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Efeito da suplementação de curcumina associada ao exercício aeróbio sobre a glicemia de jejum, a adiposidade abdominal e o estresse oxidativo em ratos obesos

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RESUMO

Introdução: A obesidade é um fator de risco para doenças crônicas não transmissíveis (DCNT) e está relacionada ao estresse oxidativo (EO), à massa corporal e ao metabolismo da glicose. O exercício físico é um potente tratamento não farmacológico para a obesidade e a prática regular estimula as defesas antioxidantes endógenas, controlando o balanço redox. Já curcumina é um composto de características antioxidantes que, também, pode auxiliar na redução do EO. **Objetivo:** Avaliar se a suplementação de curcumina associada ao exercício aeróbio de moderada intensidade resulta em melhora sobre os parâmetros metabólicos e sobre o EO em ratos obesos. **Metodologia:** 64 ratos *Wistar* machos divididos em 8 grupos. Grupos CAF receberam 12 semanas de dieta para a indução da obesidade. Após, os grupos Cur e de AE receberam suplementação de curcumina (200mg/kg/dia) e realizaram protocolo de corrida (30min/dia 5x/semana) por 8 semanas. Os animais foram divididos em grupos: dieta padrão+curcumina (STA+Cur, n=8), dieta padrão+curcumina+exercício aeróbio (STA+Cur+AE, n=8), dieta padrão+exercício aeróbio (STA+AE, n=8), dieta padrão (STA, n=8), dieta de cafeteria+curcumina, (CAF+Cur, n=8), dieta de cafeteria+curcumina+exercício aeróbio (CAF+Cur+AE, n=8), dieta de cafeteria+exercício aeróbio (CAF+AE, n=8) e dieta de cafeteria (CAF, n=8). Todos os animais realizaram teste de tolerância ao exercício (TTE) antes e após o protocolo de exercício aeróbio. Massa corporal foi aferida semanalmente e a glicemia de jejum a cada quinze dias. A avaliação da atividade das enzimas superoxido dismutase (SOD) e catalase (CAT) e a concentração de malondialdeído (MDA) dos órgãos foi realizada ao final do estudo. **Resultados:** Após a indução da obesidade, os grupos CAF tiveram maior massa corporal do que os grupos STA ($p<0,001$) e ao final do experimento os grupos CAF+Cur e CAF mantiveram maior massa corporal do que os grupos STA ($p<0,001$) e os grupos CAF+Cur+AE e CAF+AE apresentaram massa maior do que os grupos STA+Cur+AE ($p=0,0201$ e $p=0$, 0343, respectivamente), e STA ($p=0,0066$ e $p=0,0116$, respectivamente). Posterior aos protocolos de suplementação e exercício, a glicemia do grupo CAF foi mais alta do que dos grupos STA+Cur ($p=0,0203$), STA+Cur+AE ($p=0,0025$), e STA+AE ($p=0,0295$). Todos os grupos CAF apresentaram maior porcentagem de adiposidade abdominal ($p<0,001$). Os grupos que realizaram o exercício aeróbio demonstram maior tolerância no TTE (distância, tempo e velocidade) após 8 semanas. O grupo CAF+Cur apresentou maior atividade da SOD no gastrocnemio quando comparado aos grupos STA+Cur ($p=0,0329$), STA+Cur+AE ($p=0,0019$), STA+AE ($p=0,0018$), and STA ($p=0,0006$) e o grupo CAF+AE quando comparado ao STA ($p=0,0337$). **Conclusão:** A combinação de suplementação de curcumina com o exercício físico moderado não controlou o ganho de massa corporal e a adiposidade abdominal nos animais que receberam dieta de cafeteria, porém pode ter auxiliado no controle da glicemia. O exercício foi capaz de aumentar a tolerância ao exercício. Mudanças no padrão alimentar são, então, essenciais para o tratamento da obesidade.

Palavras-chave: Obesidade; Exercício aeróbio; Curcumina; Estresse Oxidativo; Massa corporal;

ABSTRACT

Introduction: Obesity is a risk factor for chronic non-communicable diseases and is related with oxidative stress, body mass and glucose metabolism. Aerobic exercise is a potent non-pharmacological treatment for obesity and regular practice stimulates endogenous antioxidant defenses that control the redox balance. Curcumin is an antioxidant compound and can reduce oxidative stress. **Objective:** To evaluate the effects of curcumin supplementation associated with continuous aerobic exercise training on metabolic variables and oxidative stress in obese rats. **Methodology:** 64 male Wistar rats divided in 8 groups: standard diet and supplemented (STA+Cur, n=8); standard diet, supplemented, and aerobic training (STA+ Cur+AE, n=8); standard diet and aerobic training (STA+AE, n=8); standard diet (STA, n=8); cafeteria diet and supplemented (CAF+Cur, n=8); cafeteria diet, supplemented, and aerobic training (CAF+Cur+AE, n=8); cafeteria diet and aerobic training (CAF+AE, n=8); cafeteria diet (CAF, n=8). The CAF groups were obesity induction by 12 weeks. After, the supplemented and exercise groups (Cur) received curcumin supplementation (200mg/kg/day) and an initiated aerobic training protocol (AE) (30 min/day, 5days/week) for 8 weeks. All the animals underwent an exercise tolerance test (ETT) before and after the aerobic training protocol. Body mass and length were measured weekly and blood glucose every fifteen days. Oxidative stress analyses of SOD and CAT activity and MDA concentration were analyzed at the end of the study in heart, liver, gastrocnemius and abdominal fat. **Results:** After obesity induction, CAF groups showed higher body mass compared to all groups that received a standard diet ($p<0.001$). At the end of study CAF+Cur e CAF groups higher body mass compared to all groups standard diet ($p<0.001$) and the groups CAF+Cur+AE and CAF+AE showed higher body mass compared to STA+Cur+AE ($p=0.0201$ and $p=0.0343$, respectively), and STA ($p=0.0066$ and $p=0.0116$, respectively) groups. CAF group demonstrated higher blood glucose than STA+Cur ($p=0.0203$), STA+Cur+AE ($p=0.0025$), and STA+AE ($p=0.0295$) groups after the protocols. Also, all CAF groups demonstrated a higher percentage of body fat compared to all standard diet groups ($p<0.001$). The groups that performed aerobic exercise demonstrated higher distance ($p<0.001$), duration ($p<0.001$), and speed ($p<0.001$) compared to untrained groups. In the gastrocnemius, the CAF+Cur group demonstrated higher SOD activity compared to STA+Cur ($p=0.0329$), STA+Cur+AE ($p=0.0019$), STA+AE ($p=0.0018$), and STA ($p=0.0006$) groups, while the CAF+AE groups showed higher SOD activity than STA group ($p=0.0337$). **Conclusion:** The combination of curcumin supplementation and aerobic moderate training did not control body mass and abdominal fat gain in animals that received cafeteria diet, however may have helped control blood glucose. The exercise was capable to increase TTE performance when compared to sedentary condition. So, changes in dietary patterns is essential for the treatment of obesity.

Keywords: Obesity; Aerobic exercise; Curcumin; Oxidative stress; body mass;

LISTA DE FIGURAS

LISTA DE ABREVIATURAS

AGL	Ácidos graxos livres
ACSM	*American College of Sports Medicine*
CAT	Catalase
COX	Ciclooxigenase
DCNT	Doenças crônicas não transmissíveis
DNA	Ácido Desoxirribonucleico
EO	Estresse oxidativo
ERO	Espécie reativa de oxigênio
ERON	Espécies reativas de oxigênio e de nitrogênio
GPx	Glutationa peroxidase
GSH	Glutationa reduzida
GSSG	Glutationa oxidada
H_2O	Água
H_2O_2	Peróxido de hidrogênio
HAS	Hipertensão arterial sistêmica
HDL	Lipoproteína de alta densidade
IL-1	Interleucina-1
IL-6	Interleucina-6
IL-8	Interleucina-8
IL-10	Interleucina-10
IMC	Índice de massa corporal
LDL	Lipoproteína de baixa densidade
LOX	lipo-oxigenase
NADPH	Fosfato de dinucleótido de nicotinamida e adenina
NF-κB	Fator nuclear κB
NO	Óxido nítrico
NOS	Óxido nítrico sintase
$O^{\cdot}{}_2^-$	Ânion radical superóxido
O_2	Oxigênio
OH-	Radical hidroxil

OMS	Organização Mundial da Saúde
PLA2	Fosfolipase A2
RENISUS	Relação Nacional de Plantas Medicinais de Interesse ao Sistema Único de Saúde
SOD	Superóxido dismutase
TAB	Tecido adiposo branco
TNF-α	Fator de necrose tumoral α
XO	Xantina oxidase

SUMÁRIO

1. INTRODUÇÃO

A obesidade é uma epidemia com grande impacto na saúde mundial. Sua principal característica é o acúmulo excessivo de gordura corporal. Além do crescente aumento de indivíduos obesos, há o prognóstico de que em dez anos mais da metade da população mundial estará com excesso de peso. A principal causa da obesidade é o desequilíbrio entre a quantidade de energia ingerida e a quantidade de energia gasta. Assim, a migração para uma dieta rica em alimentos ultra processados de alta densidade energética associada ao estilo de vida sedentário resulta na ascensão do número de pessoas obesas ao redor do mundo. É preciso ainda, considerar os fatores genéticos, ambientais, comportamentais e socioeconômicos no desenvolvimento dessa condição.

A ferramenta mais utilizada para o diagnóstico para a obesidade é o Índice de Massa Corporal (IMC), que correlaciona a massa corporal e a estatura do indivíduo e, se o resultado for maior ou igual a 30kg/m², em adultos, a classificação é de obesidade. Essa condição é o principal fator de risco para o desenvolvimento de doenças crônicas não transmissíveis (DCNT) como doenças cardiovasculares, diabetes mellitus, hipertensão arterial sistêmica (HAS), apneia do sono e neoplasias malignas. O excesso de gordura também está relacionado ao aumento da produção de interleucinas pró-inflamatórias e à regulação de enzimas antioxidantes.

Os benefícios da prática de exercícios físicos são bastante conhecidos e o sedentarismo é um fator de preocupação mundial. Dados recentes indicam que a inatividade física é responsável por mais de 3 milhões de mortes no mundo. A recomendação de, no mínimo, 150 minutos de exercício físico moderado por semana melhora a qualidade de vida, aumenta longevidade e previne diversas doenças, incluindo as DCNT. O aumento do gasto energético causado pelo exercício físico auxilia na regulação e diminuição da massa corporal. O estilo de vida ativo também gera uma modulação das defesas antioxidantes endógenas.

A literatura indica que a suplementação de curcumina pode trazer benefícios aos indivíduos obesos. Essa substância é um composto fenólico derivado da cúrcuma/açafrão que possui características antioxidantes e anti-inflamatórias. Ainda, há estudos que sugerem uma ação deste composto em parâmetros metabólicos com resultados de redução da glicemia. Redução de massa corporal e de circunferência de cintura também foram observadas.

O tratamento para a obesidade, em teoria, é simples: menor ingestão de energia e maior gasto energético, mas nenhum país conseguiu reverter o avanço do excesso de peso. Alterações no padrão alimentar focadas em promover o consumo de frutas, verduras e grãos integrais e desestimular a ingestão de alimentos ricos em açúcares e gorduras são o principal passo no combate à obesidade. Concomitante às modificações da dieta, o aumento na prática de exercício físicos regulares também auxilia o controle de ganho de massa corporal. E, como auxiliar nesse objetivo de controle da obesidade e suas consequências, a suplementação de curcumina surge como alternativa antioxidante.

Por fim, nosso estudo avaliou os efeitos a suplementação de curcumina associada ao exercício aeróbio contínuo sobre a glicemia de jejum, a gordura abdominal e o estresse oxidativo em ratos com obesidade induzida por dieta de cafeteria.

2. REVISÃO DA LITERATURA CIENTÍFICA

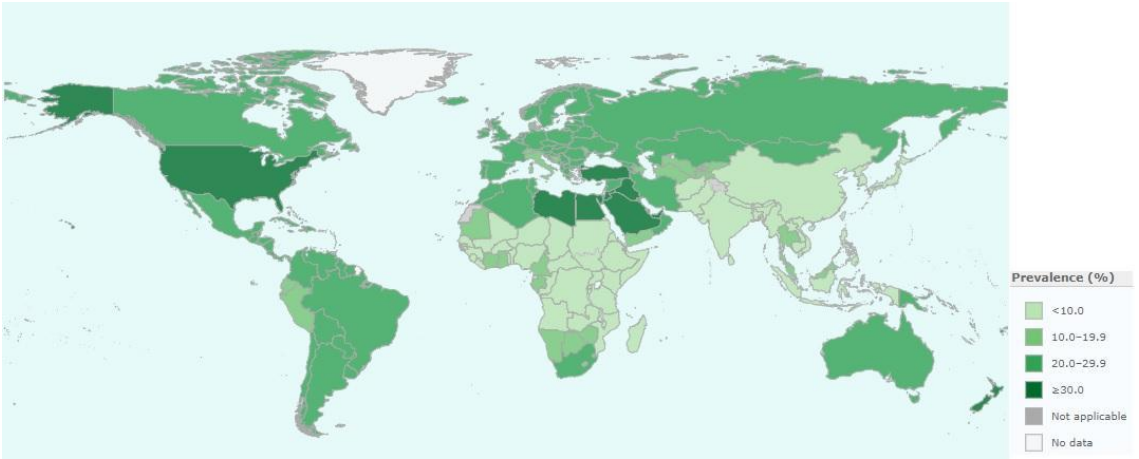
I. OBESIDADE

"A corpulência, quando em grau extraordinário, pode ser considerada uma doença, pois em alguma medida obstrui o livre exercício das funções animais; e tem tendência a encurtar a vida, abrindo caminho para doenças perigosas"

Dr. Malcolm Flemyng.

A Organização Mundial da Saúde (OMS) caracteriza, atualmente, a obesidade como uma epidemia mundial, estimando cerca de 4 milhões de mortes anuais relacionadas à obesidade e ao sobrepeso. Em 2016, 1,9 bilhões de adultos estavam com excesso de peso, destes, 650 milhões podiam ser classificados como obesos (WHO, 2020) (Figura 1). No Brasil, em 2018, 19,8% da população estava obesa. Segundo a OMS, cerca da metade da população adulta mundial estará acima do peso ideal até o ano de 2030. E, o aumento da obesidade da população pode sobrecarregar os sistemas de saúde devido ao aumento da demanda de atendimento às doenças crônicas relacionadas à essa condição (Ng, Fleming et al. 2014) (Finkelstein, Trogdon et al. 2009) (Tremmel, Gerdtham et al. 2017).

Figura 1. Prevalência global de obesidade em adultos em 2016.

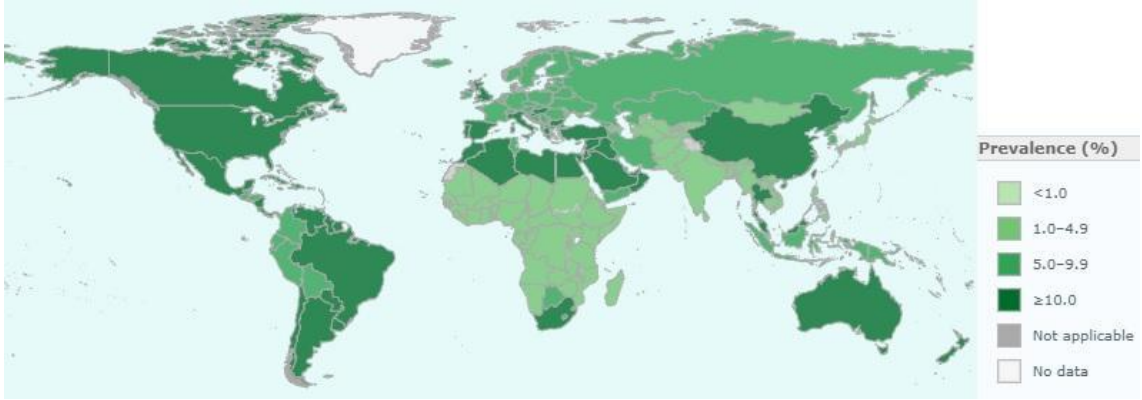


Fonte: Adaptada de OMS, 2020.

Atualmente, há mais pessoas obesas do que subnutridas na maioria das regiões do mundo, exceto África subsaariana e Ásia. O que antes era considerado um problema apenas para países desenvolvidos, agora é também uma característica de países de baixa

e média renda, especialmente em suas áreas urbanas. Crianças e adolescentes ao redor do planeta tiveram um aumento na prevalência de sobrepeso e obesidade de mais de 4 vezes ao longo de 41 anos, passando de 4% em 1975 para 18% em 2016. Grande parte deste aumento pode ser observado em países em desenvolvimento, nos quais indivíduos de até 18 anos endossam uma taxa de mais 30% de sobrepeso e obesidade quando comparados a países desenvolvidos (Figura 2).

Figura 2. Prevalência global de obesidade em crianças e adolescentes (5-19 anos) em 2016.



Fonte: Adaptada de OMS, 2020.

A OMS define obesidade como o "acúmulo anormal ou excessivo de gordura que apresenta risco à saúde", ou seja, é um fator de risco para doenças (WHO, 2020). A *World Obesity Federation*, em contraste, indica que a obesidade, em si, é uma doença recorrente crônica. A justificativa para caracterizar a obesidade como doença é feita por meio de um modelo epidemiológico no qual um agente afeta o hospedeiro e produz doença: os alimentos (agente patológico), principalmente os de alta densidade energética, e o baixo nível de atividade física interagem com a suscetibilidade genética do indivíduo (hospedeiro) para gerar balanço energético positivo e acúmulo de gordura (obesidade) (Bray, Kim et al. 2017).

A obesidade e o sobrepeso são os principais fatores de risco para DCNT, incluindo as doenças cardiovasculares que são a maior causa de morte no mundo. A deposição de gordura em tecido não adiposo, como músculos, fígado e pâncreas, prejudica a função desses órgãos (González-Muniesa, Mártinez-González et al. 2017). Além disso, estão relacionadas a diabetes mellitus tipo 2, que quando descompensada, pode gerar cegueira, amputações e insuficiência renal crônica (O'Rourke 2009). Na literatura é possível observar, também, uma forte correlação de excesso de peso com doenças ósseas como a osteoartrite, apneia do sono e alguns tipos de câncer que atingem

tecidos como mama, fígado, próstata e rins (Williams and Mummery 2015) (Lumeng and Saltiel 2011) (Figura 3).

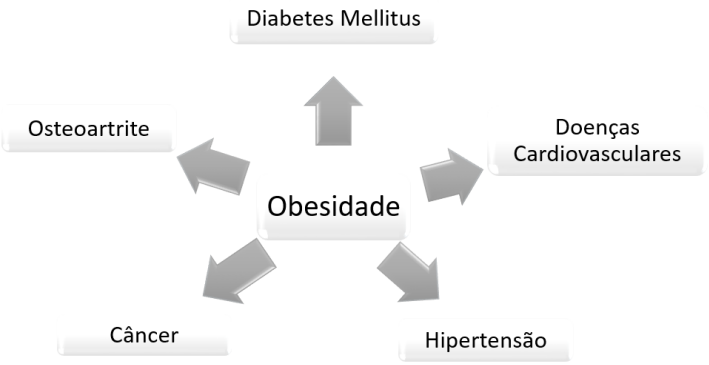


Figura 3. Doenças relacionadas à obesidade.

Fonte: Adaptado de (Bray, Kim et al. 2017).

A obesidade e o sobrepeso são definidos pelo acúmulo excessivo de gordura que pode resultar em risco à saúde. O IMC é a ferramenta que correlaciona numericamente o peso corporal do indivíduo com a estatura, sendo assim, IMC acima de 25kg/m² é classificado como sobrepeso e, acima de 30kg/m², como obesidade. É preciso salientar que apesar de o IMC não especificar as áreas de maior deposição de gordura nem as características socioeconômicas e demográficas, ele é uma ferramenta para uso de referência populacional de aplicação simples e sem custos (WHO, 2020) (Williams, Mesidor et al. 2015).

Há duas classificações para a obesidade: monogênica ou poligênica. Quando a obesidade é resultado de mutação em um único gene, a classificação é monogênica, afeta cerca 5% da população mundial e se caracteriza pelo início precoce. Já na obesidade poligênica, observa-se que cada polimorfismo é suscetível a fatores externos. Dessa forma, o estilo de vida e o ambiente obesogênico são essenciais para o desenvolvimento da obesidade. Sendo assim, o consumo de alimentos ultraprocessados, de alta densidade energética e bastante palatáveis associado a uma vida sedentária podem atuar nesses genes e determinar o aumento na quantidade de pessoas obesas ao redor do mundo (Swinburn, Sacks et al. 2011) (Albuquerque, Stice et al. 2015) (González-Muniesa, Mártinez-González et al. 2017).

A obesidade, então, pode ser considerada como uma doença crônica e multifatorial. Suas principais causas podem ser evitadas e revertidas, no entanto,

nenhum país foi capaz de reverter essa epidemia. O fator fundamental do excesso de peso é o desequilíbrio entre o consumo de energia (quilocalorias) consumida e a quantidade de energia despendida ao longo do tempo. Esse aumento no consumo de energia se deu, principalmente, em função de alterações dietéticas nas últimas décadas com o aumento no consumo de açúcares e gorduras. A disponibilidade e o consumo de alimentos com alta densidade energética – elevada quantidade de energia em pequenas porções - concomitante à redução dos níveis de atividades físicas e exercícios físicos resulta no aumento das taxas de sobrepeso e obesidade. Entretanto, o desafio no controle dessa doença é complexo porque está relacionado a fatores comportamentais, ambientais, psicológicos, socioeconômicos, bem como, aos fatores genéticos (Gregor and Hotamisligil 2011) (Swinburn, Sacks et al. 2011) (Williams, Mesidor et al. 2015).

O tecido adiposo branco (TAB) é o órgão de estoque primário de energia do organismo e, geralmente, se caracteriza por estar na forma subcutânea e visceral (Hildebrand, Stümer et al. 2018). Devido a essas características, o TAB tem função primordial na patogênese da obesidade e suas complicações. A ação endócrina do TAB está relacionada à liberação de adipocinas que estão relacionadas à regulação de funções fisiológicas como alterações da massa corporal, maior produção e liberação de leptina, o metabolismo da glicose e sensibilidade insulínica, aumento na produção e liberação de interleucinas pró-inflamatórias como interleucina 8 (IL-8), interleucina 6 (IL-6), interleucina 1 (IL-1), fator de necrose tumoral alfa (TNF-α) e a diminuição da interleucina 10 (IL-10) (Wozniak, Gee et al. 2009). O TAB ainda pode ter ação sobre a diminuição da expressão de enzimas antioxidantes como a superóxido dismutase (SOD) e a catalase (CAT) (Furukawa, Fujita et al. 2004).

Dentro de uma abordagem multidisciplinar para o tratamento da obesidade, favorecendo intervenções não farmacológicas para cessar o avanço da doença e diminuir os níveis de gordura corporal são indicados a reeducação alimentar e a prática regular de exercícios físicos. Essas medidas estão baseadas na redução no consumo de alimentos ricos em açúcares e gorduras e o incentivo a ingestão diária de frutas, vegetais, legumes, grãos e cerais integrais e sementes oleaginosas. Além disso, a prática de exercícios físicos regulares tem mostrado grande eficácia na redução de danos causados por essa doença (Williams, Mesidor et al. 2015) (González-Muniesa, Mártinez-González et al. 2017).

II. EXERCÍCIO FÍSICO

A inatividade física é o quarto fator de risco de mortes no mundo. Em todo o planeta, um em cada cinco adultos e quatro em cada cinco adolescentes são fisicamente inativos (Guthold, Stevens et al. 2020). Segundo a OMS, o sedentarismo foi responsável por cerca 3,2 milhões de mortes no mundo. A falta de atividade física, também, além de representar um prejuízo para a saúde, gera custos exorbitantes. Ainda de acordo com dados da OMS, mundialmente, US$54 bilhões são gastos em assistência médica direta e, destes, 57% provem de verba pública e o restante, US$14 bilhões, tem relação com a perda de produtividade (Ding, Lawson et al. 2016) (WHO, 2018).

O Brasil é o país mais sedentário da América Latina, cerca de 47% dos adultos brasileiros não praticam exercícios físicos regulares. Essa taxa é uma das maiores do mundo, superando, inclusive, os Estados Unidos que apresenta 40% da sua população de adultos sedentários (WHO, 2018). Esses dados são alarmantes, uma vez que existem diversas evidências sobre os benefícios da prática regular de exercício físico e sobre os prejuízos da inatividade física, que é um dos principais fatores de risco para as DCNT (Fiuza-Luces, Garatachea et al. 2013).

A recomendação da *American College of Sports Medicine* (ACSM) é de 150 minutos semanais de exercício aeróbio com intensidade moderada, 75 minutos semanais de exercício de intensidade vigorosa, em sessões de, pelo menos, 10 minutos de duração. Essa orientação, de uma prática regular de exercício físico, está associada à melhora da qualidade de vida, ao aumento da longevidade e no auxílio a prevenção de diversas doenças (WHO, 2018).

Os benefícios provenientes da prática regular de exercícios físicos são muitos e estão bastante consolidados pela literatura científica. Além dos aspectos biopsicossociais, que podem ser traduzidos em bem estar e qualidade de vida, observa-se também a capacidade do exercício físico atuar diretamente na prevenção e tratamento de acometimentos como a obesidade, a diabetes, o câncer, as doenças cardiovasculares. A literatura afirma que o exercício físico é um potente tratamento não farmacológico para a obesidade (Fiuza-Luces, Garatachea et al. 2013). Ou seja, em relação à redução do sobrepeso e obesidade, o exercício é ferramenta importante a ser utilizada em um estilo de vida capaz de atenuar o ganho de peso. Outras fontes corroboram com essa assertiva e indicam que programas de exercício aeróbio regulam o ganho de peso, reduzem a gordura corporal e a obesidade abdominal, diminuem a HAS, e atenuam o acúmulo de gordura no fígado (Finucane, Stevens et al. 2011). Ademais, a

falta de exercício físico regular está diretamente associada a maiores índices de ansiedade (Stubbs, Koyanagi et al. 2017). Sendo assim, a adição de 150 minutos de exercício físico moderado por semana, pode auxiliar na redução do ganho de peso e na diminuição de gordura corporal em indivíduos com sobrepeso e obesidade, gerando assim, benefícios à saúde.

Blair (2009) enfatiza que a inatividade física é um dos maiores impasses na saúde pública do século XXI. Este fator, deve ser considerado com atenção porque 16% das mortes são causadas pela baixa capacidade cardiorrespiratória. Além disso, pacientes obesos que realizaram exercícios de intensidade moderada ou alta morreram menos de doenças cardiovasculares relacionadas ao diabetes do que homens com peso adequado. Dessa forma, há um realce na importância da prática de exercícios, pois mais do que auxiliar no emagrecimento, o aumento da capacidade cardiorrespiratória pode diminuir a mortalidade de pacientes obesos (Blair 2009).

O sedentarismo também se caracteriza pelo aumento crônico na produção de espécies reativas de oxigênio (EROs) e pela redução da capacidade antioxidante. Esse desequilíbrio gera estresse oxidativo (EO) e, isso, provoca falha no controle e sinalização redox e danos moleculares. Esse cenário é nocivo e subsidia o desenvolvimento de doenças. Já a prática de exercícios físicos está relacionada como um dos fatores de proteção contra o EO, pois o exercício causa uma resposta de estímulo a defesa antioxidante e, outrossim, pode aumentar a síntese de proteínas específicas, amenizando o EO (Buresh and Berg 2015).

III. CURCUMINA

A cúrcuma (*Curcuma Longa L.)* é uma planta que tem origem na Índia e no sudeste da Ásia, popularmente conhecida por açafrão. Essa planta tem de longas ramificações e pertence à família das *Zingiberaceae*, sob o gênero *Curcuma L* (Prabhakaran, 2013). A parte mais utilizada é a raiz ou rizoma e sua colheita pode ser feita logo após a floração, que é o período em que a planta começa a secar e seus rizomas apresentam pigmentos mais intensos. O seu principal componente é a curcumina que se caracteriza pela coloração amarelo-alaranjada. Já transformada em um pó seco, a cúrcuma é utilizada como condimento e corante alimentar, ademais há relatos do uso farmacológico da cúrcuma desde a antiguidade (Figura 4). Além disso, o açafrão, como suplemento, já foi aprovado em diversos países em função das suas

características antioxidantes, antifúngicas, anti-inflamatórias, antibacteriana, antitumoral, antiviral, cicatrizante, hipoglicemiante neuroprotetora, antiparasitária e imunomoduladora (Marchi, Tedesco et al, 2016).

Figura 4. Cúrcuma

Fonte: Depositphotos (Disponível em https://br.depositphotos.com/stock-photos/curcuma.html; acesso em set. 2020)

Essa utilização secular de açafrão em benefício da saúde, induz ao desenvolvimento de pesquisas para comprovação de bioativos com ação farmacológica. Com a verificação dessas propriedades, as entidades governamentais podem encontrar uma alternativa mais vantajosa, economicamente, para tratar a sua população. No Brasil, por exemplo, a cúrcuma se encontra na Relação Nacional de Plantas Medicinais de Interesse ao Sistema Único de Saúde (RENISUS) como uma planta de potencial medicinal.

A curcumina, por sua vez, é um composto fenólico com características antioxidantes, possivelmente benéficas, o que gerou um significativo interesse recente nessa substância (Figura 5). Há indicações de que a curcumina possui propriedades antioxidantes, anti-inflamatórias, anticancerígenas e nefroprotetoras. Além disso, a administração de curcumina melhorou a função endotelial e diminuiu o estresse oxidativo e os marcadores inflamatórios em pacientes diabéticos (Panahi, Hosseini et al. 2015). Houve, também, redução de peso corporal e de circunferência de cintura em pacientes com Síndrome Metabólica e diminuição nos sintomas de ansiedade e depressão relacionadas com o excesso de peso (Di Pierro, Bressan et al. 2015) (Esmaily, Sahebkar et al. 2015).

Em estudos experimentais de modelo animal, a dose de 200mg/kg/dia, por dois meses, de curcumina, apresentou redução na glicemia e melhora no perfil lipídico, com a redução do colesterol total e colesterol-LDL e aumento do colesterol-HDL (HU,

2013). O uso de curcumina (200mg/kg/dia) durante oito semanas também reduziu o estresse oxidativo e marcadores inflamatórios (Kelany, Hakami et al. 2017). Sendo assim, a suplementação de curcumina pode auxiliar na redução dos principais parâmetros metabólicos como a resistência à insulina e na diminuição do estresse oxidativo e da inflamação causada pela obesidade (Sahebkar 2013) (Ganjali, Sahebkar et al. 2014).

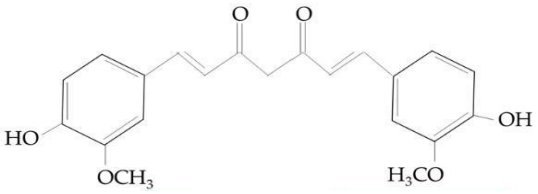


Figura 5. Estrutura química da curcumina.

Fonte: Adaptada de (Den Hartogh, Gabriel et al. 2019).

Todavia, a curcumina apresenta baixa biodisponibilidade, o que é um fator limitante na utilização clínica. A característica lipofílica da substância faz com que ela seja pouco absorvida e, outro fator que interfere na disponibilidade é a sua rápida metabolização. Além disso, a curcumina sofre metabolismo hepático e intestinal, dessa forma, há uma redução na fração livre que chega na corrente sanguínea (Ozawa, Imaizumi et al. 2017).

IV. ESTRESSE OXIDATIVO

O estresse oxidativo é resultado do desequilíbrio entre a produção de espécies reativas de oxigênio e de nitrogênio (ERON) e as defesas antioxidantes endógenas enzimáticas SOD e CAT e exógenas não enzimáticas (vitaminas A, C e E). Essa condição se caracteriza pela instabilidade do estado redox que gera radicais livres (RL) via, principalmente, cadeia transportadoras de elétrons mitocondrial e, também, através da enzima NADPH oxidase (Arcaro, Gutierres et al. 2014) (Bedard and Krause 2007).

A alta instabilidade e reatividade das EROs se dá em função de serem átomos, íons ou moléculas formadas, também, por oxigênio, e possuem um elétron não pareado em sua órbita externa. A caracterização instável e reativa é causada pela tendência de criar uma ligação entre esses elétrons não pareados e outros elétrons de estruturas

parecidas à de sua formação, assim, eles interagem sendo oxidantes/receptores ou redutores/doadores de elétrons (Lima and Abdalla, 2001). Uma vez que essas moléculas instáveis (EROs) são formadas no organismo, elas interagem com outras estruturas como o ácido desoxirribonucleico (DNA), os lipídeos e as proteínas, podendo causar danos celulares alterando conformações pré-estabelecidas, assim modificando a função da célula. Esses danos estão relacionados, por exemplo, com envelhecimento celular precoce e o desenvolvimento e progressão de doenças cardiovasculares, câncer, diabetes, doenças neurológicas (Valko, Leibfritz et al. 2007).

Uma das defesas endógenas aos EROs é superóxido dismutase SOD. A atividade desta enzima foi apresentada primeiramente pela dupla McCord e Fridovich em 1969. Quando é formado, o radical superóxido ($O^{\cdot}{}_2^-$) sofre dismutação enzimática gerando peróxido de hidrogênio (H_2O_2) e oxigênio (O_2). Essa reação ocorre pelas enzimas antioxidantes SOD (McCord and Fridovich 1969).

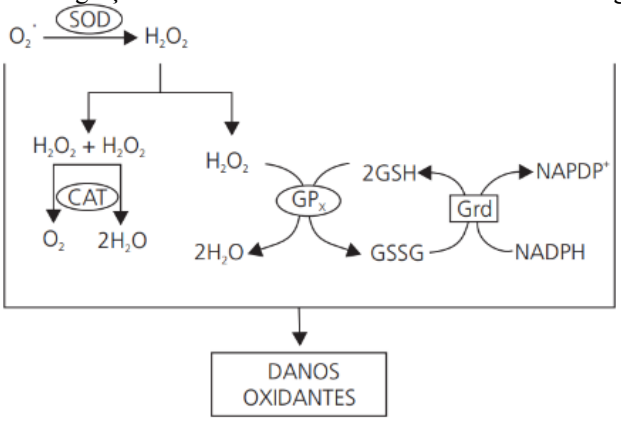
$$O^{\cdot}{}_2^- + O^{\cdot}{}_2^- + 2H^- \rightarrow SOD \rightarrow H_2O_2 + O_2$$

O peróxido de hidrogênio resultante da ação enzimática da SOD é convertido em água e oxigênio pela catalase. A CAT é uma enzima que está presente, principalmente, no citosol de células em órgãos que são mais suscetíveis aos danos provocados pela produção de EROs. O mecanismo de defesa da CAT se dá pela reação que neutraliza a ação tóxica do H_2O_2, formando duas moléculas de água e uma de oxigênio.

$$2H_2O_2 + CAT \rightarrow 2H_2O + O_2$$

A enzima glutationa peroxidase (GPx) atua com o mesmo propósito da catalase: impedir o acúmulo do peróxido de hidrogênio. A ação da GPx é dependente da continuação do estado redox da glutationa pois une a redução do H_2O_2 com a oxidação da glutationa redutase (GSH) (Limón-Pacheco and Gonsebatt 2009). A integração dessas defesas endógenas antioxidantes está na Figura 6.

Figura 6. Integração das defesas antioxidantes enzimáticas endógenas



A reação de dismutação pela enzima superóxido dismutase (SOD) gera, a partir do radical superóxido ($O^{\cdot}_2$), peróxido de hidrogênio (H_2O_2). Afim de impedir o acúmulo de H_2O_2, as enzimas catalase (CAT) e glutationa peroxidase (GPx) agem para transformá-lo em água (H_2O). A GPx realiza a redução do H_2O_2 em água por causa da conversão da glutationa reduzida (GSH) em glutationa oxidada (GSSG).
Fonte: Adaptada de Barbosa, 2010.

V. OBESIDADE E CURCUMINA

A obesidade é uma epidemia que assola o mundo todo e a adesão de um estilo de vida saudável é uma alternativa de tratamento para esta doença. Os benefícios de uma dieta adequada, com baixo consumo de açúcares e gorduras e a prática de exercícios físicos regulares já se mostraram eficazes na redução de peso corporal. Porém, muito se estuda sobre alternativas de suplementação natural que possam auxiliar no processo de emagrecimento.

A curcumina é uma das substâncias encontradas no rizoma de origem indiana denominado *Curcuma longa L.* Essa raíz é popularmente conhecida como açafrão, açafrão da terra ou gengibre dourado e se caracteriza principalmente por adicionar coloração amarela em preparações culinárias. A curcumina e seus derivados, desmetoxicurcumina e bisdesmetoxicurcumina, formam a fração fixa do açafrão e são denominados curcuminóides (Prabhakaran, 2013).

A possível característica antioxidante da curcumina fez com que essa substância fosse colocada em destaque em várias pesquisas. Estudos evidenciaram as propriedades anti-inflamatórias, anticancerígenas e nefroprotetoras da curcumina. Outro resultado de realce foi a melhora da função endotelial, diminuição do estresse oxidativo e redução dos marcadores inflamatórios em pacientes com diabetes (Panahi, Hosseini et al. 2015) (Santos-Parker, Strahler et al. 2017).

A curcumina, então, parece ser um importante fator coadjuvante na melhora de parâmetros relacionados à obesidade, como por exemplo, o estresse oxidativo (Sahebkar 2013) (Ganjali, Sahebkar et al. 2014).

VI. OBESIDADE E EXERCÍCIO FÍSICO

As EROs são moléculas bastante reativas que têm função importante no organismo. Elas ocorrem em condições e processos fisiológicos normais, porém em condições adversas que excedam a capacidade de defesa do organismo, podem causar

danos diretos ou indiretos em órgãos. Como consequência deste processo, há prejuízo para as células através de danos em proteínas, lipídios e ao DNA podendo contribuir para o desenvolvimento de inúmeras doenças, entre elas as cardiovasculares, obesidade e diabetes mellitus (Valko, Leibfritz et al. 2007).

O tecido adiposo é composto principalmente de adipócitos e, entre outros, citocinas como adipocinas e adipocitocinas. Isso resulta em um panorama de inflamação crônica que está correlacionado com a produção exagerada de EROs e gerar EO (Manna and Jain 2015). O excesso de gordura corporal gera citocinas pró-inflamatórias (TNF-α) que aumentam as EROs através dos macrófagos e monócitos. Esse aumento das EROs libera mais citocinas pró-inflamatórias pelos fatores de transcrição redox-sensível (NF-κB e NADPH via oxidase), criando, assim, um círculo vicioso que causa prejuízo ao organismo através de, por exemplo, danos teciduais, resistência à insulina (Fernández-Sánchez, Madrigal-Santillán et al. 2011, Bryan, Baregzay et al. 2013)

As defesas antioxidantes enzimáticas, bem como os agentes antioxidantes de varredura, se mostram insuficientes para minimizar o dano oxidativo em indivíduos obesos (Marseglia, Manti et al. 2014). Desta forma, alguns biomarcadores de dano oxidativo tem correlação direta com o IMC, a porcentagem de gordura corporal, a oxidação de colesterol-LDL e os níveis de triglicerídeos. Em contrapartida, menores níveis de agentes antioxidantes são observados em condições adversas. Além disso, o acúmulo de tecido adiposo induz a um aumento anormal de ácidos graxos livres (AGL) na corrente sanguínea, isso prejudica o metabolismo da glicose e favorece a deposição de substratos como gordura e glicose em tecidos periféricos. Desta forma, há a promoção de oxidação mitocondrial e peroxissômica (Fernández-Sánchez, Madrigal-Santillán et al. 2011).

Então, essa produção desregulada de adipocinas, o EO, e a escassez de moléculas antioxidantes contribuem para danos celulares estruturais, glicemia alterada, sinalização insulínica anormal e metabolismo lipídico prejudicado. Todas essas modificações podem ter como consequência a aterosclerose vascular, HAS, resistência à insulina, dislipidemia e proliferação celular inadequada (Gong, Wen et al. 2020).

VII. EXERCÍCIO FÍSICO E ESTRESSE OXIDATIVO

É bastante estabelecido que a contração muscular intensa gera estresse oxidativo (Gomez-Cabrera, Martínez et al. 2006). Em 1978, descobriu-se a primeira correlação

entre exercício físico e formação de radicais livres. Após contrações musculares repetidas, há exacerbação na produção de ERO e, posteriormente a uma corrida exaustiva, um acréscimo de 2 a 3 vezes na formação de radicais livres (Davies, Quintanilha et al. 1982) (Powers, Radak et al. 2016) (Gomez-Cabrera, Viña et al. 2020). Associado a isso, há o aumento da lipoperoxidação, a perda da integridade do retículo sarcoplasmático e a alteração na função mitocondrial (Gomez-Cabrera, 2013).

Como supracitado, o estresse oxidativo está relacionado, em função do dano que gera em âmbito celular e tecidual, a diversas condições fisiopatológicas. Entretanto, a formação de ERO também é natural e fisiológica para a sinalização e adaptação celular. Na prática do exercício físico, os radicais livres formados, atuam na modulação da contração muscular, na defesa antioxidante e no reparo de danos. A ação mediadora de regulação das moléculas antioxidantes das ERO formadas durante a contração muscular se dá pelo aumento da proteína glutationa redutase pós exercício físico (Powers and Jackson 2008, Powers, Duarte et al. 2010) (Tofas, Draganidis et al. 2019).

Oxigênio e óxido nítrico (NO) são as principais ERONs formadas nas fibras musculares e, que quando reagem com outras moléculas, produzem mais radicais livres. A dismutação do O_2^-, via SOD ou espontaneamente, gera peróxido de hidrogênio. O H_2O_2 se alastra pelas células e adentra a membrana celular, ademais, consegue reagir com diversas moléculas e têm função sinalizadora. Já o peroxinitrito (reação entre o NO e O_2^-), é bastante oxidativo e altera a sinalização da oxirredução por diminuir a biodisponibilidade do óxido nítrico e do oxigênio. Então, a formação de ERO no interior da célula é peça fundamental para que haja remodelamento celular no músculo esquelético, em função da repetição da contração durante o exercício físico (Powers and Jackson 2008, Powers, Duarte et al. 2010, Powers, Talbert et al. 2011) (Goncalves, Quinlan et al. 2015) (Powers, Radak et al. 2016).

Uma das fontes geradoras de ERO, por muito tempo considerada a principal, durante o exercício é a mitocôndria. Durante o exercício físico aeróbio pode haver um aumento de 50 a 100 vezes na formação de O_2^- porque o aumento na atividade de contração muscular que têm relação com uma maior demanda de oxigênio e ação mitocondrial. Todavia, atualmente, estudos indicam que as mitocôndrias formam mais ERO no seu estágio de repouso e não na sua fase ativa, sendo assim essa organela não seria mais a principal fonte de radicais livres durante a atividade contrátil do músculo (Jackson, Pye et al. 2007) (Gomez-Cabrera, Domenech et al. 2008) (Powers and Jackson 2008).

A enzima NADH oxidase – reticulo sarcoplasmático, túbulo T e sacolema – pode ser a principal fonte de ERO durante o exercício. A contratilidade muscular (esquelético e cardíaco) é controlada pelo cálcio liberado por causa do O_2^- gerado pela NADH. Outras enzimas, como a fosfolipase A2 (PLA2) e, em conjunto com esta as enzimas ciclooxigenase (COX) e lipo-oxigenase (LOX), são capazes de aumentar as ERO durante a função contrátil em situações de repetição e fadiga. Já em atividades intervaladas de alta intensidade a formação de radicais livres se dá pela ação da, também enzima, xantina oxidase (XO) (Jackson, Pye et al. 2007) (Powers and Jackson 2008) (Powers, Talbert et al. 2011).

A função do NO é regulação do tônus vascular e sua formação no músculo esquelético é feita pela enzima oxido nítrico sintase (NOS). A contratilidade muscular de exaustão pode aumentar a formação desse óxido por meio de suas isoformas (endotelial e induzida) e, em razão desse processo, há a produção de peroxinitrito. Sendo assim, as vias de sinalização do estado de oxirredução fundamentais para a adaptação muscular e resposta ao exercício físico, são reguladas pelo aumento da formação das espécies reativas de oxigênio e nitrogênio (Gomez-Cabrera, 2013).

O complexo protéico NF-κβ é ativado pelo exercício e fundamental para a expressão das enzimas antioxidantes. Esse complexo regula o estado redox por meio da correlação entre a sinalização das vias sensíveis ao estado oxirredução, a formação de ERO causada pelo exercício físico e o remodelamento muscular. A biogênese mitocondrial, também, é uma valiosa adaptação celular gerada pelo exercício físico e está relacionada com o acréscimo da oxidação e tolerância à contratilidade muscular (Russell, Feilchenfeldt et al. 2003) (Powers, Talbert et al. 2011) (Powers, Radak et al. 2016).

A realização do exercício físico é capaz de promover uma vida mais saudável. Quando praticado de maneira habitual e com intensidade moderada gera adequações celulares como: controle de expressão gênica, regulação de vias de sinalização, geração de força muscular e reabilitação de condições desfavoráveis causadas pelo estresse oxidativo. Dessa forma o próprio exercício estimula o pronunciamento das defesas endógenas, controlando o balanço redox. Ademais, o exercício regular moderado tem relação com a redução do risco de doenças cardiovasculares (Gomez-Cabrera, Martínez et al. 2006) (Powers and Jackson 2008) (Radak, Zhao et al. 2013) (Tofas, Draganidis et al. 2019).

VIII. CURCUMINA E ESTRESSE OXIDATIVO

Os processos naturais de respiração das células aeróbicas e reações biológicas celulares como apoptose, inflamação e secreção de substâncias geram EROs (Ponnuchamy and Khalil 2009). O acúmulo da produção demasiada de EROs causa um desequilíbrio que propicia o surgimento de DCNT, como a hipertensão arterial sistêmica, diabetes melitus, doenças cardiovasculares (Pandey and Rizvi 2009). O organismo tem mecanismos de defesa endógenos e exógenos que previnem, reparam ou inativam as reações moleculares dos elétrons desemparelhados, e dessa forma, controlam o estresse oxidativo.

Já foi demonstrado na literatura a correlação do consumo alimentar e a redução no risco de DCNT. Isso se dá devido a presença de compostos antioxidantes em determinados alimentos o que gera uma alternativa para o aumento da ação antioxidante através dos agentes exógenos encontrados na alimentação. Compostos fenólicos são estruturas que contém um grupo hidroxila (OH-) ligado a um átomo de carbono, em um anel benzênico. Frutas e vegetais podem apresentar estrutura química de 15 átomos de carbono em três anéis de benzeno, os flavonoides (Zujko, Witkowska et al. 2012) (Mason, Trewin et al. 2020).

Uma das classes pertencentes aos flavonoides é a subclasses curcuminóides. A cúrcuma faz parte dessa subclasse. A curcumina ($C_{21}H_{20}O_6$) é o pigmento mais ativo do açafrão e também o que está em maior concentração nesse rizona. Na sua forma mais estável (enólica) a curcumina atua como uma substancia doadora de elétrons, caracterizando-se como antioxidante (Santos-Parker, Strahler et al. 2017).

A curcumina pode ser considerada como um antioxidante em função do grupo dicetona encontrado na sua estrutura (Sandur, S.K., Wright, J.S). Em 1994, Joe e Lokesh determinaram que os meios mais importantes pelos quais a curcumina é capaz de promover a maioria de suas atividades é por inibição de radicais superóxidos, peróxido de hidrogênio e radical óxido nítrico. Também, uma dose de 200mg/kg/dia de curcumina aumentou a atividade da SOD e da CAT no fígado de ratos com lesão hepática (Abdel-Daim and Abdou 2015).

3. JUSTIFICATIVA

A obesidade é uma epidemia e está relacionada ao aumento do risco de doenças crônicas, como os acometimentos cardiovasculares que apresentam maiores taxas de mortalidade no mundo. Desta forma, torna-se essencial o desenvolvimento de terapias não-medicamentosas afim de atenuar o crescimento no número de obesos. O exercício físico já apresenta resultados benéficos isoladamente, enquanto a suplementação de curcumina ainda é um tópico indefinido na literatura. E, os efeitos da associação destas intervenções ainda precisam ser elucidados. Sendo assim, o presente trabalho visa verificar o efeito da associação da suplementação de curcumina com o exercício aeróbio sobre parâmetros metabólicos e sobre o estresse oxidativo na obesidade, contribuindo para o entendimento das possibilidades terapêuticas nessa condição.

4. OBJETIVOS

Objetivo Geral

Avaliar o efeito da suplementação de curcumina associada ao exercício aeróbio de moderada intensidade sobre os parâmetros metabólicos e sobre o estresse oxidativo em ratos obesos.

Objetivos Específicos

Avaliar o efeito de oito semanas de suplementação de curcumina associada ao exercício aeróbio em ratos obesos sobre:

- massa corporal total;
- glicemia de jejum;
- desempenho em teste de tolerância ao exercício;
- adiposidade abdominal;
- marcadores de estresse oxidativo em diferentes órgãos.

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6. ARTIGO

The effects of curcumin supplementation associated with aerobic exercise in obese rats: analysis of body mass, blood glucose and oxidative stress

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Abstract

Introduction: Obesity is a risk factor to chronic non-communicable disease. The adipose tissue is an endocrine organ related to oxidative stress and associated body mass and glucose metabolism. The aerobic exercise is a potent non-pharmacological treatment for obesity. Curcumin is an antioxidant compound and can reduce oxidative stress.

Objective: To evaluate the effects of curcumin supplementation associated with continuous aerobic exercise training on metabolic variables and oxidative stress in obese rats.

Methods: Male Wistar obese rats by cafeteria diet (12 weeks), supplemented with curcumin (200mg/kg/day) and underwent to a treadmill running protocol (30min/day, 5days/week) for 8 weeks. Body mass and blood glucose were measured after 12 weeks of cafeteria diet and at the end of the study. Oxidative stress analyses of superoxide dismutase (SOD) and catalase (CAT) activity and malondialdehyde (MDA) concentration were analyzed in heart, liver, gastrocnemius and abdominal fat.

Results: CAF groups showed higher body mass and percentage of body mass when compared to STA groups ($p<0.001$). CAF group demonstrated higher blood glucose than STA+Cur ($p=0.0203$), STA+Cur+AE ($p=0.0025$), and STA+AE ($p=0.0295$) groups. The aerobic exercise groups demonstrated higher distance ($p<0.001$), duration ($p<0.001$), and speed ($p<0.001$) compared to untrained groups. In the gastrocnemius, the CAF+Cur group demonstrated higher SOD activity compared to STA+Cur ($p=0.0329$), STA+Cur+AE ($p=0.0019$), STA+AE ($p=0.0018$), and STA ($p=0.0006$) groups, while the CAF+AE groups showed higher SOD activity than STA group ($p=0.0337$).

Conclusion: The exercise was capable to increase TTE performance when compared to sedentary condition. The combination of curcumin supplementation and aerobic moderate training did not control body mass and abdominal fat gain in animals that received cafeteria diet, however may have helped control blood glucose.

Keywords: obesity, curcumin, aerobic exercise, blood glucose, body mass, oxidative stress

Abbreviation list: CAF, cafeteria diet; CAT, catalase; ETT, exercise tolerance test; GPx, glutathione peroxidase; MDA, malondialdehyde; SOD, superoxide dismutase; STA, standard diet; TBARS, thiobarbituric acid reactive substances were measured;

1. Introduction

Obesity is a globally spread epidemic, responsible for 2.8 million deaths each year. This condition is defined as abnormal or excessive fat accumulation that presents a risk to health (González-Muniesa, Mártinez-González et al. 2017), which is a risk factor for the development of chronic diseases, including cardiovascular diseases, diabetes, and cancer (Tremmel, Gerdtham et al. 2017). An obesogenic environment, characterized by the consumption of high energy density foods and physical inactivity, is one of the conditions that lead to obesity (Swinburn, Sacks et al. 2011). Therefore, treatments with dietary intervention and physical exercise protocols are highly recommended. Besides, the adipose tissue is not merely a storage organ, it is also an endocrine organ composed of resident adipocytes and macrophages. These cells release a large amount of pro-inflammatory cytokines in the condition of obesity, leading to chronic inflammation that is directly related to the exacerbated production of reactive oxygen species and oxidative stress (Manna and Jain 2015) (Fernández-Sánchez, Madrigal-Santillán et al. 2011) (Bryan, Baregzay et al. 2013).

Regular aerobic exercise is especially recommended for the prevention and treatment of obesity (Jakicic, Powell et al. 2019). An active lifestyle with regular physical exercise programs is cable of attenuate weight gain, reduce body fat and abdominal obesity, and decrease systemic hypertension and the risk of developing chronic non-communicable diseases (Fiuza-Luces, Garatachea et al. 2013) (Finucane, Stevens et al. 2011). Also, physical exercise is listed as one of the protective factors against oxidative stress, as it generates a stimulus-response to improve the enzymatic antioxidant defense (Gomez-Cabrera, Domenech et al. 2008). This modulation is related to muscle contractile activity, which produces and secretes myosins that induce the regulation of antioxidant protection processes and the repair of oxidative damage (Buresh and Berg 2015).

Several antioxidant compounds, known as scavengers antioxidants, can be found in certain foods and might reduce the risk to develop chronic diseases(Zujko, Witkowska et al. 2012, Mason, Trewin et al. 2020). Curcumin, for example, is one of the substances found in the rhizome of Indian origin, *Curcuma longa L*. This root is popularly known as turmeric, saffron, or golden ginger and it is mainly characterized by adding yellow coloring to culinary preparations. Moreover, curcumin forms the fixed fraction of saffron and it is called curcuminoids, a subclass of flavonoids. In its most stable form (enolic), curcumin acts donating electron being characterized as an

exogenous antioxidant substance (Panahi, Hosseini et al. 2016) (Fleenor, Carlini et al. 2019) (Maithili Karpaga Selvi, Sridhar et al. 2015).

So, the association of curcumin supplementation and physical exercise could act in a synergic way to reduce the damage caused by oxidative stress in the condition of obesity. It is well known in the literature that physical exercise is a protective factor against oxidative stress, while the antioxidant action of curcumin is still controversial. Therefore, this study aims to evaluate the effects of curcumin supplementation associated with continuous aerobic exercise training on body mass, percentage of abdominal fat, glycemia, exercise tolerance, and oxidative stress in obesity.

2. Methodology

2.1 Animals

Sixty-four male Wistar rats were enrolled in this study (21 days old). The animals were obtained from the Animal Breeding Unit of the Universidade Federal de Ciências da Saúde de Porto Alegre (UFCSPA) and housed under standard conditions (food and water ad libitum, temperature between 22 and 24°C, light-dark cycle of 12 h). All procedures were following the Guide for the Care and Use of Laboratory Animals adopted by the National Institute of Health (NIH-USA) and obeyed resolutions of the National Council on Animal Experimentation (Animals 2011). This study was approved by CEUA/UFCSPA, under the protocol number 18-238.

2.2 Experimental design

Animals were randomly divided equally into eight experimental groups, as follows: standard diet and supplemented (STA+CUR, n=8); standard diet, supplemented, and aerobic training (STA+CUR+AE, n=8); standard diet and aerobic training (STA+AE, n=8); standard diet (STA, n=8); cafeteria diet and supplemented (CAF+CUR, n=8); cafeteria diet, supplemented, and aerobic training (CAF+CUR+AE, n=8); cafeteria diet and aerobic training (CAF+AE, n=8); cafeteria diet (CAF, n=8). Previously to the beginning of supplementation and training protocols, both diets were administrated for 12 weeks. Then, each group continues to receive the same diet and curcumin supplementation was performed daily for 8 weeks and aerobic exercise was performed for the same period (5×/week).

2.3 Protocol to induce experimental obesity

The experimental obesity induction consists of the administration of a cafeteria diet for 12 weeks (Sclafani and Springer 1976). In addition to the standard diet, the animals received sausages, crackers, vanilla cake, and white chocolate, resulting in diet composition of 60% carbohydrates, 15% proteins, 25% lipids. The control groups received a standard diet, consisting of the standard Nuvilab® diet. Animals maintain the same diets after the beginning of the aerobic exercise protocol.

2.4 Exercise tolerance test (ETT)

All animals underwent an exercise tolerance test to measure their maximal running capacity before and after the aerobic training protocol. Briefly, animals had an adaptation period to the treadmill of five days and run for 10 min/day previously to test (Marton, Koltai et al. 2016). The TTE consisted of running on an electric treadmill with an inclination of 15°. It started at a speed of 5 m/min and increasing by 5 m/min every 3 min until exhaustion. The exhaustion represents the incapacity of the animal to run for at least 15 s, even while receiving an electrical stimulus (1.5 mA) (Ferreira, Rolim et al. 2007).

2.5 Aerobic training protocol

The aerobic training protocol was performed by animals in trained groups. It consists of running in an electronic treadmill without inclination, 30 min/day, five days/week with a moderate intensity of 70% for eight weeks at the same time. The protocol was initiated with 20 min of exercise in the first week and extended to 30min/day (Emter, McCune et al. 2005).

2.6 Curcumin supplementation

Animals in supplemented groups received 200mg/kg/ml of Curcuma (presentation form: powder, with a purity of ≥ 98%, Infinity Pharma®, Brazil) in 1 ml sterile saline solution by oral gavage, five days/week for eight weeks before aerobic training (Hu, Lin et al. 2013). All animals were weighed weekly to dose adjustment. Control groups underwent the same supplementation, receiving only saline.

2.7 Glycemia

The body mass and length of the animals were measured weekly. The glycemia test was performed every fifteen days using the portable Glucotrend® equipment via the caudal vein after the animals fasted for 12h.

2.8 Tissue collection

Four days after the end of eight weeks of supplementation and aerobic training protocols, all animals were anesthetized via exposure to isoflurane in oxygen (induction 5%, 2 L/min) for 5 min in an induction chamber and then euthanized via the exsanguination method. Heart, liver, gastrocnemius, and abdominal fat were dissected and stored at −80°C for subsequent analyses.

2.9 Oxidative stress analysis

2.9.1 Tissue preparation

The tissues (heart, liver, gastrocnemius, and abdominal fat) were defrosted, weighed on an analytical balance, and homogenized in Kpi buffer (KCl 1.15%), pH 7.4, containing protein inhibitors (1µg/mL pepstatin, 1µg/mL aprotinin, 1µg/mL leupeptin, and 0.5 mM PMSF) with a ratio of 7ml/1g, 9ml/1g, 5ml/1g, 5ml/1g per tissue, respectively. For homogenization, the tissue homogenizer (CT-136.1, Cientec®) was used. After this process, the samples were centrifuged at 3000 rpm, for 10 minutes at 4ºC, to remove nuclei and cell debris, while the supernatants were collected to determine the activity of antioxidant enzymes and concentration of malondialdehyde (MDA).

2.9.2 Protein concentration

Protein concentration was performed using the Bradford method, using bovine serum albumin as the standard (Schleicher and Wieland 1978). Homogenized samples (10µl) were diluted in 190µl of distilled water for the dosage of protein in the tissue. 60µl of this solution were placed in plastic cuvettes with 2.9 ml of Bradford reagent. The sample absorbance was set at 595nm, on the Lambda 35 spectrophotometer (Perkin-Elmer of Brazil, SP, Brazil).

2.9.3 Superoxide dismutase activity

Superoxide dismutase (SOD) activity was determined by inhibiting the auto-oxidation of pyrogallol by the enzyme (Marklund and Marklund 1974). A unit of SOD is defined as the amount of enzyme capable of inhibiting 50% of the reaction. In the cuvettes, 930µl of TRIS buffer, 4µl of 30µM catalase, and 50µl of homogenized tissue were placed. Then, 16µl of 24mM pyrogallol in 10mM HCl was added to the solution. The absorbances of the samples will be determined on the Lambda 35 spectrophotometer (Perkin-Elmer do Brasil, SP, Brazil), at 420 nm in 60 and 120s. The results are expressed in units of USOD/mg of total proteins.

2.9.4 Catalase activity

Catalase (CAT) activity was determined according to the decomposition of hydrogen peroxide at 25ºC. The reaction mixture contained 2865µl of phosphate buffer (pH 7.0) and 30µl of homogenized sample afterward, 105µl of 0.02M hydrogen peroxide was added to the solution. The absorbance of the samples was determined at 240nm for 120 seconds in a Lambda 35 spectrophotometer (Perkin-Elmer do Brasil, SP, Brazil) and the results are expressed in pmol/mg of total proteins.

2.9.5 Thiobarbituric acid reactive substances

Thiobarbituric acid reactive substances were measured (TBARS) to determine lipid peroxidation by the Easterbauer and Cheeseman technique (Esterbauer and Cheeseman 1990). For protein precipitation, 250µl of the homogenized supernatant sample was added to 500µl of 10% trichloroacetic acid solution. Then, cooled on ice for 15 minutes, centrifuged at 3200 rpm for 15 minutes, at 4ºC. To 500µl of the supernatant, 500µl of 0.670% thiobarbituric acid was added. This solution was heated to 100ºC in a water bath for 10 minutes. Then, the colored supernatant was placed in micro glass cuvettes to determine the absorbance of 535 nm in a Lambda 35 spectrophotometer (Perkin-Elmer do Brasil, SP, Brazil). The concentration of MDA was expressed in nmol/mg of total proteins. The standard curve generated from the known concentrations of 1,1,3,3-tetramethoxypropane 100nmol/ml in 1% sulfuric acid solution was used. To calculate the MDA concentration.

2.10 Statistical analysis

Data are expressed as mean ± standard deviation (SD). Kolmogorov–Smirnov test was used to test the normality of the variables. One-way analysis of variance (ANOVA)

followed by the Bonferroni posthoc test was used to compare groups. P *<0.05* was considered statistically significant. Statistical analysis was performed with SigmaPlot version 12.0 for Windows (Systat Software, Inc.) and graphics created using GraphPad Prism version 8 software for Windows (GraphPad Software, San Diego, CA).

3. Results

3.1 Body mass, percentage of abdominal fat, glycemia

Posterior to the 12 weeks of obesity induction, the CAF groups showed higher body mass compared to all groups that received a standard diet (STA+Cur, p=0.0027, STA+Cur+AE, p=0.0013, STA+AE, p=0.0209; STA, p=<0.001). The CAF+Cur group demonstrated higher body mass compared to STA+Cur (p=0.0168), STA+Cur+AE (p=0.0086) and STA (p<0.001) groups, and the CAF+Cur+AE (p=0.0015) and CAF+AE (p=0.0012) groups had higher body mass compared to STA group (Figura1a). At the end of the experiment protocols, the groups CAF+Cur and CAF demonstrated higher body mass compared to all groups that received the standard diet (p<0.001). Besides, the groups CAF+Cur+AE and CAF+AE showed higher body mass compared to STA+Cur+AE (p=0.0201 and p=0.0343, respectively), and STA (p=0.0066 and p=0.0116, respectively) groups (Figure 1b).

Posterior to the obesity induction period, the blood glucose showed no difference among the groups (p=0.0895) (Figure 1c). After the 8 weeks of supplementation and training intervention, the CAF group demonstrated higher blood glucose than STA+Cur (p=0.0203), STA+Cur+AE (p=0.0025), and STA+AE (p=0.0295) groups (Figure 1d). Also, all groups that received the cafeteria diet demonstrated a higher percentage of body fat compared to all standard diet groups (p<0.001) (Figure 1e).

3.2 Exercise Tolerance Test

The ETT performed before the exercise protocol demonstrated no difference in distance (p=0.3173), duration (p=0.1020), and speed (p=0.1077) among the groups (Figure 2a). After the training, groups that performed the aerobic exercise protocol demonstrated higher distance (p<0.001), duration (p<0.001), and speed (p<0.001) compared to untrained groups (Figure 2b).

3.3 Oxidative stress

Regarding the oxidative stress analysis, the activity of SOD and CAT, and TBARS concentration demonstrated no difference among the groups in the liver (p=0.6055, p=0.3939, p=0.6931) (Figure 3), in the heart (p=0.3738, p=0.2569, p=0.4399) (Figure 4), and in the abdominal fat (p=0.2826, p=0.4225, p=0.2869) (Figure 5). In the gastrocnemius, the CAF+Cur group demonstrated higher SOD activity compared to STA+Cur (p=0.0329), STA+Cur+AE (p=0.0019), STA+AE (p=0.0018), and STA (p=0.0006) groups, while the CAF+AE groups showed higher SOD activity than STA group (p=0.0337) (Figure 6a). The CAT activity (p=0.5368) and TBARS concentration (p=0.5059) demonstrated no difference among groups in the gastrocnemius (Figure 6).

4. Discussion

Our results demonstrated that the cafeteria diet caused an increase in body mass, glycemic levels, and fat accumulation. Regarding the metabolic parameters evaluated, the eight weeks of curcumin supplementation and aerobic training did not counteract the gain of body mass and abdominal fat caused by the cafeteria diet. Also, the groups that received a cafeteria diet associated with curcumin supplementation and aerobic training demonstrated higher levels of SOD activity in gastrocnemius muscle.

The metabolic variables results showed that the maintenance of a hypercaloric dietary pattern is related to weight gain, which was greater compared to the standard diet, regardless of the intervention. Curcumin supplementation and aerobic training were not able to prevent body mass gain in cafeteria diet groups. These findings are similar to studies that used a high-fat diet and supplemented curcumin with or without white pepper. Both of them demonstrated no difference in the weight gain of the supplemented animals (Silva, Fassini et al. 2020) (Neyrinck, Alligier et al. 2013). Controversy, Dolati and colleagues observed that curcumin and exercise did not alter the body mass of overweight women, but the exclusive use of curcumin reduced body mass and BMI of the participants (Dolati, Namiranian et al. 2020).

The association of curcumin supplementation with aerobic exercise training together with a standard diet was effective in controlling body mass. The groups that received standard diet started the supplementation and exercise protocols with lower body mass compared to cafeteria diet groups. So, standard diet groups might have maintained lower mass gain after the intervention protocols. Considering that the obese

group maintained the cafeteria diet until the end of the experiment, supplementation and exercise interventions were not sufficient to cause significant changes. Thus, it is possible to emphasize the importance of changes in dietary patterns associated with additional interventions for effectively reducing body mass.

The curcumin supplementation and the aerobic exercise could act on the control of blood glucose. Curcumin emerges as an important antihyperglycemic factor, attenuating insulin resistance in skeletal muscle (Na, Zhang et al. 2011). Rashid and colleagues also showed a decrease in blood glucose after curcumin supplementation at a dose of 100mg/kg/day for 8 weeks (Rashid, Chowdhury et al. 2017). In addition, animals with metabolic syndrome induced via high fructose diet had a decrease in insulin resistance posterior supplementation of 200mg/kg/day of curcumin for 8 weeks (Kelany, Hakami et al. 2017). It is known that physical exercise leads to an improvement in glucose metabolism and insulin sensitivity in muscle tissue (Goodyear and Kahn 1998). Regardless of insulin, exercise stimulates the expression of GLUT4 in the cell membrane, promoting greater glucose uptake capacity (Lund, Holman et al. 1995). The combination of 500mg/day of curcumin and aerobic exercise for 8 weeks resulted in decreased serum concentration of insulin in overweight women who had no diet change (Dolati, Namiranian et al. 2020). Furthermore, the overexpression of SOD activity mice exposed to a high-fat diet protected the animals from glucose intolerance and insulin resistance, however, it was not observed a protective effect against obesity (Hoehn, Salmon et al. 2009) (Liu, Qi et al. 2013). These results might indicate the reason groups exposed to the cafeteria diet that received the supplementation of curcumin or performed exercise had higher SOD activity levels and improved glycemic control.

The curcumin supplementation and the aerobic exercise did not reduce the percentage of abdominal fat in our study. The consumption of a hypercaloric diet had a greater impact on the amount of abdominal adipose tissue than the proposed interventions since there was a significant difference in all cafeteria diet groups compared to the standard diet groups. Thus, the dietary pattern may be the main variable in the control of abdominal obesity. This is confirmed with the absence of difference when comparing the cafeteria diet groups. So, different from blood glucose alterations, the intervention with curcumin supplementation and/or physical exercise protocol did not change the condition of obesity without alterations on dietary patterns.

It is possible to speculate that with a more extensive exercise protocol, differences in the percentage of abdominal fat might be detected.

In the present study, only the cafeteria diet group showed higher levels of blood glucose. Therefore, both supplementation and exercise could improve glycemic control. The excessive accumulation of abdominal fat is associated with insulin resistance (Sironi, Gastaldelli et al. 2004), systemic inflammation (Brooks, Blaha et al. 2010) (Ye 2009), released of proinflammatory biomarkers, including prostaglandins and cytokines (IL-6, TNF-α, leptin) (Das 2001) (Guarner and Rubio-Ruiz 2015). The adipose tissue release of inflammatory biomarkers lead to the development of type 2 diabetes and cardiovascular diseases, thus animals that received the cafeteria diet could be more susceptible.

Among the trained groups, there was an improvement in tolerance to exercise. It was observed by the increase in distance, exhaustion time, and speed on the exercise tolerance test, which corroborates with previous experimental studies that used aerobic training (Ferreira, Rolim et al. 2007, Marton, Koltai et al. 2016, Marmett, Nunes et al. 2018). During the aerobic physical exercise, a repetitive muscle contraction occurs, generating responses such as increased aerobic metabolism capacity and muscle endurance (Powers, Talbert et al. 2011) (Radak, Zhao et al. 2013) (Steinbacher and Eckl 2015). Therefore, after the eight weeks of training, the animals might have beneficial effects caused by the practice of exercise.

The higher levels of SOD activity in the gastrocnemius muscle of the groups that consumed a cafeteria diet may be related to the time-response of antioxidant enzymes activity, since SOD is the first enzyme to act in the antioxidant defense. It is possible to assume that the animals were at the beginning of obesity and the circulation of high levels of fatty acids induced oxidative stress in the muscle tissue. During this period, the tissues aimed to neutralize the oxidative stress by increasing the expression and activity of antioxidant enzymes (Savini, Catani et al. 2013). Moreover, curcumin supplementation might help in the SOD increase, once it provided an antioxidant effect and increased this enzyme in diabetic rats (Fleenor, Carlini et al. 2019). Furthermore, the muscle adaptation after physical exercise increases the regulation of antioxidant defenses and stimulates the repair of oxidative damage (Gomes, Martinez et al. 2017), which can be noticed by the SOD levels in the gastrocnemius muscle. In a study with animals that received a high fructose diet and treatment with curcumin, attenuation of oxidative stress, and increased expression of the enzyme glutathione peroxidase (GPx)

were detected (Maithilikarpagaselvi, Sridhar et al. 2016). Therefore, the activity of the CAT enzyme in our study might have not increased due to the action of GPx.

Regardless of the absence of effects of our interventions on body mass and abdominal fat percentage, both protocols improved glycemic control, minimizing the damage caused by the cafeteria diet. Also, considering that aerobic training could induce beneficial alterations on redox status in the skeletal muscle (He, Li et al. 2016), curcumin supplementation increase antioxidant defense (Maithili Karpaga Selvi, Sridhar et al. 2015), and MDA (TBARS) concentration did not increase, it is possible to presume that there was not oxidative damage in tissues in our study.

A change in the dietary pattern together with curcumin supplementation and aerobic exercise could be a more effective intervention and it would be possible to simulate a therapeutic approach in the treatment of obesity in clinical practice. However, our findings reinforce the importance of an adequate diet associated with physical exercise to obtain better results and health benefits.

5. Conclusion

The cafeteria diet consumed for twelve weeks demonstrated a high capacity to induce obesity and damage to health, as observed by the substantial increase in body fat. The aerobic training was able to increase the performance of the exercise tolerance test when compared to a sedentary condition. However, the curcumin supplementation and physical exercise interventions were not able to control the body mass and abdominal fat gain in the animals that remained on the cafeteria diet until the end of the study. Nonetheless, these interventions may have helped control blood glucose. Thus, the present study clearly shows that the change in dietary patterns is essential for the treatment of obesity.

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Conflict of interest

The authors declare that they have no conflict of interest.

Author contributions

Fauri MB and Marmett B: study design, conduct of the study, molecular biological analysis, data collection and statistical analysis, data interpretation. Nunes RB study design, conduct of the study, data collection. All authors contributed to the manuscript writing and critical review.

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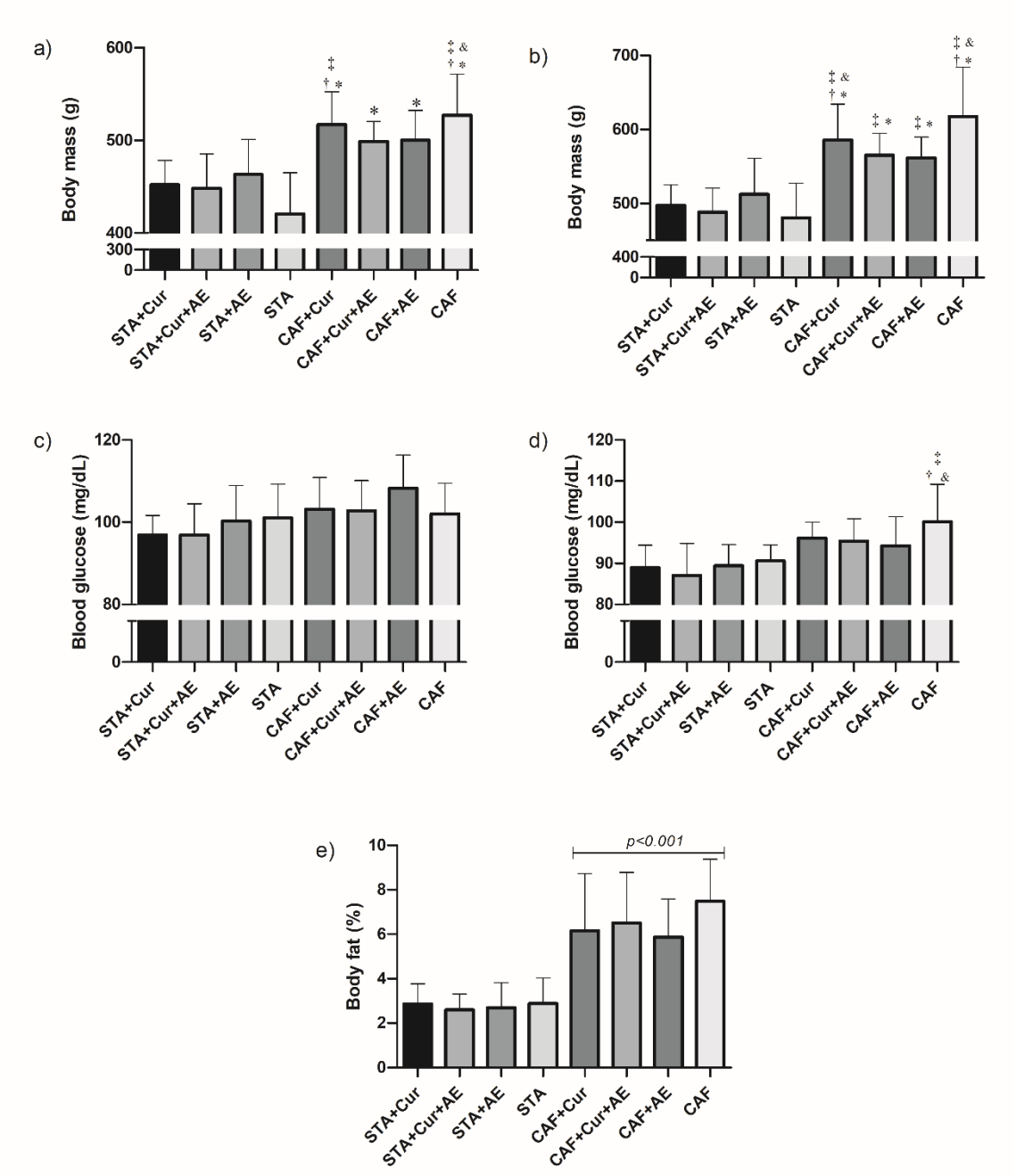

a)
Body mass (g)
600
500
400
300
0
b)
Body mass (g)
700
600
500
400
0
c)
Blood glucose (mg/dL)
120
100
80
0
d)
Blood glucose (mg/dL)
120
110
100
90
80
0
e)
Body fat (%)
10
8
6
4
2
0
p<0.001
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF

Figure 1

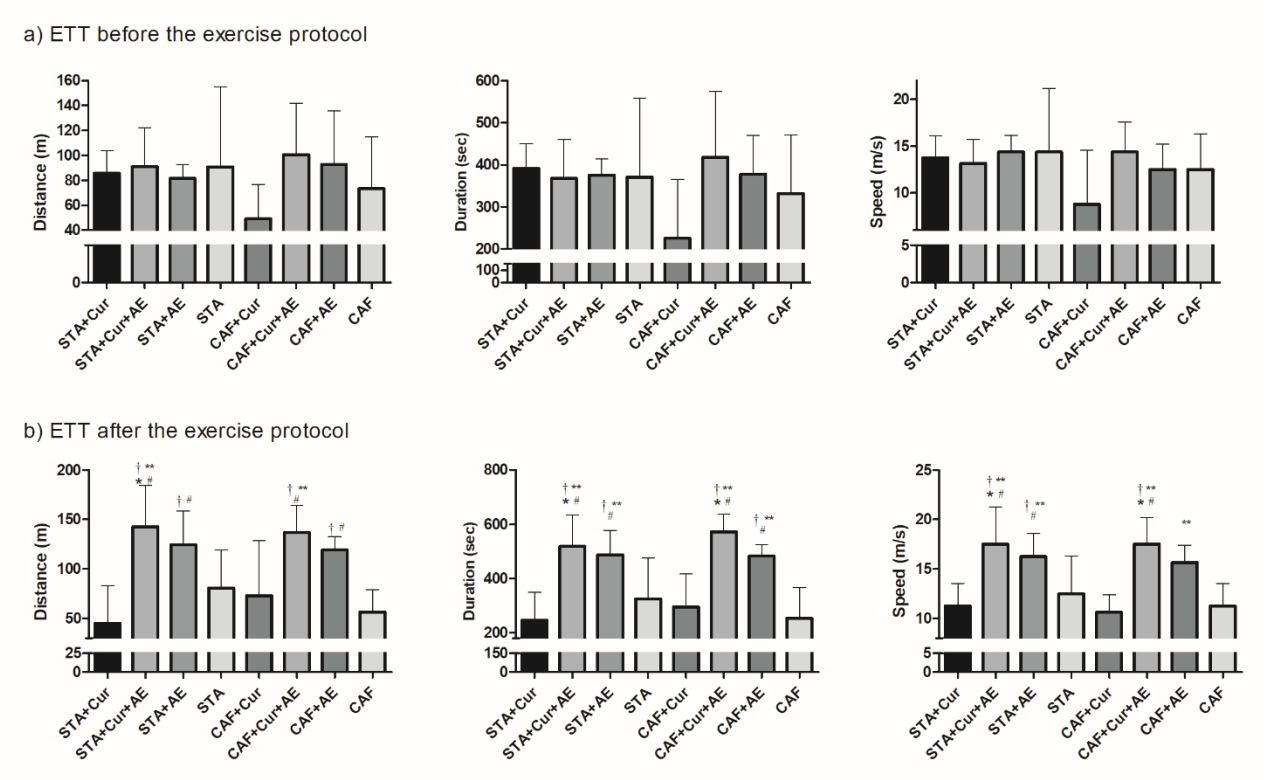

a) ETT before the exercise protocol
Distance (m)
Duration (sec)
Speed (m/s)
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF
b) ETT after the exercise protocol
Distance (m)
Duration (sec)
Speed (m/s)

Figure 2

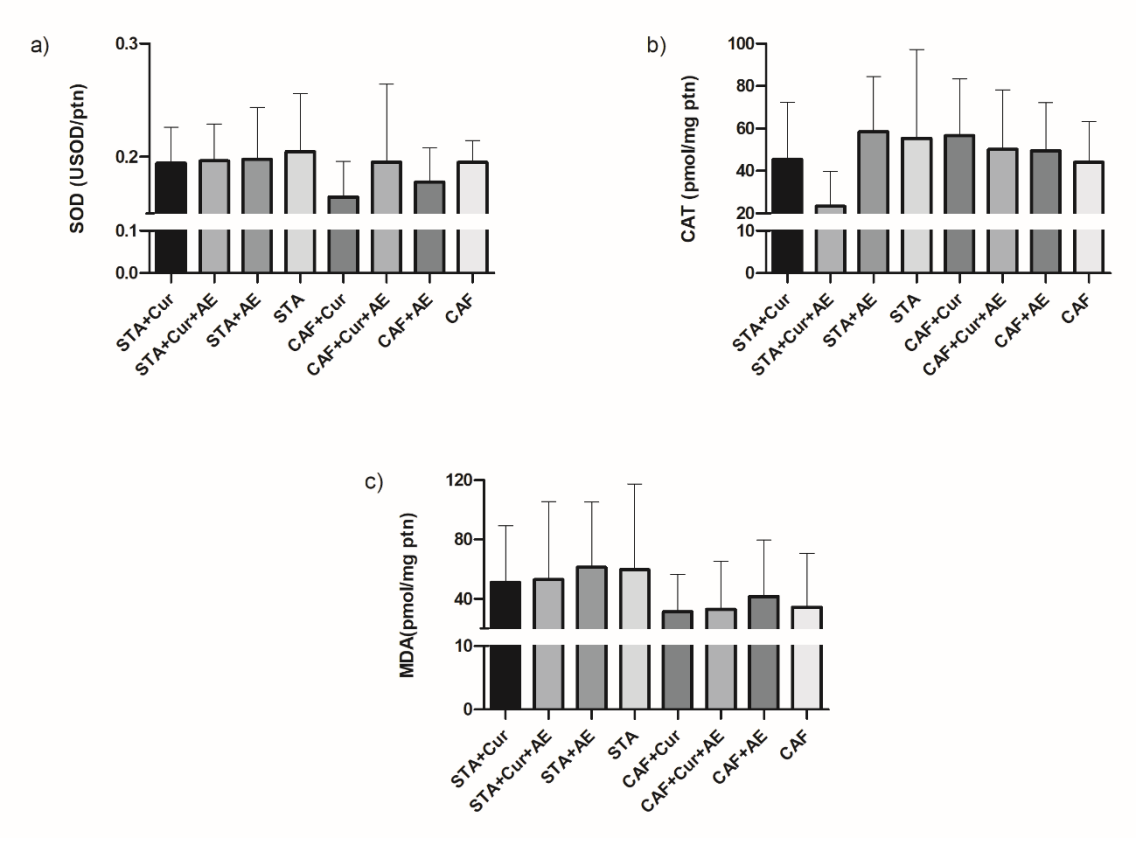
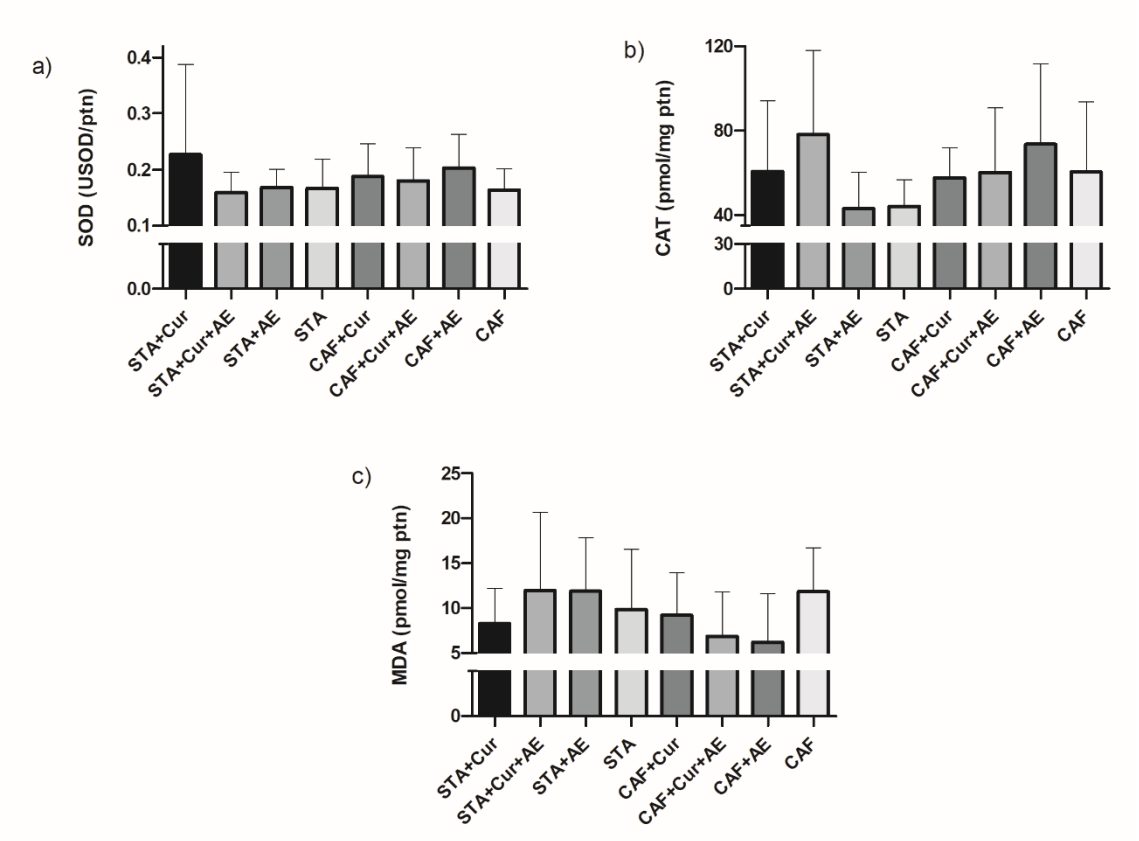

a)
SOD (USOD/ptn)
0.3
0.2
0.1
0.0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF
b)
CAT (pmol/mg ptn)
100
80
60
40
20
10
0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF
c)
MDA(pmol/mg ptn)
120
80
40
10
0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF

Figure 3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SOD (USOD/ptn)
0.4
0.3
0.2
0.1
0.0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF
b)
CAT (pmol/mg ptn)
120
80
40
30
0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF
c)
MDA (pmol/mg ptn)
25
20
15
10
5
0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF

Figure 4

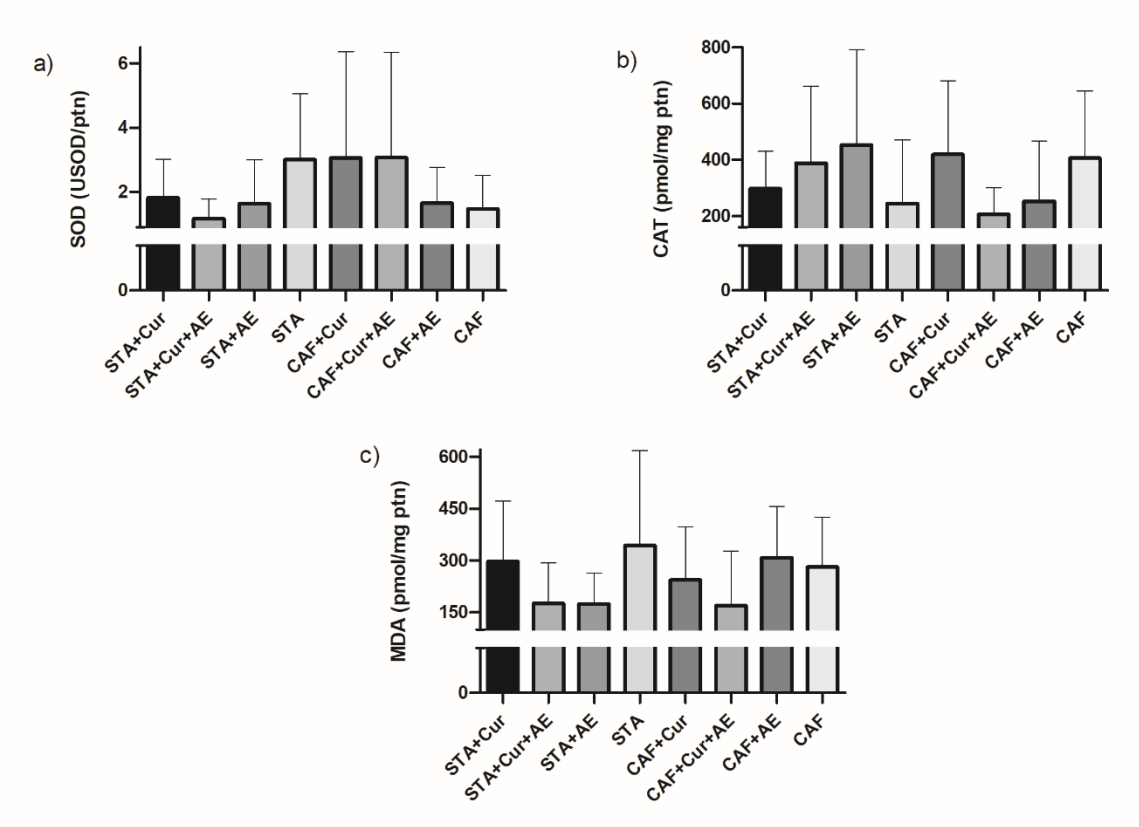
a)
SOD (USOD/ptn)
6
4
2
0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF
b)
CAT (pmol/mg ptn)
800
600
400
200
0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF
c)
MDA (pmol/mg ptn)
600
450
300
150
0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF

Figure 5

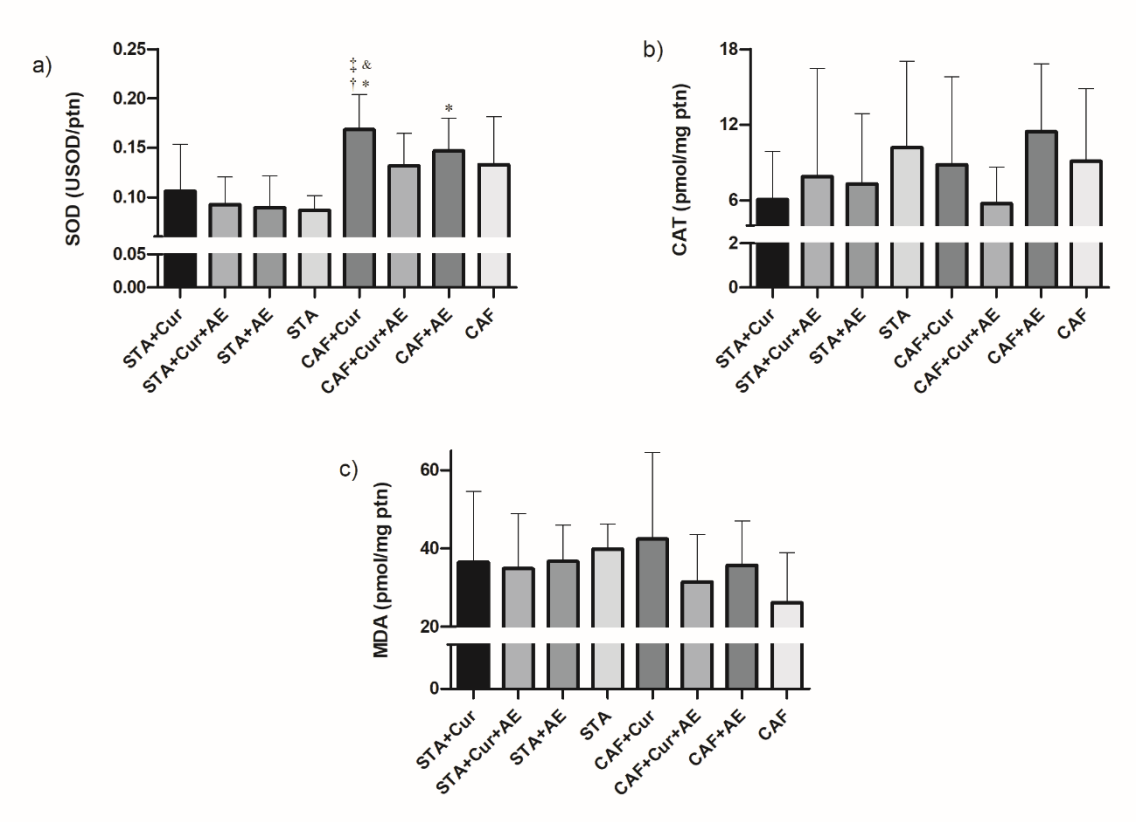
a)
SOD (USOD/ptn)
0.25
0.20
0.15
0.10
0.05
0.00
‡ &
† *
*
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF
b)
CAT (pmol/mg ptn)
18
12
6
2
0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF
c)
MDA (pmol/mg ptn)
60
40
20
0
STA+Cur
STA+Cur+AE
STA+AE
STA
CAF+Cur
CAF+Cur+AE
CAF+AE
CAF

Figure 6

Figures Legends

Figure 1. Anatomic and physiological variables of metabolic parameters
A) Body mass before. B) Body mass after. C) Glucose before. D) Glucose after. E) Body fat %**.** Data are presented as mean ± SD. Between groups differences verified by one-way ANOVA followed by Bonferroni's post hoc ($p<0.05$). † Denotes statistical difference compared to group STA+Cur ($p<0.05$). ‡ Denotes statistical difference compared to group STA+Cur+AE ($p<0.05$). & Denotes statistical difference compared to group STA+AE ($p<0.05$). * Denotes statistical difference compared to group STA ($p<0.05$).

Figure 2. Exercise tolerance test
A) Distance, duration and peed before. B) Distance after, duration and speed after. Data are presented as mean ± SD. Between groups differences verified by one-way ANOVA followed by Bonferroni's post hoc ($p<0.05$). † Denotes statistical difference compared to group STA+Cur ($p<0.05$). * Denotes statistical difference compared to group STA ($p<0.05$). ** Denotes statistical difference compared to group CAF+Cur ($p<0.05$). # Denotes statistical difference compared to group CAF ($p<0.05$)

Figure 3. Oxidative stress in liver
Concentrations of A) Superoxide dismutase (SOD) activity in liver. B) Catalase (CAT) in liver. C) Malondialdehyde (MDA) activity in liver. Data are presented as mean ± SD. Between groups differences verified by one-way ANOVA followed by Bonferroni's post hoc ($p<0.05$).

Figure 4. Oxidative stress in heart
Concentrations of A) Superoxide dismutase (SOD) activity in heart. B) Catalase (CAT) in heart. C) Malondialdehyde (MDA) activity in heart. Data are presented as mean ± SD. Between groups differences verified by one-way ANOVA followed by Bonferroni's post hoc ($p<0.05$).

Figure 5. Oxidative stress in fat
Concentrations of A) Superoxide dismutase (SOD) activity in fat. B) Catalase (CAT) in fat. C) Malondialdehyde (MDA) activity in fat. Data are presented as mean ± SD. Between groups differences verified by one-way ANOVA followed by Bonferroni's post hoc ($p<0.05$).

Figure 6. Oxidative stress in gastrocnemious
Concentrations of A) Superoxide dismutase (SOD) activity in gastrocnemius. B) Catalase (CAT) in gastrocnemius. C) Malondialdehyde (MDA) activity in gastrocnemius. Data are presented as mean ± SD. Between groups differences verified by one-way ANOVA followed by Bonferroni's post hoc ($p<0.05$). † Denotes statistical difference compared to group STA+Cur ($p<0.05$). ‡ Denotes statistical difference compared to group STA+Cur+AE ($p<0.05$). & Denotes statistical difference compared to group STA+AE ($p<0.05$). * Denotes statistical difference compared to group STA ($p<0.05$).

7. CONCLUSÃO

A realização do presente estudo demonstrou que o hábito alimentar baseado em alimentos de elevada densidade energética associado ao sedentarismo é capaz de promover obesidade e prejuízos à saúde. Tratamentos não farmacológicos podem ser uma alternativa para conter e auxiliar o ganho de massa corporal. Embora a realização do treinamento aeróbio e a suplementação de curcumina possam ter auxiliado no controle da glicemia de jejum, as intervenções não foram capazes de melhorar a condição de obesidade com o controle de ganho de massa corporal e de adiposidade abdominal quando houve conservação de uma dieta de cafeteria. Assim, é possível evidenciar claramente que a mudança para um padrão dietético saudável é fundamental na terapêutica da obesidade para que seja possível implicar melhores resultados e ganhos em saúde. Além disso, ressalta-se que estratégias multidisciplinares, tais como a combinação da nutrição e do exercício físico, podem gerar ainda mais ganhos no controle da obesidade.

ANEXOS

Anexo A

METABOLISM

Clinical and Experimental

AUTHOR INFORMATION PACK

TABLE OF CONTENTS

DESCRIPTION

Metabolism promotes excellence in research by publishing high-quality original research papers, fasttracking cutting-edge papers, research brief reports, mini-reviews, and other special articles related to all aspects of **human metabolism**. Work considered for publication in *Metabolism* includes studies in humans, animal and cellular models. Work with strong translational potential is prioritized. *Metabolism* will consider papers for publication in any aspect of translational and clinical metabolic research, including (but not limited to): **Energy Expenditure** and **Obesity Metabolic Syndrome** and **Diabetes Nutrition**, **Exercise**, and the **Environment Genetics**, **Proteomics**, and **Metabolomics Carbohydrate**, **Lipid**, and **Protein Metabolism Endocrinology** and **Hypertension Mineral** and **Bone Metabolism Cardiovascular Diseases** and **Malignancies**

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"AGREE" for Clinical practice guidelines
"STARD" for diagnostic accuracy studies
"CARE" for case reports
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tools (whether by the authors themselves or an independent vendor) will not be considered. The requirements and review process are the same as for original research articles.

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The requirements and review process are the same as for original research articles. Additional information (including references to disqualified papers and study summary tables) should be included as a supplementary appendix, to be published online.

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Reviews should be a maximum of 5000 words, excluding the title page, abstract, references, tables, and figure legends, but including the abbreviation list, acknowledgements, funding, disclosure statement, and author contributions. Subheadings in the text are recommended to highlight the content of different sections. An unstructured summary of no more than 200 words is required. Reviews should contain no more than 10 tables and figures combined and no more than 150 references. Reviews are generally commissioned by the Editors but unsolicited articles will be considered.

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Anexo B

UFCSPA

COMISSÃO CIENTÍFICA E COMISSÃO DE PESQUISA E ÉTICA EM SAÚDE

COMISSÃO DE ÉTICA NO USO DE ANIMAIS - CEUA
UFCSPA

A Comissão de Ética no uso de Animais, analisou o Projeto:

Projeto: 18-238 **Versão do Projeto:** **Versão do TCLE:**

Pesquisadores:
RAMIRO BARCOS NUNES
PEDRO DALL'AGO
CLÁUDIA RAMOS RHODEN
BRUNA MARMETT
MANOELA BOFF FAURI

Título: EFEITO DA SUPLEMENTAÇÃO DA CURCUMINA ASSOCIADA AO TREINAMENTO AO
TREINAMENTO AERÓBIO SOBRE PARÂMETROS METABÓLICOS, ESTRESSE OXIDATIVO E PERFIL INFLAMATÓRIO EM RATOS COM SÍNDROME METABÓLICA.

Este projeto foi aprovado em seus aspectos éticos e metodológicos. Todo e qualquer alteração do projeto, assim com eventos adversos graves, deverão ser comunicados a esta CEUA.

Porto Alegre, 01 de fevereiro de 2019.