UNIVERSIDADE FEDERAL DO RIO GRANDE DO SUL
FACULDADE DE MEDICINA
PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS MÉDICAS: ENDOCRINOLOGIA

Scheila Karen Graff

Dieta, atividade autonômica e efeitos do orlistat em pacientes com síndrome dos ovários policísticos

Porto Alegre, 2016

Scheila Karen Graff

Dieta, atividade autonômica e efeitos do orlistat em pacientes com síndrome dos ovários policísticos

Tese apresentada como requisito parcial para obtenção do título de Doutor em Endocrinologia, à Universidade Federal do Rio Grande do Sul, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia.

Orientadora: Profª Drª Poli Mara Spritzer

Porto Alegre, 2016

CIP - Catalogação na Publicação

Graff, Scheila Karen
Dieta, atividade autonômica e efeitos do orlistat em pacientes com síndrome dos ovários policísticos / Scheila Karen Graff. -- 2016.
82 f.

Orientadora: Poli Mara Spritzer.

Tese (Doutorado) -- Universidade Federal do Rio Grande do Sul, Faculdade de Medicina, Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Porto Alegre, BR-RS, 2016.

1. Síndrome dos ovários policísticos. 2. Dieta. 3. Orlistat. 4. Variabilidade da frequência cardíaca. 5. Modulação autonômica. I. Spritzer, Poli Mara, orient. II. Título.

Elaborada pelo Sistema de Geração Automática de Ficha Catalográfica da UFRGS com os dados fornecidos pelo(a) autor(a).

AGRADECIMENTOS

À minha orientadora, Profª Drª Poli Mara Spritzer, por seus ensinamentos e pela confiança que depositou em mim nos últimos anos.

À Fernanda Missio Mário, pelo apoio, amizade, compreensão e por tornar os meus dias de trabalho mais alegres.

Aos colegas da Unidade de Endocrinologia Ginecológica do Serviço de Endocrinologia do Hospital de Clínicas de Porto Alegre: Betânia Rodrigues dos Santos, Débora Martinho Morsch, Fabíola Satler, Gislaine Casanova, Larissa Paixão, Sheila Lecke, Ramon Bossardi Ramos, Thaís Rasia da Silva e Vitor Fabris. Obrigada por proporcionarem um excelente ambiente de trabalho e pela amizade.

À Miriam Sant'Helena e Natália Goulart, sempre incansáveis em ajudar.

Aos meus pais, Gilberto e Iris Graff, o meu agradecimento pelo amor incondicional.

À minha sogra, Vera Lúcia Ely, pelo constante incentivo e disposição de ajudar. Ao meu sogro, Fritz Birkholz, pelo apoio e confiança.

Ao meu irmão, Luiz Henrique Graff, pela amizade e companheirismo.

Ao meu marido, Frederico Birkholz, por estar sempre presente e me apoiar incondicionalmente nos momentos mais difíceis.

Aos amigos e a todas as pessoas que, direta ou indiretamente, contribuíram para a execução desta tese de doutorado.

Esta tese de doutorado segue o modelo proposto pelo Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, Faculdade de Medicina, Universidade Federal do Rio Grande do Sul, sendo apresentada na forma de três manuscritos sobre o tema da tese e considerações finais:

- Artigo de revisão: Composição da dieta no tratamento da síndrome dos ovários policísticos

- Artigo original 1: Effects of orlistat *vs*. metformin on weight loss-related clinical variables in women with PCOS: systematic review and meta-analysis

- Artigo original 2: Saturated fat intake is associated with decreased stress-related heart rate variability in women with PCOS

- Considerações finais

RESUMO

A síndrome dos ovários policísticos (PCOS) é o distúrbio endócrino mais comum em mulheres em idade reprodutiva, sendo caracterizado por anovulação crônica e manifestações de hiperandrogenismo. O sobrepeso e a obesidade afetam a maioria das mulheres com PCOS e, quando presentes, podem acentuar as alterações reprodutivas e metabólicas associadas à síndrome. Dessa forma, a redução de peso através da restrição calórica é de suma importância nas mulheres com PCOS e excesso de peso. Entretanto, ainda não está estabelecido se a composição da dieta por si só pode ter efeitos significativos sobre as alterações metabólicas e hormonais da PCOS. Poucos ensaios clínicos randomizados avaliando o efeito de diferentes intervenções dietéticas foram realizados em mulheres com PCOS, sendo que os estudos existentes apresentam, em sua maioria, curta duração e pequeno tamanho amostral. Dietas com redução de carboidratos, assim como dietas com baixo índice glicêmico e carga glicêmica têm sido o principal foco de estudo em mulheres com PCOS e, embora os resultados sejam controversos, estudos demonstram superioridade desses tipos de dieta em relação a uma dieta convencional na melhora do perfil antropométrico e da sensibilidade insulínica. Por outro lado, mudanças de estilo de vida podem não ser suficientes para promover uma redução de peso significativa e intervenções farmacêuticas podem ser necessárias. O orlistat é um fármaco usado no tratamento da obesidade que age através da inibição das lipases gástricas e pancreáticas e não tem efeitos adversos sistêmicos, sendo o único fármaco antiobesidade disponível em muitos países. Dessa forma, com o objetivo de avaliar os efeitos do orlistat nas variáveis clínicas relacionadas à perda de peso, assim como comparar esses efeitos com aqueles obtidos com o uso da metformina, em mulheres com PCOS, realizou-se uma revisão sistemática e meta-análise. Os resultados dessa revisão sistemática sugerem que o orlistat leva a uma redução significativa do peso/índice de massa corporal (IMC) em mulheres com PCOS. Além disso, os resultados da meta-análise evidenciaram que o orlistat e a metformina têm efeitos similares na redução de IMC, testosterona, *Homeostasis Model Assessment of Insulin Resistance* (HOMA-IR) e insulina em mulheres com PCOS com sobrepeso e obesidade. Outro fator a ser considerado é o aumento do risco cardiovascular associado à PCOS. Estudos demonstram que as alterações cardiovasculares pré-clínicas são mais frequentes nesta população do que em mulheres sem a síndrome de mesma idade. A variabilidade da frequência cardíaca (VFC) é a medida das variações cíclicas dos intervalos entre as batidas cardíacas (intervalo R-R), e reflete a função

cardíaca autonômica. Alterações na VFC podem refletir doença cardiovascular subclínica. A redução do consumo de gordura saturada tem um importante papel na prevenção primária e secundária de doenças cardiovasculares. Dessa forma, realizou-se um estudo com objetivo de avaliar se o consumo de ácidos graxos saturados (SFA) está associado com VFC em mulheres com PCOS. Oitenta e quatro mulheres com PCOS foram incluídas no estudo. A análise da VFC foi realizada no repouso e após teste de *stress* mental. As participantes foram estratificadas de acordo com a mediana do consumo de SFA (8,5% do consumo energético total), avaliado por questionário de frequência alimentar. Os resultados desse estudo indicam que o menor consumo de SFA combinado com menor consumo de carne vermelha e maior consumo de frutas, vegetais e feijões está associado com melhor VFC em resposta ao *stress* e níveis circulantes mais baixos de testosterona em mulheres com PCOS.

Palavras-chave: Síndrome dos ovários policísticos. Dieta. Orlistat. Metformina. Variabilidade da frequência cardíaca. Modulação autonômica. Ácidos graxos saturados.

ABSTRACT

Polycystic ovary syndrome (PCOS), the most common endocrinological disorder in women of reproductive age, is characterized by hyperandrogenism and chronic anovulation. Obesity or overweight affect most of patients with PCOS and may accentuate reproductive and metabolic issues. Thus, weight reduction through calorie restriction is extremely important in overweight/obese PCOS women. However, it remains unclear whether the diet composition per se may have significant effects on metabolic and hormonal issues of PCOS. A few randomized controlled trials (RCTs) evaluating the effect of different dietary interventions have been performed in PCOS women, and most studies have short-term and small sample size. Low-carbohydrate diets as well as diets with low glycemic index and glycemic load have been the main focus of studies in PCOS women, and although the results are controversial, studies demonstrated superiority of these diets in relation to a conventional diet in improving anthropometric profile and insulin sensitivity. On the other hand, lifestyle changes may not be sufficient to promote significant weight loss, and pharmaceutical interventions may be required. Orlistat is a drug for the treatment of obesity that acts by inhibiting gastric and pancreatic lipases. Orlistat does not have systemic adverse effects and it is currently the sole anti-obesity agent available in many countries. In this way, a systematic review and meta-analysis was performed. The aim was to assess the effects of orlistat on weight loss-associated clinical variables and to compare these effects to those obtained with metformin treatment in overweight/obese women with PCOS. The results of this systematic review indicate that orlistat leads to significant reduction in weight/body mass index (BMI) in PCOS. In addition, the results of meta-analysis indicate that orlistat and metformin have similar effects in reducing BMI, HOMA, testosterone and insulin in overweight/obese PCOS women. Another point to consider is the increased cardiovascular risk associated with PCOS. Studies have demonstrated that preclinical cardiovascular disorders are more frequent in PCOS than in women without the syndrome of same age. The heart rate variability (HRV) is a measure of the time variation between heart beats (R-R interval), and reflects autonomic cardiac function. Alterations in HRV may reflect subclinical cardiovascular disease. Reduction in saturated fat intake has an important role in primary and secondary of cardiovascular disease. Thus, we performed a study assessing whether dietary saturated fatty acids (SFA) intake is associated with stress-induced HRV in patients with PCOS. Eighty-four PCOS women were included in the study. The HRV analysis was

performed at rest and after mental stress test. Participants were stratified by median SFA intake (8.5% of daily energy intake), assessed by food frequency questionnaire. The results indicate that lower SFA intake is associated with more favorable stress-related HRV and lower testosterone in women with PCOS.

Keywords: Polycystic ovary syndrome. Diet. Orlistat. Metformin. Heart rate variability. Autonomic modulation. Saturated fatty acids.

SUMÁRIO

1. CAPÍTULO I – ARTIGO DE REVISÃO: Composição da dieta no tratamento da síndrome dos ovários policísticos…….....9

2. CAPÍTULO II – ARTIGO ORIGINAL 1: Effects of orlistat *vs*. metformin on weight loss-related clinical variables in women with PCOS: systematic review and meta-analysis…….....……..…….35

3. CAPÍTULO III – ARTIGO ORIGINAL 2: Saturated fat intake is associated with decreased stress-related heart rate variability in women with PCOS.....64

4. CONSIDERAÇÕES FINAIS.....82

CAPÍTULO I

Artigo de revisão: Composição da dieta no tratamento da síndrome dos ovários policísticos

Composição da dieta no tratamento da síndrome dos ovários policísticos

Título resumido: Dieta e PCOS

Scheila K Graff,[a] Fernanda M Mario,[a,b] Poli Mara Spritzer,[a,c]

[a]Unidade de Endocrinologia Ginecológica, Serviço de Endocrinologia, Hospital de Clínicas de Porto Alegre (HCPA), Rua Ramiro Barcelos, 2350, 90035-003, Porto Alegre, Brasil.

[b]Instituto Federal de Educação, Ciência e Tecnologia do Rio Grande do Sul, Rua Coronel Vicente, 281, 90030-041, Porto Alegre, Brasil.

[c]Laboratório de Endocrinologia Molecular, Departamento de Fisiologia, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2350, 90035-003, Porto Alegre, Brazil.

Autor correspondente:

Poli Mara Spritzer, MD, PhD

Serviço de Endocrinologia, Hospital de Clínicas de Porto Alegre, e Laboratório de Endocrinologia Molecular, Departamento de Fisiologia, Universidade Federal do Rio Grande do Sul

90035-003 - Porto Alegre, RS – Brasil

Fone: +55-51-3359.8027 – Fax: +55-51-3359.8777

e-mail: spritzer@ufrgs.br

RESUMO

A síndrome dos ovários policísticos (PCOS) é o distúrbio endócrino mais comum em mulheres em idade reprodutiva, sendo caracterizado por anovulação crônica e manifestações de hiperandrogenismo. Além dos distúrbios reprodutivos, as pacientes com PCOS apresentam frequentemente alterações metabólicas que incluem obesidade, resistência insulínica (RI), dislipidemia e hipertensão, sendo que a presença de obesidade pode exacerbar as demais alterações. Estudos têm demonstrado que uma redução de peso relativamente pequena (5%) pode melhorar a RI, o hiperandrogenismo, a função menstrual e a fertilidade em mulheres com PCOS. Dessa forma, a redução de peso através da restrição calórica é de suma importância nas mulheres com PCOS com sobrepeso e obesidade. Entretanto, ainda não está estabelecido se a composição da dieta por si só pode ter efeitos significativos sobre as alterações metabólicas e hormonais da PCOS. Poucos ensaios clínicos randomizados avaliando o efeito de diferentes intervenções dietéticas foram realizados em mulheres com PCOS, sendo que os estudos existentes apresentam, em sua maioria, curta duração e pequeno tamanho amostral. Dietas com redução de carboidratos, assim como dietas com baixo índice glicêmico e carga glicêmica têm sido o principal foco de estudo em mulheres com PCOS. Embora os resultados sejam controversos, estudos demonstram superioridade desses tipos de dieta em relação a uma dieta convencional na melhora do perfil antropométrico e da sensibilidade insulínica. Contudo, com base nas atuais evidências, não é possível definir qual o melhor tipo de dieta para essa população. Mais estudos são necessários para avaliar o efeito de diferentes tipos de dietas na redução de peso e melhora do perfil metabólico e hormonal na população com PCOS.

Palavras-chave: Síndrome dos ovários policísticos. Dieta. Obesidade. Resistência insulínica.

INTRODUÇÃO

A síndrome dos ovários policísticos (PCOS) é um distúrbio de apresentação clínica heterogênea cujas principais características clínicas são anovulação crônica e manifestações de hiperandrogenismo (1-3). De acordo com o consenso de Rotterdam (4), a síndrome é definida pela presença de pelo menos dois dos seguintes critérios: oligo ou anovulação; hiperandrogenismo clínico e/ou bioquímico; presença de ovários policísticos ao ultrasom (12 ou mais folículos com 2 a 9 mm ou aumento do volume ovariano (> 10 cm^3) em pelo menos um ovário). Ainda, devem ser excluídas outras patologias que causem hiperandrogenismo, como: tumores secretores de androgênios, hiperplasia adrenal congênita, síndrome de Cushing, hiperprolactinemia e alterações tireoidianas.

A PCOS é o distúrbio endócrino mais comum em mulheres em idade reprodutiva e sua prevalência varia de acordo com o diagnóstico utilizado, com estimativas variando de 9% a 18% das mulheres em idade reprodutiva (3, 5, 6). Além dos distúrbios reprodutivos, as pacientes com PCOS apresentam frequentemente alterações metabólicas que incluem obesidade, resistência insulínica (RI), dislipidemia e hipertensão (7-9).

Embora existam evidências que sustentem o envolvimento de fatores genéticos e ambientais/estilo de vida no desenvolvimento da PCOS, a etiologia exata permanece desconhecida. A RI e o hiperandrogenismo desempenham um papel chave na fisiopatologia da PCOS, sendo que a RI afeta em torno 85% das pacientes (75% das mulheres eutróficas e 95% das mulheres com excesso de peso) (10). Segundo alguns autores (11-13), a hiperinsulinemia resultante aumenta a produção de androgênios e reduz a globulina carreadora dos hormônios sexuais (SHBG), levando ao hiperandrogenismo.

A obesidade e o sobrepeso são altamente prevalentes na população com PCOS (14, 15) e, em comparação com mulheres sem a síndrome pareadas por índice de massa corporal (IMC), as mulheres com PCOS apresentam maior quantidade de gordura abdominal (16, 17). A presença de obesidade pode exacerbar as alterações metabólicas e reprodutivas associadas à síndrome (18). Estudos têm demonstrado que uma redução de peso relativamente pequena (5%) pode melhorar a RI, o hiperandrogenismo, a função menstrual e a fertilidade em mulheres com PCOS (19-20). Dessa forma, modificação de estilo de vida com dieta e atividade física é o tratamento de primeira linha para mulheres com sobrepeso/obesidade com PCOS (21-23). Entretanto, embora a importância da restrição calórica para redução de peso em mulheres com PCOS já esteja bem estabelecida, ainda não está claro se a composição da dieta por si só pode ter efeitos significativos sobre as alterações metabólicas e hormonais da

PCOS (24). Dessa forma, o objetivo da presente revisão foi comparar o efeito de diferentes intervenções dietéticas (Tabela 1) nas variáveis antropométricas, metabólicas (resistência insulínica e perfil lipídico) e hormonais, assim como na regularidade menstrual, em mulheres com PCOS.

DIETAS COM REDUÇÃO DE CARBOIDRATOS E AUMENTO DE PROTEÍNAS

Uma dieta moderada em proteínas (15% do valor energético total - VET), rica em carboidratos (55% do VET) e com moderado percentual de gordura (30% do VET), em conjunto com atividade física regular, tradicionalmente tem sido sugerida para redução de peso e melhora das disfunções reprodutivas e metabólicas da PCOS (25). Entretanto, apesar da consistência das recomendações tradicionais, tem havido grande interesse em abordagens alimentares alternativas destinadas à redução de peso e do risco cardiovascular e de diabetes.

Os carboidratos são o único tipo de macronutriente que afeta diretamente os níveis de glicose pós-prandial, sendo o principal determinante dietético da secreção de insulina (26). Dessa forma, os carboidratos têm sido o principal foco dos estudos de intervenção dietética em mulheres com PCOS. Ao mesmo tempo, alguns pesquisadores têm sugerido que dietas hiperprotéicas podem aumentar a redução de peso devido ao maior poder de saciedade das proteínas em relação aos carboidratos e lipídeos (27-29). Além disso, evidências demonstram que as proteínas apresentam um maior efeito termogênico (aumento no gasto de energia associado aos processos de digestão, absorção e metabolismo do alimento) em relação aos carboidratos e lipídeos (28, 30). Entretanto, os estudos de intervenção dietética com substituição de carboidratos por proteínas em mulheres com PCOS (Tabela 2) não têm resultados consistentes.

Ensaio clínico randomizado (ECR) realizado por Stamets et al. (31) examinou o efeito de 4 semanas de intervenção com dois tipos de dieta hipocalóricas, uma hiperprotéica e outra normoprotéica, ambas com mesmo percentual de lipídeos (40% carboidratos, 30% proteínas e 30% lipídeos *vs*. 55% carboidratos, 15% proteínas e 30% lipídeos, respectivamente). Treze participantes de cada grupo completaram o estudo. Não houve alteração na atividade física habitual dos participantes. Ambos os grupos tiveram redução significativa de peso, insulina de jejum, área sob a curva de insulina no teste de tolerância oral à glicose (TTG) e androgênios, sem diferença entre os tratamentos.

Da mesma forma, Moran et al. (32) e Galletly et al. (33) realizaram um ECR comparando uma dieta hiperprotéica com redução de carboidratos (40% carboidratos, 30% proteínas e 30% lipídeos) com uma dieta com menor teor de proteínas e maior percentual de carboidratos (55% carboidratos, 15% proteínas e 30% lipídeos). Nas primeiras 12 semanas de estudo as dietas tiveram restrição calórica, seguidas de 4 semanas de dieta para manutenção do peso, sendo que 14 participantes de cada grupo completaram o estudo. As participantes realizaram exercícios físicos em grupo semanalmente como parte do protocolo e foram aconselhadas a praticar atividade física pelo menos 3 vezes por semana. Ambas as dietas reduziram igualmente o peso (média geral de 7,5%) e a gordura abdominal (media geral de 12,5%). Melhoras na insulina de jejum, no *Homeostasis Model Assessment of Insulin Resistance* (HOMA-IR), na regularidade menstrual e no perfil lipídico ocorreram independentemente da composição da dieta. Ambas as dietas reduziram igualmente testosterona, índice de androgênios livres (IAL) e aumentaram o SHBG. Entretanto, na dieta normoprotéica, houve diminuição de 10% no HDL-colesterol (HDL-c) durante a fase de restrição energética, e aumento de 44% no IAL durante a fase de manutenção do peso, o que não ocorreu na dieta hiperprotéica.

Diferentemente, outros estudos mostraram benefícios da redução de carboidratos com aumento do teor protéico da dieta em mulheres com PCOS. Sorensen et al. (34) realizaram um ensaio clínico controlado de 6 meses comparando uma dieta normocalórica hiperprotéica (30% carboidratos, 40% proteínas e 30% lipídeos) com uma dieta normocalórica padrão (55% carboidratos, 15% proteínas e 30% lipídeos). As participantes de ambos os grupos receberam a recomendação de realizar 30 minutos de atividade física por dia. A dieta hiperprotéica (n=14) levou a uma redução maior de peso, de gordura corporal, da cintura, e de glicose em relação à dieta padrão (n=13). Não houve diferença entre os grupos em relação à testosterona, SHBG e níveis de lipídeos sanguíneos.

Mehrabani et al. (35) verificaram que o tratamento por 12 semanas com uma dieta hipocalórica com a combinação de alto teor de proteínas e baixa carga glicêmica (CG) (40% carboidratos de baixa e média CG, 30% proteínas e 30% lipídeos) resultou em uma redução significativamente maior no HOMA-IR e na insulina de jejum quando comparada com uma dieta hipocalórica convencional (55% carboidratos, 15% proteína e 30% lipídeos) em mulheres com PCOS. Inicialmente foram incluídas 30 participantes em cada grupo, porém 7 participantes do grupo com dieta hiperprotéica e 4 do grupo com dieta padrão não completaram o estudo. As participantes foram orientadas a não alterar sua atividade física

habitual durante o estudo. Ambas as dietas resultaram em redução significativa de peso, reduziram testosterona, sulfato de dehidroepiandrosterona (SDHEA) e aumentaram SHBG, sem diferença entre os grupos. A redução da circunferência da cintura foi significativamente maior com dieta hiperprotéica com baixa CG do que com a dieta convencional. Não houve efeito da redução de energia ou da composição da dieta nos níveos de hormônio luteinizante (LH), hormônio folículo-estimulante (FSH) e perfil lipídico, com exceção do LDL-colesterol (LDL-c), que diminuiu significativamente em ambos os grupos.

DIETAS COM REDUÇÃO DE CARBOIDRATOS E AUMENTO DE LIPÍDEOS

Ainda com foco na redução de carboidratos, estudos têm sido realizados com objetivo de avaliar os efeitos da substituição de carboidratos por lipídeos em mulheres com PCOS. O objetivo desses estudos (Tabela 2) tem sido verificar se a qualidade da dieta, independentemente da restrição calórica, traz benefícios para essa população.

Gower et al. (36) investigaram os efeitos de uma dieta normocalórica com moderada redução de carboidratos em comparação com uma dieta padrão em mulheres com PCOS (41% carboidratos, 19% proteínas e 40% lipídeos *vs*. 55% carboidratos, 18% proteínas e 27% lipídeos, respectivamente), sendo um dos critérios de exclusão a realização de mais de 2h de exercício físico estruturado por semana. O estudo teve um design *crossover* e cada dieta foi mantida por 8 semanas. Vinte e três participantes completaram o estudo com ambas as dietas e 4 realizaram apenas a intervenção com dieta com redução de carboidratos. A dieta com redução de carboidratos induziu reduções significativas na resposta basal das células β, insulina e glicose de jejum e HOMA-IR, além de aumentos significativos na sensibilidade à insulina, resposta dinâmica das células β ("primeira fase"), testosterona e todas as medidas de colesterol. Não houve melhora de nenhuma das variáveis com a dieta padrão. Resultados adicionais desse mesmo estudo foram reportados posteriormente por Goss et al. (37). O grupo com dieta com redução de carboidratos apresentou uma redução significativamente maior da gordura corporal em relação ao grupo com dieta padrão (3,7% *vs*. 2,2%, respectivamente). Somente a dieta com redução de carboidratos induziu decréscimos no tecido adiposo subcutâneo abdominal e intra-abdominal (-7,1% e -4,6%, respectivamente), enquanto a dieta padrão reduziu a massa magra total (-1,3%). Os autores sugerem que o mecanismo fisiológico subjacente à maior redução de tecido adiposo na dieta com redução de carboidratos,

independente da restrição calórica, possa estar relacionado com alterações na secreção de insulina.

Douglas et al. (38) comparam três tipos de dietas normocalóricas, uma delas com baixo teor de carboidratos, outra convencional, e outra enriquecida com ácidos graxos monoinsaturados (com distribuição padrão de macronutrientes) sendo que as participantes foram orientadas a manter sua atividade física habitual (carboidratos, proteínas, lipídeos: 43%, 15%, 45% *vs*. 56%, 16%, 31% *vs*. 55%, 15%, 33%, respectivamente). Cada participante (n=11) consumiu os três tipos de dieta, cada uma por 16 dias, com um período de *washout* de 3 semanas. A dieta com baixo teor de carboidratos reduziu mais a insulina de jejum do que a dieta padrão, e reduziu mais a resposta aguda de insulina à glicose em relação à dieta enriquecida com ácidos graxos monoinsaturados. Não foram demonstradas melhoras nos hormônios reprodutivos (testosterona total e livre, SDHEA, SHBG, LH, e FSH) com os três tipos de dietas. Houve redução significativa do colesterol total após a intervenção, sem diferença entre os tratamentos.

Entretanto, ECR de Moran et al. (39) demonstrou que uma dieta com restrição de carboidratos e uma dieta com restrição de gorduras foram igualmente eficazes na manutenção da redução de peso. As participantes seguiram uma dieta normocalórica com contagem de carboidratos (120 g de carboidratos por dia) ou contagem de lipídeos (50 g de lipídeos por dia) por 6 meses. Esse período foi precedido por 2 meses de dieta para redução de peso baseada na substituição de duas refeições diárias por substitutos de refeição, sendo essa dieta igual para os dois grupos. Vinte e três participantes completaram as duas fases do estudo. As participantes receberam um pedômetro com objetivo de realizar 8.000 passos diários. Entretanto, na semana 32 do estudo o consumo alimentar do grupo com contagem de carboidratos foi de 135 g de carboidratos e 56 g de lipídeos por dia (40% carboidratos, 21% proteínas e 35% lipídeos) e do grupo com contagem de lipídeos foi de 156 g de carboidratos e 54 g de lipídeos por dia (43% carboidratos, 21% proteínas e 31% lipídeos), diferindo da dieta prescrita.

DIETAS COM BAIXO ÍNDICE GLICÊMICO E CARGA GLICÊMICA

Os carboidratos variam em sua capacidade de aumentar os níveis circulantes de glicose e insulina pós-prandiais. O índice glicêmico (IG), proposto por Jenkins et al. (40), é um parâmetro utilizado para classificar os alimentos contendo carboidratos de acordo com a

resposta glicêmica que estes promovem, em relação à resposta observada após consumo de um alimento de referência (pão branco ou glicose). O IG é, portanto, uma medida da qualidade do carboidrato ingerido. Posteriormente, em 1997, foi introduzido o conceito de carga glicêmica (CG), por pesquisadores da Universidade de Harward, uma medida que incorpora não só a qualidade como também a quantidade dos carboidratos da dieta, sendo o produto do IG de um alimento e do teor de carboidratos disponíveis nele (41-43). A validade fisiológica e superioridade da CG dietética em relação ao conteúdo de carboidratos isolado para estimar a glicemia pós-prandial e a demanda de insulina em indivíduos saudáveis já foram demonstradas (44).

A taxa de absorção dos carboidratos após uma refeição tem efeito significativo sobre a reposta hormonal e metabólica pós-prandial. O consumo de alimentos de alto IG produz um período inicial de altos níveis de glicose e insulina, seguido, em muitos indivíduos, de hipoglicemia reativa, secreção de hormônios contrarregulatórios e elevadas concentrações séricas de ácidos graxos livres (45). Esses eventos podem promover o consumo alimentar excessivo (45). Além disso, alguns autores sugerem que a hiperinsulinemia crônica gerada por estes alimentos poderia prejudicar a função das células beta pancreáticas e, eventualmente, levar ao desenvolvimento de intolerância à glicose e diabetes mellitus tipo 2 (DM2) (46, 47).

Existem atualmente fortes evidências da relação do IG e da CG com a prevenção e o tratamento da obesidade e das doenças crônicas (45, 48, 49). Um dos mecanismos propostos para a relação entre a qualidade glicêmica da dieta e a obesidade envolve a saciedade prolongada e a consequente diminuição do consumo de energia a partir de dietas de baixo IG/CG (50). As propriedades das fibras solúveis presentes em cereais integrais e leguminosas, de formação de gel viscoso, atenuam o aumento da glicose e níveis de insulina no sangue. Alimentos ricos em fibras solúveis viscosas têm um baixo IG devido à sua capacidade de expandir e promover uma digestão prolongada aumentando a saciedade (45, 51). Além disso, sugere-se que reduzindo as concentrações de insulina pós-prandiais pode-se aumentar a oxidação de gordura após a refeição e, assim, reduzir o consumo alimentar excessivo e o ganho de peso a longo prazo (52).

Diante disso, estudos com dietas de baixo IG e CG têm sido realizados em mulheres com PCOS (Tabela 2). Marsh et al. (53) realizaram estudo de intervenção não randomizada comparando uma dieta hipocalórica padrão (IG=59%) com uma dieta hipocalórica de baixo IG (IG=40%). As participantes realizaram a intervenção por 12 meses ou até atingirem 7% de redução de peso. As dietas tiveram distribuição de macronutrientes semelhante (50%

carboidratos, 23% proteínas e 27% lipídeos), sendo que as participantes foram incentivadas a realizar 30 minutos de exercícios físicos de intensidade moderada na maioria dos dias e receberam um pedômetro com o objetivo de atingirem 10.000 passos por dia. Das 96 participantes que iniciaram o estudo apenas 49 o completaram. Considerando as participantes que completaram o estudo, o grupo com dieta de baixo IG aumentou significativamente a sensibilidade à insulina, o que não ocorreu no grupo com dieta convencional. O grupo que realizou dieta de baixo IG apresentou um maior percentual de mulheres com melhora da ciclicidade menstrual em relação ao grupo com dieta convencional (95% *vs*. 63%, respectivamente).

Estudo semelhante, porém sem objetivo de redução do peso das participantes, foi realizado por Barr et al. (54). Este estudo não randomizado consistiu em 12 semanas de dieta normocalórica com baixo IG, precedidas por 12 semanas de uma dieta habitual controle. A modificação da dieta consistiu em aconselhamento individualizado para substituir alimentos de alto e médio IG por alimentos com baixo IG, sem orientação específica para modificar o tipo e quantidade de ingestão de gorduras, proteínas e carboidratos. As participantes foram encorajadas a manter sua ingestão habitual de energia e os níveis de atividade física habituais ao longo do estudo. Vinte e uma participantes completaram o estudo. Após as 12 semanas de intervenção com dieta de baixo IG, houve melhora da sensibilidade à insulina e dos níveis de ácidos graxos não-esterificados. Não houve alterações das medidas de glicemia, colesterol total, LDL-c, peso e cintura após a fase de intervenção, com exceção de uma pequena redução no HDL-c.

Aumento significativo da sensibilidade à insulina também foi verificado no estudo de Mehrabani et al. (35), já citado anteriormente. Estes autores verificaram que o tratamento por 12 semanas com uma dieta hipocalórica com a combinação de alto teor de proteína e baixa CG causou um aumento significativo na sensibilidade à insulina em mulheres com PCOS (n=60) quando comparado com uma dieta hipocalórica convencional.

Um estudo retrospectivo com 88 mulheres com PCOS, para as quais havia sido prescrita uma dieta hipocalórica de baixa carga glicêmica, foi realizado por Herriot, Whitcroft e Jeanes (55). A dieta consistiu em orientações para consumo de alimentos de baixa CG, tendo aproximadamente 40-45% do consumo energético proveniente de carboidratos e 30% do consumo energético proveniente de proteínas, além de restrição do consumo de gordura saturada a menos de 10% do consumo energético. Em geral, as pacientes foram incentivadas a realizar 30 minutos de exercícios físicos de intensidade moderada por dia. Embora

metformina havia sido prescrita para a maioria das pacientes incluídas no estudo (87%), os autores concluíram que uma dieta de baixa CG combinada com medicamentos diminuiu significativamente o IMC e a circunferência da cintura em pacientes com sobrepeso ou obesidade.

Diferentemente, Wong et al. (56) realizaram estudo piloto comparando o impacto 6 meses de dieta de baixa CG (45% carboidratos, 20% proteínas e 35% lipídeos) *vs*. dieta com redução de lipídeos (55% carboidratos, 20% proteínas e 25% lipídeos) em adolescentes com sobrepeso e obesidade com PCOS. Não houve alteração no nível de atividade física das participantes durante o estudo. O percentual de gordura corporal diminuiu em resposta à intervenção, sem diferença entre as dietas de baixa CG e com redução de lipídeos (-1.2% *vs*. -2.2%, respectivamente). Não foi encontrada melhora significativa do hiperandrogenismo bioquímico.

DIETA DASH

A dieta DASH é caracterizada por um elevado consumo de frutas, vegetais e alimentos lácteos desnatados e por um baixo consumo de gordura saturada e total (57). Essa dieta foi baseada no ensaio clínico Dietary Approaches to Stop Hypertension (DASH), desenvolvido para avaliar os efeitos de padrões alimentares nos níveis de pressão arterial (57).

Estudos têm demonstrado efeitos benéficos desse tipo de dieta para redução do risco metabólico de indivíduos com DM2 (58, 59) e síndrome metabólica (60). Além disso, recente metanálise demonstrou que a dieta DASH resulta em maior redução de peso do que dietas padrão, principalmente em indivíduos adultos com sobrepeso e obesidade (61).

Poucos estudos avaliaram o efeito da dieta DASH em mulheres com PCOS (Tabela 2). Asemi et al. (62) realizaram um ECR comparando uma dieta DASH com uma dieta padrão por 8 semanas, ambas com a mesma distribuição de macronutrientes (52% carboidratos, 18% proteínas e 30% lipídeos). Ambas as dietas tiveram restrição de calorias e os participantes foram orientados a não alterar sua atividade física habitual. A dieta DASH baseou-se em um cardápio rico em frutas, vegetais, cereais integrais e produtos lácteos desnatados e pobre em gordura saturada, colesterol e cereais refinados. A intervenção com dieta DASH (n=24) resultou em redução significativamente maior de peso, IMC, triglicerídeos e VLDL-colesterol em relação à dieta padrão (n=24). Os mesmos pesquisadores apresentaram, no ano seguinte, resultados adicionais do mesmo estudo. Asemi e Esmaillzadeh (63) demonstraram que a

adesão à dieta DASH resultou em redução significativamente maior da insulina, do HOMA-IR, da cintura e do quadril em relação à dieta padrão.

SUPLEMENTAÇÃO DE ÁCIDOS GRAXOS POLIINSATURADOS

Ácido alfa-linolênico (ALA - *alpha-linolenic acid*), ácido eicosapentaenóico (EPA - *eicosapentaenoic acid)* e ácido docosaexaenóico (DHA - *docosahexaenoic acid*) são ácidos graxos poliinsaturados (PUFAs - *polyunsaturated fatty acids)* com 18, 20 e 22 carbonos, respectivamente. ALA é obtido a partir de fontes vegetais, tais como nozes e óleos de linhaça e chia, enquanto o EPA e o DHA, considerados de cadeia longa, estão presentes em alimentos de origem marinha, tais como peixes gordos (64).

O ALA pode ser metabolicamente convertido em vários ácidos graxos ômega-3, incluindo o EPA e o DHA. Entretanto, a conversão enzimática varia consideravelmente entre as espécies e parece ser relativamente ineficiente em humanos (65). Além do efeito antiaterogênico e anti-inflamatório do EPA e do DHA, vários estudos têm demonstrado efeitos benéficos sobre a resistência à insulina e o perfil lipídico (66-70).

Vários estudos têm sido realizados com objetivo de verificar os efeitos da suplementação de PUFAs ômega-3 em mulheres com PCOS (Tabela 2). Mohammadi et al. (71) realizaram um ECR com mulheres com PCOS com sobrepeso/obesidade no qual as participantes foram randomizadas para receber ômega-3 (4 cápsulas com 180 mg de EPA e 120 mg de DHA por dia) ou placebo por 8 semanas. Sessenta e uma participantes completaram o estudo. A suplementação de ômega-3 não teve efeitos significativos no peso, no IMC, na cintura, e na razão cintura-quadril. O grupo que recebeu ômega-3 apresentou reduções significativas da glicose (-11,4%), da insulina (-8,4%) do HOMA-IR (-21,8%), do colesterol total (-8,1%) e do LDL-c (-14,9%) quando comparado com o grupo placebo. O mesmo estudo foi relatado posteriormente por Rafraf et al. (72).

Entretanto, estudo de Cussons et al. (73) não demonstrou efeitos da suplementação de ômega-3 na sensibilidade à insulina em mulheres com PCOS. Cussons et al. (73) realizaram um estudo randomizado *crossover* com objetivo de verificar os efeitos da suplementação de EPA e DHA (4g de ômega-3/dia; 56% DHA e 27% EPA) em comparação com placebo por 8 semanas em 25 mulheres com PCOS, sem alterar a dieta habitual das pacientes. Não foram encontradas diferenças entre o grupo que recebeu ômega-3 e o grupo que recebeu placebo em relação ao HOMA-IR e à insulina e glicose de jejum. O grupo que recebeu ômega-3

apresentou reduções significativamente maiores dos triglicerídeos e da gordura hepática em relação ao grupo que recebeu placebo.

Nadjarzadeh et al. (74) avaliaram os efeitos da suplementação de ômega-3 (3 cápsulas com 180 mg de EPA e 120 mg de DHA por dia) em comparação com placebo por 8 semanas em mulheres com PCOS (78 participantes completaram o estudo). Após a intervenção o grupo que recebeu ômega-3 apresentou um percentual significativamente maior de participantes com menstruação regular e níveis de testosterona significativamente menores em relação ao grupo que recebeu placebo (47,2% *vs*. 22,9%). O SHBG e o índice IAL não se alteraram em nenhum dos grupos. Nadjarzadeh et al. (75) apresentaram resultados adicionais deste mesmo estudo. Houve redução significativa dos níveis de LH somente no grupo que recebeu suplementação. Não foram encontradas diferenças nos níveis de FSH e no perfil antropométrico após a intervenção, com exceção da razão cintura-quadril, que diminuiu no grupo que recebeu ômega 3 e não se alterou no grupo placebo.

Com o mesmo objetivo, Phelan et al. (76) realizaram um ECR *crossover* de 6 semanas em mulheres com PCOS (22 participantes completaram o estudo). A suplementação de ômega-3 consistiu em 2,4 g de ômega-3/dia (1,9 g EPA e DHA/dia, com uma razão de EPA:DHA de 1,49:1). As participantes que foram suplementadas apresentaram uma redução significativamente maior da testosterona biodisponível em relação ao grupo que recebeu placebo, sendo as maiores reduções nas participantes que exibiram maiores reduções plasmáticas da razão ômega-6/ômega-3. Entretanto não houve alterações significativas na testosterona total, no SDHEA, no SHBG, na androstenediona e nos demais hormônios reprodutivos.

Diferentemente dos estudos anteriomente citados, Kasim-Karakas et al. (77) examinou os efeitos da suplementação de PUFAs em mulheres com PCOS, porém utilizando ácidos graxos de fontes vegetais. O estudo consistiu em 12 semanas de intervenção, precedidas por período controle de 12 semanas. As participantes (n=17) foram orientadas a consumir 48 g de nozes a cada 800 kcal de consumo energético, sendo que 48 g de nozes fornecem 19 g de ácido linoléico (ômega-6) e 3,3 g de ALA. Não foram verificadas alterações no perfil hormonal das participantes.

Ainda, com o objetivo de comparar os efeitos de PUFAs ômega-3 de cadeia longa (EPA e DHA), provenientes do óleo de peixe, e PUFAs ômega-3 essenciais (ALA), provenientes do óleo de linhaça, Vargas et al. (78) realizaram um estudo prospectivo randomizado no qual as participantes receberam 3,5 g de ômega-3 por dia (óleo de peixe ou

óleo de linhaça) ou óleo de soja (placebo) por 6 semanas (17 participantes em cada grupo). Não houve alteração do consumo de macronutrientes durante o estudo. Tanto o grupo que recebeu óleo de peixe quanto o que recebeu óleo de linhaça reduziram os triglicerídeos. O grupo que recebeu óleo de peixe reduziu o índice Matsuda, porém apresentou aumento da glicose 2 h do TTG. O grupo que recebeu óleo de soja apresentou aumento dos níveis de glicose e redução dos níveis de testosterona. Glicose e insulina de jejum, HOMA, HDL-c, LDL-c e colesterol total, assim como o perfil antropométrico, não sofreram alterações pós-intervenção em nenhum dos grupos.

NÚMERO DE REFEIÇÕES E DISTRIBUIÇÃO CALÓRICA

Alguns pesquisadores têm sugerido que a distribuição das refeições diárias (número de refeições e distribuição calórica) pode influenciar o consumo alimentar e ter efeitos sobre o peso e a resistência insulínica (79-81), entretanto, poucos estudos foram realizados em mulheres com PCOS (Tabela 2).

Papakonstantinou et al. (82) realizaram estudo randomizado *crossover* com objetivo de comparar dois padrões de refeições (três *vs*. seis refeições por dia) nos níveis de glicose e de insulina de 40 mulheres com PCOS. As participantes seguiram uma dieta para manutenção do peso (40% carboidratos, 25% proteínas e 35% lipídeos), tanto com três quanto com seis refeições por dia (isocalóricas), cada uma por 12 semanas. Consumir seis refeições por dia levou a uma redução significativamente maior na sensibilidade à insulina pós TTG, independentemente da idade e do peso corporal, quando comparadas com três refeições diárias.

O efeito da ingestão calórica concentrada em diferentes horários do dia foi avaliada por Jakubowicz et al. (83) em estudo randomizado de 12 semanas com mulheres com PCOS eutróficas (51 pacientes completaram o estudo). Foram comparados dois tipos de dietas isocalóricas com objetivo de manutenção do peso: dieta do café da manhã (980 kcal no café da manhã, 640 kcal no almoço e 190 kcal no jantar) ou dieta do jantar (190 kcal no café da manhã, 640 kcal no almoço e 980 kcal no jantar). No grupo da dieta do café da manhã foram observadas diminuições significativas da área sob a curva de glicose (-7%) e da insulina (-54%), além de uma redução de 50% na testosterona livre, aumento de 105% no SHBG e aumento da taxa de ovulação. Nenhum desses parâmetros apresentou melhora no grupo com a dieta do jantar. Os autores referem que o consumo alimentar consistiu em aproximadamente

124 g de carboidrato, 191 g de proteína e 62 g de gordura por dia em uma dieta de aproximadamente 1800kcal, o que representa uma dieta hiperprotéica com grande redução de carboidratos (27% carboidratos, 42% proteínas e 31% lipídeos).

CONCLUSÕES

Poucos ECR avaliando o efeito de diferentes tipos de dietas foram realizados em mulheres com PCOS, sendo que os estudos existentes apresentam em sua maioria curta duração e, sobretudo, pequeno tamanho amostral. Dessa forma, com base nas atuais evidências não é possível definir qual o melhor tipo de dieta para a população com PCOS, embora dietas com baixa carga glicêmica pareçam ser uma boa escolha. Mais estudos são necessários para avaliar o efeito de diferentes tipos de dietas na redução de peso e melhora do perfil metabólico e hormonal na população com PCOS.

REFERÊNCIAS BIBLIOGRÁFICAS

1. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009;91(2):456-88.

2. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 2010;95(5):2038-49.

3. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 2000;85(7):2434-8.

4. Rotterdam EA-SPCWG. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81(1):19-25.

5. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89(6):2745-9.

6. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 2010;25(2):544-51.

7. Teede H, Deeks A, Moran L. Polycystic ovary syndrome: a complex condition with psychological, reproductive and metabolic manifestations that impacts on health across the lifespan. BMC Med 2010;8:41.

8. Norman RJ, Wu R, Stankiewicz MT. Polycystic ovary syndrome. Med J Aust 2004;180(3):132-7.

9. Wiltgen D, Spritzer PM. Variation in metabolic and cardiovascular risk in women with different polycystic ovary syndrome phenotypes. Fertil Steril 2010;94(6):2493-6.

10. Stepto NK, Cassar S, Joham AE, Hutchison SK, Harrison CL, Goldstein RF, et al. Women with polycystic ovary syndrome have intrinsic insulin resistance on euglycaemic-hyperinsulaemic clamp. Hum Reprod 2013;28(3):777-84.

11. Dunaif A. Insulin resistance and the polycystic ovary syndrome: mechanism and implications for pathogenesis. Endocr Rev 1997;18(6):774-800.

12 Diamanti-Kandarakis E, Dunaif A. Insulin resistance and the polycystic ovary syndrome revisited: an update on mechanisms and implications. Endocr Rev 2012;33(6):981-1030.

13. Spritzer PM, Wiltgen D. Prevalência de Síndrome Metabólica em pacientes sul-brasileiras com Síndrome dos Ovários Policísticos. Arq Bras Endocrinol Metab 2007;51:146-147.

14. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2012;18(6):618-37.

15. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. J Clin Endocrinol Metab 2015 Mar;100(3):911-9.

16. Kirchengast S, Huber J. Body composition characteristics and body fat istribution in lean women with polycystic ovary syndrome. Hum Reprod 2001;16(6):1255-60.

17. Carmina E, Bucchieri S, Esposito A, Del Puente A, Mansueto P, Orio F, et al. Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. J Clin Endocrinol Metab 2007;92(7):2500-5.

18. Lim SS, Norman RJ, Davies MJ, Moran LJ. The effect of obesity on polycystic ovary syndrome: a systematic review and meta-analysis. Obes Rev 2013;14:95–109.

19. Rondanelli M, Perna S, Faliva M, Monteferrario F, Repaci E, Allieri F. Focus on metabolic and nutritional correlates of polycystic ovary syndrome and update on nutritional management of these critical phenomena. Arch Gynecol Obstet 2014;290(6):1079-92.

20. Motta AB. The Role of Obesity in the Development of Polycystic Ovary Syndrome. Curr Pharm Des 2012;18(17):2482-91.

21. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2011;(2):CD007506.

22. Moran LJ, Teede H. Metabolic features of the reproductive phenotypes of polycystic ovary syndrome. Hum Reprod Update 2009;15(4):477-88.

23. Spritzer PM, Motta AB, Sir-Petermann T, Diamanti-Kandarakis E. Novel strategies in the management of polycystic ovary syndrome. Minerva Endocrinol 2015;40(3):195-212.

24. Moran LJ, Ko H, Misso M, Marsh K, Noakes M, Talbot M, et al. Dietary composition in the treatment of polycystic ovary syndrome: a systematic review to inform evidence-based guidelines. Hum Reprod Update 2013;19(5):432.

25. Moran L, Norman RJ. Understanding and managing disturbances in insulin metabolism and body weight in women with polycystic ovary syndrome. Best Pract Res Clin Obstet Gynaecol 2004;18(5):719-36.

26. Bell KJ, Petocz P, Colagiuri S, Brand-Miller JC. Algorithms to Improve the Prediction of Postprandial Insulinaemia in Response to Common Foods. Nutrients 2016;8(4):210.

27. Skov AR, Toubro S, Ronn B, Holm L, Astrup A 1999 Randomized trial on protein *vs.* carbohydrate in ad libitum fat reduced diet for the treatment of obesity. Int J Obes Relat Metab Disord 1999;23(5):528-36.

28. Eisenstein J, Roberts SB, Dallal G, Saltzman E. High-protein weight-loss diets: are they safe and do they work? A review of the experimental and epidemiologic data. Nutr Rev 2002;60(7 Pt 1):189-200.

29. Mikkelsen PB, Toubro S, Astrup A. Effect of fat-reduced diets on 24-h energy expenditure: comparisons between animal protein, vegetable protein, and carbohydrate. Am J Clin Nutr 2000;72(5):1135-41.

30. Tappy L. Thermic effect of food and sympathetic nervous system activity in humans. Reprod Nutr Dev 1996;36(4):391-7.

31. Stamets K, Taylor DS, Kunselman A, Demers LM, Pelkman CL, Legro RS. A randomized trial of the effects of two types of short-term hypocaloric diets on weight loss in women with polycystic ovary syndrome. Fertil Steril 2004;81(3):630-637.

32. Moran LJ, Noakes M, Clifton PM, Tomlinson L, Galletly C, Norman RJ. Dietary composition in restoring reproductive and metabolic physiology in overweight women with polycystic ovary syndrome. J Clin Endocrinol Metab 2003;88(2):812-819.

33. Galletly C, Moran L, Noakes M, Clifton P, Tomlinson L, Norman R. Psychological benefits of a high-protein, low-carbohydrate diet in obese women with polycystic ovary syndrome - A pilot study. Appetite 2007;49(3):590-593.

34. Sorensen LB, Soe M, Halkier KH, Stigsby B, Astrup A. Effects of increased dietary protein-to-carbohydrate ratios in women with polycystic ovary syndrome. Am J Clin Nutr 2012;95(1):39-48.

35. Mehrabani HH, Salehpour S, Amiri Z, Farahani SJ, Meyer BJ, Tahbaz F. Beneficial effects of a high-protein, low-glycemic-load hypocaloric diet in overweight and obese women with polycystic ovary syndrome: a randomized controlled intervention study. J Am Coll Nutr 2012;31(2):117-25.

36. Gower BA, Chandler-Laney PC, Ovalle F, Goree LL, Azziz R, Desmond RA, et al. Favourable metabolic effects of a eucaloric lower-carbohydrate diet in women with PCOS. Clin Endocrinol (Oxf) 2013;79(4):550-7.

37. Goss AM, Chandler-Laney PC, Ovalle F, Goree LL, Azziz R, Desmond RA, et al. Effects of a eucaloric reduced-carbohydrate diet on body composition and fat distribution in women with PCOS. Metabolism 2014;63(10):1257-64.

38. Douglas CC, Gower BA, Darnell BE, Ovalle F, Oster RA, Azziz R. Role of diet in the treatment of polycystic ovary syndrome. Fertil Steril 2006; 85(3):679-688.

39. Moran LJ, Noakes M, Clifton PM, Wittert GA, Williams G, Norman RJ. Short-term meal replacements followed by dietary macronutrient restriction enhance weight loss in polycystic ovary syndrome. Am J Clin Nutr 2006;84(1):77-87.

40. Jenkins DJ, Wolever TM, Taylor RH, Barker H, Fielden H, Baldwin JM, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. Am J Clin Nutr 1981;34(3):362-366.

41. Salmerón J, Ascherio A, Rimm EB, Colditz GA, Spiegelman D, Jenkins DJ, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. Diabetes Care 1997;20(4):545-50.

42. Salmerón J, Manson JE, Stampfer MJ, Colditz GA, Wing AL, Willett WC. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. JAMA 1997;277(6):472-7.

43. Liu S, Willett WC, Stampfer MJ, Hu FB, Franz M, Sampson L, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. Am J Clin Nutr 2000;71(6):1455-61.

44. Bao J, Atkinson F, Petocz P, Willett WC, Brand-Miller JC. Prediction of postprandial glycemia and insulinemia in lean, young, healthy adults: glycemic load compared with carbohydrate content alone. Am J Clin Nutr 2011;93(5):984-96.

45. Ludwig, D.S. The glycemic index. Physiological mechanisms relating to obesity, diabetes and cardiovascular disease. JAMA 2002;287(18):2414-23.

46. Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. Am J Clin Nutr 2002;76(1):274S-80S.

47. Schulze MB, Liu S, Rimm EB, Manson JE, Willett WC, Hu FB. Glycemic index, glycemic load, and dietary fiber intake and incidence of type 2 diabetes in younger and middle-aged women. Am J Clin Nutr 2004;80(2):348-56.

48. Thomas DE, Elliott EJ, Baur L. Low glycaemic index or low glycaemic load diets for overweight and obesity. Cochrane Database Syst Rev 2007;(3):CD005105.

49. Dong JY, Zhang YH, Wang P, Qin LQ. Meta-Analysis of Dietary Glycemic Load and Glycemic Index in Relation to Risk of Coronary Heart Disease. Am J Cardiol 2012;109(11):1608-13.

50. Pereira MA. Weighing in on glycemic index and body weight. Am J Clin Nutr 2006;84(4):677-9.

51. Jenkins DJ, Kendall CW, Axelsen M, Augustin LS, Vuksan V. Viscous and nonviscous fibres, nonabsorbable and low glycaemic index carbohydrates, blood lipids and coronary heart disease. Curr Opin Lipidol 2000;11(1):49-56.

52. Stevenson EL, Williams C, Mash LE, Phillips B, Nute ML. Influence of high-carbohydrate mixed meals with different glycemic indexes on substrate utilization during subsequent exercise in women. Am J Clin Nutr 2006;84(2):354-60.

53. Marsh KA, Steinbeck KS, Atkinson FS, Petocz P, Brand-Miller JC. Effect of a low glycemic index compared with a conventional healthy diet on polycystic ovary syndrome. Am J Clin Nutr 2010;92(1):83-92.

54. Barr S, Reeves S, Sharp K, Jeanes YM. An isocaloric low glycemic index diet improves insulin sensitivity in women with polycystic ovary syndrome. J Acad Nutr Diet 2013;113(11):1523-31.

55. Herriot AM, Whitcroft S, Jeanes Y. An retrospective audit of patients with polycystic ovary syndrome: the effects of a reduced glycaemic load diet. J Hum Nutr Diet 2008;21(4):337-45.

56. Wong JM, Gallagher M, Gooding H, Feldman HA, Gordon CM, Ludwig DS, et al. A randomized pilot study of dietary treatments for polycystic ovary syndrome in adolescents. Pediatr Obes 2016;11(3):210-20.

57. Appel LJ, Moore TJ, Obarzanek E, Vollmer WM, Svetkey LP, Sacks FM, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. N Engl J Med 1997;336(16):1117-24.

58. Liese AD, Nichols M, Sun X, D'Agostino RB Jr, Haffner SM. Adherence to the DASH diet is inversely associated with incidence of type 2 diabetes: the Insulin Resistance Atherosclerosis Study. Diabetes Care 2009;32(8):1434-6.

59. Azadbakht L, Fard NR, Karimi M, Baghaei MH, Surkan PJ, Rahimi M, et al. Effects of the Dietary Approaches to Stop Hypertension (DASH) eating plan on cardiovascular risks among type 2 diabetic patients: a randomized crossover clinical trial. Diabetes Care 2011;34(1):55-7.

60. Azadbakht L, Mirmiran P, Esmaillzadeh A, Azizi T, Azizi F. Beneficial effects of a Dietary Approaches to Stop Hypertension eating plan on features of the metabolic syndrome. Diabetes Care 2005;28(12):2823-31.

61. Soltani S, Shirani F, Chitsazi MJ, Salehi-Abargouei A. The effect of dietary approaches to stop hypertension (DASH) diet on weight and body composition in adults: a systematic review and meta-analysis of randomized controlled clinical trials. Obes Rev 2016;17(5):442-54.

62. Asemi Z, Samimi M, Tabassi Z, Shakeri H, Sabihi SS, Esmaillzadeh A. Effects of DASH diet on lipid profiles and biomarkers of oxidative stress in overweight and obese women with polycystic ovary syndrome: a randomized clinical trial. Nutrition 2014;30(11-12):1287-93.

63. Asemi Z, Esmaillzadeh A. DASH diet, insulin resistance, and serum hs-CRP in polycystic ovary syndrome: a randomized controlled clinical trial. Horm Metab Res 2015;47(3):232-8.

64. Wood KE, Mantzioris E, Gibson RA, Ramsden CE, Muhlhausler BS. The effect of modifying dietary LA and ALA intakes on omega-3 long chain polyunsaturated fatty acid (n-3 LCPUFA) status in human adults: a systematic review and commentary. Prostaglandins Leukot Essent Fatty Acids 2015;95:47-55.

65. Arterburn LM, Hall EB, Oken H. Distribution, interconversion, and dose response of n-3 fatty acids in humans. Am J Clin Nutr 2006;83(6 Suppl):1467S-1476S.

66. Derosa G, Cicero AF, D'Angelo A, Borghi C, Maffioli P. Effects of n-3 pufas on fasting plasma glucose and insulin resistance in patients with impaired fasting glucose or impaired glucose tolerance. Biofactors 2016;42(3):316-22.

67. Harris WS, Miller M, Tighe AP, Davidson MH, Schaefer EJ. Omega-3 fatty acids and coronary heart disease risk: Clinical and mechanistic perspectives. Atherosclerosis 2008;197(1):12-24.

68. Fedor D, Kelley DS. Prevention of insulin resistance by n-3 polyunsaturated fatty acids. Curr Opin Clin Nutr Metab Care 2009;12(2):138-46.

69. Ebbesson SOE, Risica RM, Ebbesson LOE, Kennish JM, Tejero ME. Omega-3 fatty acids improve glucose tolerance and components of the metabolic syndrome in Alaskan eskimos: The Alaska Siberia project. Int J Circumpolar Health 2005;64(4):396-408.

70. Sarbolouki S, Javanbakht MH, Derakhshanian H, Hosseinzadeh P, Zareei M, Hashemi SB, et al. Eicosapentaenoic acid improves insulin sensitivity and blood sugar in overweight type 2 diabetes mellitus patients: a double-blind randomised clinical trial. Singapore Med J 2013;54(7):387-90.

71. Mohammadi E, Rafraf M, Farzadi L, Asghari-Jafarabadi M, Sabour S. Effects of omega-3 fatty acids supplementation on serum adiponectin levels and some metabolic risk factors in women with polycystic ovary syndrome. Asia Pac J Clin Nutr 2012;21(4):511-8.

72. Rafraf M, Mohammadi E, Asghari-Jafarabadi M, Farzadi L. Omega-3 fatty acids improve glucose metabolism without effects on obesity values and serum visfatin levels in women with polycystic ovary syndrome. J Am Coll Nutr 2012;31(5):361-8.

73. Cussons AJ, Watts GF, Mori TA, Stuckey BG. Omega-3 fatty acid supplementation decreases liver fat content in polycystic ovary syndrome: randomized controlled trial employing proton magnetic resonance spectroscopy. J Clin Endocrinol Metab 2009;94(10):3842-8.

74. Nadjarzadeh A, Dehghani Firouzabadi R, Vaziri N, Daneshbodi H, Lotfi MH, Mozaffari-Khosravi H. The effect of omega-3 supplementation on androgen profile and

menstrual status in women with polycystic ovary syndrome: A randomized clinical trial. Iran J Reprod Med 2013;11(8):665-72.

75. Nadjarzadeh A, Dehghani-Firouzabadi R, Daneshbodi H, Lotfi MH, Vaziri N, Mozaffari-Khosravi H. Effect of Omega-3 Supplementation on Visfatin, Adiponectin, and Anthropometric Indices in Women with Polycystic Ovarian Syndrome. J Reprod Infertil 2015;16(4):212-20.

76. Phelan N, O'Connor A, Kyaw Tun T, Correia N, Boran G, Roche HM, Gibney J. Hormonal and metabolic effects of polyunsaturated fatty acids in young women with polycystic ovary syndrome: results from a cross-sectional analysis and a randomized, placebo-controlled, crossover trial. Am J Clin Nutr 2011;93(3):652-62.

77. Kasim-Karakas SE, Almario RU, Gregory L, Wong R, Todd H, Lasley BL. Metabolic and endocrine effects of a polyunsaturated fatty acidrich diet in polycystic ovary syndrome. J Clin Endocrinol Metab 2004;89(2):615-20.

78. Vargas ML, Almario RU, Buchan W, Kim K, Karakas SE. Metabolic and endocrine effects of long-chain versus essential omega-3 polyunsaturated fatty acids in polycystic ovary syndrome. Metabolism 2011;60(12):1711-8.

79. Morgan LM, Shi JW, Hampton SM, Frost G. Effect of meal timing and glycaemic index on glucose control and insulin secretion in healthy volunteers. Br J Nutr 2012;108(7):1286-91.

80. Froy O. Metabolism and circadian rhythms–implications for obesity. Endocr Rev 2010;31(1):1-24.

81. Arble DM, Bass J, Laposky AD, Vitaterna MH, Turek FW. Circadian timing of food intake contributes to weight gain. Obesity (Silver Spring) 2009;17(11):2100-2.

82. Papakonstantinou E, Kechribari I, Mitrou P, Trakakis E, Vassiliadi D, Georgousopoulou E, et al. Effect of meal frequency on glucose and insulin levels in women with polycystic ovary syndrome: a randomised trial. Eur J Clin Nutr 2016;70(5):588-94.

83. Jakubowicz D, Barnea M, Wainstein J, Froy O. Effects of caloric intake timing on insulin resistance and hyperandrogenism in lean women with polycystic ovary syndrome. Clin Sci (Lond) 2013;125(9):423-32.

Tabela 1. Diferentes intervenções dietéticas estudadas em mulheres com PCOS

Dietas com redução de carboidratos e aumento de proteínas
Dietas com redução de carboidratos e aumento de lipídeos
Dietas com baixo índice glicêmico/carga glicêmica
Dieta DASH
Dietas com suplementação de ômega-3
Dietas com maior número de refeições/melhor distribuição calórica

Tabela 2. Características dos estudos de intervenção dietética em mulheres com PCOS

	Autor, ano	Intervenção dietética	Delineamento	População	Duração	Atividade física
Redução de carboidratos	**Moran et al., 2003 (32); Galletly et al., 2007 (33)**	Dietas hipocalóricas (fase 1) e normocalóricas (fase 2): 1) Hiperprotéica (40% CHO, 30% PTN, 30% LIP) 2) Normoprotéica (55% CHO, 15% PTN, 30% LIP)	Ensaio clinico randomizado	País: Austrália Média de idade: 33 ± 0,84 anos IMC: ≥ 25 kg/m² n (dieta 1) = 23 iniciaram / 14 completaram n (dieta 2) = 22 iniciaram / 14 completaram	Fase 1: 12 semanas Fase 2: 4 semanas	As participantes realizaram exercícios físicos semanais em grupo e foram incentivadas a praticar atividades físicas pelo menos 3 vezes por semana.
	Stamets et al., 2004 (31)	Dietas hipocalóricas: 1) Hiperprotéica (40% CHO, 30% PTN, 30% LIP) 2) Normoprotéica (55% CHO, 15% PTN, 30% LIP)	Ensaio clinico randomizado	País: EUA Idade: 21 – 37 anos IMC: 28 – 45 kg/m² n (dieta 1) = 17 iniciaram / 13 completaram n (dieta 2) = 18 iniciaram / 13 completaram	4 semanas	Sem alteração na no nível de atividade física habitual.
	Douglas et al., 2006 (38)	Dietas normocalóricas: 1) Baixo teor de carboidratos (43% CHO, 15% PTN, 45% LIP; 8% SFAs, 17% PUFAs, 18% MUFAs) 2) Padrão (56% CHO, 16% PTN, 31% LIP; 7% SFAs, 10% PUFAs, 13% MUFAs) 3) Enriquecida em MUFAs (55% CHO, 15% PTN, 33% LIP; 7% SFAs, 6% PUFAs, 17% MUFAs)	Ensaio clínico não-randomizado *crossover*	País: EUA Idade: 19- 42 anos IMC: 24 - 37 kg/m² n = 15 (11 completaram estudo)	16 dias (cada dieta)	Participantes foram orientadas a manter o nível de atividade física habitual.
	Moran et al., 2006 (39)	Dietas normocalóricas (precedidas por período inicial de 8 semanas de dieta hipocalórica): 1) Contagem de carboidratos (objetivo de menos de 120g CHO/dia) (40% CHO, 21% PTN, 35% LIP*) 2) Contagem de lipídeos (objetivo de menos de 50g LIP/dia) (43% CHO, 21% PTN, 31 LIP*)	Ensaio clínico randomizado	País: Austrália Média de idade: 32,1 ± 5,7 anos IMC: ≥ 25 kg/m² n (dieta 1) = 21 iniciaram / 14 completaram n (dieta 2) = 22 iniciaram / 9 completaram	24 semanas (precedidas por 8 semanas de dieta hipocalórica)	As participantes receberam um pedômetro com objetivo de realizar 8.000 passos diários.
	Sorensen et al., 2012 (34)	Dietas normocalóricas: 1) Hiperprotéica (30% CHO, 40% PTN, 30% LIP) 2) Normoprotéica (55% CHO, 15% PTN, 30% LIP)	Ensaio clínico randomizado	País: Dinamarca Média de idade (dieta 1): 27,7 ± 5,5 anos Média de idade (dieta 2): 28,4 ± 5,8 anos Média de IMC (dieta 1): 30,6 ± 7,8 kg/m² Média de IMC (dieta 2): 30,5 ± 8,5 kg/m² n (dieta 1) = 29 iniciaram / 14 completaram n (dieta 2) = 28 iniciaram / 13 completaram	24 semanas	Recomendação de 30 min de atividade física por dia.
	Mehrabani et al., 2012 (35)	Dietas hipocalóricas: 1) Hiperprotéica com baixa CG (40% CHO de baixa e média CG, 30% PTN, 30% LIP) 2) Padrão (55% CHO, 15% PTN, 30% LIP)	Ensaio clínico randomizado	País: Irã Idade: 20 – 40 anos IMC: 25 – 38 kg/m² n (dieta 1) = 30 iniciaram / 23 completaram n (dieta 2) = 30 iniciaram / 26 completaram	12 semanas	Participantes foram orientadas a manter o nível de atividade física habitual.
	Gower et al., 2013 (36); Goss et al., 2014 (37)	Dietas normocalóricas: 1) Moderada redução de carboidratos (41% CHO, 19% PTN, 40% LIP) 2) Padrão (55% CHO, 18% PTN, 27% LIP)	Ensaio clínico randomizado *crossover*	País: EUA Idade: 21 - 50 anos IMC: ≤ 45 kg/m² n = 30 (23 completaram ambas as dietas e 4 completaram somente dieta 1)	8 semanas (cada dieta)	Exclusão de paciente que realizassem mais de 2 h de exercícios físicos estruturados por semana.

Índice glicêmico/ carga glicêmica	**Herriot, Whitcroft e Jeanes, 2008 (55)**	Dieta hipocalórica de baixa CG (orientação para consumo de alimentos de baixa CG; aproximadamente 40-45% de carboidratos, 30% de proteínas e menos de 10% de SFAs) (metformina havia sido prescrita para a 87% das pacientes incluídas no estudo)	Estudo retrospectivo	País: Reino Unido Média de idade: 32,4 ± 9,1 anos 58 pacientes com IMC ≤ 24,9 kg/m²; 30 pacientes com IMC ≥ 25 kg/m² n = 88 (follow-up de 59)	2 – 48 semanas	Em geral, as pacientes foram incentivadas a realizar 30 min de exercícios físicos de intensidade moderada por dia.
	Marsh et al., 2010 (53)	Dietas hipocalóricas: 1) Baixo IG (50% CHO, 23% PTN, 27% LIP; IG = 40%, CG = 74 g) 2) Padrão (50% CHO, 23% PTN, 27% LIP; IG = 59%, CG = 109 g)	Ensaio clínico não-randomizado	País: Austrália Idade: 18 - 40 anos IMC: ≥ 25 kg/m² n (dieta 1) = 50 iniciaram / 29 completaram n (dieta 2) = 46 iniciaram / 20 completaram	12 meses (ou até participantes atingirem uma redução de peso de 7%)	As participantes foram incentivadas a realizar 30 min de exercícios físicos de intensidade moderada na maioria dos dias e receberam um pedômetro com o objetivo de atingirem 10.000 passos por dia.
	Barr et al., 2013 (54)	Dieta normocalórica de baixo índice glicêmico (orientação de substituição de alimentos de alto e médio IG por alimentos com baixo IG)	Estudo de intervenção	País: Reino Unido Média de Idade: 31,5 ± 6,9 anos Média de IMC: 29,0 ± 5,9 kg/m² n = 26 (21 completaram estudo)	12 semanas (precedidas por 12 semanas de dieta controle)	Participantes foram orientadas a manter o nível de atividade física habitual.
	Wong et al., 2016 (56)	Dietas hipocalóricas: 1) Baixa carga glicêmica (45% CHO, 20% PTN, 35% LIP) (CG inicial* = 64,5 ± 8,3 g/1000 kcal; CG final* = 48,7 ± 7,6 g / 1000 kcal) 2) Redução de lipídeos (55% CHO, 20% PTN, 25% LIP) (CG inicial* = 75,4 ± 11,1 g/1000 kcal; CG final* = 69,3 ± 10,1 g/1000 kcal)	Ensaio clínico randomizado (estudo piloto)	País: EUA Idade: 13- 21 anos IMC: ≥ 25 kg/m² n (dieta 1) = 10 iniciaram / 9 completaram n (dieta 2) = 9 iniciaram / 7 completaram	24 semanas	Não houve alteração significativa do nível de atividade física durante estudo.
Dieta DASH	**Asemi et al., 2014 (62);** **Asemi e Esmaillzadeh, 2015 (63)**	Dietas hipocalóricas: 1) Dieta DASH - rica em frutas, vegetais, cereais integrais e produtos lácteos desnatados e pobre em gordura saturada, colesterol e cereais refinados (52% CHO, 18% PTN, 30% LIP) 2) Dieta padrão (52% CHO, 18% PTN, 30% LIP)	Ensaio clínico randomizado / Intenção de tratar	País: Irã Idade: 18 - 40 anos IMC: ≥ 25 kg/m² n (dieta 1) = 27 iniciaram / 24 completaram n (dieta 2) = 27 iniciaram / 24 completaram	8 semanas	Participantes foram orientadas a manter o nível de atividade física habitual.
Ômega-3	**Kasim-Karakas et al., 2004 (77)**	Substituição de gorduras da dieta por PUFAs (orientação para consumo de 48 g de nozes a cada 800 kcal de consumo energético - 19 g de LA e 3,3 g de ALA)	Estudo de intervenção	País: EUA Média de idade: 34 ± 5 anos Média de IMC: 34,0 ± 1,9 kg/m² n = 24 iniciaram / 17 completaram	12 semanas (precedidas por período controle de 12 semanas)	Participantes foram orientadas a manter o nível de atividade física habitual.
	Cussons et al., 2009 (73)	1) Suplementação de ômega-3 (4 g de ômega-3/dia; 56% DHA and 27% EPA) 2) Placebo (4 g de azeite de oliva/dia; 67% OA) As participantes foram orientadas a manter seu consumo alimentar habitual.	Ensaio clínico randomizado *crossover*	País: Austrália Média de idade: 32,7 ± 7,7 anos IMC: ≥ 25 kg/m² n = 25	8 semanas (cada dieta)	Não relatado.
	Phelan et al., 2011 (76)	1) Suplementação de ômega-3 (2,4 g de ômega-3/dia; 1.9 g EPA e DHA/dia com uma razão de EPA:DHA de 1,49:1) 2) Placebo (4 g de azeite de oliva/dia)	Ensaio clínico randomizado controlado *crossover*	País: Irlanda IMC: 18 - 50 kg/m² Idade: 18 - 40 anos n = 25 iniciaram / 22 completaram	6 semanas (cada dieta)	Participantes foram orientadas a manter o nível de atividade física habitual.

Ômega-3	**Vargas et al., 2011 (78)**	1) Suplementação de 3,5 g de PUFAs ômega-3 por dia (óleo de peixe; 6 cápsulas/dia com 358 mg de EPA e 242 mg de DHA) 2) Suplementação de 3,5 g de PUFAs ômega-3 por dia (óleo de linhaça; 6 cápsulas/dia com 545 mg de ALA) 3) Placebo (óleo de soja; 6 cápsulas/dia com 200 mg de OA, 429 mg de LA e 57 mg de ALA) Não houve alteração do consumo de macronutrientes durante o estudo.	Ensaio clínico randomizado controlado	País: EUA Idade: 20 - 45 anos IMC: 25 - 45 kg/m² n (grupo 1) = 21 iniciaram / 17 completaram n (grupo 2) = 23 iniciaram / 17 completaram n (grupo 3) = 18 iniciaram / 17 completaram	6 semanas	Não relatado.
	Mohammadi et al., 2012 (71); Rafraf et al., 2012 (72)	1) Suplementação de ômega-3 (4 cápsulas com 180 mg de EPA e 120 mg de DHA por dia) 2) Placebo	Ensaio clínico randomizado	País: Irã Idade: 20 - 35 anos IMC = 25 - 40 kg/m² n (grupo 1) = 32 iniciaram / 30 completaram n (grupo 2) = 32 iniciaram / 31 completaram	8 semanas	Participantes foram orientadas a manter o nível de atividade física habitual.
	Nadjarzadeh et al., 2013 (74); Nadjarzadeh et al., 2015 (75)	1) Suplementação de ômega-3 (3 cápsulas com 180 mg de EPA e 120 mg de DHA por dia) 2) Placebo	Ensaio clínico randomizado controlado	País: Irã Idade: 20 - 40 anos IMC = 25 - 40 kg/m² n (grupo 1) = 42 iniciaram / 39 completaram n (grupo 2) = 42 iniciaram / 39 completaram	8 semanas	Participantes foram orientadas a manter o nível de atividade física habitual.
Número de refeições e distribuição calórica	**Jakubowicz et al., 2013 (83)**	Dietas normocalóricas (27% CHO, 42% PTN e 31% LIP): 1) Dieta do café da manhã (980 kcal no café da manhã, 640 kcal no almoço e 190 kcal no jantar) 2) Dieta do jantar (190 kcal no café da manhã, 640 kcal no almoço e 980 kcal no jantar)	Ensaio clínico randomizado	País: Israel Idade: 25 - 39 anos IMC: ≤ 24,9 kg/m² n = 29 iniciaram / 25 completaram n = 31 iniciaram / 26 completaram	12 semanas	Participantes foram orientadas a manter o nível de atividade física habitual.
	Papakonstantinou et al., 2016 (82)	Dietas normocalóricas (40% CHO, 25% PTN e 35% LIP): 1) Três refeições por dia 2) Seis refeições por dia	Ensaio clínico randomizado *crossover*	País: Grécia Idade: 27 ± 6 anos IMC: 20 - 40 kg/m² n = 45 iniciaram / 40 completaram	12 semanas (cada dieta)	Participantes foram orientadas a manter o nível de atividade física habitual.

CHO = carboidratos; PTN = proteínas; LIP = lipídeos; SFAs = ácidos graxos saturados; PUFAs = ácidos graxos poliinsaturados; MUFAs = ácidos graxos monoinsaturados; EUA = Estados Unidos da América; IMC = índice de massa corporal; CG = carga glicêmica; IG = índice glicêmico; DHA = ácido docosaexaenoico; EPA = ácido eicosapentaenoico; OA = ácido oléico; LA = ácido linoléico; ALA = ácido alfa-linolênico.

*Valores definidos com base na avaliação da ingestão alimentar das pacientes durante o estudo.

CAPÍTULO II

Artigo Original 1: Effects of orlistat *vs*. metformin on weight loss-related clinical variables in women with PCOS: systematic review and meta-analysis

Artigo publicado na revista *The International Journal of Clinical Practice*, 2016

Effects of orlistat vs. metformin on weight loss-related clinical variables in women with PCOS: systematic review and meta-analysis

Running title: Orlistat and weight loss in PCOS

Scheila K Graff,[a] Fernanda M Mario,[a,b] Patrícia Ziegelmann,[c] Poli Mara Spritzer,[a,d]

[a]Gynecological Endocrinology Unit, Division of Endocrinology, Hospital de Clínicas de Porto Alegre (HCPA), Rua Ramiro Barcelos, 2350, 90035-003, Porto Alegre, Brazil.

[b]Federal Institute of Education, Science and Technology of Rio Grande do Sul, Rua Coronel Vicente, 281, 90030-041, Porto Alegre, Brazil.

[c]Department of Statistics, Federal University of Rio Grande do Sul, Avenida Bento Gonçalves, 9500, 91509-900, Porto Alegre, Brazil.

[d]Laboratory of Molecular Endocrinology, Department of Physiology, Federal University of Rio Grande do Sul, Rua Ramiro Barcelos, 2350, 90035-003, Porto Alegre, Brazil.

Corresponding author:

Poli Mara Spritzer, MD, PhD

Division of Endocrinology, Hospital de Clínicas de Porto Alegre, and Laboratory of Molecular Endocrinology, Department of Physiology, Federal University of Rio Grande do Sul

Rua Ramiro Barcelos, 2350, 90035-003 - Porto Alegre, RS – Brazil

Phone: +55-51-3359.8027 – Fax: +55-51-3359.8777

e-mail: spritzer@ufrgs.br

ABSTRACT

Aims: To assess the effects of orlistat on weight loss-related clinical variables in overweight/obese women with polycystic ovary syndrome (PCOS) and to compare treatment with orlistat vs. metformin in this group.

Methods: We conducted a systematic review and meta-analysis of the evidence about the use of orlistat in women with PCOS. We searched the literature published until May 2015 in MEDLINE, Cochrane Central Register of Controlled Trials, and LILACS.

Results: Of 3951 studies identified, nine were included in the systematic review (three prospective, non-randomized studies, and six randomized control trials). Eight studies used the Rotterdam criteria and 1 used NIH criteria to diagnose PCOS. Data suggest that orlistat promotes a significant reduction in BMI/weight in overweight/obese PCOS women. Eight studies evaluated orlistat impact on testosterone. Seven reported an improvement in testosterone levels. Eight studies evaluated impact on insulin resistance, and five reported improvement. Finally, five studies evaluated impact on lipid profile, and four reported improvement. Three randomized control trials were included in the fixed effects model meta-analysis for a total of 121 women with PCOS. Orlistat and metformin had similar positive effects on BMI (-0.65%, 95%CI: -2.03; 0.73), HOMA (-3.60%, 95%CI: -16.99; 9.78), testosterone (-2.08%, 95%CI: -13.08; 8.93), and insulin (-5.51%, 95%CI: -22.27; 11.26).

Conclusion(s): The present results suggest that orlistat leads to significant reduction in body BMI/weight in PCOS. In addition, the available evidence indicates that orlistat and metformin have similar effects in reducing BMI, HOMA, testosterone, and insulin in overweight/obese PCOS women. This study was registered in PROSPERO under number CRD42014012877.

Key Words: Polycystic ovary syndrome; Orlistat; Metformin; Systematic review; Meta-analysis.

Review criteria:

- We conducted a systematic review and meta-analysis of the evidence about the effect of orlistat on weight, BMI, androgens, and insulin resistance in women with polycystic ovary syndrome.
- We systematically searched literature published until May 2015 in electronic databases MEDLINE, Cochrane Central Register of Controlled Trials, and LILACS.
- We conducted a descriptive systematic review and a fixed effects model meta-analysis and evaluated heterogeneity using the I^2 statistics and Cochran's Q test.

Message for the clinic:

- Orlistat leads to significant reduction in BMI/weight in overweight/obese PCOS.
- Orlistat and metformin have similar effects in reducing BMI, testosterone, and insulin/HOMA in overweight/obese PCOS women.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a heterogeneous condition primarily characterized by hyperandrogenism and ovulatory dysfunction (1-3), with associated metabolic disturbances including insulin resistance, dyslipidemia, and type 2 diabetes mellitus (DM2) (1, 2, 4, 5). The prevalence of PCOS in women of reproductive age varies from 9% to 18% depending on diagnostic criteria (3, 6, 7).

Obesity and greater abdominal adiposity are also typical of PCOS and may accentuate reproductive and metabolic issues (8-15). Therefore, lifestyle measures for weight loss are the first-line treatment in obese women with PCOS (12, 16, 17). However, lifestyle changes may not be sufficient to promote significant weight loss, and pharmaceutical interventions may be required (18). Metformin, an oral antidiabetic drug that reduces glucose levels by improving insulin action, has been considered a second-line treatment for PCOS women presenting insulin resistance (19-24). While its main mechanism of action involves an improvement on insulin action, leading to an amelioration of menstrual cycles and reduction of testosterone levels, in some, but not all, insulin-resistant PCOS women these effects are similar to those obtained with weight loss (20).

The lipase inhibitor orlistat is currently the sole antiobesity agent available in many countries. Orlistat does not have systemic adverse effects and has been shown to produce significant and sustained weight loss, with improvement in cardiovascular risk factors including DM2, hypertension, and dyslipidemia in different populations (25-30). Nevertheless, only a few studies including small samples are available in the literature regarding the effects of orlistat on weight loss in women with PCOS. Therefore, the aim of this systematic review and meta-analysis was to assess the effects of orlistat on weight loss-associated clinical variables such as weight/BMI, waist circumference, insulin resistance markers, total testosterone, lipid profile, and menstrual cyclicity, and to compare these effects to those obtained with metformin treatment in overweight/obese women with PCOS.

METHODS

Search strategy and study selection

The following databases were searched for prospective studies and randomized clinical trials (RCTs) published until May 2015: Medline, Cochrane Central Register of Controlled Trials, and LILACS. No limits were set on publication date or language. This systematic review was registered in PROSPERO (http://www.crd.york.ac.uk/PROSPERO/) under

number CRD42014012877. The following basic search strategy was developed for PubMed and modified as needed for other databases: “Polycystic Ovary Syndrome” or “Ovary Syndrome, Polycystic” or “Syndrome, Polycystic Ovary” or “Stein-Leventhal Syndrome” or “Stein Leventhal Syndrome” or “Syndrome, Stein-Leventhal” or “Sclerocystic Ovarian Degeneration” or “Ovarian Degeneration, Sclerocystic” or “Sclerocystic Ovary Syndrome” or “Polycystic Ovarian Syndrome” or “Ovarian Syndrome, Polycystic” or “Sclerocystic Ovaries” or “Ovary, Sclerocystic” or “Sclerocystic Ovary” and tetrahydrolipstatin or THLP or 1-((3-hexyl-4-oxo-2-oxetanyl)methyl)dodecyl-2-formamido-4-methylvalerate or tetrahydrolipstatin or Xenical or “Roche brand of orlistat” or “Hoffmann-La Roche brand of orlistat” or Alli or “GlaxoSmithKline brand of orlistat.”

The selection criteria for the studies were as follows: diagnosis of PCOS using Rotterdam (31) or NIH criteria (32), intervention with any dose of orlistat for at least 8 weeks, and comparison of orlistat with placebo or metformin or any anti-obesity drug. Regarding studies comparing orlistat with anti-obesity drugs other than metformin in PCOS, or comparing the use of orlistat in PCOS women vs. healthy controls, only the results from the PCOS/orlistat arm were considered in the present systematic review. Studies with lifestyle interventions associated with pharmacological treatment were also included in the systematic review if all the groups in the study received the same intervention.

Primary outcomes were changes in body mass index (BMI), weight, waist circumference, insulin resistance markers and total testosterone levels following orlistat treatment. Secondary outcomes were changes in lipid profile and menstrual cyclicity, ovulation rate and ovarian morphology at ultrasound and adverse effects.

In addition, the reference lists of identified studies were searched. The most complete study was chosen to avoid duplication if the same patient populations were reported in several publications. Whenever necessary, authors were contacted in order to obtain additional data from published materials.

Data extraction and quality control assessment

Two reviewers (SKG and FMM) independently screened titles/abstracts for selection of articles for full text review. Disagreements were resolved by a third reviewer (PMS) or consensus discussion. The full text of selected articles was independently reviewed by the two initial reviewers. Cochrane Collaboration tools for assessing the risk of bias in randomized trials (33) were also independently applied by two reviewers (SKG and FMM), with

disagreements resolved by a third reviewer (PMS) or consensus discussion. The following information was extracted from studies: name of first author, publication year, country, PCOS diagnostic criteria, type of study, intervention, number of subjects in each arm, age, length of study, and lifestyle intervention.

Statistical analysis

Data are presented as mean (±SEM) at baseline and after treatment. The comparison between baseline and after-treatment data within each arm (orlistat or metformin) is presented as mean percentage change from baseline (±SEM). Data from RCTs comparing the effects of orlistat versus metformin were combined by fixed effects model meta-analysis. Variables of interest expressed as mean (±SEM) were included in the meta-analysis if they were present in at least two studies with the same unit of measurement. Mean percentage changes from baseline achieved with orlistat or metformin were recorded for each variable/outcome, and the difference (orlistat minus metformin) between these percentage changes was considered as the effect size. Therefore, results are presented as mean differences with 95% confidence intervals (95%CI). A P value < 0.05 was considered statistically significant. Heterogeneity was assessed using the I^2 statistics and Cochran's Q test. All analyses were conducted using the Meta package from R software version 3.0.

RESULTS

Flowchart of study selection

Figure 1 provides details of the study selection. The primary search identified 3951 articles. After title and abstract screening, 14 potentially eligible studies were retrieved for full text review. Of these 14 articles, 5 were excluded: one did not meet the inclusion criteria and four overlapped with other studies. Therefore, nine studies were included in the systematic review: three prospective, non-randomized studies comparing the use of orlistat in PCOS women and healthy controls (34-36) and six RCTs (4 studies comparing orlistat with metformin in PCOS women, 1 comparing orlistat with sibutramine in PCOS women, and 1 comparing orlistat with placebo in PCOS women) (37-42).

Characteristics of included studies

Table 1 summarizes the characteristics of the nine studies included in the systematic review. Two studies focused on Caucasian women from the UK (37, 38), two on Iranian

women (39, 41), one on Indian women (42), and four on Greek women (34-36, 40). Eight of these studies employed Rotterdam criteria for diagnosis of PCOS and one used NIH criteria [hyperandrogenemia (free androgen index > 8) and history of oligomenorrhea (cycle length, < 21 d or > 35 d; < 8 cycles per year) or amenorrhea and hirsutism (Ferriman-Gallwey score > 8) (37).

All nine studies included overweight/obese PCOS women. In four, orlistat was compared with metformin (37-39, 42). One study compared orlistat and sibutramine (40). In that study, a normal weight PCOS group receiving metformin for 6 months was also included. Another study compared orlistat and placebo (41). Finally, three studies compared orlistat in overweight/obese PCOS women vs. overweight/obese healthy controls (34-36).

Four studies (comparing orlistat vs. metformin or vs. sibutramine) (37-40) did not report the mean age for each group separately. Only the mean age for the overall participants was presented, and that ranged from 25.7 to 27.0 years. One study (42) included women younger than 40 years of age. In the study comparing orlistat vs. placebo (41), the mean age was 26.8 ± 5.2 in PCOS women treated with orlistat and 27.4 ± 3.3 in the placebo group. In the studies comparing PCOS and healthy controls (34-36), the age of PCOS women ranged from 25.4 to 26.1 years, vs. 30.6 to 32.1 years for controls, and study duration ranged from 12 to 24 weeks. Two 24-month studies also reported 12-week data.

The four RCTs included in the systematic review, comparing orlistat vs. metformin in PCOS women (37-39, 42), lasted 12 weeks. Three studies used the same dosages for both drugs (37-39) and one used a lower dosage of orlistat (42). One of these studies also offered general dietary guidance (37), while another provided guidance on low-calorie diet and lifestyle modification (42). The sample size ranged from 10 to 40 women for both the PCOS group treated with orlistat and the PCOS group treated with metformin.

One study compared orlistat with sibutramine in overweight/obese women with PCOS (40). These women also received low-calorie diet guidance and instructions for performing moderate intensity aerobic exercise for at least 3h/week. In that study, an additional group of lean women with PCOS received metformin for 6 months. Another study comparing orlistat vs. metformin was excluded because baseline and final results were not available (42).

Only one RCT had a placebo control group (41). Participants were instructed to follow a diet (1200-1800 kcal) and were encouraged to walk for 30 min daily.

Three additional studies included in the systematic review compared the use of orlistat in overweight/obese PCOS women and overweight/obese healthy controls (34-36). All three studies offered an energy-restricted diet and one recommended moderate-intensity aerobic exercise for at least 3h/week (35).

The risk of bias of randomized trials included in the systematic review is shown in Figure 2.

Qualitative data synthesis

Weight/BMI and waist circumference

All studies reported significant reductions in BMI and/or weight with orlistat in overweight/obese women with PCOS (34-42) (Table 2). Six studies evaluated waist circumference, and five showed significant reductions in waist or waist-to-hip ratio after orlistat treatment in women with PCOS (36, 39-42). In addition, two studies comparing the effects of orlistat and metformin showed that both treatments equally reduced waist circumference in PCOS women (39, 42).

Insulin and HOMA

While three studies found no changes in insulin resistance markers in PCOS women using orlistat (37, 41, 42), five studies did find significant decrease in HOMA and/or insulin levels (34-36, 38, 40) (Table 2).

Testosterone levels

All studies except one (40) reported a significant reduction in testosterone levels after orlistat treatment (Table 2).

Menstrual cyclicity, ovulation rate, and ovarian morphology at ultrasound

The four studies assessing menstrual cycles and/or ovarian morphology found no improvements in oligo/amenorrheic cycles or ovarian morphology at ultrasound (35, 36, 40, 41) with either orlistat or metformin. Two other studies have assessed ovulation rates (39, 42). Ghandi et al. (39) compared ovulation rates only after (and not before) the intervention with orlistat or metformin, but did not observe differences between groups. Kumar and Arora (42) also assessed ovulation rates after the intervention and found improved ovulation rates in the

orlistat and metformin groups in comparison with the control group, with no differences between orlistat and metformin users.

Lipid profile

Five studies assessed lipid profile after orlistat treatment (35, 37, 39, 41, 42) and four reported improvement in triglycerides (35, 39, 41, 42) and in LDL-cholesterol (35, 41, 42) and/or total cholesterol (35, 39, 42). One study reported improvement in HDL-cholesterol (41). Jayagopal et al. (37) observed no changes in lipid profile after orlistat treatment.

Three studies compared the effects of orlistat and metformin in lipid profile. Two found similar effects with both treatments (37, 42) and one reported that orlistat was more effective in reducing total cholesterol than metformin (39).

Side effects

Four studies described side effects of orlistat. Cramping and oily stool were reported in 5%, 20%, and 22% of participants respectively for Ghandi et al. (39), Jayagopal et al. (37), and Moini et al. (41). Jayagopal et al. (37) reported mild to moderate flatulence in 20% of participants. Occasional diarrhea with fecal urgency was observed by Diamanti-Kandarakis (34) in 43% of participants and by Moini et al. (41) in 54%. Moini et al. (41) also observed headaches in 3% of the sample.

Quantitative data synthesis and meta-analysis

A meta-analysis was performed to compare the effects of orlistat vs. metformin on BMI, HOMA, testosterone, and insulin levels (Figure 3). Fixed effects models were used because heterogeneity was not significant. The main results obtained in the three studies included in this meta-analysis (37-39) are presented in Table 2. One of the four RCTs comparing orlistat vs. metformin in PCOS women was excluded because data on baseline and final results were not available (42).

It was not possible to meta-analyze the effect of orlistat vs. placebo on clinical variables associated with weight loss because we found only one study comparing orlistat with placebo. Similarly, a meta-analysis of orlistat effects described in three prospective, non-controlled studies (before and after-treatment comparisons) (34-36) and three RCTs (40-42) was not performed because neither the measure of variability (% change) nor baseline and after-treatment values were available.

Weight/BMI

Data from 2 studies were available for BMI (38, 39), totalizing 100 women with PCOS. Orlistat and metformin produced similar BMI reduction (-0.65%, 95%CI: -2.03, 0.73). Between-study heterogeneity was moderate (I^2=58.1%, p=0.1222).

HOMA

HOMA was analyzed in two studies (37, 38), totalizing 41 women with PCOS. Orlistat and metformin produced similar reductions in HOMA (-3.60%, 95%CI: -16.99, 9.78). Between-study heterogeneity was low (I^2=0%, p=0.9994).

Testosterone

Testosterone data were available from two studies (37, 39), totalizing 101 women with PCOS. A similar reduction in testosterone levels was achieved with orlistat and metformin (-2.08%, 95%CI: -13.08, 8.93). Between-study heterogeneity was low (I^2=0%, p=0.9976).

Insulin

Two studies reported data for insulin (37, 38), totalizing 41 women with PCOS. A similar reduction in insulin levels was achieved with orlistat and metformin (-5.51%, 95%CI: -22.27, 11.26). Between-study heterogeneity was low (I^2=0%, p=0.982).

DISCUSSION

To the best of our knowledge, this is the first systematic review investigating the effects of orlistat in women with PCOS. Even though only a few studies were identified, there is agreement regarding the ability of orlistat to reduce BMI/weight in women with PCOS. In addition, most of the studies, but not all, found that orlistat treatment is associated with reduction of androgens and with improvement in insulin resistance (IR) markers and lipid profile. Our meta-analysis including three RCTs and 121 PCOS women showed that orlistat was comparable to metformin in reducing BMI, HOMA, testosterone, and insulin in overweight/obese PCOS women.

Systematic review

Our systematic review revealed that orlistat was associated with BMI reduction after 12 (ranging from 4.48% to 8.10%) and 24 weeks (12.9%) in women with PCOS. The

XENDOS study, a prospective clinical trial with obese patients from the general population, found that orlistat (120 mg three times daily) produced significantly higher weight loss as compared with placebo in 4 years (5.2% vs. 2.8%) (25).

Currently, guidelines for the treatment of obesity in the general population recommend an initial weight loss of 5% to 10% within 6 months (43). Moderate weight loss can produce health benefits, including improved glycemic control and lipid profile and reduced risk of DM2 (44-47). Studies have shown improvement in menstrual cyclicity and a higher spontaneous ovulation rate and pregnancy in obese women with PCOS following a 5% decrease in body weight (48-54).

Regarding the effects of orlistat on markers of IR, five out of eight studies showed a positive response, while three others found no significant improvement in these parameters (37, 41, 42). A difference in treatment duration may, however, help explain this discrepancy: the two studies that did not find significant changes in IR markers lasted only 12 weeks, whereas those with longer duration observed a significant effect of orlistat. In addition, the lack of statistical significance despite a marked reduction in fasting insulin (12.5%) and HOMA (10.8%) in the study of Jayagopal et al. (37) might have resulted from the small sample size, only 10 patients. In turn, Diamanti-Kandarakis et al. (34) showed that there were significant improvements in IR markers with orlistat regardless of weight loss only in the PCOS group.

In the present review, seven out of eight studies (34-37, 39, 41, 42) showed a decrease in testosterone levels in association with orlistat administration. Even though a reduction in BMI and IR markers was observed in these studies, the decrease in testosterone levels reported by Diamanti-Kandarakis et al. (34) cannot be attributed exclusively to weight reduction, because it persisted even after adjustment for changes in BMI.

None of the studies we analyzed was able to demonstrate any improvement in menstrual regularity, ovarian volume, or number of follicles with the use of orlistat. However, longer duration studies are needed to investigate the benefits of weight reduction, improved insulin resistance and androgen levels to restore or ameliorate menstrual cyclicity.

Among the five studies describing the effect of intervention with orlistat on lipid profile (35, 37, 39, 41, 42), only one was unable to show a significant beneficial effect (37), possibly because of the small sample size. The prospective XENDOS study observed that orlistat led to significantly greater improvement than placebo in total cholesterol and LDL-cholesterol after 4 years of treatment in the general population (25).

The main side effects described for orlistat were related to the drug's mechanism of action of decreasing fat absorption from the intestinal lumen – oily stool, flatulence, and diarrhea with fecal urgency occurring in around 5 to 40% of participants (34, 37, 39, 41). In contrast, although not directly assessed in the present review, the side effects of metformin (nausea, mild abdominal pain and diarrhea) are known to be dose-dependent (22, 37, 39).

Meta-analysis

Weight loss is considered the first-line treatment for obese PCOS women. Anti-obesity drugs have also been considered for these women. Orlistat promotes weight loss by partially preventing intestinal fat absorption (55, 56). Metformin improves insulin action and has been considered a second-line treatment for obese and/or insulin resistant PCOS women (19-24). Thus, the present meta-analysis was conducted to analyze the evidence for the differential effects of orlistat vs. metformin treatment on weight loss-associated clinical variables in overweight/obese women with PCOS.

The results of the present meta-analysis show that orlistat was comparable to metformin in reducing BMI. A recently published meta-analysis with more than 11,000 overweight/obese individuals from the general population showed that the use of metformin together with lifestyle change promoted a weight reduction of 1.92 kg (2.94 to 0.89; P=0.11), while orlistat plus lifestyle change reduced weight by 3.05 kg (3.75 to 2.35; P=0.0001); however, when the two drugs were compared, the difference was not statistically significant (P=0.07) (57).

We did not observe a difference between metformin and orlistat in terms of insulin and HOMA reduction. Merlotti et al. (58) recently reported an effect of various interventions in reducing the risk of DM2 in obese individuals. All strategies assessed in that meta-analysis reduced the risk of developing DM2. Similar effectiveness was found for physical activity and diet [OR 0.44 (0.36–0.52)], anti-diabetic drugs (metformin, glitazones, glinides, alpha-glucosidase inhibitors) [OR 0.53 (0.33–0.86)], and weight loss-promoting drugs (orlistat, bezafibrate, phentermine/topiramate controlled release) [OR 0.52 (0.35–0.78)].

Evidence indicates that weight reduction in PCOS improves hyperlipidemia, reduces IR, and increases SHBG concentration, thereby reducing biochemical hyperandrogenism and improving menstrual cyclicity (54, 59, 60). In the present meta-analysis, the lack of difference between the effect of metformin or orlistat on testosterone levels might be related to the lack of difference between these drugs in terms of their effect weight loss.

We observed significant heterogeneity in the analysis of BMI. This heterogeneity limits the interpretation of data and suggests similar effects of orlistat and metformin. The analyses of HOMA, insulin and testosterone levels revealed very low heterogeneity between studies. In turn, due to the limited number of studies, we were not able to determine whether there was publication bias.

One strength of this systematic review and meta-analysis is that all studies considered the Rotterdam criteria to diagnose PCOS, with the exception of one study, which employed NIH criteria. Therefore, the PCOS population was certainly homogeneous. Limitations of this meta-analysis are the reduced number of studies, the small sample sizes, and the absence of studies with long-term interventions. However, similar analyses are not available in the literature, and this study represents the first evidence for orlistat effects in women with PCOS.

Conclusion

In conclusion, the present data suggest that orlistat leads to significant reduction in weight/BMI in overweight/obese PCOS women. Most studies also reported that orlistat significantly reduced testosterone and IR markers and improved lipid profile. Regarding our meta-analysis, the evidence produced is not entirely conclusive because only three RCTs with small samples were identified. Therefore, the observed similarity between orlistat and metformin to improve BMI, HOMA, insulin, and testosterone levels in PCOS should be considered with caution, and more studies are needed in order to confirm these data.

Conflicts of interest: None.

Sources of funding: Support for this work was provided by Brazilian National Institute of Hormones and Women's Health/ Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq INCT 573747/2008-3), Brazil; the funding sources had no influence in the writing or decision to submit the article for publication.

Author contributions

Scheila K Graff: data collection, analysis/interpretation, drafting of article, critical revision of article.

Fernanda M Mario: data collection, critical revision of article.

Patrícia Ziegelmann: data analysis/interpretation, drafting of article, critical revision of article.

Poli Mara Spritzer: concept/design, data analysis/interpretation, drafting of article, securing funding, critical revision of article.

All authors read and approved the final manuscript.

Figure captions

Figure 1. Flowchart of the study selection.

Figure 2. Risk of bias summary for included studies.

Figure 3. Forrest plot showing the impact of orlistat and metformin on body mass index (BMI), homeostasis model assessment (HOMA) estimates, testosterone, and insulin levels in women with PCOS.

REFERENCES

1. Azziz R, Carmina E, Dewailly D, Diamanti-Kandarakis E, Escobar-Morreale HF, Futterweit W, et al. The Androgen Excess and PCOS Society criteria for the polycystic ovary syndrome: the complete task force report. Fertil Steril 2009;91(2):456-88.

2. Wild RA, Carmina E, Diamanti-Kandarakis E, Dokras A, Escobar-Morreale HF, Futterweit W, et al. Assessment of cardiovascular risk and prevention of cardiovascular disease in women with the polycystic ovary syndrome: a consensus statement by the Androgen Excess and Polycystic Ovary Syndrome (AE-PCOS) Society. J Clin Endocrinol Metab 2010;95(5):2038-49.

3. Asunción M, Calvo RM, San Millán JL, Sancho J, Avila S, Escobar-Morreale HF. A prospective study of the prevalence of the polycystic ovary syndrome in unselected Caucasian women from Spain. J Clin Endocrinol Metab 2000;85(7):2434-8.

4. Norman RJ, Dewailly D, Legro RS, Hickey TE. Polycystic ovary syndrome. Lancet 2007;370(9588):685-97.

5. Hart R, Doherty DA. The potential implications of a PCOS diagnosis on a woman's long-term health using data linkage. J Clin Endocrinol Metab 2015;100(3):911-9.

6. Azziz R, Woods KS, Reyna R, Key TJ, Knochenhauer ES, Yildiz BO. The prevalence and features of the polycystic ovary syndrome in an unselected population. J Clin Endocrinol Metab 2004;89(6):2745-9.

7. March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod 2010;25(2):544-51.

8. Haqq L, McFarlane J, Dieberg G, Smart N. Effect of lifestyle intervention on the reproductive endocrine profile in women with polycystic ovarian syndrome: a systematic review and meta-analysis. Endocr Connect 2014;3(1):36-46.

9. Azziz R, Sanchez LA, Knochenhauer ES, Moran C, Lazenby J, Stephens KC, et al. Androgen excess in women: experience with over 1000 consecutive patients. J Clin Endocrinol Metab 2004;89(2):453-62.

10. Diamanti-Kandarakis E, Spritzer PM, Sir-Petermann T, Motta AB. Insulin resistance and polycystic ovary syndrome through life. Curr Pharm Des 2012;18(34):5569-76.

11. Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update 2012;18(6):618-37.

12. Moran LJ, Hutchison SK, Norman RJ, Teede HJ. Lifestyle changes in women with polycystic ovary syndrome. Cochrane Database Syst Rev 2011(7):CD007506.

13. Toscani MK, Mario FM, Radavelli-Bagatini S, Wiltgen D, Matos MC, Spritzer PM. Effect of high-protein or normal-protein diet on weight loss, body composition, hormone, and metabolic profile in southern Brazilian women with polycystic ovary syndrome: a randomized study. Gynecol Endocrinol 2011;27(11):925-30.

14. Carmina E, Bucchieri S, Esposito A, Del Puente A, Mansueto P, Orio F, et al. Abdominal fat quantity and distribution in women with polycystic ovary syndrome and extent of its relation to insulin resistance. J Clin Endocrinol Metab 2007;92(7):2500-5.

15. Wiltgen D, Spritzer PM. Variation in metabolic and cardiovascular risk in women with different polycystic ovary syndrome phenotypes. Fertil Steril 2010;94(6):2493-6.

16. Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril 2009;92(6):1966-82.

17. Spritzer PM, Motta AB, Sir-Petermann T, Diamanti-Kandarakis E. Novel strategies in the management of polycystic ovary syndrome. Minerva Endocrinol 2015;40(3):195-212.

18. Panidis D, Tziomalos K, Papadakis E, Vosnakis C, Chatzis P, Katsikis I. Lifestyle intervention and anti-obesity therapies in the polycystic ovary syndrome: impact on metabolism and fertility. Endocrine 2013;44(3):583-90.

19. Chou KH, von Eye Corleta H, Capp E, Spritzer PM. Clinical, metabolic and endocrine parameters in response to metformin in obese women with polycystic ovary syndrome: a randomized, double-blind and placebo-controlled trial. Horm Metab Res 2003;35(2):86-91.

20. Naderpoor N, Shorakae S, de Courten B, Misso ML, Moran LJ, Teede HJ. Metformin and lifestyle modification in polycystic ovary syndrome: systematic review and meta-analysis. Hum Reprod Update 2015;21:560–74.

21. De Sloover Koch Y, Ernst ME. Use of metformin in polycystic ovary syndrome. Ann Pharmacother 2001;35(12):1644-7.

22. Lord JM, Flight IH, Norman RJ. Metformin in polycystic ovary syndrome: systematic review and meta-analysis. BMJ 2003;327(7421):951-3.

23. Nestler JE, Jakubowicz DJ, de Vargas AF, Brik C, Quintero N, Medina F. Insulin stimulates testosterone biosynthesis by human thecal cells from women with polycystic ovary

syndrome by activating its own receptor and using inositolglycan mediators as the signal transduction system. J Clin Endocrinol Metab 1998;83(6):2001-5.

24. Lord JM, Flight IH, Norman RJ. Insulin-sensitising drugs (metformin, troglitazone, rosiglitazone, pioglitazone, D-chiro-inositol) for polycystic ovary syndrome. Cochrane Database Syst Rev 2003(3):CD003053.

25. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L. XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. Diabetes Care 2004;27(1):155-61.

26. Rucker D, Padwal R, Li SK, Curioni C, Lau DC. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ 2007;335(7631):1194-9.

27. Sjöström L, Rissanen A, Andersen T, Boldrin M, Golay A, Koppeschaar HP, et al. Randomised placebo-controlled trial of orlistat for weight loss and prevention of weight regain in obese patients. European Multicentre Orlistat Study Group. Lancet 1998;352(9123):167-72.

28. Davidson MH, Hauptman J, DiGirolamo M, Foreyt JP, Halsted CH, Heber D, et al. Weight control and risk factor reduction in obese subjects treated for 2 years with orlistat: a randomized controlled trial. JAMA 1999;281(3):235-42.

29. Tonstad S, Pometta D, Erkelens DW, Ose L, Moccetti T, Schouten JA, et al. The effect of the gastrointestinal lipase inhibitor, orlistat, on serum lipids and lipoproteins in patients with primary hyperlipidaemia. Eur J Clin Pharmacol 1994;46(5):405-10.

30. Rissanen A. Pharmacological intervention: the antiobesity approach. Eur J Clin Invest 1998;28 Suppl 2:27-30.

31. Group REA-SPCW. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod 2004;19(1):41-7.

32. Zawadzki JF, Dunaif A. Diagnostic criteria for polycystic ovary syndrome: towards a rational approach. In: Dunaif JR, Givens FB, Haseltine GR, Merriam A, eds. Polycystic ovary syndrome. Boston: Blackwell Scientific; 1992:377-84.

33. Higgins JPT, Green S. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. 2011.

34. Diamanti-Kandarakis E, Katsikis I, Piperi C, Alexandraki K, Panidis D. Effect of long-term orlistat treatment on serum levels of advanced glycation end-products in women with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2007;66(1):103-9.

35. Panidis D, Tziomalos K, Papadakis E, Chatzis P, Kandaraki EA, Tsourdi EA, et al. The role of orlistat combined with lifestyle changes in the management of overweight and obese patients with polycystic ovary syndrome. Clin Endocrinol (Oxf) 2014;80(3):432-8.

36. Spanos N, Tziomalos K, Macut D, Koiou E, Kandaraki EA, Delkos D, et al. Adipokines, insulin resistance and hyperandrogenemia in obese patients with polycystic ovary syndrome: cross-sectional correlations and the effects of weight loss. Obes Facts 2012;5(4):495-504.

37. Jayagopal V, Kilpatrick ES, Holding S, Jennings PE, Atkin SL. Orlistat is as beneficial as metformin in the treatment of polycystic ovarian syndrome. J Clin Endocrinol Metab 2005;90(2):729-33.

38. Cho LW, Kilpatrick ES, Keevil BG, Coady AM, Atkin SL. Effect of metformin, orlistat and pioglitazone treatment on mean insulin resistance and its biological variability in polycystic ovary syndrome. Clin Endocrinol (Oxf) 2009;70(2):233-7.

39. Ghandi S, Aflatoonian A, Tabibnejad N, Moghaddam MH. The effects of metformin or orlistat on obese women with polycystic ovary syndrome: a prospective randomized open-label study. J Assist Reprod Genet 2011;28(7):591-6.

40. Koiou E, Tziomalos K, Katsikis I, Delkos D, Tsourdi EA, Panidis D. Disparate effects of pharmacotherapy on plasma plasminogen activator inhibitor-1 levels in women with the polycystic ovary syndrome. Hormones (Athens) 2013;12(4):559-66.

41. Moini A, Kanani M, Kashani L, Hosseini R, Hosseini L. Effect of orlistat on weight loss, hormonal and metabolic profiles in women with polycystic ovarian syndrome: a randomized double-blind placebo-controlled trial. Endocrine 2015;49(1):286-9.

42. Kumar P, Arora S. Orlistat in polycystic ovarian syndrome reduces weight with improvement in lipid profile and pregnancy rates. J Hum Reprod Sci 2014;7(4):255-61.

43. Jensen MD, Ryan DH, Apovian CM, Ard JD, Comuzzie AG, Donato KA, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation 2014;129(25 Suppl 2):S102-38.

44. Lindström J, Peltonen M, Eriksson JG, Ilanne-Parikka P, Aunola S, Keinänen-Kiukaanniemi S, et al. Improved lifestyle and decreased diabetes risk over 13 years: long-term follow-up of the randomised Finnish Diabetes Prevention Study (DPS). Diabetologia 2013;56(2):284-93.

45. Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. Lancet 2008;371(9626):1783-9.

46. Unick JL, Beavers D, Bond DS, Clark JM, Jakicic JM, Kitabchi AE, et al. The long-term effectiveness of a lifestyle intervention in severely obese individuals. Am J Med 2013;126(3):236-42, 42.e1-2.

47. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, et al. Association of an intensive lifestyle intervention with remission of type 2 diabetes. JAMA 2012;308(23):2489-96.

48. Crosignani PG, Colombo M, Vegetti W, Somigliana E, Gessati A, Ragni G. Overweight and obese anovulatory patients with polycystic ovaries: parallel improvements in anthropometric indices, ovarian physiology and fertility rate induced by diet. Hum Reprod 2003;18(9):1928-32.

49. Norman RJ, Noakes M, Wu R, Davies MJ, Moran L, Wang JX. Improving reproductive performance in overweight/obese women with effective weight management. Hum Reprod Update 2004;10(3):267-80.

50. Mahoney D. Lifestyle modification intervention among infertile overweight and obese women with polycystic ovary syndrome. J Am Assoc Nurse Pract 2014;26(6):301-8.

51. Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD. The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J Clin Endocrinol Metab 2008;93(9):3373-80.

52. Clark AM, Ledger W, Galletly C, Tomlinson L, Blaney F, Wang X, et al. Weight loss results in significant improvement in pregnancy and ovulation rates in anovulatory obese women. Hum Reprod 1995;10(10):2705-12.

53. Hollmann M, Runnebaum B, Gerhard I. Effects of weight loss on the hormonal profile in obese, infertile women. Hum Reprod 1996;11(9):1884-91.

54. Huber-Buchholz MM, Carey DG, Norman RJ. Restoration of reproductive potential by lifestyle modification in obese polycystic ovary syndrome: role of insulin sensitivity and luteinizing hormone. J Clin Endocrinol Metab 1999;84(4):1470-4.

55. Dixon JB. Weight loss medications--where do they fit in? Aust Fam Physician 2006;35(8):576-9.

56. Padwal RS, Majumdar SR. Drug treatments for obesity: orlistat, sibutramine, and rimonabant. Lancet 2007;369(9555):71-7.

57. Peirson L, Douketis J, Ciliska D, Fitzpatrick-Lewis D, Ali MU, Raina P. Treatment for overweight and obesity in adult populations: a systematic review and meta-analysis. CMAJ Open 2014;2(4):E306-17.

58. Merlotti C, Morabito A, Ceriani V, Pontiroli AE. Prevention of type 2 diabetes in obese at-risk subjects: a systematic review and meta-analysis. Acta Diabetol 2014;51(5):853-63.

59. Andersen P, Seljeflot I, Abdelnoor M, Arnesen H, Dale PO, Løvik A, et al. Increased insulin sensitivity and fibrinolytic capacity after dietary intervention in obese women with polycystic ovary syndrome. Metabolism 1995;44(5):611-6.

60. Hamilton-Fairley D, Kiddy D, Anyaoku V, Koistinen R, Seppälä M, Franks S. Response of sex hormone binding globulin and insulin-like growth factor binding protein-1 to an oral glucose tolerance test in obese women with polycystic ovary syndrome before and after calorie restriction. Clin Endocrinol (Oxf) 1993;39(3):363-7.

Table 1. Characteristics of studies in the systematic review

Name, Year	Ethnicity (country)	PCOS criteria	Types of studies and intervention	Dosage	Length (weeks)	N (PCOS-orlistat/ comparison group)	Age (PCOS-orlistat group vs. comparison group) Mean ± SD	Lifestyle intervention
Cho et al., 2009 (38)	Caucasian (UK)	Rotterdam	Randomized, open-label parallel study comparing the use of orlistat with metformin in obese PCOS women	Orlistat: 120mg three times per day; Metformin: 500mg once daily for the first week, 500mg twice daily for the next week and 500mg three times daily for the remainder of the study period	12	10/10	26.4 ± 6.7 (all participants)	No
Diamanti-Kandarakis et al., 2007 (34)	European (Greece)	Rotterdam	Prospective study comparing the use of orlistat in obese PCOS women and obese healthy controls	Orlistat: 120mg three times per day	12/24	29/18	25.5 ± 5.8 vs. 32.1 ± 5.6	Normal protein, energy-restricted diet (BMR – 600kcal; 50% CHO, 30% FAT, 20% PTN)
Ghandi et al., 2011 (39)	Iranian (Iran)	Rotterdam	Randomized, open-label parallel study comparing the use of orlistat with metformin in obese PCOS women	Orlistat: 120mg three times per day; Metformin: 500mg once daily for the first week, 500mg twice daily for the next week and 500mg three times daily for the remainder of the study period	12	40/40	27.0 ± 44.0 (all participants)	No
Jayagopal et al., 2005 (37)	Caucasian (UK)	*	Prospective, randomized, open-label study comparing the use of orlistat with metformin in overweight/obese PCOS women	Orlistat: 120mg three times per day; Metformin: 500mg once daily for the first week, 500mg twice daily for the next week and 500mg three times daily for the remainder of the study period	12	10/11	27.0 ± 4.12 (all participants)	Weight maintenance diet (50% CHO, 30% FAT, 20% PTN, 300mg cholesterol)
Koiou et al., 2013 (40)	European (Greece)	Rotterdam	Prospective, randomized study comparing the use of orlistat with sibutramine in PCOS overweight/obese women	Orlistat: 120mg three times per day; Sibutramine: 10mg qd	24	22/28	25.7 ± 5.9 (all participants)	Normal protein, energy-restricted diet (BMR – 600kcal; 50% CHO, 30% FAT, 20% PTN) and instruction for exercise (moderate intensity aerobic exercise) for at least 3h/week
Kumar and Arora, 2014 (42)	Indian	Rotterdam	Randomized controlled trial comparing the use of orlistat with metformin in overweight/obese PCOS women	Orlistat: 120mg two times per day; Metformin was incremented stepwise to maximum 500 mg 3 times a day	12	30/30	N/A	Normal protein, energy-restricted diet (1200-1800 kcal/day; 55% CHO, 30% FAT, 15% PTN) and exercise (1h/day)

Moini et al., 2015 (41)	Iranian	Rotterdam	Randomized double-blind placebo-controlled clinical trial comparing the use of orlistat with placebo in overweight/obese PCOS women	Orlistat: 120mg three times per day	12	43/43	26.8 ± 5.2 vs. 27.4 ± 3.3	Normal protein, energy-restricted diet (1200-1800 kcal/day; 55% CHO, 30% FAT, 15% PTN) and patients encouraged to walk for 30 min daily
Panidis et al., 2014 (35)	European (Greece)	Rotterdam	Prospective study comparing the use of orlistat in overweight/obese PCOS women and overweight/obese healthy controls	Orlistat: 120mg three times per day	12/24	101/29	26.1 ± 6.4 vs. 31.5 ± 4.7	Normal protein, energy-restricted diet (BMR – 600kcal; 50% CHO, 30% FAT, 20% PTN) and instruction to exercise (moderate intensity aerobic exercise) at least 3h/week
Spanos et al., 2012 (36)	European (Greece)	Rotterdam	Prospective study comparing the use of orlistat in overweight/obese PCOS women and overweight/obese healthy controls	Orlistat: 120mg three times per day	24	60/48	25.4 ± 6.2 vs. 30.6 ± 6.3	Normal protein, energy-restricted diet (BMR – 600kcal; 50% CHO, 30% FAT, 20% PTN)

BMR =basal metabolic rate; CHO= carbohydrate; PTN= protein; BMI=body mass index; N/A: not available
*Presence of hyperandrogenemia (free androgen index >8) with a history of oligomenorrhea (cycle length, <21 d or >35 d; <8 cycles per year) or amenorrhea and hirsutism (Ferriman-Gallwey score >8).

Table 2. Changes in BMI, HOMA, insulin, and testosterone with orlistat vs. metformin treatment in PCOS women

			Orlistat				Metformin				
	Study	**Length (weeks)**	**Baseline**	**After treatment**	**Delta (%) ± SEM**	**P**	**Baseline**	**After treatment**	**Delta (%) ± SEM**	**P**	**Unit**
BMI	**Cho et al., 2009 (38)**	12	37.40 ± 2.70	35.20 ± 2.40	(-5.70) ± 0.80	<0.050	34.30 ± 1.80	33.20 ± 1.90	(-3.40) ± 1.00	<0.050	kg/m²
	Diamanti-Kandarakis et al., 2007 (34)	12	35.43 ± 5.31	31.52 ± 4.80		<0.001					kg/m²
	Diamanti-Kandarakis et al., 2007 (34)	24	35.43 ± 5.31	29.70 ± 4.57		<0.001					kg/m²
	Ghandi et al., 2011 (39)	12	34.88 ± 4.90	33.24 ± 4.19	(-4.48) ± 0.47	<0.001	32.49 ± 3.06	31.03 ± 3.43	(-4.55) ± 0.70	<0.001	kg/m²
	Jayagopal et al., 2005 (37)	12									
	Koiou et al., 2013 (40)	24	33.70 ± 6.60	29.90 ± 6.40		<0.001					kg/m²
	Kumar and Arora, 2014 (42)	12			(-8.12) ± 6.71	<0.001			(-8.40) ± 0.65	<0.001	kg/m²
	Moini et al., 2015 (41)	12	29.10 ± 2.09	27.16 ± 1.93		<0.010					kg/m²
	Spanos et al., 2012 (36)	24	34.90 ± 5.90	30.40 ± 5.80		<0.001					kg/m²
HOMA	**Cho et al., 2009 (38)**	12	5.00 ± 0.80	3.70 ± 0.50	(-19.70) ± 6.40	0.013	3.60 ± 0.50	3.10 ± 0.60	(-16.10) ± 6.80	0.170	
	Diamanti-Kandarakis et al., 2007 (34)	12	4.75 ± 2.48	3.10 ± 1.68		0.008					
	Diamanti-Kandarakis et al., 2007 (34)	24	4.75 ± 2.48	2.67 ± 1.23		0.006					
	Ghandi et al., 2011 (39)	12									
	Jayagopal et al., 2005 (37)	12	4.32 ± 1.20	3.58 ± 0.70	(-10.80) ± 6.00	>0.050	4.27 ± 0.60	4.09 ± 0.70	(-7.19) ± 8.40	>0.050	
	Koiou et al., 2013 (40)	24	4.39 ± 2.34	2.97 ± 2.74		0.002					
	Kumar and Arora, 2014 (42)	12			(10.56) ± 7.45	>0.050			(-3.78) ± 3.78	>0.050	
	Moini et al., 2015 (41)	12	3.46 ± 1.99	3.43 ± 1.11		0.430					
	Panidis et al., 2014 (35)	12	4.78 ± 3.12	2.97 ± 1.59							
	Panidis et al., 2014 (35)	24	4.78 ± 3.12	2.72 ± 1.85		<0.001					
	Spanos et al., 2012 (36)	24	4.85 ± 3.48	2.82 ± 2.08		<0.001					

Insulin	**Cho et al., 2009 (38)**	12	23.60 ± 3.90	17.70 ± 2.30	(-18.40) ± 5.60	<0.050	16.80 ± 2.30	15.10 ± 2.90	(-12.80) ± 7.70	>0.050	mUI/mL
	Diamanti-Kandarakis et al., 2007 (34)	12	127.37 ± 61.12	88.13 ± 47.36		0.014					pmol/L
	Diamanti-Kandarakis et al., 2007 (34)	24	127.37 ± 61.12	76.40 ± 34.93		0.008					pmol/L
	Ghandi et al., 2011 (39)	12									
	Jayagopal et al., 2005 (37)	12	19.00 ± 4.60	15.70 ± 8.00	(-12.50) ± 5.80	0.155	19.40 ± 2.50	18.20 ± 2.60	(-7.39) ± 8.20	0.527	mUI/mL
	Koiou et al., 2013 (40)	24	17.30 ± 8.40	12.30 ± 10.60		0.004					mUI/mL
	Kumar and Arora, 2014 (42)	12			8.35 ± 5.54	>0.050			(0.86) ± 4.12	>0.050	nmol/L
	Moini et al., 2015 (41)	12	17.24 ± 6.49	17.20 ± 6.72		0.210					mUI/mL
	Panidis et al., 2014 (35)	12	18.70 ± 10.80	12.40 ± 6.40							mUI/mL
	Panidis et al., 2014 (35)	24	18.70 ± 10.80	11.30 ± 7.10		<0.001					mUI/mL
	Spanos et al., 2012 (36)	24	18.70 ± 11.70	11.50 ± 8.00		<0.001					mUI/mL
Testosterone	**Cho et al., 2009 (38)**	12									
	Diamanti-Kandarakis et al., 2007 (34)	12	3.01 ± 0.94	2.44 ± 0.91		0.001					nmol/L
	Diamanti-Kandarakis et al., 2007 (34)	24	3.01 ± 0.94	2.28 ± 0.65		<0.001					nmol/L
	Ghandi et al., 2011 (39)	12	0.80 ± 0.23	0.63 ± 0.22	(-19.37) ± 3.52	<0.001	0.78 ± 0.44	0.66 ± 0.34	(-17.30) ± 5.30	0.053	ng/mL
	Jayagopal et al., 2005 (37)	12	114.50 ± 11.50	93.50 ± 11.50		0.039	120.00 ± 8.70	97.20 ± 11.50		0.048	ng/dL
	Koiou et al., 2013 (40)	24	69.10 ± 29.20	56.30 ± 26.40		0.067					ng/dL
	Kumar and Arora, 2014 (42)	12			(-17.68) ± 4.18	<0.050			(-12.89) ± 3.12	<0.050	nmol/L
	Moini et al., 2015 (41)	12	83.46 ± 5.08	63.95 ± 1.63		<0.010					ng/dL
	Panidis et al., 2014 (35)	12	73.90 ± 28.80	63.30 ± 24.60							ng/dL
	Panidis et al., 2014 (35)	24	73.90 ± 28.80	60.50 ± 22.40		<0.001					ng/dL
	Spanos et al., 2012 (36)	24	75.50 ± 29.10	64.20 ± 24.00		<0.001					ng/dL

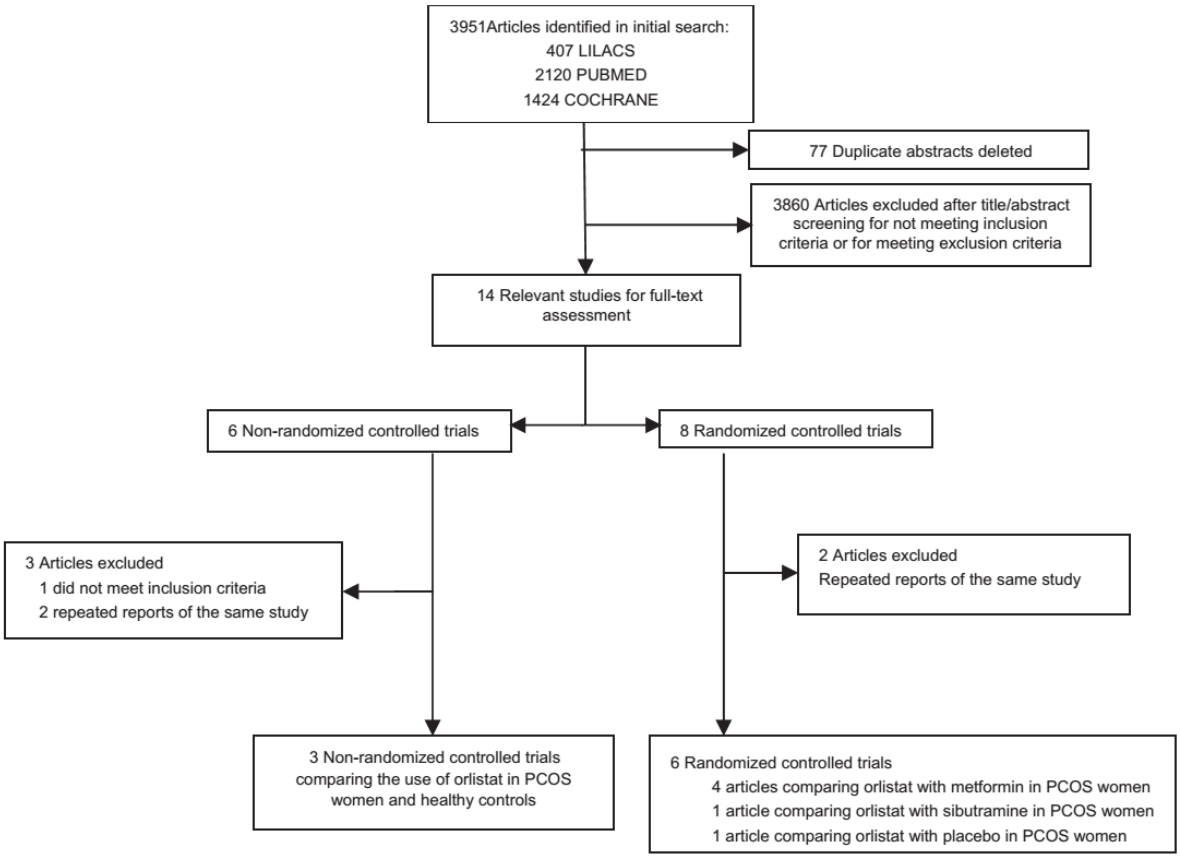

Figure 1. Flowchart of the study selection.

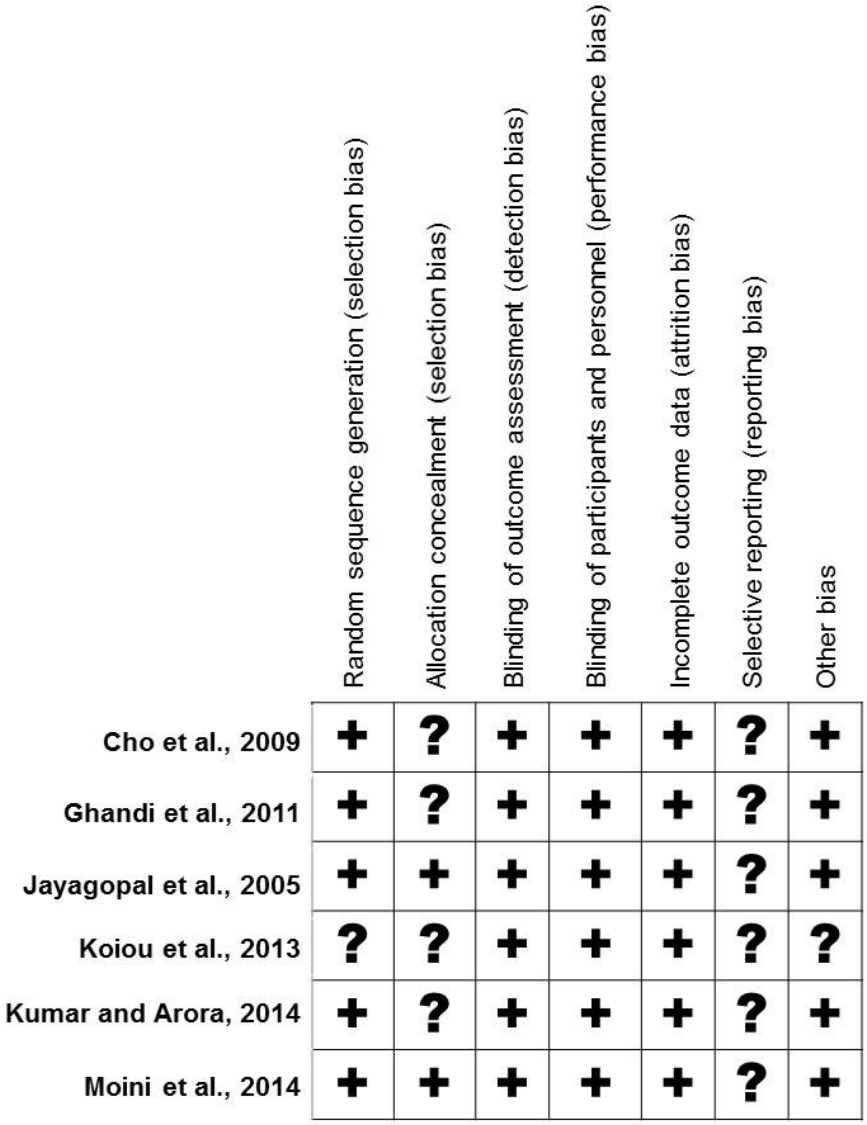

Figure 2. Risk of bias summary for included studies.

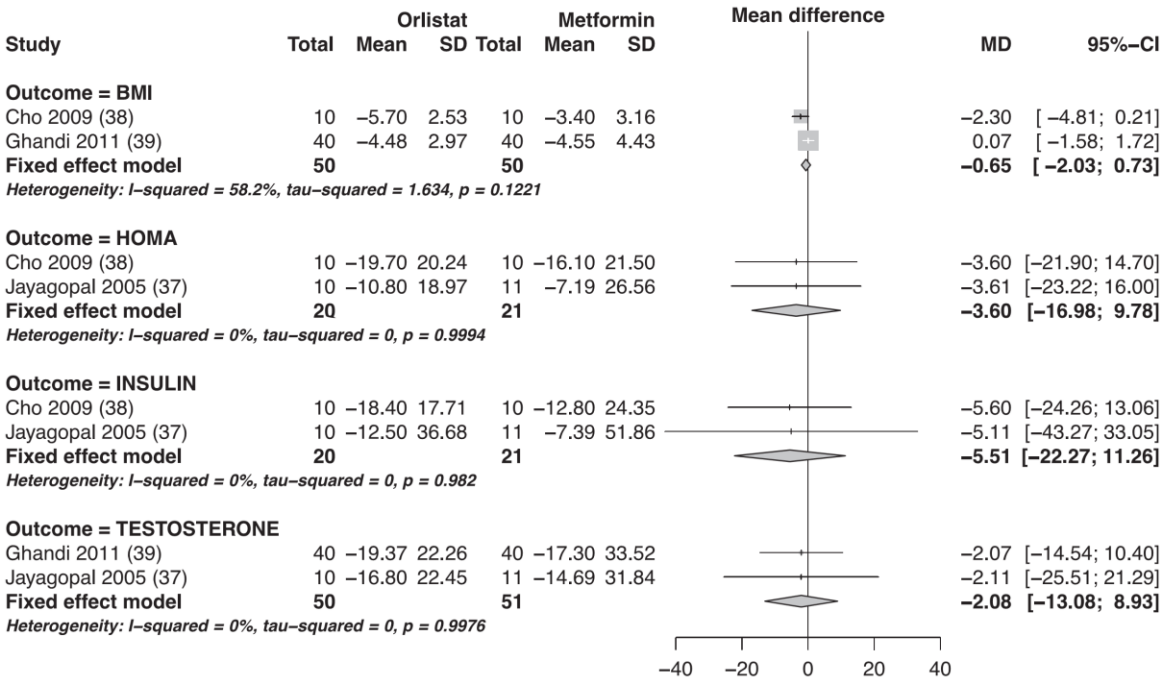

Figure 3. Forrest plot showing the impact of orlistat and metformin on body mass index (BMI), homeostasis model assessment (HOMA) estimates, testosterone, and insulin levels in women with PCOS.

CAPÍTULO III

Artigo Original 2: Saturated fat intake is associated with decreased stress-related heart rate variability in women with PCOS

Artigo submetido à revista *Nutrition, Metabolism and Cardiovascular Diseases*, 2016

Saturated fat intake is associated with stress-related heart rate variability in women with polycystic ovary syndrome

Graff SK,[a] Mario FM,[a] Magalhães JA,[b] Moraes RS,[c] Spritzer PM,[a,d]

[a]Gynecological Endocrinology Unit, Division of Endocrinology, [b]Division of Gynecology and Obstetrics, and [c]Division of Cardiology, Hospital de Clínicas de Porto Alegre, RS, Brazil. [d]Laboratory of Molecular Endocrinology, Department of Physiology, Federal University of Rio Grande do Sul, Porto Alegre, Brazil.

Corresponding author:

Poli Mara Spritzer, MD, PhD

Division of Endocrinology, Hospital de Clínicas de Porto Alegre

Rua Ramiro Barcelos, 2350

90035-003 - Porto Alegre, RS – Brazil

Phone: +55-51-3359.8027 – Fax: +55-51-3359.8777

e-mail: spritzer@ufrgs.br

Abstract

Background and Aims: Women with polycystic ovary syndrome (PCOS), characterized by hyperandrogenism and chronic anovulation, present higher prevalence of insulin resistance (IR) and cardiovascular risk factors. Alterations in heart rate variability (HRV) may reflect subclinical cardiovascular disease, and an association has been proposed between HRV and dietary fat. The aim of this study was to assess whether saturated fatty acid (SFA) intake is associated with HRV, in PCOS.

Methods and Results: Eighty-four women with PCOS according to the Rotterdam criteria were studied. Biochemical and hormonal profile, body composition, resting metabolic rate, physical activity status (pedometer), HRV, and food frequency were assessed. Participants were stratified by median SFA intake (8.5% of daily energy intake). Mean age was 23.5 ± 6.3 years and mean BMI was 29.4 ± 6.4 kg/m². Anthropometric and metabolic profiles were similar between groups. Total testosterone was higher in the group with SFA > 8.5%. Frequency domain HRV indices response to mental stress showed higher delta LF-to-HF and delta LFnu and lower delta HFnu values in the group with SFA < 8.5%. Time domain indices, such as mean R-R intervals, pNN50, and rMSSD values were lower during mental stress in the group with SFA < 8.5%.

Conclusion: The present results indicate that lower SFA intake is associated with more favorable stress-related HRV and lower testosterone in women with PCOS.

Keywords: Polycystic ovary syndrome, heart rate variability, autonomic modulation, diet, saturated fatty acids

Acronyms: BMI, body mass index; DHEAS, dehydroepiandrosterone; ECG, electrocardiogram; FAI, free androgen index; GI, glycemic index; GL, glycemic load; HDL-C, high-density lipoprotein cholesterol; HF, high frequency; HFnu, high frequency in normalized units; HOMA, homeostasis model assessment; HRV, heart rate variability; IR, insulin resistance; LF, low frequency; LFnu, low frequency in normalized units; PCO, polycystic ovary; PCOS, polycystic ovary syndrome; pNN50, percentage of successive differences between normal adjacent R-R intervals exceeding 50 ms; rMSSD, root mean square of successive differences of normal adjacent R-R intervals; SFA, saturated fatty acid; SHBG, sex hormone-binding globulin; TC, total cholesterol; TG, triglycerides; TT, total testosterone.

INTRODUCTION

Polycystic ovary syndrome (PCOS), the most common endocrinological disorder in women of reproductive age [1], is characterized by hyperandrogenism and chronic anovulation and is often associated with insulin resistance (IR), obesity, dyslipidemia, and hypertension, and consequently increased cardiovascular risk [2]. Preclinical cardiovascular alterations such as decreased cardiac output, diastolic dysfunction, endothelial dysfunction and elevation of inflammatory cytokines, [3,4] are more frequent in PCOS patients than in non-PCOS women of the same age.

In patients without established cardiovascular disease, previous studies have shown an association of IR, metabolic syndrome, and pro-inflammatory state [5] with heart rate variability (HRV) –oscillations in the interval between consecutive heart beats (R-R interval). HRV is a simple, non-invasive measure of autonomic modulation [6]. In PCOS, studies have shown lower HRV when compared to controls [7,8]. Our group has also reported stress-induced alterations in heart autonomic function in women with classic PCOS phenotype in comparison to age-matched healthy controls [9].

Dietary pattern plays an important role in primary and secondary prevention of cardiovascular disease [10], with a reduction in the intake of saturated fatty acids (SFA) being recommended [10]. An association between HRV and dietary fat has been investigated in healthy subjects [11] and overweight adults with risk for coronary disease [12]. However, no studies have analyzed this relationship in PCOS.

Therefore, the aim of the present study was to assess whether dietary SFA is associated with stress-induced heart rate variability in patients with PCOS.

MATERIALS AND METHODS

Participants

The present study included participants recruited by advertisement in the media between 2009 and 2015. Hirsute volunteers with irregular or regular menses were recruited, and 84 met the inclusion criteria: presence of PCOS according to the Rotterdam criteria [13], body mass index (BMI) < 40 kg/m^2, age between 14 and 37 years, and menarche at least two years before enrollment. Fifty-nine patients were classified as classic PCOS (biochemical and/or clinical hyperandrogenism, oligo/amenorrheic [< nine cycles/year] or anovulatory cycles, with or without polycystic ovary [PCO] appearance at ultrasound) and 25 as ovulatory PCOS (clinical or laboratory hyperandrogenism, regular ovulatory cycles confirmed by luteal-phase progesterone > 3.8 ng/mL, and PCO).

No participants had received any drugs known to interfere with hormonal levels for ≥ 3 months before the study. Women diagnosed with other hyperandrogenic disorders, thyroid disorders, or hyperprolactinemia were excluded [13]. Other exclusion criteria were diabetes mellitus, pregnancy, smoking, blood pressure > 160/100 mmHg, and use of antihypertensive medications. The study protocol was approved by the Institutional Review Board. Written informed consent was obtained from all subjects.

Study Protocol

Anthropometric measurements were performed in duplicate and included body weight, height, and waist circumference. BMI was calculated by dividing weight in kilograms by square of height in meters.

Hirsutism was defined as a modified Ferriman-Gallwey score ≥ 8 [13]. Blood pressure was measured after a 10-minute rest, in the sitting position, with feet on the floor and the arm supported at heart level. All participants underwent transvaginal ultrasound or, if they were sexually inactive, transabdominal pelvic ultrasound. Hormonal and metabolic assessments were made between the 2nd and 10th days of the menstrual cycle or on any day if the patient was amenorrheic. Samples were obtained between 8 and 10 a.m. Blood samples were drawn after an overnight 12-hour fast for determination of plasma cholesterol (TC), high-density lipoprotein cholesterol (HDLc), and triglycerides (TG). Glucose was measured before and 2 hours after the ingestion of a 75-g oral glucose load.

Blood samples were also drawn for measurements of insulin, sex hormone-binding globulin (SHBG), androstenedione, dehydroepiandrosterone sulphate (DHEAS), and total testosterone (TT). IR was estimated by homeostasis model assessment (HOMA). HOMA index was calculated by multiplying insulin (mIU/mL) by glucose (mmol/L) and dividing the product by 22.5. Free androgen index (FAI) was estimated by dividing TT (nmol/L) by SHBG nmol/L) and multiplying by 100.

Biochemical and Hormonal Assays

TC, HDLc, TG, and glucose levels were determined by colorimetric-enzymatic methods (Advia 1800 Siemens). LDLc was determined indirectly with the formula LDLc = TC - HDLc - TG / 5. Plasma insulin levels were measured by electrochemiluminescence (Centaur XP Siemens), with a sensitivity of 0.50 U/mL and intra- and interassay CVs of 2.8% and 2.1% respectively. TT levels were measured by chemiluminescence (Centaur XP Siemens), with a sensitivity of 0.10 ng/mL and intra- and interassay coefficients of variation

(CVs) of 3.3% and 7.5% respectively. SHBG, androstenedione and DHEAS were measured by chemiluminescence (Immulite 2000 Siemens).

Assessment of Habitual Physical Activity and Rest Metabolic Rate

Habitual physical activity was estimated with the use of a digital pedometer (BP 148 Techline), as previously reported [14]. The participants were instructed not to modify their usual physical activity during the study.

Rest metabolic rate was obtained by indirect calorimetry (Fitmate®, Cosmed, Rome, Italy). Patients were evaluated in the morning, after a fast of ≥ 5 hours, in a quiet, low-light, temperature-controlled environment. Patients were instructed to avoid exercise and consumption of caffeine and alcohol the day before and on the day of the test [14].

Assessment of Food Consumption

Dietary intake during the preceding month was assessed with a validated food frequency questionnaire consisting of 121 items, as previously reported [14]. Nutritional composition was calculated using the Brazilian Table of Food Composition [15]. Participants were stratified by median of SFA intake (above or below group median).

Classification of food groups was based on the Feeding Guide for the Brazilian Population [16]. Glycemic index (GI) and glycemic load (GL) were calculated as previously described [14].

Heart Rate Variability

Participants were submitted to a 30-minute electrocardiogram recording (ECG) with a SEER Light digital recorder (GE Medical Systems Information Technologie, Milwaukee, WI, USA) for HRV analysis. ECG data were analyzed with a MARS 8000 analyzer (GE Medical Systems Information Technologies) by an experienced investigator (R.S.M.).

ECG recording was performed in the morning, after a minimum 2-hour fast. Participants were instructed not to consume alcoholic beverages, caffeine, or other products containing stimulants, and not to perform heavy exercise for 24 hours before the test.

The participants rested quietly in the supine position, in a silent, semi-dark room for 20 minutes. After resting, they underwent a Stroop color-word conflict test during 10 minutes. HRV was evaluated during the last 5 minutes of the rest and mental stress periods. In the color-word test, subjects are shown the printed names of colors on screens of a different color

(e.g., the word ‘‘blue’’ on a red screen), and are asked to name the color of the screen rather than the word [9].

The following time and frequency domain HRV indices were calculated using 5-minute segments [6]: mean of all normal R-R intervals (mean R-R), root mean square of successive differences of normal adjacent R-R intervals (rMSSD), percentage of successive differences between normal adjacent R-R intervals exceeding 50 ms (pNN50), low frequency (LF) component (0.04 – 0.15 Hz), high frequency (HF) component (0.15 – 0.5 Hz), and LF-to-HF ratio. Spectral components were expressed in normalized units. The difference between HRV results obtained during rest and stress (delta) for each variable was calculated by subtracting the value obtained at rest from the value obtained during stress.

Statistical Analysis

Estimation of sample size was based on the study by Yildirir et al. [7], considering a power of 80% and alpha of 5%. To detect a difference of 0.6 in LF/HF between groups, 28 women would be required in each group.

Results are presented as mean ± SD or median and interquartile range. Comparisons between group means were analyzed by Student t test; comparisons between median values were analyzed with the Mann-Whitney U test. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, version 18). Data from FFQ were entered in duplicate in Epidata software, version 3.1 (Epidata Association) and subsequently transported to SPSS for analysis. Data were considered to be significant at $P < 0.05$.

RESULTS

Mean age was 23.5 ± 6.3 years, and mean BMI was 29.4 ± 6.4 kg/m². Of 84 participants, 92.9% were white. The remaining subjects were of mixed African and European ancestry.

Median SFA intake was 8.5% of daily energy intake. Table 1 summarizes clinical, anthropometric, hormonal, and metabolic features of patients with PCOS stratified by SFA intake (< or ≥ 8.5%). Only TT differed significantly between the groups, being higher in the group with SFA ≥ 8.5%. The groups had similar prevalence of classic PCOS (71.4 vs. 69.0%; $P = 0.811$), obesity (47.6 vs. 40.5%; $P = 0.510$), and metabolic syndrome (27.0 vs. 24.4%; $P = 0.790$).

Table 2 shows dietary intake stratified by SFA categories. Protein and calorie intake was similar between the groups. The percentage of total fat was slightly higher in the group

with SFA ≥ 8.5% (24.4 ± 4.0 vs. 29.9 ± 4.7, P < 0.001); consequently, the percentage of carbohydrates was slightly lower in this group (58.4 ± 6.1 vs. 52.0 ± 7.8, P < 0.001). However, the two groups did not differ in terms of consumption (servings per day) of whole and refined grains, sweets, and sweet beverages. GI (57.0 ± 5.1 vs. 58.5 ± 5.7, P = 0.209 respectively) and GL [182 (107-272) vs. 163 (110-256) P = 0.886 respectively] were also similar. The group with SFA < 8.5% consumed less red meat and more beans, fruits, and vegetables. The groups had similar intake of other food groups.

Heart rate variability indices in response to mental stress test stratified by SFA intake are shown in Figure 1. Mental stress promoted a significant change in time and frequency domain indices in both groups, suggesting induction of vagal withdrawal and sympathetic stimulation (data not shown).

Concerning frequency-domain HRV indices, participants with lower SFA intake had higher delta LF-to-HF ratio (Figure 1A), delta LFnu (Figure 1B) and lower delta HFnu (Figure 1C) than participants with higher SFA intake. The two groups had similar LF/HF ratio, LFnu, and HFnu at rest, whereas during stress LF/HF ratio and LFnu values were significantly higher and HFnu values were significantly lower in the group with SFA < 8.5% [3.94 (2.60 – 6.21) vs. 2.66 (1.52 – 3.56), P = 0.012; 0.75 ± 0.12 vs. 0.67 ± 0.14, P = 0.011; 0.21 ± 0.11 vs. 0.29 ± 0.12, P = 0.016].

Participants with lower SFA intake had lower mean R-R intervals (Figure 1D), pNN50 (Figure 1E), and rMSSD (Figure 1F) values during the stress test when compared with the group with higher SFA intake. The groups had similar R-R intervals, pNN50 and rMSSD at rest.

DISCUSSION

In the present study, PCOS women with lower SFA intake achieved better results in HRV testing. To the best of our knowledge, this is the first study evaluating the association between HRV indices and dietary intake in PCOS women.

Indeed, while during rest, time and frequency domain HRV indices mainly reflect vagal activity, [17], under controlled sympathetic stimulation, a pronounced reduction in time domain indices and HF component is related with vagal withdrawal, and increases in LF component and LF-to-HF ratio are associated with sympathetic modulation [18]. Thus, the evaluation of HRV derived from ECG recordings during rest and after mental stress enabled us to assess both parasympathetic and sympathetic modulation in young women with PCOS.

We observed that PCOS women with higher SFA consumption had an impaired sympathetic response to the mental stress test, as shown by a significantly lower increase in LFnu and LF-to-HF ratio. Furthermore, in response to the mental stress test, the group with higher consumption of SFA showed less reduction in predominantly vagal HRV indices, such as HFnu, mean R-R, pNN50, and rMSSD. Differences in HRV between the groups were detected in response to mental stress, but not during rest – perhaps because the young women in our sample were still healthy, without alterations in autonomic modulation during rest conditions. Meanwhile, during the stress test, which demanded fast and effective autonomic modulation, an impaired response was produced by the group with higher SFA intake. This autonomic imbalance denotes a failure in the adaptation to stress that may predispose to the development of a sustained perturbation of sympathovagal balance over time, possibly with higher risk of hypertension and IR.

In the present study, although the groups were similar in relation to hormonal and metabolic profile, the group with higher SFA intake had higher testosterone levels, as previously described [19-21].

Using controlled diets with low fat (20-25% calories as fat) and high fiber (40 g/day) content, Goldin et al. [19] observed a significant decrease of 9-15% in testosterone and androstenedione concentrations, along with a decrease in serum estrogen and SHBG concentration, in premenopausal women. In that study, the consumption of a low-fat diet was the major determinant for the decline in serum concentrations of androgens, possibly through a reduction in the synthesis of adrenal and/or ovarian androstenedione. The study of Adlercreuts et al. [20], which evaluated the usual diet in post-menopausal women, showed that saturated and total fat intake were positively related to total and free testosterone. Recently, Mumford et al. [21] assessed the usual diet in regularly menstruating women and demonstrated that total fat intake, as well SFAs, MUFAs and PUFAs, were significantly and positively associated with total and free testosterone concentrations, highlighting that women in the highest tertile of percentage of energy from fat also had a significantly higher mean percentage of energy from SFAs, MUFAs, PUFAs.

Interestingly, increasing evidence suggests a regulation of androgens by dietary fat [22]. A controlled, randomized, crossover trial has shown an increase in adrenal androgen precursors DHEA, DHEAS, androstenedione, and in androgens testosterone and 5α–dihydrotestosterone during lipid infusion in healthy young women [22]; this effect appears to be independent of subsequent changes in insulin sensitivity.

Conversely, it is possible that higher testosterone levels influence the relationship between higher saturated fat intake and lower HRV. Some authors have indicated an association between testosterone and HRV [9,23]. A previous study by our group [9] had already demonstrated a negative correlation between testosterone levels and frequency domain HRV indices during stress in PCOS women. Similarly, Neufeld et al. [23] demonstrated that, in premenopausal women, testosterone was correlated with HRV (SDNN, PNN50, RMSSD, and power of HF band).

Because a perfect comparison between the groups regarding all macro and micronutrients in the usual diet was not possible, the overall dietary pattern was considered. The group with lower SFA intake consumed less red meat and more beans, fruits and vegetables. In addition, this group had a slightly lower intake of total fat and slightly higher intake of carbohydrates.

The percent intake of total dietary fat and carbohydrates in both groups met the Dietary Reference Intakes (DRIs) – 20-35% and 45-65% of total energy intake respectively [24]. Regarding the consumption of beans, fruits, and vegetables, only the lower SFA intake group met the Brazilian recommendations (1 serving of beans, 3 servings of fruits, and 3 servings of vegetables per day) [16]. While the link between dietary components and risk of cardiovascular diseases is still not fully understood, vegetables, fruits, and beans are sources of key nutrients, such as fiber, vitamins, minerals (calcium, magnesium, selenium and zinc), and antioxidants, which have been associated with lower risk of cardiovascular disease [25].

In the present study, the total meat and egg intake in the group with higher SFA intake was almost twice the daily recommended allowance (one serving of meat, preferably chicken and low-fat meats, fish, and eggs) [16]. De Oliveira Otto et al. [26] suggested that associations of saturated fat with health might depend on food-specific fatty acids or other nutrient constituents in foods that contain this fat. In their study with a large multiethnic cohort, only intake of saturated fat from meat was associated with higher CVD risk [26]. Siri-Tarino et al. [27] also suggest that the choice of macronutrient to replace fat is of crucial importance, and that saturated fat should ideally be replaced with polyunsaturated fat and minimally processed grains. Evidence from a meta-analysis suggests that high intake of red meat may be related to increased risk of cardiovascular mortality [28]. A possible mechanism for the negative effect of red meat consumption has been described as the partial degradation by intestinal bacteria of phosphatidylcholine [29] and carnitine [30], generating potentially atherogenic trimethylamine-N-oxide (TMAO).

Strengths of the present study include the absence of earlier analyses of dietary intake and HRV in PCOS women and the use of a robust validated FFQ that assesses 121 items of food consumption during the preceding month. A limitation is the relatively small sample size, which could not be stratified according to PCOS phenotype, and the cross-sectional nature of the study, which does not allow causal inferences.

In conclusion, the present results indicate that lower consumption of saturated fat combined with lower intake of meat and higher intake of fruits, vegetables, and beans is associated with better autonomic response to mental stress and lower testosterone in women with PCOS. Although more research is needed, our data suggest that diets low in saturated fat and high in fruit, vegetables, and beans may help to reduce the risk of subclinical cardiovascular disease through favorable changes in HRV.

Acknowledgments

This work was supported by the Brazilian National Institute of Hormones and Women's Health/Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq INCT 573747/2008-3) and Fundo de Apoio à Pesquisa do Hospital de Clínicas de Porto Alegre (FIPE-HCPA 15-0209). We thank Kristhiane Di Domenico for their support with data collection, and Thais Rasia da Silva for their support with setting up the nutritional database.

REFERENCES

[1] March WA, Moore VM, Willson KJ, Phillips DI, Norman RJ, Davies MJ. The prevalence of polycystic ovary syndrome in a community sample assessed under contrasting diagnostic criteria. Hum Reprod. 2010;25:544-51.

[2] de Groot PC, Dekkers OM, Romijn JA, Dieben SW, Helmerhorst FM. PCOS, coronary heart disease, stroke and the influence of obesity: A systematic review and meta-analysis. Hum Reprod Update. 2011;17(4):495-500.

[3] Yarali H, Yildirir A, Aybar F, Kabakçi G, Bükülmez O, Akgül E, et al. Diastolic dysfunction and increased serum homocysteine concentrations may contribute to increased cardiovascular risk in patients with polycystic ovary syndrome. Fertil Steril 2001;76:511-516.

[4] Toulis KA, Goulis DG, Mintziori G, Kintiraki E, Eukarpidis E, Mouratoglou SA, et al. Meta-analysis of cardiovascular disease risk markers in women with polycystic ovary syndrome. Hum Reprod Update 2011;17(6):741-760.

[5] Min KB, Min JY, Paek D, Cho SI. The impact of the components of metabolic syndrome on heart rate variability: using the NCEP-ATP III and IDF definitions. Pacing Clin Electrophysiol. 2008 May;31(5):584-91.

[6] Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology. Heart rate variability. Standards of measurement, physiologic interpretation, and clinical use. Circulation 1996;93:1043-1065.

[7] Yildirir A, Aybar F, Kabakci G, Yarali H, Oto A. Heart rate variability in young women with polycystic ovary syndrome. Ann Noninvasive Electrocardiol 2006;11:306-12.

[8] Saranya K, Pal GK, Habeebullah S, Pal P. Assessment of cardiovascular autonomic function in patients with polycystic ovary syndrome. J Obstet Gynaecol Res 2014;40(1):192-9.

[9] Di Domenico K, Wiltgen D, Nickel FJ, Magalhães JA, Moraes RS, Spritzer PM. Cardiac autonomic modulation in polycystic ovary syndrome: does the phenotype matter? Fertil Steril 2013;99(1):286-92.

[10] Committee American Heart Association Nutrition, Lichtenstein AH, Appel LJ, Brands M, Carnethon M, Daniels S, Franch HA, Franklin B, Kris-Etherton P, Harris WS, Howard B, Karanja N, Lefevre M, Rudel L, Sacks F, Van Horn L, Winston M, WylieRosett J. Diet and lifestyle recommendations revision 2006: a scientific statement from the American Heart Association Nutrition Committee. Circulation 2006;114(1):82-96.

[11] Mozaffarian D, Stein PK Prineas RJ, Siscovick DS. Dietary Fish and w-3 Fatty Acid Consumption and Heart Rate Variability in US Adults. Circulation 2008;117:1130-1137.

[12] Ninio DM, Hill AM, Howe PR, Buckley JD, and Saint DA. Docosahexaenoic acid-rich fish oil improves heart rate variability and heart rate responses to exercise in overweight adults. Br. J. Nutr 2008*;*100:1097-1103.

[13] Rotterdam EA-SPCWG. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril 2004;81:19-25.

[14] Graff SK, Mário FM, Alves BC, Spritzer PM. Dietary glycemic index is associated with less favorable anthropometric and metabolic profiles in polycystic ovary syndrome women with different phenotypes. Fertil Steril 2013;100(4):1081-8.

[15] Center for Studies and Research in Food: Brazilian table of food composition. Campinas: NEPA-UNICAMP 2011, São Paulo.

[16] Brasil. Ministério da Saúde. Secretaria de Atenção à Saúde. Guia alimentar para a população brasileira: promovendo a alimentação saudável / Ministério da Saúde, Secretaria de

Atenção à Saúde, Departamento de Atenção Básica. – Brasília: Ministério da Saúde, 2008. 210 p. – (Série A. Normas e Manuais Técnicos).

[17] Polanczyk CA, Rohde LE, Moraes RS, Ferlin EL, Leite C, Ribeiro JP. Sympathetic nervous system representation in time and frequency domain indices of heart rate variability. Eur J Appl Physiol Occup Physi 1998;79:69-73.

[18] Ahmed MW, Kadish AH, Parker MA, Goldberger JJ. Effect of physiologic and pharmacologic adrenergic stimulation on heart rate variability. J Am Coll Cardiol 1994;24:1082-90.

[19] Goldin BR, Woods MN, Spiegelman DL, Longcope C, Morrill-LaBrode A, Dwyer JT, et al. The effect of dietary fat and fiber on serum estrogen concentrations in premenopausal women under controlled dietary conditions. Cancer 1994;74(3 Suppl):1125-31.

[20] Adlercreutz H, Hämäläinen E, Gorbach SL, Goldin BR, Woods MN, Dwyer JT. Diet and plasma androgens in postmenopausal vegetarian and omnivorous women and postmenopausal women with breast cancer. Am J Clin Nutr 1989;49(3):433-42.

[21] Mumford SL, Chavarro JE, Zhang C, Perkins NJ, Sjaarda LA, Pollack AZ, et al. Dietary fat intake and reproductive hormone concentrations and ovulation in regularly menstruating women. Am J Clin Nutr 2016;103:868-77.

[22] Mai K, Bobbert T, Reinecke F, Andres J, Maser-Gluth C, Wudy SA, et al. Intravenous Lipid and Heparin Infusion-Induced Elevation in Free Fatty Acids and Triglycerides Modifies Circulating Androgen Levels in Women: A Randomized, Controlled Trial. J Clin Endocrinol Metab 2008;93:3900-3906.

[23] Neufeld IW, Kiselev AR, Karavaev AS, Prokhorov MD, Gridnev VI, Ponomarenko VI, et al. Autonomic control of cardiovascular system in pre- and postmenopausal women: a cross-sectional study. J Turk Ger Gynecol Assoc 2015;16:11-20.

[24] IOM (Institute of Medicine). Dietary reference intakes for energy, carbohydrate, fiber, fat, fatty acids, cholesterol, protein and amino acids (Macronutrients). Washington, DC: The National Academies Press; 2005.

[25] Wang JB, Fan JH, Dawsey SM, Sinha R, Freedman ND, Taylor PR, et al. Dietary components and risk of total, cancer and cardiovascular disease mortality in the Linxian Nutrition Intervention Trials cohort in China. Sci Rep 2016;6:22619.

[26] De Oliveira Otto MC, Mozaffarian D, Kromhout D, Bertoni AG, Sibley CT, Jacobs DR Jr, et al. Dietary intake of saturated fat by food source and incident cardiovascular disease: the Multi-Ethnic Study of Atherosclerosis. Am J Clin Nutr 2012;96(2):397-404.

[27] Siri-Tarino PW, Sun Q, Hu FB, Krauss RM. Saturated Fatty Acids and Risk of Coronary Heart Disease: Modulation by Replacement Nutrients. Curr Atheroscler Rep 2010;12(6):384-390.

[28] Abete I, Romaguera D, Vieira AR, Lopez de Munain A, Norat T. Association between total, processed, red and white meat consumption and all-cause, CVD and IHD mortality: a meta-analysis of cohort studies. Br J Nutr 2014;112:1-14.

[29] Tang WHW, Wang Z, Levison BS, Koeth RA, Britt EB, Fu X, et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013; 368:1575-1584.

[30] Koeth RA, Wang Z, Levison BS, Buffa JA, Org E, Sheehy BT, et al. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013;19:576-585.

Legend of Figure 1.

Figure 1. Heart rate variability indices in response to mental stress test in PCOS, stratified by median saturated fatty acid intake.

(A) Delta (Δ) of low-frequency to high-frequency (LF/HF) ratio. (B) Delta of low-frequency component (LF) in normalized units (nu). (C) Delta of high-frequency component (HF) in normalized units. (D) Normal R-R intervals during the stress test. (E) Root mean square of successive differences of normal adjacent R-R intervals (rMSSD) during the stress test. (F) Percent differences between normal adjacent R-R intervals exceeding 50 ms (pNN50) during the stress test.

Delta is the difference between the results obtained in heart rate variability for each variable during stress - value obtained at rest. *$P<0.05$ by Mann-Whitney test. Values are expressed as median and 25%–75% interquartile range.

Table 1. Clinical, anthropometric, hormonal, and metabolic features of patients with PCOS stratified by saturated fatty acids intake

Variable	SFA < 8.5% (n=42)	SFA ≥ 8.5% (n=42)	P
Age (y)	23.9 ± 6.6	23.0 ± 6.1	0.539
BMI (kg/m^2)	29.8 ± 6.1	29.1 ± 6.8	0.615
Waist circumference (cm)	87.6 ± 14.2	85.7 ± 14.1	0.537
Resting metabolic rate (kcal/d)	1483 (1283 – 1675)	1424 (1250 – 1536)	0.134
Steps/d	5959 (3982 – 7964)	5579 (3699 – 7548)	0.571
Systolic blood pressure (mmHg)	118.1 ± 10.2	118.4 ± 15.2	0.937
Diastolic blood pressure (mmHg)	77.9 ± 9.2	77.0 ± 10.6	0.690
Glucose 0' (mg/dL)	89.1 ± 9.8	85.8 ± 6.5	0.081
Glucose 120' (mg/dL)	109.0 ± 36.9	98.4 ± 24.4	0.134
Total cholesterol (mg/dL)	177.3 ± 36.3	170.2 ± 32.3	0.353
HDL-cholesterol (mg/dL)	44.0 ± 10.1	47.5 ± 13.8	0.193
Triglycerides (mg/dL)	104 (62 – 140)	84 (60 – 133)	0.183
LDL-cholesterol (mg/dL)	109.8 ± 29.6	103.4 ± 25.0	0.297
HOMA-IR	3.6 (2.0 – 4.6)	2.8 (1.4 – 5.0)	0.453
Total testosterone (ng/mL)	0.61 ± 0.22	0.73 ± 0.27	**0.031**
SHBG (nmol/L)	28.4 (18.2 – 41.7)	28.1 (19.5 – 38.1)	0.899
Free androgen index	7.1 (5.1 – 11.0)	7.9 (5.8 – 15.9)	0.395
Androstenedione (ng/mL)	2.5 (1.9 – 3.2)	2.7 (2.0 – 3.9)	0.228
DHEAS (ug/dL)	215 (117 – 306)	225 (162 – 317)	0.620
Classic PCOS diagnosis (%/n)	71.4 (30)	69.0 (29)	0.811
Metabolic syndrome diagnosis (%/n)	25.0 (10)	24.4 (10)	0.790
White (%/n)	92.9 (39)	92.9 (39)	1.000

Values are expressed as mean ± SD (Student t test) or median (interquartile range) (Mann-Whitney test) or percentage/n (Chi-square test). PCOS = polycystic ovary syndrome; BMI = body mass index; HDL=high-density lipoprotein; LDL= low-density lipoprotein; DHEAS = dehydroepiandrosterone sulfate; HOMA-IR = homeostasis model assessment of insulin resistance; *SHBG* = sex hormone-binding globulin; SFA= saturated fatty acids intake; 8.5% is the median SFA value of all sample.

Table 2. Dietary intake of patients with PCOS stratified by saturated fatty acids intake

	SFA < 8.5% (n=42)	**SFA ≥ 8.5% (n=42)**	P
MACRONUTRIENTS and ENERGY			
Carbohydrate (%)	58.4 ± 6.1	52.0 ± 7.8	**0.000**
Protein (%)	16.2 ± 3.0	17.2 ± 5.0	0.270
Fat (%)	24.4 ± 4.0	29.9 ± 4.7	**0.000**
Energy intake (kcal/d)	2295 (1522 – 2981)	2232 (1674 – 3492)	0.610
Polyunsaturated fatty acids (%)	3.3 ± 1.1	3.8 ± 1.3	0.066
Saturated fatty acids (%)	7.0 ± 1.2	10.2 ± 2.2	**0.000**
Fiber (g/d)	26.7 (17.8 – 39.6)	24.7 (13.9 – 28.4)	0.071
FOOD GROUPS			
Fruits and vegetables (servings/d)	6.0 (2.6 – 9.3)	4.4 (1.7 – 6.7)	**0.041**
Beans (servings/d)	1.4 (0.6 – 2.8)	0.6 (0.3 – 1.7)	**0.017**
Whole grains (servings/d)	0.7 (0.2 – 1.3)	0.5 (0.2 – 0.9)	0.295
Refined grains (servings/d)	3.4 (2.0 – 5.0)	3.4 (1.5 – 5.0)	0.635
Fried and Fast food (servings /d)	1.0 (0.6 – 1.9)	1.2 (0.5 – 2.6)	0.700
Processed meat (servings /d)	0.2 (0.0 – 0.4)	0.3 (0.1 – 0.5)	0.074
Sweets (servings/d)	1.8 (1.1 – 3.2)	2.8 (1.4 – 5.1)	0.054
Sweet beverages (servings/d)	0.8 (0.3 – 2.3)	1.0 (0.3 – 2.9)	0.687
Total meat and eggs (servings/d)	1.3 (0.9 – 2.0)	1.9 (0.9 – 2.8)	0.081
Red meat (servings/d)	0.9 (0.5 – 1.5)	1.4 (0.6 – 2.2)	**0.047**
White meat (servings/d)	0.4 (0.1 – 0.6)	0.3 (0.1 -0.6)	0.604
Dairy/dairy products (servings/d)	1.1 (0.6 – 2.3)	1.1 (0.5 – 2.1)	0.658
Alcoholic beverage (drinks/d)	0.0 (0.0 – 0.2)	0.01 (0.0 – 0.2)	0.764

Values are expressed as mean ± SD (Student t test) or median (interquartile range) (Mann-Whitney test).
PCOS = polycystic ovary syndrome; SFA= saturated fatty acids intake; 8.5% is the median SFA value of all sample.

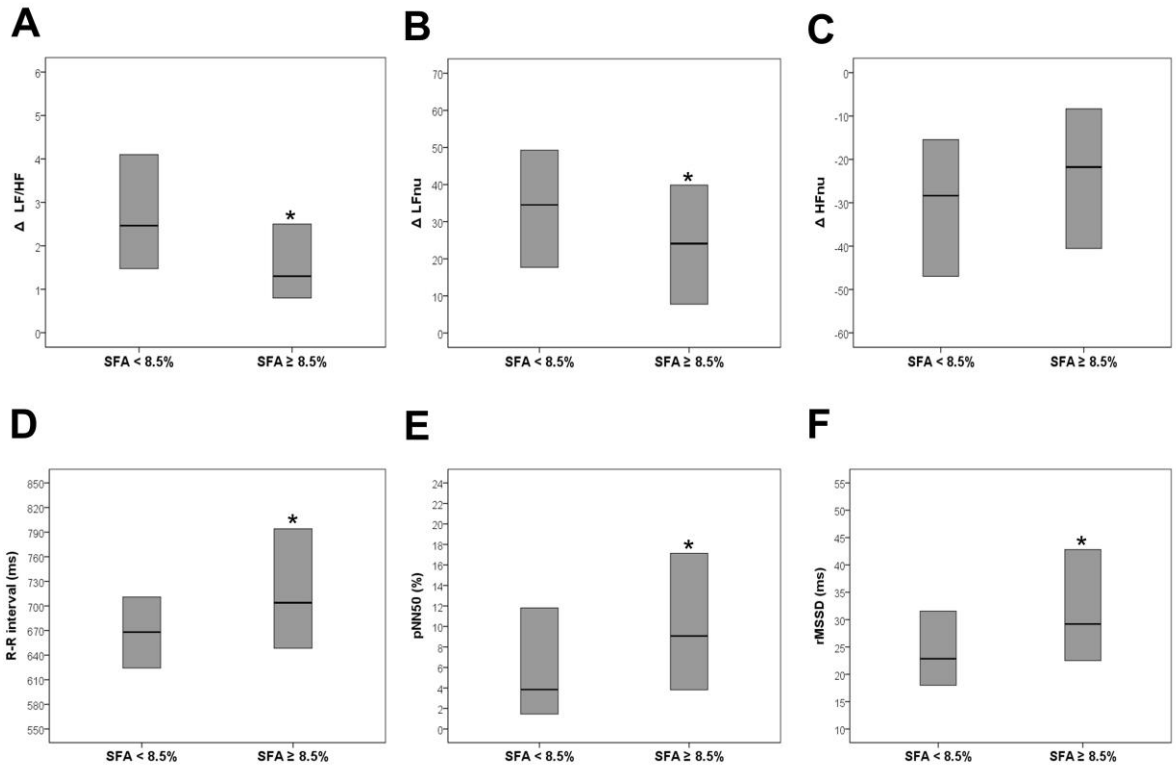

Figure 1. Heart rate variability indices in response to mental stress test in PCOS, stratified by median saturated fatty acid intake.

CONSIDERAÇÕES FINAIS

A redução de peso através da restrição calórica é de suma importância nas mulheres com PCOS com sobrepeso e obesidade, visto que uma redução de peso relativamente pequena (5%) pode reduzir a resistência insulínica e o hiperandrogenismo, levando a melhoras da função reprodutiva. Entretanto, ainda não está estabelecido se a composição da dieta por si só pode ter efeitos significativos sobre as alterações metabólicas e hormonais da PCOS, independentemente da redução do peso. Poucos ensaios clínicos randomizados avaliando o efeito de diferentes intervenções dietéticas foram realizados em mulheres com PCOS, sendo que os estudos existentes apresentam, em sua maioria, curta duração e pequeno tamanho amostral. Dessa forma, com base nas atuais evidências, não é possível definir qual o melhor tipo de dieta para essa população.

No presente estudo concluiu-se, através de revisão sistemática e meta-análise, que o uso de orlistat pode trazer benefícios comparáveis aos da metformina na redução de peso/IMC, testosterona, HOMA-IR e insulina em pacientes com PCOS com sobrepeso ou obesidade que não atingirem a redução necessária apenas com mudanças de estilo de vida. Além disso, demonstrou-se que o menor consumo de gordura saturada combinado com menor consumo de carne vermelha e maior consumo de frutas, vegetais e feijões está relacionado com maior variabilidade da frequência cardíaca em resposta ao *stress* e níveis circulantes mais baixos de testosterona em mulheres com PCOS, podendo desta forma contribuir para redução de alterações cardiovasculares subclínicas.