Universidade Federal do Rio Grande Do Sul
Faculdade de Medicina
Programa de Pós-Graduação em Ciências Médicas: Endocrinologia

SÍNDROME DOS OVÁRIOS POLICÍSTICOS: ASPECTOS NUTRICIONAIS

Mariana Kirjner Toscani

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Tese apresentada ao Programa de Pós-Graduação em Ciências Médicas: Endocrinologia, como requisito parcial para obtenção do título de Doutor

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- Artigo de revisão: Síndrome dos Ovários Policísticos: aspectos nutricionais.

- Artigo original 1: Diet pattern in patients with Polycystic Ovary Syndrome and healthy controls (submetido para *Annals of Nutrition and Metabolism, 2009).*

- Artigo original 2: Effect of high-protein or normal protein diet on weight loss, body composition, hormone and metabolic profile in PCOS patients and controls: a randomized study (submetido para *Fertility and Sterility, 2009).*

SUMÁRIO

RESUMO

A Síndrome dos Ovários Policísticos (PCOS) é uma das doenças endocrinológicas mais comuns, afetando de 5-10% das mulheres em idade reprodutiva.

Mulheres com PCOS, independentemente do peso corporal, têm predisposição à resistência insulínica (RI) e hiperinsulinemia, obesidade (predominantemente abdominal), alterações no perfil lipídico, além de um aumento na pressão arterial. O aumento de peso está associado com a piora dos sintomas associados à PCOS, enquanto que a redução melhora os sintomas e os perfis metabólico e endócrino.

A relação entre consumo alimentar e PCOS ainda apresenta dados inconclusivos. Alguns estudos mostram que mulheres com PCOS apresentam menor consumo de carboidratos e fibras e maior consumo de gorduras e alimentos com elevado índice glicêmico. Em estudo comparando PCOS e controles pareados por IMC observamos, não haver diferença no valor calórico total e distribuição de macronutrientes comparando PCOS e controles. Entretanto, PCOS consumiam menor quantidade de proteína de elevado valor biológico, além de possuírem maior percentual de gordura corporal total, maior soma das dobras cutâneas do tronco e maior circunferência da cintura. Também encontramos menores níveis séricos da globulina carreadora dos hormônios sexuais e maiores valores de testosterona, índice de androgênios livres, glicose pós-prandial, insulina em jejum e pós-prandial, HOMA (*Homeostasis Model Assessment*), triglicerídeos, colesterol total e LDL-colesterol nessas pacientes. Assim, os resultados sugerem que pacientes com PCOS apresentam maior suscetibilidade à RI mas as preferências alimentares e a ingestão parecem não estar diretamente associadas com as anormalidades metabólicas em PCOS.

Apesar da redução de peso ser benéfica no tratamento da PCOS, a definição de qual a composição mais adequada da dieta ainda é controversa. Há um aumento do interesse por dietas hiperproteicas no tratamento da PCOS, tendo sido observado em alguns estudos maior redução de peso e saciedade e melhora dos fatores de risco cardiometabólicos, perfil hormonal e função reprodutiva. Em nosso estudo, quando comparamos uma dieta hiperproteica *versus* normoproteica em PCOS e controles, ambos os grupos reduziram peso, índice de massa corporal, circunferência da cintura, percentual de gordura, soma das dobras cutâneas do tronco. Além disso, houve redução dos níveis de testosterona, independente da composição da dieta, pelo menos a curto prazo. Concluímos que a restrição calórica

per se, parece estar mais relacionada com a melhora do perfil hormonal e da composição corporal do que a quantidade de proteína da dieta. Estudos de mais longo prazo e testando diferentes dietas são ainda necessários para definir o melhor manejo nutricional de pacientes com PCOS.

Parte I

SÍNDROME DOS OVÁRIOS POLICÍSTICOS: ASPECTOS NUTRICIONAIS

SÍNDROME DOS OVARIOS POLICÍSTICOS: ASPECTOS NUTRICIONAIS

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RESUMO

A Síndrome dos Ovários Policísticos (PCOS) é uma doença de apresentação clínica heterogênea cujas principais características clínicas são anovulação crônica e manifestações de hiperandrogenismo. Além dos distúrbios reprodutivos, mulheres com PCOS apresentam freqüentemente alterações metabólicas que incluem resistência insulínica, obesidade e dislipidemia.

A obesidade atinge cerca de 30 a 70% das PCOS e pode exacerbar as anormalidades metabólicas e reprodutivas associadas. O controle do peso corporal e a dieta são componentes importantes no tratamento da PCOS.

É possível que a qualidade da dieta possa interferir com as anormalidades endócrinas e metabólicas presentes na PCOS, embora não exista um consenso atual sobre a melhor composição de macronutrientes da dieta. Estudos que avaliaram o padrão alimentar de mulheres com PCOS e controles observaram menor consumo de carboidratos e fibras e maior consumo de gorduras (total e saturada), além de maior ingestão de alimentos com elevado índice glicêmico em pacientes com PCOS, não havendo diferença nas calorias. Mulheres com PCOS têm tendência à elevada ingestão de alimentos, por causas emocionais ou biológicas. Alguns estudos observaram que PCOS apresentaram termogênese pós-prandial reduzida, e a redução de peso estava associada com a melhora nos parâmetros metabólicos e reprodutivos. A redução de peso por dieta hipocalórica leva à melhora da composição corporal, reduzindo massa adiposa, gordura abdominal e circunferência da cintura em PCOS com sobrepeso e obesidade.

Embora esteja claro que a redução de peso seja benéfica no tratamento da PCOS, a composição adequada da dieta para que a redução de peso seja alcançada ainda é controversa. Há um aumento do interesse por dietas para redução de peso que visam à modificação do perfil de macronutrientes no tratamento de PCOS, como as dietas hiperproteicas com redução ou modificação da quantidade de carboidratos. Essas dietas contribuem para a redução mais efetiva de peso e maior poder de saciedade, além de promoverem melhora dos fatores de risco cardiometabólicos, perfil hormonal e função reprodutiva. Porém, são necessários mais estudos na tentativa de esclarecer qual opção dietoterápica seria mais eficaz no manejo de peso corporal dessas pacientes.

Palavras chave: Dieta normoproteica, Dieta hiperproteica, Padrão alimentar, Redução de peso, PCOS.

ABSTRACT

Polycystic ovary syndrome (PCOS) is a heterogeneous endocrine disease with simptoms such as chronic anovulation and hyperandrogenism. Besides the reproductive disorders, PCOS patients often present metabolic alterations that include insulin resistance, obesity, and dyslipidemia.

Obesity affects about 30 to 70% of PCOS women and may exacerbate the metabolic and reproductive abnormalities associated. The control of body weight and diet are important components in the treatment of PCOS.

It is possible that the quality of the diet can interfere with the endocrine and metabolic abnormalities in the PCOS but there is no current consensus on the best composition of macronutrients of the diet. Studies assessing dietary patterns between PCOS and controls women have shown lower carbohydrates and fiber consumption, and higher fats ingestion (total and saturated). There were also an increased amount of high glycemic index food in PCOS women, but no difference in the calories comsumed. Women with PCOS have a tendency to overeat for emotional or biological causes. Some studies have found that PCOS had reduced postprandial thermogenesis, with the weight loss being associated with improvement in metabolic and reproductive parameters. Weight reduction by hypocaloric diet leads to improvement in body composition by reducing fat mass, abdominal fat, and waist circumference in overweight and obese PCOS patients.

However, although it is clear that the weight reduction is beneficial in the treatment of PCOS, the appropriate diet composition to achieve the weight loss is still controversial. It has increased the interest in diets for weight reduction that aim the modification of nutrients profile in the treatment of PCOS, such as high-protein diets with reduction or modification of the amount of carbohydrates. These diets contribute to more effective weight loss and satiety, and have also showed improvement of cardiometabolics risk factors, hormonal profile and reproductive function. Further studies are needed to clarify which dietetic option would be more effective in the weight management of these patients.

Key words: Normal protein diet, High-protein diet, Diet pattern, Loss weight, PCOS.

INTRODUÇÃO

A Síndrome dos Ovários Policísticos (PCOS) é uma doença de apresentação clínica heterogênea cujas principais características clínicas são anovulação crônica e manifestações de hiperandrogenismo (Ehrmann, 1995). Estima-se que de 5-10% das mulheres em idade reprodutiva apresentam esta síndrome (Ehrmann, 1995; (Knochenhauer, Key et al. 1998; Asuncion, Calvo et al. 2000). Além dos distúrbios reprodutivos, as pacientes com PCOS apresentam frequentemente, alterações metabólicas que incluem resistência insulínica (RI), obesidade e dislipidemia (Carmina, Bucchieri et al. 2007).

A obesidade é uma característica prevalente em PCOS, atingindo cerca de 30 a 70% destas mulheres, dependendo da população estudada (Azziz, Woods et al. 2004; Spritzer and Wiltgen 2007; Moran, Brinkworth et al. 2008). A patogênese da obesidade em PCOS ainda não é totalmente conhecida (Dunaif, 1999). A obesidade pode ser conseqüência de fatores genéticos e/ou do estilo de vida adotado, em função da dieta e do sedentarismo (Bringer, Lefebvre et al. 1999).

O controle do peso corporal e a dieta são componentes importantes no tratamento da PCOS, embora não exista um consenso atual sobre a melhor composição de macronutrientes da dieta. A redução de peso por dieta hipocalórica leva à melhora da composição corporal, reduzindo massa adiposa, gordura abdominal e circunferência da cintura em mulheres com PCOS com sobrepeso e obesidade (Huber-Buchholz, Carey et al. 1999; Moran, Noakes et al. 2003).

Teoricamente, é possível que a qualidade da dieta possa interferir com as anormalidades endócrinas e metabólicas presentes em mulheres com PCOS, embora poucos estudos tenham investigado esse assunto (Pasquali and Casimirri 1993; Gambineri, Pelusi et al. 2002; Pasquali, Pelusi et al. 2002). Existe, de fato, uma complexa inter-relação entre diferentes fatores nutricionais e condições endócrinas. Está claro que a dieta desempenha um importante papel na regulação do metabolismo dos esteróides sexuais e secreção de hormônio luteinizante (LH). Dietas ricas em fibra reduzem os níveis de estrogênio em mulheres na pós-menopausa e acredita-se que uma alimentação com baixo teor de fibras possa levar ao aumento das

concentrações de estrogênio e androgênios circulantes. Além disso, a elevada ingestão de lipídios parece diminuir os níveis da globulina carreadora de hormônios sexuais (SHBG), aumentando, em consequência, a disponibilidade de androgênios e estrogênios nos tecidos alvo (Gambineri et al., 2002).

Na presença da obesidade ocorre o aumento dos níveis de androgênios, sendo que a redução de peso melhora a fertilidade e sinais clínicos de hiperandrogenismo. Estudos com diferentes macronutrientes é útil na tentativa de tentar esclarecer qual dieta é mais eficaz no tratamento da PCOS. Assim, é de fundamental importância o conhecimento do padrão alimentar em PCOS para detecção de hábitos e preferências dietéticas.

PADRÃO ALIMENTAR E PCOS

Diversos estudos mostram associação de padrão alimentar com o desenvolvimento de comorbidades. Evidências sugerem uma relação positiva entre consumo de sódio e pressão arterial (Sacks, Svetkey et al. 2001) e entre consumo de alimentos com elevado índice glicêmico e aumento na incidência de diabetes mellitus tipo 2 (DM2) (Colditz, Manson et al. 1992). A alimentação excessiva em gordura trans está associada ao aumento de risco para desenvolvimento de doença arterial coronariana, em razão do aumento do LDL-colesterol e da diminuição do HDL-colesterol ou pelo aumento das concentrações séricas de triglicerídeos (Troisi, Willett et al. 1992).

A relação entre o consumo alimentar e a PCOS ainda apresenta dados inconclusivos. Estudo realizado com 68 mulheres do Reino Unido (37 com PCOS e 31 controles), avaliando o padrão alimentar e a atividade física, mostrou que mulheres com PCOS apresentaram menor consumo de carboidratos e maior de gorduras, tanto gordura total quanto gordura saturada, não havendo diferença nas calorias diárias ingeridas e no padrão de atividade física entre os grupos (Barr, 2008). Wild e colaboradores (Wild, Painter et al. 1985) encontraram que pacientes com PCOS, quando comparadas às controles, consumiam uma dieta com elevada quantidade de ácido graxo saturado e com quantidades de fibra abaixo do recomendado. Outro estudo, comparando mulheres italianas e americanas portadoras de

PCOS, não encontrou diferença entre o consumo energético e de macronutrientes, exceto que as PCOS americanas consumiam quase o dobro a mais de ácido graxo saturado, fato que poderia explicar, pelo menos parcialmente, o maior grau de obesidade encontrado nas mulheres americanas (Carmina, Legro et al. 2003). Douglas e colaboradores (Douglas, Norris et al. 2006) verificaram que o grupo de mulheres com PCOS ingeria maior quantidade de alimentos com elevado índice glicêmico (pão branco, biscoitos, bolos entre outros), comparado ao grupo sem PCOS (pareadas por idade, raça e índice de massa corporal). Em relação ao consumo de micronutrientes, esses mesmos autores não encontraram diferenças na ingestão de magnésio e de sódio entre os grupos, porém ambos apresentaram consumo de sódio acima dos 2400 mg/dia recomendados pela *American Heart Association*. Nesse mesmo estudo, uma relação inversa entre o consumo de magnésio e insulina de jejum foi encontrada apenas no grupo controle.

Alguns pesquisadores têm sugerido que mulheres com PCOS têm tendência à elevada ingestão de alimentos por causas emocionais (depressão, desejo por alimentos que “confortam”) (McKittrick 2002) ou razões biológicas. Holte e pesquisadores (Holte, Bergh et al. 1995) observaram que mulheres com PCOS resistentes à insulina apresentavam hipoglicemia recorrente. Os episódios hipoglicêmicos provocam desejo pelo consumo de carboidratos e diminuição da sensação de saciedade pós-refeição, o que pode levar ao aumento de consumo alimentar e obesidade.

DIETA E REDUÇÃO DE PESO EM PCOS

Estudos que investigaram a presença de distúrbio metabólico em pacientes com PCOS são controversos (Ravussin and Zawadzki 1987; Robinson, Chan et al. 1992). Robinson e colaboradores (Robinson, Chan et al. 1992) observaram que mulheres de peso normal e obesas com PCOS apresentaram termogênese pós-prandial reduzida comparadas com mulheres sem PCOS, de mesmo índice de massa corporal (IMC). Além disso, a redução da termogênese pós-prandial em mulheres com PCOS correlacionou-se com a baixa sensibilidade à insulina. Porém, outros estudos

(Segal and Dunaif 1990) não encontraram diferença estatística na taxa de metabolismo basal entre mulheres com ou sem PCOS.

A obesidade pode exacerbar as anormalidades metabólicas e reprodutivas associadas à PCOS (Dunaif 1999). As diferenças clínicas e bioquímicas entre pacientes obesas e não-obesas têm sido associadas à prevalência de fatores de risco metabólico e cardiovascular na PCOS (Kiddy, Sharp et al. 1990; Ehrmann, Sturis et al. 1995; Arroyo, Laughlin et al. 1997; Gambineri, Pelusi et al. 2002; Salehi, Bravo-Vera et al. 2004). Por esse motivo, o tratamento objetiva a redução do peso corporal, com estudos que mostram que a redução de peso através da restrição calórica (Hoeger 2001) está associada com a melhora nos parâmetros metabólicos e reprodutivos entre a população de mulheres com PCOS (Kiddy, Hamilton-Fairley et al. 1989; Pasquali, Gambineri et al. 2000).

Assim, o manejo do peso corporal em mulheres com PCOS tem sido vigorosamente recomendado por vários autores (Hoeger 2001; Norman, Davies et al. 2002). Existem relatos de que a restrição energética *per se*, independente da redução de peso, também leva à melhora dos distúrbios reprodutivos em mulheres com PCOS (Moran, Noakes et al. 2003). Evidências sugerem que as modificações alimentares estão relacionadas à melhora da infertilidade, além da prevenção de comorbidades de longo prazo (Andersen, Seljeflot et al. 1995; Huber-Buchholz, Carey et al. 1999). A redução de peso a curto prazo pode ser alcançada em pacientes com sobrepeso que apresentam PCOS através de dietas de muito baixo valor calórico (VLCD) (em torno de 700-800 kcal/dia) (Kiddy, Hamilton-Fairley et al. 1989; Hamilton-Fairley, Kiddy et al. 1993; Andersen, Seljeflot et al. 1995; Wahrenberg, Ek et al. 1999) e moderada restrição calórica (1000-1500 kcal/dia por 3-6 meses) (Pasquali, Fabbri et al. 1986; Pasquali, Antenucci et al. 1989; Kiddy, Hamilton-Fairley et al. 1992; Andersen, Seljeflot et al. 1995; Holte, Bergh et al. 1995; Jakubowicz and Nestler 1997; Pasquali, Gambineri et al. 2000; Moran, Noakes et al. 2003). Um estudo que incluiu o tratamento dietético combinado a exercícios físicos mostrou benefícios similares em mulheres com PCOS. Todas as intervenções (somente dieta, dieta com exercício aeróbico e dieta com exercício aeróbico e de resistência combinados) levaram à redução do peso corporal independente do

tratamento. Além disso, reduções de pressão arterial, níveis de triglicerídeos, colesterol total, LDL-colesterol, glicose e insulina de jejum, além das concentrações de testosterona e índice de androgênios livres e melhora nos níveis de SHBG e da função reprodutiva ocorreram em todos os grupos (Thomson, Buckley et al. 2008).

Uma redução de 5-10% no peso corporal por 4 semanas é suficiente para melhorar as alterações presentes na PCOS, apesar das pacientes permanecerem ainda com sobrepeso ou obesidade (Clark, Thornley et al. 1998). Esse percentual de redução de peso reduz os níveis de androgênios, levando à melhora da fertilidade (Franks, Robinson et al. 1996); (Huber-Buchholz, Carey et al. 1999; Crosignani, Colombo et al. 2003) e dos sinais clínicos do hiperandrogenismo (Kiddy, Hamilton-Fairley et al. 1992; Lefebvre, Bringer et al. 1997; Pasquali and Filicori 1998; Chou, von Eye Corleta et al. 2003). São observadas melhoras também nas taxas de concepção, redução de abortos, dislipidemia, hiperglicemia e RI (Kiddy, Hamilton-Fairley et al. 1989; Holte, Bergh et al. 1995; Clark, Thornley et al. 1998; Moran, Noakes et al. 2003; Hoeger 2006) em mulheres com PCOS (Holte, Bergh et al. 1995; Clark, Thornley et al. 1998), além da redução dos fatores de risco cardiovascular (Moran, Noakes et al. 2003). Com a redução de peso, os níveis da SHBG aumentam 2 vezes e a concentração de testosterona livre diminui, com alterações nos níveis de insulina e fator de crescimento associado à insulina tipo 1 (IGF-1) (Kiddy, Hamilton-Fairley et al. 1989). Por todos esses motivos é que as modificações no estilo de vida e a redução do peso corporal são escolhidas como alternativas imediatas no tratamento de pacientes obesas com PCOS (Cussons, Stuckey et al. 2005).

Sendo assim, o controle alimentar é essencial para as pacientes com hiperandrogenismo, principalmente na presença de hiperinsulinemia. A redução de carboidratos é necessária, e por vezes também o uso de drogas sensibilizadoras de insulina (NIH 1998), para a melhora da sensibilidade à insulina nestas pacientes (Piatti, Monti et al. 1994; Mavropoulos, Yancy et al. 2005). Muitos estudos têm mostrado que a redução de peso por restrição alimentar leva à melhora da composição corporal, reduzindo a quantidade de gordura corporal e abdominal e a circunferência da cintura em mulheres com sobrepeso com PCOS (Moran, Noakes et al. 2003); (Huber-Buchholz, Carey

et al. 1999). No entanto, embora esteja claro que a redução de peso é benéfica no tratamento da PCOS, a composição ideal da dieta para que a redução de peso seja alcançada é ainda controversa.

DIFERENÇAS NA COMPOSIÇÃO DIETÉTICA E DESFECHOS CLÍNICOS EM PCOS

Evidências sugerem que os fatores dietéticos que afetam a sensibilidade à insulina podem desempenhar um importante papel na etiologia de algumas formas de infertilidade (Chavarro, Rich-Edwards et al. 2007; Chavarro, Rich-Edwards et al. 2007; Chavarro, Rich-Edwards et al. 2007; Chavarro, Rich-Edwards et al. 2009). A melhora na sensibilidade à insulina, que pode ser influenciada pela dieta (Kitabchi, Temprosa et al. 2005), é um importante determinante da função ovulatória e da fertilidade (Hjollund, Jensen et al. 1999; Azziz, Ehrmann et al. 2001). Em geral, terapias que reduzem os níveis de insulina e a RI e promovem a redução de peso são úteis no tratamento da PCOS (Mavropoulos, Yancy et al. 2005).

Os ácidos graxos insaturados trans da dieta aumentam o risco de infertilidade quando consumidos no lugar de carboidratos ou de ácidos graxos insaturados, encontrados principalmente em óleos vegetais (Chavarro, Stampfer et al. 2007). Por outro lado, o consumo de alimentos com elevado teor de ácidos graxos poli-insaturados (PUFAs) costuma ser recomendado para pacientes com PCOS, embora os efeitos destes sobre as alterações endócrinas e metabólicas não tenham sido ainda estudados nessa população. Evidências experimentais indicam que os PUFAs melhoram a ação da insulina em tecidos periféricos e diminuem a secreção de insulina pelo pâncreas (Kasim-Karakas, Almario et al. 2000; Storlien, Higgins et al. 2000).

O aumento da ingestão de ácidos graxos insaturados cis (comumente encontrados em óleos vegetais não hidrogenados) tem sido associado com redução da concentração de marcadores inflamatórios (Pischon, Hankinson et al. 2003; Baer, Judd et al. 2004) e menor risco para DM2 (Salmeron, Hu et al. 2001), bem como com melhora de características endócrinas e metabólicas em mulheres com PCOS.

Em termos gerais, a dieta balanceada com restrição calórica moderada é a recomendada para redução e manejo da obesidade e comorbidades relacionadas e melhora da sensibilidade à insulina (NIH 2000). Esta dieta é constituída por 30% de lipídio, 10% de gordura saturada, < 300 mg de colesterol, 15% de proteína, 55% de carboidrato em conjunto com exercícios regulares moderados e aumento do consumo de fibras, cereais integrais, frutas e vegetais (NIH 2000). Estas indicações estão de acordo com o recomendado pelo National Institute of Health (NIH) na terapia dietética para redução e manutenção de peso (NIH 1998) e também são utilizadas na intervenção em pacientes diabéticos (Tuomilehto, Lindstrom et al. 2001; Knowler, Barrett-Connor et al. 2002).

No entanto, não há consenso sobre a constituição ideal da dieta em mulheres com PCOS (Marsh and Brand-Miller 2005). Por outro lado, tem aumentado o interesse por dietas para redução de peso que visam a modificação do perfil de macronutrientes no tratamento de mulheres com PCOS, tais como dietas hiperproteicas com redução ou modificação da quantidade de carboidratos (Moran, Brinkworth et al. 2008). Estas dietas contribuem para a redução mais efetiva de peso, somado ao maior poder de saciedade das proteínas, se comparadas a carboidratos e lipídios (Mikkelsen, Toubro et al. 2000). Embora este tema ainda não seja consensual, pacientes com sobrepeso e obesas com PCOS que seguiram uma dieta hipocalórica hiperproteica mostraram melhora dos fatores de risco cardiometabólicos, perfil hormonal e função reprodutiva (Thomson, Buckley et al. 2008). O termo “hiperproteico” (HP) refere-se a aproximadamente 30% de proteína, 40% de carboidrato e 30% de lipídio; e o termo “normoproteica” (NP) deve conter 15% de proteína, 55% de carboidrato e 30% de lipídio (Moran, Noakes et al. 2004).

A quantidade e a origem das proteínas da dieta podem modificar a sensibilidade à insulina (Gannon, Nuttall et al. 1988; Lavigne, Marette et al. 2000).

No entanto, não se sabe se o percentual de proteína na dieta influencia na função ovulatória e fertilidade em mulheres saudáveis que não estão em tratamento dietético para redução de peso. Por outro lado, o consumo de proteína de origem vegetal em substituição à ingestão de

proteína de origem animal ou carboidratos foi associado com um menor risco de infertilidade (Chavarro, Rich-Edwards et al. 2008). A escolha de fontes de vegetais e gordura para compor a dieta pode também reduzir moderadamente o risco de doença coronariana (Halton, Willett et al. 2006).

O aumento moderado de proteína na dieta pode levar à diminuição da fome e do "desejo de comer" (Westerterp-Plantenga 2003; Lejeune, Kovacs et al. 2005), além de aumentar a longo prazo a saciedade após as refeições (Poppitt, McCormack et al. 1998; Poppitt and Swann 1998; Poppitt, Swann et al. 1998; Eisenstein, Roberts et al. 2002; Johnston, Tjonn et al. 2004; Moran, Noakes et al. 2004). A dieta rica em proteinas pode também reduzir o consumo alimentar (Skov, Toubro et al. 1999), aumentar a termogênese pós-prandial e o gasto energético basal pelo efeito termogênico das proteínas, comparada com dietas compostas por percentual mais elevado de carboidratos e lipídios, mas com o mesmo valor calórico (Tappy 1996; Lejeune, Westerterp et al. 2006). Essa dieta preserva a massa magra corporal na redução de peso (Krieger, Sitren et al. 2006). Em pacientes com PCOS, a dieta hipocalórica suplementada com proteína reduziu a massa adiposa, colesterol e apoproteína B, mais do que na dieta suplementada apenas com açúcar simples (Kasim-Karakas, Almario et al. 2008).

Foi também demonstrado que a dieta HP leva à melhora do peso corporal, dos níveis de testosterona, da razão hormônio luteinizante/hormônio folículo-estimulante (LH/FSH) e da insulina de jejum em mulheres obesas com PCOS em tratamento por 24 semanas (Mavropoulos, Yancy et al. 2005). Dieta HP tem sido associada também à melhora da dislipidemia, e da hiperglicemia pós-prandial (Moran, Noakes et al. 2003), e à melhora da sensibilidade à insulina independente da redução de peso (Samaha, Iqbal et al. 2003), com manutenção da massa magra corporal (Piatti, Monti et al. 1994; Layman, Shiue et al. 2003). A dieta HP levou a uma maior redução dos níveis de triglicerídeos em indivíduos que reduziram mais de 5% do seu peso basal (Samaha, Iqbal et al. 2003). Outros estudos sugerem que a dieta HP possa diminuir as concentrações de SHBG, com consequente aumento na disponibilidade de androgênios e estrogênios nos tecidos-alvo (Gambineri, Pelusi et al. 2002; Gapstur, Gann et al. 2002). Entretanto, a dieta HP parece não influenciar em parâmetros reprodutivos, apesar dos efeitos na redução

de peso em mulheres com PCOS (Moran, Noakes et al. 2003; Stamets, Taylor et al. 2004).

Estudo de Sacks FM e colaboradores (Sacks, Bray et al. 2009) compararam dieta de lipídeo reduzido versus lipídeo aumentado; valor de proteína padrão versus proteína aumentada, além disso, compararam conteúdo de carboidrato aumentado e reduzido. Todas as dietas resultaram em redução significativa de peso, independente do conteúdo da dieta.

Com relação a outras dietas, um trabalho de revisão recente observou que a redução de peso e a adesão a uma dieta com baixo teor de lipídios foram similares a outras abordagens nutricionais (Pirozzo, Summerbell et al. 2002). Nesta mesma linha, outros estudos demonstraram uma piora do perfil metabólico com a dieta NP, particularmente quando a redução de peso não foi alcançada (Piatti, Monti et al. 1994; Moran, Noakes et al. 2003). Farnsworth e colaboradores (Farnsworth, Luscombe et al. 2003) observaram um aumento dos níveis de insulina pós-prandial e da glicose em pacientes em dieta NP. Dieta com baixo percentual de carboidratos levou a uma maior redução de peso (diferença absoluta de aproximadamente 4%) do que a dieta convencional nos 6 primeiros meses de tratamento, mas essa diferença não foi significativa em 1 ano. A dieta com redução de carboidratos foi associada com melhora de fatores de riscos para doença coronariana (Foster, Wyatt et al. 2003). Por outro lado, existem evidências que indicam que o peso é mantido mais eficazmente e a obediência é aumentada na dieta NP seguida por longo período (Moran, Noakes et al. 2004).

Um estudo realizado com a população em geral observou que as dietas NP e HP se mostraram igualmente efetivas para a redução de peso após 12 (McAuley, Smith et al. 2006) ou 24 meses de dieta (Due, Toubro et al. 2004) em mulheres com RI (McAuley, Smith et al. 2006). No entanto, outros grupos (Baba, Sawaya et al. 1999; Moran, Noakes et al. 2003) observaram uma maior redução e manutenção do peso na dieta HP comparada à NP, além de redução da adiposidade abdominal e total em mulheres com sobrepeso, com DM2 (Luscombe, Clifton et al. 2002; Foster, Wyatt et al. 2003). Após 12 semanas, uma dieta com baixo teor de carboidrato levou à redução de peso, à melhora da acne e a alterações de testosterona, proteina ligadora de IGF tipo 1 e HOMA (*Homeostasis Model*

Assessment), quando comparada com dieta convencional rica em carboidratos (Smith, Mann et al. 2007). Nordmann e pesquisadores (Nordmann, Nordmann et al. 2006) observaram que a dieta com baixo carboidrato parece ser, pelo menos, tão efetiva quanto a dieta com baixo lipídio em relação à redução de peso por um período maior do que 1 ano.

Na ausência de evidência de nível I, a recomendação dietética para mulheres obesas com PCOS é qualquer dieta hipocalórica (com déficit de 500 Kcal/dia), com redução da carga glicêmica e qualquer restrição calórica que as pacientes possam cumprir e atingir uma redução de peso de 5% (Consensus 2008; Jeanes, Barr et al. 2009).

Estudos preliminares em pacientes sem PCOS mostraram que dietas com diferentes perfis de macronutrientes poderiam ser mais eficazes para alcançar a perda de peso em indivíduos com RI. No entanto, até o momento não existem evidências consistentes de que determinada composição dietética seja particularmente mais benéfica no tratamento da PCOS. São necessários mais estudos sobre os efeitos das dietas com diferentes composições de macronutrientes na redução de peso e nos distúrbios reprodutivos e metabólicos em mulheres com PCOS, como tratamento inicial (Pasquali, Gambineri et al. 2000).

CONCLUSÃO

A redução de peso leva à redução dos níveis de androgênios e resistência à insulina, bem como à melhora do perfil lipídico, conferindo benefícios reprodutivos e na fertilidade de um grande número de mulheres com PCOS. No entanto, a composição dietética mais adequada para o tratamento destas mulheres é ainda um assunto controverso.

Além disso, uma redução moderada de carboidratos na dieta pode reduzir as concentrações de insulina de jejum e pós-sobrecarga com glicose entre mulheres com PCOS, levando à melhora dos fatores reprodutivos, hormonais e metabólicos.

Modificações no estilo de vida com redução modesta de 5 a 10% do peso corporal parecem ser igualmente efetivas para restaurar a fertilidade, e podem ser mais consistentes para alcançar o sucesso em longo prazo. Mais

estudos são necessários para determinar se alguma composição dietética é particularmente mais benéfica do que outras no tratamento da PCOS.

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Parte II

Artigo Original 1:

DIET PATTERN IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME AND HEALTHY CONTROLS

DIET PATTERN IN PATIENTS WITH POLYCYSTIC OVARY SYNDROME AND HEALTHY CONTROLS

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Running title: Diet pattern in PCOS

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ABSTRACT

Background/Aims: Obesity occurs in 60% of patients with Polycystic ovary syndrome (PCOS), associated with insulin resistance (IR) and risk for diabetes. Whether dietary factors are associated with these metabolic abnormalities is a controversial issue. We compared patients with PCOS and BMI-matched, ovulatory, non-hirsute controls in terms of body fat, metabolic and hormonal variables and diet composition.

Methods: Forty-three PCOS patients and 37 controls with age between 14 and 38 years underwent anthropometric, laboratory and nutrition assessment.

Results: The groups had a similar intake of energy [1707kcal (1294-2332) and 2002kcal (1416-2402)], carbohydrate (53.51 ± 8.36 and 51.83 ± 10.06), protein [15 (12–18) and 16 (13–19)] and total fat (30.51 ± 7.90 and 30.80 ± 7.97) percentages. PCOS patients consumed lower amounts of high biological value protein (p=0.031) and presented higher total body fat (p=0.007), sum of trunk skinfolds (p=0.002) and waist circumference (p=0.029). SHBG was lower (p=0.030) whereas total testosterone (p=0.001), free androgen index (p=0.001), postprandial glucose (p=0.001), fast (p=0.001) and postprandial insulin (p=0.001), HOMA (p=0.001), triglycerides (p=0.043), total (p=0.019) and LDL cholesterol (p=0.031) were higher in PCOS than in the control group.

Conclusions: The susceptibility to insulin resistance observed in PCOS might be independent of caloric intake or dietary composition.

Key words: dietary intake, central obesity, insulin resistance, clinical nutrition, macronutrients, nutritional endocrinology, steroid hormone.

INTRODUCTION

Polycystic ovary syndrome (PCOS) is a very common endocrine disorder, affecting 5 to 10% of women of reproductive age [1-5]. It is characterized by hyperandrogenism and anovulation [6] in the absence of other diseases affecting pituitary and/or adrenal glands. PCOS is a major cause of anovulatory infertility, menstrual disturbances and hirsutism and is frequently associated with metabolic abnormalities and insulin resistance [7-11].

The obesity (predominantly abdominal) observed in 30 to 75% of women with PCOS [4,5] is associated with the metabolic and reproductive disorders usually found in these patients. Also, insulin resistance may be present in PCOS independently of body mass index (BMI), with an adverse impact on lipid profile and blood pressure [8,12-15].

Feeding behavior and an unhealthy lifestyle are probably the main causes of increasing overweight worldwide. In Brazil, the highest rates of obesity and overweight in women (14.4% and 42.4%, respectively) occur in the South [16], but few data are available concerning the prevalence of obesity in PCOS [8,11,17].

It has been speculated that women with PCOS are obese due to a tendency to overeating, particularly sweet or starchy foods [18]. Studies examining diet composition have shown that subjects with PCOS eat significantly more saturated fat [13,19] and less monounsaturated fat [19]. In addition, they have a lower intake of dietary fiber [13] compared with healthy control women.

The study of how dietary composition influences fertility is a largely unexplored field, although there is a substantial body of evidence concerning the effects of underweight and excess weight on fertility [20]. Specifically concerning PCOS, even though the possibility of an influence of the quality of diet on metabolic and endocrine control has been acknowledged, very few studies have addressed this

issue [21]. In contrast, weight loss has been consistently shown to improve the clinical status of PCOS women [22,23].

Therefore, the aim of this study was to determine body fat, hormonal and metabolic variables and diet composition in patients with PCOS vs. a control group of ovulatory, non-hirsute, BMI-matched women.

MATERIALS AND METHODS

Patients and controls

This case-control study was carried out with women at reproductive age, consulting at the Gynecological Endocrinology Unit at Hospital de Clínicas de Porto Alegre, Brazil. Forty-three hirsute women presenting oligo/amenorrheic cycles (9 or less cycles/year), increased levels of serum testosterone and/or free androgen index (FAI), and absence of other disorders causing hirsutism [24,25] were enrolled in the study. Thirty-seven BMI and race-matched non-hirsute women with regular and ovulatory cycles (luteal phase progesterone levels higher than 3.8 ng/mL) were recruited to participate in the study as a control group. None of the women from either group had received any drugs known to interfere with hormone levels for at least 3 months before the study. Women with BMI higher than 40 kg/m^2 or type 2 diabetes were excluded. The study protocol was approved by the local Ethics Committee (Institutional Review Board-equivalent), and written informed consent was obtained from all subjects.

Study protocol

Anthropometric measurements were performed in duplicate and included body weight, height, BMI (current kg/m^2), waist circumference (measured at the midpoint between the lower rib margin and the iliac crest, perpendicularly to the long axis of the body, with the subject standing balanced on both feet, spread

approximately 20cm apart, with both arms hanging freely) [11,26,27], hip circumference (widest circumference over the buttocks) [28] and waist to hip ratio. Obesity was defined as BMI ≥30 kg/m^2. Hirsutism was defined as a modified Ferriman-Gallwey score of 8 or more [29-31]. Blood pressure was measured after a rest period of 10 minutes, with the woman in the supine position. Hormonal and metabolic evaluation was performed between days 2 and 10 of the menstrual cycle or on any day if the patient was amenorrheic. After an overnight 12h fast, blood samples were drawn from an antecubital vein for determination of plasma cholesterol, high-density lipoprotein (HDL) cholesterol and triglycerides at baseline, and glucose and insulin before and 2h after the ingestion of a 75g oral glucose load. Impaired glucose tolerance was determined by glucose levels between 140 and 200 mg/dL, as defined by the World Health Organization (WHO) [32]. Blood samples were also drawn for measurement of sex hormone binding globulin (SHBG) and total testosterone (TT). All samples were obtained between 8 and 10 a.m. FAI was estimated by dividing TT (nmol/L) by SHBG (nmol/L) X 100. Homeostasis model assessment (HOMA) index was calculated by multiplying insulin (mIU/mL) by glucose (mmol/L) and dividing this product by 22.5 [33]. The cutoff point to define insulin resistance was arbitrarily defined as a HOMA index ≥3.8 [27].

Biochemical and hormonal assays

Total cholesterol, HDL-cholesterol, triglycerides and glucose were determined by colorimetric-enzymatic methods using the Bayer 1650 Advia System (Mannheim, Germany). Non-HDL cholesterol (non-HDL-c) levels were calculated by subtracting HDL-cholesterol from total cholesterol values. Low-density lipoprotein (LDL) cholesterol was estimated indirectly using: LDL = total cholesterol - HDL - triglycerides/5. Serum LH was measured by a specific immunometric assay (Diagnostic Products Corporation-DPC, Los Angeles, CA, USA) with sensitivity of

0.05 mIU/mL, and intra- and inter-assay coefficients of variation (CV) of 3.6 and 6.7%, respectively. TT levels were measured by radioimmunoassay (ICN, Costa Mesa, CA, USA) with an intra- and inter-assay CV of 10 and 11.6%, respectively. SHBG was measured by chemiluminescent enzyme immunoassay (DPC) with a sensitivity of 0.2 nmol/L, and intra- and interassay CV of 6.1 and 8.0%, respectively. Serum insulin levels were measured with an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, D-68298 Mannhein, Germany) with sensitivity of 0.20 mIU/mL and intra- and inter-assay CV of 1.8 and 2.5%, respectively.

Measurement of skinfold thicknesses

Skinfold thickness was estimated using a caliper (Cescorf, Mitutoyo, Porto Alegre, Brazil) with 0.1mm scale and pressure of 10 g/mm^2. Measurements were performed at the triceps and subscapular, abdominal and suprailiac regions. Percentage body fat was calculated using the Faulkner (1968) formula: % total body fat = (triceps + subscapular + suprailiac + abdominal skinfolds x 0.153) + 5.783. To estimate truncal adiposity, the sum of three skinfold measurements (subscapular, suprailiac and abdominal) was used, referred to as “sum of trunk skinfolds” and expressed in mm, as previously reported [27].

Nutritional assessment

In order to determine amounts and quality of all foods and beverages consumed the day before, a validated 24h dietary recall was used, based on individual interviews [34-36]. Each participant responded to the questionnaire specifying details about the brand, size and volume of each portion consumed, based on food replicas, drawing and photographs and home utensils (such as glasses, cups, mugs, spoons and shells) displayed during the interview.

To estimate the protein intake of macronutrients and the reliability of the information obtained by the 24-hour dietary recall, urea and creatinine were determined in 24-hour urine samples. Agreement was observed by estimating the protein intake achieved. Protein balance was estimated by determination of 24-hour urinary urea with the formula protein intake (g of protein/day) = nitrogen intake x 6.25, where nitrogen intake = urinary urea nitrogen (urinary urea / 2) + non-urea nitrogen (losses through skin, hair, nails and others = 0.031 g/kg current weigh). This calculation was used taking into account that almost the totality of the nitrogen derived from amino acids produced by protein catabolism is excreted in the urine [37].

Statistical analysis

Results are presented as means ± standard deviation (SD). Non-parametric data are presented as medians and interquartile range. Two-tailed Student t-tests were used to compare the differences between means of parametric continuous variables whilst the Mann Whitney U-test was used for comparisons of non-parametric data. Statistical significance for categorical variables was calculated by Pearson's χ^2 test. Spearman's rank correlation coefficient was calculated between variables using a two-tailed significance test for variables with non-Gaussian distribution. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA). Data were considered to be significant at $p<0.05$.

RESULTS

Twenty-eight (90%) of 31 PCOS patients and 26 (74%) of 35 controls were Caucasian, while the others were of mixed race. Participants in both groups were

predominantly obese (57% and 50% for PCOS and controls, respectively, *versus* 25% and 31% overweight and 18% and 19% normal weight for PCOS and controls).

Table I summarizes the clinical and anthropometric profile of each group. Controls were older than PCOS patients (p=0.001). While BMI was similar in both groups, PCOS patients had higher percentage body fat (p=0.007), sum of trunk skinfolds (p=0.002) and increased waist circumference (p=0.029) and waist to hip ratio (p=0.001) in relation to control women.

Table II shows the hormonal and metabolic profile of the PCOS and control groups. PCOS patients presented significantly lower SHBG and higher TT, FAI, post-prandial glucose, fasting and post-prandial insulin, HOMA index, triglycerides, total cholesterol and LDL-c compared to control women. No differences between the groups were found for fasting glucose or HDL-cholesterol. Twenty-two (50%) of 44 PCOS patients and only 2 (5.5%, p< 0.05) of 36 controls presented insulin resistance (HOMA≥3.8).

Regarding food intake (Table III), there were no statistical differences in energy, carbohydrate, protein and lipid intake between the groups. Patients with PCOS had a slightly lower protein intake than the control group (p=0.05) and ingested less high biological value protein (p=0.03). The consumption of macronutrients was in accordance with NIH recommendations [38], although both soluble (5-10 g/d) and insoluble fiber intake (15-20 g/d) was lower than recommended [39].

Other nutrients were found to be within the normal range [38]: carbohydrate ≥55%, protein = 15% and total fat ≤30% of the total caloric intake (Table IV). Also within the normal range was the intake of cholesterol (<300 mg/d) and saturated fatty acids (8-10%). Intake of monounsaturated fatty acids >15% and polyunsaturated fatty acids >10% were slightly lower than the recommendation [38].

HOMA was positively associated with BMI (r=0.680, p=0.0001 in PCOS and r=0.645, p=0.0001 in controls), percentage body fat (r=0.709, p=0.0001 in PCOS and

r=0.623, p=0.0001 in controls), and sum of trunk skinfolds (r=0.715, p=0.0001 in PCOS and r=0.635, p=0.0001 in controls). These associations remained significant after adjustment for FAI. No correlations were observed between total energy intake and androgens.

DISCUSSION

The present study shows that PCOS and control women had a similar dietary intake. However, despite being younger than controls, PCOS patients had more central obesity as measured by the sum of trunk skinfolds, waist circumference and waist to hip ratio. Central obesity, defined as increased fat in the abdominal region, is considered a marker of insulin resistance and a risk factor for cardiovascular disease [40,41]. The PCOS group also presented lower SHBG and higher androgens as well as a worse metabolic profile than the control group, confirming previous observations made by us [8,27] and others [42-44]. In PCOS patients, the compensatory hyperinsulinemia that follows insulin resistance leads to both an increase in ovarian androgen secretion and a reduction in SHBG concentration. Because of that, obese PCOS women often are more hyperandrogenic that non-obese ones [8,45-49].

There are few data on the diet preferences of women with PCOS. We did not observe statistical differences between the groups in terms of the intake of carbohydrate and lipids. This may have resulted, at least partially, from the high prevalence of obese women in both groups, leading to a lower discriminative effect. Douglas et al., studying PCOS patients and controls matched by age, sex and BMI (with BMI values that were similar to those of our patients), observed a higher ingestion of high glycemic index foods in the PCOS group [19].

It should be noted that while the method of 24-hour dietary recall has been validated and is widely employed, the information reported by participants and changes in the food consumption pattern on the day of the recall may yield

somewhat inaccurate information. Nevertheless, in the present study, patients with PCOS consumed lower amounts of proteins of high biological value than controls.

A study comparing Italian and American women with PCOS found no statistical differences in the intake of energy and macronutrients between the two groups. In turn, American women presented higher ingestion of saturated fatty acids (almost 2 fold increase) compared to the Italian ones [50]. However, the fact that American participants had higher BMI than the Italians might have affected this result. In another study, patients with PCOS ingested more carbohydrates and lipids (total and saturated fat) than controls, but the daily caloric intake was similar in both groups [19].

Some investigators have suggested that women with PCOS have a tendency to overeat, either for emotional (depression, a craving for 'comfort foods') [51] or biological reasons. Holte et al. [47] postulated that insulin-resistant PCOS patients experience recurrent hypoglycemia. The hypoglycemic episodes could cause carbohydrate cravings and a decreased feeling of satiation after eating, which in turn could lead to overeating and obesity. Other studies investigating whether PCOS patients experience disordered metabolism have produced contradictory findings [52,53]. Robinson et al. [53] found that obese and lean women with PCOS displayed reduced postprandial thermogenesis (a measure of metabolic efficiency) compared to obese and lean women without PCOS; the reduction in postprandial thermogenesis in the women with PCOS correlated with reduced insulin sensitivity. In contrast, other studies [54] found no difference in resting metabolic rate or postprandial thermogenesis between obese women with and without PCOS.

In conclusion, the presence of PCOS in this group of patients does not seem to interfere with the amount or quality of dietary intake. Women with PCOS, however, had greater waist circumference and waist to hip ratio than the control group, which may be associated with the increased susceptibility to insulin resistance observed in

these patients. This suggests that dietary preferences and intake are not directly associated with metabolic abnormalities in PCOS.

CONFLICT OF INTEREST STATEMENT

The authors declare they have no conflicts of interest concerning the publication of this article.

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TABLES

Table I. Clinical and anthropometric features of patients with PCOS and non-hirsute ovulatory controls

Variable	PCOS (n=43)	Controls (n=37)	p
Age (years)	22.67 ± 5.55	29.70 ± 4.93	0.001
Weight (kg)	79.64 ± 15.04	77.03 ± 13.95	0.420
BMI (kg/m²)	30.92 ± 5.48	29.66 ± 5.16	0.290
Systolic BP (mmHg)	121.45 ± 15.81	116.32 ± 9.56	0.080
Diastolic BP (mmHg)	77.56 ± 11.7	74.03 ± 10.18	0.171
Skinfold thickness total body fat (%)	30.71 ± 6.67	26.8 ± 5.85	0.007
Sum of trunk skinfolds (mm)	127.92 ± 36.51	104.34 ± 29.95	0.002
Waist circumference (cm)	90.83 ± 11.33	85.48 ± 9.94	0.029
Hip (cm)	110.19 ± 10.56	110.90 ± 10.60	0.740
Waist to hip ratio	0.82 ± 0.07	0.77 ± 0.05	0.001

BP: blood pressure; BMI: body mass index; PCOS: polycystic ovary syndrome.

Values are expressed as mean ± SD (Student's t-test).

Table II. Hormonal and metabolic features of patients with PCOS and non-hirsute ovulatory controls

Variable	PCOS (n=43)	Controls (n=37)	p
Total testosterone (ng/mL)	1.10 (0.90 – 1.40)	0.32 (0.21 – 0.39)	0.001
SHBG (nmol/L)	28.50 (14.80 – 50.60)	44.60 (29.55 – 56.04)	0.030
Free androgen index	19.90 (9.93 – 29.96)	2.76 (1.70 – 4.70)	0.001
Fasting glucose (mg/dL)	88.69 ± 8.92	88.89 ± 7.08	0.910
Glucose 120' (mg/dL)	118.15 ± 28.72	96.43 ± 18.24	0.001
Fasting insulin µUI/mL	17.75 (10.95 – 33.60)	10.57 (5.97 – 13.73)	0.001
Insulin 120' µUI/mL	126.90 (56.45 – 190.60)	49.86 (27.70 – 85.48)	0.001
HOMA index	3.85 (2.30 – 7)	2.13 (1.30 – 3.16)	0.001
Triglycerides (mg/dL)	86 (60 – 1420)	63 (48.50 – 97.50)	0.043
Total cholesterol (mg/dL)	170 ± 47.84	162.91 ± 35.05	0.019
HDL-c (mg/dL)	51.34 ± 10.19	52.02 ± 12.83	0.790
LDL-c (mg/dL)	155.56 ± 42.92	136.42 ± 33.41	0.031

HDL: high-density lipoprotein; HOMA: homeostasis model assessment; LDL: low-density lipoprotein; PCOS: polycystic ovary syndrome; SHBG: sex hormone binding globulin.

Values are expressed as mean ± SD (Student's *t* test) or median and interquartile range (25% to 75%) (Mann-Whitney *U* test).

Table III. Macronutrient intake of patients with PCOS and non-hirsute ovulatory controls.

Variable	PCOS (n=43)	Controls (n=37)	p
Energy intake (kcal/d)	1707 (1294 – 2332)	2002 (1416.49 – 2401.73)	0.50
Protein (g/kg)	0.88 ± 0.42	1.05 ± 0.39	0.05
Proteins of high biological value (g/d)	40.16 (28.92 – 63.70)	58.39 (36.28 – 77.79)	0.03
Vegetable protein (g/d)	17.31 (13.50 – 25.12)	18.68 (13.59 – 24.69)	0.54
Saturated fatty acid (g/d)	18.42 (12.79 – 24.42)	21.58 (12.37 – 26.91)	0.43
% saturated fatty acid	8.87 ± 2.84	9.71 ± 3.46	0.23
Monounsaturated fatty acid (g/d)	17.99 (12.02 – 24.71)	18.17 (11.84 – 26.02)	0.92
% Monounsaturated fatty acid	9.44 ± 3.04	9.01 ± 3.51	0.56
Polyunsaturated fatty acids (g/d)	13.29 (7.56 – 19.08)	12.98 (9.1 – 21.28)	0.56
% Polyunsaturated fatty acids	6.53 (3.89 – 8.69)	6.69 (4.97 – 10.54)	0.49
Cholesterol (mg/d)	150 (105.9 – 257.6)	202.6 (122.94 – 314.93)	0.09
Total fiber (g/d)	11.62 (7.18 – 15.49)	11.02 (6.44 –18.45)	0.825
Soluble fiber (g/d)	3.99 (2.09 – 4.86)	3.57 (1.72 – 4.97)	0.790
Insoluble fiber (g/d)	7.17 (4.95-11.51)	7.56 (4.41-11.74)	0.965

PCOS: polycystic ovary syndrome.

Values are expressed as mean ± SD (Student's *t* test) or [a] median and inter quartile range (25% to 75%) (Mann-Whitney *U* test).

Table IV. Macronutrient distribution in patients with and without PCOS

Variable	PCOS (n=43)	Controls (n=37)	p
Carbohydrate (%)	53.51 ± 8.36	51.83 ± 10.06	0.41
Protein (%)	15 (12 – 18)	16 (13 – 19)	0.17
Total fat (%)	30.51 ± 7.90	30.80 ± 7.97	0.88

PCOS: polycystic ovary syndrome.

Values are expressed as mean ± SD (Student's *t* test) or median and inter quartile range (25% to 75%) (Mann-Whitney *U* test).

Parte III

Artigo Original 2:

Effect of High-protein or normal protein diet on weight loss, body composition, hormone and metabolic profile in PCOS patients and controls: a randomized study

EFFECT OF HIGH-PROTEIN OR NORMAL PROTEIN DIET ON WEIGHT LOSS, BODY COMPOSITION, HORMONE AND METABOLIC PROFILE IN PCOS PATIENTS AND CONTROLS: A RANDOMIZED STUDY

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Capsule: In this randomized study, calorie restriction rather than protein content had an impact on body composition and hormone profile in patients with PCOS and BMI-matched controls on an eight-week diet.

ABSTRACT

Objective

To assess the effects of a high protein (HP) and a normal protein diet (NP) on patients with polycystic ovary syndrome (PCOS) and BMI-matched controls.

Design

Eight week randomized trial.

Setting

University gynecological endocrinology clinic.

Patients

Eighteen PCOS patients and 23 controls.

Intervention

Patients were randomized to receive HP (30% protein, 40% carbohydrate, 30% lipid) or NP (15% protein, 55% carbohydrate, 30% lipid). The energy content was estimated for each individual patient at 20-25 kcal/kg current weight/day.

Main Outcome Measures

Changes in weight, body composition and hormone and metabolic profile.

Results

Waist-to-hip ratio, physical activity, blood pressure, HOMA index, and fasting and 2-hour glucose and insulin remained similar during the intervention in PCOS and controls, even in the presence of weight loss. There were no changes in lipid profile in either group. In contrast, body weight, BMI, waist circumference, % of body fat and sum of trunk skinfolds decreased significantly after both diets in both groups. Total testosterone also decreased in PCOS and controls regardless of diet.

Conclusions

Calorie reduction, rather than protein content, seemed to affect body composition and hormonal profile in this study.

Keywords: High-protein diet, hypocaloric diet, PCOS, central adiposity, obesity, hyperandrogenism.

INTRODUCTION

Polycystic ovary syndrome (PCOS), an endocrine disorder affecting 7 to 10% of women of reproductive age, is often associated with obesity, insulin resistance (IR) and compensatory hyperinsulinemia(1-5). Dyslipidemia, high blood pressure and higher risk for type 2 diabetes (4,6-10) – a cluster of symptoms referred to as the metabolic syndrome – are also common features of PCOS (11-13).

It is known that the control of weight in PCOS through calorie restriction diets (14) improves clinical features (15, 16), lipid profile, menstrual cycle and fertility, in addition to decreasing abdominal fat, hyperandrogenism and IR (17, 18). Normal protein (NP) diets containing 30% lipid, 55% carbohydrate and of 15% protein (19, 20) have been used for the management of weight and improvement of metabolic and reproductive aspects in PCOS (21). In turn, high protein (HP) diets containing 30% protein, 40% carbohydrate and 30% fat have been reported to promote greater weight loss and weight maintenance compared with NP (22). In overweight people, HP has been associated with a decrease in total abdominal adiposity and in the prevalence of type 2 diabetes (23, 24). Also, previous studies report that HP improves insulin sensitivity (25), increases basal metabolism and postprandial energy expenditure, and decreases post-prandial glucose (26). However, other investigators have shown that fasting insulin (22, 24, 27), postprandial insulin and HOMA (22) are not affected by dietary content. Thus, there is no consensus regarding which diet, NP or HP, is more indicated for PCOS (22, 28, 29).

The aim of the present study was to assess the effects of HP and NP on weight loss, body composition and hormone and metabolic profile in patients with PCOS and in a group of BMI-matched control women.

MATERIALS AND METHODS

Participants

This randomized trial was carried out with women of reproductive age consulting at the Gynecological Endocrinology Unit at Hospital de Clínicas de Porto Alegre, Brazil. Women with BMI ranging from 18.5 to 39.9 kg/m² and age between 14 to 35 years were selected. Eighteen hirsute women presenting oligo/amenorrheic cycles (9 or less cycles/year), increased levels of serum testosterone and/or free androgen index (FAI), and absence of other disorders causing hirsutism (30, 31) were enrolled. A control group was set up with 23 BMI-matched non-hirsute women with regular ovulatory cycles (luteal phase progesterone higher than 3.8 ng/ml). None of the women from either group had received any drugs known to interfere with hormone levels for at least 3 months before the study. Women with type 2 diabetes, liver or renal disease or thyroid dysfunction were excluded. The study protocol was approved by the local Ethics Committee (Institutional Review Board-equivalent), and written informed consent was obtained from all subjects.

Study protocol

Anthropometric measurements were performed in duplicate by two investigators (M.K.T. and F.M.M.), and included body weight, height, BMI (current kg/m^2), waist circumference (WC) (waist measured at the midpoint between the lower rib margin and the iliac crest, perpendicularly to the long axis of the body, with the subject standing balanced on both feet, spread approximately 20cm apart, with both arms hanging freely) (32-34), hip circumference (widest circumference over the buttocks), and waist to hip ratio (WHR) (waist measured at the midpoint between the lower rib margin and the iliac crest) (34).

Skinfold thickness was estimated with a caliper (Cescorf, Mitutoyo, Porto Alegre, Brazil) with 0.1 mm scale and pressure of 10 g/mm^2. Measurements were

performed at the triceps, subscapular, abdominal and suprailiac regions. To estimate truncal adiposity, the sum of three skinfold measurements – subscapular, suprailiac and abdominal – was considered (referred to as “sum of trunk skinfolds,” expressed in mm) (33).The percentage of total body fat was calculated by the Faulkner formula: percentual total body fat = (triceps + subscapular + suprailiac + abdominal skinfolds x 0.153) + 5.783.

Medical interview and physical examination were performed as described (5, 35) and included the measurement of blood pressure and the evaluation of the severity of hirsutism by the modified Ferriman and Gallwey score (36).

Hormonal and metabolic assessment was made between days 2 and 10 of the menstrual cycle or on any day when the patients were amenorrheic. After an overnight fast, blood samples were drawn from an antecubital vein for determination of plasma cholesterol, HDL-cholesterol and triglycerides at baseline and glucose and insulin before and 2 hours after the ingestion of 75 g of oral glucose (OGTT). Impaired glucose tolerance (IGT) was determined by glucose levels between 140 and 200 mg/ml, as defined by the WHO (37, 38).

Blood samples were also drawn for measurements of sex hormone binding globulin (SHBG) and total testosterone (TT). All samples were obtained between 8 and 10 am. The free androgen index (FAI) was estimated using the formula T (nmol/l)/SHBG (nmol/l) x 100. HOMA was calculated by multiplying insulin (µIU/ml) by glucose (mmol/l) and dividing the product by 22.5. The cutoff point to define IR was arbitrarily defined as a HOMA index ≥ 3.8 (33, 39).

Assays

Total cholesterol, HDL-cholesterol, triglycerides and glucose were determined by colorimetric-enzymatic methods using the Bayer 1650 Advia System (Mannheim, Germany). Non-HDL cholesterol (non-HDL-c) levels were calculated by subtracting HDL-cholesterol from total cholesterol values. Low-density lipoprotein (LDL)

cholesterol was estimated indirectly using: LDL = total cholesterol - HDL + triglycerides / 5. Serum LH was measured by a specific immunometric assay (Diagnostic Products Corporation-DPC, Los Angeles, CA, USA) with sensitivity of 0.05 mIU/ml, and intra- and inter-assay coefficients of variation (CV) of 3.6 and 6.7%, respectively. TT levels were measured by radioimmunoassay (ICN, Costa Mesa, CA, USA) with an intra- and inter-assay CV of 10 and 11.6%, respectively. SHBG was measured by chemiluminescent enzyme immunoassay (DPC) with a sensitivity of 0.2 nmol/l, and intra- and interassay CV of 6.1 and 8.0%, respectively. Serum insulin levels were measured with an electrochemiluminescence immunoassay (Roche Diagnostics GmbH, D-68298 Mannhein, Germany) with sensitivity of 0.20 mIU/ml and intra- and inter-assay CV of 1.8 and 2.5%, respectively.

Nutritional assessment, evaluation of physical activity and diet intervention

Pre-treatment energy and macronutrient intake were evaluated using a validated 24h dietary recall (24hR) twice prior to the diet intervention. The recall serves to quantify the ingestion of food and beverages on the day before the interview based on detailed information about brand, size and volume of each portion ingested. Food replicas, pictures and household utensils were used to ensure an accurate description. The 24hR was also applied after 1 and 2 months of diet. Renal function and validation of the 24hR, as well as diet adherence were evaluated by urinary creatinine and 24h-urea measurements (40) before and after the diet intervention. Food intake based on the information obtained with the 24hR was calculated with the Nutribase 7 software (NB7 Professional Edition, version 7.18, United States Department of Agriculture, USDA).

Adherence to the diet was verified by estimating protein intake in 24h urinary urea samples using the formula protein intake (g of protein / day) = nitrogen X 6.25. Ingestion of urea nitrogen = urinary nitrogen (urinary urea / 2) + non-urea nitrogen (losses through the skin, hair, nails and etc) = 0.031g / kg of current weight. The

measurement of 24h urinary nitrogen excretion is considered a standard criterion for evaluation of protein intake (41), since almost all the nitrogen derived from amino acids produced by protein catabolism is excreted in the urine (42).

Energy needs were estimated by using 20-25 kcal/kg current weight/day for overweight and obese women and 25-30 kcal/kg current weight/day for normal weight participants (43, 44). Patients were randomized to receive one of two diets: HP (30% protein, 40% carbohydrate, and 30% lipid) or NP (15% protein, 55% carbohydrate, and 30% lipid).

Participants were required to exercise no more than 3 times per week and were asked to maintain their level of physical activity constant during the 8 weeks of study. The level of habitual physical activity was assessed by the use of a digital pedometer (BP 148 Techline). This equipment records the number of steps taken during a certain period of time, and is capable of recording the distance traveled daily by each individual. Patients were not encouraged to walk more than usually. The device was configured individually according to the participant's weight (kg) and step length (recorded with a measuring tape between the calcaneus and the left calcaneus in cm). Participants who walked fewer than 6,000 steps daily were classified as sedentary (45), while those walking 6,000 to 9,999 steps/day were considered to have a light level of physical activity, and those walking more than 10,000 steps per day were classified as active.

Statistical analysis

Results are presented as means ± standard deviation (SD). Non-parametric data are presented as medians and interquartile range. Logarithmic transformation was performed for variables presenting non-normal distribution. Two-tailed Student t-tests were used to compare the means of two continuous variables. ANOVA for repeated measures was performed to the groups before and after nutritional

treatment. All analyses were performed using the Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA). Data were considered to be significant at $p < 0.05$.

RESULTS

Fifteen of 18 (83.3%) PCOS patients and 16 of 23 (69.6%) controls were Caucasian. The remaining participants were of mixed (African and European) descent. The mean age in the PCOS group was 22.72 ± 5.68 years vs. 29.35 ± 5.74 years for controls ($p = 0.001$).

Table 1 shows the anthropometric, metabolic and hormonal profile of PCOS patients and non-hirsute, ovulatory controls before the diet. While the groups had a similar BMI, fasting glucose and level of physical activity (number of steps), PCOS patients presented increased waist circumference, WHR, body fat and sum of trunk skinfolds. The PCOS group also had a higher HOMA index and insulin and androgen levels, and lower SHBG serum concentrations than the control group.

The effect of 2 months of HP and NP on anthropometric, metabolic and hormonal variables in PCOS and controls is described in Table 2. Weight loss was observed in all the groups. WHR, level of physical activity, blood pressure, fasting and 2-hour glucose and insulin levels, and HOMA index remained similar during the diet treatment in both the PCOS and control groups, even in the presence of weight loss. There were no changes in lipid profile regardless of diet (HP or NP) or group (PCOS or controls). Body weight, BMI, waist circumference, % of body fat and sum of trunk skinfolds decreased significantly after the diet intervention in both the PCOS and control groups (Figure 1), but no differences were observed between HP and NP.

Figure 2 shows androgen and SHBG levels in response to the diet intervention in the two groups. While no differences were observed in SHBG levels or

FAI, total testosterone levels decreased in both PCOS and control women, with no difference between the diets.

DISCUSSION

In this study, we observed that body weight, BMI and central adiposity decreased in both PCOS patients and controls following weight loss resulting from a hypocaloric diet regardless of protein content. Moreover, despite the short intervention time, both diets reduced serum androgen levels.

Control of diet and weight is an important component of the treatment of PCOS, although no consensus exists concerning the best distribution of dietary contents. For this reason, in the present study, we chose to assess the short-term effects of a drug-free HP or NP treatment in order to rule out the influence of conventional pharmacological treatment; thus, the clinical phenotype changes observed in our patients are a result exclusively of the diets offered to these women.

No differences were observed between HP and NP during the two months of treatment. This result might be due, at least in part, to the short duration of the intervention, which only allowed us to detect acute metabolic responses. However, other studies with non-PCOS populations have also reported absence of differences in terms of body weight and body fat after NP or HP diets (22, 46). Also, in insulin-resistant women, weight loss with the HP diet has been shown to be similar to that obtained with moderate protein intake over 12 or 24 months in the general population (47). Both NP and HP have been reported to decrease body fat (27). Parker et al. (48) have described a reduction in total lean mass in a group of type 2 diabetes patients independently of diet composition.

In turn, there is evidence suggesting greater loss of weight and body fat with HP after 6 months (23) and higher reduction and maintenance of weight with HP compared with NP after 4 weeks (22, 27). This is important for obese PCOS patients, who often report greater difficulty in losing weight and maintaining weight loss(49). Kasim-Karakas et al. (50) have shown that a group of PCOS patients on a protein diet lost more weight and more fat mass than the group receiving a high carbohydrate content diet.

In should also be considered that the fat and carbohydrate content might influence the response to diets with different protein intake (51). Low-fat, energy-restricted diets of varying protein content (15 or 30%) have been shown to promote healthy weight loss compared to high-carbohydrate diets (52, 53). Due et al. (54) have observed more favorable effects on weight loss in overweight and obese subjects after 6 months of a low-fat, high-protein diet compared to a medium-protein diet.

Regardless of dietary content, weight loss induced by energy restriction improves body composition by reducing fat mass, abdominal fat mass and waist circumference in overweight women with PCOS (18, 22).Interestingly, in the present study there was a remarkable decrease in central adiposity, as shown by the sum of trunk skinfolds, with both diets, in both the PCOS and control groups. We have previously reported that the sum of trunk skinfolds has an excellent correlation with trunk fat mass measured by dual-energy x-ray absorptiometry (DXA) (33). The present results indicate that the sum of trunk skinfolds is also a simple and useful tool to assess the effectiveness of diet treatment in PCOS patients.

We observed a reduction in testosterone levels in PCOS patients and BMI-matched controls, independently of the diet composition. This result is in accordance with previous studies showing that a reduction of 5-10% in body weight over as little as 4 weeks may be sufficient to improve the presentation of PCOS even if subject remain clinically overweight or obese (55). This percentage of weight loss reduces blood androgens levels, improving fertility (18, 56, 57) and clinical signs of hyperandrogenism (15, 58-60).

In conclusion, the present data suggest that calorie restriction rather than dietary content was associated with metabolic and hormonal improvement in the short term, and emphasize the role of non-pharmacological interventions to reduce weight and ameliorate the anthropometric and clinical phenotype in PCOS. Further

studies are needed to determine the ideal composition of hypocaloric diets for use in women with PCOS.

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TABLES

Table 1. Basal anthropometric, hormonal and metabolic data of PCOS and controls women

Variable	PCOS (n = 18)	Controls (n = 23)	*P*
BMI (kg/m²)	31.01±5.51	29.03±5.11	0.247
Waist circumference (cm)	90.82±10.96	83.8±9.47	0.036
Waist/Hip ratio	0.82±0.06	0.75±0.06	0.001
Total body fat (%)	30.48±6.91	25.63±6.74	0.031
Sum of trunk skinfolds (mm)	126.51±36.14	99.39±35.27	0.022
Number of steps	6279 (3827-11297)	5435 (3705-8683)	0.441
Fasting glucose (mg/dl)	88.83±6	89.45±7.69	0.781
Fasting insulin (µUI/ml)	15.67 (10.72-26.49)	8.45(4.84-11.89)	0.001
HOMA index	3.25 (2.24-6.08)	1.9 (1.02-2.71)	0.001
Testosterone (ng/ml)	1.37 (1.13-1.58)	0.62 (0.53-0.74)	0.001
SHBG (mmol/l)	25.9 (16.37-42.65)	46.83 (36.45-63.22)	0.008
Free androgen index	24.19 (13.5-32.34)	5.82 (4.86-8.17)	0.001

Values are expressed as mean ± SD or median and interquartile range (25% to 75%) (Student t test); BMI: Body mass index; HOMA: Homeostasis model assessment; SHBG*:* Sex hormone-binding globulin.

Table 2. Clinical, hormonal and metabolic characteristics of PCOS and Control women before and after the diet Intervention

	Prediet				Postdiet			
	PCOS		Controls		PCOS		Control	
Data	HP (n = 9)	NP (n = 9)	HP (n = 13)	NP (n = 9)	HP (n = 9)	NP (n = 9)	HP (n = 13)	NP (n = 9)
Body weight (kg)	74.62±18.18	82.85±15.18	75.89±13.49	77.51±13.31	71.4±15.45 [a]	79.82±16.51 [b]	74.54±13.71 [c]	74.31±13.88 [d]
Hip (cm)	107.24±11.3	112.25±9.12	110±10.58	112.02±9.8	105.24±11.4 [a]	108.97±10.62 [b]	108.04±11.18 [c]	108.74±9.56 [d]
Waist/Hip Ratio	0.81±0.06	0.82±0.06	0.76±0.05	0.75±0.005	0.82±0.07	0.81±0.05	0.76±0.05	0.75±0.06
Number of steps	7793 (3462-13111)	5528 (3906-8278)	6363 (4057-9738)	4248 (1145-8683)	9870 (4833-14265)	7181 (3921-9708)	6738 (2762-8529)	6798 (1726-10243)
Systolic BP (mmHg)	125.7±19.0	119.1±16.4	116.1±10.41	116.43±10.3	126±23.1	119.36±15.38	117.85±10.18	110.71±7.32
Diastolic BP (mmHg)	77.9±10.75	78±11.83	74.6±8.46	75.14±9.6	80±11.2	77.82±12.02	74±8.83	72.57±7.72
Fast glucose (mg/dl)	89.62±6.07	88.33±6.55	89.23±8.16	89.78±7.43	90.5±7.23	89.78±6.38	91.08±9.72	90.44±6.38
2 h Glucose (mg/dl)	113±28.79	118±26.97	90.54±17.76	97.44±18.38	124.62±35.98	119.68±39	101.38±28.07	93.33±18.35

Fast Insulin (µUI/ml)	10.95 (8.64-17.77)	18.55 (13.4-30.71)	8.33 (4.06-12.23)	8.58 (5.91-12.17)	8.88 (7.59-15.67)	18 (10.73-32.48)	8.17 (4.78-14.1)	6.69 (4.34-11.17)
2 h Insulin (µUI/m)	84.1 (45.79-170.8)	131.1 (91.01-236.7)	34.87(23.87-83.12)	42.83 (28.17-65)	76.4 (43.76-117.1)	131.85 (85.84-248.65)	50.65 (31.74-80.11)	34.78 (17.96-51)
HOMA	2.59 (1.88-3.79)	4.11 (2.82-7.1)	1.8 (0.88-2.61)	2.01 (1.25-2.73)	2.06 (1.77-3.33)	3.59 (2.28-7.35)	1.71 (1.05-3.04)	1.61 (0.92-2.63)
TC (mg/dl)	177.78±44.36	166.33±40.21	163.84±27.23	156.55±43.74	166.78±43.26	155.11±31.64	161.61±31.84	149±52.45
HDL (mg/dl)	50±7.2	46±12.5	52.23±14.63	53.78±10.22	49±7.89	45.44±12.38	51.69±15.13	58±9.82
LDL (mg/dl)	150.93±41.94	139.62±36.87	141.35±23.65	127.6±42.92	145.8±42.32	128.49±29.05	136.64±29.34	121±51.56
NHDL (mg/dl)	127.78±39.62	120.33±35.51	111.61±18.51	102.77±43.37	117.77±39.68	109.66±24.52	109.92±21.85	91±49.52
Triglycerides (mg/dl)	76 (42-130)	86 (59-115)	60 (41.5-67.5)	63 (36.5-143.5)	49 (43.5-62.5)	83 (72-102)	81 (49-90.5)	78 (57-107.5)

[a]p<0.001 vs. basal data of HP diet PCOS group; [b]p<0.001 vs. basal data of LP diet PCOS group; [c]p<0.001 vs. basal data of HP diet control group; [d]p<0.001 vs. basal data of LP diet control group(ANOVA for repeated measures). BP: Blood pressure; HOMA: Homeostasis model assessment; SHBG*:* Sex hormone-binding globulin; FAI: Free androgen index; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; NHDL: Non-high-density lipoprotein; TC: Total cholesterol.

FIGURES

FIGURE 1

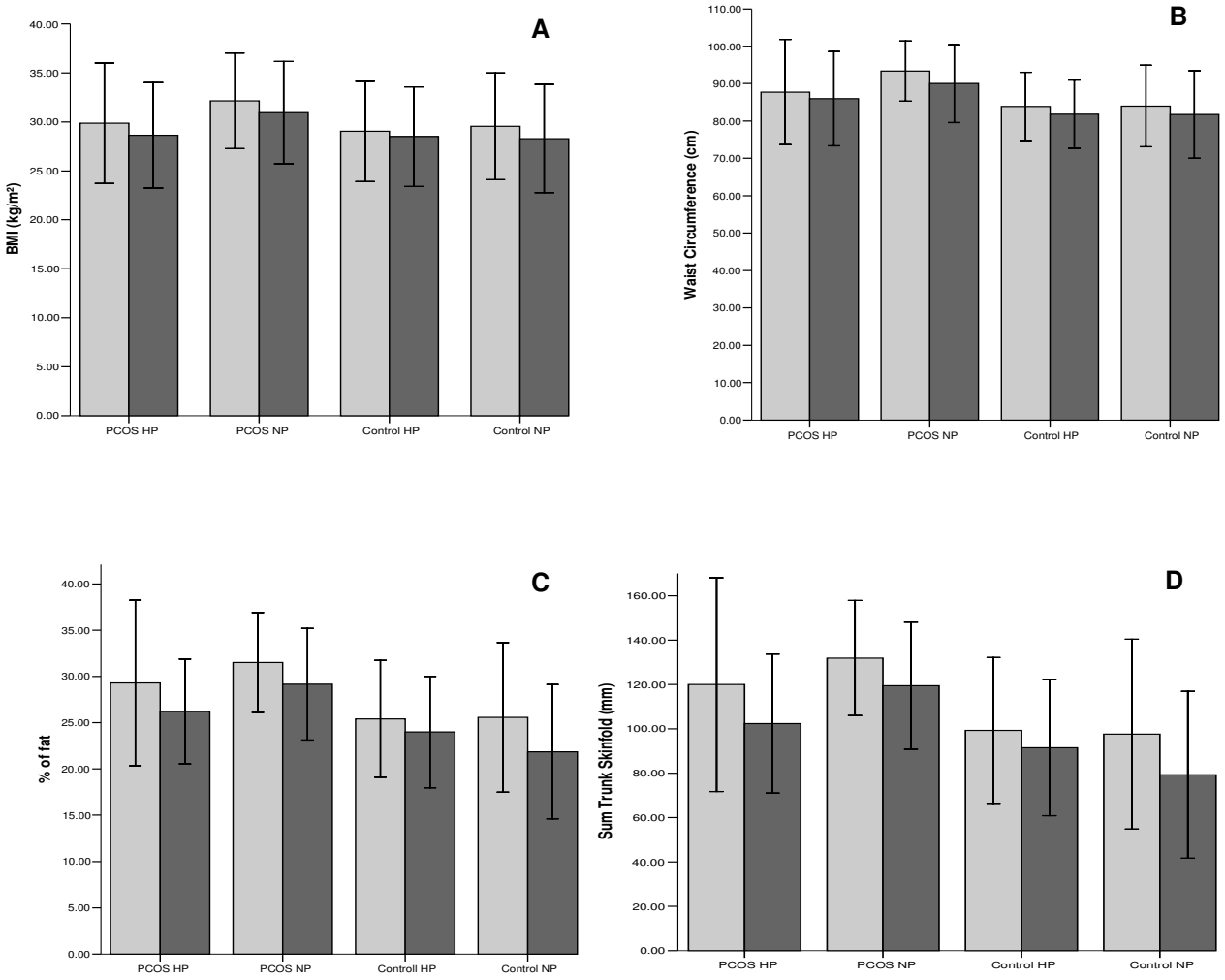

FIGURE 2

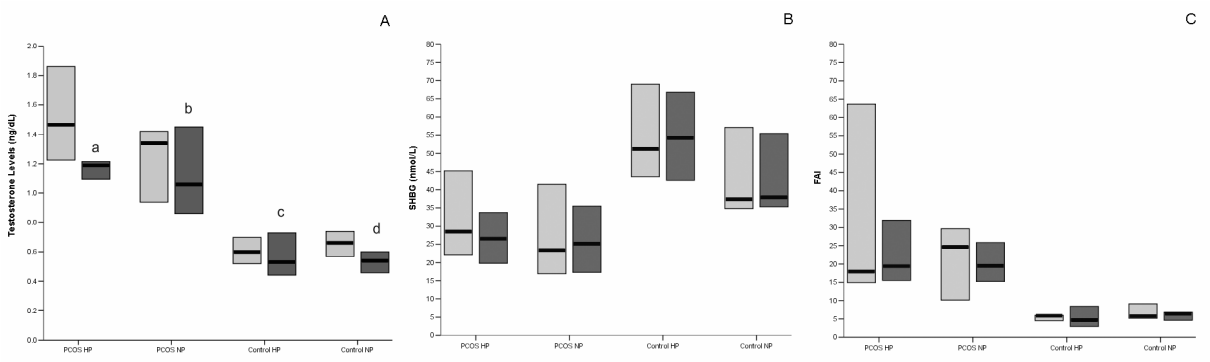
A
Testosterone Levels (ng/dL)
a
b
c
d
PCOS HP
PCOS NP
Control HP
Control NP
B
SHBG (nmol/L)
C
FAI

FIGURE LEGENDS

Figure 1. Changes in A) body mass index, B) waist circumference, C) % of body fat and D) sum of trunk skinfolds after 2 months of high protein or normal protein diet intervention in PCOS and controls.

▒ Before diet intervention.

■ After diet intervention.

[a]p<0.001 vs. basal PCOS data for high protein diet; [b]p<0.001 vs. basal PCOS data for normal protein diet; [c]p<0.001 vs. basal control data for high protein diet; [d]p<0.001 vs. basal control data for normal protein diet.

Figure 2. Changes in A) total testosterone, B) SHBG and C) FAI after 2 months of high protein or normal protein diet intervention in PCOS and controls.

▒ Before diet intervention.

■ After diet intervention.

[a]p<0.03 vs. basal PCOS data for high protein diet PCOS; [b]p<0.03 vs. basal PCOS data for normal protein; [c]p<0.03 vs. basal control data for high protein diet; [d]p<0.03 vs. basal control data for normal protein diet.

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