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# MARCADORES DE RISCO CARDIOMETABÓLICO, ATIVIDADE FÍSICA HABITUAL E ANDROGÊNIOS EM MULHERES COM A SÍNDROME DOS OVÁRIOS POLICÍSTICOS

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**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.**

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- **Introdução**

- **Capítulo 1:** Artigo original: Adiposity indexes as phenotype-specific markers of preclinical metabolic alterations and cardiovascular risk in polycystic ovary syndrome: a cross-sectional study. Aceito para publicação na revista *Experimental and Clinical Endocrinology & Diabetes*

- **Capítulo 2:** Artigo original: Habitual physical activity is associated with improved anthropometric and androgenic profile in PCOS: a cross-sectional study. Publicado na revista Journal of Endocrinological Investigation 2016 Oct 22. [Epub ahead of print]

- **Considerações finais**

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**ARTIGO ORIGINAL 2**

## LISTA DE ABREVEATURAS

17 βHSD: 17β-hydroxysteroid dehydrogenase [17β-hidroxiesteroide desidrogenase]

ANOVA: analysis of variance [análise de variância]

AUC: area under the curve [área sob a curva]

BMI: body mass index [índice de massa corporal]

C-index: conicity index [índice de conicidade]

CLIA: chemiluminescence immunoassay [imunoensaio por quimioluminescência]

c-PCOS: classic polycystic ovary syndrome phenotype [fenótipo clássico da síndrome dos ovários policísticos]

CV: cardiovascular risk [risco cardiovascular]

DHEAS: dehydroepiandrosterone sulfate [sulfato de dehidroepiandrosterona]

FAI: free androgen index [índice de androgênios livres]

FG: Ferriman-Gallwey score [escala de Ferriman-Gallwey]

HDL: high-density lipoprotein cholesterol [lipoproteína de alta densidade]

HOMA-IR: homeostasis model assessment of insulin resistance [modelo de homeostasia de resistência à insulina]

IGT: impaired glucose tolerance [tolerância diminuída à glicose]

IR: insulin resistance [resistência insulínica]

LAP: lipid accumulation product [produto da acumulação lipídica]

LDL: low-density lipoprotein cholesterol [lipoproteína de baixa densidade]

oGTT: oral glucose tolerance test [teste oral de tolerância à glicose]

ov-PCOS: ovulatory polycystic ovary syndrome phenotype [fenótipo ovulatório da síndrome dos ovários policíticos]

NPV: negative predictive value [valor preditivo negativo]

PA: physical activity [atividade física]

PCO: polycystic ovary appearance [aparência policística do ovário]

PCOS: polycystic ovary syndrome [síndrome dos ovários policísticos]

PPV: positive predictive value [valor preditivo positivo]

ROC: receiver operating characteristic curve [curva de característica de operação do receptor]

S: sensitivity [sensibilidade]

SD: standard deviation [desvio-padrão]

SHBG: sex hormone-binding globulin [globulina carreadora dos hormônios sexuais]

SP: specificity [especificidade]

T2DM: type 2 diabetes [diabete mellito tipo 2]

VAI: visceral adiposity index [índice de adiposidade visceral]

WC: waist circumference [circunferência abdominal]

WHtR: waist-to-height ratio [razão cintura-estatura]

## RESUMO

A Síndrome dos Ovários Policísticos (PCOS), caracterizada por disfunção ovulatória e hiperandrogenismo, é a endocrinopatia mais frequente entre mulheres em idade reprodutiva, afetando aproximadamente de 6 a 19% desta população, conforme o critério diagnóstico empregado. Além dos distúrbios reprodutivos, as mulheres com PCOS frequentemente apresentam maior prevalência de fatores de risco cardiometabólico como obesidade abdominal, dislipidemia, hipertensão, tolerância diminuída à glicose e diabetes *mellitus* tipo 2. A resistência insulínica e a hiperinsulinemia compensatória são consideradas como o ponto central destas alterações metabólicas.

Os critérios atuais para diagnóstico de PCOS, a partir do Consenso de Rotterdam, indroduziram diferentes fenótipos. Os mais frequentes são o fenótipo “clássico” (hiperandrogenismo e anovulução, com ou sem a aparência policística do ovário), e o fenótipo “ovulatório” (hiperandrogenismo e aparência policística do ovário). Evidências sugerem que as mulheres com PCOS fenótipo “clássico” tenham alterações metabólicas mais severas comparadas às mulheres com o fenótipo ovulatório.

Em razão disto, o objetivo do primeiro artigo original foi avaliar o desempenho da circunferência abdominal, da razão cintura-estatura, do índice de conicidade, do produto da acumulação lipídica (LAP) e do índice de adiposidade visceral (VAI) com base no modelo de homeostasia de resistência à insulina (HOMA-IR)≥ 3,8 como padrão de referência para rastreamento de alterações metabólicas pré-clínicas e fatores de risco cardiovascular nos diferentes fenótipos de PCOS. Este estudo mostrou que, dentre os índices de adiposidade avaliados, os que apresentaram maior acurácia foram o LAP entre as mulheres com PCOS fenótipo “clássico” e o VAI entre as com fenótipo “ovulatório”. Aplicando o ponto de corte do LAP< 34, identificamos um subgrupo de pacientes sem alterações cardiometabólicas no grupo de mulheres com PCOS com fenótipo “clássico”, população com maior risco de hipertensão, de dislipidemia e de tolerância diminuída à glicose. Dentre as mulheres com PCOS classificadas com o fenótipo “ovulatório”, VAI≥ 1,32 foi capaz de detectar mulheres

com pressão arterial significativamente mais alta e variáveis glicêmicas e lipídicas menos favoráveis em relação às mulheres com PCOS com fenótipo “ovulatório” com VAI abaixo deste ponto de corte.

Atualmente, mudanças de estilo de vida (dieta e/ou exercício físico) são consideradas como primeira opção de tratamento não farmacológico nas mulheres com PCOS. Embora a prática de, pelo menos, 30 minutos por dia de exercício físico estruturado seja recomendada e tenha mostrado um potencial efeito na melhora da resistência insulínica e das variáveis antropométricas e hormonais, a manutenção deste hábito a longo prazo permanece como um ponto crítico. Neste sentido, o objetivo do segundo artigo foi avaliar o efeito da atividade física habitual (AFH) nos perfis metabólico e hormonal de mulheres com PCOS e controles pareadas por idade e índice de massa corporal (IMC). A AFH das participantes foi avaliada por meio de pedômetro digital e, conforme o número de passos diário, a participante foi classificada como ativa (≥ 7500 passos/dia) ou sedentária (< 7500 passos/dia). Mulheres ativas, em ambos os diagnósticos, apresentaram menor IMC, circunferência abdominal e LAP. No grupo PCOS, as mulheres ativas apresentaram menores valores de testosterona total, androstenediona e índice de androgênios livres (IAL) em comparação às sedentárias. Além disto, o aumento de 2000 passos foi um preditor independente de redução do IAL nas mulheres com a síndrome. Este estudo mostrou que ser mais ativa foi associado a um perfil antropométrico e metabólico mais saudável, portanto encorajar um estilo de vida mais ativo pode ser benéfico para mulheres com PCOS, especialmente para as obesas e sedentárias.

**Palavras-chave:** Síndrome dos Ovários Policísticos, índices de adiposidade, risco cardiometabólico, sedentarismo, atividade física, androgênios

## ABSTRACT

Polycystic Ovary Syndrome (PCOS) is characterized by ovulatory dysfunction and hyperandrogenism. The prevalence of PCOS in women of reproductive age range from 6-19%. Women with PCOS present higher prevalence of cardiometabolic risk factors as abdominal obesity, dyslipidemia, hypertension, impaired glucose tolerance and diabetes mellitus type 2. These metabolic abnormalities have been primarily linked to insulin resistance.

Currently, the diagnosis of PCOS is confirmed according the Rotterdam Consensus. The more frequent phenotypes are the classic phenotype (hyperandrogenism and anovulation with or without polycystic ovary appearance), and the ovulatory phenotype (hyperandrogenism and polycystic ovary appearance). Evidence suggests that women with classic PCOS phenotype present more severe metabolic alterations compared to women with ovulatory PCOS phenotype.

The aim of the first study was to evaluate the performance of the waist circumference (WC), waist-to-height ratio, conicity index, lipid accumulation product (LAP), and visceral adiposity index (VAI) based on homeostasis model assessment of insulin resistance (HOMA-IR)≥ 3.8 as standard reference for screening preclinical metabolic alterations and cardiovascular risk factors in classic PCOS and ovulatory PCOS phenotypes. Among these indexes, LAP had the best accuracy for screening metabolic alterations in classic PCOS phenotype, while VAI had the best accuracy for ovulatory PCOS phenotype. Applying the cutoff point of LAP< 34, we identified a subgroup of patients without cardiometabolic alterations in the group with classic PCOS, a phenotype which is characterized by higher risk for hypertension, dyslipidemia, and impaired glucose tolerance. In ovulatory PCOS, VAI≥ 1.32 was useful to detect women with significantly higher blood pressure and less favorable glycemic and lipid variables as compared to ovulatory PCOS with lower VAI.

In addition, lifestyle intervention (diet and/or exercise) is the first-line treatment for

PCOS. Although structured exercise (at least 30 minutes daily) has been recommended and has shown a potential effect on improving insulin resistance, anthropometric, and hormonal variables, the long-term maintenance of exercise remains a critical point. Therefore, the aim of the second study was to objectively examine the effect of habitual PA on metabolic, hormonal, BMI, and anthropometric variables of women with PCOS and a control group, matched by age and BMI. The PA was assessed by digital pedometer, and according to the number of steps/day, participants were classified as active (≥ 7500 steps) or sedentary (< 7500 steps). This study showed that BMI, WC, and LAP were lower in active women in both groups. In the PCOS group, total testosterone, free androgen index (FAI), and androstenedione levels were lower in active when compared to sedentary women. Besides that, a 2,000 daily step increment was an independent predictor of the FAI reduction in PCOS group. The present study showed that a more active lifestyle is associated with healthier anthropometric and metabolic profile, and may be beneficial to women with PCOS, especially for those which are obese and sedentary.

**Keywords:** polycystic ovary syndrome; adiposity indexes; cardiometabolic risk; sedentary lifestyle; physical activity; androgens

## INTRODUÇÃO

### SÍNDROME DOS OVÁRIOS POLICÍSTICOS: DEFINIÇÃO E CRITÉRIOS

A Síndrome dos Ovários Policísticos (PCOS), caracterizada por disfunção ovulatória e hiperandrogenismo, é a endocrinopatia mais frequente entre mulheres em idade reprodutiva, afetando aproximadamente de 6 a 19% desta população, conforme o critério diagnóstico empregado [1,2].

A etiologia da PCOS não está completamente elucidada. Acredita-se que ela seja determinada por diversos fatores genéticos e ambientais, como exposição a androgênios no período pré-natal, condição nutricional na vida intrauterina, etnia, resistência insulínica (RI) e/ou adrenarca exagerada durante a puberdade e alterações no peso corpóreo [3-5].

Atualmente, há três critérios propostos para o diagnóstico da síndrome, conforme tabela abaixo [6,7]:

**Tabela 1.** Critérios de diagnóstico para PCOS

| ***National Institute of Health* (NIH) (1990)[8]** | **Consenso de Rotterdam (2003)[9]** | ***Androgen Excess and PCOS Society* (2006)[10]** |
|---|---|---|
| Todos os critérios são necessários | Dois de três critérios | Hiperandrogenismo associado a outro critério |
| Hiperandrogenismo clínico e/ou bioquímico | Hiperandrogenismo clínico e/ou bioquímico | Hiperandrogenismo clínico e/ou bioquímico |
| Oligo/amenorreia ou anovulação | Oligo/amenorreia ou anovulação | Oligo/amenorreia ou anovulação |
| | Aparência policística do ovário ao exame de ultrassom | Aparência policística do ovário ao exame de ultrassom |

Adaptado de Spritzer, 2014 [7]

Em todos os critérios, há a necessidade de exclusão prévia de doenças que mimetizam a síndrome como: hiperplasia adrenal congênita não clássica, Síndrome de Cushing, tumores secretores de androgênios, hiperprolactinemia, doenças tireoidianas além de outras causas de oligomenorreia ou de anovulação, bem como uso de medicamentos que causem excesso de androgênios. Há a indicação, baseado no parecer de painel de especialistas, do uso do critério de Rotterdam para o diagnóstico de PCOS [6].

O crescente reconhecimento da complexidade da síndrome levou à caracterização de vários fenótipos de PCOS [9] além do previamente descrito pelo NIH, de 1990, conhecido como fenótipo “clássico” [mulheres com hiperandrogenismo (hiperandrogenemia e/ou hirsutismo) e disfunção ovulatória com ou sem aparência policística do ovário]. Os novos fenótipos estabelecidos incluem o fenótipo “ovulatório" (hiperandrogenismo e aparência policística do ovário, sem disfunção ovulatória) e o fenótipo “não hiperandrogênico" (disfunção ovulatória e aparência policística do ovário, sem hiperandrogenismo).

## FATORES DE RISCO CARDIOVASCULAR E PCOS

Além dos distúrbios reprodutivos, as mulheres com PCOS frequentemente apresentam fatores de risco para doenças cardiovasculares como obesidade [11,12], principalmente obesidade abdominal [13,14], dislipidemia [15], síndrome metabólica [16,17], tolerância diminuída à glicose [18,19] e RI [20,21]. Além destes, mulheres com PCOS apresentam diminuição do débito cardíaco [22], elevação de citocinas inflamatórias [23], disfunção diastólica e endotelial [24,25], aumento do enrijecimento vascular [26], alterações dos níveis de fibrinogênio e de óxido nítrico vascular [27] e elevação do antígeno ativador do plasminogênio [28].

Evidências sugerem que as mulheres com PCOS fenótipo “clássico” tenham alterações clínicas, hormonais e metabólicas mais severas comparadas às mulheres com o fenótipo “ovulatório” [29]. A maioria dos estudos comparando PCOS fenótipo “clássico” com

o “ovulatório” relata a presença de um pior perfil metabólico nas primeiras, incluindo elevado índice de massa corporal (IMC), circunferência abdominal [29-33] e níveis pressóricos [29], perfil lipídico mais adverso [29,30], aumento de RI [29,30,32,33] e do produto da acumulação lipídica (LAP) [29,33], alteração da modulação simpática após estresse mental [33], além de maior prevalência de síndrome metabólica [29,32]. Entretanto, ao realizar ajuste para IMC, algumas diferenças (níveis pressóricos e perfil lipídico) entre os dois fenótipos desaparecem [29,32], sinalizando que a presença da obesidade (prevalência de até 43%) pode estar relacionada mais diretamente com o perfil metabólico mais adverso encontrado no fenótipo “clássico” [29].

A RI é uma condição prevalente na população com PCOS, presente em cerca de 85% destas mulheres (75% das mulheres eutróficas e 95% das mulheres com excesso de peso) [21]. Os mecanismos moleculares envolvidos na RI em PCOS ainda não estão completamente esclarecidos, mas parecem ser diferentes dos outros estados resistentes à insulina, como o diabetes *mellitus* tipo 2, e incluem um defeito intrínseco da sinalização do receptor insulínico, resultante do aumento da fosforilação à serina, e, por isto, acredita-se que esta condição exerça papel chave na fisiopatologia da PCOS [21,34]. A RI e a hiperinsulinemia compensatória são consideradas como o ponto central das alterações metabólicas vistas na síndrome [35]. A RI extrínseca (relacionada ao IMC) ocorre tanto em mulheres controles como nas mulheres com a síndrome, no entanto o IMC, nas mulheres com PCOS, tem um impacto mais potente na RI extrínseca do que o observado nas controles [21].

A obesidade é outra característica frequente em mulheres com PCOS, presente em cerca de 12,5% [36] a 70% [37] desta população, apresentando uma prevalência combinada estimada de 49% de acordo com uma recente meta-análise [12]. Mulheres com PCOS exibem maior deposição de gordura na região central em comparação a mulheres controles, independente do IMC [13,38,39] e, em média, 54% das mulheres PCOS apresentam obesidade central [12] a qual está mais intimamente relacionada às alterações vistas na

síndrome [39].

## ÍNDICES DE ADIPOSIDADE E RISCO CARDIOVASCULAR

Em razão da elevada prevalência de RI e da sua importância no desenvolvimento de alterações metabólicas na síndrome, o rastreamento de mulheres com PCOS com fatores de risco cardiometabólico é fundamental para medidas de prevenção e/ou tratamento ativo das comorbidades metabólicas. Neste sentido, torna-se relevante a busca por indicadores simples, não invasivos e de baixo custo que detectem alterações pré-clínicas.

Dentre os índices associados à adiposidade central, podemos citar a circunferência abdominal, uma medida antropométrica clássica, amplamente utilizada devido à praticidade e ao baixo custo, a qual reflete indiretamente a gordura visceral [40]. Em mulheres com PCOS, a circunferência abdominal isolada, além de ser considerada um importante marcador de obesidade central e de RI [14], também apresenta correlação positiva com gordura visceral [41]. Embora a circunferência abdominal correlacione-se fortemente com gordura visceral (mensurada por técnicas de imagem acuradas), quando utilizada isoladamente, é um índice de adiposidade total que pode não distinguir a gordura abdominal visceral da subcutânea, já que também apresenta correlação positiva com esta última [42]. Além disto, esta medida isolada pode super ou subestimar risco cardiovascular em indivíduos com diferentes alturas e circunferência abdominal semelhante [43]. Neste sentido, a utilização da razão cintura-estatura (RCE) para avaliação de risco cardiovascular poderia ser vantajosa. Este índice tem sido empregado para avaliação de risco cardiovascular tanto em crianças [44] quanto em adultos [45], sendo considerado um marcador de risco precoce mais sensível do que a combinação de IMC e circunferência abdominal [43]. Uma meta-análise publicada em 2012, incluindo dados de mais de trezentos mil indivíduos de diversos grupos étnicos, mostrou a superioridade da RCE sobre circunferência abdominal e IMC em detectar risco cardiometabólico tanto em homens quanto em mulheres [46]. Em mulheres

com PCOS, este indicador tem sido proposto para identificação de síndrome metabólica [47] e de dislipidemia [48,49]. No entanto, no estudo de Gateva e Kamenov (2012), embora a RCE tenha mostrado um ótimo desempenho na identificação de um conjunto de fatores de risco cardiovascular em mulheres com PCOS, a circunferência abdominal isolada também apresentou o mesmo desempenho [48].

O LAP, índice que relaciona níveis séricos de triglicerídeos e circunferência abdominal, foi descrito a primeira vez por Kahn em 2005 em um estudo que mostrou a superioridade deste marcador em identificar risco cardiovascular na população adulta americana comparado ao tradicional IMC [50]. Segundo Kahn (2009), o LAP refletiria a acumulação excessiva de lipídeos em outros tecidos que não o adiposo (como o tecido hepático, muscular, cardíaco) e por isto predizeria melhor que o IMC doença cardiovascular e diabetes *mellitus* tipo 2, visto que a superacumulação lipídica produz consequências cardiovasculares mais graves comparada à acumulação total de gordura [50,51]. Com relação a estudos em mulheres com PCOS, o LAP mostrou-se um índice acurado na identificação de risco cardiometabólico, utilizando diversos fatores como RI [52-54], tolerância diminuída à glicose [55], síndrome metabólica [56-58] e esteatose hepática não alcoólica [59]. Na menopausa, cujo risco para desenvolvimento de doença cardiovascular é aumentado comparado ao de mulheres em idade fértil [60], o LAP também pode ser considerado um marcador adequado para discriminar este risco, além de ser associado a níveis mais elevados de androgênios, diminuição da globulina carreadora dos hormônios sexuais (SHBG), marcadores de inflamação e RI nestas mulheres [61].

Em 2010, Amato e colaboradores propuseram o índice de adiposidade visceral (VAI), o qual combina medidas antropométricas (circunferência abdominal e IMC) e variáveis metabólicas [triglicerídeos e lipoproteína de alta densidade (HDL colesterol)], sendo considerado um indicador de alterações no tecido adiposo, de sensibilidade à insulina e de risco para eventos cardio e cerebrovasculares em indivíduos adultos saudáveis com IMC entre 20 e 30 kg/m² [62]. Em mulheres com PCOS, o VAI apresentou associação com

severidade de alterações menstruais [63], RI (avaliada por *clamp* euglicêmico hiperinsulinêmico) [64], além der ser um prático marcador para identificar tolerância diminuída à glicose em mulheres sem fatores de risco clássicos para diabetes [65]. Este indicador também se mostrou eficaz em distinguir um perfil metabólico mais favorável de um mais adverso ao aplicar o ponto de corte de 1,675 em mulheres com PCOS [66].

O índice de conicidade (índice C), proposto por Valdez em 1991, combina três medidas antropométricas em sua fórmula: peso, altura e circunferência abdominal [67]. A fundamentação para este modelo matemático é que algumas pessoas possuem padrão central de acumulação de gordura, alterando o desenho corporal de um cilindro para dois cones dispostos um sobre o outro, enquanto aquelas que não possuem padrão de acumulação de gordura ao redor do abdômen teriam aparência de um cilindro [68]. Estudos comparando índice C e diversos indicadores de obesidade como preditores de risco cardiovascular são contraditórios, relatando vantagem [68,69], igualdade [70] e até desvantagem [71] da utilização deste índice em comparação a outros marcadores de adiposidade. Em mulheres com PCOS, este índice, até o momento, foi pouco estudado, e, assim como na população em geral, também apresenta resultados divergentes sobre acurácia na identificação de risco cardiovascular [47,72,73].

Embora haja alguns estudos avaliando a acurácia da circunferência abdominal, da RCE, do LAP, do VAI e do índice C, todos foram compostos por um grupo geral de mulheres com PCOS, sem diferenciação entre os fenótipos. Considerando-se a heterogeneidade fenotípica das manifestações clínicas, hormonais e metabólicas [29,30,32,33], é plausível ponderar que exista diferença no desempenho destes marcadores nos diferentes fenótipos de PCOS. Neste sentido, tornam-se interessantes estudos que visem identificar o melhor índice que detecte precocemente sinais subclínicos de alterações metabólicas, ou seja, antes do estabelecimento da doença, permitindo a introdução de medidas terapêuticas adequadas, diminuindo, provavelmente, o risco de doença cardiovascular no futuro [52].

## HIPERANDROGENISMO, RESISTÊNCIA INSULÍNICA E OBESIDADE

O hiperandrogenismo é causado por secreção excessiva de androgênios pelos ovários e/ou adrenais (maiores sítios de produção androgênica nas mulheres) e está associado a manifestações clínicas como hirsutismo, acne e calvície de padrão masculino, resultado de anormalidades em todos os níveis do eixo hipotálamo-hipófise-ovário (figura 1) [74]. Na PCOS, há a produção exagerada destes hormônios, cujos mecanismos primários da produção androgênica ovariana são o aumento do hormônio luteinizante (LH) e a hiperinsulinemia devido à RI [75,76]. O aumento da frequência de pulsos de LH, vistos na PCOS, parece ser decorrente da frequência aumentada de pulsos do hormônio liberador de gonadotrofina hipotalâmica (GnRH). O favorecimento da produção de LH em detrimento da produção do hormônio folículo estimulante (FSH) ocasiona elevação na relação LH/FSH, estimulando a produção de androgênios pelas células da teca do ovário [74]. O aumento da eficiência na conversão de precursores androgênicos nas células da teca aumenta a produção de androstenediona, a qual é então convertida pela 17 β-hidroxiesteroide desidrogenase (17-βHSD) em testosterona ou aromatizada pela enzima aromatase para formar estrona. Dentro da célula da granulosa, a estrona é convertida em estradiol pela 17-βHSD [74,77]. Este excesso de androgênios inibe o crescimento do folículo dominante, ocasionando irregularidade menstrual, acúmulo de vários (>12) pequenos folículos (< 10 mm) na periferia do ovário (aparência policística) e anovulação, características da síndrome [77].

A insulina desempenha papel direto e indireto no hiperandrogenismo na PCOS [34,35]. Embora estas mulheres apresentem resistência periférica à insulina, a esteroidogênese ovariana parece ser hipersensível a este hormônio [78]. A hiperinsulinemia (decorrente da RI) estimula diretamente a produção de androgênios nos ovários ao ligar-se ao seu receptor nas células da teca, aumentando LH e fator de crescimento semelhante à insulina (IGF-1) [35,79]. A ação indireta da insulina ocorre pelo aumento da bioatividade

sérica do IGF-1, por meio da supressão da proteína de ligação do IGF-1, e pela redução da SHBG, principal proteína circulante que se liga à testosterona, resultando no aumento de androgênios biologicamente disponíveis [35,79].

A obesidade, principalmente a obesidade central, também age na produção de androgênios exacerbando a RI [34] e também aumentando a esteroidogênese periférica [80]. A obesidade central atua como estimulante para a atividade da 17-βHSD favorecendo a conversão de androstenediona em testosterona nos tecidos periféricos, como o adiposo [80], além de superestimular a ação da 5 α-redutase, aumentando a conversão de testosterona em dihidrotestosterona no tecido adiposo e no fígado [81,82].

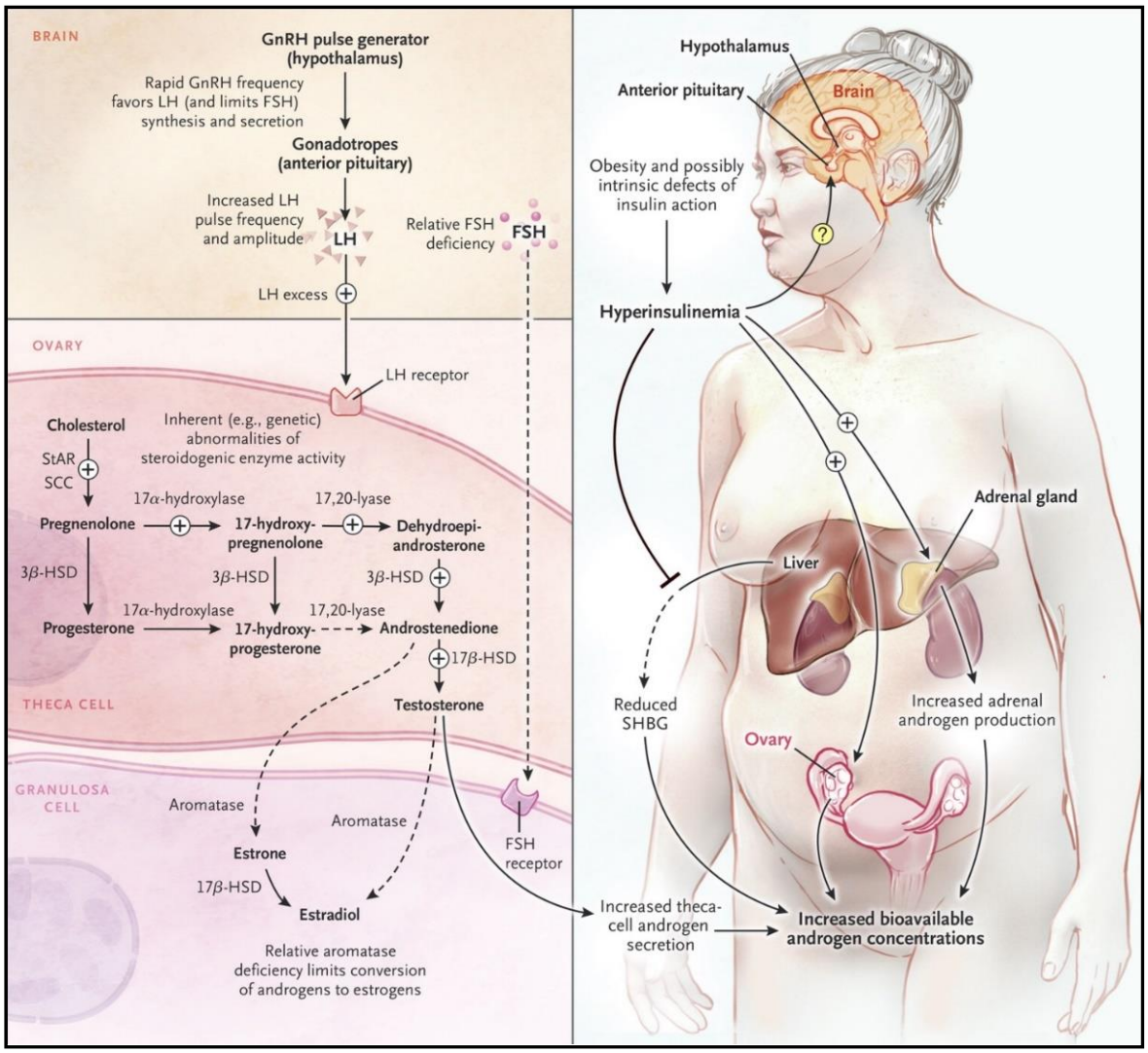


**Figura 1**. Fisiopatologia do hiperandrogenismo na PCOS [83]

Corbould e colegas demonstraram que pré-adipócitos rapidamente convertem androstenediona em testosterona e que a razão entre 17-βHSD tipo 3/aromatase no tecido adiposo omental possui correlação positiva com IMC [80]. Pesquisas recentes têm sugerido que a 17-βHSD tipo 5, e não a tipo 3, desempenha ação fundamental na síntese de androgênios no tecido adiposo [84,85].

Nos últimos anos tem sido demonstrada a capacidade do tecido adiposo em secretar uma variedade de proteínas com função hormonal conhecidas como adipocinas [86,87]. Em situações de estresse metabólico, como hiperandrogenismo ou ganho de peso, a expansão do tecido adiposo é alterada, sendo o processo de hipertrofia maior que o de hiperplasia, condição mais deletéria, visto que adipócitos hipertrofiados são mais suscetíveis a processos inflamatórios, apoptose, fibrose e liberação de ácidos graxos livres, situações que contribuem para a RI e consequente hiperinsulinemia vistas na PCOS [86]. Este distúrbio no processo de expansão do tecido adiposo também promove alteração na secreção de adipocinas, o que poderia influenciar a síntese de hormônios esteroides na PCOS [86,88,89].

Dentre as adipocinas, podemos destacar a leptina e a adiponectina, produzidas em maior quantidade pelo tecido adiposo e mais estudadas em PCOS [90]. A leptina age no controle do apetite, no gasto calórico por meio da sinalização entre o tecido adiposo e o sistema nervoso central [91,92], enquanto a adiponectina está envolvida na homeostase da glicose e dos lipídeos ao promover sensibilização à insulina, na resposta inflamatória (papel anti-inflamatório) e na regulação do balanço energético (papel anorexígeno) [92].

Em mulheres com PCOS, níveis séricos de leptina apresentam correlação negativa (independente do IMC e da razão insulina/glicose) com os níveis de LH, porém a mesma associação não é verificada no grupo de mulheres sem a síndrome [93]. Além disto, esta adipocina também é associada à obesidade e distúrbios metabólicos nestas mulheres [31,89,93,94]. Estudo de Lecke e colaboradores mostrou que mulheres com sobrepeso/obesidade, independente do diagnóstico de PCOS, quando comparadas a

mulheres de IMC eutrófico, apresentam valores maiores de leptina, sugerindo que esta adipocina está associada à adiposidade e não à presença de PCOS [94]. Outros estudos não verificaram diferença nos níveis de leptina entre mulheres com PCOS e controles com pesos semelhantes [31,89], no entanto, houve correlação positiva com IMC e com insulina e negativa com marcador de sensibilidade à insulina [89]. A presença de valores mais elevados nas mulheres com PCOS com sobrepeso/obesidade sugere que haja um estado de resistência à leptina [93]. Em relação aos níveis de adiponectina, estudos mostram diminuição [89] ou semelhança [94] nos valores entre mulheres com a síndrome e participantes controles. Um estudo considerando os diferentes fenótipos mostrou que mulheres com PCOS fenótipo "clássico" apresentam níveis inferiores de adiponectina, quando comparadas ao fenótipo "ovulatório" e a mulheres controles pareadas por IMC, no entanto este estudo não encontrou diferença entre mulheres com o fenótipo "ovulatório" e controles para esta adipocina [31]. Alguns autores sugerem que a relação leptina/adiponectina seja mais importante para a RI vista nas PCOS, do que níveis de adiponectina e leptina isolados [94,95].

## EXERCÍCIO FÍSICO E PCOS

Mudanças de estilo de vida (dieta e/ou exercício) são indicadas como primeira opção de tratamento para mulheres com PCOS objetivando a perda ou prevenindo o ganho de peso [96]. Reduções entre 5% a 10% do peso promovem melhora da RI, do hiperandrogenismo, do ciclo menstrual e da fertilidade nestas mulheres [97-99]. A prática de exercício físico estruturado é um importante componente para o tratamento do sobrepeso/obesidade na PCOS, sendo recomendados, pelo menos, 30 minutos diários, conforme diretriz da *Androgen Excess and Polycystic Ovary Syndrome Society* [100].

Ensaios clínicos randomizados que avaliaram o efeito do exercício físico estruturado (treino aeróbico, de resistência ou combinado) como única terapia não farmacológica

mostraram redução do IMC [101,102], da circunferência abdominal [101,103,104], da RI [101,103,105] e dos androgênios séricos [105,106], além de melhora do perfil lipídico [colesterol total [103], HDL colesterol [102,103,105], lipoproteína de baixa densidade (LDL colesterol) [103] e triglicerídeos [102,107] após intervenções com duração entre 8 a 16 semanas. Nestes estudos, foram selecionadas mulheres com PCOS eutróficas e com sobrepeso/obesidade, sugerindo que a prática do exercício físico estruturado produz alterações benéficas não somente às mulheres com excesso de peso, mas também às eutróficas. Os benefícios da prática de exercício físico estruturado em mulheres com PCOS também é evidenciado com diminuições discretas no IMC (2-5%) [108] e, até mesmo, na ausência de perda de peso [105,107]. Recentes meta-análises confirmam os dados de estudos individuais, de que o exercício físico estruturado é eficaz na redução do IMC, da circunferência abdominal, da razão cintura-quadril [109], além de melhora da aptidão física (105) e dos parâmetros do hiperandrogenismo, como redução dos níveis de testosterona total e do hirsutismo e aumento de SHBG em mulheres com PCOS [110].

Orio e colaboradores (2008) avaliaram o efeito do exercício físico em dois grupos de mulheres com PCOS por 12 semanas. Após este período, um grupo permaneceu realizando exercício físico por mais 12 semanas, enquanto o outro cessou o treinamento durante o mesmo tempo. Os pesquisadores relataram que, após estas 12 semanas sem exercício, houve perda completa das adaptações favoráveis produzidas pelo treinamento, mostrando a importância da manutenção deste hábito nas mulheres com PCOS [111].

Embora o exercício físico estruturado promova perda de peso e melhora dos parâmetros hormonal e metabólico e da fertilidade, a continuidade desta prática a longo prazo é um ponto crítico deste tipo de intervenção. Entre mulheres em idade reprodutiva (18 a 44 anos), menos de um terço relata praticar exercício físico regularmente [112], sendo este percentual também não adequado quando consideradas apenas mulheres com PCOS [113]. Estudos sobre o efeito do exercício físico em mulheres com PCOS apresentam taxas de desistência de até 45% [107], comprometendo a manutenção, a longo prazo, dos benefícios

adquiridos durante a intervenção [111]. Neste sentido, a busca por atividades que se insiram dentro do cotidiano é uma alternativa para a incorporação e a manutenção, a longo prazo, de um estilo de vida mais ativo.

## ATIVIDADE FÍSICA HABITUAL

Segundo Caspersen, Powell e Christensen (1985), a atividade física é definida como qualquer movimento corporal produzido pelo músculo esquelético que resulte em gasto energético, diferenciando-se do exercício físico em razão deste ser uma atividade física planejada, repetitiva e estruturada com o objetivo de manter ou melhorar a capacidade física [114].

Como a caminhada é a forma mais comum de atividade diária e está inserida em outros tipos de atividade física [115], é possível estimar de forma objetiva e com acurácia aceitável [116], através do uso do pedômetro, a atividade física habitual de uma pessoa [117,118]. Além disto, a caminhada permanece como atividade de lazer mais comumente praticada [119]. Dados de 37.878 mulheres do *Women's Health Study* mostrou que caminhar entre duas a três horas/semana está associado à redução de 34% na incidência de diabetes *mellitus* tipo 2 em quase sete anos de acompanhamento [120].

O pedômetro é um dispositivo simples, relativamente barato e de fácil uso, utilizado para mensurar atividades ambulatoriais (caminhadas, corridas) por meio da contagem do número de passos, em razão da sua sensibilidade às acelerações verticais do centro de gravidade corporal [121]. Além de ser mais sensível a atividades ambulatoriais, ele oferece tecnologia mais acessível, facilidade de manuseio e de interpretação de dados, tanto para o pesquisador quanto para o usuário [122]. Recomendações para atividade física baseada na contagem de passos podem ser mais apropriadas e melhor recebidas pelo grande segmento da população que não se envolve em qualquer esporte ou exercício, exceto a caminhada [123]. O pedômetro, inicialmente utilizado como uma ferramenta para mensurar atividade

física, tem sido amplamente utilizado como um instrumento de intervenção para estimulá-la [124]. Maior nível de atividade física, mensurada por pedômetro, está associado a menor risco de disglicemia [125], síndrome metabólica [126], além de ser inversamente associado à mortalidade por todas as causas [127]. O estilo de vida mais ativo, em uma população de mulheres em idade fértil sem comorbidades, está associado a menor IMC e a escolhas alimentares mais saudáveis [128].

Em razão da variablidade entre os grupos etários, Tudor-Locke e Bassett (2004) propuseram pontos de corte para classificação do nível de atividade física conforme cada faixa etária, sendo indicado para adultos (entre 20 e 65 anos) o descrito na tabela 2 [129].

**Tabela 2.** Pontos de corte para classificação do nível de atividade física em adultos (20 a 65 anos)

| Número de passos/dia | Classificação |
|---|---|
| < 5000 | Sedentário |
| 5000-7499 | Baixa atividade |
| 7500-9999 | Com algum grau de atividade |
| 10000-12499 | Ativo |
| 12500 | Muito ativo |

Adaptado de Tudor-Locke e Bassett, 2004 [129]

Embora o objetivo de 10000 passos/dia possa ser considerado factível para adultos e seja associado a benefícios à saúde, algumas populações menos ativas ou com alguma incapacidade podem apresentar dificuldades em atingi-lo [130]. Neste sentido, o ponto de corte de 7500 passos/dia está emergindo como uma meta viável, em razão dos benefícios relacionados e por atingir as recomendações para prática de exercício físico [123,131].

O ponto de corte de 7500 passos/dia foi associado à redução de 50% na prevalência de depressão comparado a 5000 passos diários, não sendo verificado nenhum benefício

adicional para depressão em níveis mais elevados de atividade física em mulheres [132]. Na pós-menopausa, níveis diários de atividade física entre 7500 e 9999 foram associados a um IMC significativamente menor comparados a níveis inferiores a 7500 passos, não sendo encontrado benefício adicional, em relação ao IMC, em quem caminha mais de 10000 passos/dia [132]. No entanto, para algumas populações com alto risco para doença cardiovascular, como diabéticos tipo 2 ou hipertensos, 10000 passos/dia têm sido recomendados para obtenção de melhora na sensibilidade à insulina [133], na pressão arterial e na atividade simpática [134]. Pontos de corte mais baixos, como 6000 passos/dia, têm sido associados à diminuição do risco de doença cardiovascular e de diabetes tipo 2 em mulheres de meia-idade, independentemente do *status* menopausal, numa coorte do sul do Brasil [135]. Este mesmo ponto de corte também é associado a um perfil cardiovascular mais favorável em mulheres na menopausa em uso de terapia hormonal [136].

O resultado de uma meta-análise, cujo objetivo foi avaliar a associação entre o uso do pedômetro e o nível de atividade física na população adulta, evidenciou que o estabelecimento de metas é uma forma de estimular a prática de exercício físico, sendo o pedômetro um instrumento eficaz na promoção do aumento da atividade física [137]. Esta mesma meta-análise concluiu que o aumento da atividade física promovida pelo uso do pedômetro (aproximadamente 2500 passos/dia) está associado à diminuição da pressão arterial e do peso [137]. Este incremento no número de passos reduziria entre 37 a 45 minutos/dia o tempo gasto em atividades sedentárias [138]. Na população jovem, uma revisão sistemática também sugeriu que o uso do pedômetro associado a uma meta é ferramenta útil de incentivo à prática de atividade física, especialmente entre adolescentes sedentários, no entanto, somente o uso do dispositivo não é suficiente para promover mudanças neste comportamento [139].

Dados de um grande estudo internacional (*Nateglinide And Valsartan in Impaired Glucose Tolerance Outcomes Research* - NAVIGATOR) mostraram que o aumento de 2000 passos/dia também é associado à redução do escore de síndrome metabólica [140], do risco

para eventos cardiovasculares (10%) e de doença cardiovascular (8%), independente do peso corporal e do nível de atividade física basal, em indivíduos com alto risco para diabetes *mellitus* tipo 2 [141]. Em mulheres menos ativas (que caminham diariamente menos de 10000 passos) o aumento de 2000 passos/dia está associado a maiores reduções da circunferência abdominal e do IMC, sendo este declínio maior para aquelas que eram sedentárias ou apresentavam menor contagem de passos diários [142]. Dois mil passos podem ser traduzidos, grosseiramente, como 20 minutos de caminhada de intensidade moderada [129], meta factível para populações com maior risco cardiovascular, como obesos e sedentários.

Considerando-se que a RI desempenha um papel central nas alterações metabólicas e hormonais associadas à PCOS e que a heterogeneidade entre os fenótipos impacta diretamente as manifestações clínicas, hormonais e metabólicas, na presente tese realizamos dois estudos relacionados com índices de adiposidade central e atividade física habitual, respectivamente, em mulheres com PCOS.

O objetivo do primeiro estudo foi avaliar o desempenho da circunferência abdominal, RCE, índice C, LAP e VAI, utilizando o modelo de homeostasia de resistência à insulina (HOMA-IR)≥ 3,8 como padrão de referência para o rastreamento de alterações metabólicas pré-clínicas e fatores de risco cardiovascular nos fenótipos “clássico” e “ovulatório” de PCOS. Em razão da alta prevalência de obesidade e de outras comorbidades associadas em mulheres com a síndrome, intervenções baseadas em mudanças de estilo de vida, incluindo dieta e/ou exercício físico, são consideradas primeira opção de tratamento não farmacológico. A prática de, pelo menos, 30 minutos diários de exercício é recomendada pela *Androgen Excess and Polycystic Ovary Syndrome Society*, no entanto, a manutenção deste hábito a longo prazo ainda é um ponto crítico. Neste contexto, a atividade física habitual, até o momento não avaliada nesta população, pode ser uma alterantiva viável para que estas mulheres adotem um estilo de vida mais ativo e obtenham os benefícios proporcionados pelo exercício físico. Desta forma, o objetivo do segundo estudo

foi avaliar o efeito da atividade física habitual (avaliada com o uso do pedômetro) no perfil antropométrico, metabólico e hormonal das mulheres com PCOS.

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## CAPÍTULO 1

# Adiposity indexes as phenotype-specific markers of preclinical metabolic alterations and cardiovascular risk in polycystic ovary syndrome: a cross-sectional study

**Running title:** Adiposity indexes in PCOS phenotypes

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**Abstract**

Polycystic ovary syndrome (PCOS) is a common condition in women of reproductive age. Two PCOS phenotypes (classic and ovulatory) are currently recognized as the most prevalent, with important differences in terms of cardiometabolic features. We studied the performance of different adiposity indexes to predict preclinical metabolic alterations and cardiovascular risk in 234 women with PCOS (173 with classic and 61 with ovulatory PCOS) and 129 controls. Performance of waist circumference, waist-to-height ratio, conicity index, lipid accumulation product, and visceral adiposity index was assessed based on HOMA-IR ≥ 3.8 as reference standard for screening preclinical metabolic alterations and cardiovascular risk factors in each group. Lipid accumulation product had the best accuracy for classic PCOS, and visceral adiposity index had the best accuracy for ovulatory PCOS. By applying the cutoff point of lipid accumulation product < 34, we identified a subgroup of patients without cardiometabolic alterations ($P<0.05$) in the group with classic PCOS, a population at higher risk for hypertension, dyslipidemia, and impaired glucose tolerance. In ovulatory PCOS, visceral adiposity index ≥ 1.32 was capable of detecting women with significantly higher blood pressure and less favorable glycemic and lipid variables as compared to ovulatory PCOS with lower visceral adiposity index ($P< 0.05$). These results suggest LAP ≥ 34 as the best marker for classic PCOS, and VAI ≥ 1.32 for ovulatory PCOS women. Both indexes can be easily calculated with measures obtained in routine clinical practice and may be useful to detect cardiometabolic risk and secure early interventions.

**Keywords** PCOS, insulin resistance, anovulation, lipid accumulation product, visceral adiposity index, accuracy test.

## Introduction

Polycystic ovary syndrome (PCOS), characterized by clinical and/or biochemical androgen excess, ovulatory dysfunction, and polycystic ovaries, is the most prevalent endocrine disorder among women of reproductive age, affecting an estimated 6% to 19% of this population, depending on diagnostic criteria [1,2]. PCOS is associated with higher cardiometabolic risk resulting from the presence of obesity [3,4], abdominal obesity [5-7], dyslipidemia [8], metabolic syndrome [9-11], impaired glucose tolerance (IGT) [9,12,13], and insulin resistance (IR) [14,15]. The risk of type 2 diabetes (T2DM) is also higher in PCOS [9,12]. IR and the ensuing compensatory hyperinsulinemia, which play a key role in the pathophysiology of PCOS, have been linked to cardiovascular (CV) risk factors in these women [16,17]. In this sense, there is great interest in screening women with PCOS for cardiometabolic risk in order to actively prevent and/or treat metabolic comorbidities.

Growing recognition of the complexity of PCOS has led to the characterization of several PCOS phenotypes [18]. Among these phenotypes, classic PCOS (c-PCOS) is characterized by the presence of oligo/amenorrheic or anovulatory cycles associated with clinical or biochemical hyperandrogenism, with or without polycystic ovary appearance (PCO) on ultrasound. In turn, the ovulatory PCOS phenotype (ov-PCOS) is defined by the presence of hyperandrogenism and PCO appearance at ultrasound in ovulatory women [19]. Hyperandrogenism is a key factor in the pathophysiology of PCOS, with more pronounced androgen excess status linked to more “severe” features that are found more often in c-PCOS as compared to ov-PCOS, along with higher prevalence of cardiometabolic risk factors [7,20-24].

There have been recent reports regarding the potential usefulness of various adiposity indexes for the screening of cardiometabolic risk in PCOS [6,10,25-32]. These inexpensive and simple to use indexes include waist circumference (WC) [6], lipid accumulation product (LAP) [10,29,30,33,34], visceral adiposity index (VAI) [25,31,32,34], waist-to-height ratio (WHtR) [26,28], and the conicity index (C-index) [27]. However, until

now, no study has assessed the accuracy of these indexes to determine cardiometabolic risk in different PCOS phenotypes.

Therefore, the aim of the present study was to assess the performance of WC, WHtR, C-Index, LAP, and VAI for the screening of preclinical metabolic alterations and cardiovascular risk factors in women with the c-PCOS and ov-PCOS phenotypes.

## Materials and Methods

*Patients and controls*

This cross-sectional study was carried out at the Gynecological Endocrinology Unit of Hospital de Clínicas de Porto Alegre, Brazil. Candidates with PCOS were recruited through public advertisement (woman of reproductive age with hirsutism and irregular menses or hirsutism and regular menses) or referred to our outpatient clinic for investigation of menstrual dysfunction or hair excess during the period between 2007 and 2012. Inclusion criteria were body mass index (BMI) ranging from 18.5 to 39.9 kg/m$^2$, age between 14-40 years, onset of menarche at least two years before enrollment, and no intake of drugs known to interfere with hormonal profile for at least 3 months before the study. Exclusion criteria were non-classic congenital adrenal hyperplasia, Cushing's syndrome, androgen-secreting neoplasms, thyroid disorders, hyperprolactinemia, and diabetes (fasting glucose levels ≥126 mg/dL or 2-hour glucose levels ≥ 200 mg/dL or previous use of antidiabetic drugs beyond metformin). Women with liver or renal disease, and pregnancy were also excluded.

PCOS diagnosis was based on Rotterdam criteria [18]. c-PCOS was defined as oligo- or amenorrheic cycles (9 or fewer cycles/year) associated with hirsutism and/or increased levels of serum testosterone and/or free androgen index (FAI) (testosterone levels and/or FAI above + 2 standard deviation of levels detected in the control group) [7] , and absence of other disorders causing hirsutism, with or without PCO at ultrasound. ov-PCOS was considered in women with clinical or biochemical hyperandrogenism, PCO and ovulatory cycles (confirmed by luteal phase progesterone levels higher than 3.8 ng/mL). The diagnosis

of PCOS in adolescent girls was defined by the presence of clinical and/or biochemical hyperandrogenism and persistent oligomenorrhea [22].

The control group was recruited through public advertisement. As with the PCOS group, women with BMI ranging from 18.5 to 39.9 kg/m$^2$ and age between 14-40 years were enrolled at least two years after menarche. Participants in the control group did not have hyperandrogenism, and had regular and ovulatory menstrual cycles (luteal phase progesterone higher than 3.8 ng/mL) as well as normal appearance of the ovaries at pelvic ultrasound. The exclusion criterion was diabetes (fasting glucose levels ≥126 mg/dL or 2-hour glucose levels ≥ 200 mg/dL or previous use of antidiabetic drugs beyond metformin).

All women gave written informed consent for the scientific use of their data, and the study protocol was approved by the local Institutional Review Board.

*Study protocol*

Anthropometric measures included weight (in kg, patients dressed light clothes), height (m) and WC (measured at the midpoint between the lower rib margin and the iliac crest). A digital sphygmomanometer with an appropriate cuff for the arm diameter (Omron HEM 742, Rio de Janeiro, Brazil) was used to determine systolic and diastolic blood pressure. Blood pressure was measured twice for each patient and anthropometric measurements were performed in duplicate by two trained investigators. The mean of two measurements was considered for the study.

The following adiposity indexes were calculated: BMI (current weight in kg divided by height in m$^2$); WHtR (waist circumference in cm divided by height in cm); LAP index ([waist circumference in cm – 58] x triglyceride concentration in mmol/L) [10,35]; and VAI (waist circumference in cm/36.58 + [1.89 x BMI in kg/m$^2$] x [triglycerides/0.81] x [1.52 / high-density lipoprotein cholesterol in mmol/L]) [36]. The C-index was calculated according to the formula: C-index = WC (in m) / 0.109 x square root of weight (in kg) / height (in m) [37].

Hirsutism was defined as a Ferriman-Gallwey score ≥ 8 [38]. Homeostasis model assessment of insulin resistance (HOMA-IR) index was used as a surrogate measure of IR.

The cutoff point to define IR was HOMA-IR ≥ 3.8 [6,39].

Total testosterone, sex hormone-binding globulin (SHBG), total and high-density lipoprotein (HDL) cholesterol, triglycerides, oral glucose tolerance test (oGTT), and insulin levels were determined based on a 12h fasting blood sample. All samples were obtained between 8AM and 10AM. Laboratory tests were performed in the follicular phase (between days 2 and 8 of the menstrual cycle) of a spontaneous menstrual cycle or on any day if the patient was in amenorrhea. Progesterone was determined in the luteal phase (between days 20-24 for participants with regular cycles) or on any day if the patient was in amenorrhea. The metabolic syndrome was diagnosed based on the Joint Scientific Statement [40]. The maximum interval between anthropometric measures and carrying out laboratory tests for the calculation of adiposity indices and for HOMA-IR was 2 weeks.

*Assays*

Total cholesterol, HDL cholesterol, and triglycerides were determined by colorimetric-enzymatic methods (Bayer 1800 Advia System, Mannheim, Germany), with intra and interassay coefficients of variation (CV) < 3%. Glucose was determined by the hexokinase method (Bayer 1800 Advia System, Mannheim, Germany) with intra-assay CV < 3.4% and interassay CV < 2.1%. Total testosterone levels were measured by chemiluminescence immunoassay (CLIA) (Siemens Centaur XP, Deerfield, USA), with sensitivity of 0.10 ng/mL and intra and interassay CV of 3.3% and 7.5% respectively. SHBG was measured by CLIA (Immulite 2000 Siemens, Deerfield, USA), with sensitivity of 0.02 nmol/L and intra- and interassay CV of 5.3% and 6.6% respectively. Progesterone was measured by CLIA (Siemens Centaur XP, Deerfield, USA) with a sensitivity of 0.21 ng/mL and intra- and interassay CV of 7.2% and 5.7% respectively. Serum insulin levels were measured using CLIA (Siemens Centaur XP, Deerfield, USA), with a sensitivity of 0.2 μIU/mL and intra- and interassay CV of 2.0% and 4.3% respectively. FAI was estimated by dividing total testosterone (nmol/L) by SHBG (nmol/L) × 100. Low-density lipoprotein (LDL) cholesterol was determined indirectly using the Friedewald formula: LDL = total cholesterol – HDL

cholesterol – (triglycerides / 5) [41]. HOMA-IR index was calculated by multiplying insulin (μIU/mL) by glucose (mmol/L) and dividing this product by 22.5 [42].

*Pelvic ultrasound*

Ovarian morphology was assessed in all participants by transvaginal ultrasound (or transabdominal ultrasound in girls who were not sexually active) between the 2nd and 8th day in women with regular cycles and on any day for those with oligo- or amenorrhea. PCO was defined by the presence of 12 or more follicles (measuring 2-9 mm in diameter) and/or ovarian volume greater than 10 mL [18].

*Statistical analysis*

Data were expressed as means ± standard deviation (SD), or medians and inter-quartile range (25-75). Categorical variables were expressed as percentage and absolute number. Comparisons between percentages were performed by using Chi-square or Fisher's exact test when appropriate. Analyses were adjusted for BMI by Poisson regression. Variables without normal distribution were log-transformed for statistical analysis and back-transformed into their original units for presentation. One-way ANOVA followed by Tukey test was performed for comparisons between the three groups (c-PCOS, ov-PCOS, and controls), and analyses were adjusted for BMI by ANCOVA and Bonferroni test. Pearson correlation coefficients were calculated between adiposity indexes and HOMA-IR.

Receiver operating characteristic (ROC) curve analyses were performed for LAP, WC, WHtR, C-index, and VAI to assess cardiometabolic risk defined as HOMA-IR ≥ 3.8 [43]. The highest sensitivity and specificity indicated the optimal cutoff value for each adiposity index, estimated by the Youden index [44]. The performance of each adiposity index cutoff point was determined by sensitivity (S), specificity (SP), positive (PPV) and negative (NPV) predictive values. The choice of the best adiposity index in each group was based on the balance between sensitivity and specificity, and on decreasing misclassification cost [45].

Associations between adiposity indexes and HOMA-IR≥ 3.8 were analyzed by Poisson regression with robust variance (adjusted for BMI) and expressed as prevalence

ratio. Student's t-test was performed to compare metabolic and hormonal variables into c-PCOS women stratified by the cutoff of LAP and in ov-PCOS participants stratified by the cutoff of VAI.

The Statistical Package for the Social Sciences (SPSS version 20) (Armonk, NY, USA) was used for analysis. A P-value < 0.05 was considered to be statistically significant.

## Results

*Clinical, hormonal and metabolic features*

Two hundred and thirty-four women were diagnosed with PCOS: 173 were classified as c-PCOS and 61 as ov-PCOS. The control group included 129 ovulatory, non-hirsute women with normal androgen levels. HOMA-IR was assessed in 169 c-PCOS (98%), 58 ov-PCOS (95%) and 106 controls (82%) because of missing values in some participants. Table 1 presents the clinical, metabolic, and hormonal features of women in the three groups. Mean age was similar in all groups. c-PCOS participants had higher BMI, blood pressure, FAI, and total testosterone, and a worse lipid profile than participants in other groups. After adjustment for BMI, all variables except total, HDL, and LDL cholesterol remained significantly higher in the c-PCOS group. Fasting glucose was similar in the three groups, but 2-hour glucose, fasting insulin, and HOMA-IR were higher in c-PCOS. Metabolic syndrome was significantly more prevalent in c-PCOS than in the other groups. After adjustment for BMI, fasting insulin and HOMA remained significantly higher in c-PCOS, but 2-hour glucose and metabolic syndrome lost significance.

*Correlations between HOMA-IR and adiposity indexes*

In the three groups, adiposity indexes presented moderate and positive correlations with HOMA-IR, except for C-index, which presented a weak, but still significant, positive correlation with HOMA-IR (Table 2).

*ROC curves*

ROC curves including all participants were generated (participants with missing

values for HOMA-IR were not included) (Figure 1A). This analysis revealed that the best marker of cardiometabolic risk defined as HOMA-IR ≥ 3.8 was LAP, with an area under the curve (AUC) of 0.78 (95% CI: 0.72-0.84), followed by WC, with AUC of 0.75 (95% CI: 0.69-0.82), WHtR (AUC: 0.75; 95% CI: 0.65-0.79), VAI (AUC: 0.72; 95% CI: 0.67-0.78), and C-index (AUC: 0.68; 95% CI: 0.61-0.75) (Figure 1B). After adjustment for BMI, all AUC for adiposity indexes maintained moderate accuracy: LAP (AUC: 0.78, 95% CI: 0.72-0.83), VAI (AUC: 0.77, 95% CI: 0.71-0.83), WHtR (AUC: 0.76, 95% CI: 0.71-0.82), WC (AUC: 0.75, 95% CI: 0.69-0.81), and C-index (AUC: 0.75, 95% CI: 0.69-0.80). Based on ROC curve analysis, the optimal cutoff point was 34 for LAP, 87.3 cm for WC, 0.56 for WHtR, 1.32 for VAI, and 1.19 for C-index (Figure 1B).

*Sensitivity, specificity, positive and negative predictive values for adiposity indexes according to PCOS phenotypes and control group*

Table 3 summarizes S, SP, PPV, and NPV for adiposity indexes in all groups, using the cutoff values obtained with ROC curve analysis. In the c-PCOS group, the best combination between sensitivity and specificity was obtained for LAP, whereas in the ov-PCOS group, the best combination was obtained for VAI. Thus, LAP ≥ 34 presented the best performance to detect cardiometabolic risk in c-PCOS, while VAI ≥ 1.32 performed better in the ov-PCOS and normal control groups.

*Prevalence ratio of HOMA-IR ≥ 3.8 among adiposity indexes in c-PCOS and ov-PCOS*

In c-PCOS, the prevalence ratio of HOMA-IR≥ 3.8 was higher by using the LAP [2.6 (95% CI: 1.6-4.1)] that other adiposity indexes (Table 4). In ov-PCOS, only VAI presented significant prevalence ratio of HOMA-IR ≥ 3.8 [3.3 (95% CI: 1.2-9.1)] (Table 4).

*Screening of cardiometabolic risk using the cutoff points for LAP and VAI in PCOS phenotypes*

c-PCOS and ov-PCOS women were analyzed according to the LAP and VAI cutoff points on order to test the ability of these indexes to detect cardiometabolic risk in each specific phenotype (Tables 5 and 6). c-PCOS women with LAP ≥ 34 presented a significantly

worse lipid profile as well as higher waist circumference, fasting and 2-hour glucose levels, and HOMA-IR than c-PCOS with LAP < 34, even after adjustment for BMI (Table 5). Among ov-PCOS women, those with VAI ≥1.32 had significantly higher diastolic blood pressure levels and HOMA-IR, as well as worse lipid profile than those with lower VAI (P< 0.05); these differences remained significant after adjustment for BMI (Table 6).

**Discussion**

In the present study, we found that the ability of adiposity indexes to predict cardiometabolic risk varied according to PCOS phenotype: in c-PCOS, LAP was the best marker of cardiometabolic risk, vs. VAI in ov-PCOS. To the best of our knowledge, this is the first study to specifically examine the performance of adiposity indexes according to PCOS phenotype.

The selection of the most appropriate adiposity index relied on balancing maximum sensitivity and specificity to address specific features of each phenotype. c-PCOS patients are likely to have higher prevalence of cardiometabolic risk factors [7,20-24], and the early recognition of this condition facilitates primary prevention. Hence, higher specificity may decrease the number of false-positive cases or, in other words, c-PCOS with LAP ≥ 34 have a low probability of not presenting cardiometabolic risk.

In contrast, ov-PCOS patients are less prone to present metabolic comorbidities. Thus, beyond the balance between sensitivity and specificity, screening measures should present the highest possible sensitivity; the present results indicate that ov-PCOS with VAI < 1.32 have low probability of having cardiometabolic risk.

Consistent with this approach, we chose a high HOMA-IR cutoff point of at least 3.8 as the reference indicator of cardiometabolic risk for testing the performance of adiposity indexes in order to prevent overestimate the presence of IR. Indeed, previous studies have employed similar [6,39] or lower values [33,34]. In addition, PCOS women with diabetes were excluded from this study because the presence of diabetes *per se* implies increased

cardiometabolic risk. Moreover, it is well recognized that HOMA-IR is not accurate in diabetic subjects, as they present a mixed condition of insulin resistance and decreased β-cell function [46].

We have previously shown that LAP is useful for screening IR in PCOS [10]. In that first study, which included both c- and ov-PCOS patients, we found that LAP ≥ 34.5 was more accurate than BMI, non-HDL cholesterol, or WC as predictor of increased HOMA-IR. Not only was that observation confirmed in the present study, it was also enhanced by the finding that specific markers should probably be used for different phenotypes, with VAI presenting higher accuracy in ov-PCOS.

In addition, a population-based study comparing various adiposity indexes for screening IR and metabolic syndrome in PCOS has reported that while LAP and VAI were equally adequate to identify IR, WC and VAI were better markers of the metabolic syndrome [34]. However, despite the stratification of PCOS participants into three different phenotypes, the performance of the indexes was analyzed in that study only for the overall PCOS group. Other studies also found LAP to be a reliable index to identify metabolic syndrome in PCOS [30,47,48]. Indeed, although WC presents good correlation with abdominal adipose tissue, it cannot differentiate subcutaneous from visceral fat [49], an aspect that has major implications for cardiovascular disease [50,51]. In contrast, VAI and LAP have been reported to positively correlate with visceral adipose tissue [31,36,52].

Wehr *et al.* have evaluated the accuracy of LAP, WC, and BMI to estimate the risk of IGT and their relationship with metabolic parameters and body fat distribution in PCOS and control women [29]. LAP was found to be the best predictor of IGT in both groups and was better correlated with body fat, glucose, and HOMA-IR than BMI and waist-hip ratio [29]. In that study, both PCOS and control patients were older than our patients; also, ROC curves were generated to predict IGT and not IR. These aspects may explain the higher LAP cutoff of 44.1 reported by Wehr *et al.* (2011) [29].

In the present study, VAI presented good performance for screening IR in ov-PCOS

patients and normal controls. These groups were similar in terms of some metabolic variables. In fact, evidence suggests that the clinical impact and severity of metabolic alterations is mild in ov-PCOS [7,20,53]. Because of this milder risk, it is possible to speculate that an index including more risk factors in its formula, such as VAI, may offer additional information about risk. Interestingly, when ov-PCOS women were stratified by VAI cutoff point, those in the higher VAI *stratum* clearly presented a worse cardiometabolic profile, with higher diastolic blood pressure levels and less favorable lipid variables and HOMA-IR, even after adjustment for BMI. A recent study has shown that LAP, and mainly VAI, were better than anthropometric markers of obesity (BMI, WC, waist-to-hip ratio, WHtR) to identify metabolically obese normal-weight individuals [54].

Previous studies in PCOS have shown that VAI is an independent predictor of IR (assessed by euglycemic hyperinsulinemic clamp) [31] and a practical index for detecting altered glucose tolerance in PCOS women without traditional risk factors for diabetes [55]. A prior study evaluating metabolically healthy *versus* metabolically unhealthy women with PCOS evidenced that VAI was the best predictor for detecting an adverse metabolic profile in these women [25]. In the general population, VAI presented a strong positive correlation with insulin sensitive (euglycemic hyperinsulinemic clamp) and was independently associated with cardio- and cerebrovascular events [36].

Our c-PCOS group had worse metabolic profile in comparison with ov-PCOS and control participants, even after adjustment for BMI. This is in agreement with many other studies [5,7,12,19-24,53,56]. Interestingly, applying the LAP cutoff point allowed us to identify a subgroup with no altered cardiometabolic variables in this population at higher risk for hypertension, dyslipidemia, and IGT.

One of the limitations of the present study is that euglycemic hyperinsulinemic clamping [57], the gold standard for assessment of IR, was not employed. Nevertheless, HOMA-IR is well correlated with the clamp [58] and has been shown to be significantly and independently associated with risk of CV disease [59-61]. Another limitation of this study is its

cross-sectional design, which does not allow conclusions regarding cause and effect. Finally, because PCOS women with both classic and ovulatory phenotypes were hyperandrogenic, we were unable to analyze the accuracy of adiposity indexes in the normoandrogenic PCOS phenotype. However, current evidence [21, 24, 39] indicates that the prevalence of cardiovascular risk factors and metabolic comorbidities in normoandrogenic PCOS women is lower than that of hyperandrogenic PCOS phenotypes.

In conclusion, considering the heterogeneity between PCOS phenotypes, which impacts clinical and metabolic manifestations, the present findings suggest that different adiposity indexes should be used to predict cardiometabolic risk in c-PCOS and ov-PCOS. Data from the present study suggest LAP ≥ 34 as the best marker for c-PCOS, and VAI ≥ 1.32 for ov-PCOS and non-hirsute ovulatory women. Both these indexes, which can be easily calculated with measures commonly obtained in clinical practice, may be useful to detect cardiometabolic risk and secure early interventions.

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**Conflict of interest**

The authors declare that they have no competing interests**.**

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**Table 1.** Clinical, hormonal, and metabolic features of classic and ovulatory PCOS phenotypes and controls

| Variables | PCOS (n=234) | | Controls (n=129) | P | P* |
|---|---|---|---|---|---|
| | Classic (n=173) | Ovulatory (n=61) | | | |
| **Age (years)** | 23±6 | 23±7 | 24±7 | 0.132 | - |
| **BMI (kg/m²)** | 31.4±6.9[a] | 26.6±4.8[b] | 26.5±5.9[b] | 0.001 | - |
| **WC (cm)** | 92.6±15.6[a] | 81.0±10.9[b] | 80.5±12.4[b] | 0.001 | 0.003 |
| **SBP (mmHg)** | 122±16[a] | 117±12[b] | 110±12[b] | 0.031 | 0.001 |
| **DBP (mmHg)** | 79±10[a] | 74±12[b] | 71±9[b] | 0.001 | 0.001 |
| **Fasting glucose (mg/dL)** | 90±16 | 85±9.3 | 87±7 | 0.058 | 0.370 |
| **Glucose 2 hour (mg/dL)** | 110±26[a] | 98±24[b] | 95±20[b] | 0.007 | 0.052 |
| **Fasting insulin (µUl/mL)** | 18 (12-28)[a] | 12 (6-18)[b] | 11 (7-15)[b] | 0.001 | 0.001 |
| **HOMA-IR index** | 3.9 (2.5-6.6)[a] | 2.5 (1.4-4.0)[b] | 2.1 (1.4-3.1)[b] | 0.001 | 0.001 |
| **Total cholesterol (mg/dL)** | 179±40[a] | 164±28[b] | 170±29[b] | 0.012 | 0.309 |
| **HDL-c (mg/dL)** | 46±11[a] | 52±11[b] | 51±11[b] | 0.003 | 0.117 |
| **LDL-c (mg/dL)** | 109±33[a] | 95±26[b] | 102±25[a,b] | 0.005 | 0.263 |
| **Triglycerides (mg/dL)** | 101 (67-138)[a] | 74 (57-96)[b] | 71 (51-99)[b] | 0.001 | 0.009 |
| **Total testosterone (ng/mL)** | 0.9 (0.6-1.2)[a] | 0.6 (0.5-0.7)[b] | 0.5 (0.4-0.6)[c] | 0.037 | 0.001 |
| **SHBG (nmol/L)** | 23.3(14.2-31.5)[a] | 31.0 (17.5-45.3)[a] | 39.9 (29.3-59.2)[b] | 0.030 | 0.001 |
| **FAI** | 11.5 (5.5-20.6)[a] | 4.6 (3.1-7.9)[b] | 2.2 1.1-4.1)[c] | 0.001 | 0.001 |
| **Metabolic syndrome[#] %(n)** | 20 (32)[a] | 9 (5)[b] | 4 (4)[b] | 0.002 | 0.303 |

Values are expressed as mean ± SD or median and inter-quartile range (25% to 75%) (one-way ANOVA - *post hoc* Tukey test) or percentage (absolute number) ([#] Fisher's exact test); different superscript letters indicate statistical difference. BMI, body mass index; DBP, diastolic blood pressure; FAI, free androgen index; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment – insulin resistance; LDL-c - low-density lipoprotein cholesterol; PCOS - polycystic ovary syndrome; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin; WC, waist circumference. [*] P adjusted for BMI (ANCOVA and Bonferroni test or Poisson Regression).

**Table 2.** Correlations between HOMA-IR and adiposity indexes in classic and ovulatory PCOS phenotypes and controls

| Variable | c-PCOS | | ov-PCOS | | Controls | |
|---|---|---|---|---|---|---|
| | r | P | r | P | r | P |
| **VAI** | 0.44 | 0.001 | 0.48 | 0.001 | 0.33 | 0.002 |
| **LAP** | 0.57 | 0.001 | 0.59 | 0.001 | 0.41 | 0.001 |
| **WHtR** | 0.55 | 0.001 | 0.44 | 0.001 | 0.36 | 0.001 |
| **WC** | 0.53 | 0.001 | 0.46 | 0.001 | 0.38 | 0.001 |
| **C-index** | 0.39 | 0.001 | 0.31 | 0.02 | 0.25 | 0.001 |

Pearson correlation test. C-Index, conicity index; c-PCOS, classic PCOS phenotype; LAP, lipid accumulation product; ov-PCOS, ovulatory PCOS phenotype; VAI, visceral adiposity index; WHtR, waist-to-height ratio.

**Table 3.** Sensitivity, specificity, and predictive values for adiposity indexes in classic and ovulatory PCOS phenotypes and controls according to cutoff values

| Index | Cutoff value | c-PCOS | | | | Ov-PCOS | | | | Controls | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | S (%) (95%CI) | SP (%) (95%CI) | PPV (%) (95%CI) | NPV (%) (95%CI) | S (%) (95%CI) | SP (%) (95%CI) | PPV (%) (95%CI) | NPV (%) (95%CI) | S (%) (95%CI) | SP (%) (95%CI) | PPV (%) (95%CI) | NPV (%) (95%CI) |
| LAP | 34 | 79.5 (69.5-87.6) | 69.2 (57.7-79.2) | 73.3 (62.9-82.1) | 76.1 (64.5-85.4) | 46.6 (21.3-73.4) | 90.2 (76.8-97.8) | 63.6 (30.8-89.0) | 82.2 (67.9-92.0) | 38.4 (13.8-68.4) | 89.8 (81.0-95.5) | 38.4 (13.8-68.4) | 89.8 (81.0-95.5) |
| WC | 87.3 | 78.5 (68.2-86.8) | 58.9 (47.2-69.9) | 67.3 (57.1-76.5) | 71.8 (59.2-82.4) | 46.6 (21.3-73.4) | 85.7 (71.5-94.5) | 53.8 (25.1-80.8) | 81.8 (67.3-91.8) | 56.2 (29.8-80.2) | 75.8 (65.5-84.4) | 30.0 (14.7-49.4) | 90.4 (81.2-96.0) |
| WHtR | 0.56 | 72.6 (61.8-81.8) | 67.1 (55.3-77.4) | 70.9 (60.1-80.2) | 68.9 (57.1-79.1) | 40.0 (16.3-67.7) | 87.5 (73.2-95.8) | 54.5 (23.3-83.2) | 79.5 (64.7-90.2) | 53.8 (25.1-80.8) | 90.2 (80.9-96.0) | 50.0 (23.0-76.9) | 91.5 (82.5-96.8) |
| VAI | 1.32 | 81.9 (71.9-89.5) | 52.6 (40.8-64.2) | 65.3 (55.4-74.4) | 72.7 (59.0-83.8) | 73.3 (44.9-92.2) | 74.3 (57.8-86 .9) | 52.4 (29.8-74.3) | 87.9 (71.8-96.6) | 66.6 (34.9-90.1) | 64.8 (52.5-75.7) | 24.2 (11.1-42.4) | 92.0 (80.7-97.8) |
| C-index | 1.19 | 65.5 (54.1-75.5) | 70.5 (59.1-80.3) | 70.5 (59.1-80.3) | 65.5 (54.1-75.5) | 40.0 (16.3-67.7) | 80.9 (65.9-91.4) | 42.8 (17.6-71.1) | 70.1 (63.9-89.9) | 50.0 (24.6-75.3) | 85.3 (75.8-92.2) | 40.0 (19.1-63.9) | 89.7 (80.8-95.4) |

LAP, lipid accumulation product; WC, waist circumference; WHtR, waist-to-height ratio; VAI, visceral adiposity index; C-index, conicity index; S, sensitivity; SP, specificity; PPV, positive predictive value; NPV, negative predictive value; c, classic PCOS phenotype; ov, ovulatory PCOS phenotype

**Table 4.** Prevalence ratio of HOMA-IR ≥ 3.8 among adiposity indexes in c-PCOS and ov-PCOS

| | c-PCOS | | Ov-PCOS | |
|---|---|---|---|---|
| **Index** | **Prevalence ratio (95% IC)[a]** | **P** | **Prevalence ratio (95% IC)[a]** | **P** |
| **LAP ≥ 34** | 2.6 (1.6-4.1) | 0.001 | 2.3 (0.9-6.0) | 0.066 |
| **WC ≥ 87.3** | 1.7 (1.1-2.8) | 0.023 | 1.6 (0.5-4.7) | 0.403 |
| **WHtR ≥ 0.56** | 1.7 (1.1-2.7) | 0.019 | 1.1 (0.3-3.6) | 0.870 |
| **VAI ≥ 1.32** | 1.9 (1.2-3.0) | 0.005 | 3.3 (1.2-9.1) | 0.016 |
| **C-index ≥ 1.19** | 1.6 (1.1-2.2) | 0.008 | 1.4 (0.5-3.8) | 0.443 |

LAP - lipid accumulation product; WC - waist circumference; WHtR – waist-to-height ratio; VAI - visceral adiposity index; C-index – conicity index; c, classic PCOS phenotype; ov, ovulatory PCOS phenotype

[a] Prevalence ratio calculated by Poisson regression with robust variance, adjusted for BMI

**Table 5.** Metabolic and hormonal profile of women with classic PCOS phenotype according to LAP cutoff

| Variable | LAP < 34 | LAP ≥ 34 | P | P* |
|---|---|---|---|---|
| **BMI (kg/m²)** | 26.4±4.9 | 35.3±5.7 | 0.001 | - |
| **Age (years)** | 21±5 | 25±6 | 0.001 | - |
| **Waist circumference (cm)** | 80.3±10.4 | 101.9±12.3 | 0.001 | 0.001 |
| **SBP (mmHg)** | 118±13 | 126±17 | 0.004 | 0.835 |
| **DBP (mmHg)** | 76±10 | 82±10 | 0.001 | 0.419 |
| **Fasting glucose (mg/dL)** | 85±10 | 92±16 | 0.001 | 0.005 |
| **2 hours glucose (mg/dL)** | 97±22 | 129±41 | 0.001 | 0.001 |
| **HOMA-IR index** | 2.5 (1.4-3.7) | 5.3 (3.7-7.7) | 0.001 | 0.001 |
| **Total cholesterol (mg/dL)** | 160±31 | 192±39 | 0.001 | 0.001 |
| **HDL-c (mg/dL)** | 51±11 | 42±9 | 0.001 | 0.001 |
| **LDL-c (mg/dL)** | 95±24 | 119±33 | 0.001 | 0.001 |
| **Triglycerides (mg/dL)** | 66 (51-81) | 132 (104-185) | 0.001 | 0.001 |
| **Total testosterone (ng/mL)** | 0.9±0.3 | 0.9±0.4 | 0.890 | 0.337 |
| **SHBG (nmol/L)** | 29.2 (17.4-41.9) | 22.1 (13.4-28.0) | 0.001 | 0.303 |
| **FAI** | 9.1 (4.2-18.7) | 14.3 (5.7-21.3) | 0.128 | 0.568 |
| **Metabolic syndrome[#] % (n)** | 7 (5) | 29 (27) | 0.001 | 0.181 |

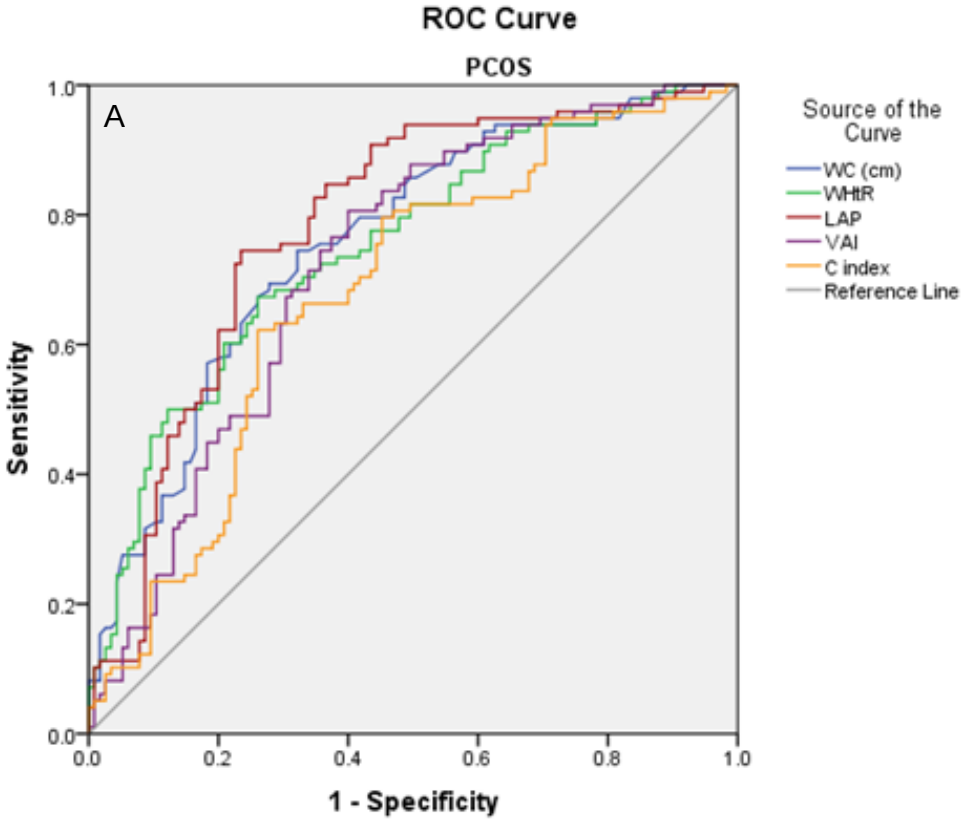
Values are expressed as mean ± standard deviation or median and interquartile range (25% -75%) (Student's t test) or percentage (absolute number) ([#]Chi-square). P value of nonparametric variables was obtained after logarithmic transformation. BMI, body mass index; DBP, diastolic blood pressure; FAI, free androgen index; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment – insulin resistance; LAP, lipid accumulation product; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin. [*] P adjusted for BMI (ANCOVA and Bonferroni test or Poisson regression).

**Table 6.** Metabolic and hormonal profile of women with ovulatory PCOS phenotype according to VAI cutoff

| Variable | VAI < 1.32 | VAI ≥ 1.32 | P | P* |
|---|---|---|---|---|
| **BMI (kg/m²)** | 25.1± 4.6 | 28.2±3.9 | 0.011 | - |
| **Age (years)** | 23±7 | 24±7 | 0.466 | - |
| **Waist circumference (cm)** | 78.3±11.3 | 85.7±9.3 | 0.015 | 0.597 |
| **SBP (mmHg)** | 114±11 | 122±13 | 0.018 | 0.051 |
| **DBP (mmHg)** | 70±9 | 80±11 | 0.001 | 0.004 |
| **Fasting glucose (mg/dL)** | 83±6 | 89±12 | 0.042 | 0.254 |
| **2 hours glucose (mg/dL)** | 92±19 | 109±28 | 0.012 | 0.059 |
| **HOMA-IR index** | 1.8 (1.0-2.8) | 4.0 (2.5-5.2) | 0.001 | 0.001 |
| **Total cholesterol (mg/dL)** | 161±25 | 166±32 | 0.563 | 0.938 |
| **HDL-c (mg/dL)** | 57±10 | 43±7 | 0.001 | 0.001 |
| **LDL-c (mg/dL)** | 92±26 | 97±27 | 0.429 | 0.845 |
| **Triglycerides (mg/dL)** | 61 (50-75) | 120 (86-136) | 0.001 | 0.001 |
| **Total testosterone (ng/mL)** | 0.6±0.2 | 0.5±0.2 | 0.217 | 0.653 |
| **SHBG (nmol/L)** | 38.4 (22.5-47.9) | 20.0 (12.5-30.1) | 0.012 | 0.052 |
| **FAI** | 3.8 (2.2-7.52) | 5.4 (4.5-8.6) | 0.174 | 0.204 |
| **Metabolic syndrome[#] % (n)** | 3 (1) | 19 (4) | 0.074 | 0.244 |

Values are expressed as mean ± standard deviation or median and interquartile range (25% -75%) (Student's t test) or percentage (absolute number) ([#] Fisher's exact test). P value of nonparametric variables was obtained after logarithmic transformation. BMI, body mass index; DBP, diastolic blood pressure; FAI, free androgen index; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostasis model assessment – insulin resistance; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; SHBG, sex hormone-binding globulin; VAI, visceral adiposity index. [*] P adjusted for BMI (ANCOVA and Bonferroni test or Poisson regression).

**Figure 1.** A. ROC curves for WC, WHtR, LAP, VAI, and C-index to detect cardiometabolic risk expressed as HOMA-IR ≥ 3.8 in the overall population; B. Sensitivity (S) and specificity (SP) of adiposity indexes according to the cutoff value obtained for overall participants in the ROC curve




B

| Index | AUC (95%CI) | P | Cutoff value | S (%) (95%CI) | SP (%) (95%CI) |
|---|---|---|---|---|---|
| **LAP** | 0.78 (0.72-0.84) | 0.001 | 34 | 70.2 (61.2-77.9) | 81.8 (75.8-86.5) |
| **WC (cm)** | 0.75 (0.69-0.82) | 0.001 | 87.3 | 71.3 (62.4-78.8) | 71.5 (65.0-77.2) |
| **WHtR** | 0.75 (0.65-0.79) | 0.001 | 0.56 | 66.0 (56.9-74.2) | 80.3 (74.0-85.3) |
| **VAI** | 0.72 (0.67-0.78) | 0.001 | 1.32 | 79.1 (70.5-85.6) | 61.8 (54.6-68.5) |
| **C-index** | 0.68 (0.61-0.75) | 0.001 | 1.19 | 60.0 (51.7-69.3) | 78.7 (71.5-82.9) |

## CAPÍTULO 2

# Habitual physical activity is associated with improved anthropometric and androgenic profile in PCOS: a cross-sectional study

**Running title:** Physical activity and androgens in PCOS

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**Abstract**

*Purpose:* To examine the effect of habitual physical activity (PA) on the metabolic and hormonal profiles of women with polycystic ovary syndrome

*Material and methods:* Anthropometric, metabolic, and hormonal assessment and determination of habitual PA levels with a digital pedometer were evaluated in 84 women with PCOS and 67 age- and body mass index (BMI)-matched controls. PA status was defined according to number of steps (≥7,500 steps, active, or <7,500 steps, sedentary).

*Results:* BMI was lower in active women from both groups. Active PCOS women presented lower waist circumference (WC) and lipid accumulation product (LAP) values vs. sedentary PCOS women. In the control group, active women also had lower WC, lower values for fasting and 120-minute insulin, and lower LAP than sedentary controls. In the PCOS group, androgen levels were lower in active vs. sedentary women (p=0.001). In the control group, free androgen index (FAI) was also lower in active vs. sedentary women (p=0.018). Homeostasis model assessment of insulin resistance and 2,000 daily step increments were independent predictors of FAI. Each 2,000 daily step increment was associated with a decrease of 1.07 in FAI.

*Conclusion:* Habitual PA was associated with a better anthropometric and androgenic profile in PCOS.

**Keywords:** androgens; sedentary lifestyle; exercise; polycystic ovary syndrome.

## Introduction

Polycystic ovary syndrome (PCOS) is a common endocrine disease that affects an estimated 6% to 19% of women of reproductive age, depending on diagnostic criteria [1,2]. In addition to being regarded as a major cause of anovulatory infertility, PCOS is also recognized for its cardiometabolic implications, such as increased obesity [3] and abdominal obesity [4], dyslipidemia [5], metabolic syndrome [6-8], insulin resistance (IR) [9], impaired glucose tolerance, and diabetes [6].

Nonpharmacological interventions, especially diet and exercise, are the first-line treatment for preventing cardiometabolic risk factors and reproductive dysfunction [10]. Medical guidelines recommend at least 150 minutes weekly of moderate or 60 minutes of vigorous aerobic activity [11]. Free-living habitual physical activity (PA), which encompasses routine activities such as walking for transportation, shopping, or moderate movement, without concern for intensity, has also been linked to favorable health outcomes [12,13]. Indeed, higher levels of habitual PA have been associated with more favorable anthropometric, and body composition profiles [14], lower glycated hemoglobin [15] and blood pressure [16] in different populations. In combination with aerobic exercise, habitual PA could potentiate the cardiometabolic benefits of exercise alone [17].

In PCOS, structured exercise (at least 30 minutes/day) has been recommended for obesity management [10]; also, there is evidence of clinical, and metabolic benefits associated with different types of structured exercise programs involving PA of various intensities and durations [18-24]. However, the impact of habitual PA has not yet been examined in PCOS. Therefore, the aim of this study was to objectively examine the effect of habitual PA on the metabolic, hormonal, BMI and anthropometric profiles of women with PCOS and controls.

## Patients and methods

*Patients and controls*

This cross-sectional study was carried out at the Gynecological Endocrinology Unit of Hospital de Clínicas de Porto Alegre, Brazil, during the period between 2010 and 2015, with women aged between 15-40 years enrolled at least two years after menarche. All participants had to be off oral contraceptives, insulin sensitizers or antiandrogens for at least 3 months before the study. Women with diabetes, renal or liver disease, or those who were pregnant or breastfeeding were also excluded.

PCOS patients were recruited among those referred to our outpatient clinic and through public advertisement. Eighty-four women were enrolled following diagnosis of PCOS according to the Rotterdam criteria [25].

Anovulation was defined as 9 or fewer cycles/year (confirmed by luteal phase progesterone levels lower than 12 nmol/L). Biochemical hyperandrogenism was considered when serum total testosterone and/or free androgen index (FAI) were 2 standard deviations higher than the mean levels detected in the control group [4]. Clinical hyperandrogenism was defined by a modified Ferriman-Gallwey score (FG) ≥8 [26].

Ovarian morphology was assessed in all women using transvaginal/transabdominal ultrasound between the 2nd and 8th day of the menstrual cycle or on any day if the patient was amenorrheic [25]. The diagnosis of PCOS in adolescent participants was based on the presence of all three Rotterdam criteria, hyperandrogenism in combination with persistent oligomenorrhea, and PCO [27].

Sixty-seven women matched by age and BMI were recruited for the control group through public advertisement. These women did not have PCO or evidence of clinical or biochemical hyperandrogenism; they presented regular and ovulatory menstrual cycles (confirmed by progesterone levels higher than 12 nmol/L).

Written informed consent was obtained from each participant before evaluation, and the study protocol was approved by the local Institutional Review Board.

*Study protocol*

Anthropometric measures were performed in duplicate and included weight (kg), height (m) and waist circumference (WC). Systolic and diastolic blood pressure was measured after a 10-minute rest, twice for each patient, using an automatic blood pressure monitor with an appropriate cuff for the arm diameter (Omron HEM 742, Rio de Janeiro, Brazil).

The following indexes were calculated: BMI (current weight in kg divided by the square of height in m) and LAP index for women ([WC in cm – 58] x triglyceride concentration in mmol/L) [28].

*Assessment of habitual physical activity*

Habitual PA was measured using a digital pedometer (BP 148 Techline, São Paulo, Brazil), configured individually for each participant with information about the weight (in kg) and step length (in cm) [29]. Step length was obtained by measuring the distance covered in one step from heel to heel. Participants were instructed to wear the pedometer attached to a waistband during waking hours (except in water-based activities) for six consecutive days (including Saturdays and Sundays). Patients were asked to keep a daily record of total number of steps and time of pedometer placement and removal [29], and were instructed to maintain their PA habits during the study.

Participants were classified as active (7,500 daily steps or more) or sedentary (maximum of 7,499 daily steps) [30]. In addition, we assessed the impact of 2,000-step increases in average daily steps [31] on FAI values.

*Laboratory evaluation*

Blood samples for metabolic and hormonal assessment were collected between 8 a.m. and 10 a.m. and were determined after a 12h fast. Total testosterone, sex hormone-binding globulin (SHBG), dehydroepiandrosterone sulfate (DHEAS), androstenedione, estradiol, total and high-density lipoprotein (HDL) cholesterol, and triglycerides were

measured in all participants in the follicular phase (between days 2 and 8 of the menstrual cycle) of a spontaneous menstrual cycle or on any day if the patient was in amenorrhea. Progesterone was determined in all control and PCOS women in the luteal phase (between days 20-24 for participants with regular cycles). Glucose and insulin were measured before and after a 75 g oral glucose tolerance test. Metabolic syndrome diagnosis was based on the Joint Scientific Statement [32]. The maximum interval between anthropometric measures and laboratory tests was 2 weeks.

*Assays*

Total cholesterol, HDL cholesterol, and triglycerides were determined by colorimetric-enzymatic methods (Bayer 1800 Advia System, Mannheim, Germany). Glucose was determined by the hexokinase method (Bayer 1800 Advia System, Mannheim, Germany). DHEAS and androstenedione were determined by chemiluminescence immunoassay (CLIA) (Immulite 2000 Siemens, Deerfield, USA), with sensitivity of 0.08 μmol/L and 0.01 nmol/L, respectively and intra and interassay CV of less than 13%. Total testosterone levels were measured by CLIA (Siemens Centaur XP, Deerfield, USA), with sensitivity of 0.001 nmol/L and intra and interassay CV of 3.3% and 7.5% respectively. SHBG, progesterone and insulin were measured by CLIA, as previously reported [4]. FAI was estimated by dividing total testosterone (nmol/L) by SHBG (nmol/L) × 100. Low-density lipoprotein (LDL) cholesterol was determined indirectly using the Friedewald formula: LDL = total cholesterol – HDL cholesterol – (triglycerides/5). HOMA-IR index was calculated by multiplying insulin (μIU/mL) by glucose (mmol/L) and dividing this product by 22.5 [33].

**Statistical analysis**

Since there were no previous studies investigating the association between habitual PA and clinical and laboratory variables in PCOS, the sample size was determined using an interim analysis. Considering a power of 80% and alpha of 5% to detect a difference of 3.5 in

BMI between the total of sedentary and active women (PCOS plus controls), the sample size was calculated as 40 sedentary and 40 active women. In addition, to detect a difference of 4.5 in FAI between sedentary and active PCOS participants, 27 women were required in each PCOS group.

Results are presented as mean ± standard deviation (SD), or median and interquartile range, depending on the Gaussian or non-Gaussian distribution of variables. Student's t-test was used to compare the differences between two independent groups. Categorical variables were expressed as percentage and absolute number. The chi-square test or Fisher's exact test were used for comparisons between percentages as appropriate. Variables without normal distribution were log-transformed for statistical analysis and back-transformed into their original units for presentation. The relationship between diagnostic status (PCOS or non-PCOS) and PA status was investigated by two-way ANOVA followed by Bonferroni test.

Multiple linear regression analyses were carried out with age, 2,000-step increases in average daily steps, and HOMA-IR as independent variables and FAI as the dependent variable in the PCOS group.

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS version 20) (Armonk, NY, USA). A *p*-value <0.05 was considered to be statistically significant.

**Results**

Of the 151 women enrolled, 107 were classified as sedentary and 44 as active. BMI was lower in active vs. sedentary women (26.5±5.0 vs 30.0±5.9 kg/m², p=0.001).

Eighty-four women met the criteria for PCOS, and 67 were enrolled as controls. Anthropometric and clinical data of PCOS and control women are shown in table 1. Age, BMI, WC, and number of steps/day did not differ between the groups. PCOS women had higher systolic and diastolic blood pressure and a higher FG score than controls.

Table 2 presents clinical, hormonal, and metabolic characteristics of PCOS and

control women according to PA status. Thirty-three percent (n=28) of women in the PCOS group and 24% (n=16) of women in the control group were classified as active (≥7,500 steps/day). As expected, BMI was lower in active women from both groups as compared to their sedentary counterparts. In addition, active women with PCOS presented lower WC and LAP values compared with sedentary PCOS women. In the control group, active women also had lower WC, lower values for fasting and 120-minute insulin, and lower LAP than sedentary women. When adjusted for BMI, these differences lost statistical significance. There was no interaction between PA status and diagnostic status.

Androgen levels are shown in figure 1. In the PCOS group, total testosterone, FAI, and androstenedione levels were lower in active vs. sedentary women, even when adjusted for BMI. In the control group, FAI was also lower in active vs. sedentary women, but this difference did not remain significant after adjustment for BMI.

Multiple linear regression analysis was performed to examine the independent contribution of age, HOMA-IR, and 2,000 daily step increments to FAI in the PCOS group (table 3). In this model, HOMA-IR and 2,000 daily step increments were independent predictors of FAI, explaining 40.8% of the variance in FAI values in PCOS. Each 2,000 daily step increment was associated with a decrease of 1.07 in FAI.

**Discussion**

In the present study, active PCOS women had a better anthropometric and metabolic profile than sedentary PCOS women of the same age. Moreover, an increment of 2,000 steps/day in habitual PA (regardless of PA status) was independently associated with decreased FAI in these women. While the association between structured exercise and reductions in androgen levels has been previously noted [20-22], this is the first study to describe a positive impact of habitual PA on PCOS, expressed by an association with lower androgen levels.

BMI is often elevated in PCOS women [34,35], and a sedentary lifestyle along with

high energy intake can further aggravate this problem [34]. A systematic review has shown beneficial effects of exercise interventions on reproductive and cardiometabolic outcomes in PCOS [36]. However, while the studies included in that review focused mainly on the effects of exercise training, in the present study we objectively assessed habitual PA with the use of a motion sensor. The 7,500 steps used to determine PA status in this and other studies cover both habitual and structured activities [30]; the present results suggest that like exercise programs, non-structured PA may benefit women with PCOS.

Cross-sectional studies have reported an association between lower BMI and higher PA levels in both the general population [29,37] and PCOS [38,39]. In line with our results, previous research in PCOS has detected lower BMI, waist circumference [38,39], glucose levels, and reduced weight fluctuations in active PCOS women [38]. Nevertheless, androgens levels were not evaluated in earlier studies.

In the present study, total testosterone, FAI and androstenedione were lower in active vs. sedentary PCOS participants. In addition, a 2,000-step increase in average daily steps (which roughly translates into about 20 minutes of moderate-intensity walking) [30,40] was independently associated with a reduction in FAI in PCOS women. Interestingly, FAI was also significantly lower in active control women as compared to sedentary ones, supporting recent data from a meta-analysis [41]. Evidence suggests that androgens may be associated with cardiovascular risk factors in PCOS [42-44]. It is known that obesity, and mainly central obesity, contributes both directly (through over-activation of 17beta-hydroxysteroid dehydrogenase and 5alfa-reductase) [45,46] and indirectly (exacerbating IR, resulting compensatory hyperinsulinemia) to higher androgen levels [47]; also, weight loss and physical activity may determine improvements in hormonal profile and ovulatory function in women with PCOS. However, the mechanisms underlying these processes are not completely understood. Some studies suggest that the reduction of adipose tissue and IR results in a more favorable endocrine profile, with subsequent increases in SHBG and decreases in free androgens [19,21,22,48,49]. In our study, the reductions in FAI levels

associated with 2,000-step increases in average daily steps could be mediated by a reduction in BMI given that active women, in both groups, presented lower BMI. In the present study, both IR and habitual PA were independent predictors of FAI in PCOS. Indeed, while structured exercises are effective for improving anthropometric and metabolic profile in women with PCOS, the compliance at long-term is often a critical point. In this sense, the present results encourage a simple and more feasible active behavior, i.e. moving more during the day to PCOS women that are not engaged in structured exercises or sports.

The finding of lower fasting and 120-minute insulin in active vs. sedentary women was observed only in the control group. Even though walking 7,500 steps a day or more is accepted as mild physical activity in healthy adults [30], this cutoff may not be sufficient to improve metabolic outcomes in PCOS women, who are often obese and insulin resistant. In populations at higher risk for cardiovascular disease, such as individuals with type 2 diabetes or hypertension, a cutoff of 10,000 steps/day has been related to improvements in insulin sensitivity [50], blood pressure and sympathetic nerve activity [51].

Data from a large observational study have shown beneficial effects of increased habitual PA (independent of baseline level) in reducing cardiovascular risk factors [31]. In individuals at high risk for type 2 diabetes, an addition of 2,000 steps daily reduced the risk of cardiovascular events in 10%. After 12 months, this increase in 2,000 steps/day was associated with an additional 8% difference in the rate of cardiovascular events after adjustment for potential confounding variables [31]. In less active women, a 2,000-step increase in average daily steps is associated with greater reductions in BMI and WC [13]. In pedometer-based interventions in adults, additions of 2,500 steps/day have been associated with a decrease in blood pressure levels and BMI [52].

One limitation of the present study is that PA was assessed by a pedometer that does not discriminate intensity, cadence, or type of PA. The equipment is also unsuitable to measure non-ambulatory activities, like swimming or bicycling, for example. Nevertheless, walking is the most common and preferred PA [53], and corresponds to nearly 62% of time

spent in moderate-vigorous PA [54]. Moreover, the pedometer, which is capable of assessing vertical oscillations, has been validated for estimating and encouraging habitual PA [30]. The lack of information about dietary intake to assess weight and BMI variation in active and sedentary groups is another limitation of our study, since energy balance is directly related to BMI [55]. The third limitation is the cross-sectional design, which does not allow inferences about causal relationships regarding habitual PA and androgen levels in PCOS. Therefore, randomized and controlled studies with larger sample sizes are needed to further establish causality among these outcomes.

## Conclusions

In conclusion, sedentary women with PCOS presented a worse anthropometric and metabolic profile as well as higher androgen levels compared to active women with PCOS. Given that cardiovascular risk factors are more prevalent in PCOS and hyperandrogenism may exacerbate these risk factors, encouraging a more active behavior lifestyle, especially in obese and sedentary PCOS women, may prove beneficial.

## Compliance with ethical standards


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### Conflict of interest

The authors declare that they have no conflict of interest.

**Ethical approval**

All procedures performed were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Informed consent**

Informed consent for the scientific use of the data was obtained from all participants included in the study.

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**Table 1** Clinical features of PCOS and control women

| Variable | PCOS (n=84) | Controls (n=67) | *p* |
|---|---|---|---|
| **Age (years)** | 24.6±5.8 | 26.4±5.4 | 0.058 |
| **BMI (kg/m²)** | 29.4±5.9 | 28.4±5.9 | 0.290 |
| **Waist (cm)** | 87.1±12.8 | 83.7±12.3 | 0.105 |
| **SBP (mmHg)** | 118±13 | 113±11 | 0.024 |
| **DBP (mmHg)** | 77±9 | 73±10 | 0.018 |
| **Ferriman-Gallwey score** | 13 (9-19) | 3 (1-5) | <0.001 |
| **Steps/day** | 5931 (3686-8887) | 5810 (3884-7326) | 0.631 |

Values are expressed as mean±SD or median and interquartile range (25% to 75%).
BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure

**Table 2** Clinical, hormonal, and metabolic characteristics of PCOS and control women according to physical activity status

| Variable | PCOS | | *p* | Controls | | *p* |
|---|---|---|---|---|---|---|
| | Sedentary (56) | Active (28) | | Sedentary (51) | Active (16) | |
| **Age (years)** | 23.8±5.4[a] | 26.1±6.3 | 0.078 | 26.7±5.1[b] | 25.4±6.3 | 0.431 |
| **Ethnicity, % (n)** | | | 0.473 | | | 0.217 |
| **White** | 91.1 (51) | 85.7 (24) | | 88.2 (45) | 73.3 (11) | |
| **Nonwhite** | 8.9 (5) | 14.3 (4) | | 11.8 (6) | 26.7 (5) | |
| **BMI (kg/m²)** | 30.7±5.9 | 26.9±5.0 | 0.005 | 29.2±5.9 | 25.7±5.0 | 0.040 |
| **Waist (cm)** | 89.4±12.8 | 82.5±11.8 | 0.017 | 85.0±12.4 | 79.3±11 | 0.012 |
| **SBP (mmHg)** | 120±1[a] | 115±16 | 0.071 | 114±12[b] | 114±10 | 0.838 |
| **DBP (mmHg)** | 78±8 | 76±10 | 0.302 | 74±10 | 71±8 | 0.432 |
| **Ferriman-Gallwey score** | 14 (9-20)[a] | 12 (8-16)[a] | 0.396 | 3 (1-4)[b] | 1 (0-5)[b] | 0.769 |
| **Steps/day** | 4366 (3387-5945) | 9743 (8837-11768) | 0.001 | 4844 (3577-6415) | 10079 (8776-11729) | 0.001 |
| **Fasting glucose (mmol/L)** | 4.8±0.4 | 4.9±0.4 | 0.153 | 4.9±0.4 | 4.7±0.3 | 0.207 |
| **2-hour glucose (mmol/L)** | 5.8±1.4 | 5.9±1.5 | 0.892 | 5.5±1.1 | 5.1±1.0 | 0.307 |
| **Fasting insulin (pmol/L)** | 118 (49-153) | 90 (55-118)[a] | 0.136 | 76 (55-111) | 42 (28-69)[b] | 0.003 |
| **2 hour insulin (pmol/L)** | 625 (312-1347) | 451 (312-805)[a] | 0.219 | 486 (278-792) | 236 (194-472)[b] | 0.024 |
| **HOMA-IR** | 3.6 (1.4-5.0) | 2.6 (1.7-4.1) | 0.231 | 2.4 (1.6-3.4) | 1.3 (1.0-1.9) | 0.074 |
| **Estradiol (ng/L)** | 51 (41-65) | 54 (44-69) | 0.612 | 53 (36-82) | 53 (39-65) | 0.870 |
| **SHBG (nmol/L)** | 27.4 (17.7-38.6)[a] | 33.9 (22.1-43.5) | 0.123 | 35.7 (26.3-52.9)[b] | 51.2 (33.1-71.4) | 0.698 |
| **DHEAS (µmol/L)** | 6.2 (4.3-8.6) | 6.0 (2.9-7.7) | 0.424 | 4.2 (2.7-5.7) | 4.8 (2.6-5.7) | 0.973 |
| **LAP** | 35.2 (22.0-67.5) | 17.8 (10.5-41.1) | 0.041 | 23.8 (11.6-33.5) | 13.6 (7.1-35.3) | 0.033 |
| **MS, % (n)** | 29.4 (15) | 10.7 (3) | 0.058 | 14.9 (7) | 0 | 0.134 |
| **Classic PCOS, % (n)** | 73.2 (41) | 71.4 (20) | 0.863 | - | - | - |

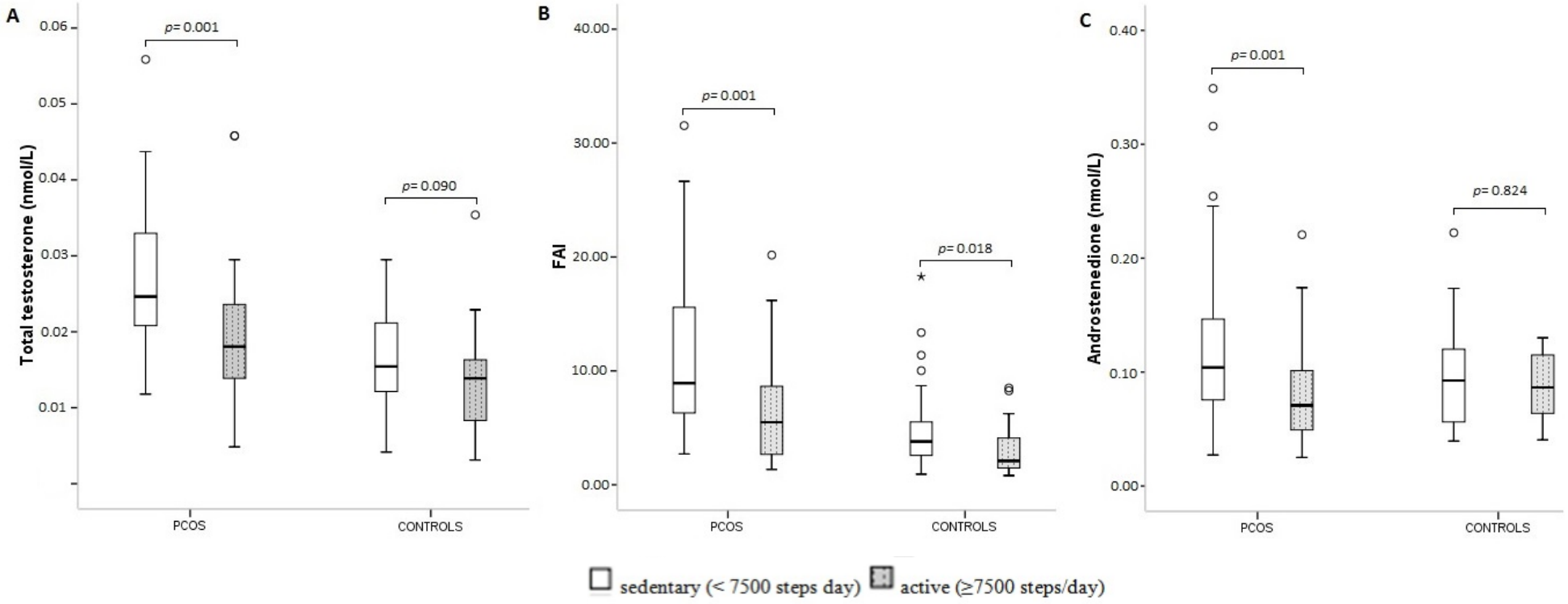
Values are expressed as mean±standard deviation, median and interquartile range (25%–75%) or percentage (absolute number)
Lower-case letters indicate statistical difference between PCOS and control patients with the same physical activity status
BMI, body mass index; SBP; systolic blood pressure; DBP, diastolic blood pressure; HOMA-IR, homeostasis model assessment – insulin resistance; LAP, lipid accumulation product; MS, metabolic syndrome; SHBG, *sex hormone-binding globulin; DHEAS,* dehydroepiandrosterone sulfate

**Table 3** Multiple linear regression analysis of the impact of age, HOMA-IR, and 2,000-step increases in average daily steps on FAI

| **FAI *vs.*** | **B (95% CI)** | ***P*** | **$R^2$ adjusted** |
|---|---|---|---|
| Age (years) | -0.038 (-0.21; 0.17) | 0.722 | 0.408 |
| HOMA-IR | 1.29 (0.88; 1.70) | <0.001 | |
| 2,000-step increases in average daily steps | -1.07 (-1.86; -0.27) | 0.010 | |

FAI, free androgens index; HOMA-IR, homeostasis model assessment – insulin resistance

**Fig. 1** Androgen levels in PCOS and control women according to physical activity status



## CONSIDERAÇÕES FINAIS

A síndrome dos ovários policísticos (PCOS) é a endocrinopatia de maior prevalência em mulheres em idade reprodutiva e, considerando a heterogeneidade entre os diferentes fenótipos, o qual impacta a severidade das manifestações clínicas e metabólicas, o estudo da acurácia de diferentes índices de adiposidade para identificação de alterações subclínicas e risco cardiometabólico sugere que índices distintos devam ser considerados para melhor identificar risco cardiometabólico nos fenótipos “clássico” e “ovulatório”. Em mulheres com PCOS com o fenótipo “clássico”, o produto da acumulação lipídica≥ 34 mostrou-se como o melhor índice, enquanto que, para aquelas classificadas com o fenótipo “ovulatório”, o marcador que melhor discriminou o risco cardiometabólico foi o índice de adiposidade visceral≥ 1,32. Ambos os indicadores são de baixo custo, fácil cálculo e interpretação, sendo úteis na prática clínica para o rastreamento precoce de risco cardiometabólico, permitindo a adoção de intervenções antes da instalação de doenças, reduzindo, provavelmente, risco futuro de doença cardiovascular.

Considerando-se medidas não farmacológicas no manejo da obesidade e das comorbidades associadas na PCOS, mudanças de estilo de vida, incluindo a recomendação para a prática de exercício físico, são consideradas a primeira opção de tratamento. No entanto, a manutenção deste hábito a longo prazo é uma limitação deste tipo de intervenção. Neste sentido, o estímulo à prática de atividade física habitual pode ser uma alternativa para mulheres com PCOS. Os dados do segundo trabalho mostram que mulheres com PCOS mais ativas apresentam um perfil antropométrico, hormonal e metabólico mais saudável. Em razão dos fatores de risco cardiovascular serem mais prevalentes nesta população e do hiperandrogenismo poder exacerbar estes fatores de risco, encorajar a adoção de um estilo de vida mais ativo pode ser benéfico para estas mulheres, especialmente as com sobrepeso/obesidade.