literature. Our hypothesis is this that training method would induce adaptations on redox status and remodeling mitochondrial functionality markers that might be relevant to treatment of PBMCs patient's impaired by the MetS. In this work, we discuss the effectiveness to functional training protocol under mitochondrial metabolism and redox state modulation of PBMCs, as well as aspects associated with chronic diseases and exercise.

3.4 MATERIALS AND METHODS

Participants and experimental design

Through institutional website advertisements, 30 untrained middle-age women volunteered to participate in this study. Functional and anthropometric measurements (**Table 1**) and anamnesis (**Table 2**) were performed to characterize and classify the MetS, as previously described (NATIONAL CHOLESTEROL EDUCATION PROGRAM (NCEP) EXPERT PANEL ON DETECTION EVALUATION AND TREATMENT OF HIGH BLOOD CHOLESTEROL IN ADULTS (ADULT TREATMENT PANEL III), 2002). Participants were selected based on the following criteria: (1) presence of at least 3 clinical sings for MetS, (2) >45 y.o. women (middle-aged), (3) non-smokers, and (4) a clinical medical examination and authorization for physical exercise practices. The participants that changed their medication throughout the training protocol were excluded. Volunteers signed an informed written consent before enrolment in the study, which was approved by the Ethics Committee of Universidade Federal de Santa Maria (57249916.3.0000.5346). The ethical standards set forth in the Declaration of Helsinki for clinical settings have been respected throughout the study.

From the initial sample, (n=7) participants do not meet the inclusion criteria, (n=9) did not complete the training protocol and (n=4) no obtained 85% of presence in training. Only

(n=10) participants performed all functional training protocols during the 12 weeks and the blood collections. Immune cells were obtained from subject's blood with MetS, it was performed at before training (baseline) and 72 hours after the end of the training protocol to avoid acute exercise effects (after training) (**Figure 1**).

Blood pressure, anthropometry and maximal oxygen uptake ($VO_{2máx}$)

Participants were weighed with a digital scale (Plenna, São Paulo, Brazil) and heighted with a stadiometer (Cardiomed, Curitiba, Brazil). Waist circumference was measured at the midpoint between the lowest rib and iliac crest. Blood pressure was measured with a digital sphygmomanometer (Omron, Kyoto, Japan), after the individuals remain resting state for 5 min. The maximal exertion test was assessed on treadmill (Inbramed®, Porto Alegre, Brazil) using a gas analyzer VO2000 according to Bruce's modified protocol (BRUCE; KUSUMI; HOSMER, 1973). Additionally, the heart rate was monitored before exercise, during each workload, and for 5 minutes of recovery using frequency meter Polar®-plus Accurex. The perceived exertion was measured through Borg scale (BORG, 1982).

Training protocol

Participants performed a functional training program for 12 weeks for 1 hour/day and 3 days/week. The 12-week of training were adapted of others training protocols that offers a time-efficient to achieve outcomes beneficial in women with MetS (FARINHA et al., 2015; STENSVOLD; SLØRDAHL; WISLØFF, 2012). Training intensity was 50–70% reserve heart rate (HR_{res}) obtained as the difference between the resting heart rate (HR_{rest}) and maximum heart rate ($HR_{máx}$), as recommended (BRANDÃO; BRANDÃO; NOGUEIRA, ARMANDO DA ROCHA; SUPLICY, HENRIQUE; GUIMARÃES, JORGE ILHA; OLIVEIRA, 2005). Additionally, the heart rate was monitored before exercise (HR_{rest}) and during workload ($HR_{máx}$) to control the training intensity. The training protocol was according to that previously

described (DELIA, 2013) with brief modifications. Each training session consisted of (1) general heating (core and neuromuscular activation, dynamic heating), (2) circuit (knee and hip dominance, pull, push, shifting gears, stabilization, flexion and extension of the core, fast force, and proprioception), (3) recovery, and (4) stretching. The circuits contained 5 different exercises, each one executed for 30 seconds, 3 repetitions, and 5 minutes rest intervals. To be included of the study, participants had to complete 85% of the sessions. All sessions were supervised by a physical education professional.

Blood sampling and PBMC separation

The volunteers were recommended to avoid intense exercise during 48 h before the blood sampling. The baseline samples before training and after training were collected during the morning after overnight fasting to avoid confounders. After training, the samples were obtained after 72 hours last day of training protocol. Blood samples were collected from the antecubital vein into 16 mL tubes with ethylenediamine tetraacetic acid (EDTA). PBMCs were separated from whole blood by density gradient centrifugation with a Histopaque®-1077 solution (Sigma-Aldrich, St. Louis, USA), as previously described (JIMÉNEZ-JIMÉNEZ et al., 2008) with brief modifications. For each sample, four 15-mL centrifuge tubes were used to layer 16 mL of blood onto 8 mL of Histopaque®-1077. The suspension was centrifuged for 30 min at 275 × g at room temperature. The layer of PBMCs was removed, washed in phosphate buffered saline (PBS) (136 mM NaCl, 2.7 mM KCl, 7.8 mM Na_2HPO_4, 1.7 mM KH_2PO_4, pH 7. 4) and centrifuged for 10 min at 450 × g. Then, supernatants were discarded and the PBMCs pellets were dried out with lysing solution of erythrocyte (150 mM NH_4Cl, 10 mM $NaHCO_3$, 1 mM EDTA) and centrifuged for 3 min at 300 × g. The pellets were frozen at −80 °C for further analysis.

Preparing PBMCs homogenate

The pellets (layer of PBMCs) were unfrozen, added (500 µL) in PBS (pH 7.4) and sonicated for 30 seconds into the ice. Then, PBMCs homogenate were utilized for biochemical analyses.

PBMC homogenate assays

Methyl-tetrazolium (MTT) reduction levels

The MTT assay was carried out as previously described (MOSMAN, 1983). PBMCs homogenate (27 µL) were incubated in MTT (0.5 mg/mL) for 60 min at 37 °C. MTT reduction reaction was stopped by the addition of dimethylsulfoxide (DMSO). The formed formazan (purple) levels were determined spectrophotometrically, reported as the difference in absorbance between 570 and 630 nm and corrected by the protein content.

2′, 7′-dichlorofluorescein diacetate (DCFH-DA) oxidation

ROS was estimated in PBMCs homogenate for oxidation of the DCFH-DA, as previously described (MYHRE et al., 2003), with modifications. After PBMC suspension, the homogenate (5 µL) were incubated in TRIS buffer and in the presence of DCFH-DA no fluorescent (1 mM) for 60 min. The DCFH-DA is enzymatically hydrolyzed by intracellular esterase to form no fluorescent DCFH, which is then rapidly oxidized to form highly fluorescent 2′, 7′-dichlorofluorescein (DCF) in the presence of ROS. DCF fluorescence intensity is proportional to the amount of ROS formed. Fluorescence was measured using excitation and emission wavelengths of 488 and 525 nm, respectively. A calibration curve was established with standard DCF (0.1 mM), and ROS levels were corrected by the protein content.

Hydrogen peroxide (H_2O_2) production

H_2O_2 release was measured in PBMCs homogenate (5 µL) with Amplex Red (Molecular

Probes) as a trapper of H2O2 in the presence of horseradish peroxidase (HRP). The resorufin generation, a highly fluorescent compound was measured at excitation and emission wavelengths of 560 nm and 590 nm described (MAYNARD et al., 2013) with slight modifications. The released H_2O_2 was quantified and expressed as area under curve, H_2O_2 production were corrected by the protein content.

Catalase (CAT) activity

CAT activity was determined following the decrease in H_2O_2 concentration by the method of Aebi with short modifications (AEBI, 1984). The spectrophotometric determination was initiated by the addition of H_2O_2 (0.3 M) in a cuvette containing potassium phosphate buffer (TFK) (50 mM and pH 7.0) and PBMCs homogenate (20 µL). The change in absorbance at 240 nm was measured for 4 min, unit was defined in µmol and corrected by the protein content.

Citrate synthase (CS) activity

CS activity was determined spectrophotometrically in PBMCs homogenate according to the method previously described (SRERE, 1969). The enzyme activity was measured for amount product resulting from acetyl-CoA and oxaloacetate, and determined at 412 nm and 37 °C, CS activity were corrected by the protein content.

Lactate dehydrogenase (LDH) activity

The activity of the enzyme LDH was measured in homogenate of PBMCs using commercial assay kits (Labtest®, Lagoa Santa, Brazil), through kinetic method according with manufacturer's instructions and corrected by the protein content.

Mitochondrial complexes

Mitochondrial electron transfer capacity at the mitochondrial complexes was measured at 37 ° C in the Oxygraph-2k High-Resolution Respirometer (Oroboros Instruments, Innsbruck, Austria) in 2-ml chambers. A high-resolution oxygraph is a device uses polarographic oxygen sensors to measure oxygen concentration with very high resolution and sensitivity. Oxygen consumption rates are calculated and expressed as picomol/mg. This device has been applied to measure respiration in a wide range of cell types and may also provide information on mitochondrial quality and integrity, and mitochondrial respiratory electron transport capacity. In this protocol was utilized respiration medium MIR05 (0.5 mM EGTA, 3 mM $MgCl_2$, 60 mM K-MES, 20 mM taurine, 10 mM KH_2PO_4, 20 mM HEPES, 110 mM sucrose, BSA fat free 1 g/L, pH 7.1). After device stabilization, PBMCs homogenate (50 µL) were added and experimental protocol to measure the complex I (CI), complex II (CII) and complex IV (CIV), respectively, was proceeded. A titration protocol was used to mimetic favorable conditions and environment for acting of mitochondrial complexes from following sequence of reagents: NADH 1.5 mM, succinate 10 mM and rotenone (inhibitor of the CI) 0.5 µM, malonic acid (inhibitor of the CII) 5 mM, antimycin A (inhibitor of the complex III (CIII)) 2.5 µM, cytochrome c 1 mM, ascorbate 0.8 M, N,N,N′,N′-tetramethyl-p-phenylenediamine (TMPD) 0.2 M and potassium cyanide (KCN) (inhibitor of the CIV) 1 mM. The CIII was performed separately with following sequence of reagents: succinate 10 mM, rotenone (inhibitor of the CI) 0.5 µM, KCN (inhibitor of the CIV) 1 mM, coenzyme Q 12.5 mM, cytochrome c 1 mM and antimycin A (inhibitor of the CIII) 2.5 µM. The method previously described Gnaiger with modifications (GNAIGER, 2014). Mitochondrial electron transfer capacity (ETC) was estimated from equation: [ETC= (S_P-M_P)] by CI, CII, CIII and CIV, at where stable point (S_P) after titrations with specific inhibitors and maximum point (M_P) after complexes maximum stimulation. Data were express at O_2 flux and corrected by the CS activity.

Protein determination

The protein content was determined as described (BRADFORD, 1976) using bovine serum albumin (BSA) as standard.

Statistical analysis

The analyses were performed using GraphPad (version 6.0 for Macintosh OSX, GraphPad Software, San Diego, CA). The Shapiro-Wilk test was used to confirm the normality of quantitative variables. A paired Student's *t* or the Wilcoxon test was performed, depending on normality of the data. Significance was set at $p < 0.05$ and data were expressed as mean ± standard deviation of the mean (SD).

3.5 RESULTS

Maximal aerobic capacity and anthropometric measurements

Participants had no differences in body weight (81.3±12.22 kg) (**Figure 2A**) and body mass index (31.50±4.02 kg/cm²) (**Figure 2B**) after intervention (79.33±11.21 and 31.23±4.08 kg/cm², respectively). However, the training protocol resulted in a significant increase in $VO_{2máx}$ (21.08±4.72 mL kg^{-1} min^{-1}) (**Figure 2C**) after training (24.5±4.62 mL kg^{-1} min^{-1}).

Glycolytic and oxidative metabolism and dehydrogenases activity

As demonstrate in **Figure 3**, the PBMCs of the subjects after training had higher LDH activity (E.s 1.47, p=0.002) (**Figure 3A**) when compared to before training, while the activity of citrate synthase (E.s –0.15, p=0.49) (**Figure 3B**) did not show significant changes. The MTT reduction percentage (E.s 1.87, p=0.02) in PBMCs increased after training when compared to before training (**Figure 3C**).

Relative capacity of the mitochondrial complexes to transfer electrons

Electron transfer capability from CI (E.s 2.01, p=0.002) (**Figure 4A**), CII (E.s 1.64, p= 0.046) (**Figure 4B**), and CIII (E.s 0.62, p= 0.046) (**Figure 4C**) increased after training. However, no changes in CIV (E.s –0.05, p=0.72) were observed (**Figure 4D**).

Oxidative stress biochemical markers and antioxidant system

Figure 5 demonstrates that training increased the DCF levels (E.s 1.95, p=0.002) (**A**) in PBMCs after 12 weeks. Despite no changes in H_2O_2 levels (E.s 0.37, p=0.35) (**B**), the training protocol also demonstrated increased CAT activity (E.s 1.22, p=0.005) (**C**) when compared to before training.

3.6 DISCUSSION

Physical exercise has been recognized as a key factor in the improvement and primary prevention against chronic conditions that might lead to accelerated aging/death pathways (BOOTH; ROBERTS; LAYE, 2012; PEDERSEN; SALTIN, 2015). Here, we established for the first time a physical training model that positively modulated cell metabolism, mitochondria functional capability and antioxidant system in middle-aged women's PBMCs, in addition to improving participant's aerobic capacity after the 12-week intervention. Regarding PBMCs, we provided data that they could be susceptible to adaptation responsiveness to exercise training methods linked to skeletal muscle adaptations (ROBINSON et al., 2017).

When inflammation signs are detected by immune system cells, the metabolic demand is accelerated in order to become more efficient (GRIFFITHS; GAO; PARARASA, 2017), providing faster energy to the cell (GALVÁN-PEÑA; O'NEILL, 2014). This turnover triggers macrophage activation to pro-inflammatory and glycolytic metabolic phenotype (M1) (KRAMER et al., 2014). This fact was evident here in the PBMCs, which were demonstrated

to be efficient when responding to metabolic stress during pathological situations or, as depicted, exercise-induced stress. Indeed, we observed a glycolic metabolism stimulation from the highest LDH activity after training women's cells when compared to the training before. This can indicate an overload of this metabolic pathway compared to the aerobic citric acid cycle because, despite the higher amount of energy produced by aerobic pathways, the anaerobic glycolytic pathway is faster for cell demands, which is mainly related to the macrophage switch phenotype (M2 to M1) (KRAMER et al., 2014). Moreover, especially during exercise, recruitment of fast-glycolytic pathways cause an increase in lactate flux, which is released into systemic circulation and taken up by distal tissues and organs, demonstrating lactate as an important redox signalling molecule, as described previously (BROOKS, 2009; GARCIA-ALVAREZ; MARIK; BELLOMO, 2014). Then, lactate is converted to pyruvate and totally oxidized into the mitochondrial matrix (JACOBS et al., 2013). These intra- and extra-cellular effects of lactate production and removal have been linked to the 'lactate shuttle' hypothesis (BROOKS, 1985). Moreover, it was recently demonstrated that lactate is the main metabolite produced in high-energy demands states in white/glycolytic and red/oxidative muscle fibres, heart, brain, liver, and kidneys (BROOKS, 2018).

Coincidentally, PBMC's CS activity remained unaltered after 12 weeks of training. In this regard, recent studies have suggested that high exercise levels are associated with an increase in mitochondrial function (measured by mitochondrial respiration capacity, complexes I–IV) (BISHOP; GRANATA; EYNON, 2014). In addition, the CS activity is not correlated with individual mitochondrial respiration capacity, but with mitochondrial total content (LARSEN et al., 2012). Some studies indicate that muscle mitochondrial content is mainly related to training volume, while mitochondrial capacity depends on training intensity (JACOBS; LUNDBY, 2013b; LUNDBY; JACOBS, 2016; WALSH; TONKONOGI; SAHLIN, 2001). Thus, the CS activity observed in the current study demonstrates that a moderate

intensity without change at training volume does not induce increases in mitochondrial content but contributes to mitochondrial respiration capacity improvement.

Furthermore, our results illustrate that 12 weeks a moderate intensity no change body composition is might indicated a relation with CS activity. On the other hand, an increase in $VO_{2máx}$ in response to training intensity may be related to mitochondrial capability improvement in PBMCs from patients with MetS. It was demonstrated previously that aerobic exercise increases at the same time the PBMC mitochondrial respiration and aerobic capacity ($VO_{2máx}$) in HIV-infected individuals (KOCHER et al., 2017b). Further considerations in regard to higher $VO_{2máx}$, a change that may not depend an increase in mitochondrial content (CS activity), but it is likely maximize improvements in mitochondrial respiration at the exercise intensity (GRANATA; JAMNICK; BISHOP, 2018b).

In concurrency, we revealed that our protocol increased MTT reduction and this could be associated with an increase in electron transfer on the mitochondrial respiratory chain complexes. In addition, MTT reduction is an indicator of mitochondrial functionality and depends on the dehydrogenases activities; therefore, functional impairment might be related to those enzyme activities since most dehydrogenases are mitochondrial enzymes (BERRIDGE; TAN, 1993; YAKES; VAN HOUTEN, 1997). Our results showed that functional exercise increases PBMC's mitochondrial function by both dehydrogenases activities and mitochondrial respiration capacity methods (WIBOM et al., 1992), specifically through CI, CII, and CIII. However, the training intensity (50–70% HR_{res}) used did not produce enough stimulus to reach the complex IV threshold. In addition, it was demonstrated that at high intensity (80% HR_{res}), PBMC's mitochondrial respiratory capacity was augmented (KOCHER et al., 2017a), resulting in an increased substrate amount and electron transport taxes for the high energy demand. In this sense, recent studies reported that training intensity is important for increasing mitochondrial respiration by improving mitochondrial function in human skeletal muscle

(GRANATA et al., 2016a; ROBINSON et al., 2017) when training volume leads to greater mitochondrial content (GRANATA et al., 2016b).

In contrast, we believe that an increase in ROS could be linked to mitochondrial complexes, as consequence of the reverse electron transfer. Interestingly, studies suggests that the reverse electron transfer is associated with the generation of high levels of ROS (LIU; FISKUM; SCHUBERT, 2002; STOWE; CAMARA, 2009). One study suggests that reverse electron transfer - ROS is suited to detecting metabolic changes that require adaptations, it is sensitive to changes in the redox state (SCIALÒ; FERNÁNDEZ-AYALA; SANZ, 2017).

In addition, we demonstrated that functional training also modulates the PBMCs redox status. Physiologically, CI and CIII are the major source of ROS production (BRAND, 2010), while succinate dehydrogenase has been recognized as an indirect modulator of superoxide production by CI and CIII (MØLLER; SWEETLOVE, 2010). However, it is known that chronic exercise training attenuates oxidative stress processes (HENRIKSEN; DIAMOND-STANIC; MARCHIONNE, 2011) and concomitantly increases the amount and activity of antioxidant enzymes (BROOKS et al., 2008; FERRER et al., 2009), which was corroborated by our data. Despite the constant H_2O_2 production, increased DCFH-DA oxidation levels were detected. Possibly, the elevation in CAT activity led to ROS (especially H_2O_2) neutralization, illustrating the training modulation on the antioxidant defence system. Furthermore, moderate ROS production is associated with molecular signalling, leading to adaptive responses, while higher ROS levels are considered harmful and associated with senescence and apoptosis processes (BUSQUETS-CORTÉS et al., 2016).

3.7 CONCLUSIONS

In conclusion, we provided novel evidence that a 12-week functional exercise-training program modifies PBMCs redox state and mitochondrial electron transfer capability in response to metabolism stimulation and energy demand, and this may be related to aerobic capacity improvement in middle-aged women with MetS. Therefore, this may be essential for demonstrating good cell functionality and the adaptive responses of exercise training models, and consequently to treatment of cardiometabolic diseases.

3.8 CONFLICT OF INTEREST

The authors declare no conflicts of interests.

3.9 FINANCIAL SUPPORT

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3.11 TABLES

Table 1- Functional and anthropometric characteristics of the middle-age women before training

Parameter	n=10
Age (years)	56.9±7.30
Body Weight (Kg)	81.3±12.22
Height (cm)	160.05±0.06
Waist Circumference (cm)	99.2±10.08
Resting Heart Rate (bpm)	68.22±7.80
Systolic Blood Pressure (mmHg)	134.77±55.30
Diastolic Blood Pressure (mmHg)	89.88±32.86

Values are given as means ± SD; n=10

Table 2- Clinical sings of the study participants. Note that the subject numbers listed here are used from anamnesis of the middle-age women before training

Features	n=10
Menopause	5
Obesity	8
Hypertension[1]	3
Diabetes[2]	2
High Cholesterol[3]	5
High Triglycerides[4]	2
Medicines	8

Women's number with MetS features and the use of their medications: [1]Hydrochlorothiazide, losartan potassium and atenolol; [2]Metformin; [3]Simvastatin; [4]Atorvastatin.

3.12 FIGURES

Figure 1- Flow diagram of participants and experimental design of the study.

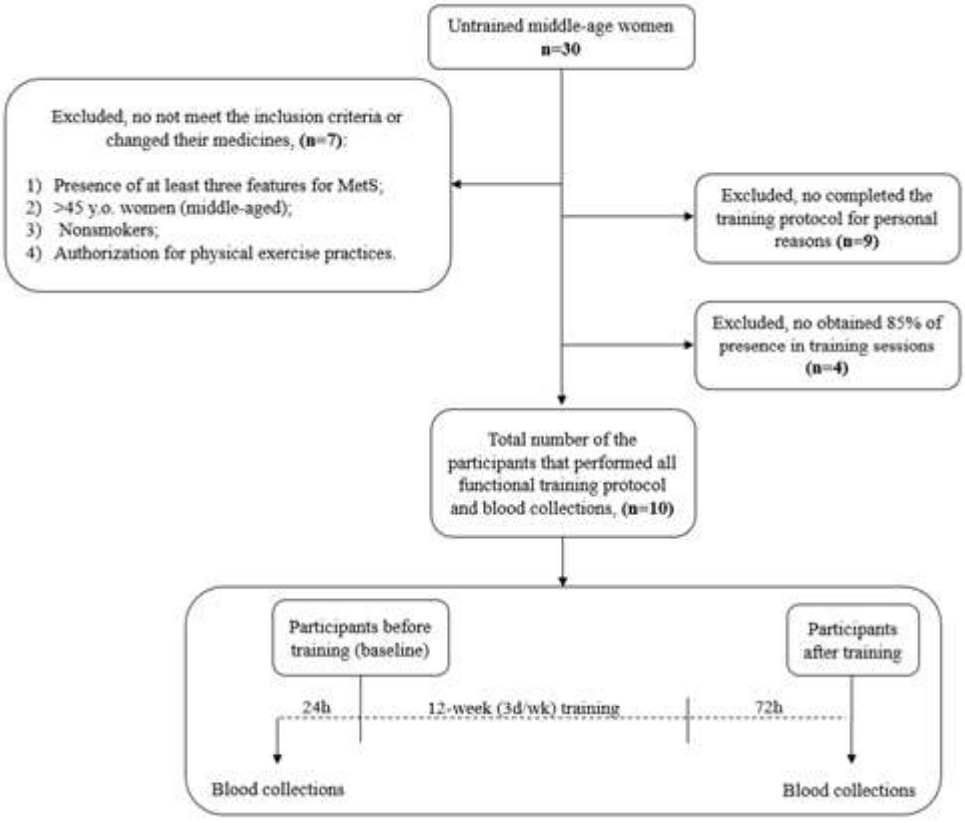


Figure 2- Effect of training on maximal aerobic capacity ($VO_{2máx}$) and anthropometric measurements for women with MetS.

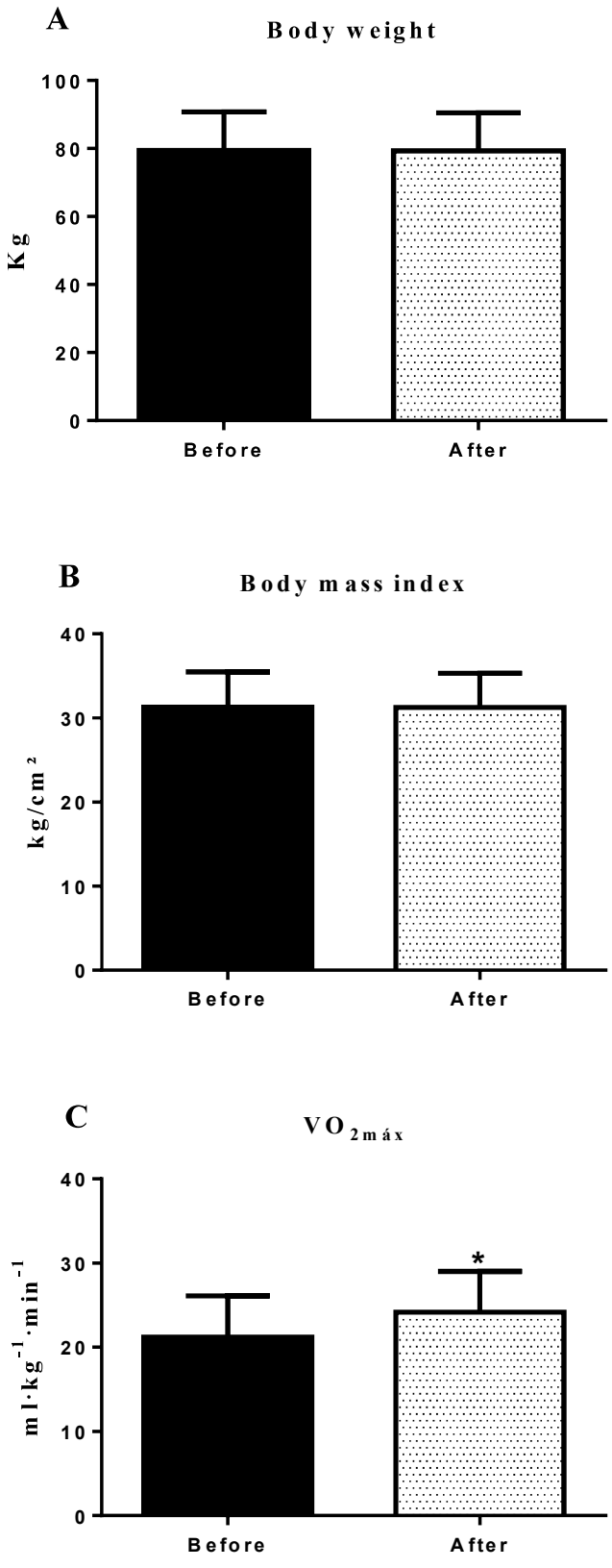


Figure 3 - Effect of training in LDH activity, CS activity and dehydrogenases activity for women's PBMCs.

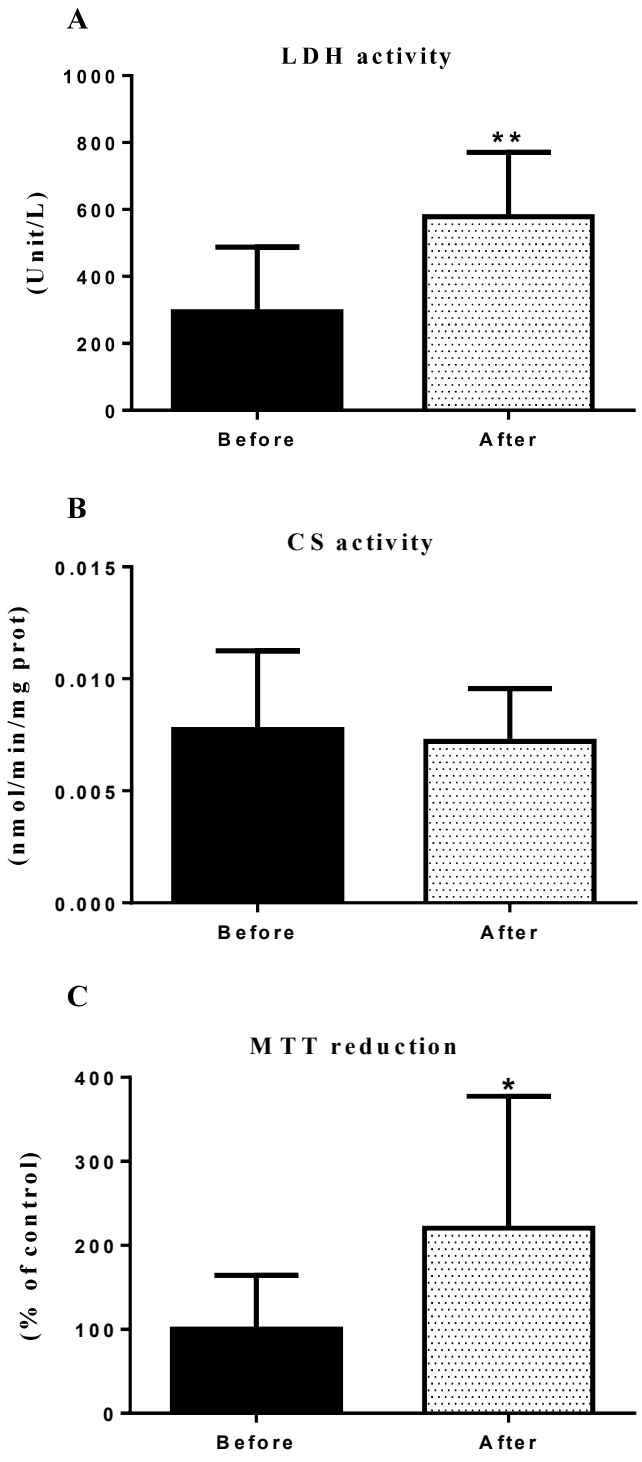


Figure 4 - Effect of training on mitochondrial electron transfer capability in women's PBMCs.

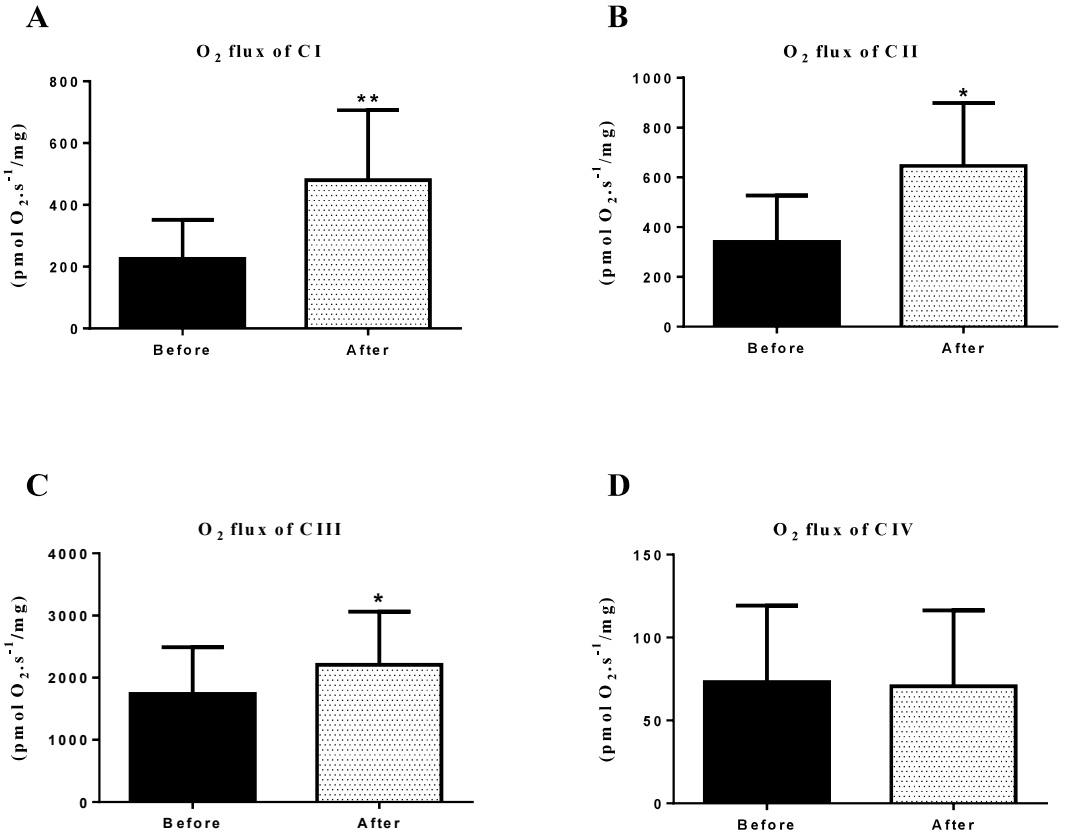
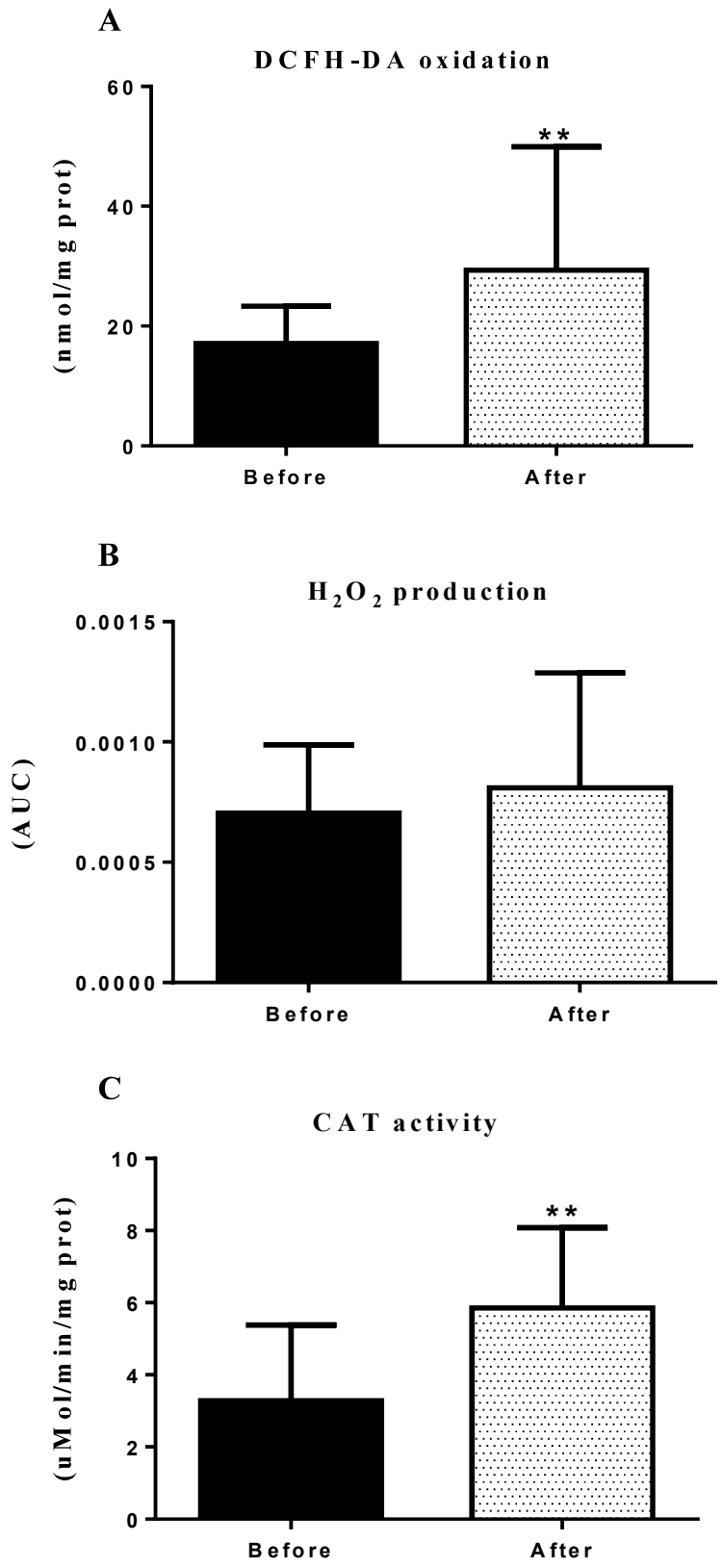


Figure 5 - Effect of training on oxidative stress biochemical markers and antioxidant system in women's PBMCs.



3.13 FIGURE LEGENDS

Figure 1. Flow diagram of participants and experimental design of the study.

Figure 2. Effect of training on maximal aerobic capacity and anthropometric measurements for women with MetS. Body weight (**A**), body mass index (**B**) and $VO_{2máx}$ (**C**). Data expressed as mean ± SD for n=10 in each group. *p < 0.05 after vs. before training.

Figure 3. Effect of training in LDH activity, CS activity and dehydrogenases activity for women's PBMCs. LDH activity (**A**), CS activity (**B**) and MTT reduction levels (**C**). Data expressed as mean ± SD for n=10 in each group. *p < 0.05 and **p < 0.01 after vs. before training.

Figure 4. Effect of training on mitochondrial electron transfer capability in women's PBMCs. The mitochondrial capability was measured after the addition of the substrates: NADH, succinate and rotenone (inhibitor of the CI) (**A**), malonic acid (inhibitor of the CII) (**B**), antimycin A (inhibitor of the CIII), cytochrome c, ascorbate, TMPD and KCN (inhibitor of the CIV) (**D**). The CIII (**C**) was performed separately with following sequence of reagents: succinate, rotenone (inhibitor of the CI), KCN (inhibitor of the CIV), coenzyme Q, cytochrome c and antimycin A (inhibitor of the CIII). Data expressed as mean ± SD for n=7–8 in each group. *p < 0.05 and **p < 0.01 after vs. before training.

Figure 5. Effect of training on oxidative stress biochemical markers and antioxidant system in women's PBMCs. DCFH-DA oxidation levels (**A**), H_2O_2 production (**B**) and CAT activity (**C**). Data expressed as mean ± SD for n=9–10 in each group. **p < 0.01 after vs. before training.

4 CONCLUSÕES ESPECÍFICAS

- Observamos um aumento na estimulação do metabolismo, a partir do aumento da atividade da LDH enquanto a CS das PBMCs permaneceu inalterada após 12 semanas de treinamento funcional;
- O treinamento funcional aumenta a função mitocondrial das PBMCs tanto pela redução do MTT quanto pelo método da capacidade respiratória mitocondrial, especificamente, através dos complexos I, II e III;
- O treinamento também aumentou os níveis de DCF em PBMCs após 12 semanas de treinamento, entretanto, a elevação da atividade da CAT levou à neutralização de EROs (especialmente H_2O_2), ilustrando a modulação do sistema de defesa antioxidante;
- Em relação aos parâmetros de treinamento, o treinamento funcional promoveu a melhora da capacidade aeróbica ($VO_{2máx)}$ de mulheres com SM, entretanto, não houve alterações no peso corporal;
- Nossos resultados demonstram que as PBMCs são altamente responsivas a um programa de treinamento funcional de 12 semanas, portanto, a sua responsividade as adaptações geradas pelo exercício sugerem o uso das PBMCs como uma boa fonte de biomarcadores de exercício físico.

5 CONCLUSÃO GERAL

De acordo com os resultados apresentados nesta dissertação, pode-se concluir que as 12 semanas de treinamento funcional de intensidade moderada aumenta o sistema de defesa antioxidante e a eficiência dos componentes da cadeia respitatória mitocondrial em resposta ao estímulo do metabolismo glicolítico sobre as PBMCs, além de melhorar a capacidade aeróbica de mulheres com SM, mesmo na ausência de perda de peso. Considerando a modulação do metabolismo energético das PBMCs, concluímos que exercício físico induz adaptações nestas células, e, desta forma, indicamos que as alterações detectadas nos parâmetros estudados nas PBMCs podem ser consideradas uma promissora e efetiva fonte de biomarcador de treinamento.

6 PERSPECTIVAS

A partir dos resultados obtidos, mais estudos são necessários para identificar precisamente os perfis metabólico e disfunções mitocondriais em PBMCs associadas às doenças, e assim, comprovar a eficácia e efetividade destas células na saúde e doença. Além disso, em um próximo estudo tentaremos examinar o impacto da alternância da intensidade e/ou do volume em um programa de treinamento físico em PBMCS para avaliar a eficiência do treinamento físico no desempenho e performance do indivíduo.

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