UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL

FACULDADE DE MEDICINA

PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: ENDOCRINOLOGIA

TESE DE DOUTORADO

EFEITOS DA PERDA DE PESO ATRAVÉS DE RESTRIÇÃO ENERGÉTICA COM OU SEM TREINAMENTO FÍSICO SOBRE PARÂMETROS VASCULARES E METABÓLICOS DE INDIVÍDUOS COM OBESIDADE

ANA PAULA TRUSSARDI FAYH

PORTO ALEGRE

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Orientador: Dr Rogério Friedman

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RESUMO

INTRODUÇÃO: Evidências suportam uma importante contribuição da obesidade abdominal e da inflamação sobre a resistência à insulina (RI) e o risco cardiovascular. A redução da massa corporal a partir da modificação do estilo de vida pode diminuir a inflamação e a RI, mas estudos não esclarecem o efeito adicional do treinamento físico na melhora desses parâmetros.

OBJETIVO: Verificar o impacto da redução de 5% do peso inicial com ou sem treinamento físico sobre o tecido adiposo visceral (TAV), RI, perfil lipídico, função endotelial e inflamação em indivíduos obesos.

MÉTODOS: Neste ensaio clínico randomizado, 48 indivíduos obesos (idade 31,8 $\pm$ 6 anos, IMC 34,8 $\pm$ 2,7 kg/m^2) reduziram 5% da massa corporal inicial com dieta isolada (DI) ou acompanhada de treinamento físico (DI+EXE). Antes e após a redução do peso, foram dosados o colesterol total e frações, triglicerídeos, glicemia e insulina para o cálculo do HOMA-IR e proteína C-reativa ultrassensível (PCR-us) no sangue. A função endotelial foi avaliada pela técnica de dilatação mediada pelo fluxo (DMF), com determinação ecográfica do diâmetro arterial e o TAV foi quantificado pela tomografia computadorizada de abdômen. O treinamento físico consistiu de três sessões semanais de cicloergometria durante 45 minutos a 70% da frequência cardíaca de reserva.

RESULTADOS: Treze indivíduos desistiram de participar do estudo antes de atingir redução ponderal. Nos grupos DI (n=18) e DI+EXE (n=17), colesterol total (-15,8 $\pm$ 4,8 mg/dL e -10,5 $\pm$ 4,9 mg/dL, respectivamente), triglicerídeos (-33,8 $\pm$ 10 mg/dL e -39,4 $\pm$ 10,3 mg/dL, respectivamente), PCR-us (-1,4 $\pm$ 0,4 mg/L e -0,5 $\pm$ 0,4 mg/L, respectivamente), HOMA-IR (-1,38 $\pm$ 0,37 e -0,95 $\pm$ 0,14mg/dL respectivamente) e TAV (-23,6 $\pm$ 19,4 cm^2 e -35,4 $\pm$ 35 cm^2 respectivamente) diminuiu significativamente e de forma similar (*general linear model*).

CONCLUSÃO: A perda de 5% da massa corporal reduziu a resistência à insulina, o TAV e a inflamação, além de melhorar alguns parâmetros do perfil lipídico nos indivíduos obesos. A função endotelial não foi alterada, e as alterações nos parâmetros foram independentes do treinamento físico.

Palavras-chave: dieta, exercício, inflamação, gordura abdominal, risco cardiovascular

Esta Tese de Doutorado segue o formato proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia da UFRGS, sendo apresentada na forma de três manuscritos sobre o tema da Tese, sendo:

* Um (1) artigo de revisão geral do tema a ser submetido para publicação em periódico científico nacional (*Arquivos Brasileiros de Cardiologia*).

* Dois (2) artigos originais referentes ao trabalho de pesquisa propriamente dito a ser submetido para publicação em periódico científico de circulação internacional (*American Journal of Clinical Nutrition* e *Metabolism*).

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LISTA DE ABREVIATURAS

BMI: *Body Mass Index*

DAC: Doença Arterial Coronariana

DI: Orientação dietética para redução ponderal

DI+EXE: Orientação dietética para redução ponderal acompanhada de treinamento físico

DMF: Dilatação mediada pelo fluxo

EID – TNG: *Endothelium independent dilation after administration of sublingual nitroglycerin*

FMD: *Flow mediated dilation*

FvW: Fator von Willebrand

HDL-C: lipoproteína de alta densidade (HDL-colesterol)

HOMA: *Homeostasis Model Assessment* index

HC: *Hip circumference*

hs-CRP: *High sensitivity C-reactive protein*

IL-6: Interleucina 6

IMC: Índice de Massa Corporal

IR: *Insulin resistance*

LDL-C: Lipoproteína de baixa densidade (LDL-colesterol)

NO: Óxido nítrico

PAI-I: Inibidor do ativador do plasminogênio I

PCR-us: Proteína C-reativa ultra-sensível

RCQ: Razão cintura-quadril

RI: Resistência à insulina

SAT: *Subcutaneous abdominal tissue*

TAT: *Total abdominal tissue*

TASB: Tecido adiposo subcutâneo

TAV: Tecido adiposo visceral

TAT: *Total abdominal tissue*

TCA: Tomografia computadorizada de abdômen

TNF- α: Fator de Necrose Tumoral – α

VAT: *Visceral abdomina tissue*

vWf – *von Willebrand factor*

WC – w*aist circumference*

WHR – *waist-to-hip ratio*

ARTIGO 1

RESISTÊNCIA À INSULINA E DISFUNÇÃO ENDOTELIAL EM OBESOS: IMPACTO DA DIETA E DO TREINAMENTO FÍSICO

A ser submetido ao periódico *Arquivos Brasileiros de Cardiologia*
Seção "Atualização Clínica"

Resistência à insulina e disfunção endotelial na obesidade: impacto da dieta e do treinamento físico

Insulin Resistance and Endothelial Dysfunction in Obesity: Impact of Diet and Physical Training

Resistência à Insulina, Endotélio e Obesidade

Descritores: perda de peso, aterosclerose, inflamação, tratamento, exercício
Key words: weight loss, atherosclerosis, inflammation, treatment, exercise

RESUMO

A obesidade situa-se entre os maiores fatores de risco de doença arterial coronária, ao lado de dislipidemia, hipertensão, tabagismo e diabetes. O objetivo deste estudo é revisar o papel da resistência à insulina sobre a função endotelial, e o impacto da redução da massa corporal, por meio da modificação do estilo de vida, sobre o risco cardiovascular. Evidências recentes destacam a importância da gordura abdominal como o principal fator desencadeante de anormalidades metabólicas e suas complicações. A produção excessiva de adipocinas pode induzir resistência à insulina e complicações vasculares associadas à obesidade. De uma forma geral, a função endotelial apresenta melhora significativa em indivíduos obesos após redução ponderal. Independente do método utilizado para a perda de peso, os pacientes apresentam melhora na dilatação mediada pelo fluxo e na resistência à insulina. O treinamento físico pode reduzir a obesidade abdominal, principal responsável pela resistência à insulina e disfunção endotelial, mas os resultados ainda são inconsistentes. Com isso, novos estudos são recomendados para melhor compreensão sobre os mecanismos envolvidos na relação entre exercício e endotélio vascular; de qual seria a intensidade e o volume ideais de exercício, entre outras questões.

Introdução

A obesidade situa-se entre os maiores fatores de risco de doença arterial coronariana (DAC), ao lado de dislipidemia, hipertensão, tabagismo e diabetes, e a sua prevalência vem crescendo progressivamente [1]. Esta situação tem sido atribuída à mudança nos hábitos alimentares – com aumento do consumo energético, principalmente à custa de gordura e açúcar – e à redução considerável no gasto energético diário relacionado à atividade física [2]. O diagnóstico clínico de obesidade se faz por pontos de corte do Índice de Massa Corporal (IMC, em kg/m^2) [3-4]. Um indivíduo é considerado obeso quando o seu índice de massa atinge ou supera os 30 kg/m^2.

Nos indivíduos obesos, observa-se resistência à insulina (RI), hiperinsulinemia, alterações na atuação de enzimas hepáticas e no metabolismo lipídico [5]. Estas alterações metabólicas são ainda mais notáveis quando a obesidade é predominantemente abdominal. O mecanismo pelo qual a distribuição central da adiposidade causa RI vem sendo extensamente pesquisado. A hiperinsulinemia é considerada um fator de risco independente para a doença cardiovascular, já que tem um papel importante no desenvolvimento de outros fatores associados a risco cardiovascular, como a dislipidemia, a hipertensão e a hiperuricemia [6-7]. Alterações na função endotelial são demonstráveis precocemente, antes da detecção de placa aterosclerótica ou de manifestações clínicas de aterosclerose. A disfunção endotelial está associada à maioria dos fatores de risco cardiovascular clássicos, que, por sua vez, se associam com RI. Por esta razão, poderia representar o primeiro indicador de dano vascular [8]. As relações entre RI e função endotelial ainda não estão totalmente conhecidas.

O objetivo deste estudo foi revisar o papel da RI sobre a função endotelial, e o impacto da perda de peso sobre a redução do risco cardiovascular. Adicionalmente, objetivou-se discutir os efeitos independentes do exercício sobre o risco cardiovascular durante o processo de redução ponderal com dieta.

O papel da resistência à insulina na disfunção endotelial

Evidências epidemiológicas provenientes de estudos de coorte prospectivos observacionais apontam que a obesidade constitui importante fator de risco

cardiovascular [9-12]. No entanto, alguns indivíduos com obesidade não desenvolvem anormalidades metabólicas ou eventos cardiovasculares. Dessa forma, a obesidade não pode ser considerada uma condição homogênea [13]. Sugere-se que a distribuição da gordura corporal seja determinante sobre o desenvolvimento de doenças cardiometabólicas relacionadas à obesidade, e o excesso de gordura na região abdominal tem sido apontado como um dos motivos desencadeadores dessas doenças [14]. Com isso, a inclusão de outras medidas antropométricas, como a circunferência abdominal e relação cintura-quadril, pode ajudar na determinação de risco cardiovascular em pacientes com obesidade [15], uma vez que o IMC pode não ser o parâmetro mais adequado na prática clínica por não diferenciar a massa corporal magra da massa de gordura. Desta forma, homens e mulheres que apresentem circunferência abdominal superior a 102 cm e 88 cm, respectivamente, são considerados de alto risco para o desenvolvimento de doenças metabólicas [3].

Nesta última década, evidenciou-se a importância da gordura abdominal como um dos maiores fatores de risco para as doenças metabólicas e suas complicações [16]. Neste sentido, a identificação da distribuição e diferenciação desta gordura, especialmente o tecido adiposo visceral (TAV) e o tecido adiposo subcutâneo (TASB), é de suma importância para a descrição de um conjunto de anormalidades metabólicas diabetogênicas, aterogênicas, pró-trombóticas e inflamatórias, atualmente reconhecida como a síndrome metabólica [15]. Ainda, está bem estabelecida a relação entre o excesso de TAV e a RI, elevação da pressão arterial, diminuição da concentração do HDL colesterol (HDL-C) e a elevação das triglicérides [15].

Antigamente considerado apenas um local de armazenamento de gordura, o tecido adiposo atualmente é reconhecido como um órgão endócrino, com participação ativa na homeostase energética e outras funções fisiológicas. O tecido adiposo secreta uma variedade de novas adipocinas que têm sido implicadas no desenvolvimento da RI e aterosclerose [17]. Dentre estas adipocinas, pode-se citar a leptina, a resistina e a adiponectina, sendo que esta última pode ser a ligação entre obesidade e RI [18]. Outras adipocinas afetam especialmente o sistema cardiovascular, como o inibidor do ativador de plasminogênio-I (PAI-I) e o angiotensinogênio. Atribui-se ao PAI-I o papel de principal inibidor fisiológico da fibrinólise e envolvimento nos eventos tromboembólicos, enquanto o angiotensinogênio está envolvido no aumento da pressão arterial [19].

Apesar dos estudos apontarem a importância de diferenciar o tipo de gordura na região abdominal, esta diferenciação é possível apenas com sofisticadas técnicas de imagem, como a tomografia computadorizada ou a ressonância magnética. Estudos que utilizaram estas técnicas reúnem evidências que o TAV é um preditor independente de infarto do miocárdio e da RI em adultos e idosos [20-22]. Por serem métodos onerosos e pouco aplicáveis na prática clínica, a circunferência abdominal tem sido amplamente utilizada como marcador de gordura abdominal (TAV e TASB), e correlaciona-se com o aumento no risco de doenças cardiovasculares [14].

A obesidade abdominal leva à progressão de vários fatores de risco cardiometabólicos independentes do IMC, através da secreção alterada de adipocinas e exacerbação da RI [23]. Alguns desses produtos derivados do tecido adiposo, tais como ácidos graxos livres, fator de necrose tumoral-α (TNF- α) e interleucina 6 (IL-6) também podem afetar função vascular, além de induzir RI [24]. Esses produtos são um forte estímulo para a produção de proteína C-reativa ultra-sensível (PCR-us) no fígado, um biomarcador plasmático para inflamação de baixo grau que pode ser responsável pro algumas comorbidades associadas à obesidade. Devido ao fato de os produtos derivados do tecido adiposo serem medidos através de técnicas sofisticadas e onerosas, a dosagem de PCR-us no sangue é uma técnica acessível de representar a magnitude da inflamação como preditor de risco para DAC [25]. Com isso, a investigação da disfunção endotelial e da RI no paciente obeso é fundamental na prevenção do diabetes tipo 2 e das doenças cardiovasculares.

O aperfeiçoamento das imagens arteriais bidimensionais, obtidas por ultrassonografia de alta resolução aliada ao sistema Doppler, permite, de forma acurada, a análise estrutural e funcional do vaso, com melhor entendimento das alterações hemodinâmicas [26]. Evidências crescentes sugerem que a integridade do endotélio vascular é fundamental na prevenção da aterosclerose, provavelmente através da liberação de fatores derivados do endotélio, que conferem propriedades antiproliferativa, antiinflamatória e antitrombóticas, além de vasodilatação [27-28]. A função endotelial anormal, representada pela redução da dilatação mediada pelo fluxo (DMF) é um marcador precoce de doença cardiovascular e um fator de prognóstico para futuros eventos cardiovasculares [29-30].

Além das técnicas de imagem, parâmetros bioquímicos podem auxiliar no diagnóstico da disfunção endotelial. Marcadores inflamatórios como a contagem total

de leucócitos, fibrinogênio, PCR-us e moléculas de adesão são atualmente reconhecidos por serem marcadores de risco cardiovascular na população em geral [31-33]. O Fator von Willebrand (FvW) é um polímero sintetizado nas células endoteliais e nos megacariócitos que têm sido utilizado para verificar a função endotelial com excelente sensibilidade. Este polímero liga-se ao colágeno e a outros componentes da parede vascular e, portanto, serve de mediador da adesão das plaquetas ao subendotélio dos vasos lesados. Em casos de disfunção endotelial, a secreção do FvW pode aumentar de duas a 10 vezes [8], e este aumento das concentrações séricas está associado com uma série de condições patológicas, como o diabetes mellitus, hepatopatias, infarto agudo do miocárdio, neoplasias malignas e outras condições que cursam com o aumento da proliferação endotelial e dano vascular [34].

Estudos têm demonstrado que a inflamação participa de todas as etapas da evolução da aterosclerose [35]. Dentre os marcadores inflamatórios envolvidos, a PCR-us tem sido a mais utilizada [36], pois os métodos utilizados para a dosagem de outros marcadores como as citocinas são, em geral, inadequados para o uso clínico rotineiro, além do fato dessas proteínas possuírem uma meia-vida muito curta. Adicionalmente, a PCR-us é um marcador estável, com uma meia-vida longa (18 a 20 horas) e cuja dosagem pode ser feita tanto em plasma congelado quanto fresco, sem a exigência de cuidados especiais para coleta [37-38]. Ridker [39] sugere que a mensuração da PCR-us, junto com o perfil lipídico, pode contribuir no aprimoramento do método para a avaliação do risco cardiovascular em indivíduos adultos.

Impacto da perda de peso na redução do risco cardiovascular

De uma forma geral, a função endotelial apresenta melhora significativa em indivíduos obesos após a redução ponderal [40]. No entanto, os resultados acerca da associação entre as mudanças na função endotelial com os parâmetros bioquímicos e antropométricos ainda são controversos. Alguns estudos apontam uma melhora na função endotelial após a redução da massa corporal [28, 40-42], já outros não encontraram associação entre as mudanças na função endotelial com a perda de peso [43-44]. Além da função endotelial, a redução da massa corporal através da restrição calórica pode diminuir marcadores inflamatórios sistêmicos [45] e melhorar a

RI [46]. Em pacientes com excesso de peso, uma redução de 7% do peso inicial reduziu componentes da síndrome metabólica, como a pressão arterial sistólica e níveis plasmáticos de glicose, triglicerídeos e HDL-C [47]. Estes benefícios estão relacionados com a redução dos níveis de adipocinas no plasma, como a adiponectina, resultado da redução da gordura corporal [48].

Considera-se sucesso no tratamento da obesidade a habilidade de atingir e manter uma perda de peso, que resulte em efeitos benéficos sobre doenças associadas, como diabetes tipo 2, hipertensão e dislipidemia [1,14]. A orientação de uma perda de peso pequena e sustentada, através de uma dieta planejada individualmente para criar um déficit de 500 a 1.000 kcal, deveria ser parte integrante de qualquer programa de perda de peso que objetive diminuição de 0,5 a 1 kg por semana [48]. Qualquer dieta prescrita para reduzir peso deve considerar, além da quantidade de calorias, as preferências alimentares do paciente, o aspecto financeiro, o estilo de vida e o requerimento energético para a manutenção da saúde.

A redução da massa corporal é um fator importante para a redução do risco cardiovascular, e parece que o tempo é indiferente para promover este benefício. Mavri e colaboradores [40] encontraram melhora significativa da função endotelial, resistência à insulina e perfil lipídico de um pequeno grupo de obesos após uma semana de restrição alimentar (1200kcal/dia) e redução de 5% na massa corporal. Estes mesmos indivíduos foram acompanhados por mais cinco meses, período no qual reduziram mail 8% da sua massa corporal e aumentaram sua DMF. No entanto, nenhum efeito significativo adicional foi observado nos parâmetros de perfil lipídico e RI após a primeira semana. Com uma população semelhante, Sasaki e colaboradores [49] observaram uma melhora na vasodilatação estimulada pela acetilcolina após duas semanas de dieta hipocalórica. Com isso, pode-se hipotetizar que uma modesta perda de peso melhora a função endotelial em indivíduos obesos, e esta alteração pode reduzir o risco cardiovascular.

A diminuição da ingestão calórica diária de 500 kcal ocasiona uma redução do peso corporal inicial entre 5 a 10%, e uma diminuição do IMC entre 2 a 2,9 kg/m^2 [50-52]. Outros estudos apontam que, para uma melhora significativa do perfil lipídico e parâmetros inflamatórios, seria necessária uma restrição energética de até 1.000 kcal por dia, com redução peso inicial entre 7 a 12% [47,53]. Avaliando o impacto da de duas diferentes intervenções sobre a DMF em um pequeno grupo de obesos,

Gokce e colaboradores [54] observaram que a cirurgia bariátrica foi mais efetiva do que a modificação do estilo de vida, provavelmente pela maior perda de peso apresentada pelo grupo que realizou a cirurgia. Em mulheres obesas, a redução da massa corporal através do aconselhamento nutricional de longo prazo (um ano) reduziu citocinas inflamatórias em níveis observados no grupo de mulheres não obesas [28]. Também foi observado que a redução de adiponectina em indivíduos obesos e com RI pode ser parcialmente revertida por meio da redução de peso [53,55].

Com parâmetros bioquímicos frequentemente utilizados na prática clínica, Bobbert e colaboradores [18] realizaram um estudo com obesos, que participaram de um programa de redução de peso durante seis meses, através de uma dieta hipocalórica. Após o período de seis meses, os indivíduos apresentaram redução média de 6% na massa corporal, alteração benéfica na composição corporal analisada através da bioimpedância, e um pequeno, mas significativo aumento, nos níveis de HDL-C. No entanto, não foram observadas alterações significativas nos parâmetros de colesterol total e LDL colesterol (LDL-C), triglicerídeos, glicemia e proteína C-reativa após a perda de peso. Os autores sugerem que a redução na massa corporal foi pequena para produzir alterações benéficas nesses parâmetros.

Uma dieta nutricionalmente balanceada, que promova um déficit energético, igualmente melhora a função endotelial de indivíduos não obesos [56]. Também já é conhecido que uma dieta do tipo Mediterrânea, rica em gorduras monoinsaturadas e antioxidantes, pode melhorar a função endotelial independente da alteração da massa corporal ou da adição de exercícios físicos [57-58]. Outro estudo apontou prejuízo na função endotelial e aumento em parâmetros de estresse oxidativo com uma infusão aguda de lipídeos na circulação em voluntários saudáveis [59]. Em indivíduos com síndrome metabólica, intervenções para modificações do estilo de vida em longo prazo (um ano) [60] e curto prazo (16 semanas) [61] foram eficazes na redução de leptina plasmática mesmo sem a redução esperada na massa de gordura corporal.

Apesar de não haver controvérsia sobre o fato de que balanço energético negativo causado por redução na ingestão calórica e a prática de exercícios físicos resulte em diminuição da massa corporal, há muita divergência sobre a melhor maneira de colocar em prática essas estratégias. Sabe-se que o tratamento dietético é mais bem-sucedido quando aliado a aumento no gasto energético e a um pro-

grama de modificação comportamental [41-43]. Uma recente revisão sistemática com a inclusão de quatro estudos de coorte, verificou que é possível prevenir o diabetes tipo 2 com a modificação do estilo de vida [62]. Este mesmo estudo aponta as limitações das dietas para a perda de peso sobre a adequação de nutrientes específicos e ressalta a importância de aliar treinamento físico com dispêndio energético semanal de, no mínimo 2000 kcal, para a manutenção da perda de peso. Já em uma recente metanálise, que identificou 17 ensaios clínicos randomizados relevantes em 8084 indivíduos com intolerância à glicose, foi verificado que o número necessário para tratar, no intuito de prevenir um caso de diabetes pela modificação do estilo de vida, foi 6,4 (IC95% 5,0-8,4) [63].

Efeitos do exercício físico no processo de redução ponderal e redução do risco cardiovascular

Sendo a obesidade um fator de risco para DAC, estratégias de redução de peso devem ser implementadas, com orientações para modificação do estilo de vida e, se necessário, o uso de fármacos deve ser avaliado [4]. Estas estratégias podem promover a perda de peso de duas formas, basicamente: uma diminuição concomitante da gordura corporal e da massa muscular ou uma redução da gordura corporal com manutenção da massa magra. O principal fator que determina esta diferença na composição corporal com o emagrecimento induzido pela restrição calórica ou fármacos é o exercício físico [40-42]. No entanto, durante um programa de redução de peso, nem sempre é possível distinguir os efeitos isolados da dieta ou do exercício, uma vez que o paciente deve ser orientado a mudar estilo de vida, aumentando as atividades físicas diárias.

Exercícios moderados são conhecidos como estimuladores da liberação de óxido nítrico (NO), um dos fatores relaxantes derivados do endotélio de maior importância, diretamente relacionado à integridade da função endotelial [64-65]. Resultados de estudos têm demonstrado que o treinamento físico provoca melhora expressiva na perfusão miocárdica [66]. Entre os componentes envolvidos nessa melhora da circulação coronariana podem-se citar: a função endotelial [67]; a velocidade de produção e oxidação do NO [66]; a regressão de lesões aterosclerótica e a neoformação de vasos colaterais [68-69]; além da redução da viscosidade sanguínea e do aumento do tempo de perfusão diastólica [69]. Embora esteja definido que o exercício físico produza esses benefícios em indivíduos com DAC, os

processos pelos quais as melhoras se estabelecem ainda não foram totalmente esclarecidos. Estudos sugerem que o mecanismo pelo qual o exercício físico faz reduzir a progressão da aterosclerose e o risco de eventos recorrentes está relacionado à melhora no tônus vascular e da função endotelial [70].

A relação entre exercício físico e prevenção da DAC vem sendo amplamente discutida [71-72]. Em indivíduos obesos, o treinamento pode reduzir a obesidade abdominal, principal responsável pela RI e disfunção endotelial [60,69], mas os resultados ainda são inconsistentes. Sujeitos com síndrome metabólica e previamente treinados têm concentrações significativamente mais baixas de PCR-us em comparação com aqueles com baixo nível de condicionamento [73], e este efeito deve-se, provavelmente, ao efeito anti-inflamatório do exercício. No entanto, outro estudo mostrou que o treinamento físico não alterou significativamente a PCR-us em indivíduos não diabéticos em com RI [74]. Oberbach e colaboradores [75] também não encontraram redução significativa das concentrações de glicemia e insulina em 20 indivíduos sem intolerância à glicose após quatro semanas de treinamento aeróbico. No entanto, estes autores verificaram alterações benéficas no perfil lipídico destes indivíduos, com redução dos níveis de LDL-C e PCR-us, e manutenção dos níveis de HDL-C.

A melhora nos parâmetros de gordura abdominal e RI com a realização de exercícios são independentes da melhora na aptidão física. Kim e colaboradores [25], em um estudo transversal, avaliaram 160 indivíduos adultos com IMC de 25 kg/m^2. Destes, metade relatou praticar exercícios de forma regular nos últimos seis meses. Os autores não encontraram diferenças significativas na composição corporal e aptidão física entre os indivíduos que realizavam ou não exercícios regularmente. No entanto, avaliando a adiposidade abdominal através da tomografia computadorizada, os indivíduos que praticavam exercícios físicos tinham menores valores TAV e TASB quando comparados aos indivíduos que não se exercitavam e, consequentemente, menores valores de gordura abdominal total. Mesmo com níveis glicêmicos em jejum sem diferença significativa entre os grupos, os autores também verificaram que o grupo que se exercitava tinha menores valores de insulina plasmática e hemoglobina glicada.

Fisher e colaboradores [76] avaliaram os efeitos independentes da perda de peso e do treinamento físico sobre o TAV e parâmetros inflamatórios em 126 indivíduos com excesso de peso. A amostra foi randomizada em três grupos (dieta

apenas, dieta mais exercício aeróbico e dieta mais treino de força), e as avaliações ocorreram no momento basal e após os indivíduos atingirem a meta de redução de peso (IMC< 25 kg/m^2). Com a perda de peso, os indivíduos reduziram o TAV e parâmetros inflamatórios, mas o treinamento físico não proporcionou efeitos adicionais nesta redução. Estes achados demonstram a necessidade de investigar os efeitos adicionais do treinamento físico sobre a redução do risco cardiovascular durante o processo de perda de peso.

A avaliação dos estudos que comparam os efeitos da redução ponderal através da dieta isolada ou associada com exercício é difícil pelas suas diferenças metodológicas. Fatores como tipo de exercício, duração e intensidade, são de difícil padronização, e podem afetar as respostas metabólicas e hormonais. Ainda, é igualmente difícil avaliar a adesão ao tratamento dietético, e com isso questiona-se se o sucesso da perda de peso ocorre pela restrição calórica ou pelo aumento do gasto energético do treinamento. Não se observa uma nítida diferença do TAV e da composição corporal com o treinamento físico, quando comparado à restrição alimentar [77], e resta a dúvida se a melhora da RI com o exercício de curta duração se dá pelo efeito da perda de peso em si.

O treinamento físico, de forma ideal, deve incluir todas as aptidões físicas individuais. Tanto o treinamento aeróbico quanto o treinamento de força são importantes na redução do risco cardiometabólico, especialmente em indivíduos obesos [65]. O treino de força aumenta a massa magra e eleva a taxa metabólica basal, o que pode acelerar o processo de perda de peso, enquanto o treino aeróbico possui impacto positivo sobre o perfil bioquímico, como os lipídeos plasmáticos e a RI [62].

O que parece incerto, ainda, são os efeitos de diferentes intensidades de exercício na função endotelial [70]. Em pacientes com DAC estabilizada, a vasorreatividade mostrou-se aumentada em níveis elevados de exercício [78]; entretanto, diminuiu significativamente no limiar aeróbico. Outros estudos também concluem que níveis moderados de exercício (próximo ao limiar anaeróbico) podem ser considerados terapêuticos e preventivos para pacientes coronarianos [79]. Em nosso laboratório, Schaun e colaboradores [80] demonstraram que o treinamento aeróbico de baixa intensidade (50% do $VO_{2máx}$) é suficiente para induzir melhoras na DMF, porém não afeta significativamente a capacidade antioxidante e a função imune. Independentemente disso, novos estudos são recomendados para melhor

entendimento dos mecanismos envolvidos na relação entre exercício e endotélio vascular.

Perspectivas

Mudanças no estilo de vida que levam à perda de peso são capazes de promover melhorias significativas na RI e disfunção endotelial em indivíduos com obesidade. No entanto, os estudos acerca do papel da perda de peso sobre a RI e a função endotelial, em humanos, possuem como limitação um baixo período de seguimento. Ainda, as diferentes intervenções dietéticas e intensidades do treinamento físico dificultam a comparação das respostas metabólicas. Desta forma, a comunidade científica deve unir esforços para reforçar a importância de financiamento de estudos clínicos sobre esta temática. Com isso, poderemos entender melhor a patogênese da RI e disfunção endotelial na obesidade, e esclarecer os efeitos da modificação do estilo de vida sobre estas variáveis. As intervenções para a promoção da perda de peso devem estar incluídas nas políticas de saúde pública para o combate desta epidemia global, e a necessidade de aliar o treinamento físico à restrição energética deve ser avaliada para maximizar o benefício cardiovascular.

REFERÊNCIAS

1. Padwal RS, Sharma AM. Prevention of cardiovascular disease: obesity, diabetes and the metabolic syndrome. Can J Cardiol 2010; 26(Suppl C):18C-20C.

2. Hill JO, Peters JC. Environmental contributions to the obesity epidemic. Science 1998; 280(5368):1371-74.

3. World Health Organization. Obesity: preventing and managing the global epidemic. Report of a WHO Consultation on Obesity. Geneva: World Health Organization, 1998.

4. National Institutes of Health, National Heart, Lung, and Blood Institute. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults—The Evidence Report. Obes Res 1998; 6(suppl):51S–209S.

5. Després JP, Lemieux I, Tchernof A, Coullard C, Pascot A, Lemieux S. Distribution et métabolisme des masses grasses. Diabetes Metab 2001; 27(2):209-14.

6. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, et al. Insulin resistance in essential hypertension. N Engl J Med 1987; 317(6):350-7.

7. Sheehan MT, Michael DJ. Metabolic complications of obesity. Med Clin North Am 2000; 84(2):363-85.

8. Butt M, Dwivedi G, Blann A, Khair O, Lip G. Endothelial dysfunction: methods of assessment and implications for cardiovascular diseases. Curr Pharm Des 2010; 16(31):3442-54.

9. Hubert HB, Feinleib M, McNamara PM, Castelli WP. Obesity as an independent risk factor for cardiovascular disease: a 26-year follow-up of participants in the Framingham Heart Study. Circulation. 1983; 67(5):968-77.

10. Manson JE, Colditz GA, Stampfer MJ, Willett WC, Rosner B, Monson RR, et al. A prospective study of obesity and risk of coronary heart disease in women. N Engl J Med 1990; 322(13):882-9.

11. Rimm EB, Stampfer MJ, Giovannucci E, Ascherio A, Spiegelman D, Colditz GA, et al. Body size and fat distribution as predictors of coronary heart disease among middle-aged and older US men. Am J Epidemiol 1995; 141(12):1117-27.

12. Dorn JM, Schisterman EF, Winkelstein W, Jr., Trevisan M. Body mass index and mortality in a general population sample of men and women. The Buffalo Health Study. Am J Epidemiol 1997; 146(11):919-31.

13. Lemieux I, Poirier P, Bergeron J, Alméras N, Lamarche B, Cantin B et al. Hypertriglyceridemic waist: A useful screening phenotype in preventive cardiology? Can J Cardiol 2007; 23(Suppl B):23B-31B.

14. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, et al. Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Diabetes Care 2007; 30(6):1647-52.

15. Kashihara H, Lee JS, Kawakubo K, Tamura M, Akabayashi A. Criteria of Waist Circumference According to Computed Tomography-Measured Visceral Fat Area and the Clustering of Cardiovascular Risk Factors. Circ J 2009; 73(10):1881 –86.

16. Hauner H. The new concept of adipose tissue function. Physiol Behav 2004; 83(4):653-8.

17. Funahashi T, Nakamura T, Shimomura I, Maeda K, Kuriyama H, Takahashi M et al. Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med 1999; 38(2):202–6.

18. Bobbert T, Rochlitz H, Wegewitz U, Akpulat S, Mai K, Weickert Mo et al. Changes of Adiponectin Oligomer Composition by Moderate Weight Reduction. Diabetes 2005; 54(9):2712–19.

19. Guimarães DED, Sardinha FLC, Mizurini DM, Carmo MGT.Adipocitocinas: uma nova visão do tecido adiposo. Rev Nutr 2007; 20(5):549-59.

20. Ross R, Aru J, Freeman J, Hudson R, Janssen I. Abdominal adiposity and insulin resistance in obese men. Am J Physiol Endocrinol Metab 2002; 282(3):E657-63.

21. Kuk JL, Katzmarzyk PT, Nichaman MZ, Church TS, Blair SN, Ross Rl. Visceral fat is an independent predictor of all-cause mortality in men. Obes 2006; 14(2):336-41.

22. Nicklas BJ, Penninx BW, Cesari M, Kritchevsky SB, Newman AB, Kanaya AB et al. Association of visceral adipose tissue with incident myocardial infarction in older men and women: The Health, Aging and Body Composition Study. Am J Epidemiol 2004; 160(8):741-9.

23. Despres JP. Abdominal obesity: the most prevalent cause of the metabolic syndrome and related cardiometabolic risk. Eur Heart J Suppl 2006; 8(Supplement B):B4-B12.

24. Yudkin SJ, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999; 19(4):972-8.

25. Kim K, Valentine RJ, Shin Y, Gong K. Associations of visceral adiposity and exercise participation with C-reactive protein, insulin resistance, and endothelial dysfunction in Korean healthy adults. Metabolism 2008; 57(9)1181–89.

26. Corretti, MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the Ultrasound Assessment of Endothelial-Dependent Flow-

Mediated Vasodilation of the Brachial Artery A Report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002; 39(2):257–65.

27. de Jongh S, Lilien MR, Bakker HD, Hutten BA, Kastelein JJ, Stroes ES. Family history of cardiovascular events and endothelial dysfunction in children with familial hypercholesterolemia. Atherosclerosis 2002; 163(1):193–97.

28. Ziccardi P, Nappo F, Giugliano G, Esposito K, Marfella R, Cioffi M, et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. Circulation 2002; 105(7):804–09.

29. Patti G, Pasceri V, Melfi R, Goffredo C, Chello M, D'Ambrosio A, et al. Impaired flow-mediated dilation and risk of restenosis in patients undergoing coronary stent implantation. Circulation 2005; 111(1):70–5.

30. Yoshida T, Kawano H, Miyamoto S, Motoyama T, Fukushima H, Hirai N et al. Prognostic value of flow-mediated dilation of the brachial artery in patients with cardiovascular disease. Intern Med 2006; 45(9):575–79.

31. Grimm RH, Neaton JD, Ludwig W. Prognostic importance of the white blood cell count for coronary, cancer, and all-cause mortality. JAMA 1985; 254(14):1932-7.

32. Danesh J, Collins R, Appleby P, Peto R. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998; 279(18):1477-82.

33. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR. Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. N Engl J Med 2002; 347(20):1557-65.

34. Schwartsmann G, Damin DC & Roisemberg I. Malignant disease and von Willebrand factor. The Lancet Oncol 2001; 2(12):716-7.

35. Libby P, Ridker P, Maseri A. Inflammation and atherosclerosis. Circulation 2002; 105:1135-43.

36. Ridker PM. C-reactive protein, inflammation and cardiovascular disease - Clinical Update. Tex Heart Inst J 2005; 32(3):384-6.

37. Macy EM, Hayes TE, Tracy RP. Variability in the measurement of C-reactive protein in healthy subjects: implications for reference interval and epidemiological applications. Clin Chem1997; 43(1):52-8.

38. Roberts WL, Moulton L, Law TC, Farrow G, Cooper-Anderson M, Savory J, et al. Evaluation of nine automated high sensitivity C-reactive protein methods: implication for clinical and epidemiological applications. Part 2. Clin Chem 2001; 47(3):418-25.

39. Ridker PM, Danielson E, Fonseca FA, Genest J, Gotto AM Jr, Kastelein JJ, et al. Reduction in C-reactive protein and LDL cholesterol and cardiovascular event rates after initiation of rosuvastatin: a prospective study of the JUPITER trial. Lancet 2009; 373(9670):1175-82.

40. Mavri A, Poredos P, Suran D, Gaborit B, Juhan-Vague I, Poredos P. Effect of diet-induced weight loss on endothelial dysfunction: early improvement after the first week of dieting. Heart Vessels 2011; 26(1):31–38.

41. Sciacqua A, Candigliota M, Ceravolo R, Scozzafava A, Sinopoli F, Corsonello A, et al. Weight loss in combination with physical activity improves endothelial dysfunction in human obesity. Diabetes Care 2003; 26(6):1673–78.

42. Hamdy O, Ledbury S, Mullooly C, Jarema C, Porter S, Ovalle K, et al. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. Diabetes Care 2003; 26(7):2119–2125.

43. Brook RD, Bard RL, Glazewski L, Kehrer C, Bodary PF, Eitzman DL, et al . Effect of short-term weight loss on the metabolic syndrome and conduit vascular endothelial function in overweight adults. Am J Cardiol 2004; 93(8):1012–16.

44. Raitakari M, Ilvonen T, Ahotupa M, Lehtimaki T, Harmoinen A, Suominen P, et al. Weight reduction with very-low-caloric diet and endothelial function in overweight adults: role of plasma glucose. Arterioscler Thromb Vasc Biol 2004; 24(1):124–8

45. Bougoulia M, Triantos A, Koliakos G. Plasma interleukin-6 levels, glutathione peroxidase and isoprostane in obese women before and after weight loss. Association with cardiovascular risk factors. Hormones 2006; 5(3):192-9.

46. Weinstock RS, Dai H, Wadden TA. Diet and exercise in the treatment of obesity: effects of 3 interventions on insulin resistance. Arch Intern Med 1998; 158(22):2477-83.

47. Xydakis AM, Case CC, Jones PH, Hoogeveen RC, Liu MY, Smith EO, et al. Adiponectin, inflammation, and the expression of the metabolic syndrome in obese individuals: the impact of rapid weight loss through caloric restriction. J Clin Endocrinol Metab 2004; 89(6):2697-703.

48. Westerink J, Visseren FLJ. Pharmacological and non-pharmacological interventions to influence adipose tissue function. Cardiovasc Diabetol 2011; 10(1):1-12.

49. Sasaki S, Higashi Y, Nakagawa K, Kimura M, Noma K, Sasaki S, et al. A low-calorie diet improves endothelium-dependent vasodilation in obese patients with essential hypertension. Am J Hypertens 2002; 15(4 Pt 1):302–9.

50. Miller GD, Nicklas BJ, Davis CC, Ambrosius WT, Loeser RF, Messier SP. Is serum leptin related to physical function and is it modifiable through weight loss and exercise in older adults with knee osteoarthritis? Int J Obes Relat Metab Disord 2004; 28(11):1383-90.

51. Nicklas BJ, Ambrosius W, Messier SP, Miller GD, Penninx BW, Loeser RF, et al: Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. Am J Clin Nutr 2004; 79(4):544-51.

52. Weiss EP, Racette SB, Villareal DT, Fontana L, Steger-May K, Schechtman KB, et al. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. Am J Clin Nutr 2006; 84(5):1033-42.

53. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000; 20(6):1595-9.

54. Gokce N, Vita JA, McDonnell M, Forse AR, Istfan N, Stoeckl M, et al. Effect of medical and surgical weight loss on endothelial vasomotor function in obese patients. Am J Cardiol 2005; 95(2):266–8.

55. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, et al. Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. J Clin Endocrinol Metab 2001; 86(8):3815–9.

56. Brook RD. Obesity, weight loss, and vascular function. Endocrine 2006; 29(1):21–5.

57. Fuentes F, López-Miranda J, Sánchez E, Sánchez F, Paez J, Paz-Rojas E, et al. Mediterranean and low-fat diets improve endothelial function in hypercholesterolemic men. Ann Intern Med 2001; 134(12):1115–9.

58. Esposito K, Marfella R, Ciotola M, Di Palo C, Giugliano F, Giugliano G, et al. Effect of a mediterranean-style diet on endothelial dysfunction and markers of vascular inflammation in the metabolic syndrome: a randomized trial. JAMA 2004; 292(12):1440–6.

59. Tripathy D, Mohanty P, Dhindsa S, Syed T, Ghanim H, Aljada A, et al. Elevation of free fatty acids induces inflammation and impairs vascular reactivity in healthy subjects. Diabetes 2003; 52(12):2882–7.

60. Reseland JE, Anderssen SA, Solvoll K, Hjermann I, Urdal P, Holme I, et al. Effect of long term changes in diet and exercise on plasma leptin concentrations. Am J Clin Nutr 2001; 73(2):240–5.

61. Brekke HK, Lenner RA, Taskinen MR, Mansson JE, Funahashi T, Matsuzawa Y, et al. Lifestyle modification improves risk factors in type 2 diabetes relatives. Diabetes Res Clin Pract 2005; 68(1):18–28.

62. Walker KZ, O´Dea K, Gomez M, Girgis S, Colagiuri R. Diet and exercise in the prevention of diabetes. J Hum Nutr Diet 2010; 23(4):344–352.

63. Gillies CL, Abrams KR, Lambert PC, Cooper NJ, Sutton AJ, Hsu RT, et al. Pharmacological and lifestyle interventions to prevent or delay type 2 diabetes in people with impaired glucose tolerance: systematic review and meta-analysis. BMJ 2007; 334(7588): 299.

64. Vanhoutte PM, Shimokawa H, Tang EHC, Feletou M. Endothelial dysfunction and vascular disease. Acta Physiol 2009; 196(2):193-222.

65. Goto C, Higashi Y, Kimura M, Noma K, Hara K, Nakagawa K, et al. Effect of different intensities of exercise on endothelium-dependent vasodilatation in humans: role of endothelium-dependent nitric oxide and oxidative stress. Circulation 2003; 108(5):530-5.

66. Gielen S, Hambrecht R. Effects of exercise training on vascular function and myocardial perfusion. Cardiol Clin 2001; 19(3): 357-68.

67. Rush JWE, Denniss SG, Graham DA. Vascular nitric oxide and oxidative stress: determinants of endothelial adaptations to cardiovascular disease and to physical activity. Can J Appl Physiol 2005; 30(4):442-74.

68. Hilberg T. Physical activity in the prevention of cardiovascular diseases: epidemiology and mechanisms. Hamostaseologie 2008; 28(1-2): 9-15.

69. Duncker DJ, Bache RJ. Regulation of coronary blood flow during exercise. Physiol Rev 2008; 88(3):1009-86.

70. Ghisi GLM, Durieux A, Pinho R, Benetti M. Exercício Físico e Disfunção Endotelial. Arq Bras Cardiol 2010; 95(5):130-37.

71. Sasaki JE, Santos MG. O papel do exercício aeróbico sobre a função endotelial e sobre os fatores de risco cardiovasculares. Arq Bras Cardiol 2006; 87(5):227-33.

72. Schumacher A, Peersen K, Sommervoll L, Seljeflot I, Arnesen H, Otterstad JE. Physical performance is associated with markers of vascular inflammation in patients with coronary heart disease. Eur J Cardiovasc Prev Rehabil 2006; 13(3):356-62.

73. Aronson D, Sella R, Sheikh-Ahmad M, Kerner A, Avizohar O, Rispler S, et al. The association between cardiorespiratory fitness and C-reactive protein in subjects with the metabolic syndrome. J Am Coll Cardiol 2004; 44(10):2003-7.

74. Marcell TJ, McAuley KA, Traustadottir T, Reaven PD. Exercise training is not associated with improved levels of C-reactive protein or adiponectin. Metabol 2005; 54(4):533–41.

75. Oberbach A, Tönjes A, Klöting N, Fasshauer M, Kratzsch J, Busse MW, et al. Effect of a 4 week physical training program on plasma concentrations of inflammatory markers in patients with abnormal glucose tolerance. Eur J Endocrinol 2006; 154(4):577–85.

76. Fisher G, Hyatt TC, Hunter GR, Oster RA, Desmond RA, Gower BA. Effect of Diet With and Without Exercise Training on Markers of Inflammation and Fat Distribution in Overweight Women. Obes 2011; 19(6):1131–6.

77. Nicklas BJ, Wang X, You T, Lyles MF, Demons J, Easter L, et al: Effect of exercise intensity on abdominal fat loss during calorie restriction in overweight and

obese postmenopausal women: a randomized, controlled trial. Am J Clin Nutr 2009; 89(4):1043-52.

78. Farsidfar F, Kasikcioglu E, Oflaz H, Kasikioglu D, Meric M, Umman S. Effects of different intensities of acute exercise on flow-mediated dilatation in patients with coronary heart disease. Int J Cardiol 2008; 124(3):372-4.

79. Frick M, Weidinger F. Endothelial function: a surrogate endpoint in cardiovascular studies? Curr Pharm Des 2007; 13(17):1741-50.

80. Schaun MI, Dipp T, Rossato JS, Wilhelm EN, Pinto R, Rech A et al. The effects of periodized concurrent and aerobic training on oxidative stress parameters, endothelial function and immune response in sedentary male individuals of middle age. Cell Biochem Funct 2011; 29:534-542.

ARTIGO 2

Impact of weight loss with or without exercise on abdominal fat and insulin resistance in obese patients: a randomized clinical trial

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Title: Impact of weight loss with or without exercise on abdominal fat and insulin resistance in obese individuals: a randomized clinical trial

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Short Title: Weight loss in obese individuals

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Abbreviations list: DI - diet group, DI+EXE – diet and exercise group, hs-CRP – high sensitivity C-reactive protein, HOMA - Homeostasis Model Assessment index, IL-6 - interleukin-6 , IR – insulin resistance, TAT – total abdominal tissue, TNF-α - tumor necrosis factor-α, VAT – visceral abdominal tissue, WC – waist circumference, WHR – waist-to-hip ratio.

ABSTRACT

BACKGROUND: Evidence supports an important contribution of abdominal obesity and inflammation on the development of insulin resistance (IR) and cardiovascular diseases. The weight loss in obese individuals can reduce inflammation and, consequently, IR, but the role of training remains unclear.

OBJECTIVE: To evaluate effects of body weight reduction with and without exercise over abdominal fat tissue and IR.

DESIGN: In this randomized clinical trial, 48 obese individuals (age 31.8 $\pm$ 6 years, BMI 34.8 $\pm$ 2.7 kg/m^2) were randomized to either a diet only group (DI) or a diet and exercise group (DI+EXE). Treatment was maintained until 5% of the initial body weight was lost. At baseline and upon completion, the following parameters were analyzed: biochemical parameters such as glycemia and insulin for determination of HOMA-IR, high-sensitivity C-reactive protein (hs-CRP), and abdominal computed tomography for determination for visceral (VAT) and subcutaneous abdominal tissue (SAT).

RESULTS: Thirteen individuals dropped out before completing the weight loss intervention and did not repeat the tests. In both DI (n=18) and DI+EXE (n=17), insulin (-3.53 $\pm$ 1.26 µUI/mL and -2.47 $\pm$ 1.3 µUI/mL respectively, p=0.01), HOMA-IR (-1.38 $\pm$ 0.37 and -0.95 $\pm$ 0.14mg/dL respectively, p=0.01) and VAT (-23,62 $\pm$ 19,41 cm^2 and -35,43 $\pm$ 34,96 cm^2 respectively, p<0.00) decreased significantly, and it was similar (repeated measures ANOVA).

CONCLUSION: In this study**,** 5% weight loss reduces abdominal fat and IR in obese individuals, and physical training did not improve changes in these parameters.

Key-words: weight loss, diet, physical training, obese, insulin resistance.

INTRODUCTION

Evidence points to an important association of abdominal obesity and the development of metabolic and cardiovascular diseases [1], favoring the occurrence of hypertension, diabetes mellitus and clinical atherosclerotic disease [2-4], affecting the quality of life. Abdominal fat is the sum of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in the abdominal region. VAT holds the highest association with the development of cardiovascular disease, and it is related to insulin resistance (IR), and secretion of proinflammatory cytokines [5].

Some of the products derived from adipose tissue, such as free fatty acids, tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6), are a strong stimulus for the production of high sensitive C-reactive protein (hs-CRP) by the liver, a biomarker for low-grade inflammation that is associated with some comorbidities of obesity and has been regarded as a risk predictor for coronary artery disease [6]. To measure abdominal fat and to estimate cardiovascular risk, anthropometric techniques are often used in clinical practice, particularly the waist circumference (WC) and waist-to-hip ratio (WHR). However, they do not differentiate VAT from SAT. Furthermore, their clinical importance seems to be less significant in obese individuals [7]. Measuring VAT accurately is important in the setting of obesity if one wishes to detect changes in this metabolically important tissue. Among the existing imaging methods, computed tomography of the abdomen is the gold standard for measuring VAT [5].

An intentional reduction of body weight by caloric restriction reduces systemic inflammatory markers [8] and improves IR [9]. In overweight patients, a reduction of 7% of initial body weight improves systolic blood pressure, plasma glucose, and insulin [10]. Physical training can also be associated with lower levels of inflammation due to its ability to reduce

abdominal obesity and IR [6,11]. Individuals with the metabolic syndrome that are highly physically active have a lower concentration of hs-CRP than their sedentary counterparts [12]. Recent studies have explored the behavior of inflammatory parameters and IR after physical training, but the results are still contradictory [6,13]. Thus, the aim of this study was to compare the behavior of hs-CRP, insulin resistance and VAT in obese patients who lose weight through diet therapy alone or combined with physical training.

SUBJECTS AND METHODS

Design and subjects

This is a randomized clinical trial involving obese adults (body mass index - BMI - 30 to 39.9 kg/m^2), of both sexes, aged between 22 and 41 years, previously sedentary and without use of drugs. Invitations to volunteers were advertised in newspapers, radio and TV. Active smokers, patients with overt hypothyroidism, diabetes mellitus, grade III obesity, arterial hypertension, anemia, active infection, or cancer were excluded. The project was approved by the Ethics Committee, and all participants gave written informed consent.

Procedures

Logistic:

On admission to the study, we assessed anthropometric parameters, aerobic capacity, biochemistry, and abdominal fat. A complete food history provided the parameters for the calculation of individual diets.

After these evaluations, the patients were allocated randomly to receive two different interventions: dietary counseling for weight reduction (DI) or dietary counseling for weight reduction accompanied by physical training (DI + EXE). The intervention was continued until the patients had lost 5% of their initial body weight. During the follow up, patients had several outpatient visits where adherence to the diet was checked and stimulated.

When the 5% weight loss was reached, the baseline assessments were repeated.

Intervention:

The diet plan was individually calculated to provide a reduction of between 500 and 1000 kcal \ day energy needs of the subject. The prescribed diet was balanced and rich in fiber, according to current Brazilian guidelines for the treatment of obesity [14]. Every two weeks, we

measured body weight, waist circumference (WC) and, if necessary, adjustments were made to the diet to improve compliance.

The DI group received a standard orientation for light, informal, physical activity, at least 3 times a week, aimed at maintaining a healthy lifestyle [14]. In the outpatient visits, the practice of physical activity was always stimulated.

The DI + EXE group was enrolled in a training program. Three times a week, the participants attended the University gymnasium where they were supervised while training on a stationary bicycle, during 45 minutes, at a 70% intensity of the heart rate reserve [15].

Measurements:

Aerobic Power

To determine the intensity of exercise, aerobic power was assessed by means of a protocol in cycle ergometer (Cybex, The Byke, USA). This consisted of a warm-up period of 3 minutes with a load of 25 W, followed by lifting the load a further 25 W per minute until exhaustion. The hart rate was monitored by a heart rate monitor (Polar, S810) and oxygen consumption and carbon dioxide production were measured using the CPX-D System (Medical Graphics - St Paul Minnesota) during the test. The maximum oxygen consumption was measured at maximal exercise, defined as the inability to continue exercising despite vigorous encouragement and confirmed by the respiratory exchange ratio> 1.1, heart rate > 95% of maximum predicted for age and presence of plateau oxygen consumption even with increased load [16].

Abdominal Fat:

To assess abdominal fat, anthropometric techniques and abdominal computed tomography were used.

Anthropometric measurements were: body mass, height, WC and hip circumference (HC), to calculate the WHR.

Height was measured with a fixed stadiometer (Tonelli, Ltda, SC, Brasil), with a 1 mm precision. Body weight was measured, with light indoor clothes, on a digital scale (MEA-03200, Plenna, Brasil). WC was measured with an inelastic tape measure (Sanny, SP, Brazil), halfway between the last rib and the iliac crest. The nutritional status was classified by BMI [17].

Computed tomography (Philips Brilliance CT, Cleveland, USA) was used for determination of cross-sectional abdominal adipose tissue from a single tomographic slice at L4-L5 level, as described by Seidell et al. [18]. To define the VAT (cm^2), a continuous line was traced out by an electronic cursor, along the fascia transversalis, and along the fascia of the quadratus lumborum muscle, excluding the vertebral body. In the area so defined, retroperitoneal, mesenteric and omental fat was included. The total abdominal adipose tissue area (TAT) was measured in a similar way, but outlined over the outer limits of the tomographic image of the abdominal wall [18]. SAT was calculated by subtracting VAT from TAT. All exams were carried out by a single, blinded technician.

Biochemical Measurements:

Venous blood samples were obtained after an overnight fast. hs-CRP was determined by nephelometry (Boehringer, German), plasma glucose by a glucose-peroxidase, automated method (Advia, Bayer, USA), plasma insulin by eletrochemiluminescence (Elecsys, Roche, EUA) and uric acid by colorimetric enzymatic method (Advia, Bayer, USA). IR was calculated by the *Homeostasis Model Assessment* index (HOMA-IR), as proposed by Matthews an collaborators [19]: *HOMA-IR* = fasting insulin (μU/ml) X fasting glucose (mmol/L) / 22,5.

Statistical Analysis

Statistical analyses were conducted using SPSS for Windows version 19.0. All variables were examined for their normality in distribution by the Kolmogorov-Smirnov test. Because of nonsymmetrical distributions, HOMA-IR and hs-CRP were log-transformed for the statistical analyses. Nevertheless, for the sake of clarity, values are presented in the original scale. Descriptive statistics were used to identify sample characteristics and provide summary indices of selected measures. Baseline demographic and clinical characteristics were compared using either Student's t-test or Wilcoxon's tests for continuous variables. Categorical variables were analyzed using the Chi Square test. Changes in outcomes were analyzed by General linear model (GLM) for repeated measurements, with measurements at different interventions as a within-subjects factor. A one-way ANCOVA, using the baseline measurements as the covariates, was conducted to evaluate differences between the DI and DI+EXE. Results were considered significant if P-value was < 0.05.

RESULTS

Figure 1 shows the flow diagram of patient recruitment and randomization. In total, 48 subjects performed all baseline assessments. **Table 1** shows the baseline clinical and biochemical characteristics of the groups after randomization, where it is clear that the groups were similar in all the variables. After performing the initial assessments, 13 subjects dropped out (seven – 2 men - from the DI group and six – one man – from the DI+EXE group). Individuals who dropped out did not differ significantly from those who completed the study in their baseline values ($p > 0.05$ for all variables). After exclusion of dropouts, the groups did not show statistically significant differences in baseline values ($p > 0.05$ for all).

The time required for reduction of 5% of initial body weight was 79.7 days (63-95) for the DI group and 65.9 days (55-76) for the DI+EXE group, and this difference was not statistically significant ($p = 0.16$).

Table 2 shows the effect of interventions on anthropometric and biochemical parameters. After weight reduction, the groups significantly reduced BMI, WC and WHR, with no difference between groups. After the weight loss, there was a significant reduction in insulin and HOMA , of similar magnitude in both groups. There were no changes in glycemia and uric acid.

Figure 2 shows the effect of interventions in abdominal fat evaluated by CT. After 5% body weight reduction, both groups reduced TAT (from 660.3 $\pm$ 137.1 cm^2 to 608.5 $\pm$ 147.5 cm^2 and from 622.8 $\pm$ 128.5 cm^2 to 576.9 $\pm$ 137.2 cm^2 in DI and DI+EXE, respectively, $p<0.00$) and VAT (from 136.1 $\pm$ 64cm^2 to 112.5 $\pm$ 54 cm^2 and from 154.23 $\pm$ 60.6 cm^2 to 118,80 $\pm$ 55,36 cm^2 in DI and DI+EXE, respectively, $p=0.02$). This change was not statistically different between groups ($p>0.05$). Neither treatment alter significantly the SAT ($p>0.05$).

DISCUSSION

In this study, a 5% reduction in body weight was associated with a reduction in visceral fat, hs-CRP and IR in obese individuals. Previous studies have shown an improvement in insulin sensitivity and inflammatory parameters with this percentage of weight loss in obese patients undergoing caloric restriction (500 to 800 kcal/day) without physical training [10,20]. However, other studies suggest that a significant improvement in these parameters would require a reduction of up to 1000 kcal/day by dietary restriction accompanied by increased energy expenditure through physical training. Thus, it would be possible to reduce the initial weight between 7 and 12% [21-22]. Our results indicate that, at least in the short run, a modest weight loss, via a limited caloric restriction, with our without physical training, is associated with improvement in inflammatory parameters, VAT and IR. In the long run, increasing energy expenditure may be required.

VAT has greater cardiometabolic impact than SAT [23-24]. However, because it has greater total mass, SAT can contribute to the relationship between central adiposity, IR and cardiovascular disease [25]. Few studies have investigated the effects of diet and exercise on these tissues, and the impact on cardiovascular risk reduction. Marques et al [27] suggest that VAT areas with values above 100cm ² increase the risk of metabolic complications such as raised plasma glucose, total cholesterol and high blood pressure. When the VAT area exceeds 150 cm² the risk of developing coronary artery disease is increases about three fold [27]. Kim et al [6] measured the abdominal fat of 160 middle-aged Korean adults, both eutrophic and overweighed. The VAT average these adults was 89.5$\pm$46.3 cm^2, and men showed higher values than women. Our patients had baseline VAT of 141.6$\pm$62.1 cm^2, suggesting a higher risk of metabolic complications, corroborated by IR and elevated hs-CRP. IR and the accompanying high fasting plasma insulin are frequently found in obese individuals and appear to be the first signs of the future development of type 2 diabetes [13, 28].

Physical exercise is associated with reduced cardiovascular risk, especially in individuals with diabetes, improving endothelial function and inflammatory markers [29,30]. The effects of exercise on markers of inflammation may be more pronounced in individuals with features of the metabolic syndrome if compared with those without metabolic abnormalities [12]. We did not find a significant additional effect of exercise training on markers of inflammation or IR. In women that lose weight through diet, hs-CRP, TNF-α, and IL-6 are reduced in a similar fashion in those exercising or not [33]. In a randomized clinical trial with older obese adults, hs-CRP was significantly lowered in the subjects on diet only [20]. It is possible that the length of exposure to exercise was not enough to promote cardiovascular protection. Alternatively, the acute generation of free radicals induced by acute exercise could have contributed to these findings [20,31]. Speculatively, the relatively short time period between the last exercise session and the final biochemical analyses of the studies could have contributed to the findings [20,31]. The amount of exercise was not enough to elicit the antioxidant protection of physical training [31]. It is therefore likely that the process of ischemia-reperfusion of aerobic exercise caused a rapid increase in blood flow (reperfusion) and the generation of free radicals [32].

Previous studies suggest that the levels of hs-CRP may bear an important association with variations in insulin sensitivity [34-35]. In obese but otherwise metabolically healthy individuals, low levels of hs-CRP may contribute to the favorable glucose profile, even with increased body adiposity [36]. Our patients had relatively benign glucose profile, but somewhat elevated hs-CRP. This could have had an impact on the results, minimizing effects that could otherwise be significant in those patients with more evident metabolic disturbances.

In our study, losing weight was associated with improved insulin levels and HOMA, but exercise did not contibute additional improvement. Oberbach et al [13] did not find significant reductions in glucose and insulin concentrations in 20 subjects with normal glucose

tolerance after four weeks of aerobic training. The training program adopted by the authors was shorter than ours and involved a concurrent training (aerobic + resistance), while our protocol was just aerobic. Although further exploration is much needed, such results suggest that different exercise regimens can bring different effects on these parameters.

The strength of this study was the use of the same percentage weight loss goal for all subjects, in order to evaluate eventual differential effects of the inclusion of physical training in the therapeutic regime. If the design were based on a fixed duration of treatment, the results in terms of weight loss and body composition change might have been different in the two groups. Interestingly, the time needed to achieve the 5% goal was not different in the 2 regimens. The use of computer imaging techniques for the evaluation of abdominal fat distribution gave the study more power to accurately identify the effect of weight loss in different types of adipose tissue.

The limitation of this study was the absence of a control group (similar follow up without weight loss, with or without physical training). However, it was considered unethical to treat a group of obese individuals without stimulating them to lose weight during any given period of time. With this design, we believe that it was possible to test the hypothesis of a differential effect of exercise on several parameters. Since the results are negative, one cannot avoid looking into issues such as sample size and duration of the interventions. Although the sample size was initially estimated to allow for eventual differences to be found in the 5% significance area, a larger sample might have led to different findings. This will have to be clarified in further studies.

In summary, a reduction of 5% of initial body weight resulted in significant decreases in VAT and TAT in these obese individuals. Additionally, this weight loss decreased HOMA-IR and hs-CRP. Physical training did not add any measurable benefit in as far as the variables in this study are considered.

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REFERENCES

1. Lemieux I, Poirier P, Bergeron J, Alméras N, Lamarche B, Cantin B, Dagenais GR, Després J-P. Hypertriglyceridemic waist: A useful screening phenotype in preventive cardiology? Can J Cardiol 2007; 23: 23B-31B.

2. Rexrode KM, Carey VJ, Hennekens CH, Walters EE, Colditz GA, Stampfer MJ, Willet WC, Manson JE. Abdominal adiposity and coronary heart disease in women. JAMA 1998; 280: 1843-8.

3. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L, et al. Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: A case-control study. Lancet 2005; 366: 1640-9.

4. Kuk JL, Katzmarzyk PT, Nichaman MZ, Church TS, Blair SN, Ross R. Visceral fat is an independent predictor of all-cause mortality in men. Obes Res 2006; 14: 336-41.

5. Klein S, Allison DB, Heymsfield SB, Kelley DE, Leibel RL, Nonas C, Kahn R, Association for Weight Management and Obesity Prevention, NAASO, Obesity Society, American Society for Nutrition et al. . Waist circumference and cardiometabolic risk: a consensus statement from shaping America's health: Association for Weight Management and Obesity Prevention; NAASO, the Obesity Society; the American Society for Nutrition; and the American Diabetes Association. Diabetes Care 2007; 30: 1647-52.

6. Kim K, Valentine RJ, Shin Y, Gong K. Associations of visceral adiposity and exercise participation with C-reactive protein, insulin resistance, and endothelial dysfunction in Korean healthy adults. Metabol Clin Exp 2008; 57: 1181–9.

7. Snijder MB, Visser M, Dekker JM, Seidell JC, Fuerst T, Tylavsky F, Cauley J, Lang T, Nevitt M, Harris TB. The prediction of visceral fat by dual-energy X-ray absorptiometry in the elderly: a comparison with computed tomography and anthropometry. Int J of Obes 2002; 26: 984-993.

8. Bougoulia M, Triantos A, Koliakos G. Plasma interleukin-6 levels, glutathione peroxidase and isoprostane in obese women before and after weight loss. Association with cardiovascular risk factors. Hormones 2006; 5: 192-9.

9. Weinstock RS, Dai H, Wadden TA. Diet and exercise in the treatment of obesity: effects of 3 interventions on insulin resistance. Arch Intern Med 1998; 158: 2477-83.

10. Xydakis AM, Case CC, Jones PH, Hoogeveen RC, Liu MY, Smith EO, Nelson KW, Ballantyne CM. Adiponectin, inflammation, and the expression of the metabolic syndrome in obese individuals: the impact of rapid weight loss through caloric restriction. J Clin Endocrinol Metab 2004; 89: 2697-703.

11. Geffken DF, Cushman M, Burke GL, Polak JF, Sakkinen PA, Tracy RP. Association between physical activity and markers of inflammation in a health elderly population. Am J Epidemiology 2001; 153: 242-50.

12. Aronson D, Sella R, Sheikh-Ahmad M, Kerner A, Avizohar O, Rispler S, Bartha P, Markiewicz W, Levy Y, Brook GJ. The association between cardiorespiratory fitness and Creactive protein in subjects with the metabolic syndrome. J Am Coll Cardiol 2004 ;44: 2003-7.

13. Oberbach A, Tonjes A, Kloting N, Fasshauer M, Kratzsch J, Busse MW, Paschke R, Stumvoll M, Blüher M. Effect of a 4 week physical training program on plasma concentrations of inflammatory markers in patients with abnormal glucose tolerance. Eur J Endocrinol 2006; 154: 577-85.

14. Sposito AC, Caramelli B, Fonseca FAH, Bertolami, MC. IV Diretriz Brasileira sobre Dislipidemias e Prevenção da Aterosclerose: Departamento de Aterosclerose da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol 2007; 88: 2-19 .

15. Karvonen JJ, Kentala E, Mustala O. The effects of training on heart rate: a “longitudinal” study. Ann Med Exp Biol Fenn 1957; 35: 307-15.

16. McGuire DK, Levine BD, Williamson JW, Snell PG, Blomqvist CG, Saltin B, Mitchell JH. A 30-year follow-up of the Dallas Bed Rest and Training Study: I. Effect of age on the cardiovascular response to exercise. Circulation 2001; 104: 1350-7.

17. Organização Mundial da Saúde / Organização Pan-Americana da Saúde. Doenças crônico-degenerativas e Obesidade: estratégia mundial sobre alimentação saudável, atividade física e saúde. Brasília, 2003. Version current 2 may 2009. Internet: http://www.opas.org.br/sistema/arquivos/d_cronic.pdf. (accessed 2 may 2009).

18. Seidell JC, Oosterlee A, Thijssen MA, Burema J, Deurenberg P, Hautvast JG, Ruijs JH. Assessment of intra-abdominal and subcutaneous abdominal fat: relation between anthropometry and computed tomography. Am J Clin Nutr 1987; 45: 7-13.

19. Mathews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetol 1985; 28: 412-9.

20. Nicklas BJ, Ambrosius W, Messier SP, Miller GD, Penninx BW, Loeser RF, Palla S, Bleecker E, Pahor M. Diet-induced weight loss, exercise, and chronic inflammation in older, obese adults: a randomized controlled clinical trial. Am J Clin Nutr 2004; 79: 544-51.

21. Weiss EP, Racette SB, Villareal DT, Fontana L, Steger-May K, Schechtman KB, Klein S, Holloszy JO and *Washington University School of Medicine CALERIE Group*. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. Am J Clin Nutr 2006; 84: 1033-42.

22. Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, Iwahashi H, Kuriyama H, Ouchi N, Maeda K et al. Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. Arterioscler Thromb Vasc Biol 2000; 20: 1595-9.

23. Fox CS, Massaro JM, Hoffmann U, Pou KM, Maurovich-Horvat P, Liu CY, Vasan RS, Murabito JM, Meigs JB, Cupples LA, et al. Abdominal Visceral and Subcutaneous Adipose Tissue Compartments: Association With Metabolic Risk Factors in the Framingham Heart Study. Circulation 2007; 116: 39-48.

24. Saijo Y, Kiyota N, Kawasaki Y, Miyazaki Y, Kashimura J, Fukuda M, Kishi R. Relationship between C –reactive protein and visceral adipose tissue in healthy Japanese subjects. Diab Obes Metabol 2004; 6: 249-58.

25. Kullberg J, Below CV, Lönn L, Lind L, Ahlström H, Johansson L. Practical approach for estimation of subcutaneous and visceral adipose tissue. Clin Physiol Funct Imaging 2007; 27: 148-53.

26. Yudkin SJ, Stehouwer CD, Emeis JJ, Coppack SW. C-reactive protein in healthy subjects: associations with obesity, insulin resistance and endothelial dysfunction: a potential role for cytokines originating from adipose tissue? Arterioscler Thromb Vasc Biol 1999; 19: 972-8.

27. Marques MD, Santos RD, Parga JR, Rocha-Filho JA, Quaglia LA, Miname MH, Avila LF. Relation between visceral fat and coronary artery disease evaluated by multidetector computed tomography. Atherosc J 2010; 209: 481-6.

28. Weyer C, Bogardus C, Mott DM, Pratley RE. The natural history of insulin secretory dysfunction and insulin resistance in the pathogenesis of type 2 diabetes mellitus. J Clin Invest 1999; 104: 787-94.

29. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. Circulation 2003; 107: 2435–39.

30. Stewart KJ. Exercise training: can it improve cardiovascular health in patients with type 2 diabetes? Brit J Sports Med 2004; 38: 250–2.

31. Sureda A, Tauler P, Aguilo A, Cases N, Fuentespina E, Córdova A, Tur JA, Pons A. Relation between oxidative stress markers and antioxidant endogenous differences during exhaustive exercise. Free Rad Res 2005; 39: 1317-24.

32. Cooper CE, Vollaard NB, Choueiri T, Wilson MT. Exercise, free radicals and oxidative stress. Biochem Soc Trans 2002; 30: 280-4.

33. Fisher G, Hyatt TC, Hunter GR, Oster RA, Desmond RA, Gower BA. Effect of diet with and without exercise training on markers of inflammation and fat distribution in overweight women. Obes 2011; 19: 1131–6.

34. Festa A, D'Agostino Jr R, Howard G, Mykkanaen L, Tracy RP, Haffner SM. Chronic subclinical inflammation as part of the insulin resistance syndrome: the Insulin Resistance Atherosclerosis Study (IRAS). Circulation 2000; 102: 42-7.

35. Rutter MK, Meigs JB, Sullivan LM, D'Agostino Sr RB, Wilson PW. C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. Circulation 2004; 110: 380-5.

36. Karelis AD, Faraj M, Bastard JP, St-Pierre DH, Brochu M, Prud'homme D, Rabasa-Lhoret R. The metabolically healthy but obese individual presents a favorable inflammation profile. J Clin Endocrinol Metab 2005; 90: 4145-50.

Table 1- Baseline clinical and biochemical characteristics of study group after randomization

Variables	DI (n=24)	DI+EXE (n=24)
Male (n/%)	8 (33.3)	8 (33.3)
Age (years)	31.4 ± 5.6	32.3 ± 6.4
Body Weight (kg)	95.4 ± 12.1	99.1 ± 12.0
Height (m)	1.65 ± 0.09	1.69 ± 0.07
Body Mass Index (kg/m^2)	34.8 ± 2.4	34.7 ± 2.2
Obesity grade I (n/%)	14 (58.3)	13 (54.17)
Waist Circumference (cm)	111.7 ± 7.7	110.8 ± 6.6
Hip Circumference (cm)	118.9 ± 8.6	120.9 ± 6.0
Waist-to-hip Ratio	0.84 ± 0.09	0.85 ± 0.08
Uric Acid (mg/dL)	5.2 ± 1.2	5.1 ± 1.4
Fasting glucose (mg/dL)	90.9 ± 8.8	91.1 ± 8.9
Insulin (µUI/mL)	16.6(14.5-20.9)	14.1(11.4-18.6)
HOMA-IR	3.8(3.1-5.1)	3.2(2.5-4.5)
hs-CRP (mg/L)	3.8 (2.6–5.8)	4.1 (1.4-7.1)
Total Adipose Tissue (cm^2)	646.7 ± 127.3	625.6 ± 122.9
Visceral Adipose Tissue (cm^2)	136.0 ± 65.6	148.1 ± 57.9
Subcutaneous Adipose Tissue (cm^2)	510.7 ± 127.3	477.6 ± 126.6

Data are presented in n(%), mean ± sd or median (interquartile range)

HOMA-IR: Homeostasis Model Assessment hs-CRP: high sensitivity C-reactive protein

P>0.05 for all comparisons

Table 2 – Anthropometric and biochemical changes with different interventions

	DI (n=18)			DI+EXE (n=17)					
	Before	**After**	**Change**	**Before**	**After**	**Change**	**P [1]**	**P [2]**	**P[3]**
Body weight (kg)	95.8 ± 13.7	91.5 ± 14.2	-4.31 ± 0.5	98.7 ± 13.0	94.0 ± 13.0	-4.66 ± 0.52	0.00	0.64	0.63
Body Index Mass (kg/m^2)	34.7 ± 2.4	33.1 ± 2.6	-1.58 ± 0.17	34.7 ± 2.4	33.1±2.1	-1.62 ± 0.17	0.00	0.79	0.79
Waist circumference (cm)	112.0 ± 8.7	108.3 ± 8.7	-3.42 ± 0.44	110.9 ± 7.4	107.0 ± 7.8	-3.92 ± 0.45	0.00	0.76	0.76
Hip circumference (cm)	120.4 ± 8.8	117.1 ± 8.6	-3,31 ± 1,18	120.2 ± 5.1	117.0 ± 4.7	-3.18 ± 2.2	0.00	0.83	0.84
Waist-to-hip ratio	0.83 ± 0.09	0.83 ± 0.09	0.00 ± 0.00	0.86 ± 0.08	0.85 ± 0.07	0.01 ± 0.00	0.06	0.05	0.09
Glycemia (mg/dL)	92.4 ± 9.2	89.7 ± 9.2	-2.06 ± 1.78	90.4 ± 9.7	90.4 ± 6.8	-0.64 ± 1.83	0.42	0.40	0.59
Insulin (µUI/mL)	17.3(14.7-21.6)	15.4 (7.8-19.6)	-3.53 ± 1.26	15.5(11.4-18.7)	13.4(8.8-19.8)	-2.47 ± 1.30	0.01	0.39	0.56
HOMA	4.1 (3.1-5.6)	3.3 (1.7-4.3)	-1.30 ± 0.37	3.1 (2.5-4.7)	3.2 (2.0-4.4)	-0.95 ± 0.41	0.01	0.32	0.53
Uric Acid (mg/dL)	5.4 ± 1.3	5.3 ± 1.1	-0.05 ± 0.13	5.4 ± 1.6	5.4 ± 1.1	-0.04 ± 0.14	0.65	0.99	0.95
hs-RCP (mg/L)	3.3 (2.4-6.4)	2.8(1.5-4.8)	-1.35 ± 0.41	3.5 (1.5-5.8)	3.0 (1.1-5.9)	-0.45 ± 0.43	0.01	0.13	0.14

Data are presented in mean ± sd or median (interquartile range)

P[1] for intervention with repeated measures analyses of variance

P[2] for intervention x group with repeated measures analyses of variance

P[3] with analyses of covariance adjusted for baseline measures

HOMA-IR: Homeostasis Model Assessment; hs-CRP: high sensitivity C-reactive protein

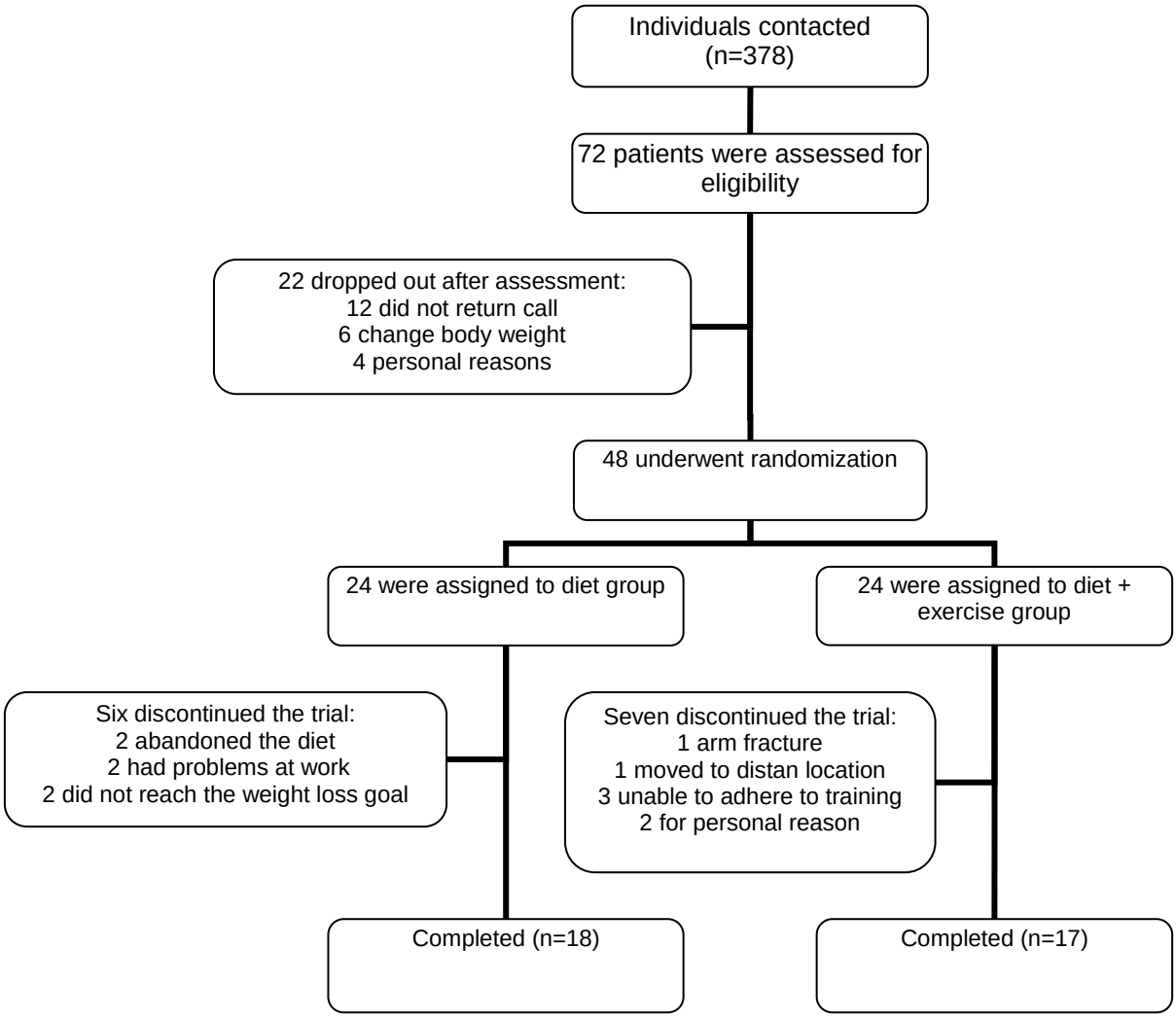

Figure 1 – Flow diagram of patient recruitment and randomization

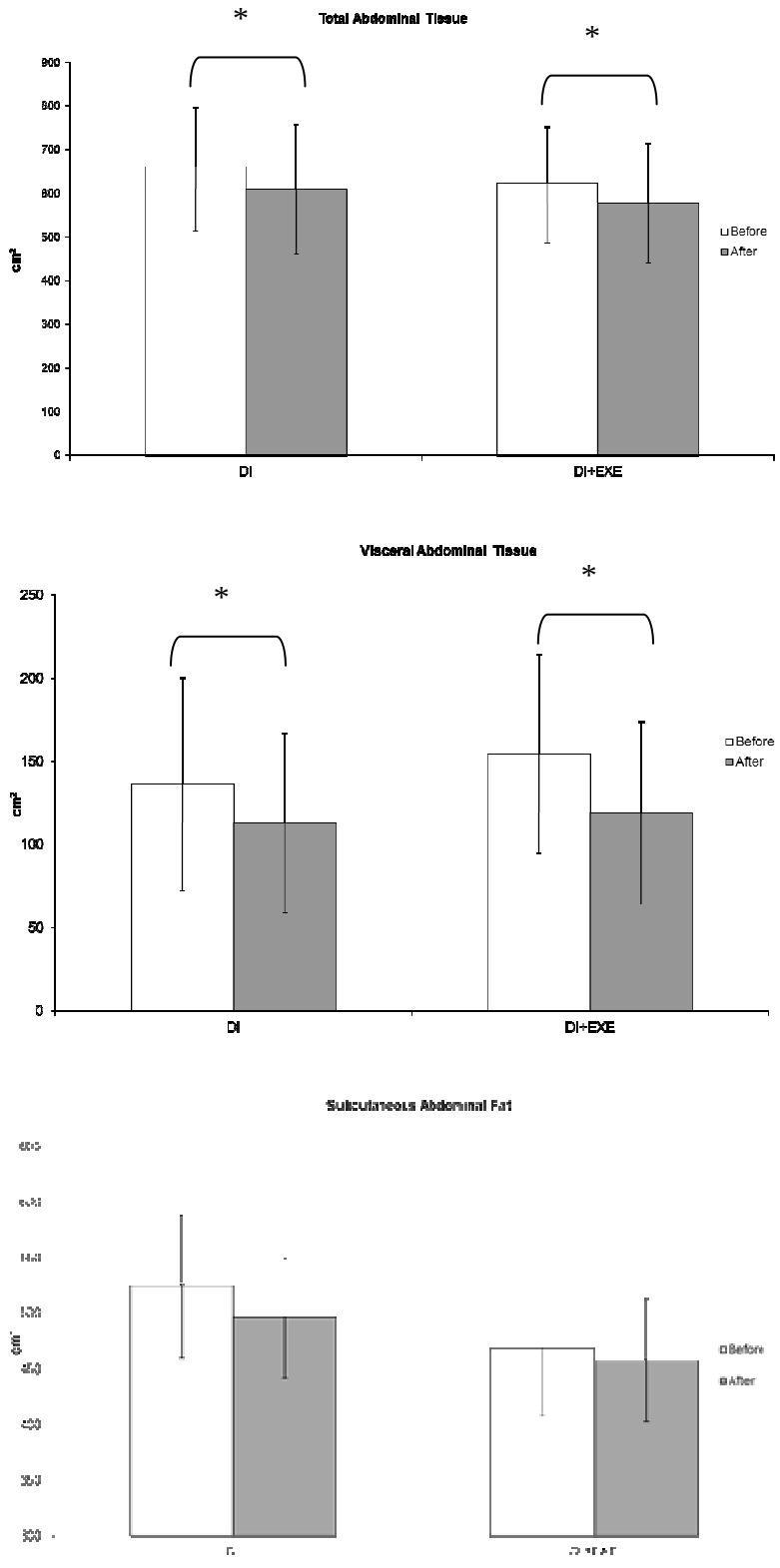

Figure 2 – Effect of interventions in abdominal fat evaluated by computed tomography. DI: diet group; DI+EXE: diet and exercise group. *p< 0.05 for GLM repeated measures.

ARTIGO 3

DOES PHYSICAL TRAINING ADD ADDITIONAL BENEFIT IN THE INITIAL MANAGEMENT OF OBESITY? A RANDOMIZED CLINICAL TRIAL.

A ser submetido para a revista *Metabolism – Clinical and Experimental*

Title: Does physical training add additional benefit in the initial management of obesity? A randomized clinical trial.

Short running title: Exercise in managing obesity

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http://clinicaltrials.gov/show/NCT00929890

ABSTRACT

OBJECTIVE: The aim of this study was to evaluate the effects of 5% weight loss, through diet only or diet plus physical training, on lipid profile, inflammation and endothelial function in obese individuals.

METHODS: In this randomized clinical trial, 48 obese individuals (age 31.8 ± 6 years, BMI 34.8 ± 2.7 kg/m^2) were randomized to either a diet only group (DI) or a diet and exercise group (DI+EXE). Treatment was maintained until 5% of the initial body weight was lost. At baseline and upon completion, the following parameters were analyzed: total cholesterol and fractions, triglycerides, fibrinogen, von Willebrand factor (vWf) and high sensitive C-reactive protein (hs-CRP), and arterial endothelial function (brachial artery flow-mediated vasodilation (FMD)).

RESULTS: Thirteen individuals dropped out before completing the weight loss intervention and did not repeat the tests. In both DI (n=18) and DI+EXE (n=17), total cholesterol (-15.83 ± 4.75mg/dL and -10.47 ± 4.89 mg/dL respectively), triglycerides (-33.8 ± 10.0mg/dL and -39.4 ± 10.3mg/dL respectively), and hs-CRP (-1.35mg/L ± 0.41 and -0.45 ± 0.43mg/L, respectively) decreased significantly, and in a similar fashion (repeated measures ANOVA). Weight loss did not decrease significantly the fibrinogen (p= -5.59 ± 13.23mg/dL and -5.79 ± 13.61, respectively, for both DI and DI+EXE) and FMD (0.73 ± 1.11% and 2.08 ± 1.15%, respectively).

CONCLUSION: A 5% weight loss improves lipid profile and reduces inflammation in obese individuals. Endothelial function remains unchanged. Weight loss has a significant impact on these cardiovascular risk factors in obese individuals, and this is independent of physical training.

Keywords: obesity, lipid profile, inflammation, diet, exercise.

LIST OF ABBREVIATIONS:

BMI: Body index mass

DI: diet only group

DI+EXE: diet and exercise group

EID-NTG: endothelium-independent dilation after administration of sublingual nitroglycerin

FMD: flow mediated dilation

HDL-C: HDL cholesterol

hs-CRP: high sensitivity C-reactive protein

LDL-C: LDL cholesterol

vWf: von Willebrand factor

WC: waist circumference

WHR: waist-to-hip ratio

INTRODUCTION

Obesity is associated with increased cardiovascular morbidity and mortality due to a wide spectrum of prevalent metabolic, inflammatory and fibrinolytic abnormalities that can accelerate the process of atherosclerosis [1]. The secretion of adipocytokines by the adipose tissue and consequent insulin resistance may be underlying abnormalities [2].

Endothelial function may also be altered in the presence of obesity [3]. Endothelial dysfunction can be detected early in the process of atherosclerotic plaque formation**,** by examining the ability of the endothelium to respond to both exogenous and endogenous stimuli [4-5]. Flow-mediated dilation (FMD) of the brachial artery is a functional marker of endothelial function, recognized as an early indicator of cardiovascular risk [6]. The mechanisms involved in the control of endothelial function are multiple, and may be altered in the event of a disease process. Endothelial dysfunction increases the vasoconstrictor response, proliferation and migration of vascular smooth muscle cells, platelet and leukocyte adhesion and expression of adhesion molecules [6]. This loss of the functional integrity of endothelium is associated with risk factors for cardiovascular disorders such as hypertension and dyslipidemia [7]. Inflammatory (e.g. high-sensitivity C-reactive protein, hs-CRP) [8,9] and biochemical parameters (e.g. von Willebrand factor (vWf) and fibrinogen) [10] are often altered in the presence of endothelial dysfunction.

Previous clinical trials have shown that weight loss can reduce the levels of hs-CRP [11-12]. Physical fitness is also associated with lower levels of hs-CRP, leukocytes and fibrinogen [13-14]. Since the inflammatory markers are strongly influenced by body fat, it is possible that lower levels of these markers may be an indirect consequence of the effect of exercise on body fat [15].

The potential role of the contribution of physical training to the amelioration of endothelial function during the process of weight reduction is still largely under-evaluated. The aim of this study was to compare endothelial and biochemical responses of two strategies for weight loss in obese patients.

METHODS

Design and subjects

This is a randomized clinical trial involving obese adults (body mass index - BMI - 30 to 39.9 kg/m^2), of both sexes, aged between 22 and 41 years, previously sedentary and without use of drugs. Invitations to volunteers were advertised in newspapers, radio and TV. **Figure 1** shows the flow of recruitment and randomization of participants. Active smokers, patients with overt hypothyroidism, diabetes mellitus, grade III obesity, arterial hypertension, anemia, active infection, or cancer were excluded. The project was approved by the local Ethics Committee, and all participants gave written informed consent.

Procedures

Logistics:

On admission to the study, we assessed anthropometric parameters, aerobic capacity, biochemistry, and endothelial function. A complete food history provided the parameters for the calculation of individual diets.

After these evaluations, the patients were allocated randomly to receive two different interventions: dietary counseling for weight reduction (DI), or dietary counseling for weight reduction accompanied by physical training (DI + EXE). The intervention was continued until the patients had lost 5% of their initial body weight. During the follow up, patients had multiple outpatient visits where adherence to the diet was checked and stimulated.

When the 5% weight loss was reached, the baseline assessments were repeated.

Intervention:

The diet plan was individually calculated to provide a reduction from 500 to 1000 kcal / day energy needs of the subject. The prescribed diet was balanced and rich in fiber, according to current Brazilian guidelines for the treatment of obesity [16]. Every two weeks, we measured body weight, waist circumference (WC) and, if necessary, adjustments were made to the diet to improve compliance.

The DI group received a standard orientation for light, informal, physical activity, at least 3 times a week, aimed at maintaining a healthy lifestyle [16]. In the outpatient visits, the practice of physical activity was always stimulated.

The DI + EXE group was enrolled in a training program. Three times a week, the participants attended the University gymnasium where they were supervised while training on a stationary bicycle, during 45 minutes, at a 70% intensity of the heart rate reserve [17].

Measurements

Aerobic power:

To determine the intensity of exercise, aerobic power was assessed with the use of a protocol in cycle ergometer (Cybex, The Byke, USA), which consisted of a warm-up period of 3 minutes with a load of 25 W, followed by lifting the load at 25 W per minute until exhaustion. The hart rate was monitored by a heart rate monitor (Polar, S810) and oxygen consumption and carbon dioxide production were measured using the CPX-D System (Medical Graphics - St Paul Minnesota) during the test. The maximum oxygen consumption was measured at maximal exercise, defined as the inability to continue exercising despite vigorous encouragement and confirmed by the respiratory exchange ratio> 1.1, heart rate > 95% of maximum predicted for age and presence of plateau oxygen consumption even with increased load [18].

Anthropometric parameters:

Height was measured with a fixed stadiometer (Tonelli, Ltda, SC, Brasil), with a 1 mm precision. Body weight was measured, with light indoor clothes, on a digital scale (MEA-03200, Plenna, Brasil). WC was measured with an inelastic tape measure (Sanny, SP, Brazil), halfway between the last rib and the iliac crest. Hip circumference was measured to calculate the waist-to-rip ratio (WHR). The nutritional status was classified by BMI [19].

Endothelial function:

To evaluate endothelium dependent vasodilation, flow mediated vasodilation (FMD) was measured according to international guidelines [20], with a high resolution vascular ultrasound (EnVisor CHD, Philips, Bothell, WA, USA) and a 3-12 MHz linear-array transducer (L12-3, Philips, Bothell, WA, USA). With the transducer positioned at 5 cm from the antecubital fossa, the baseline diameter of the brachial artery was measured at the anterolateral aspect of the vessel. FMD was measured as the percent change in brachial artery diameter from baseline after 60 s of reactive hyperemia (provoked by inflating a cuff at a pressure 50 mmHg above the systolic for 5 min and then deflating it rapidly). A midartery pulsed Doppler signal was obtained to evaluate basal flow and upon immediate cuff release, and no later than 15 s after cuff deflation to assess hyperemic flow.

The arterial diameter increases after a 0.4 mg sublingual nitroglycerin spray (NTG) was used as a measure of endothelium-independent vasodilation (EID-NTG). The percent vessel diameter response to the drug administration was used as the estimate of EID-NTG.

All the volunteers were instructed not to consume products that can alter endothelial function, such as alcohol, caffeine and fatty foods, for at least 24 hours before testing. All images were analyzed by the same blinded investigator.

Biochemical Measurements

Venous blood samples were obtained during the morning hours after an overnight fast. Triglycerides, total cholesterol, HDL-cholesterol (HDL-C) and fibrinogen were determined by automated enzymatic methods (Advia, Bayer, USA), and LDL-cholesterol (LDL-C) was calculated by the Friedewald formula [21]. High sensitivity C-reactive protein (hs-CRP) was determined by nephelometry (Boehringer, Germany), and Von-Willebrand factor (vWf) was measured by an enzyme-linked immunosorbent assay.

Statistical Analyses

Statistical analyses were conducted using SPSS for Windows version 17.0. All variables were examined for their normality in distribution by the Kolmogorov-Smirnov test. Because of the nonsymmetrical distributions, triglycerides and hs-PCR were log transformed. Nevertheless, for the sake of clarity, values are presented in the original scale. Descriptive statistics were used to identify sample characteristics and to provide summary indices of selected measures. Baseline demographic and clinical characteristics were compared using either Student's t test or Wilcoxon's test for continuous variables. Categorical variables were analyzed using the Chi-square test. Changes in outcomes were analyzed by General linear model (GLM) for repeated measurements, with measurements at different interventions as a within-subjects factor. A one-way ANCOVA, using the baseline measurements as the covariates, was conducted to evaluate differences between DI and DI+EXE. Results were expressed as

means (SD), median (interquartile range), or number of patients with the characteristic (%) and were considered statistically significant if the P-value was < 0.05.

RESULTS

In total, 48 subjects performed all baseline assessments. **Table 1** shows the baseline clinical and laboratory characteristics of the groups after randomization. The groups were similar in all the variables. After the initial assessments, 13 subjects dropped out before completing the study (seven – 2 men - of the DI group, and six – one man - in the DI+EXE group). Individuals who dropped out did not differ significantly in their baseline values when compared with those who completed the intervention ($p > 0.05$ for all). After exclusion of dropouts, the groups still did not show statistically significant differences in baseline values ($p > 0.05$ for all).

The time required for reduction of 5% of initial body weight was 79.7 days (63 - 96) for the DI group and 65.9 days (56 - 76) for the DI+EXE group ($p = 0.16$).

Table 2 shows the effect of interventions on anthropometric and biochemical parameters. After weight reduction, both groups significantly and similarly reduced BMI, WC, WHR, total cholesterol, HDL-C, triglycerides and hs-CRP. LDL-C remained unchanged in both groups.

Table 3 shows the results of interventions on the biochemical and ultrasound parameters of vascular function. There was a significant reduction of vWf in the two groups after weight loss, with no statistical difference between groups. However, plasma fibrinogen, the basal arterial diameter and both the endothelium dependent and independent vasodilation remained unchanged after the weight reduction, and this was the same for either treatment.

DISCUSSION

The purpose of this study was to assess a possible beneficial, independent effect of exercise training on vascular function in obese subjects who were still free from clinical cardiovascular disease, engaged in a weight-loss treatment. Studies show that individuals that combine diet and training over a pre-determined period of time have improvements in cardiovascular parameters when compared with those who only undergo diet [22]. However, these studies cannot isolate the contribution of physical training, because the weight loss was often magnified by adding exercise to diet. Thus, we tried to correct for the confounding effect of a differential weight loss by adopting as a target a percent loss of the initial weight. Even with this precaution, the length of treatment was similar between the two groups.

Obesity is associated with an increased prevalence of cardiovascular disease. A modest and sustained loss of initial weight (approximately 5-7%) is associated with improvement in clinical indicators of cardiovascular diseases [23]. In the present study, cardiovascular and metabolic responses to weight reduction of 5% of initial body weight were not different with the two strategies.

However, some of our findings, although lacking statistical significance, may point to some avenues to be explored. Muscle activity has an oxidative potential, and acute exercise is a physiological stress, causing heat release and metabolic changes with a concomitant increase in free radicals production. Nevertheless, regular, chronic exposure to exercise (physical training) promotes a set of morphological and functional adaptations that give the body greater capacity to respond to the stress of exercise [24]. Our data suggest that in patients undergoing exercise, hs-CRP and vWF are less importantly reduced than in those subjected to diet only. Our study lacks the power to confirm this impression. This could eventually be related to the relatively short duration

of training in our sample, or to the sample size. Further studies are required to clarify this issue.

There was a significant reduction of HDL-C with weight loss in both groups. This contradicts other studies in the literature [11,25-26], but may have been caused by the concomitant reduction in total cholesterol. Other studies have found similar reduction in HDL-C with a low-carbohydrate diet [3] and the maintenance of HDL-C levels after one-year intervention for weight loss [12]. Although statistically significant, the reduction in HDL-C did not reach pathological levels, and both groups still remained with desirable levels of the lipoprotein [5]. A non-significant reduction in LDL-C was also observed. The effects of physical training over longer periods of time, and of sustained weight loss on lipid profile have to be further explored. The effects of exercise on plasma lipoproteins are more pronounced in individuals with metabolic syndrome compared with those without metabolic abnormalities [27]. Although the results of our study did not show differences with both interventions, it is well acknowledged that a physically active lifestyle can contribute to the prevention of cardiovascular disease and that this may be mediated by improvements in lipid profile [28].

Previous studies have shown an inverse association between hs-CRP levels and arterial diameter in healthy [29] and hypercholesterolemic subjects [30]. The majority of subjects in our sample, all of them obese, had high levels of hs-CRP. Although without diagnosed coronary artery disease, 31.2% of them had endothelial dysfunction (FMD <8%) [20]. High sensitivity CRP is considered a good marker of low-grade inflammation in the vessel wall, has a role in the mechanism of atherosclerosis, through the activation and adhesion of monocytes, and contributes to the vulnerability of the atheromatous plaque (through increased proteolysis) [31]. Trained subjects with the

metabolic syndrome have lower concentrations of hs-CRP compared with those with low fitness level [28], and this effect may be related to the anti-inflammatory effect of exercise.

In general, endothelial function improves significantly after weight loss in obese subjects [32]. However, the results on the association between changes in endothelial function with anthropometric and biochemical parameters are still controversial. Some studies indicate an improvement in endothelial function after reduction of body weight [33-34], while others fail to show vascular benefits with weight loss [35]. We have shown a non-statistically significant increase in FMD in the group that performed exercise training (DI+EXE), suggesting that exercise may promote vascular benefit. The reduction of vWf, a biochemical marker of endothelial function, gives further support to the hypothesis of a beneficial effect of weight loss on vascular function in these individuals.

The relationships between endothelial function, diet and exercise are still controversial. In a cross-sectional study examining 160 eutrophic and overweight adult subjects, half of which reported exercising regularly, Kim and co-workers [36] found no significant differences in BMI and percentage body fat between those who exercised or not. However, individuals who exercised had lower levels of fibrinogen and hs-CRP and higher HDL-cholesterol, with no significant difference in other plasma lipids and endothelial function. Mavri et al [32] found a significant improvement of endothelial function and lipid profile in a small group of obese patients after one week of severe dietary restriction and reduction of 5% in body mass. After a further five months follow up, the subjects lost 8% of their body mass and increased their FMD. However, no additional effect was observed in the lipid profile after the first week. In our study, the lack of change in endothelial function after weight loss could be related to the

maintenance of LDL-cholesterol levels, since high levels of this lipoprotein have been associated to a reduction in FMD [37].

Our data did not show changes in the endothelium-independent vasodilation after the weight reduction interventions. This is in agreement with previous studies [33-35, 38]. Obese individuals without known cardiovascular disease have endothelial dysfunction in association with a reduced production of nitric oxide, an endothelium-dependent metabolite; this low yield may be due to increased oxidative stress or to insulin resistance [39]. Though we did not measure oxidative stress parameters, previous studies suggest that weight reduction decreases oxidative stress in obese subjects [40].

This study has several limitations. As in several other studies, the dropout rates in both groups were relatively high, and this limits the extrapolation of results. The sample size was small, and we did not have a control group. Therefore, we could not exclude a seasonal effect of metabolic disorders. Furthermore, it was not possible to predict the length of time that individuals would take to reduce body weight to the desired target. We cannot rule out that the amount of exercise (intensity and duration) was insufficient to promote beneficial cardiovascular effects.

In conclusion, our findings indicate that, in obese adults, clinically free from cardiovascular disease, a 5% reduction of body weight is associated with beneficial changes on total cholesterol, triglycerides and hs-CRP. Biochemical parameters of endothelial function (vWF) also improve after weight loss, but this is not reflected in a change of FMD. Based on these findings, we could confirm that the non-pharmacological treatment of obesity (lifestyle change and diet) is effective in reducing inflammation and blood coagulation parameters, and improves some parameters of lipid profile in these patients. At least during the first very few months of treatment, weight

loss seems to be the key variable, and physical training added little or no beneficial effect.

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Author contributions: Ana Paula Trussardi Fayh participated in all stages of the study, including, study design, data collection and analysis, and writing of the manuscript. Rogerio Friedman supervised the study, and had active part in designing the project, analyzing data and writing the manuscript. Alvaro Reischak-Oliveira contributed with data analysis and writing of the manuscript. Andre Lopes and Antonio Marcos Vargas da Silva assisted in data collection and analysis.

REFERENCES

1. National Task Force on the Prevention, Treatment of Obesity. Overweight, obesity and health risk. Arch Intern Med 2000; 160: 898–904.

2. Funahashi T, Nakamura T, Shimomura I, et al. Role of adipocytokines on the pathogenesis of atherosclerosis in visceral obesity. Intern Med 1999; 38: 202–6.

3. Keogh JB, BrinkworthGD, Clifton PM. Effects of weight loss on a low-carbohydrate diet on flow-mediated dilatation, adhesion molecules and adiponectin. Br J Nutr 2007; 98: 852–9.

4. de Jongh S, Lilien MR, Bakker HD, et al. Family history of cardiovascular events and endothelial dysfunction in children with familial hypercholesterolemia. Atherosclerosis 2002; 163: 193-7.

5. Sposito AC, Caramelli B, Fonseca FAH, et al. IV Diretriz Brasileira sobre Dislipidemias e Prevenção da Aterosclerose: Departamento de Aterosclerose da Sociedade Brasileira de Cardiologia. Arq Bras Cardiol 2007; 88: 2-19 .

6. Rossi R, Nuzzo A, Origliani G, et al. Prognostic role of flow-mediated dilation and cardiac risk factors in post-menopausal women. J Am Coll Cardiol 2008;51:997–1002.

7. Mombouli JV, Vanhoutte PM. Endothelial dysfunction: from physiology to therapy. J Mol Cell Cardiol 1999; 31: 61-74.

8. Jialal I, Devaraj S, Venugopal SK. C-reactive protein: risk marker or mediator in atherosclerosis? Hypertension 2004; 44: 6-11.

9. Koenig W. Predicting risk and treatment benefit in atherosclerosis: the role of C-reactive protein. Int J Cardiol 2005; 98: 199-206.

10. Danesh J, Collins R, Appleby P, et al. Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. JAMA 1998; 279: 1477- 82.

11. Tchernof A, Nolan A, Sites CK, et al. Weight loss reduces C-reactive protein levels in obese postmenopausal women. Circulation 2002; 105: 564-9.

12. Ziccardi P, Nappo F, Giugliano G, et al. Reduction of inflammatory cytokine concentrations and improvement of endothelial functions in obese women after weight loss over one year. Circulation 2002; 105: 804-9.

13. LaMonte MJ, Durstine JL, Yanowitz FG, et al. Cardiorespiratory fitness and C-reactive protein among a tri-ethnic sample of women. Circulation 2002; 106: 403-6.

14. Church TS, Barlow CE, Earnest CP, et al. Associations between cardiorespiratory fitness and C-reactive protein in men. Arterioscler Thromb Vasc Biol 2002; 22: 1869-76.

15. Hammett CJ, Prapavessis H, Baldi JC, et al. Effects of exercise training on 5 inflammatory markers associated with cardiovascular risk. Am Heart J 2006; 151: 367.e7-367.e16.

16. ABESO - Associação Brasileira para o Estudo da Obesidade e da Síndrome Metabólica. Diretrizes brasileiras de obesidade 2009/2010. 3.ed. Itapevi : AC Farmacêutica, 2009.

17. Karvonen JJ, Kentala E, Mustala O. The effects of training on heart rate: a “longitudinal” study. Ann Med Exp Biol Fenn 1957; 35: 307-15

18. McGuire DK, Levine BD, Williamson JW, et al. A 30-year follow-up of the Dallas Bed Rest and Training Study: I. Effect of age on the cardiovascular response to exercise. Circulation 2001; 104: 1350-7.

19. OMS. Organização Mundial da Saúde / Organização Pan-Americana da Saúde. Doenças crônico-degenerativas e Obesidade: estratégia mundial sobre alimentação saudável, atividade física e saúde. Brasília, 2003. [Access in: 2009 Maio 2]. Available in: http://www.opas.org.br/sistema/arquivos/d_cronic.pdf.

20. Corretti, MC, Anderson TJ, Benjamin EJ, et al. Guidelines for the Ultrasound Assessment of Endothelial-Dependent Flow-Mediated Vasodilation of the Brachial Artery A Report of the International Brachial Artery Reactivity Task Force. J Am Coll Cardiol 2002; 39: 257–65.

21. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. Clin Chem 1972; 18: 499-502.

22. Franz, MJ, VanWormer JJ, Crain AL, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc 2007; 107: 1755-67.

23. National Institute of Health. National Heart, Lung and Blood Institute. North American Association for the Study of Obesity. The Practical Guide Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. [Access in: 01 Set 2009] Available in: http://www.nhlbi.nih.gov/guidelines/obesity/prctgd_c.pdf.

24. Leung FP, Yung LM, Laher I, et al. Exercise, vascular wall and cardiovascular diseases: an uptade (part1). Sports Med 2008; 38: 1009-24.

25. Barbato KBG, Martins RCV, Rodrigues MLG, et al. Efeitos da redução de peso superior a 5% nos perfis hemodinâmico, metabólico e neuroendócrino de obesos grau 1. Arq Bras Cardiol 2006; 87: 12-21.

26. Bobbert T, Rochlitz H, Wegewitz U, et al. Changes of adiponectin oligomer composition by moderate weight reduction. Diabetes 2005; 54: 2712–9.

27. Aronson D, Sella R, Sheikh-Ahmad M, et al. The association between cardiorespiratory fitness and C-reactive protein in subjects with the metabolic syndrome. J Am Coll Cardiol 2004; 44: 2003-7.

28. National Cholesterol Education Program (NCEP). Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) final report. Circulation 2002; 106: 3143-421.

29. Yasmin, McEniery CM, Wallace S, et al. C-reactive protein is associated with arterial stiffness in apparently healthy individuals. Arterioscler Thromb Vasc Biol 2004; 24: 969-74.

30. Pirro M, Schillaci G, Savarese G, et al. Low-grade systemic inflammation impairs arterial stiffness in newly diagnosed hypercholesterolaemia. Eur J Clin Invest 2004; 34: 335-41.

31. Montero I, Orbe J, Varo N, et al. C-reactive protein induces matrix metalloproteinase-1 and -10 in human endothelial cells: implications for clinical and subclinical atherosclerosis. J Am Coll Cardiol 2006; 47: 1369-78.

32. Mavri A, Poredos P, Suran D, et al. Effect of diet-induced weight loss on endothelial dysfunction: early improvement after the first week of dieting. Heart Vessels 2011; 26: 31–8.

33. Hamdy O, Ledbury S, Mullooly C, et al. Lifestyle modification improves endothelial function in obese subjects with the insulin resistance syndrome. Diabetes Care 2003; 26: 2119–25.

34. Raitakari M, Ilvonen T, Ahotupa M, et al. Weight reduction with very-low-caloric diet and endothelial function in overweight adults: role of plasma glucose. Arterioscler Thromb Vasc Biol 2004; 24: 124–8.

35. Williams IL, Wheatcroft SB, Shah AM, et al. Obesity, atherosclerosis and the vascular endothelium: mechanisms of reduced nitric oxide bioavailability in obese humans. Int J Obes Relat Metab Disord 2002; 26: 754–64.

36. Kim K, Valentine RJ, Shin Y, et al. Associations of visceral adiposity and exercise participation with C-reactive protein, insulin resistance, and endothelial dysfunction in Korean healthy adults. Metabolism 2008; 57: 1181–9.

37. Kuvin JT, Patel AR, Sliney KA, et al. Comparison of flow-mediated dilatation of the brachial artery in coronary patients with low-density lipoprotein cholesterol levels 80 mg／dl versus patients with levels <80 to 100 mg/dl. Am J Cardiol 2005; 95: 93–5.

38. Wicherley TP, Brinkworth GD, Keogh JB, et al. Long-term effects of weight loss with a very low carbohydrate and low fat diet on vascular function in overweight and obese patients. J Intern Med 2010; 267: 452–61.

39. Cangemi R, Angelico F, Loffredo L, et al. Oxidative stress-mediated arterial dysfunction in patients with metabolic syndrome: effect of ascorbic acid. Free Radic Biol Med 2007; 43: 853–9.

40. Dandona P, Mohanty P, Ghanim H, et al. The suppressive effect of dietary restriction and weight loss in the obese on the generation of reactive oxygen species by leukocytes, lipid peroxidation, and protein carbonylation. J Clin Endocrinol Metab 2001; 86: 355–62.

Table 1 - Baseline clinical and laboratory characteristics of study group after randomization

Variables	DI (n=24)	DI+EXE (n=24)
Male (n/%)	8 (33.3)	8 (33.3)
Age (years)	31.4 ± 5.6	32.3 ± 6.4
Body Weight (kg)	95.4 ± 12.1	99.1 ± 12.0
Height (m)	1.65 ± 0.09	1.69 ± 0.07
Body Mass Index (kg/m^2)	34.8 ± 2.4	34.7 ± 2.2
Obesity grade I (n/%)	14 (58.3)	13 (54.17)
Waist Circumference (cm)	111.7 ± 7.7	110.8 ± 6.6
Hip Circumference (cm)	118.9 ± 8.6	120.9 ± 6.0
Waist-to-hip Ratio	0.84 ± 0.09	0.85 ± 0.08
Total Cholesterol (mg/dL)	192.4 ± 35.5	182.2 ± 30.3
HDL Cholesterol (mg/dL)	47.7 ± 9.8	48.0 ± 12.5
LDL Cholesterol (mg/dL)	114.3 ± 28.4	106.4 ± 27.4
Triglycerides (mg/dL)	119 (93 –203)	127 (69,5-186)
High-sensitive C-reactive Protein (g/dL)	3.8 (2.6 - 5,8)	4.1 (1,4-7.1)
von Willebrand factor (%)	117.4 ± 34.4	124.6 ± 41.6
Fibrinogen (mg/dL)	388.0 ± 96.3	376.3 ± 91.5
Basal diameter of vessel (mm)	3.23 ± 0.48	3.48 ± 0.53
FMD (%)	10.47 ± 4.90	8.20 ± 5.05
EID – TNG (%)	18.37 ± 6.18	16.16 ± 5.71

Values are n (%), mean ± SD or median (interquartile range). DI and DI+EXE groups did not differ, $P > 0.05$ for all comparations. FMD: flow mediated dilation, EID – TNG: endothelium-independent dilation after administration of sublingual nitroglycerin

Table 2 – Anthropometric and biochemical changes with interventions

	DI (n=18)			DI+EXE (n=17)					
	Before	**After**	**Change**	**Before**	**After**	**Change**	**P [a]**	**P [b]**	**P[c]**
Body weight (kg)	95.8 ± 13.7	91.5 ± 14.2	-4.31 ± 0.5	98.7 ± 13.0	94.0 ± 13.0	-4.66 ± 0.52	0.00	0.64	0.63
Body Mass Index (kg/m^2)	34.7 ± 2.4	33.1 ± 2.6	-1.58 ± 0.17	34.7 ± 2.4	33.1±2.1	-1.62 ± 0.17	0.00	0.79	0.79
Waist circumference (cm)	112.0 ± 8.7	108.3 ± 8.7	-3.42 ± 0.44	110.9 ± 7.4	107.0 ± 7.8	-3.92 ± 0.45	0.00	0.76	0.76
Hip circumference (cm)	120.4 ± 8.8	117.1 ± 8.6	-3,31 ± 1,18	120.2 ± 5.1	117.0 ± 4.7	-3.18 ± 2.2	0.00	0.83	0.84
Waist-to-hip ratio	0.83 ± 0.09	0.83 ± 0.09	0.00 ± 0.00	0.86 ± 0.08	0.85 ± 0.07	0.01 ± 0.00	0.06	0.05	0.09
Total cholesterol (mg/dL)	191.4 ± 31.5	175.4 ± 37.1	-15.83 ± 4.75	185.5 ± 31.2	175.3 ± 32.6	-10.47 ± 4.89	0.00	0.40	0.44
HDL cholesterol (mg/dL)	45.5 ± 7.6	42.1 ± 9.3	-3.55 ± 1.60	47.2 ± 11.6	44.6 ± 11.2	-2.47 ± 1.65	0.02	0.75	0.64
LDL cholesterol (mg/dL)	115.4 ± 27.2	109.5 ± 29.1	-5.23 ± 4.13	108.8 ± 29.0	107.8 ± 27.3	-1.67 ± 4.25	0.27	0.43	0.55
Triglycerides (mg/dL)	122 (94-206)	94 (65-177)	-33.8 ± 10.0	142 (83-202)	104 (67-158)	-39.4 ± 10.3	0.00	0.81	0.70
hs-RCP (mg/L)	3.3 (2.4-6.4)	2.8(1.5-4.8)	-1.35 ± 0.41	3.5 (1.5-5.8)	3.0 (1.1-5.9)	-0.45 ± 0.43	0.01	0.13	0.14

Data are presented in mean ± sd or median (interquartile range)

P[a] for intervention with repeated measures General Linear Model

P[b] for intervention x group with repeated measures General Linear Model

P[c] with analysis of covariance adjusted for baseline measures

hs-CRP: high sensitivity C-reactive protein

Table 3 – Changes in vascular parameters with interventions

	DI (n=18)			DI+EXE (n=17)					
	Before	**After**	**Change**	**Before**	**After**	**Change**	**P [a]**	**P [b]**	**P [c]**
Fibrinogen (mg/dL)	386.2±104.8	380.0 ±110.2	-5.59 ± 13.23	377.5 ± 90.0	372.4±85.3	-5.79 ± 13.61	0.56	0.95	0.99
Von Willebrand factor (%)	120.8 ± 37.0	103.5 ± 29.2	-17.63 ± 4.77	124.1 ± 39.4	119.4 ± 41.0	-4.27 ± 4.91	0.01	0.10	0.06
Basal diameter of artery (mm)	3.21 ± 0.46	3.15 ± 0.42	-0.07	3.51 ± 0.63	3.34 ± 0.55	-0.74	0.07	0.64	0.88
FMD (%)	9.9 ± 3.4	10.1 ±5.8	0.73 ± 1.11	8.1 ± 3.6	10.7 ± 3.6	2.08 ± 1.15	0.10	0.17	0.41
EID - TNG (%)	18.2 ± 5.5	19.4 ± 6.7	1.7 ± 1.21	15.9 ± 3.9	17.6 ± 4.2	1.06 ± 1.25	0.14	0.83	0.72

P[a] for intervention with repeated measures General Linear Model

P[b] for intervention x group with repeated measures General Linear model

P[c] with analyses of covariance adjusted for baseline measures

FMD: Flow mediated dilation measured by vascular ultrasound

EID-TNG: Endothelium-independent dilation after administration of sublingual nitroglycerin (NTG) spray

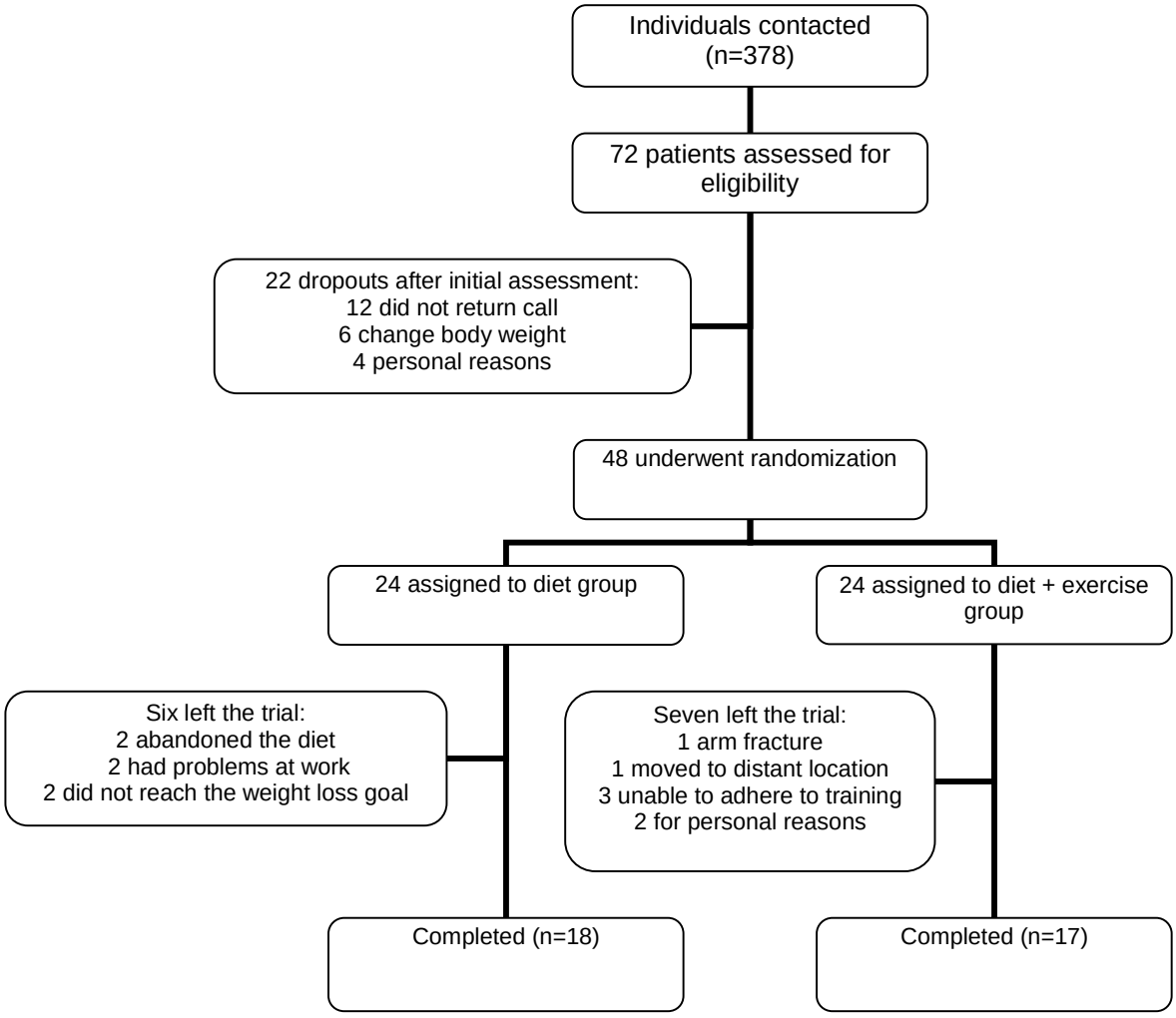

Figure 1 – Flow diagram of patient recruitment and randomization

CONSIDERAÇÕES FINAIS E PERSPECTIVAS

Os dados desta tese permitem concluir que uma perda de peso modesta (5% do peso inicial) através da dietoterapia isolada ou adicionada a treinamento físico diminui a gordura abdominal e a RI, além de melhorar alguns parâmetros do perfil lipídico em indivíduos obesos. Não foram observadas alterações significativas na função vascular após a redução de peso com as diferentes estratégias, exceto nos valores do FvW. O treinamento físico não agregou benefícios nas modificações dos parâmetros basais quando comparado ao grupo que realizou apenas dieta.

Os mecanismos fisiológicos que sustentam estes achados se relacionam com a inflamação de baixo grau observada em indivíduos obesos. Estudos têm demonstrado que a inflamação participa de todas as etapas da evolução da RI e aterosclerose. O tecido adiposo abdominal tem sido considerado um preditor de elevadas concentrações de PCR-us, devido à significativa expressão desta proteína nos depósitos de gordura abdominal, visceral e subcutâneo. Ainda, a hiperinsulinemia é considerada um fator de risco independente para a doença cardiovascular, já que tem um papel importante no desenvolvimento de outros componentes da síndrome metabólica, como a dislipidemia, a hipertensão e a hiperuricemia.

Apesar de não haver controvérsia sobre o fato de que balanço energético negativo causado por redução na ingestão calórica e a prática de exercícios físicos resulte em diminuição da massa corporal, há muita divergência sobre a melhor maneira de colocar em prática essas estratégias. Sabe-se que o tratamento dietético é mais bem-sucedido quando aliado a aumento no gasto energético e a um programa de modificação comportamental. No entanto, durante um programa de redução de peso, nem sempre é possível distinguir os efeitos isolados da dieta ou do exercício, uma vez que o paciente deve ser orientado a mudar estilo de vida, aumentando as atividades físicas diárias.

Devido ao fato de não ter sido observado diferença entre os tipos de tratamento, pode-se hipotetizar que, em um primeiro momento do tratamento da obesidade, a redução da massa corporal pode ser mais efetiva na prevenção das complicações metabólicas do que o treinamento físico.

Como outros ensaios clínicos, as limitações deste estudo merecem ser levadas em consideração. O pequeno tamanho amostral não nos permite a extrapolação dos resultados. Estudos clínicos com a utilização de exames potencialmente danosos à saúde do paciente, mesmo com baixo risco, como no caso desta tomografia computadorizada que utiliza apenas um corte, devem ser criteriosamente planejados em relação aos seus participantes. Sempre que possível, o menor número de indivíduos arrolados nestes estudos garantem a segurança clínica do protocolo de estudo e reduzem as chances de efeitos adversos. O uso da tomografia computadorizada na prática clínica é limitado pelo alto custo e pela complexidade. Para avaliar a composição corporal na clínica diária, as variáveis antropométricas são satisfatórias. Desta forma, a tomografia computadorizada para avaliar gordura abdominal tem seu uso restrito à pesquisa, dentro de estritos critérios de segurança.

Outra limitação do presente estudo é a ausência de um grupo controle. A decisão de não incluir este grupo foi tomada a partir da premissa de que não seria correto não oferecer tratamento aos indivíduos com intenção de reduzir a massa corporal. Sendo a obesidade um fator de risco independente para doença arterial coronariana, estratégias de redução de peso devem ser incentivadas, com orientações para modificação do estilo de vida. Desta forma, seria questionável propor a manutenção da massa corporal nos indivíduos do grupo controle durante o seguimento.

A avaliação dos estudos que comparam os efeitos da redução ponderal através da dieta isolada ou associada com exercício é difícil em função das diferentes abordagens metodológicas. Fatores como o tipo de exercício, a

duração e a intensidade, são de difícil padronização, e podem afetar as respostas metabólicas e hormonais. Ainda, é igualmente difícil avaliar a adesão ao tratamento dietético, e com isso questiona-se se o sucesso da perda de peso ocorre pela restrição calórica ou pelo aumento do gasto energético do treinamento. No entanto, as intervenções para a promoção da perda de peso devem ser estimuladas para o combate desta epidemia global, e a necessidade de aliar o treinamento físico à restrição energética deve ser avaliada para maximizar o benefício cardiovascular.

Como perspectivas futuras a estudos clínicos, o aumento do tempo de seguimento destes pacientes poderia esclarecer aspectos que ficaram obscuros no presente estudo. Provavelmente a duração do treinamento foi insuficiente para promover as alterações vasculares já amplamente descritas na literatura e não encontradas neste estudo. A alteração do marcador bioquímico FvW indica esta possibilidade, uma vez que é considerado um marcador precoce de disfunção endotelial. Ainda, aumentando a magnitude da perda de peso, provavelmente seria possível observar alterações na glicemia destes pacientes, e não apenas na insulinemia e no HOMA-IR. Desta forma, períodos de tempo mais longos, que proporcionem maior perda de peso relativa, tornam-se necessários para complementar os achados deste estudo.