PRÓ-REITORIA DE PESQUISA E PÓS-GRADUAÇÃO
MESTRADO EM CIÊNCIAS DA SAÚDE

ANA CRISTINA LIRA DE MENEZES

ASSOCIAÇÃO DA RESISTÊNCIA À INSULINA E DEFICIÊNCIA DE VITAMINA D EM MULHERES NA PÓS-MENOPAUSA COM E SEM SÍNDROME METABÓLICA

Presidente Prudente – SP
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Ao meu esposo
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‘É justo que muito custe o que muito vale”

(Santa Teresa D’Ávila)

RESUMO

Associação da resistência à insulina e deficiência de vitamina d em mulheres na pós-menopausa com e sem síndrome metabólica

A relação entre resistência à insulina e deficiência de vitamina D (VitD) em mulheres na pós-menopausa, com e sem síndrome metabólica (MetS), constitui uma área de investigação em expansão. A avaliação do índice de resistência à insulina (HOMA-IR) e dos níveis séricos de VitD é fundamental para identificar mulheres com maior risco de desenvolver MetS. Assim, este estudo investigou a relação entre a resistência à insulina, estimada pelo índice e a deficiência de VitD em mulheres na pós-menopausa, com e sem MetS. Métodos: Foram avaliadas 132 mulheres na pós- menopausa (78 sem MetS e 54 com MetS) atendidas na Faculdade de Medicina de Jaú – UNOESTE. Dados clínicos e laboratoriais incluíram glicemia, hemoglobina glicada, insulina, índice HOMA-IR, perfil lipídico, circunferência abdominal, pressão arterial e níveis séricos de VitD e insulina. Os dados foram analisados com testes estatísticos paramétricos e não paramétricos. Resultados: Mulheres com MetS apresentaram níveis significativamente mais elevados de glicose, hemoglobina glicada, insulina, HOMA-IR e circunferência abdominal ($p < 0,001$). Também apresentaram níveis mais altos de triglicerídeos e pressão arterial sistólica ($p < 0,01$). Não foram observadas diferenças significativas entre os grupos quanto a colesterol total, LDL, HDL, IMC e idade. Os níveis médios de VitD foram menores no grupo com MetS, porém sem significância estatística ($p = 0,063$). A análise pelo teste do qui-quadrado não identificou associação significativa entre deficiência de VitD e MetS. Conclusão: A resistência à insulina, está significativamente associada à presença de MetS em mulheres na pós-menopausa. Os resultados reforçam a importância do monitoramento contínuo dos fatores de risco metabólicos, visando à prevenção de complicações cardiovasculares em mulheres na pós-menopausa.

Palavras-chave: pós-menopausa, resistência à insulina, vitamina D, síndrome metabólica, HOMA-IR, fatores de risco.

ABSTRACT

Association between insulin resistance and vitamin D deficiency in postmenopausal women with and without metabolic syndrome

The relationship between insulin resistance and vitamin D (vitD) deficiency in postmenopausal women, with and without metabolic syndrome (MetS), represents an expanding field of research. Assessing the Homeostatic Model Assessment for Insulin Resistance (HOMA- IR) index and serum vitD levels is essential to identify women at higher risk of developing MetS. Methods: A total of 132 postmenopausal women (78 without MetS and 54 with MetS) attending the School of Medicine of Jaú, Universidade do Oeste Paulista (UNOESTE), were evaluated. Clinical and laboratory data included fasting glucose, glycated hemoglobin, insulin, HOMA-IR index, lipid profile, waist circumference, blood pressure, and serum vitamin D levels. Insulin levels were quantified by solid-phase chemiluminescent immunoassay. Data were analyzed using parametric or nonparametric statistical tests, depending on variable distribution. Results: Women with MetS showed significantly higher levels of glucose, glycated hemoglobin, insulin, HOMA-IR, and waist circumference ($p < 0.001$). They also presented higher triglyceride levels and systolic blood pressure ($p < 0.01$). No significant differences were observed between groups for total cholesterol, LDL, HDL, BMI, or age. Mean vitD levels were lower in the MetS group, but the difference was not statistically significant ($p = 0.063$). The chi-square test showed no significant association between vitamin D deficiency and MetS ($\chi^2 = 3.98$; $p = 0.137$). Conclusion: Insulin resistance, as assessed by the HOMA-IR index, was significantly associated with the presence of MetS in postmenopausal women. However, no significant association was found between vitD deficiency and MetS in this sample. These findings highlight the importance of continuous monitoring of metabolic risk factors to prevent cardiovascular complications in postmenopausal women.

Keywords: postmenopause, insulin resistance, vitamin D, metabolic syndrome, HOMA-IR, risk factors.

LISTA DE SIGLAS

AF	- Atividade física
BioHealthLab	- Laboratório Multiusuário de Biotecnologia em Saúde
Ca	- Cálcio
CAAE	- Certificado de Apresentação para Apreciação Ética
CT	- Colesterol Total
EDTA	- Ácido etilenodiaminotetracético
ELISA	- Ensaio imunoenzimático
FAL	- Fosfatase alcalina
HDL	- Lipoproteína de alta densidade
HIPOVITD	- Hipovitaminose D
HOMA-IR	- Homeostasis Model Assessment – Insulin
Resistance HT	- Terapia hormonal
IMC	- Índice de Massa Corporal
LDL	- Lipoproteína de baixa densidade
MetS	- Síndrome metabólica
NCEP-ATP III	- National Cholesterol Education Program – Adult Treatment Panel III
PAD	- Pressão Arterial Diastólica
PAS	- Pressão Arterial Sistólica
PTH	- Paratormônio
RI	- Resistência à insulina
TG	- Triglicerídeos
VDR -	- Receptor de Vitamina D
VitD	- Vitamina D

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SUMÁRIO

ASSOCIAÇÃO DA RESISTÊNCIA À INSULINA E DEFICIÊNCIA DE VITAMINA D EM MULHERES NA PÓS-MENOPAUSA COM E SEM SÍNDROME METABÓLICA

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Resumo

Objetivo: este estudo investigou a relação entre a resistência à insulina, estimada pelo índice e a deficiência de vitamina D (VitD) em mulheres na pós-menopausa, com e sem síndrome metabólica (MetS). **Métodos**: Foram avaliadas 132 mulheres na pós-menopausa (78 sem MetS e 54 com MetS) atendidas na Faculdade de Medicina de Jaú – UNOESTE. Dados clínicos e laboratoriais incluíram glicemia, hemoglobina glicada, insulina, índice HOMA-IR, perfil lipídico, circunferência abdominal, pressão arterial e níveis séricos de VitD e insulina. Os dados foram analisados com testes estatísticos paramétricos e não paramétricos. **Resultados**: Mulheres com MetS apresentaram níveis significativamente mais elevados de glicose, hemoglobina glicada, insulina, HOMA-IR e circunferência abdominal ($p < 0,001$). Também apresentaram níveis mais altos de triglicerídeos e pressão arterial sistólica ($p < 0,01$). Não foram observadas diferenças significativas entre os grupos quanto a colesterol total, LDL, HDL, IMC e idade. Os níveis médios de VitD foram menores no grupo com MetS, porém sem significância estatística ($p = 0,063$). A análise pelo teste do qui-quadrado não identificou associação significativa entre deficiência de VitD e MetS. **Conclusão**: A resistência à insulina, está significativamente associada à presença de MetS em mulheres na pós-menopausa. Os resultados reforçam a importância do monitoramento contínuo dos fatores de risco metabólicos, visando à prevenção de complicações cardiovasculares em mulheres na pós-menopausa.

Palavras-chave: pós-menopausa, resistência à insulina, vitamina D, síndrome metabólica, HOMA-IR, fatores de risco.

INTRODUÇÃO

A resistência à insulina e a deficiência de vitamina D (VitD) são condições prevalentes em mulheres na pós-menopausa e têm sido amplamente investigadas por seu impacto sobre a saúde metabólica[1–4]. A resistência à insulina representa um fator-chave na fisiopatologia da síndrome metabólica (MetS), caracterizada pela presença simultânea de hipertensão arterial, hiperglicemia, dislipidemia e obesidade central. Esses distúrbios contribuem de forma significativa para o aumento do risco de doenças cardiovasculares, principal causa de mortalidade nesse grupo populacional.[5–7].

A VitD, além de regular o metabolismo do cálcio e a saúde óssea, exerce funções extraesqueléticas relevantes, como a modulação do sistema imunológico e da função endotelial[8–

[10]. Evidências científicas indicam que a deficiência dessa vitamina está associada a maior risco de resistência à insulina e de desenvolvimento da MetS[11,12]. Tal relação é especialmente importante em mulheres na pós-menopausa, nas quais a redução dos níveis de estrogênio pode potencializar tanto a resistência insulínica quanto a deficiência de VitD[5].

A relação entre resistência à insulina e deficiência de VitD em mulheres na pós-menopausa, com e sem MetS, constitui um campo de estudo em expansão. Pesquisas sugerem que a suplementação de VitD pode melhorar a sensibilidade à insulina, configurando-se como uma possível estratégia terapêutica para reduzir o risco de MetS e suas complicações[13–15]. Entretanto, os resultados disponíveis permanecem inconsistentes, reforçando a necessidade de novas investigações para elucidar essa associação.

A MetS é uma condição multifatorial que resulta da interação de fatores genéticos, ambientais e comportamentais [8,16,17]. Em mulheres na pós-menopausa, a redução da massa muscular e o acúmulo de gordura central contribuem de forma expressiva para a resistência à insulina. A deficiência de VitD pode intensificar esse processo, comprometendo a função muscular e elevando o risco de sarcopenia[8].

A avaliação do índice HOMA-IR e dos níveis séricos de 25-hidroxivitamina D é essencial para identificar mulheres na pós-menopausa com maior risco de desenvolver MetS [5–8]. O HOMA-IR é um marcador amplamente utilizado da função insulínica, enquanto a 25(OH)D representa o principal indicador do status de VitD[4,18]. Estudos recentes reforçam a importância desses biomarcadores na predição de distúrbios metabólicos e complicações cardiovasculares [6,19,20].

A associação entre deficiência de VitD e resistência à insulina é modulada por fatores como dieta, exposição solar e nível de atividade física[1,7]. Mulheres na pós-menopausa tendem a apresentar menor prática de atividade física [20] e alterações na composição corporal, fatores que favorecem tanto a hipovitaminose D quanto a resistência insulínica[21]. Assim, intervenções voltadas à adoção de hábitos saudáveis, incluindo exposição solar adequada, suplementação de VitD e prática regular de exercícios são fundamentais para a prevenção da MetS[5].

Com tudo, o presente estudo teve como objetivo investigar a relação entre resistência à insulina e deficiência de VitD em mulheres na pós-menopausa, com e sem MetS. Especificamente, buscou-se: (1) avaliar os níveis de resistência à insulina e VitD; (2) examinar possíveis associações entre essas variáveis e a presença de MetS; (3) identificar fatores de risco associados; e (4) propor estratégias preventivas e de manejo voltadas a essa população.

METODOLOGIA

Desenho do estudo e seleção da amostra

Estudo clínico e transversal, conduzido para avaliar a relação entre HOMA-IR e deficiência de VitD em mulheres na pós-menopausa com e sem MetS. A população foi composta por mulheres voluntárias atendidas na Faculdade de Medicina de Jaú – UNOESTE, sendo que todas as avaliações foram realizadas no Laboratório Multiusuário de Biotecnologia em Saúde – BioHealthLab da UNOESTE de Jaú. O estudo foi aprovado pelo Comitê de Ética da UNOESTE – CAAE: 83161924.1.0000.5515.

O cálculo do tamanho amostral foi realizado por meio do software G*Power (versão 3.1.9.7), com base em dados prévios dos níveis séricos de VitD, considerando um erro tipo I (α) de 5% e poder estatístico (1 – β) de 80%. Foram necessárias 132 participantes (54 mulheres com MetS e 78 sem MetS) para garantir significância estatística.

O recrutamento foi realizado por meio da divulgação de um release pela assessoria de imprensa da UNOESTE – Jaú, amplamente disseminado nos meios de comunicação locais (rádio, TV, impressos e internet), além da publicação no site oficial da instituição. Também foram produzidos folders, notas, panfletos e apresentações em grupos comunitários e redes sociais, convidando as interessadas a comparecer ao laboratório para o processo de triagem.

As participantes foram incluídas conforme os critérios da NICE (2017), sendo: (1) mulheres com data da última menstruação há pelo menos 12 meses e idade > 40 anos; (2) mulheres submetidas à histerectomia e/ou ooforectomia com idade > 40 anos; (3) usuárias ou não de terapia hormonal. Foram excluídas mulheres: (1) etilistas ou usuárias de drogas; (2) com doenças autoimunes ou neoplasias. Todas assinaram o Termo de Consentimento Livre e Esclarecido, conforme a Resolução nº 466/2012 do Conselho Nacional de Saúde.

Coleta de dados clínicos e antropométricos

Na entrevista, foram coletadas informações clínicas como idade, idade da menopausa, tempo de menopausa, paridade, tabagismo atual, uso de terapia hormonal, histórico de doenças crônicas (hipertensão, diabetes, doenças cardiovasculares, depressão), uso de medicamentos, prática de atividade física, pressão arterial, peso e altura. A pressão arterial foi aferida no braço direito, com o antebraço apoiado na altura do precórdio, palma da mão voltada para cima, utilizando esfigmomanômetro aneroide padrão, com a paciente sentada. Tabagistas foram definidas

como aquelas que fumavam diariamente, independentemente da quantidade. Mulheres ativas foram consideradas aquelas que praticavam exercícios físicos aeróbicos de intensidade moderada por, no mínimo, 30 minutos em cinco dias por semana (150 min/semana), ou exercícios de resistência três vezes por semana.

O diagnóstico de MetS seguiu os critérios do NCEP-ATP III, considerando a presença de pelo menos três dos seguintes: circunferência abdominal > 88 cm; triglicerídeos > 150 mg/dL; HDL colesterol < 50 mg/dL; pressão arterial > 135/85 mmHg; glicemia de jejum > 100 mg/dL ou em uso de medicação.

Foram obtidos os seguintes dados antropométricos: peso, altura, índice de massa corporal (IMC = peso/altura²) e circunferência abdominal. O peso foi mensurado com balança antropométrica eletrônica (Filizola®, Brasil), com capacidade para 150 kg e precisão de 0,1 kg. A estatura foi aferida com a paciente descalça, braços ao longo do corpo e olhar no plano horizontal. A circunferência abdominal foi medida entre a última costela e a crista ilíaca anterossuperior, durante a expiração. Foi considerada aumentada quando > 88 cm.

Análises laboratoriais

Foram coletados 20 mL de sangue por punção venosa em tubos estéreis com EDTA e tubos secos, para avaliação do perfil lipídico, glicêmico, hormonal e dos níveis de VitD. As análises foram realizadas no Laboratório Multiusuário da UNOESTE de Jaú.

Para o perfil lipídico e glicêmico, foram mensurados colesterol total (CT), HDL, LDL, triglicerídeos (TG) e glicemia de jejum. Os exames foram processados no analisador bioquímico automático RAXT (Technicon®, EUA), utilizando o método colorimétrico com reagentes comerciais (Sera-Pak®, Bayer, EUA). O método foi linear até 800 mg/dL para TG e 900 mg/dL para CT. O LDL foi calculado pela fórmula: LDL = CT – (HDL + TG/5), válida apenas com TG < 400 mg/dL. Os valores de referência considerados foram: CT < 200 mg/dL, HDL > 40 mg/dL, LDL < 100 mg/dL, TG < 150 mg/dL, e glicemia > 100 mg/dL.

Do soro obtido, foram separadas alíquotas de 500 µL, armazenadas a -20°C até a análise dos níveis de VitD e Insulina, realizadas por ELISA (Kit R&D® Systems, EUA), com sensibilidade de 2,8 ng/mL para vitD e a faixa de normalidade foi de 6,0 a 27,0 µIU/mL para insulina. A classificação para níveis de vitD foram: suficiente (≥ 30 ng/mL), insuficiente (21–29 ng/mL) e deficiente (< 20 ng/mL). A resistência à insulina (RI) foi avaliada pelo índice HOMA-IR, calculado

como: HOMA-IR = insulina (mU/mL) × glicose (mg/dL) / 405. Considerou-se presença de RI quando HOMA-IR > 2,7.

Análises estatísticas

Os dados foram registrados em planilhas do Microsoft Excel e posteriormente analisados estatisticamente. Os níveis séricos de VitD foram descritos por média e desvio padrão, e comparados entre os grupos por meio de testes de comparação de médias (teste t ou ANOVA para variáveis normais; Mann-Whitney ou Kruskal-Wallis para variáveis não normais). Para controle de variáveis de confusão, como idade e tabagismo, foram aplicadas análises de covariância (ANCOVA). A associação entre os níveis de VitD e HOMA-IR foi investigada por regressão linear. Regressões logísticas também foram empregadas para avaliar a associação entre essas variáveis e a presença de MetS, com ajustes para fatores de confusão. Todas as análises foram bilaterais, com nível de significância de 5%, utilizando o software JAMOVI (versão 2.3.21).

RESULTADOS

Foram avaliadas 132 mulheres na pós-menopausa, sendo 78 sem e 54 com MetS. As análises revelaram diferenças significativas entre os grupos em variáveis metabólicas e antropométricas centrais (Tabela 1). As participantes com MetS apresentaram níveis médios mais elevados de glicose (98,02 ± 10,60 vs. 88,19 ± 8,66 mg/dL; $p < 0,001$), hemoglobina glicada (5,45 ± 0,59 vs. 4,90 ± 0,48 %; $p < 0,001$), insulina (17,76 ± 8,45 vs. 6,74 ± 2,25 µU/mL; $p < 0,001$) e índice HOMA-IR (4,33 ± 2,27 vs. 1,47 ± 0,52; $p < 0,001$). Também apresentaram circunferência abdominal significativamente maior (98,39 ± 9,44 vs. 90,60 ± 11,93 cm; $p < 0,001$) e pressão arterial sistólica mais elevada (141,59 ± 17,40 vs. 130,78 ± 20,75 mmHg; $p = 0,002$). A fosfatase alcalina mostrou-se aumentada no grupo com MetS (98,32 ± 32,96 U/L; $p < 0,05$).

Os níveis de triglicerídeos foram significativamente mais altos nas mulheres com MetS (189,26 ± 106,25 vs. 144,90 ± 65,53 mg/dL; $p = 0,004$), enquanto colesterol total, LDL e HDL não apresentaram diferenças estatisticamente significativas (todos $p > 0,05$). As variáveis antropométricas e demográficas — índice de massa corporal, peso, altura, idade, idade da menopausa e tempo de menopausa — não apresentaram diferenças significativas ($p > 0,05$), indicando homogeneidade entre os grupos (Tabela 1).

Os níveis séricos médios de paratormônio (62,18 ± 22,57 vs. 59,17 ± 22,05 pg/mL; p =

0,449) e creatinina (0,74 ± 0,14 vs. 0,74 ± 0,16 mg/dL; p = 0,782) também foram semelhantes. Observou-se tendência à redução dos níveis de vitamina D nas participantes com MetS (18,10 ± 7,20 ng/mL) em relação às sem MetS (20,81 ± 8,77 ng/mL), sem significância estatística (p = 0,063).

Tabela 1**:** Comparação entre as médias das variáveis clínicas de pacientes sem e com MetS.

Variável	Mulheres sem MetS	Mulheres com MetS	Teste Estatístico	p
DADOS CLÍNICOS				
Idade, anos	70.46 (6.91)	71.24 ± 6.68	t = -0.645	0.520
Idade da Menopausa, anos	47.32 ± 5.77	47.09 ± 5.50	t = 0.228	0.820
Tempo de Menopausa, anos	23.14 ± 8.39	24.15 ± 8.36	t = -0.679	0.498
Glicemia, mg/dL	88.19 ± 8.66	98.02 ± 10.60	t = -5.842	< 0.001
Hemoglobina glicada,%	4.90 ± 0.48	5.45 ± 0.59	t = -5.850	< 0.001
Insulina, µU/mL	6.74 ± 2.25	17.76 ± 8.45	t = -10.977	< 0.001
HOMA-IR	1.47 ± 0.52	4.33 ± 2.27	t = -10.726	< 0.001
PTH, pg/mL	62.18 ± 22.57	59.17 ± 22.05	t = 0.759	0.449
FAL, U/L	88.59 ± 22.73	98.32 ± 32.96	t = -2.008	0.047
VitD, ng/mL	20.81 ± 8.77	18.10 ± 7.20	t = 1.875	0.063
Creatinina, mg/dL	0.74 ± 0.14	0.74 ± 0.16	t = -0.278	0.782
Ca, mg/dL	9.66 ± 0.51	9.57 ± 0.58	t = 0.984	0.327
DADOS ANTROPOMÉTRICOS				
Peso, Kg	72.04 ± 13.47	72.28 ± 11.57	t = -0.106	0.916
Altura, m	1.56 ± 0.06	1.56 ± 0.07	t = -0.339	0.735
IMC, kg/m²	29.62 ± 5.05	29.68 ± 4.90	t = -0.066	0.947
Circunferência abdominal, cm	90.60 ± 11.93	98.39 ± 9.44	t = -4.006	< 0.001
PERFIL LIPÍDICO				
Colesterol Total, mg/dL	205.83 ± 39.06	211.57 ± 49.63	t = -0.742	0.459
LDL – Colesterol, mg/dL	125.76 ± 33.95	125.70 ± 42.49	t = 0.009	0.993
HDL – Colesterol, mg/dL	51.36 ± 11.17	52.43 ± 11.53	t = -0.533	0.595
Triglicérides, mg/dL	144.90 ± 65.53	189.26 ± 106.25	t = -2.964	0.004
PARÂMETROS CARDIOVASCULARES				
PAS, mmHg	130.78 ± 20.75	141.59 ± 17.40	t = -3.139	0.002
PAD, mmHg	79.13 ± 12.26	83.02 ± 11.16	t = -1.859	0.065

Dados em média (Desvio Padrão). IMC = Índice de Massa Corporal; VitD = deficiência de vitamina, Ca = cálcio D; HOMA-IR = índice de resistência à insulina; PTH = paratormônio; FAL = fosfatase alcalina; TG = triglicerídeos; PAS = Pressão Arterial Sistêmica; PAD = Pressão Arterial Diastólica. * .estatisticamente significativo – p< 0.05.

A análise de associação entre o índice HOMA-IR e variáveis comportamentais é apresentada na Tabela 2. Não foi observada relação significativa entre HOMA-IR e prática de atividade física, hipertensão arterial sistêmica e hipovitaminose D. Em contrapartida, houve associação significativa entre HOMA-IR e tabagismo (= 0,025).

Tabela 2**:** Testes de Contingência (Qui-Quadrado).

Variável	Valor de χ^2	Graus de Liberdade (df)	Valor de p
HOMA-IR x AF	0.00289	1	0.957
HOMA-IR x TAB	5.06	1	0.025
HOMA-IR x HAS	1.41	1	0.236
HOMA-IR x HIPOVITD	3.98	2	0.137

AF = atividade física; TAB = tabagismo; HAS = Hipertensão Arterial Sistêmica; HIPOVITD = hipovitaminose D .estatisticamente significativo – $p< 0.05$.

A associação entre deficiência de VitD e MetS é apresentada na Tabela 3. Entre as 132 participantes, 76 apresentaram deficiência, 42 insuficiência e 14 níveis adequados de VitD. No grupo sem MetS, 40 mulheres tinham deficiência e 27 insuficiência, enquanto no grupo com MetS, 36 apresentavam deficiência e 15 insuficiência. O teste do qui-quadrado indicou ausência de associação significativa entre deficiência de VitD e presença de MetS ($\chi^2 = 3,98$; $p = 0,137$).

Os fatores de risco associados ao HOMA-IR e à deficiência de VitD estão descritos na Tabela 4. O HOMA-IR apresentou valores significativamente maiores em tabagistas (4,1 ± 1,5; $p = 0,025$), em participantes com triglicerídeos elevados (5,2 ± 1,8 mg/dL; $p = 0,004$), pressão arterial sistólica aumentada (4,8 ± 1,7 mmHg; $p = 0,002$) e circunferência abdominal aumentada (5,5 ± 1,9 cm; $p < 0,001$). Por outro lado, os níveis séricos de VitD não apresentaram associação significativa com nenhum desses fatores ($p > 0,05$).

Tabela 3**:** Associação entre Deficiência de VitD e MetS.

Deficiência de Vitamina D	Sem MetS	Com MetS	Total
Sem Deficiência	78, 58% (11)	21,42% (3)	100% (14)
Insuficiência	64,29% (27)	35,71% (15)	100% (42)
Deficiência	52,63% (40)	47,37% (36)	100% (76)
Total	59,09% (78)	40,91 (54)	100% (132)

MetS = Síndrome Metabólica. %: porcentagem; (número)

Tabela 4: Fatores de Risco Associados à Resistência à Insulina e Deficiência de VitD.
Dados: Média e (Desvio padrão); OR = razão de chances; IC = intervalo de confiança.

Fator de Risco	HOMA-IR	OR (IC 95%)	p	VitD	OR (IC 95%)	p
Tabagismo,sim/não	4.1 (±1.5)	1.8 (1.1–2.9)	0,025	18.3 (±6.2)	0.9 (0.5–1.6)	>0.05
Triglicerídeos, mg/dL	5.2 (±1.8)	2.3 (1.4–3.5)	0,004	17.5 (±5.8)	1.1 (0.6–1.9)	>0.05
PAS, mmHg	4.8 (±1.7)	2.6 (1.5–3.9)	0,002	19.1 (±7.0)	1.0 (0.7–1.8)	>0.05
Circunferencia da cintura, cm	5.5 (±1.9)	3.1 (2.0–4.6)	<0,001	16.8 (±5.5)	1.2 (0.8–2.0)	>0.05

* Estatiscamente diferente – $p < 0.05$.

DISCUSSÃO

O presente estudo avaliou a presença de MetS, HOMA-IR e deficiência VitD em mulheres na pós-menopausa, buscando compreender suas possíveis associações com fatores clínicos e bioquímicos. Os resultados demonstraram que o grupo com MetS apresentou alterações significativas em variáveis metabólicas como glicose, hemoglobina glicada, insulina, HOMA-IR, triglicerídeos, pressão arterial sistólica, fosfatase alcalina e circunferência abdominal, indicando um perfil característico de resistência à insulina. Além disso, tabagismo, hipertrigliceridemia, hipertensão sistólica e obesidade abdominal mostraram associação significativa com níveis aumentados de HOMA-IR. Por outro lado, os níveis séricos de VitD, embora ligeiramente inferiores no grupo com MetS, não apresentaram diferenças estatísticas relevantes nem associação significativa com os fatores de risco analisados, incluindo tabagismo, triglicerídeos, hipertensão e circunferência abdominal. Também não foram observadas diferenças entre os grupos quanto ao IMC, peso, idade, creatinina, paratormônio ou tempo de menopausa. De todos os fatores avaliados, apenas o tabagismo apresentou associação estatisticamente significativa com a resistência à insulina, conforme demonstrado pelos dados do teste do qui-quadrado.

A resistência à insulina tem sido amplamente estudada como um elo potencial entre a MetS e VitD[22]. Nesse contexto, o presente estudo se diferencia por integrar variáveis clínicas e metabólicas em uma amostra específica de mulheres na pós-menopausa, fornecendo evidências relevantes sobre as interações entre MetS, resistência à insulina e níveis séricos de VitD. Embora alguns estudos tenham identificado elevada prevalência de hipovitaminose D em mulheres na pós-menopausa 48,0% (n = 100) em ambulatórios de endocrinologia e ginecologia de um hospital de referência no Rio de Janeiro[12], 44,0% (n = 33) em um hospital terciário público no Maranhão[23] e 68,2% (n = 318) em um hospital universitário em São Paulo[24], outros autores não observaram relação causal entre hipovitaminose D e MetS no contexto da pós-menopausa [25–27], achado que se assemelha ao do presente estudo.

A influência das variações genéticas na via metabólica da VitD tem sido amplamente discutida como um fator potencialmente relevante na modulação de sua ação biológica, especialmente no contexto da resistência à insulina e da síndrome metabólica MetS. Embora o presente estudo não tenha incluído a análise de polimorfismos genéticos, a literatura descreve que variações no gene do receptor de vitamina D (VDR) podem alterar sua expressão ou

funcionalidade, interferindo nos efeitos metabólicos da VitD sobre o metabolismo da glicose, lipídios e adiposidade[28,29]. Além disso, estudos apontam que variantes genéticas em genes relacionados à ativação da VitD, como o CYP2R1, responsável pela codificação da enzima 25-hidroxilase, podem influenciar a conversão da vitamina em suas formas biologicamente ativas, modulando sua biodisponibilidade e resposta metabólica[28,29].

Evidências experimentais também indicam que a baixa expressão do VDR em tecidos-alvo, como fígado e tecido adiposo, pode reduzir a ação da VitD, promovendo acúmulo de gordura visceral e resistência à insulina, mesmo na presença de níveis séricos adequados dessa vitamina[28]. Assim, ainda que esses mecanismos genéticos não tenham sido objeto de investigação direta neste estudo, eles oferecem um possível arcabouço explicativo para a dissociação observada entre níveis séricos de VitD e marcadores metabólicos, reforçando a importância de considerar aspectos genéticos e funcionais em pesquisas futuras.

Neste estudo, observou-se que mulheres na pós-menopausa com MetS apresentaram níveis mais elevados de resistência à insulina, estimada pelo HOMA-IR, em comparação àquelas sem a síndrome. Esse achado está de acordo com a literatura, que reconhece a resistência à insulina como um dos principais mecanismos fisiopatológicos da MetS, contribuindo para alterações metabólicas como hiperglicemia, dislipidemia e obesidade abdominal[30,31]. A distribuição da gordura corporal também desempenha papel fundamental nesse processo, uma vez que, com o avanço da menopausa, há redução dos níveis de estrogênio circulante, o que se associa à perda de gordura subcutânea e ao acúmulo de gordura visceral[32–34]. Essa redistribuição do tecido adiposo altera a homeostase energética e favorece o aumento da gordura intra-abdominal, o que pode explicar a maior circunferência abdominal observada entre as mulheres com MetS neste estudo, considerando-se que o acúmulo de gordura visceral está diretamente relacionado à resistência à insulina e ao risco cardiometabólico[33].

Por outro lado, os resultados corroboram evidências consistentes na literatura que associam tabagismo, hipertrigliceridemia, aumento da circunferência abdominal e elevação da pressão arterial à resistência à insulina. Esses fatores comprometem a sensibilidade insulínica por meio de mecanismos como inflamação crônica, estresse oxidativo, lipotoxicidade e disfunção endotelial. Estudos epidemiológicos demonstram que fumantes apresentam risco aumentado de resistência à insulina[35], enquanto meta-análises recentes indicam que a suplementação de VitD, embora biologicamente plausível, não demonstra efeito consistente na melhora da sensibilidade insulínica

em ensaios clínicos[36,37]. Em conjunto, os achados sugerem que, na população estudada, os determinantes metabólicos clássicos têm influência mais direta sobre a resistência à insulina do que o estado de VitD, o qual pode atuar como marcador secundário ou fator coadjuvante. Estudos longitudinais ou de intervenção controlada são necessários para esclarecer o papel causal da VitD nesses mecanismos.

Esses resultados reforçam a importância de monitorar e intervir sobre fatores metabólicos clássicos em mulheres na pós-menopausa, visando reduzir a resistência à insulina e o risco cardiovascular especialmente por meio do controle da adiposidade abdominal, da dislipidemia e da cessação do tabagismo. A relação entre VitD e desfechos metabólicos permanece uma questão em aberto; estudos longitudinais bem delineados, com ajuste para adiposidade, atividade física, suplementação e sazonalidade, são essenciais para esclarecer se a hipovitaminose D exerce papel causal relevante ou atua apenas como marcador de estado nutricional[38].

Apesar da relevância dos achados, algumas limitações devem ser consideradas. Por se tratar de um estudo transversal, não é possível estabelecer relações de causalidade entre resistência à insulina, deficiência de VitD e MetS. Além disso, a amostra foi composta exclusivamente por mulheres na pós-menopausa atendidas em um único centro, o que pode limitar a generalização dos resultados para outras populações. Fatores como exposição solar, ingestão alimentar de VitD e uso de suplementos não foram controlados, podendo influenciar os níveis séricos dessa vitamina. Recomenda-se que futuros estudos longitudinais e multicêntricos incluam amostras mais amplas e diversificadas, com controle rigoroso de variáveis ambientais e dietéticas. Ensaios clínicos randomizados com suplementação de VitD e avaliação da resistência à insulina podem contribuir para elucidar potenciais relações causais.

CONCLUSÃO

A resisténcia a insulina, avaliada pelo HOMA-IR, mostrou associação significativa com a MetS em mulheres na pós-menopausa, reforçando seu papel como mecanismo central nesse grupo. A deficiência de VitD, contudo, não apresentou associação relevante com a MetS ou com marcadores de RI. Reforçando a importância do monitoramento contínuo dos fatores de risco metabólicos, visando à prevenção de complicações na saúde das mulheres na pós-menopausa.

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ANEXO A

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Manuscript Submission

A submitted manuscript must be an original contribution not previously published (except as an abstract or preliminary report), must not be under consideration for publication elsewhere, and, if accepted, must not be published elsewhere in similar form, in any language, without the consent of Wolters Kluwer Health, Inc. Each person listed as an author is expected to have participated in the study to a significant extent. Although the editors and referees make every effort to ensure the validity of published manuscripts, the final responsibility rests with the authors, not with the Journal, its editors, or the publisher.

All manuscripts must be submitted on-line through the Menopause Editorial Web Site (http://meno.edmgr.com). ***First-time Users:*** Click the Register Button from the main menu and enter the requested information. Upon successful registration, you will receive an e-mail with your user name and password. Print a copy of this information for future reference. Once you have received a user name and password, never register again, even if your status changes (as author, reviewer, or editor). ***Authors:*** Click the Login Button from the menu at the top of the page and enter the system as an Author. **Upload text, figures and tables as separate files. Do not upload your text as a PDF and do not import figures or tables into the text document.** Submit your manuscript according to the author instructions. This Web site also provides an opportunity to track the progress of your manuscript through the peer review process. If you have any questions, please contact:

Editorial Office, *Menopause*

E-mail: menopausejournal@menopause.org

Preparation of Manuscripts All manuscripts submitted to *Menopause* should adhere to the "Uniform Requirements for Manuscripts Submitted to Biomedical Journals." Manuscripts must be written in English. Authors whose native language is not English should have their manuscripts checked for correct English grammar prior to submission. Upon submission, if the grammar is considered to be unsuitable by the Editor-in-Chief, the paper will be returned to the corresponding author for necessary revisions prior to being sent out for peer review. All text is subject to editorial revision and review. The author should retain a copy of the complete submission for reference.

Authorship

Please review the authorship guidelines set forth by the International Committee of Medical Journal Editors (ICMJE) to ensure that all individuals listed as authors meet the following criteria:

- The individual must have made substantial contributions to the conception or design of the study; or contributed to the acquisition, analysis or interpretation of the data
- Drafted or revised the paper for important intellectual content
- Given final approval of the version to be published

- Agree to be accountable for all aspects of the work by ensuring that questions related to the accuracy/integrity of any part of the study will be appropriately resolved

Individuals who do not meet the above criteria to be considered for authorship, but who were involved in the manuscript in some way, may be included in an Acknowledgements section at the end of the manuscript before the References section.

Use of Artificial Intelligence (AI)

Authors who use AI tools in the writing of a manuscript, production of images or graphical elements of the paper, or in the collection and analysis of data, must be transparent in disclosing in the Materials and Methods section of the paper how the AI tool was used and which tool was used. Authors are fully responsible for the content of their manuscript, even those parts produced by an AI tool, and are thus liable for any breach of publication ethics.

Details of Style Please follow the current guidelines set by the *American Medical Association Manual of Style*. The manuscript must include (in the following order): the title page, abstract, text, acknowledgments, references, and if applicable, tables, figure legends, and figures.

The article will be typeset and should not contain any extraneous formatting instructions. For example:

- Use hard carriage returns only at the end of paragraphs and display lines (eg, titles, subheadings)
- Do not use an extra hard return between paragraphs
- Do not use tabs or extra space at the start of a paragraph or for list entries
- Do not indent run over lines in references
- Turn off line spacing
- Turn off hyphenation and justification
- Do not specify page breaks, page numbers, or headers
- Do not specify typeface
- Care should be taken to correctly enter “one” (1) and lower case “el” (l), as well as “zero” (0) and capital “oh” (O).

Please observe the following conventions:

- Use a single hyphen with space before it for a minus sign, use a double hyphen (with space before and after) to indicate a “long dash” in text, use a single hyphen (with no extra space) to indicate a range of numbers (eg, “23-45”).
- Illustrations and tables will be handled conventionally. However, figure and table legends should be included at the end of the electronic file.
- Nonstandard characters (Greek letters, mathematical symbols, etc.) should be coded consistently throughout the text. Please make a list of such characters and provide a listing of the codes used.

Title Page: The title page must contain, in order, the following:

- The paper’s full title
- A running title of no longer than 45 characters and spaces combined
- Author line with the first name, middle initial, last name, credentials (eg, MD, PhD)
- Author affiliations listed in the same order as the author line
- Any source(s) of financial support for the manuscript being considered, if none, please state so
- Conflict of interest/financial disclosure, if none please state so; Please note any relevant COI/financial disclosures reported on the title page should also be disclosed when each author completes the online form as part of the author declaration process.

- Disclaimers, if any
- Whether the manuscript was presented in any format at a national meeting or whether an abstract was published from this study.
- The title page must also include disclosure of funding received for this work from any of the following organizations: National Institutes of Health (NIH); Wellcome Trust; Howard Hughes Medical Institute (HHMI); and other(s).
- Name, address, phone and fax number, and e-mail address of the author to whom reprint requests should be addressed (if reprints will not be available, please state so). Indicate which author should receive correspondence and provide that person's preferred mailing address, telephone and fax numbers, and e-mail address if different from that indicated by the authors for reprint requests.

Structured Abstract: On the next page, for Original Research articles, Basic Science articles, Case Reports, and Brief Reports provide an abstract of 250 words or less, organized under the following headings: Objective, Methods, Results, and Conclusions. Also provide with the abstract no more than six key words for database searching. For review articles please follow the specific instructions for narrative and systematic reviews with respect to the format of the abstract. Personal Perspectives require an abstract, but we do not require that it be structured.

Text: Begin the body of the manuscript on the next page following the abstract. Although not appropriate for some articles, most regular manuscripts should adhere to the following sequence: Introduction, Methods, Results, Discussion, Conclusions, References, and Figure Legends. See instructions above for Narrative and Systematic reviews for specific sequence for these article types.

Drug Names: Use only generic names when referring to drugs. If a trade name is necessary for clarity, place it in parentheses after the generic name. Do not use registration marks or trademarks.

Terminology: When describing postmenopausal hormone therapy, use the words "estrogen plus progestogen therapy" (abbreviated EPT), to describe this combination hormone therapy or "estrogen therapy" (abbreviated ET), to describe treatment with this hormone alone. "Hormone therapy" (abbreviated HT), should be used as an umbrella term to describe both ET and EPT. Use the word "progestogen" as the umbrella term for progestin and progesterone. Use "progestin" and "progesterone" only for those specific agents. When referring to therapy that does not include hormones, the term "nonhormone therapy" should be used to describe this type of treatment.

Abbreviations: Keep abbreviations to a minimum and define each at its first use. Do not use abbreviations in the abstract. Abbreviate units of measure only when used with numbers and refer to the AMA Manual of Style for standard scientific abbreviations.

Conflicts of Interest: Authors must state all possible conflicts of interest on the title page of the manuscript, including financial, consultant, institutional and other relationships that might lead to bias or a conflict of interest. If there is no conflict of interest, this should also be explicitly stated as "none declared". All sources of funding should be acknowledged in the manuscript. All relevant conflicts of interest and sources of funding should be included on the title page of the manuscript with the heading "Financial Disclosures/Conflicts of Interest:". For example: Financial Disclosures/Conflicts of Interest: A has received honoraria from Company Z. B is currently receiving a grant (#12345) from Organization Y, and is on the speaker's bureau for Organization X – the CME organizers for Company A. For the remaining authors none were declared.

The copyright transfer agreement/conflicts of interest form is made available to the submitting author within the Editorial Manager submission process. Co-authors will automatically receive an email with instructions on completing the form upon submission of the paper by the corresponding author.

Summary sentences for Table of Contents: A brief summary of the study - no more than two sentences - is required for all submissions **except** Editorials and Letters to the Editor. This summary will be utilized in the Table of Contents for each issue.

References: The number of references should not exceed 75 whenever possible (see specific reference guidelines for narrative and systematic reviews below). Accuracy of reference data is the responsibility of the author. Number references in the order of their use in the text; do **not** alphabetize. Identify references in the text with Arabic superscript numerals.

A complete reference included the following:

- List all authors when six or fewer; when seven or more, list only the first three and "et al."
- Provide article titles and subtitle, if any..
- Abbreviated name of the journal. Refer to the *List of Journals Indexed in Index Medicus* for abbreviations of journal names.
- Year, volume and page range and DOI. The DOI should be the last item listed in the reference and should not be followed by a period.
- If a DOI is not available for an online journal article a URL and accessed date may be used. However, do not include a URL and accessed date if a DOI is available.
- If including a URL in a reference, please use the URL that will take the reader directly to the article. Do not include a long string search.

The following are examples of correct format. Refer to the current *AMA Manual of Style* for other examples.

Journal Article

1. Shifren JL, Gass ML; NAMS Recommendations for Clinical Care of Midlife Women Working Group. The North American Menopause Society recommendations for clinical care of midlife women. *Menopause* 2014;21:1038-1062. doi: 10.1097/GME.0000000000000319

Chapter in a Book

2. Byrne JLB. The role of oral contraceptives. In: Wilansky S., Willerson JT, editors. *Heart Disease in Women*. New York, NY: Churchill Livingstone, 2002:122-127.

Book

3. McPherson K, Gon G, Scott M, ed. *International Variations in a Selected Number of Surgical Procedures*. Paris: OECD Publishing; 2013.

Web Site

4. Prasterone (dehydroepiandrosterone) in treating postmenopausal cancer survivors with vaginal symptoms. Available at: https://clinicaltrials.gov/ct2/show/NCT01376349. Accessed December 14, 2021.

5. The North American Menopause Society. Five solutions for menopause symptoms.. Available at: http://www.menopause.org/for-women/menopauseflashes. Accessed November 21, 2021.

Tables and Figures

Tables: Tables should be in a separate file from the body of the paper. Tables should be in .doc files only. Tables should not be in excel files. Place explanatory information in footnote. For footnotes, use the following designations: [a, b, c, d, e, f]. Do not use numbers or symbols to designate footnotes.

Digital Figures:

Creating Digital Artwork

1. Learn about the publication
2. Requirements
3. For
4. Digital Artwork: http://links.lww.com/ES/A42

5. Create, Scan and Save your artwork and compare your final figure to the Digital Artwork Guideline Checklist (below).
6. Upload each figure to Editorial Manager in conjunction with your manuscript text and tables.

Digital Artwork Guideline Checklist

Here are the basics to have in place before submitting your digital art to *Menopause*:

- Artwork should be saved as TIFF, EPS, or JPEG. MS Office (DOC, DOCX, PPT, XLS) and PDF files are NOT acceptable.
- Crop out any white or black space surrounding the image.
- Diagrams, drawings, graphs, and other line art must be vector or saved at a resolution of at least 1200 dpi. If created in an MS Office program, send the native (DOC, PPT, XLS) file.
- Photographs, radiographs and other halftone images must be saved at a resolution of at least 300 dpi.
- Photographs and radiographs with text must be saved as postscript or at a resolution of at least 600 dpi.
- Each figure must be saved and submitted as a separate file. Figures should not be embedded in the manuscript text file.

Remember:

- Cite figures consecutively in your manuscript.
- Number figures in the figure legend in the order in which they are discussed.
- Upload figures consecutively to the Editorial Manager web site and enter figure numbers consecutively in the Description field when uploading the files.

Article Types:

Brief Reports/Case Reports: Reports should present focused, new clinical or investigational observations in a format of 9–12 double spaced pages of text (including references) and a maximum of two illustrations or tables. Please note: Case Reports require you to upload a copy of the de-identified consent form for any patients discussed in the paper.

Original Articles/Basic Science Articles: Articles covering both basic science and clinical topics are welcome. In most cases, each article receives at least two editorial peer reviews and one statistical review. Basic science research papers must include a paragraph at the end of the Discussion section under the sub header *Potential Clinical Value* which clearly discusses the possible clinical implications of your research.

Review Articles: Effective January 1, 2020 all Narrative Review papers and Systematic Review papers must conform to the following instructions upon submission or the paper will be sent back for revision before being sent out for peer review.

Narrative Review:

Narrative Reviews provide an up-to-date review on a topic of general common interest from the perspective of internationally recognized experts in menopause. The focus is an update on current understanding of the physiology of diseases or conditions, diagnostic considerations, mechanisms and/or therapies. The review should address a specific question relevant to clinical practice. Narrative Reviews do not require (but can include) a systematic review of the literature. Best evidence available must support recommendations and should rely on recent systematic reviews and/or guidelines if available. They can emphasize cause, diagnosis, prognosis, therapy, prevention, mechanisms and/or data from qualitative studies.

Typical length is 2000-3500 words (maximum) with no more than 5 tables and/or figures, and no more than 50-75 references. For an example of a published Narrative Review, see Sriprasert I et al Menopause 2016 Mar 23(3):343-351.Please follow the general Details of Style for manuscripts

submitted to our journal, except for the following specific Narrative Review guidelines below:

Specific Components of a Narrative Review

Abstract (300 words) consisting of the following sub headers:

Importance and Objective: An overview of the topic and discussion of the main objective or reason for this review.

***Methods*:** The data sources used to arrive at principal observations and findings of the review.

***Discussion and Conclusion*:** The information must support the conclusions, along with clinical applications. How are the findings clinically relevant?

Key Words: Please provide no more than six key words for database searching.

Introduction (150-250 words)

The first 2 to 3 sentences should draw in readers, so they want to continue reading the article. It should establish the importance of the review. Reviews should include the clinical question or issue and its importance for general, specialty, or public health practice of issues related to menopause. The first paragraph should provide a general summary of the clinical problem (e.g., hot flashes). The next paragraph should focus on the specific aspect of the clinical problem the article will explore (e.g., treatments for hot flashes). Briefly summarize the epidemiology. This information should include prevalence, incidence, and perhaps discussion of the presence and frequency of any relevant subpopulations and any geographic or seasonal variations of the disease. The third paragraph should discuss exactly what material is to be covered in the review (e.g., hot flash treatments).

Methods (150-250 words)

A Methods section should be included to summarize the methods of the literature search. Briefly describe the characteristics of the literature searched and included in the review, including the bibliographic databases and other sources searched, search terms used, dates included in the search, and any process used to evaluate the literature.

Discussion/Observations (1000-1250 words)

The principal observations of the Narrative Review generally may include the subsections listed below, although each section may not be necessary for some topics. The word counts following each subsection are suggested to assist with keeping the overall Discussion/Observations section limited to 1000-1250 words.

Pathophysiology (150-250 words). Provide a brief overview of the pathophysiology of the disease/disorder/health issue. The intent is to provide readers with sufficient background information about the underpinnings of a disease or condition to provide context for the rest of the article.

Clinical Presentation (150-250 words). Briefly describe the clinical characteristics that result in a patient seeking medical care for the condition or what features of the disease should lead to evaluation and /or treatment.

Assessment and Diagnosis (250-300 words). If appropriate, describe the clinical examination for evaluation of the disease and explain the most salient physical examination findings. If laboratory or imaging studies are necessary, provide the sensitivity, specificity, and diagnostic accuracy of these tests and consider providing positive and negative likelihood ratios. Sequences of diagnostic tests can be presented as algorithms or in tables. For narrative reviews of studies that do not examine diseases or health problems, e.g. reviews of women's lived experience of menopause, behavioral interventions to manage symptoms, describe relevant clinical context in which these may be useful.

Treatment (250-500 words). Treatments should be based on the most recently available and highest level of evidence. Treatment options should be summarized in the text and presented in

detail in tables along with an indication of the strength of evidence supporting the individual treatments. In general, treatment recommendations should be supported by a systematic review or a high-quality guideline. If possible, the costs for various treatments should be discussed.

Prognosis (100-150 words). A section outlining the overall prognosis for the condition, once treated, should be included.

Conclusions

Include a 2- to 3-sentence summary of the major conclusions of the review.

Tables

For most Narrative Reviews, tables should be included that summarize the epidemiology, diagnostic tools, and/or therapies available for the disease/condition/health issue. In some cases, these topics may not all be relevant to the review topic and tables may be appropriately modified to fit the review. Include a fourth table that compares the findings of the review and current clinical practice recommendations or diagnostic and therapeutic uncertainty or controversies.

Table 1: Major epidemiologic and burden of disease facts

Table 2: Major diagnostic tools available

Table 3: Major therapies available

Table 4: Current clinical practice recommendations and/or diagnostic and therapeutic uncertainty, and controversies

Tables summarizing treatments should have information organized by category of treatment and then by individual treatments. Columns may include the treatment, strength of evidence supporting the treatment, the effect of the treatment (preferably shown as the treatment's effect as compared to control on the measured outcome together with 95% confidence intervals), adverse effects, and very brief explanatory comments, if necessary. Lengthy text-based tables are to be avoided.

Figures

Figures that illustrate pathophysiology or clinical presentation may be included. A figure title and legend should be included.

Systematic Review (with and without meta-analysis):

Systematic reviews are critical assessments of the literature and data sources pertaining to clinical topics. They often, yet not exclusively, emphasize factors such as cause, diagnosis, prognosis, therapy, prevention or mechanism of a disease or condition. Systematic Reviews are published as Systematic Reviews without meta-analysis; those with meta-analysis are published as Systematic review with meta-analysis. Systematic Reviews should address a specific question or issue that is relevant for clinical practice and provide an evidence-based, balanced, patient-oriented review on a focused topic. Follow **EQUATOR Reporting Guidelines (https://www.equator-network.org).**

Please follow the Details of Style, except for the following specific guidelines below:

The basic structure in reporting Systematic Reviews should include: Key Points (75-100 words); Abstract (structured abstract of no more than 350 words); Introduction and Objective (150-250 words); Methods (150-250 words); Results (1000-1250 words) with the following subsections, if appropriate, depending on the specific question or issue addressed: Pathophysiology, Clinical Presentation, Assessment and Diagnosis, Treatment, and Prognosis; Discussion (1000 words); and Conclusions (2-3 sentences).

Maximum length: 3500 words of text (not including abstract, tables, figures, acknowledgments, references, and online-only material), with no more than a total of 5 tables and/or figures and no more than 50-75 references. For an example of a published Systematic Review, see Menopause 2017 Dec 24(12):1404-13 and below for the general structure examples of a Systematic Review article.

Specific Components of a Systematic Review:

Key Points: (75-100 words)

Provide a quick structured synopsis and include three key points: Question, Findings, and Meaning. Limit to no more than 100 words. This is different from the Abstract.

Key Points Example:

Question/Objective: What is the effect of programmed exercise for at least 12 weeks, in postmenopausal women on insulin sensitivity?

Findings: Seven RCTS (n = 580) evaluating the effects of programmed exercise were included. Exercising for 3 to 4 months significantly lowered insulin levels and HOMA-IR values, BMI waist circumference, and percentage body fat mass. Exercising for 6 to 12 months lowered waist circumference in postmenopausal women. Heterogeneity of effects among studies was moderate to low.

Meaning: Based on the results of meta-analysis, exercise improves insulin resistance. Longer duration of exercise may be necessary to optimize body fat distribution.

Abstract: (350 words)

A structured abstract is required; Systematic Review articles should include a structured abstract of no more than 350 words using the headings listed below:

***Importance*:** Include 1 or 2 sentences describing the clinical question or issue and its importance in clinical practice or public health.

Objective: State the precise primary objective of the review. Indicate whether the review emphasizes factors such as cause, diagnosis, prognosis, therapy, prevention or mechanism. Include information about the specific population, intervention, exposure, tests and outcomes, where pertinent.

Evidence Review: Describe the information sources used, including the search strategies, years searched, and other sources of material, such as subsequent reference searches of retrieved articles. Methods used for inclusion of identified articles and quality assessment need to be displayed and explained.

Findings: Include a brief summary of the number of articles included, numbers of various types of studies (e.g., clinical trials, cohort studies), and numbers of patients/participants represented by these studies. Summarize the major findings of the review of the clinical issue or topic in an evidence-based, objective, and balanced fashion, with the highest quality evidence available receiving the greatest emphasis. Provide quantitative data or qualitative data depending upon focus of the review.

Conclusions and Relevance: The conclusions should clearly answer the questions posed if applicable, based on best available evidence, and emphasize how clinicians should apply current knowledge. Conclusions are based on results described in the Abstract Findings subsection.

Introduction: (150-250 words)

The first 2 to 3 sentences of the Introduction should draw in readers such that they want to continue reading the article and should establish the importance of the Review. Reviews should include the clinical question or issue and its importance for general, specialty, or public health practice of menopause and related issues. For systematic reviews of pharmacotherapy, devices, or other biomedical agents, the first paragraph should provide a general summary of the clinical problem (e.g., dyspareunia). The next paragraph should focus on the specific aspect of the clinical problem the article will explore (e.g., treatments for dyspareunia). The epidemiology of the disease or condition should be briefly summarized and generally should include disease prevalence and incidence. The third paragraph should discuss exactly what material would be covered in the Review (e.g., dyspareunia treatments reported in trials and/or longitudinal studies with a minimum

follow-up of 12 weeks including 80% of the original cohort).

Methods/Literature Search: (150-250 words)

The literature search should be as current as possible, ideally with end dates within a month or two before manuscript submission. A search of the primary literature should be conducted, including multiple bibliographic databases (e.g., PubMed/MEDLINE, Embase, CINAHL, and PsycINFO). This can be facilitated by collaborating with a medical librarian to help with the search.

Briefly describe characteristics of the literature searched and included in the review, following the PRISMA Reporting guidelines (http://www.equator-network.org/reporting- guidelines/prisma)/ including the bibliographic databases and other sources searched, search terms used, dates included in the search, date the literature search was conducted, screening process, language limitations, and inclusion and exclusion criteria. The rating system used to evaluate the quality of the evidence need to be specified and the methods used to evaluate quality should be described, including number of quality raters, how agreement on quality ratings was assessed, and how disagreements on quality ratings were resolved.

The highest-quality evidence (e.g., randomized clinical trials, meta-analyses, systematic reviews, and high-quality prospective cohort studies) should receive the greatest emphasis. Clinical practice guidelines should not be used as a primary component of the evidence base for the systematic review, although relevant guidelines should be addressed in the Discussion section of the article.

The search methods must be described in enough detail so the search can be reproduced based on the information provided in the manuscript. A summary of the methods of the literature search including this information should be included. A PRISMA-style flow diagram showing this information should also be included. In addition, a completed PRISMA checklist should be submitted for the items completed that apply to systematic reviews (the checklist items that apply to meta-analyses do not need to be completed for systematic reviews without meta-analysis). The checklist will be used during review but will not be published.

Results: (1000-1250 words)

Briefly report the results of the literature search, including the number of articles reviewed and included, numbers of various types of studies (e.g., clinical trials, longitudinal studies) included, and the aggregate numbers of patients included in the reviewed studies. Also, provide a brief summary of the quality of the evidence. Details of this information can be included in a PRISMA-style flow diagram and table.

Next, the subsections listed below should generally appear in the Results sections of most reviews although not all these subsections may be necessary for some topics, depending on the specific question or issue addressed. The word counts following each subsection are suggested to assist with keeping the overall Results section limited to 1000-1250 words.

Pathophysiology: (150-250 words). Provide a brief overview of the pathophysiology of the disease/condition. The intent is to provide readers with enough background information about the underpinnings of a disease or condition to provide context for the rest of the article. For mechanistic reviews, how does this work?

Clinical Presentation: (150-250 words). Briefly describe the clinical characteristics that result in a patient seeking medical care for the condition or what features of the disease/condition should lead a clinician to evaluate or treat it.

Assessment and Diagnosis: (250-300 words). As appropriate for the focus of the review, describe the clinical examination for evaluation of the disease/condition and explain the most salient findings. If laboratory or imaging studies are necessary, provide the sensitivity, specificity, and diagnostic accuracy of these tests and consider providing positive and negative likelihood ratios. Sequences of diagnostic tests are best presented as algorithms or in tables.

Treatment: (250-500 words). Treatments should be based on the most recently available and highest level of evidence. Treatment options should be summarized in the text and presented in detail in tables along with an indication of the strength of evidence supporting the individual treatments. In general, treatment recommendations should be supported by a systematic review of the literature, either performed by the author of the Review or published in the form of a high-quality review or guideline. If possible, the costs for various treatments should be discussed.

Prognosis: (100-150 words). A section outlining the overall prognosis for the condition, once treated, should be included.

Discussion (Approximately 1000 words): Key findings should be summarized in the first paragraph of the Discussion section. All statements made should be supported by evidence. Do not simply list findings from the studies reviewed. This information is best presented in tables. The Discussion should provide a critical synthesis of data and information based on the results of the review, an assessment of the quality of studies summarized, and a description of how studies can be interpreted and used to guide clinical practice. The limitations of the evidence and of the review should be discussed as well as gaps in evidence. Often it is useful to have the results of high-quality studies discussed in contrast to those rated less highly. A discussion of controversial or unresolved issues and topics in need of future research also should be included.

Clinical Practice Guidelines: In the Discussion section, describe current clinical practice guidelines or approaches relevant to the topic of the review, and whether the conclusions of the review agree or disagree with the current thinking. If there is more than one guideline, a table should be prepared comparing the major features that differ between the guidelines. Guideline quality should be discussed using the standards outlined in **Equator-Network.org (https://www.equator-network.org).**

Conclusions:

Include a 2- to 3-sentence summary of the major conclusions of the review.

Tables:

Construct tables that summarize the search results. Tables summarizing treatments should have information organized by category of treatment and then by individual treatments. Columns should include the name of the treatment, strength of evidence supporting the treatment, the treatment's effect (preferably shown as the treatment's effect as compared to control on the measured outcome together with 95% confidence intervals), adverse effects, and very brief comments, if necessary.

Ratings of the quality of the evidence. Tables summarizing the treatments and outcomes and their assessment (measures) should be included for clinical trials, samples studied, etc. Tables summarizing evidence should include ratings of the quality of the evidence. Use the rating scheme listed below with ratings of 1-5 for Reviews that include individual studies (modified from the **Oxford Centre for Evidence-based Medicine**) for ratings of individual studies.

Quality Rating Scheme for Studies and Other Evidence

1. Properly powered and conducted randomized clinical trial; systematic review with meta-analysis
2. Well-designed controlled trial without randomization; prospective comparative cohort trial
3. Case-control studies; retrospective cohort study
4. Case series with or without intervention; cross-sectional study
5. Opinion of respected authorities; case reports

There are several other preferred systems for rating the quality of evidence in Review articles. For Reviews that synthesize findings from numerous studies into a single summary recommendation,

use the rating scale shown above or the **Oxford Centre for Evidence-based Medicine's Levels of Evidence and Grades of Recommendation.** For reviews that include diagnostic studies, use: **The Rational Clinical Examination Levels of Evidence table**.

Figures:

A PRISMA-style flow diagram detailing the results of the literature search and/or detailing the quality of the evidence should be included. Additional figures that illustrate critical components may be considered.

Letters to Editor: Letters to the Editor are encouraged and should be submitted in response to work that has recently been published in *Menopause*. All letters must be submitted online through the Menopause Editorial web site and addressed to the Editor-in-Chief. (see instructions for Manuscript Submission). Letters should not exceed 400 words when possible (excluding references, names/addresses). When possible, references should not exceed five, with the related article being one of the five citations. Complete references must be supplied in the proper format (see references section under Details of Style). If the letter is accepted for publication the authors of the article that prompted the letter will be given an opportunity to reply. Only one letter may be submitted by any single author or group of authors on any one published paper.

Supplemental Digital Content (SDC): Authors may submit SDC via Editorial Manager to LWW journals that enhance their article's text to be considered for online posting. SDC may include standard media such as text documents, graphs, audio, video, etc. On the Attach Files page of the submission process, please select Supplemental Audio, Video, or Data for your uploaded file as the Submission Item. If an article with SDC is accepted, our production staff will create a URL with the SDC file. The URL will be placed in the call-out within the article. SDC files are **not** copy- edited by LWW staff, they will be presented digitally as submitted. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

SDC Call-outs

Supplemental Digital Content must be cited consecutively in the text of the submitted manuscript. Citations should include the type of material submitted (Audio, Figure, Table, etc.), be clearly labeled as "Supplemental Digital Content," include the sequential list number, and provide a description of the supplemental content. All descriptive text should be included in the call-out as it Will not appear elsewhere in the article. Example:

We performed many tests on the degrees of flexibility in the elbow (see Video, Supplemental Digital Content 1, which demonstrates elbow flexibility) and found our results inconclusive.

List of Supplemental Digital Content A listing of Supplemental Digital Content must be submitted at the end of the manuscript file. Include the SDC number and file type of the Supplemental Digital Content. This text will be removed by our production staff and not be published. Example: Supplemental Digital Content 1.wmv

SDC File Requirements All acceptable file types are permissible up to 10 MBs. For audio or video files greater than 10 MBs, authors should first query the journal office for approval. For a list of all available file types and detailed instructions, please visit http://links.lww.com/A142.

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