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

ESTADO MENOPÁUSICO E SÍNDROME METABÓLICA EM MULHERES NO CLIMATÉRIO ATENDIDAS EM UM AMBULATÓRIO NO SUL DO BRASIL

KARINA GIANE MENDES

Porto Alegre, 2012

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

Porto Alegre, 2012

Este trabalho é dedicado àquelas pessoas que viveram intensamente este momento comigo. Essa é uma recompensa pelas horas em que estive ausente: **Caian**, meu marido/parceiro/companheiro, obrigada pela paciência, conforto e compreensão nesse período; **mãe**, obrigada por me incentivar e acreditar em mim, sempre prá sempre; **pai**, obrigada por me tratar com tanto carinho e amor; Diego, meu **irmão** querido, desculpa o estresse do último ano e obrigada por estar sempre ao meu lado... Amo vocês!

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

1. Artigo de revisão: Prevalência de Síndrome Metabólica e seus componentes na transição menopáusica (publicado nos Cadernos de Saúde Pública)
2. Artigo original 1: Estado Menopáusico e Síndrome Metabólica em mulheres no climatério atendidas em um ambulatório no sul do Brasil (publicado no Open Journal of Endocrine and Metabolic Diseases)
3. Artigo original 2: Produto de Acumulação Lipídica (LAP) e sua relação com características socioeconômicas, reprodutivas e risco cardiometabólico em mulheres no climatério (será submetido à Revista de Saúde Pública)

SUMÁRIO

RESUMO

A síndrome metabólica (SM) é um transtorno complexo, caracterizado por um agrupamento de fatores de risco cardiovasculares. Sugere-se que a fase da transição menopáusica possa ser um determinante importante no aumento da prevalência da SM. Foi realizado um estudo transversal com 551 mulheres de 40 a 65 anos atendidas em um ambulatório no sul do Brasil, excluídas as mulheres histerectomizadas e que faziam terapia de reposição hormonal.

No artigo de revisão, o objetivo foi avaliar, por meio de uma revisão sistemática, a prevalência de SM e dos seus componentes na transição menopáusica. Com base nos estudos analisados, a prevalência de SM aumenta na comparação do período da pré para a pós-menopausa, independente da população e do delineamento do estudo. As maiores prevalências de SM foram encontradas nos estudos transversais de base populacional, quando comparados aos estudos transversais realizados em ambulatório. Quanto aos componentes, a alteração foi mais expressiva nas medidas de CC e PA. Sugere-se que esses componentes sejam os que exercem maior influência na prevalência de SM.

No artigo original I, os objetivos foram conhecer a relação entre estado menopáusico e a presença de Síndrome Metabólica em mulheres de 40 a 65 anos, bem como descrever a distribuição de cada um dos componentes da Síndrome Metabólica segundo o estado menopáusico. A prevalência de Síndrome Metabólica na amostra foi de 56,1% ($IC_{95\%}$ 51,9 a 60,2), sendo mais frequente entre as mulheres mais velhas (56 a 65 anos), com baixa escolaridade, menarca $\leq$ 11 anos de idade, com 3 ou mais gestações e que estavam na pós-menopausa. Quanto à análise dos componentes isolados na amostra, os componentes alterados mais prevalentes foram: hipertensão arterial (84,8%; $IC_{95\%}$: 81,7 a 87,8), circunferência da cintura (66,4%; $IC_{95\%}$: 62,5 a 70,4) e HDL-colesterol (51,7%; $IC_{95\%}$: 47,5 a 55,9). Na análise multivariada, observou-se aumento das razões de prevalência, comparando perimenopausa e pós com a pré-menopausa; entretanto, os intervalos de confiança incluem a unidade.

No artigo original II, o objetivo do estudo foi verificar a associação do índice LAP com características socioeconômicas, demográficas, reprodutivas e de qualidade de vida, investigar sua relação com estado menopáusico e avaliar o LAP como rastreador de diabetes mellitus e síndrome metabólica. A síndrome metabólica foi avaliada conforme os critérios do NCEP-ATPIII *(National Cholesterol Education Program's Adult Treatment Panel III)*. As mulheres com glicose em jejum acima de 100mg/dl/presença de

Diabetes Mellitus também foram avaliadas separadamente. A média do LAP foi de 61,31 cm.mmol/L ($IC_{95\%}$ 59,9 a 64,7). Idade entre 56 e 65 anos, três ou mais gestações e ser ex-fumante mostraram-se positivamente associados ao aumento do LAP, mesmo após o ajuste nos modelos multivariados. A prevalência do LAP elevado (≥34,5 cm.mmol/L) foi de 71,3% ($CI_{95\%}$: 67,6 a 75,1). Mulheres com LAP elevado apresentaram probabilidade 4,6 vezes maior de desenvolver SM ($CI_{95\%}$ 3,2 a 6,6) e 2,4 vezes maior de ter glicose elevada ou presença de DM ($CI_{95\%}$ 1,6 a 7,4), quando comparadas às mulheres com LAP < 34,5 cm.mmol/L.

Em conclusão, através deste estudo, foi possível evidenciar que, além da pressão arterial e da circunferência da cintura, a alteração na glicemia e nos triglicerídeos séricos exerce um papel importante no aumento da Síndrome Metabólica durante o climatério. Também foi possível observar que o LAP pode ser uma nova alternativa para predizer risco cardiometabólico, pois, além da medida da circunferência da cintura, inclui a medida dos triglicerídeos, que nas mulheres parece representar um risco aumentado para mortalidade cardiovascular, independentemente de outras frações lipídicas.

ABSTRACT

Metabolic syndrome (MetS) is a complex disorder represented by a cluster of cardiovascular risk factors. Menopausal transition may be a key factor in the increase of prevalence of MetS.A cross-sectional study was conducted with 551 women from 40 to 65 years treated at a clinic in southern Brazil. Hysterectomized women and women who were submitted to hormone replacement therapy were excluded from the study.

The review article aimed to evaluate, through a systematic review, the prevalence of MetS and its components in the menopausal transition. Based on the studies analyzed, the MetS prevalence increases when comparing pre- and post menopausal periods, regardless of the population and study design. The highest evidences were found in a population-based, cross-sectional study when compared to cross-sectional studies performed at a clinic. Regarding to the components, the change was more significant for WC and BP measurements. It is suggested that these components may be those which have more influence on the prevalence of MetS.

The original article I aimed to understand the relationship between menopausal status and the presence of Metabolic Syndrome in women from 40 to 65 years, as well as to describe the distribution of each component of Metabolic Syndrome according to menopausal status.. The prevalence of Metabolic Syndrome in the sample was 56.1% ($CI_{95\%}$ 51.9 to 60.2), being more common among older women (56 to 65 years), with low education, menarche $\leq$ 11 years old, with three or more pregnancies and in the post-menopausal period. Regarding the analysis of isolated components in the sample, the most prevalent altered components were: hypertension (84.8%; $CI_{95\%}$: 81.7 to 87.8), waist circumference (66.4%; $CI_{95\%}$: 62.5 to 70.4) and HDL cholesterol (51.7%; $CI_{95\%}$: 47.5 to 55.9). In multivariate analysis, there was an increase of prevalence ratios when comparing perimenopause and post-menopause with pre-menopause; however, the confidence intervals include the unit.

The original article II aimed to verify the association of LAP index with socioeconomic, demographic, reproductive and quality of life characteristics, to investigate its relation with menopausal status, as well as to assess the LAP as a tracker of diabetes mellitus and metabolic syndrome. Metabolic syndrome was assessed according to NCEP-ATPIII's (National Cholesterol Education Program's Adult Treatment Panel III) criteria. Women with fasting glucose above 100 mg/dl / presence of Diabetes Mellitus were also evaluated separately. LAP mean was 61.31 cm.mmol/L

($CI_{95\%}$ 59.9 to 64.7). Ages from 56 to 65 years, three or more pregnancies and being former smoker was positively associated with increased LAP, even after adjustment in the multivariate models. The prevalence of high LAP (≥34.5 cm.mmol/L) was 71.3% ($IC_{95\%}$: 67.6 to 75.1). Women with high LAP had 4.6 times more likely to develop MetS ($IC_{95\%}$ 3.2 to 6.6) and 2.4 times more likely to have high glucose or presence of DM ($IC_{95\%}$ 1.6 to 7.4) compared with women with LAP <34.5 cm.mmol/L.

Data from the present study demonstrate that, in addition to blood pressure and waist circumference, the change in blood glucose and serum triglycerides play an important role in increasing Metabolic Syndrome during climacteric. It was also possible to notice that LAP can be a new alternative to predict cardiometabolic risk, since besides the waist circumference measurement, it includes triglyceride measurement, which in women appears to represent an increased risk for cardiovascular mortality, regardless of other lipid fractions.

Parte I

Artigo de revisão

PREVALÊNCIA DE SÍNDROME METABÓLICA E SEUS COMPONENTES NA TRANSIÇÃO MENOPÁUSICA

TÍTULO: Prevalência de Síndrome Metabólica e seus componentes na transição menopáusica

TÍTULO EM INGLÊS: Prevalence of metabolic syndrome and its components in the menopausal transition

TÍTULO CORRIDO: Síndrome metabólica e transição menopáusica

PALAVRAS-CHAVE:
Síndrome Metabólica. Menopausa. Pré-menopausa. Perimenopausa. Pós-menopausa.
Metabolic Syndrome. Menopause. Premenopause. Perimenopause. Postmenopause.

INFORMAÇÕES SOBRE FINANCIAMENTO E CONFLITO DE INTERESSES:
- O projeto não teve financiamento.
- Declaramos que não há conflito de interesses.

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RESUMO:

A síndrome metabólica (SM) é um transtorno complexo, caracterizado por um agrupamento de fatores de risco cardiovasculares. Sugere-se que a fase da transição menopáusica possa ser um determinante importante no aumento da prevalência da SM. O presente estudo teve como objetivo avaliar, por meio de uma revisão sistemática, a prevalência de SM e dos seus componentes na transição menopáusica. Três revisores fizeram a busca dos artigos na base de dados do Pubmed. A qualidade dos artigos foi avaliada através do *Strengthening the Reporting of Observational Studies in Epidemiology* (STROBE). Com base nos estudos analisados, a prevalência de SM aumenta na comparação do período da pré para a pós-menopausa, independente da população e do delineamento do estudo. As maiores prevalências de SM foram encontradas nos estudos transversais de base populacional, quando comparados aos estudos transversais realizados em ambulatório. Quanto aos componentes, a alteração foi mais expressiva nas medidas de CC e PA. Sugere-se que esses componentes sejam os que exercem maior influência na prevalência de SM.

ABSTRACT:

Metabolic syndrome (MetS) is a complex disorder represented by a cluster of cardiovascular risk factors. Menopausal transition may be a key factor in the increase of prevalence of MetS. This study aims to evaluate, through a systematic review, prevalence of MetS and its components in the menopausal transition. Three reviewers searched for articles in PubMed database. The quality of the articles was evaluated according to Strengthening the Reporting of Observational Studies in Epidemiology (STROBE). Based on the studies analyzed, the MetS prevalence increases when comparing pre- and post menopausal periods, regardless of the population and study design. The highest evidences were found in population based cross-sectional studies when compared to cross-sectional studies performed on an outpatient basis. Regarding to the components, the change was more significant for WC and BP measurements. It is suggested that these components may be those which have more influence on the prevalence of MetS.

PREVALÊNCIA DE SÍNDROME METABÓLICA E SEUS COMPONENTES NA TRANSIÇÃO MENOPÁUSICA

A Síndrome Metabólica

A síndrome metabólica (SM) é um transtorno complexo, caracterizado por um agrupamento de fatores de risco cardiovasculares.

De acordo com o *National Cholesterol Education Program's Adult Treatment Panel III* (NCEP-ATP III)[1], a SM resulta da ocorrência de pelo menos três das cinco desordens a seguir: obesidade abdominal (≥ 88cm), hipertensão arterial (≥ 130 mmHg ou ≥ 85 mmHg), elevação da glicemia (≥ 100mg/dl ou com diagnóstico de Diabetes Mellitus), triglicerídeos elevados (≥ 150mg/dl ou em tratamento) e redução de colesterol HDL (≤ 50mg/dl ou em tratamento). Já o *International Diabetes Federation* (IDF) enfatiza a presença de obesidade abdominal (≥80cm) acrescida de mais dois dos componentes já citados para o diagnóstico de SM.

Recentemente, a *American Diabetes Association* (ADA) e a *European Association for the Study of Diabetes* (EASD) publicaram um documento de reflexão sobre a SM, aconselhando uma reorientação sobre os componentes individuais da síndrome, sem considerá-la de forma agregada[2]. Levantaram-se várias questões com base em uma crítica aos critérios anteriores da Organização Mundial da Saúde (OMS) e do NCEP-ATP III: 1) seria de fato uma síndrome, especialmente porque a causa é desconhecida? 2) teria um propósito útil? 3) estaria sendo atribuído um "rótulo" (e consequente medicalização) às pessoas?[2]. Tem-se sugerido que o reconhecimento da SM foi em grande parte impulsionado pela indústria para o desenvolvimento de novos medicamentos[3, 4]. Mas, segundo o IDF, independentemente das incertezas de definição e etiologia, seria aconselhável considerar a SM como um todo[2]. Alberti, Zimmet & Shaw (2005)[3] defendem que o conceito da SM existe há cerca de 80 anos e a crescente epidemia de Diabetes Melittus tipo 2 (DM2) e doenças cardiovasculares (DCV) em todo o mundo, particularmente nos países em desenvolvimento, parecem razões suficientes para identificar e tratar as pessoas com a síndrome.

A Síndrome Metabólica na transição menopáusica

Estudos realizados em diferentes populações do mundo revelaram altas prevalências de SM, dependendo do critério diagnóstico empregado e das características da população observada, como gênero, idade, etnia e morbidades associadas, variando as

taxas de 8% a 24% em homens e de 7% a 46% em mulheres[5]. Alguns estudos demonstram que a prevalência de SM aumentou com a idade em ambos os sexos[6, 7]. No entanto, entre 20 e 50 anos de idade, os homens apresentam uma maior prevalência de SM, a partir dos 50 anos, a prevalência torna-se maior entre as mulheres. Sugere-se que a fase da transição menopáusica possa ser um determinante importante no aumento dessa prevalência[8].

A transição menopáusica é caracterizada por três períodos, sendo eles: a pré-menopausa, que inicia geralmente aos 40 anos, com redução da fertilidade em mulheres com ciclos menstruais regulares; a perimenopausa, que inicia dois anos antes do último ciclo menstrual e estende-se até um ano após, caracterizado por ciclos menstruais irregulares e alterações endócrinas; e a pós-menopausa, que inicia um ano após o último ciclo menstrual[9].

Alguns autores consideram que a pós-menopausa é um período de hiperandrogenismo relativo como consequência da maior queda de estrogênios, em comparação com os andrógenos, que pode levar à formação da aterosclerose, com aumento dos níveis de colesterol LDL e uma diminuição nos níveis de HDL[10-12]. De acordo com Janssen et al. (2010)[13], mulheres na pós-menopausa possuem maior acúmulo de gordura visceral do que as mulheres que ainda menstruam, sendo independente do processo de envelhecimento. O estrogênio é considerado como fator protetor para DCV nas mulheres pré-menopáusicas e devido a redução deste hormônio em mulheres após a menopausa, ocorre maior suscetibilidade ao aumento de gordura na região abdominal. Outro hormônio sexual relacionado a este aumento é a testosterona, sendo um forte preditor de gordura visceral e, como tal, associado a um maior risco cardiovascular em mulheres na transição menopáusica.

A temporalidade entre a ocorrência dos componentes da SM e menopausa tem sido questionada[14]. Não é claro se a ocorrência da menopausa aumenta o risco da SM ou se a idade é que eleva a prevalência. O aumento da idade estaria relacionado com o processo fisiológico do envelhecimento, principalmente pela redução do metabolismo basal, alteração da composição corporal e estilo de vida inadequado[15, 16].

Considerando que não é clara na literatura científica a relação entre ocorrência de SM e a distribuição dos componentes segundo as alterações hormonais na transição menopáusica, bem como a idade das mulheres, o presente estudo tem como objetivo avaliar, por meio de uma revisão sistemática, a prevalência de SM e dos seus componentes na transição menopáusica, ou seja, nas etapas de pré-menopausa, perimenopausa e pós-menopausa.

MATERIAIS E MÉTODOS

Revisão - Fase 1

Foi realizada uma busca em maio de 2011 nas bases de dados: PubMed, Lilacs, Science Direct, Cochrane, Scielo e Scopus. Os termos usados para busca foram retirados do MeSH (*Medical Subject Heading*) e DeCS (Descritores em Ciências da Saúde). Os termos usados foram *"Metabolic syndrome X" and "climacteric"* e *"Metabolic syndrome" and "climacteric"* (Tabela 1). A busca nessas bases totalizou 402 documentos. Lendo os títulos, foi observado que 86 estavam repetidos nas diferentes bases de dados, ficando para análise do resumo 316. Desses 316 documentos, foram retirados estudos especificamente com homens, revisões sistemáticas, ensaios clínicos com animais, ensaios clínicos em laboratórios, livros, resumos de eventos, relatos de caso e outros (consensos, editoriais, guias, correspondência).

Com a retirada desses documentos, restaram 71 (ensaios clínicos com humanos e estudos observacionais - transversal, caso-controle e coorte). Desses, 8 foram excluídos por abordarem questões genéticas e disfunções sexuais.

Ao final, 63 artigos foram lidos na íntegra para a revisão sistemática. Nesta etapa da busca observou-se que seria necessária a utilização de outros descritores para atingir os objetivos do estudo. Portanto, iniciamos a Revisão - Fase 2.

Revisão - Fase 2

Para esta fase da revisão, três revisores realizaram as buscas, seleção e análise dos artigos e o crítico fez a revisão final do artigo. O fluxograma da busca está apresentado na Figura 1.

Foi observado na Revisão - Fase 1 que a maioria dos artigos elegíveis para serem lidos integralmente estavam na base de dados do Pubmed (US National Library of Medicine). Por esse motivo, os revisores utilizaram somente a base de dados do PubMed para essa nova pesquisa. Optou-se por analisar somente os artigos encontrados nesta busca.

Os termos usados para descrever a SM foram retirados do MeSH (*Medical Subject Heading*) e DeCS (Descritores em Ciências da Saúde). Os termos usados foram *metabolic syndrome x or metabolic syndrome and menopause or climacteric or perimenopause or postmenopause or premenopause.*

Foram ativados alguns limites na busca: humanos, adultos com mais de 19 anos, feminino; língua: inglês, espanhol, português; período: últimos 10 anos; exclusão: artigos de revisão e metanálises.

Utilizando os termos e os limites, 262 artigos foram encontrados.

Seleção dos artigos

Os títulos e resumos dos 262 artigos foram lidos.

Foram incluídos em uma pré-análise todos os artigos que, pelo resumo, apresentassem resultados relacionados a mulheres na transição menopáusica, com a descrição dos componentes da síndrome e com divisão dos períodos da transição menopáusica (pré, peri e pós-menopausa). Foram excluídos os artigos onde o objetivo do estudo era estudar a SM em uma população que já possuía alguma doença pré-existente (câncer, transplantados, HIV, Síndrome dos Ovários Policísticos, Síndrome de Cushing, pacientes com distúrbios do sono, diabéticos, Doença Arterial Coronariana, usuários de TRH).

Depois da utilização desses critérios de inclusão e exclusão, restaram 25 artigos para serem lidos na íntegra.

Entre os 25 artigos, foram excluídos oito, por não apresentarem a divisão no estado menopáusico ou o desfecho da SM era referente a outros fatores (adiponectina, transtornos mentais, etc) e em um artigo faltava um componente da SM (HAS). Assim, restaram 17 artigos para serem avaliados. Desses 17, os revisores selecionaram os artigos conforme os dois objetivos da revisão: a prevalência de SM no estado menopáusico e a análise dos componentes da SM segundo as fases da transição menopáusica.

Para a análise da prevalência da SM, dos 17, quatro artigos foram excluídos, pois só apresentarem a divisão do estado menopáusico dos componentes da SM, e não da prevalência, ou seja, 13 artigos foram selecionados.

Para a análise dos componentes da SM na transição menopáusica, dentre os 17 artigos, seis foram excluídos por não apresentarem os componentes divididos por estado menopáusico, ou seja, 11 artigos foram selecionados para investigar o segundo objetivo do estudo. Entre o total de artigos, sete estiveram incluídos em ambas as análises (Figura 1).

Pontuação do STROBE (Strengthening the Reporting of Observational Studies in Epidemiology)

Todos os 17 artigos selecionados foram avaliados pelos critérios do STROBE[17], onde cada um dos 22 critérios recebeu uma pontuação de 0 a 1. Depois da avaliação de todos os critérios, cada artigo recebeu uma nota de 0 a 22 de cada revisor. Para a nota final, foi realizada uma média das três notas, sendo que a variação das notas entre os revisores não foi superior a 1. De acordo com a nota final, realizou-se a classificação ordinal apresentada na Tabela 3. A pontuação foi transformada em percentual para melhor avaliar a qualidade dos artigos. Os revisores definiram que os artigos que atingissem um percentual superior a 50% seriam considerados de boa qualidade.

DISCUTINDO OS RESULTADOS

Avaliação do STROBE

Avaliando a Tabela 2, todos os artigos selecionados para a revisão atingiram percentuais maiores que 50%. Observa-se que a maioria dos estudos que atingiram percentuais acima de 80% segundo os critérios do STROBE[17] foram estudos transversais de base populacional e estudos de coorte. Esses foram os estudos que apresentaram as maiores prevalências de SM das mulheres na transição menopáusica, denunciando a magnitude do problema nas mulheres nesta fase da vida.

Prevalência de Síndrome Metabólica

Na tabela 3 estão apresentados os artigos que avaliaram a prevalência de SM na transição menopáusica. Observa-se que os estudos que compararam os critérios NCEP e IDF apresentam resultados semelhantes. O IDF apresenta prevalências maiores do que o NCEP[20, 23, 26]. Essa diferença ocorre devido ao ponto de corte para a obesidade abdominal – enquanto no NCEP é definido em 88cm, no IDF o ponto de corte é 80cm. Logo, devemos interpretar os achados considerando que o critério do NCEP é mais específico, enquanto o IDF torna-se um critério mais sensível.

Entre os estudos longitudinais, em Porto Rico foi encontrada uma prevalência de SM no início do estudo de 23,8%[23], enquanto nos EUA a incidência foi de 13,7% no final do período da menstruação entre as 949 mulheres avaliadas[14]. Neste estudo com mulheres americanas, houve diferença em relação à etnia dessas mulheres: caucasianas apresentaram 42,3%, seguidas de afro-americanas com 34,6%, sendo as menores incidências em chinesas e japonesas (8,5% cada) e em hispânicas (6,2%)[14]. Este resultado

corrobora com os achados nos estudos transversais, onde mulheres asiáticas apresentaram menores prevalências de SM.

Analisando estudos transversais, observa-se que as prevalências em estudos de base populacional (63%[31], 27.5%[29]) são maiores do que aqueles realizados em ambulatórios (6.2%[28], 17.9%[24]). Esperava-se que as maiores prevalências fossem encontradas nos estudos em ambulatórios, no entanto, isto não ocorreu. As menores prevalências encontradas nos estudos em ambulatórios foram realizados com mulheres asiáticas, o que demonstra uma diferença na prevalência de SM de acordo com a etnia.

Há um aumento na prevalência de SM de acordo com o estado menopáusico, como observado em estudo transversal de base populacional realizado com iranianas (53%, 54% e 69% na pré, peri e pós-menopausa, respectivamente)[31]. Porém, estudo com imigrantes soviéticas nos EUA apresentou uma pequena variação entre pré (13%) e peri (11%), enquanto a pós-menopausa teve uma prevalência elevada (68%). Ressalta-se que o número de mulheres na perimenopausa neste estudo foi reduzido (n=15), o que pode ter diminuído o efeito da prevalência da SM na perimenopausa[29]. Entre os transversais em ambulatório, apenas dois artigos apresentaram as prevalências da perimenopausa, as quais assemelham-se aos da pós-menopausa (12.4% para 16.9%[19]; 20.5 para 22%[30]).

Quanto às comparações realizadas entre pré e pós-menopausa, notou-se um aumento progressivo na prevalência entre essas duas fases. Heterogeneidade étnica, idade, fatores socioeconômicos, estilo de vida, idade da menarca e número de gestações são possíveis fatores que podem influenciar no aumento da prevalência da SM em mulheres[33]. A relação da idade com SM ficou claramente evidenciada. A associação foi diretamente proporcional, sendo que quanto maior a idade, maior a probabilidade da SM, como resultado do processo fisiológico do envelhecimento[18, 34, 35]. Entretanto, em estudo longitudinal realizado nos EUA, foi encontrado um aumento significativo na prevalência de SM durante a perimenopausa e pós-menopausa, independente da idade e de outros fatores de risco cardiovasculares, incluindo ganho de peso e hábito de fumar[14]. Essa relação entre idade e SM deve ser objeto de outros estudos longitudinais para maiores esclarecimentos sobre essa questão.

Avaliação dos componentes da SM e transição menopáusica

Na tabela 4 estão descritos os estudos que avaliaram separadamente os componentes da SM no período da transição menopáusica, segundo o desenho de estudo e a população alvo.

Obesidade Abdominal

Durante a transição menopáusica, a forma de distribuição de gordura corporal das mulheres parece se modificar, apresentando tendência de acumular-se na região abdominal[36, 37]. Com base nos artigos selecionados, verificaram-se elevadas prevalências de obesidade abdominal, sendo que os maiores percentuais foram encontrados nos estudos realizados em ambulatórios. Entre esses, as prevalências mais elevadas foram encontradas no estudo realizado no nordeste brasileiro, sendo de 76.6% nas que estavam na pré-menopausa e 85.2% em mulheres na pós-menopausa[26]. As menores prevalências foram encontradas entre as mulheres asiáticas, as quais apresentaram 16.4% na pré-menopausa e 29.1% na pós-menopausa[28], sendo que esses dois estudos utilizaram o ponto de corte de 80cm para obesidade abdominal.

Já nos estudos de base populacional, houve discrepância nos resultados encontrados. Em estudo realizado com 2671 mulheres coreanas, encontrou-se uma prevalência de obesidade abdominal na pós-menopausa de 67.1%[8], enquanto o estudo com 940 mulheres iranianas apresentou 11.5%, sendo menor do que a prevalência em mulheres na pré-menopausa (13.2%)[21]. Este achado pode ser devido à amplitude da faixa etária (20 a 76 anos, média de idade de 33.1) das participantes, que reduziu o efeito da transição menopáusica sobre o acúmulo de gordura central. Quando comparadas as médias de circunferência da cintura (CC) destes estudos de base populacional, a diferença na transição menopáusica é pequena, não ultrapassando 4cm entre a pré e pós-menopausa[18, 22, 31].

Na transição menopáusica, a pós-menopausa tem apresentado maior prevalência de obesidade abdominal, fato consistente com os estudos analisados. Na Coréia, o aumento da prevalência de obesidade abdominal na pós-menopausa foi aproximadamente de 40% em relação às mulheres na pré-menopausa[8], semelhantemente em estudo realizado por Cho e colaboradores também na Coréia, no qual este aumento foi superior a 30%[24]. Na avaliação da média da CC, o estudo de coorte com 1276 mulheres na Holanda verificou um aumentou na transição menopáusica. Na pré-menopausa a média da CC foi de 78,4 cm (± 11,3) enquanto que na pós-menopausa foi de 86,1 cm (±11,5)[25].

Elevação da Pressão Arterial

Outro critério importante para o diagnóstico de SM é a elevação da pressão arterial (PA) que representa um fator de risco independente, linear e contínuo para DCV[38]. Os valores ótimos para pressão arterial, sistólica e diastólica, são <120 e <80 mmHg, respectivamente. Valores a partir de 130 e/ou 85 mmHg são considerados alterados e de 140 e/ou 90 mmHg permitem classificar os indivíduos adultos, acima de 18 anos, como hipertensos[39].

Analisando as prevalências de PA alterada de mulheres na transição menopáusica, percebeu-se que estas foram mais elevadas na pós do que na pré-menopausa. Entre todos os estudos, aquele realizado no Brasil[26] foi o que apresentou maior prevalência de PA elevada, tanto na pré (55,8%) como na pós-menopausa (73,4%). As menores prevalências foram encontradas em ambulatório na Polônia, (7,0% na pré e 30,0% na pós-menopausa)[32].

Naqueles estudos que apresentaram seus resultados por médias, também se percebeu elevação nos valores da PA sistólica e diastólica. No estudo de coorte realizado na Holanda[25] e em um estudo transversal de base populacional na Índia[22] as variações mostraram-se semelhantes. A sistólica e a diastólica aumentaram na transição menopáusica, sendo que na pós-menopausa a sistólica apresentou níveis acima de 140mmHg, enquanto a diastólica aumentou na transição, atingindo 87.6 mmHg[22]. As menores médias de pressão arterial foram encontradas na China[18] e na Argentina[30].

Alteração da Glicemia em jejum

A presença de resistência à ação da insulina tem sido considerada um fator fisiopatogênico importante para a SM[40]. O Diabetes Mellitus tipo 2 (DM2), que apresenta como principal característica a hiperglicemia, é resultado de defeitos na ação da insulina, na secreção de insulina ou em ambos. O DM2 pode ocorrer em qualquer idade, mas é geralmente diagnosticado após os 40 anos, sendo que a maioria dos pacientes apresenta sobrepeso ou obesidade[41]. Assim como os outros componentes já avaliados, o aumento da glicemia na transição menopáusica foi observado em todos os estudos.

Os estudos que demonstraram maiores prevalências de glicemia em jejum alterada na transição menopáusica foram o de base populacional no Irã[21], passando de 25.5% para 60.3% da pré para a pós-menopausa, e o de ambulatório na Polônia[32], aumentando de 13.0% para 55.0% após a ocorrência da menopausa. Entre os estudos ambulatoriais, na

Coréia[24] foi encontrada a menor prevalência de glicemia em jejum na pré-menopausa (1.9%), enquanto no Taiwan[28], encontrou a menor prevalência na pós-menopausa (5.6%).

Avaliando os resultados através das médias da glicemia em jejum, menores valores foram verificados em estudo de coorte co holandesas[25], passando de 75.6 para 84.6 mg/dl da pré para a pós-menopausa. Resultados mais elevados foram observados por estudos de base populacional no Irã[31] e na Índia[22], passando de 103 a 114[31] e 102 a 123 mg/dl[22], respectivamente, da pré para a pós-menopausa. Entre os estudos transversais realizados em ambulatório, Argentina[30] e Coréia[24] avaliaram as médias de glicemia em jejum, apresentando aumento no período da transição menopáusica, com pequena variação e não ultrapassando o ponto de corte de 100 mg/dl.

Dislipidemias

Quanto às dislipidemias na transição menopáusica, de acordo com Ferin *et al.* (1993), o hipoestrogenismo associa-se à dislipidemia, pois pode aumentar o colesterol total e o LDL-colesterol, que é aterogênico, por diminuir os receptores hepáticos[42].

Nos artigos selecionados para esta revisão, foi possível observar o aumento dos TG na transição menopáusica. Assim como encontrado na análise da prevalência geral de SM, os estudos transversais de base populacional apresentaram maiores prevalências de TG aumentados quando comparados aos transversais realizados em ambulatório. Entre os estudos que apresentaram as prevalências de TG aumentados, o maior percentual encontrado, tanto na pré quanto na pós-menopausa, foi em um estudo transversal de base populacional realizado com 940 mulheres iranianas de 20 a 76 anos (79,4% na pré, 95,4% na pós-menopausa)[21]. As menores prevalências de TG aumentados foram encontradas em estudo realizado no Brasil (9.1% na pré; 15.4% na pós)[26]. Quando os estudos apresentaram seus dados através de médias, também foi possível notar o aumento no valor dos TG na transição menopáusica. Em estudo no Irã[31], já na pré-menopausa, as mulheres apresentavam um valor médio acima do recomendado (182mg/dl), sendo que esse valor foi aumentando no período (195 e 211mg/dl, na peri e na pós, respectivamente). As menores médias foram encontradas em estudo transversal de base populacional realizado com chinesas (103 mg/dl na pré, 118 mg/dl na pós)[18].

Quanto ao colesterol HDL, a maioria dos estudos apresenta uma redução no valor na transição menopáusica, o que não é adequado, pois quanto maiores os valores de HDL, melhor a saúde cardiovascular. As maiores prevalências de HDL abaixo de 50mg/dl foram encontradas no Brasil (76.0% na pré, 82.8% na pós)[26] e na Coréia (54.2% na pré,

69.8% na pós)[8]. As menores prevalências de HDL abaixo de 50mg/dl foram encontradas em estudo com mulheres iranianas (11.2% na pré, 13.4% na pós)[21]. Quando os resultados foram apresentados através das médias de HDL, o estudo de coorte que avaliou 1276 mulheres holandesas apresentou os menores valores, sem diferenças no período da transição menopáusica (40.21mg/dl na pré e na pós-menopausa)[25]. As maiores médias de HDL (60.71 na pré, 54.14 na pós), foram encontradas no estudo com polonesas[32].

CONCLUSÃO

Com base nos estudos analisados, a prevalência de SM aumenta na comparação do período da pré para a pós-menopausa, independente da população. Essa tendência foi observada na maioria dos estudos, independentemente do delineamento. As maiores prevalências de SM foram encontradas nos estudos transversais de base populacional, quando comparados aos estudos transversais realizados em ambulatório. As menores prevalências foram encontradas nos estudos realizados com populações asiáticas.

Quanto aos componentes, a maioria dos estudos apresentou na transição menopáusica aumento na medida da CC, da PA, da glicemia em jejum, do TG e redução do HDL. Essa alteração foi mais expressiva nas medidas de CC e PA. Os estudos com maiores prevalência de SM foram os mesmos que apresentaram as maiores prevalências ou médias de CC e PA. Sugere-se que esses componentes sejam os que exercem maior influência na prevalência de SM.

Quanto à relação entre SM, estado menopáusico e idade, as conclusões dos estudos apontam para uma maior influência da menopausa na presença da SM. Entre os estudos que fizeram a análise desta relação, a maioria demonstrou que o estado menopáusico foi preditor independente para a SM[8, 14, 21, 24, 29]. Outros encontraram que o principal fator de risco para o aumento da prevalência de SM foi a idade [26, 30].

Para a análise da prevalência da SM e de seus componentes foram utilizados apenas os artigos encontrados através da busca no Pubmed, sem utilizar outras bases de dados ou busca nas referências dos artigos selecionados. Estas podem ser consideradas limitações deste estudo. É importante destacar que se torna difícil avaliar o efeito da menopausa sobre a SM e seus componentes em estudos transversais, visto que ambas as situações sofrem influências de muitos fatores, tais como IMC, etnia, classe socioeconômica, atividade física, alimentação e tabagismo.

Destacamos a importância da realização de estudos longitudinais com mulheres desde o início da vida reprodutiva para maiores esclarecimentos sobre a relação entre a

idade, a menopausa, a SM e seus componentes. Estudos que considerem as características sociodemográficas e de estilo de vida das mulheres poderão oferecer subsídios para a melhor compreensão dessa relação e contribuir para a proposição de medidas de prevenção.

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Tabela 1. Número de documentos encontrados na busca da Revisão – Fase 1.

"Metabolic syndrome X" and "climacteric"		*"Metabolic syndrome" and "climacteric"*	
Base de dados	**N**	**Base de dados**	**N**
PubMed	15	PubMed	31
Lilacs	5	Lilacs	16
Science Direct	12	Science Direct	288
Cochrane	2	Cochrane	0
Scielo	1	Scielo	1
Scopus	14	Scopus	17

Figura 1. Fluxograma da Fase 2 da revisão bibliográfica

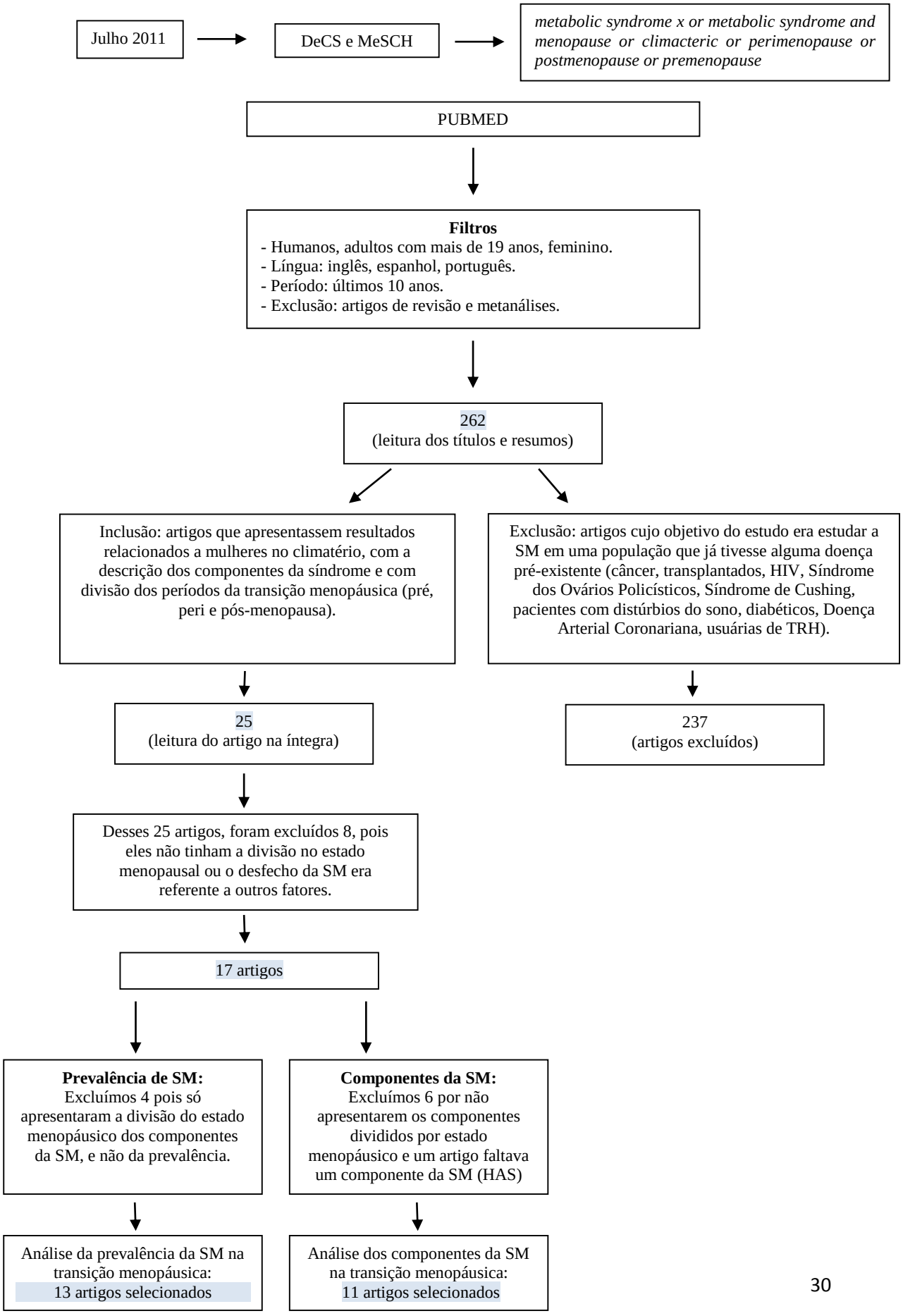

Tabela 2. Pontuação e percentual de qualidade dos artigos a partir dos critérios do STROBE.

Publicação	Autor	Título	Tipo de estudo	Pontos	%
Atherosclerosis. 2008 Feb;196(2):590-7. Epub 2007 Aug 6	Feng Y et al[18]	Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases.	Transversal de base populacional	20.8	94.5%
Climacteric. 2011 Feb;14(1):58-65. Epub 2010 May 7	Indhaviva-dhana, S[19]	Predictors for metabolic syndrome in perimenopausal and postmenopausal Thai women	Transversal em ambulatório	20.5	93.2%
Medicina (B Aires). 2009;69(2):246-52.	Coniglio RI et al[20]	Metabolic syndrome in employees in Argentina	Transversal de base populacional	19.6	89.0%
Arch Intern Med. 2008 Jul 28; 168(14):1568-75.	Janssen I et al[14]	Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation.	Coorte	19.6	89.0%
Maturitas. 2010 Mar;65(3):262-6. Epub 2009 Dec 3.	Eshtiaghi R et al[21]	Menopause is an independent predictor of metabolic syndrome in Iranian women	Transversal de base populacional	19.0	86.3%
Cardiovasc J Afr. 2008 Jul-Aug; 19(4):183-7	Ghosh A.[22]	Comparison of risk variables associated with the metabolic syndrome in pre- and postmenopausal Bengalee women	Transversal de base populacional	18.8	85.5%
Menopause. 2010 Mar;17(2):388-92.	Romaguera J et al[23]	Factors associated with metabolic syndrome in a sample of women in Puerto Rico.	Coorte	18.1	82.3%
Menopause. 2008 May-Jun; 15(3):524-9	Cho GJ et al[24]	Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome	Transversal em ambulatório	17.7	80.5%
J Intern Med. 2010.Apr;267(4):402-9. Epub 2009 Aug 26	Henneman P et al[25]	Menopause impacts the relation of plasma adiponectin levels with the metabolic syndrome.	Coorte	16.0	72.7%
Arq Bras Cardiol. 2010 Sep;95(3):339-45. Epub 2010 Jul 23.	Figueiredo Neto JA et al[26]	Metabolic syndrome and menopause: cross-sectional study in gynecology clinic	Transversal em ambulatório	15.9	72.3%
Climacteric. 2011 Feb;14(1):83-91. Epub 2010 May 5	Lejsková M et al[27]	Menopause: clustering of metabolic syndrome components and population changes in insulin resistance.	Transversal de base populacional	15.8	71.8%
Diabetes Care. 2007 Mar;30(3):701-6	Kim HM et al[8]	The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001.	Transversal de base populacional	15.7	71.4%
Int J Obes (Lond). 2006. Jun; 30(6):912-7	Lin WY et al[28]	Insulin resistance, obesity, and metabolic syndrome among non-diabetic pre- and post-menopausal women in North Taiwan.	Transversal em ambulatório	15.7	71.4%
Women Health. 2003;38(3):19-36	Miller AM et al[29]	Cardiovascular disease risk factors and menopausal status in midlife women from the former Soviet Union.	Transversal de base populacional	14.5	65.9%
Climacteric. 2006 Feb;9(1):40-8	Mesch VR et al[30]	Metabolic syndrome throughout the menopausal transition: influence of age and menopausal status.	Transversal em ambulatório	14.3	65.0%
Maturitas. 2007 Oct 20;58(2):150-5. Epub 2007 Sep 4	Ainy E et al[31]	Prevalence of metabolic syndrome during menopausal transition Tehranian women: Tehran Lipid and Glucose Study (TLGS).	Transversal de base populacional	14.0	63.6%
Endokrynol Pol. 2006 Jan-Feb;57(1):15-22	Siemińska L et al[32]	The relation of serum adiponectin and leptin levels to metabolic syndrome in women before and after the menopause	Estudo transversal em ambulatório	13.0	59.1%

Tabela 3. Estudos com a prevalência de SM no período da transição menopáusica.

Publicação	Autor	Título	Desenho / população e local de estudo	Prevalência de Síndrome Metabólica	
Climacteric. 2011. Feb;14(1):83-91. Epub 2010 May 5.	Lejsková M et al[27]	Menopause: clustering of metabolic syndrome components and population changes in insulin resistance.	Transversal – base populacional. Residentes em Praga. 909 mulheres de 45 a 54 anos.	Prevalência geral Pré-menopausa Pós-menopausa	- 22.9% (± 2.6) 38.3% (± 4.0)
Climacteric. 2011. Feb;14(1):58-65. Epub 2010 May 7.	Indhavivadhana S et al[19]	Predictors for metabolic syndrome in perimenopausal and postmenopausal Thai women	Transversal – ambulatorial. Clínica de menopausa de um hospital. 971 mulheres com idade média de 50,8 anos.	Prevalência geral Peri-menopausa Pós-menopausa	NCEP: 15.9% (CC asiáticos) IDF: 16% NCEP: 12.4% (IC 9.4-15.4) IDF: 16% (IC 15.1-24.3) NCEP: 16.9% (IC 14.0-19.8) IDF: 15.9% (IC 13.6-18.2)
Arq Bras Cardiol. 2010. Sep;95(3):339-45. Epub 2010 Jul 23.	Figueiredo Neto JA et al[26]	Metabolic syndrome and menopause: cross-sectional study in gynecology clinic	Transversal – ambulatorial. Ambulatório de ginecologia de um hospital público terciário no Brasil. 323 pacientes de 40 a 65 anos, idade média de 49,7 anos.	Prevalência geral Pré-menopausa Pós-menopausa	NCEP: 34.7% IDF: 49.8% NCEP: 24% IDF: 37% NCEP: 44.4% IDF: 61.5%
J Intern Med. 2010. Apr;267(4):402-9. Epub 2009 Aug 26	Henneman P et al[25]	Menopause impacts the relation of plasma adiponectin levels with the metabolic syndrome.	Coorte. Holanda. 695 (id média de 37,8) na pré-menopausa e 581 (id média de 60,2) na pós-menopausa.	Prevalência geral Pré-menopausa Pós-menopausa	- IDF: 17% IDF: 43.2%
Menopause. 2010. Mar;17(2):388-92.	Romaguera J et al[23]	Factors associated with metabolic syndrome in a sample of women in Puerto Rico.	Coorte. Porto Rico. 214 mulheres de 36 a 82 anos acompanhadas por 3 anos.	Prevalência geral Pré-menopausa Pós-menopausa	NCEP: 23.8% IDF: 32.7% NCEP: 21.5% IDF: 30.4% NCEP: 29% IDF: 45.2%
Maturitas. 2010. Mar;65(3):262-6. Epub 2009 Dec 3.	Eshtiaghi R et al[21]	Menopause is an independent predictor of metabolic syndrome in Iranian women	Transversal – base populacional. Irã, 940 mulheres de 20 a 76 anos.	Prevalência geral Pré-menopausa Pós-menopausa	NCEP: 26.4% NCEP 18% NCEP: 54%
Medicina (B Aires).2009 69(2):246-52.	Coniglio RI et al[20]	Metabolic syndrome in employees in Argentina	Transversal – base populacional. Diferentes regiões geográficas da Argentina. 1203 mulheres de 40 a 65 anos.	Prevalência geral Pós-menopausa	NCEP: 22% IDF: 27% NCEP: OR 1.61 (1.18-2.19) IDF: OR 1.41 (1.06-1.87)

Tabela 3. Estudos com a prevalência de SM no período da transição menopáusica.

Publicação	Autor	Título	Desenho / população e local de estudo	Prevalência de Síndrome Metabólica	
Arch Intern Med. 2008. Jul 28; 168(14):1568-75.	Janssen I et al[14]	Menopause and the metabolic syndrome: the Study of Women's Health Across the Nation.	Coorte. SWAN – EUA. 949 participantes, alinhadas na última menstrução. Foram recrutadas quando estavam na pré ou peri.	Prevalência geral Peri-menopausa Pós-menopausa	NCEP: 13.7% (<80cm CC de japoneses e chineses) OR 1.45 (1.35-1.56) (risco por ano de desenvolver SM na perimenopausa) OR 1.24 (1.18-1.30) (risco por ano de desenvolver SM na pós-menopausa)
Menopause. 2008. May-Jun; 15(3):524-9	Cho GJ et al[24]	Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome	Transversal – ambulatorial. Participantes de exames anuais no Anam Hospital in Seoul, Korea, de janeiro a outubro de 2006. 618 na pré-menopausa (média id 40.5) e 384 na pós-menopausa (média id 59.0).	Prevalência geral Pré-menopausa Pós-menopausa	NCEP: 17.9% NCEP: 6.6% NCEP: 35.9%
Maturitas. 2007. Oct 20;58(2):150-5. Epub 2007 Sep 4	Ainy E et al[31]	Prevalence of metabolic syndrome during menopausal transition Tehranian women: Tehran Lipid and Glucose Study (TLGS).	Transversal – base populacional. Participantes do Tehran Lipid and Glucose Study (TLGS). 2182 mulheres, 537 pré-menopausa (média id 47,0), 311 na peri (média id 53.0), 1334 pós (média id 61), de 45 a 66 anos.	Prevalência geral Pré-menopausa Peri-menopausa Pós-menopausa	NCEP: 63% NCEP: 53% NCEP: 54% NCEP: 69%
Int J Obes (Lond). 2006. Jun; 30(6):912-7	Lin WY et al[28]	Insulin resistance, obesity, and metabolic syndrome among non-diabetic pre- and post-menopausal women in North Taiwan.	Transversal – ambulatorial. Mulheres que participaram do levantamento de fatores de risco de DCV em um centro médico no Norte de Taiwan. 594 mulheres, 40 a 64 anos.	Prevalência geral Pré-menopausa Pós-menopausa	NCEP: 6.2% NCEP modif: 8.9% (CC >80cm) NCEP: 4.2% NCEP modif: 5.8% (CC >80cm) NCEP: 9.4
Climacteric. 2006. Feb;9(1):40-8	Mesch VR et al[30]	Metabolic syndrome throughout the menopausal transition: influence of age and menopausal status.	Transversal – ambulatorial. Unidade de Climatério na Divisão de Ginecologia da Clínica do Hospital da Universidade de Buenos Aires. 124 mulheres divididas em 4 grupos (pré, peri hemorragia, peri amenorréia, pós).	Prevalência geral Pré-menopausa Peri-menopausa Pós-menopausa	- NCEP: 0% NCEP: 20-21% NCEP: 22%
Women Health. 2003. 38(3):19-36	Miller AM et al[29]	Cardiovascular disease risk factors and menopausal status in midlife women from the former Soviet Union.	Transversal – base populacional. Coorte de mulheres imigrantes da União Soviética. 35 na pré, 15 na peri, 116 na pós-menop natural e 29 menop cirúrgica. 40 a 70 anos. Média de idade: 57,26 anos	Prevalência geral Pré-menopausa Peri-menopausa Pós-menopausa	NCEP: 27.5% NCEP: 13% NCEP: 11% NCEP: 68%

Tabela 4. Componentes da SM na transição menopáusica.

Publicação	Autor	Título	Desenho / População	Componentes da Síndrome Metabólica na transição menopáusica									
Arq Bras Cardiol. 2010. Sep;95(3):339-45. Epub 2010 Jul 23.	Figueiredo Neto JA et al[26]	Metabolic syndrome and menopause: cross-sectional study in gynecology clinic	Ambulatório de ginecologia de um hospital público terciário no Brasil. 323 pacientes de 40 a 65 anos, idade média de 49,7 anos.	**CC pré**	IDF: 76.6% NCEP: 29.9%	**PA pré**	55.8%	**Gli pré**	9.1%	**TG pré**	9.1%	**HDL pré**	76%
				CC pós	IDF: 85.2% NCEP: 50.9%	**PA pós**	73.4%	**Gli pós**	14.2%	**TG pós**	15.4%	**HDL pós**	82,8%
J Intern Med. 2010. Apr;267(4):402-9. Epub 2009 Aug 26	Hennemann P et al[25]	Menopause impacts the relation of plasma adiponectin levels with the metabolic syndrome.	Coorte. Holanda. 695 (id média de 37,8) na pré-menopausa e 581 (id média de 60,2) na pós-menopausa.	**CC pré**	IDF: 78.4 ± 11.3	**PA pré**	IDF Diast: 76.5 ± 9.6 IDF Sist: 126.7 ± 15.2	**Gli pré**	*75.6 mg/dl**	**TG pré**	97 mg/dl	**HDL pré**	40.2 mg/dl
				CC pós	IDF: 86.1 ± 11.5	**PA pós**	IDF Diast: 80.9 ± 9.4 IDF Sist: 147.4 ± 21.8	**Gli pós**	*84.6 mg/dl**	**TG pós**	123.9 mg/dl	**HDL pós**	40.2 mg/dl
Maturitas. 2010. Mar;65(3):262-6. Epub 2009 Dec 3.	Eshtiaghi R et al[21]	Menopause is an independent predictor of metabolic syndrome in Iranian women	Transversal – base populacional. Irã, 940 mulheres de 20 a 76 anos.	**CC pré**	IDF 85.5cm: 13.2%	**PA pré**	NCEP Diast: 9.7% NCEP Sist: 15.3%	**Gli pré**	NCEP: 25.8%	**TG pré**	NCEP: 79.4%	**HDL pré**	NCEP: 11.2%
				CC pós	IDF 85.5cm:11.5%	**PA pós**	NCEP Diast: 8.3% NCEP Sist: 17.3%	**Gli pós**	NCEP: 60.3%	**TG pós**	NCEP: 95.4%	**HDL pós**	NCEP: 13.4%
Cardiovasc J Afr. 2008. Jul-Aug; 19(4):183-7	Ghosh A [22]	Comparison of risk variables associated with the metabolic syndrome in pre- and postmenopausal Bengalee women	Transversal – base populacional. 100 na pré-menopausa (média id 40.2) e 100 na pós-menopausa (média id 55.4)	**CC pré**	84.8cm ±3.2cm	**PA pré**	S: 134.5 ±18.0 D: 82.4 ±13.4	**Gli pré**	102.4 mg/dl ± 12.6	**TG pré**	108.2 mg/dl ± 14.4	**HDL pré**	45.2 mg/dl ± 4.6
				CC pós	88.6cm ±2.8cm	**PA pós**	S: 145.0 ± 17.4 D: 87.6 ±14.6	**Gli pós**	123.0 mg/dl ± 14.3	**TG pós**	122.4 mg/dl ± 16.3	**HDL pós**	43.6 mg/dl ± 4.2

*Resultados transformados de mmol em mg/dl para comparação de resultados.

Tabela 4. Componentes da SM na transição menopáusica.

Publicação	Autor	Título	Desenho / População	Componentes da Síndrome Metabólica na transição menopáusica									
Menopause. 2008. May-Jun; 15(3):524-9	Cho GJ et al[24]	Postmenopausal status according to years since menopause as an independent risk factor for the metabolic syndrome	Participantes de exames anuais no Anam Hospital in Seoul, Korea, de janeiro a outubro de 2006. 618 na pré-menopausa (média id 40.5) e 384 na pós-menopausa (média id 59.0).	**CC pré**	46.1% 80.3 ± 7.9 cm	**PA pré**	6.0% S: 113.4 ± 10.7 D: 69.5 ± 8.8	**Gli pré**	1.9% 85.4 ± 9.1 mg/dl	**TG pré**	12.3% 96.5 ± 55.6 mg/dl	**HDL pré**	22.5% 60.9n ± 13.5 mg/dl
				CC pós	78.9% 86.6 ± 8.0 cm	**PA pós**	40.6% S: 120.9 ±10.9 D: 76.7 ± 9.1	**Gli pós**	15.1% 93.8 ± 17.3 mg/dl	**TG pós**	32.8% 138.1 ± 84.4 mg/dl	**HDL pós**	37.5% 57.1 ± 13.5 mg/dl
Atherosclerosis. 2008. Feb;196(2):590-7. Epub 2007 Aug 6	Feng Y et al[18]	Effects of age at menarche, reproductive years, and menopause on metabolic risk factors for cardiovascular diseases.	Transversal – base populacional. 9097 mulheres de dois condados na província de Anhui, China.	**CC pré**	74.4 + 8.1	**PA pré**	Sist: 117 ± 17 Diast: 75 ± 10	**Gli pré**	*99 mg/dl**	**TG pré**	*103mg/dl**	**HDL pré**	*53.7mg/dl**
				CC pós	74.5 + 8.3	**PA pós**	Sist: 123 ± 21 (dif <0.001) Diast: 77 ± 12	**Gli pós**	*102.4 mg/dl**	**TG pós**	*118mg/dl**	**HDL pós**	*57.2mg/dl**
Maturitas. 2007. Oct 20;58(2):150-5. Epub 2007 Sep 4	Ainy E et al[31]	Prevalence of metabolic syndrome during menopausal transition Tehranian women: Tehran Lipid and Glucose Study (TLGS).	Transversal – base populacional. Participantes do Tehran Lipid and Glucose Study (TLGS). 2182 mulheres, 537 pré-menopausa (média id 47,0), 311 na peri (média id 53.0), 1334 pós (média id 61), de 45 a 66 anos.	**CC pré**	92 ± 11 cm	**PA pré**	S: 121 ± 18 D: 80 ± 10	**Gli pré**	103 ± 37 mg/dl	**TG pré**	182 ± 115 mg/dl	**HDL pré**	47± 12 mg/dl
				CC peri	94 ± 12 cm	**PA peri**	S: 127 ± 20 D: 82 ± 11	**Gli peri**	106 ± 44 mg/dl	**TG peri**	195 ± 118 mg/dl	**HDL peri**	46± 11 mg/dl
				CC pós	95 ± 11 cm 72%	**PA pós**	S: 136 ± 23 D: 83 ± 11 69%	**Gli pós**	114 ± 49 mg/dl 30%	**TG pós**	211 ± 133 mg/dl 67%	**HDL pós**	43 ± 11 mg/dl 79%
Diabetes Care. 2007. Mar;30(3):701-6	Kim HM et al[8]	The effect of menopause on the metabolic syndrome among Korean women: the Korean National Health and Nutrition Examination Survey, 2001.	Transversal – base populacional. The Korean National Health and Nutrition Examination Survey (KNHANES). 1893 mulheres na pré-menopausa (média id 35.4) e 778 na pós-menopausa (média id 65.1).	**CC pré**	28.1% (>80cm OMS)	**PA pré**	13.7%	**Gli pré**	9.8%	**TG pré**	18.9%	**HDL pré**	54.2%
				CC pós	67,1% (>80cm OMS)	**PA pós**	63.6%	**Gli pós**	26%	**TG pós**	39.3%	**HDL pós**	69.8%

*Resultados transformados de mmol em mg/dl para comparação de resultados.

Tabela 4. Componentes da SM na transição menopáusica.

Publicação	Autor	Título	Desenho / População	Componentes da Síndrome Metabólica na transição menopáusica									
Int J Obes (Lond). 2006. Jun; 30(6):912-7	Lin WY et al[28]	Insulin resistance, obesity, and metabolic syndrome among non-diabetic pre- and post-menopausal women in North Taiwan.	Mulheres que participaram do levantamento de fatores de risco de DCV em um centro médico no Norte de Taiwan. 594 mulheres, 40 a 64 anos.	**CC pré**	NCEP modif (80cm): 16.4%	**PA pré**	19.4%	**Gli pré**	5.0%	**TG pré**	9.2%	**HDL pré**	35.6%
				CC pós	NCEP modif (80cm): 29.1%	**PA pós**	37.2%	**Gli pós**	5.6%	**TG pós**	20.5%	**HDL pós**	23.9%
Endokrynol Pol. 2006. Jan-Feb;57(1):15-22	Siemińska L et al[32]	The relation of serum adiponectin and leptin levels to metabolic syndrome in women before and after the menopause	Polônia. 56 mulheres na pós-menopausa (média id 53.9) e 75 na pré-menopausa (média id 28.2)	**CC pré**	78.0 (76.0-85.0)	**PA pré**	7%	**Gli pré**	13%	**TG pré**	*127mg/dl**	**HDL pré**	*60.7mg/dl**
				CC pós	89.0 (84-94.5)	**PA pós**	30%	**Gli pós**	55%	**TG pós**	*160mg/dl**	**HDL pós**	*54.1mg/dl**
Climacteric. 2006 Feb;9(1):40-8	Mesch VR et al[30]	Metabolic syndrome throughout the menopausal transition: influence of age and menopausal status.	Unidade de Climatério na Divisão de Ginecologia da Clínica do Hospital da Universidade de Buenos Aires. 124 mulheres divididas em 4 grupos (pré, peri hemorragia, peri amenorréia, pós).	**CC pré**	77.8+12	**PA pré**	D: 72.3+9.3 S: 110+32	**Gli pré**	*82.8mg /dl**	**TG pré**	*66.4mg/dl**	**HDL pré**	*56.8mg/dl**
				CC peri	Hemor: 88.0+10.9 Ameno: 90.6+10.2	**PA peri**	Hemor: D: 80+9.2 S: 127+18 Amen: D: 84.8+13.5 S: 129+14	**Gli peri**	Hemor: *86.4mg /dl** Amen: *88.2mg /dl**	**TG peri**	Hemor: *105mg/dl** Amen: *113mg/dl**	**HDL peri**	Hemor: *54.5mg/dl** Amen: *59.5mg/dl**
				CC pós	88.1+10.8	**PA pós**	D: 78.3+7.0 S: 125+10	**Gli pós**	*93.6mg /dl**	**TG pós**	*125mg/dl*	**HDL pós**	*57.2mg/dl*

*Resultados transformados de mmol em mg/dl para comparação de resultados.

Parte II

Artigo original I

MENOPAUSAL STATUS AND METABOLIC SYNDROME IN WOMEN IN CLIMACTERIC PERIOD TREATED AT A CLINIC IN SOUTHERN BRAZIL

MENOPAUSAL STATUS AND METABOLIC SYNDROME IN WOMEN IN CLIMACTERIC PERIOD TREATED AT A CLINIC IN SOUTHERN BRAZIL

Menopausal status and metabolic syndrome

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ABSTRACT

This study aims to understand the relationship between menopausal status and the presence of Metabolic Syndrome in women from 40 to 65 years, as well as to describe the distribution of each component of Metabolic Syndrome according to menopausal status. A cross-sectional study was conducted with women from 40 to 65 years treated at a clinic in southern Brazil. Hysterectomized women and women who were submitted to hormone replacement therapy were excluded from the study. The prevalence of Metabolic Syndrome in the sample was 56.1% ($CI_{95\%}$ 51.9 to 60.2), being more common among older women (56 to 65 years), with low education, menarche $\leq$ 11 years old, with three or more pregnancies and in the post-menopausal period. Regarding the analysis of isolated components in the sample, the most prevalent altered components were: hypertension (84.8%; $CI_{95\%}$: 81.7 to 87.8), waist circumference (66.4%; $CI_{95\%}$: 62.5 to 70.4) and HDL cholesterol (51.7%; $CI_{95\%}$: 47.5 to 55.9). In multivariate analysis, there was an increase of prevalence ratios when comparing perimenopause and post-menopause with pre-menopause; however, the confidence intervals include the unit. This study has shown that, in addition to blood pressure and waist circumference, the change in blood glucose and serum triglycerides play an important role in increasing Metabolic Syndrome during climacteric.

Keywords: Metabolic Syndrome. Climacteric. Menopause. Pre-menopause. Perimenopause. Post-menopause.

INTRODUCTION

Climacteric is defined as the period of transition from the reproductive stage to the non-reproductive stage. This period is characterized by endocrine changes, such as the hypoestrogenism and relative hyperandrogenism, due to the decline of ovarian activity, biological changes because of decreased fertility, and clinical changes resulting from changes in the menstrual cycle and a number of factors [1]. The climacteric is divided into three periods, which define women's menopausal status. The menopausal status is established according to the menstrual cycle characteristics or the time of amenorrhea, and can be divided into pre-menopause, perimenopause and post-menopause, based on the last menstrual period (menopause) [2].

MetS is a complex disorder, characterized by a grouping of cardiovascular risk factors related to the resistance to insulin action, central obesity, dyslipidemia (increased triglycerides and decreased HDL cholesterol) and altered blood pressure [3].

It is estimated that 47 million American adults have MetS [4]. Data from Framingham's study indicates that 20 to 30% of middle-aged adults are affected by MetS [5]. In Brazil, some studies show even higher prevalence of MetS. In a 2007 study, the prevalence of MetS was 35.5% [6]. In another study conducted in Vitória, state of Bahia, the prevalence of MetS was 29.8% and an increase in prevalence as the age increases was noticed [7]. In a study by Figueiredo Neto (2010)[8], women between 40 and 45 years had a prevalence of MetS of 14.1%, while for women between 56 and 64 years the prevalence was 66.7%. In this study, the increase in the prevalence of MetS in post-menopausal women was caused mainly by the increase of age. On the other hand, some studies have shown a relationship between menopausal status and presence of Metabolic Syndrome (MetS) regardless of age, suggesting that menopause contributes to the increase in this prevalence [9-12].

The increase in prevalence of obesity and MetS in post-menopausal women has attracted considerable interest, since women in this situation tend to develop cardiovascular diseases [13, 14]. However, there are few studies exploring the relationship between menopausal status and MetS [8, 9, 11, 12, 15-20].

Thus, this study aims to understand the relationship between menopausal status and the presence of MetS in women from 40 to 65 years, as well as to describe the distribution of each component of MetS according to menopausal status.

METHODS

A cross-sectional study was conducted with women from 40 to 65 years treated at the clinic of Climacteric and of Gynecological Surgery, belonging to the Central Clinic of the University of Caxias do Sul (AMCE-UCS), during the period from January 2010 to May 2011. Both clinics are part of the Unified Health System and serve the population of the municipality and region. Hysterectomized women and women who were submitted to hormone replacement therapy were excluded from the study, because they have their normal metabolism altered.

The sample size was calculated for the association between menopausal status and MetS. Thus, a sample of 687 women would allow identifying an odds ratio of 1.6 [9], with a confidence level of 95%, a statistical power of 80% and a ratio of unexposed:exposed maintained at 2:1. The unexposed are the pre-menopausal women, and the exposed are the post-menopausal women.

All interviews were conducted in the clinics, prior medical consultation, by trained interviewers. A standardized, pre-coded and pre-tested questionnaire was applied, containing socioeconomic, demographic, previous reproductive and behavioral characteristic questions. The demographic characteristics evaluated were: age (40 to 45 years; 46 to 50 years; 51 to 55 years; 56 to 65 years); skin color (white or not white); and marital status (married / in union and not married). The socioeconomic characteristics evaluated were: schooling (0 to 4, 5 to 8, 9 to 11 and ≥ 12 full years of study), family income (0 to 2, 2.01 to 3.00, 3.01 to 5.00; ≥ 5.01 minimum wages; value at the time: R$ 510.00); and paid work (yes / no). Schooling was recategorized for bivariate and multivariate analysis (0 to 4; 5 to 8; ≥ 9 full years of study). This recategorization occurred because of the small number of women in the category ≥ 12 full years of study. As behavioral characteristics, smoking and physical activity were evaluated. Smoking habit was classified as smoker, former smoker and nonsmoker. As to physical activity, the women were classified as sedentary (women who reported no physical activity) and non-sedentary (those practicing any physical activity at least once a week for at least 30 minutes). The women's previous reproductive characteristics were evaluated using the following variables: menarche (≥ 14; 12-13; ≤ 11 years of age); number of pregnancies (0 to 1; 2; and ≥ 3 pregnancies).

The MetS was evaluated through each of its components: waist circumference, blood pressure, blood glucose, levels of HDL cholesterol and triglycerides. Waist circumference (WC) was measured by the survey coordinators. To this measure, a standardization training was performed in order to reduce intra- and inter-observer error.

The WC was measured with a non-flexible tape measure directly on the skin at the midpoint between the last rib and the iliac crest, and the readings were made at the end of a normal expiration [21]. Abdominal obesity was obtained by the average between two WC measurements. The blood pressure levels were measured at the wrist with a validated automatic digital device (BP3AF1-3), according to the guidelines of Association for the Advancement of Medical Instrumentation (AAMI) and British Hypertension Society (BHS) [22]. The woman remained sitting, without speaking, and at rest for at least 5 minutes. This procedure was performed two non-consecutive times in a minimum interval of 5 minutes, and the average value between the two measurements was used for analysis.

Laboratory tests (fasting blood glucose, levels of HDL cholesterol and triglycerides) were collected from participants' medical records, with a limit of four months. Since the request of these tests was part of the clinic routine, most women already had them. For those women who had old tests, new tests were requested by the physician responsible for the clinic.

MetS was defined according to diagnostic criteria of NCEP-ATP III [3]. Thus, MetS would be present in women with at least three of the following criteria: waist circumference $\geq$88 cm, blood pressure $\geq$130 mmHg or $\geq$85 mmHg, fasting blood glucose $\geq$100mg/dl, triglycerides $\geq$150mg/dl, HDL cholesterol $\leq$50 mg/dl or in use of medication to treat these conditions.

For classification of menopausal status, the study participants were asked if they were still menstruating. If so, whether they were regular menstrual cycles, similarly to what had occurred during their reproductive life, they were classified as pre-menopausal women. If menstrual cycles were irregular in relation to flow and time intervals, they were classified as perimenopausal women. If they reported they did not menstruate, i.e., with amenorrhea for at least 12 consecutive months, they were classified as post-menopausal women [2].

To ensure the quality control of information, 10% of the interviews were redone through phone calls, using a simplified questionnaire. In this questionnaire, some perennial questions (with answer with no possibility of change since the time of the survey) were repeated by the research coordinators. The encoding of the information was also carried out by the research coordinators.

The typing of data followed the procedure of double entry, being performed with EPI-DATA 3.1 software. Comparisons of typing and analysis of consistency between

them were made. Bivariate and multivariate analysis were performed in STATA 9.0 (Stata Corp.,College Station, USA) software, according to a pre-established analysis plan.

The chi-square test and the test for linear trend were used to describe the characteristics of the sample according to menopausal status. The MetS components were also evaluated individually, both in terms of relative frequency and measures of central tendency and dispersion, according to menopausal status.

Estimates of prevalence ratios crude and adjusted with confidence intervals of 95% were calculated by Poisson Regression with robust variance. To investigate the relationship between menopausal status and MetS, the control of potential confounding factors in the multivariate model was based on the conceptual framework from Victora et al (1997) [23, 24], based on levels of determination. Models I, II and III included the most distal level of determination. The model I was adjusted for demographic variables; the model II, for the socio-economic variables; and model III, for the variables of models I and II that remained associated. The model IV includes the most proximal variables to determine MetS, and the reproductive and behavioral variables. Both to join multivariate analysis as a potential confounding factor and to remain in the model, a variable should have a p-value <0.20 in the bivariate analysis and in its level of determination, respectively. In each model, those variables with p-value <0.05 were considered statistically associated with the outcome. Since nutritional status assessed by body mass index is directly related to MetS components, it was used only for the bivariate analysis.

This study was submitted and approved by the Research Ethics Committee of the University of Caxias do Sul, under opinion No. 124/08.

RESULTS

During the collection period, from January 2010 to April 2011, 658 women who consulted in the clinic were eligible for the study; 41 (6.2%) were refused and 66 (10%) did not perform the laboratory tests. The following results refer to 551 women with average age of 51.1 years (sd 6.5).

Table 1 presents the sample characteristics and the distribution according to menopausal status. Most women said they were white and being married / in union, 28% had low education (less than 4 years of study) and 48.7% had low family income (less than 3 minimum wages). Sedentariness was present in 67.9% of the sample, and most women never smoked (52.6%). As for reproductive variables, menarche between 12 and 13 years (44.6%) and three or more pregnancies (63.5%) prevailed in the sample. Most women (80.6%) were overweight.

Among all women in the study, 17% were pre-menopausal, 42% were perimenopausal and 38% were post-menopausal women. Table 1 shows, as expected, the advance of menopausal status as the age increases, and among women from 56 to 65 years, 88% were post-menopausal. Women with low education and without paid work were proportionally more in the post-menopausal period than the other groups of schooling and among those with paid work (Table 1).

The prevalence of MetS in the sample was 56.1% ($CI_{95\%}$ 51.9 to 60.2), being more common among older women (56 to 65 years), with low education, menarche $\leq$ 11 years old, with three or more pregnancies and in the post-menopausal period (Table 2). The prevalence of MetS increased gradually as menopausal status, showing a linear association, with 26% greater likelihood of MetS in post-menopausal women compared to pre-menopausal women (Table 2). Obese women had six times more MetS than the eutrophic women (78.8% vs. 13.1%).

Figure 1 shows the isolated components of MetS according to the menopausal status. Among all women, the most prevalent altered components were: hypertension (84.8%; $CI_{95\%}$: 81.7 to 87.8), waist circumference (66.4%; $CI_{95\%}$: 62.5 to 70.4) and HDL cholesterol (51.7%; $CI_{95\%}$: 47.5 to 55.9). The increase in the proportions of high blood glucose and blood pressure showed a clear linear trend. The largest increase in waist circumference (>88 cm) occurs between the pre-menopause to perimenopause, suggesting a later stabilization at a level slightly less than 70%. The proportion of women with low HDL remained unchanged between the three periods.

Comparing the average values of the components according to the presence or absence of MetS (Table 3), it was observed that the largest increase was in values of serum triglycerides (51.5%), followed by blood glucose (21%).

Table 4 presents the multivariate models for MetS according to the three periods of the menopausal status. Regarding behavioral variables, physical activity was not included and smoking habit remained in the multivariable models, due to lack of statistical significance. There was an increase of prevalence ratios when comparing perimenopause and post-menopause with pre-menopause; however, the confidence intervals include the unit (Table 4).

DISCUSSION

The present study investigated the relationship between menopausal status and presence of Metabolic Syndrome in women from 40 to 65 years treated at a clinic of climacteric and Gynecological Surgery in southern Brazil. The prevalence of MetS in this population was high, showing an increasing trend in relation to periods of pre-, peri- and post-menopause. In the multivariate model, this trend lost statistical significance. Among MetS components isolatedly, there was a linear increase in the occurrence of high blood pressure and blood glucose over the three periods of the menopausal status, but the proportion of low HDL remained unchanged.

The study found a prevalence of MetS of 56.1%, considerably higher than other studies conducted in clinics and similar to population studies in Brazil. Cross-sectional population-based studies showed prevalence similar to that found in our study - 56.9% (among women over 45 years) in the semi-arid region of Bahia [25] and 59.9% (in women over 60 years) in Novo Hamburgo, state of Rio Grande do Sul [26]. However, Figueiredo Neto (2010)[8], investigating women in climacteric period in a gynecology clinic in Maranhão, found lower prevalence, of 34.7%[8]. This study, like ours, was performed in public health service, with the average age of women of 49.7 years, slightly lower than ours.

Just as within the country, the prevalence of MetS in women in climacteric period varies widely around the world. In Taiwan [17] and Korea [12], in studies performed in clinics, the prevalence of MetS were even lower (6.2% and 17.9%, respectively). On the other hand, population-based studies show higher prevalence rates of MetS. In Iran, Ainy et al (2007) [18] conducted a study with 2,182 women in menopausal transition and found a prevalence of MetS of 63%. In addition to differences in culture and lifestyle, which are not evaluated, the difference between the prevalence on this study and ours may be partly attributed to the higher age averages of the study performed in Iran.

In our study, an increase in the prevalence of Metabolic Syndrome was observed between the periods of pre- to peri- and post-menopause, although this effect has missed statistical significance in multivariate analysis. These findings are consistent with recent studies that demonstrate increased prevalence of MetS in women in climacteric period, and a greater increase in post-menopause when compared to pre-menopause was observed [8, 11, 12, 20, 27]. Miller et al (2003)[28], through a cross-sectional population-based study in the USA women with a cohort of immigrant women from the Soviet Union, presented an even bigger difference than the other studies in the prevalence of MetS in the period (13% in pre-menopause, 68% in post-menopause). This increased prevalence in post-menopause may have occurred because the average age was higher in the study by Miller

(57.3 years) when compared with the average age of our study (51.1 years). In a study performed on a gynecology clinic in Brazil[8], with women with an average age of 49.7 years, the prevalence of MetS in pre-menopausal women was 24%, while in post-menopausal women was 44.4%, prevalence lower than of our study. These findings show the age as a participating factor when the relationship of menopausal status and the occurrence of MetS is studied. Although the risk of MetS increases with age, cross-sectional population-based and cohort studies show that post-menopausal women are at greater risk of having MetS, regardless of age [9, 11, 29].

Establishing the effect of climacteric as an independent risk factor for MetS has been a tough challenge to researchers, given the difficulty of separating the effects of natural aging process of menopause [27]. The predominance of testosterone is being indicated as a hormonal change that is directly associated with the incidence of MetS, regardless of aging and other standard risk factors of CVD [29]. Other studies support the hypothesis that the reduction of estrogen would be the main factor for the increase of this incidence, directly associated with aging and biological aging, which itself already contributes to the increase of health problems. However, Kok et al (2006) [30] conducted a study with Framingham's data to investigate whether cardiovascular risk profile could accelerate menopause. The results showed that the risk of heart disease determines the age of menopause. This offers an explanation for the inconsistent results in the cardiovascular disease rates in relation to the age of menopause.

By investigating the characteristics of women, it was observed that there was a similar behavior in association with both the MetS outcome and the menopausal status exposure, namely: age, schooling, number of pregnancies and nutritional status. Moreover, menarche was only associated with MetS, not with menopausal status.

Socioeconomic characteristics such as low schooling and income are factors associated with an increased prevalence of MetS in most studies that evaluate women in climacteric period [29, 31]. Romaguera et al (2010) [31], using data from a longitudinal study, showed that higher schooling seems to provide a protective effect, even after adjustment for confounding factors. Number of pregnancies has often been studied in relation to MetS. By assessing Iranian women, Mousavi et al. (2009) [32] found that the number of pregnancies in women with MetS was significantly higher than in those without MetS (5.2 ± 3.1 vs. 3.5 ± 2.6, $p < 0.001$). The prevalence of MetS in nulliparous women, mothers with 1-4 children and more than 4 children was 15.2%, 26.2% and 49.6%, respectively. As to menarche, Feng et al. (2008) [19] also found that women with early menarche (8-13 years) have significantly increased risk for MetS (OR = 1.32; CI 95% 1.14–1.53) than

women with menarche from 14 years. Heys et al. (2007) [33] evaluated the effect of menarche in the development of MetS in 7,349 Chinese women with 50 years or more of a historical cohort. Adjusted for age, schooling and number of pregnancies, the lower age of menarche (<12.5 years), when compared to the older (≥14.5 years), was associated with a higher risk of MetS (OR = 1.49; CI 95% 1.22–1.82). Regarding the nutritional status, obese and overweight women had higher prevalence rates of MetS when compared with eutrophic women. One of the components of MetS is abdominal obesity, directly related to overall obesity. In a study conducted with the 1982 Pelotas cohort, obesity increased the risk of young adults having MetS by about 40 times [34].

As for the prevalence of MetS components, altered blood pressure (130/85) was the most common characteristic observed in the population studied, followed by increased waist circumference and low HDL. Other studies showed that waist increased circumference and blood pressure had the highest prevalence among the MetS components, suggesting that these are the components that most influence the prevalence of MetS [9, 12]. Specifically in relation to blood pressure, the region where the study was conducted is considered one of the biggest consumers of sodium-rich foods and, consequently, a high prevalence of hypertension is found in this population. While the average sodium consumption in Brazil is 4.5 g, in southern Brazil is 5 g [35]. A national population survey showed that the female population that resides in southern Brazil consumes 64% more sodium than the recommended [36].

When the occurrence of the altered components during different periods of climacteric was observed, there were gradual increases in the prevalence of altered blood pressure and high glucose when comparing pre-, peri- and post-menopause periods. The increase in blood pressure during climacteric is common in many studies in different countries [8, 9, 12, 17]. Sièminksa et al (2006) [16], investigating Polish women, found in pre-menopausal women a prevalence of 7% of hypertension, while in post-menopausal women this percentage increased to 30%. High glucose (above 100 mg/dl) has also increased its prevalence in climacteric period [8, 9, 11]. In a study by Kim et al. (2007) [9], with Korean women, the prevalence found in pre-menopausal women was 9.8%, while among post-menopausal women the prevalence of altered glucose was 26%. It was observed that high waist circumference had its highest prevalence during the perimenopause period. Few studies assess the perimenopause; most evaluates the difference between pre- and post-menopause. Low HDL cholesterol did not present change in prevalence between the three periods.

In our study, the average values of the components were evaluated according to the presence or absence of MetS. An increase in the average value of those with MetS was observed. The biggest variation (increase of 51%) occurred in the average of serum triglycerides, 111.5 vs. 158.9, respectively, in women without and with MetS – followed by blood glucose (increase of 20%) and serum HDL cholesterol (reduction of 18%). The smallest average variation occurred in the blood pressure levels, an increase of 6% among women without and with MetS. In the study by Janssen (2010) [29], which also compared the data between women with and without MetS, the same trend in the variation of components is observed. It is noteworthy that in our study the averages in women with and without MetS are higher, and all the component values among women with MetS were higher than the recommended by NCEP[3]. These results reinforce the need to investigate the components of MetS both aggregate and isolatedly in this period of life of women.

Our findings should be interpreted with some observations. First, the way in which the three periods of menopausal status were analyzed, i.e., based on self-reported information. Perimenopausal women reported being with irregular menstrual cycles or less than twelve months without menstruating. Since this is a cross-sectional study, we only have information from the current moment of these women. One year after the collection, we contacted 55 women, who at the time of the survey reported that were not menstruating for less than 12 months, which were classified in perimenopause for that reason. Even classifying as post-menopausal the women who reported being more than 12 months without menstruating at the time of phone call, the analysis showed no differences. Therefore, we chose to use the data collected during the interview. A second aspect that deserves attention refers to the sample size both in terms of total size and the number within the categories of exposure. In subsequent calculations we found that 594 women would be needed to identify significant difference of MetS between pre- and post-menopause. In addition, we obtained a small number of classified women in the pre-menopause period, and in our sample calculation, we expected to find a greater number of these women. Most of our sample was in perimenopause. It is also important to assess that, among those who were post-menopausal, the average age was 57 years ($\pm$4.9), demonstrating that exposure to post-menopause on these women was small. In several studies the average age in post-menopause is greater than what was found in our study [12, 18, 20]. The study by Cho et al (2009) [12] presents results that support the hypothesis that the risk of having MetS increases with the years since menopause, and tends to decrease after 14 years from the last menstruation. The highest prevalence of MetS would be around 60

years, value greater than the average age we found. By analyzing the results of these other studies, it is possible to infer that there were no statistically significant differences in our multivariate analysis because our sample has a greater number of perimenopausal women and because of the small exposure of women to menopause.

Another point to highlight relates to the generalization of our findings, mainly regarding the prevalence of MetS. Our sample came from a health service specialized in women in climacteric period, which serve only users of the Unified Health System, with low schooling and income. Since this sample is not population-based, the results should not be generalized to the general population.

The last observation is about the percentage of rejections and losses caused by failure to carry out the laboratory tests. However, in a comparative analysis of the main characteristics of the studied group (551) and such losses / rejections, there were no statistically significant differences between the characteristics investigated.

This study stands out not only for being one of the few studies conducted in Brazil in a secondary level public clinic, as well as for evaluating the relationship of menopausal status with each of the isolated components of MetS. Thus, it was possible to demonstrate that, in addition to blood pressure and waist circumference, the change in blood glucose and serum triglycerides play an important role in increasing Metabolic Syndrome during climacteric. Certainly, further studies with this type of approach should be conducted to improve understanding and targeting of actions and programs focusing on women in this period of life.

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Table 1. Demographic, socioeconomic, behavior and reproductive characteristics of the sample and relationship with the menopausal status of women in climacteric period at a clinic in southern Brazil.

Variables	n (%)		Pre		Peri		Post		P
	551 (100)		96 (17.6)		250 (45.7)		201 (36.7)		
Age (years) Quartile									< 0.001**
40 to 45	119	(21.6)	47	(39.8)	69	(58.5)	2	(1.7)	
46 to 50	155	(28.1)	40	(25.8)	100	(64.5)	15	(9.7)	
51 to 55	143	(26.0)	9	(6.4)	65	(46.1)	67	(47.5)	
56 to 65	134	(24.3)	0	(0)	16	(12.0)	117	(88.0)	
Skin Color									0.42*
White	395	(71.8)	74	(18.9)	176	(45.0)	141	(36.1)	
Not White	155	(28.2)	22	(14.2)	74	(47.7)	59	(38.1)	
Marital status									0.06*
Not Married	191	(34.7)	25	(13.2)	85	(44.7)	80	(42.1)	
Married / in union	360	(65.3)	71	(19.9)	165	(46.2)	121	(33.9)	
Schooling (years) Quartile									0.03**
0 to 4	154	(28.1)	16	(10.5)	66	(43.1)	71	(46.4)	
5 to 8	250	(45.5)	53	(21.4)	119	(48.0)	73	(30.6)	
9 to 11	127	(23.1)	24	(19.9)	53	(42.1)	49	(38.9)	
≥ 12	18	(3.3)	3	(16.7)	11	(61.1)	4	(22.2)	
Family Income (MS) Quartile									0.07**
0 to 2	153	(27.9)	20	(13.1)	70	(45.8)	63	(41.2)	
2.01 to 3.00	114	(20.8)	18	(15.9)	52	(46.0)	43	(38.1)	
3.01 to 5.00	151	(27.5)	34	(22.7)	66	(44.0)	50	(33.3)	
5.01 or more	131	(23.9)	23	(17.8)	62	(48.1)	44	(34.1)	
Paid work									<0.001*
No	257	(46.6)	41	(16.0)	93	(36.3)	122	(47.7)	
Yes	294	(53.4)	55	(18.9)	157	(54.0)	79	(27.1)	
Physical Activity									0.002*
Sedentary	374	(67.9)	69	(18.6)	184	(49.6)	118	(31.8)	
Non-sedentary	177	(32.1)	27	(15.3)	66	(37.5)	83	(47.2)	
Smoking Habit									0.60*
Non-smoker	290	(52.6)	55	(19.0)	125	(43.3)	109	(37.7)	
Former Smoker	158	(28.7)	22	(14.0)	77	(49.0)	58	(36.9)	
Smoker	103	(18.7)	19	(18.8)	48	(47.5)	34	(33.7)	
Menarche (years)									0.70*
≥ 14	190	(34.5)	37	(19.5)	82	(43.2)	71	(37.4)	
12 to 13	246	(44.6)	43	(17.8)	110	(45.5)	89	(36.8)	
≤ 11	115	(20.9)	16	(13.9)	58	(50.4)	41	(35.7)	
Number of pregnancies									<0.001*
0 to 1	72	(13.1)	23	(31.9)	20	(27.8)	29	(40.3)	
2	129	(23.4)	27	(21.1)	53	(41.4)	48	(37.5)	
≥ 3	350	(63.5)	46	(13.3)	177	(51.0)	124	(35.7)	
Nutritional status (BMI)									0.04**
Eutrophic (< 24.9)	107	(19.4)	24	(22.6)	43	(40.6)	39	(36.8)	
Overweight (25 to 29.9)	189	(34.3)	39	(20.7)	89	(47.3)	60	(31.9)	
Obesity (≥ 30)	255	(46.3)	33	(13.0)	118	(46.6)	102	(40.3)	

* P-value for Pearson
** P-value Linear Association

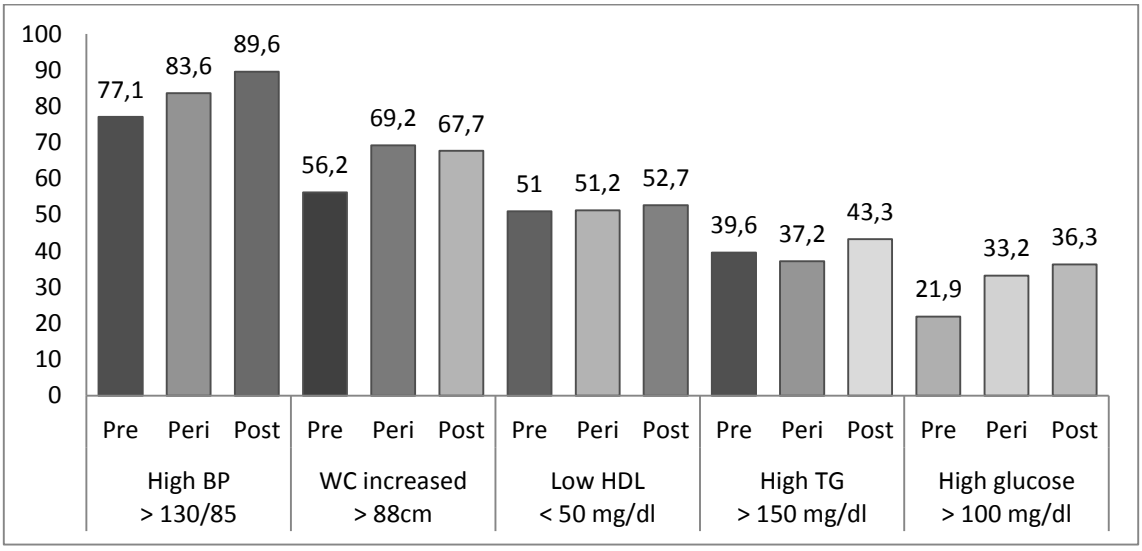
Table 2. Prevalence and prevalence ratios of Metabolic Syndrome according to demographic, socioeconomic, behavioral, reproductive and nutritional status characteristics of women in climacteric period at a clinic in southern Brazil. (n= 551 women)

Variables	MetS n (%)		P-value	PR	CI (95%)	P-value
Age (years) Quartile			0.04**			0.04
40 to 45	60	(50.4)		1		
46 to 50	85	(54.8)		1.09	0.87-1.35	
51 to 55	78	(54.5)		1.08	0.86-1.37	
56 to 65	86	(64.2)		1.27	1.02-1.58	
Skin Color			0.47*			0.50
White	225	(57.0)		1		
Not White	83	(53.5)		0.94	0.79-1.11	
Marital status			0.10**			0.11
Not Married	98	(51.3)		1		
Married / in union	211	(58.6)		1.14	0.97-1.34	
Schooling (years) Quartile			0.04**			0.04
0 to 4	97	(63.0)		1		
5 to 8	137	(54.8)		0.87	0.74-1.03	
≥ 9	74	(51.0)		0.81	0.66-0.99	
Family Income (MS R$510) Quartile			0.04*			0.06
0 to 2	87	(56.9)		1		
2.01 to 3.00	75	(65.8)		1.16	0.96-1.40	
3.01 to 5.00	83	(55.0)		0.97	0.79-1.18	
5.01 or more	62	(47.3)		0.83	0.66-1.04	
Paid work			0.18*			0.18
No	152	(59.1)		1		
Yes	157	(53.4)		0.90	0.78-1.05	
Physical Activity			0.38*			0.38
Sedentary	205	(54.8)		1		
Non-sedentary	104	(58.8)		1.07	0.92-1.25	
Smoking Habit			0.02*			0.10
Non-smoker	166	(57.2)		1		
Former Smoker	97	(61.4)		1.07	0.91-1.26	
Smoker	46	(44.7)		0.78	0.62-0.99	
Menarche (years)			0.05**			0.04
≥ 14	100	(52.6)		1		
12 to 13	134	(54.5)		1.03	0.87-1.24	
≤ 11	75	(65.2)		1.24	1.02-1.50	
Number of pregnancies			0.01**			0.02
0 to 1	34	(47.2)		1		
2	64	(49.6)		1.05	0.78-1.42	
≥ 3	211	(60.3)		1.28	0.99-1.65	
Nutritional status (BMI)			<0.001**			<0.001
Eutrophic (< 24.9)	14	(13.1)		1		
Overweight (25 to 29.9)	94	(49.7)		3.80	2.28-6.33	
Obesity (≥ 30)	201	(78.8)		6.02	3.68-9.86	
Menopausal status			0.05**			0.06
Pre-menopause	46	(47.9)		1		
Perimenopause	140	(56.0)		1.17	0.92-1.48	
Post-menopause	121	(60.2)		1.26	0.99-1.60	

* P-value for Pearson

** P-value Linear Association

Figure 1. Prevalence of altered components of MetS according to menopausal status in women in climacteric period at a clinic in southern Brazil. (n=551)



HDL (high density lipoprotein) and TG (triglycerides): P-value >0.05
BP (blood pressure) and glucose: P-value < 0.05 (linear trend)
WC (waist circumference): P-value =0.07 (Pearson)

Table 3. Average values and standard deviation (sd) of the components of MetS in women treated at a climacteric clinic in southern Brazil according to the presence or absence of Metabolic Syndrome (n = 242) and with Metabolic Syndrome (n = 307)

Component	Without MetS (n=242) Average (sd) (a)	With MetS (307) Average (sd) (b)	Variation (a:b)	P-value
Diastolic BP	137.2 (± 17.87)	145.6 (± 18.98)	↑ 6.1%	<0.001
Systolic BP	87.2 (± 12.21)	92.2 (± 12.67)	↑ 5.7%	<0.001
Waist circumference	86.7 (± 11.70)	101.0 (± 12.20)	↑ 16.5%	<0.001
HDL	57.1 (± 11.97)	46.4 (± 10.75)	↓ 18.7%	<0.001
Triglycerides	111.5 (± 52.41)	168.9 (± 74.54)	↑ 51.5%	<0.001
Glucose	88.5 (± 10.37)	107.0 (± 36.40)	↑ 20.9%	<0.001

Test: t-test
BP: blood pressure
HDL: high density lipoprotein

Table 4. Multivariate models and CI95% of MetS in relation to menopausal status in women in climacteric period at a clinic in southern Brazil.

Exposures	Model I	Model II	Model III	Model IV
P-value	0.38	0.12	0.47	0.55
Pre	1	1	1	1
Peri	1.15 (0.90-1.46)	1.16 (0.92-1.48)	1.13 (0.87-1.44)	1.08 (0.85-1.38)
Post	1.15 (0.85-1.55)	1.22 (0.96-1.57)	1.12 (0.83-1.52)	1.10 (0.81-1.48)

I - Controlled for age and marital status
II - Controlled for schooling, income, and paid work
III - Controlled for age, marital status and schooling
IV - Controlled for age, marital status, schooling and number of pregnancies

Parte III

Artigo original II

LIPID ACCUMULATION PRODUCT (LAP) AND ITS RELATION WITH CARDIOMETABOLIC RISK, SOCIOECONOMIC AND REPRODUCTIVE CHARACTERISTICS IN WOMEN IN CLIMACTERIC PERIOD

Lipid Accumulation Product (LAP) and its Relation with Cardiometabolic Risk, Socioeconomic and Reproductive Characteristics in Women in Climacteric Period
LAP and cardiometabolic risk in climacteric period

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ABSTRACT

The aim of this study is to verify the association of LAP index with socioeconomic, demographic, reproductive and quality of life characteristics, to investigate its relation with menopausal status, as well as to assess the LAP as a tracker of diabetes mellitus and metabolic syndrome. A cross-sectional study was conducted with a sample of 551 women from 40 to 65 years. Metabolic syndrome was assessed according to NCEP-ATPIII's (National Cholesterol Education Program's Adult Treatment Panel III) criteria. Women with fasting glucose above 100 mg/dl / presence of Diabetes Mellitus were also evaluated separately. LAP mean was 61.31 cm.mmol/L ($CI_{95\%}$ 59.9 to 64.7). Ages from 56 to 65 years, three or more pregnancies and being former smoker was positively associated with increased LAP, even after adjustment in the multivariate models. The prevalence of high LAP ($\geq$34.5 cm.mmol/L) was 71.3% ($IC_{95\%}$: 67.6 to 75.1). Women with high LAP had 4.6 times more likely to develop MetS ($IC_{95\%}$ 3.2 to 6.6) and 2.4 times more likely to have high glucose or presence of DM ($IC_{95\%}$ 1.6 to 7.4) compared with women with LAP <34.5 cm.mmol/L. LAP can be a new alternative to predict cardiometabolic risk, since besides the waist circumference measurement, it includes triglyceride measurement, which in women appears to represent an increased risk for cardiovascular mortality, regardless of other lipid fractions.

INTRODUCTION

Climacteric is the period of transition from the reproductive stage to the non-reproductive stage of women. At the onset of menopause (last menstrual period) it is common to gain weight and change the fat distribution (1-2). Longitudinal studies have shown an association between menopausal status and obesity, especially central obesity, suggesting that there is an increased deposition of abdominal fat associated with changes in hormonal milieu, which is characteristic of the menopausal transition, with a drop in estrogen levels and consequent relative hyperandrogenism (3). This deposit of fat, in turn, is a risk factor for developing metabolic syndrome (MetS) (4) and diabetes mellitus (DM) (5).

Although the body mass index (BMI) is the most commonly used marker to assess obesity, central obesity measurements have been proposed because they are better correlated with cardiometabolic risk (6). There are several ways to estimate abdominal obesity; the waist circumference (WC) measurement is the more effective for clinical practice and epidemiological studies (7). Recently, the lipid accumulation product (LAP) has been proposed as abdominal adiposity marker index and cardiovascular risk marker (8-9-10-11). LAP relates the WC measurement with triglycerides (TG) levels.

This index was first described by Kahn in 2005, from National Health and Nutrition Examination Survey (NHANES III) data (10), being a strong marker for the diagnosis of diabetes and a better cardiovascular risk indicator than BMI in the general population and also in subpopulations such as women in menacme and postmenopausal women (12-13-14-15). LAP was considered modestly higher than BMI to predict glucometabolic variables, but far superior to identify adults with diabetes. Although the risk of diabetes is associated with abdominal adiposity and circulating triglycerides, the combination of these two variables into a single continuous index (LAP) seems to better summarize how the lipid accumulation can lead to the disease (12). In non-diabetic adults, LAP showed a strong and reliable accuracy of diagnosis for Metabolic Syndrome (16).

In literature, there are not studies that describe the LAP distribution according to population group characteristics. There are few published studies that use LAP as a risk indicator for cardiometabolic diseases, focusing on the menopausal transition (9-13-14).

Therefore, we intend to verify the association of LAP index with socioeconomic, demographic, reproductive and quality of life (smoking and physical activity) characteristics, to investigate its relation with menopausal status, as well as to assess the LAP as a tracker of diabetes mellitus (high fasting glucose) and metabolic syndrome.

METHODS

A cross-sectional study was conducted with women from 40 to 65 years treated at the clinic of Climacteric and of Gynecological Surgery, belonging to the Central Clinic of the University of Caxias do Sul (AMCE-UCS), from January 2010 to May 2011. Both clinics are part of the Unified Health System and serve the population of the municipality and region. Hysterectomized women and women who were submitted to hormone replacement therapy were excluded from the study.

The sample size was calculated for the association between menopausal status and MetS, because this study is part of a larger project entitled "Menopausal status and metabolic syndrome in women in climacteric period treated at a clinic in southern Brazil". Thus, a sample of 687 women would allow identifying an OR of 1.6 (17), with a confidence level of 95%, a statistical power of 80% and a ratio of unexposed:exposed maintained at 2:1. The unexposed are the pre-menopausal women, and the exposed are the post-menopausal women.

A standardized, pre-coded and pre-tested questionnaire was applied, containing socioeconomic, demographic, reproductive and behavioral characteristic questions, presented by trained interviewers. The demographic characteristics evaluated were: age (40 to 45 years; 46 to 50 years; 51 to 55 years; 56 to 65 years); skin color (white or not white); and marital status (married / in union and not married). The socioeconomic characteristics evaluated were: schooling (0 to 4, 5 to 8, 9 to 11 and ≥ 12 full years of study), family income (0 to 2, 2.01 to 3.00, 3.01 to 5.00; ≥ 5.01 minimum wages; value at the time: R$ 510.00); and paid work (yes / no). As behavioral characteristics, smoking and physical activity were evaluated. Smoking habit was classified as smoker, former smoker and nonsmoker. As to physical activity, the women were classified as: sedentary (women who reported no physical activity) and non-sedentary (those practicing any physical activity at least once a week for at least 30 minutes.

The women's previous reproductive characteristics were evaluated using the following variables: menarche (≥ 14; 12-13; ≤ 11 years of age); number of pregnancies (0 to 1; 2; and ≥ 3 pregnancies). For classification of menopausal status, the study participants were asked if they were still menstruating. If so, whether they were regular menstrual cycles, similarly to what had occurred during their reproductive life, they were classified as pre-menopausal women. If menstrual cycles were irregular in relation to flow and time intervals, they were classified as perimenopausal women. If they reported they

did not menstruate, i.e., with amenorrhea for at least 12 consecutive months, they were classified as post-menopausal women (18).

Anthropometric measurements were performed by nutritionists with previous training and standardization. The weight was obtained in kilograms (kg), in an anthropometric beam scale with non-detachable weights, Welmy® brand, with capacity of 150 kg and precision of 100 g. To measure the height, the fixed anthropometric of the scale ranging from 95 to 190 cm was used. Both procedures were performed with the patient barefoot and without excess clothing. To define obesity, the body mass index (BMI) was calculated by dividing weight (kg) by squared height (m). Women with BMI $\geq$ 30.0 kg/m^2 were classified as obese, with BMI between 25.0 and 29.9 kg/m^2 were classified as overweight, and with BMI <24.9 kg/m^2 were classified as eutrophic (19).

For WC measurement, standardization training was performed in order to reduce intra- and inter-observer error. The WC was measured with a non-flexible tape measure directly on the skin at the midpoint between the last rib and the iliac crest, and the readings were made at the end of normal expiration (19). Abdominal obesity was obtained by the mean between two WC measurements.

The MetS was evaluated through each of its components: blood pressure, blood glucose, levels of HDL cholesterol, triglycerides and waist circumference – measured as described above. The blood pressure levels were measured at the wrist with an automatic digital device (BP3AF1-3), validated according to the guidelines of Association for the Advancement of Medical Instrumentation (AAMI) and British Hypertension Society (BHS) (20). The woman remained sitting, without speaking, and at rest for at least 5 minutes. This procedure was performed two non-consecutive times in a minimum interval of 5 minutes, and the mean value between the two measurements was used for analysis. Laboratory tests (fasting blood glucose, levels of HDL cholesterol and triglycerides) were collected from participants' medical records, with a limit of four months. Since the request of these tests was part of the clinic routine, most women already had them. For those women who had old tests, new tests were requested by the physician responsible for the clinic. MetS was assessed according to NCEP-ATPIII's (National Cholesterol Education Program's Adult Treatment Panel III) criteria (21). Women were considered with SM having at least three of the following criteria: waist circumference >88 cm, triglycerides >150mg/dl, HDL cholesterol <50 mg/dl, blood pressure $\geq$130 mmHg or $\geq$85 mmHg, fasting blood glucose >100mg/dl, or in use of medication to treat these conditions.

Diabetes mellitus was defined as women with fasting glucose >100 mg/dl or with diagnosis of diabetes mellitus made by a physician.

LAP combines an anthropometric measurement (waist circumference) and a biochemical measurement (concentration of triglycerides). Its determination in women is given by the following equation: (waist circumference [cm] - 58) x (triglycerides [mmol/L]). The TG results were transformed from mmg/dl into mmol for LAP calculation.

The typing of data followed the procedure of double entry and subsequent comparison, being performed with EPI-DATA 3.1 software. Simple and multiple regression analyses were performed using STATA 9.0 software (Stata Corp., College Station, USA). To assess the existence of associations between the outcome as continuous numerical variable (LAP) and the categorical independent variables, the mean comparison tests ANOVA and T Student was used. Simple and multiple linear regressions were conducted including the LAP outcome with the other sample characteristics. Variables with $p<0.20$ were entered into the multivariate model. Multivariate analysis was performed using a pre-established hierarchical model. Model I was adjusted for socioeconomic and demographic variables, model II was adjusted for model I and lifestyle and reproductive variables. Model III was adjusted for models I and II and nutritional status and menopausal status.

To investigate the association of LAP with MetS and glucose $\geq$100 mg/dl / presence of diabetes mellitus, the prevalence ratio and confidence interval of 95% were calculated through Poisson regression. In this analysis, the cutoff point for LAP was $\geq$34.5 (9).

This study was submitted and approved by the Research Ethics Committee of the University of Caxias do Sul, under opinion No. 124/08.

RESULTS

Among the 658 women eligible for the study; 41 (6.2%) were refused and 66 (10%) did not perform the laboratory tests. Thus, this study counted with 551 women, with average age of 51.1 years ($CI_{95\%}$ 50.5 to 52.4). Table 1 shows that most women said they are white and married. More than half of women (53.4%) had some paid work, 28% had low schooling (less than 4 years of study), and 48.7% had low family income (less than 3 minimum wages). Sedentariness was present in about two-thirds of the sample and about half of women have never smoked (52.6%). As for reproductive variables, menarche between 12 and 13 years (44.6%) and three or more pregnancies (63.5%) prevailed in the sample. Most women (80.6%) were overweight / had obesity.

Among all women, LAP mean was 61.31 cm.mmol/L ($CI_{95\%}$ 59.9 to 64.7). Still in table 1, it is possible to observe the distribution of the LAP means according to the sample characteristics. LAP directly increases as the age increases and inversely increases with increased incomes and schooling. Women with paid work have lower LAP, when compared to those without paid work. Smokers have a lower LAP mean (56.6) when compared to nonsmokers and former smokers, while those physically active showed a larger LAP mean than the sedentary women (64.8 and 59.7, respectively). Women with three or more pregnancies and the post-menopausal women showed LAP means greater than those nulliparous / primiparous or who were in pre- or perimenopause.

Table 2 presents the crude and adjusted regression coefficients of the sample characteristics according to the LAP. Ages from 56 to 65 years, three or more pregnancies and being former smoker was positively associated with increased LAP, even after adjustment in the multivariate models. It is noteworthy that overweight women had an increase of 20.55 cm.mmol/L in the LAP, while obese women presented an increase of 51.45 cm.mmol/L, compared with eutrophic women. The relation between menopausal status and the LAP lost statistical significance and effect after the adjustment in the model III (table 2).

The prevalence of high LAP ($\geq$34.5) was 71.3% ($IC_{95\%}$: 67.6 to 75.1) (data not presented in the table). Figure 1 shows the reasons for the prevalence of high LAP for high fasting glucose and MetS/DM, adjusted to the age of women. Women presenting high LAP had 4.6 times more likely to develop MetS ($IC_{95\%}$ 3.2 to 6.6) and 2.4 times more likely to have high glucose or presence of DM ($IC_{95\%}$ 1.6 to 7.4), when compared with women with LAP < 34.5 cm.mmol/L.

DISCUSSION

Our study stands out for being the first to investigate the LAP distribution according to socioeconomic, demographic, reproductive and quality of life characteristics in a sample of women in climacteric period. Age (56 to 65 years), being former smoker, having overweight/obesity and more than three pregnancies were strongly associated with increased LAP. LAP proved to be a predictor of risk for metabolic syndrome and diabetes mellitus.

As to the socio-demographic characteristics, just the age remained in the multivariate analysis – the higher the age, the greater the LAP mean. Women, over 50 years old, showed a tendency to weight gain, which can be related to the reduction of resting energy requirements, concomitant to an inadequate nutrition and low levels of

physical activity (1-2-22). The studies indicate a trend of increase in WC and TG as the age increases (23-24-25-26). In contrast, some studies show that post-menopause is, regardless of aging, the responsible for increased levels of WC, TG, and also of the other MetS components (17-27-28).

Women who said they were former smokers had a higher LAP mean when compared to non-smokers and smokers. This relation was found when studies evaluating isolated WC were analyzed. Several studies show an inverse association between smoking and WC; however, in former smoker women there seems to be a potentiating effect for abdominal obesity. In a cross-sectional study performed in Pelotas (state of Rio Grande do Sul), an inverse association between smoking and abdominal obesity was found. The study identified that the WC mean in former smokers was 93.6 cm (± 14.1) and in smokers it was 88.9 cm (± 13.6) (29). According to the study of Olinto and collaborators (30), former smoker women showed prevalence of abdominal obesity of 47.1%, and for the smoker women it was 27.3% ($p < 0.01$).

In our study, the greater the number of pregnancies, the higher the LAP mean. This difference remained in the multivariate analysis. Parity has also been cited as a factor that directly and positively associated with weight gain in women of older age. Moreover, it is associated with increased deposition of intra-abdominal fat after the gestational period, possibly due to excess of weight gain during pregnancy (31). Studies show that the increase of parity is associated with the decrease of hip circumference and increase of waist circumference (32-33). In a subsample of the *Coronary Artery Risk Development in Young Adults* (CARDIA) study, with 122 pre-menopausal women followed for five years, subjected to analysis of body composition using DEXA and computed tomography, pregnancy was associated with the gain in postpartum central and visceral adiposity. Throughout the follow-up, nulliparous women increased by 14% their visceral adipose tissue, while those with at least one childbirth increased by 40%. There was no significant difference in relation to BMI, but the parity was associated with increased WC ($p = 0.05$). It is suggested that after pregnancy there is a preference for fat accumulation in the visceral adipose tissue (31). The *Guangzhou Biobank Cohort Study,* conducted with the Chinese population, evaluated the reproductive factors of 7,352 women and 3,065 men aged 50-93 years between 2003 and 2004. In women, BMI, waist-hip ratio, triglycerides and glucose were positively associated with number of children, even after adjusting for confounding factors. (34).

As to the nutritional status, studies show that LAP presents a better performance than BMI for identifying cardiovascular risk in adults (10). In this study, LAP showed an

association with nutritional status, and the greater the value of LAP, the higher the BMI. It is common the overall obesity to be related to abdominal obesity and increased triglycerides. In a study performed in Brazil with postmenopausal women, overweight and obesity were present in 77.1%, and abdominal obesity occurred in 87.3% of participants. In 45.8% of women, the mean values of TG were higher than the recommended. The authors concluded that the association between WC and BMI was efficient for the proper diagnosis of obesity related to metabolic changes in postmenopausal women (3). Janssen and collaborators, with NHANES data, evaluated the BMI and WC and showed that, in the different BMI categories, those with increased WC were more likely to have hypertension, diabetes, dyslipidemia and MetS (35).

One of our hypotheses was that menopausal status would be related to LAP. Our data demonstrated that postmenopausal women had a LAP mean of 67.1, higher than perimenopausal and premenopausal women, and in the crude analysis this relation was statistically significant**.** However, when controlled for age, income, smoking, physical activity, menarche and number of pregnancies, the association lost its significance. The study carried out with data from the Korean National Health and Nutrition Examination Survey (2001) found that increased TG and WC were significantly associated with post-menopause stage, after adjustment for age, and women at this stage were 60% (OR: 1.61; $CI_{95\%}$ 1.15 a 2.25) more likely to have abdominal obesity and 28% (OR: 1.28; $CI_{95\%}$ 0.89 to 1.83) more likely to have high triglycerides than premenopausal women (17). In Brazil, a high prevalence of abdominal obesity has been identified during post-menopause. Another study in southern Brazil showed the gradual increase in the prevalence of abdominal obesity according to menopausal status. Women in the menopausal transition were twice (OR: 2.07; $CI_{95\%}$ 1.09 to 3.96), while post-menopausal women were about three times more (OR: 2.83; $CI_{95\%}$ 1.17 to 6.88) likely to have abdominal obesity compared to premenopausal women (36).

In this study, we used the same cutoff point used initially by Wiltgen et al, in a study published in 2009, among women in menacme (15). In this study, the LAP rate $\geq$ 34.5 showed better performance than HDL-c, WC, or BMI to identify insulin resistance in patients with Polycystic Ovary Syndrome (PCOS) and controls, suggesting that LAP $\geq$ 34.5 may be considered as an additional risk factor in patients with PCOS. In a recent study in postmenopausal women, Maturana et al., using the same cut-off point described above, showed a positive association between LAP and endogenous androgens, SHBG and cardiovascular risk factors in women with favorable metabolic profile, suggesting that LAP seems to be an appropriate method to assess cardiovascular risk in

postmenopausal women (9). Using the cutoff point of Wiltgen et al. in our study, 71.3% of the selected women were with LAP above 34.5. This difference may be due to the difference in age of women in both studies (14 to 35 years in the study of women with PCOS; 40 to 65 years in our study). Therefore, our prevalence may be overestimated due to the cutoff point, which could be higher when the assessment is among women in climacteric period.

LAP is being described in the literature as an important marker for diabetes and cardiovascular risk in postmenopausal women (13-37). Recent studies address LAP as an index in the joint assessment of waist circumference and triglycerides through a specific calculation already described in the methods, but these two parameters have been investigated for a long time, individually or jointly, to predict cardiovascular risk. Tanko and collaborators (38) used the EWET (Enlarged Waist (88 cm) Combined with Elevated Triglycerides (1.45 mmol/L)) dichotomous indicator and compared it with the metabolic syndrome defined by NCEP-ATPIII. The authors found that central obesity and lipid overaccumulation are important risk factors for cardiovascular disease in postmenopausal women. Hypertriglyceridemia in women seems to represent an increased risk for cardiovascular mortality, regardless of other lipid fractions (38). In a cohort study in Swedish women conducted in 1993, the findings had already shown that the concentration of serum triglycerides was independent and significantly correlated with the incidence of myocardial infarction, cerebrovascular accident and death in general. In the study, the authors also claim that the location of adipose tissue is more important than its total amount (39). In non-diabetic adults, LAP has a rugged and reliable diagnostic precision for Metabolic Syndrome (International Diabetes Federation) and, especially, Metabolic Syndrome- NCEP/ATP III among women (16). These findings corroborate this study, in which LAP was associated with MetS and high fasting glucose / presence of DM in this population of women in climacteric period with low socioeconomic profile, with a high prevalence of overweight and sedentariness. LAP can be a new alternative to predict cardiometabolic risk, since it includes the measurement of triglycerides, which in women appears to represent an increased risk for cardiovascular mortality, regardless of other lipid fractions (38). With these findings, it is possible to suggest the reassessment of the use of MetS diagnosis in primary care, since it requires two more laboratory tests and blood pressure measurement. The LAP index, although it requires a fasting venipuncture, may be a useful estimator of obesity and cardiometabolic risk for the assessment of people whose weight or height can be difficult to measure (e.g. amputees) (40).

One of the limitations of our study refers to its cross-sectional design, which facilitates the occurrence of reverse causality bias between the investigated associations. In this study, the hypothesis of association between practice of physical activity and LAP was not confirmed. Non-sedentary women had a LAP mean lower than sedentary women. This finding may be a reflection of this bias, in which the presence of chronic diseases (dyslipidemia, obesity, hypertension, diabetes) would lead these women to make physical activity as part of treatment. Another limitation of this study refers to the generalization of our findings, especially in relation to the LAP mean. Our sample came from a health service specialized in women in climacteric period, which serve only users of the Unified Health System, women with low schooling and income. Since this sample is not population-based, any generalization of our findings for the general population must be done with restrictions. For losses caused by failure to carry out the laboratory tests by some women eligible for the study, it is noteworthy that in a comparative analysis between the main characteristics of the studied group (551) and these losses, there were no statistically significant differences between the characteristics investigated.

Finally, our findings contribute to better understand how LAP is distributed in women in climacteric period, as well as show consistency with other studies regarding the role of LAP as a predictor of cardiometabolic risk. However, further studies are needed to investigate the distribution of LAP in different population groups, both demographically and geographically, in order to better understand the specifics of this indicator in predicting cardiometabolic risk.

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Table 1. Description of the sample, means and standard deviations of LAP according to socio-demographic, behavioral and reproductive characteristics in women in climacteric period at a clinic in southern Brazil.

Variables	n (%) 551 (100)		Mean (DP)	P-value
Age (in years) quarters				0.001*
40 to 45	119	(21.6)	55.7 (40.51)	
46 to 50	155	(28.1)	56.5 (37.41)	
51 to 55	143	(26.0)	62.2 (39.13)	
56 a 65	134	(24.3)	70.9 (45.53)	
Skin color				0.87**
White	395	(71.8)	61.2 (41.12)	
Other	155	(28.2)	61.8(40.72)	
Marital Status				0.75**
Without partner	191	(34.7)	62.1 (45.46)	
With partner	360	(65.3)	60.9 (38.40)	
Schooling (in years) quarters				0.03***
0 to 4	154	(28.1)	69.6 (49.12)	
5 to 8	250	(45.5)	57.7 (33.32)	
9 to 11	127	(23.1)	59.8 (43.60)	
≥ 12	18	(3.3)	54.6 (33.85)	
Family income (quarters)				<0.001***
0 to 2	153	(27.9)	62.7 (44.11)	
2,01 to 3,00	114	(20.8)	74.5 (47.57)	
3,01 to 5,00	151	(27.5)	57.0 (36.75)	
5,01 or over	131	(23.9)	53.5 (32.45)	
Paid work				0.03**
Yes	257	(46.6)	65.3 (42.30)	
No	294	(53.4)	57.9 (39.47)	
Physical Activity				
Sedentary	374	(67.9)	59.7 (38.26)	0.16**
No sedentaty	177	(32.1)	64.8 (40.04)	
Smoking				0.02***
Non-smoker	290	(52.6)	58.9 (40.61)	
Former smoker	158	(28.7)	68.9 (43.20)	
Smoker	103	(18.7)	56.6 (36.97)	
Menarche (years)				0.16***
≥ 14	190	(34.5)	56.8 (37.89)	
12 to 13	246	(44.6)	63.3 (44.68)	
≤ 11	115	(20.9)	64.6 (36.95)	
Number of pregnacies				0.03*
0 to 1	72	(13.1)	52.7 (43.15)	
2	129	(23.4)	57.9 (37.63)	
≥ 3	350	(63.5)	64.3 (41.42)	
Nutritional status (BMI)				<0.001*
Eutrophic (18.5 to 24.4)	107	(19.4)	29.5 (21.05)	
Overweight (25 to 29.9)	189	(34.3)	50.2 (26.15)	
Obese (≥ 30)	255	(46.3)	83.0 (44.15)	
Menopausal Status				0.006*
Premenopausal	96	(17.6)	53.3 (38.78)	
Perimenopausal	250	(45.7)	59.2 (37.20)	
Postmenopausal	201	(36.7)	67.1 (43.64)	

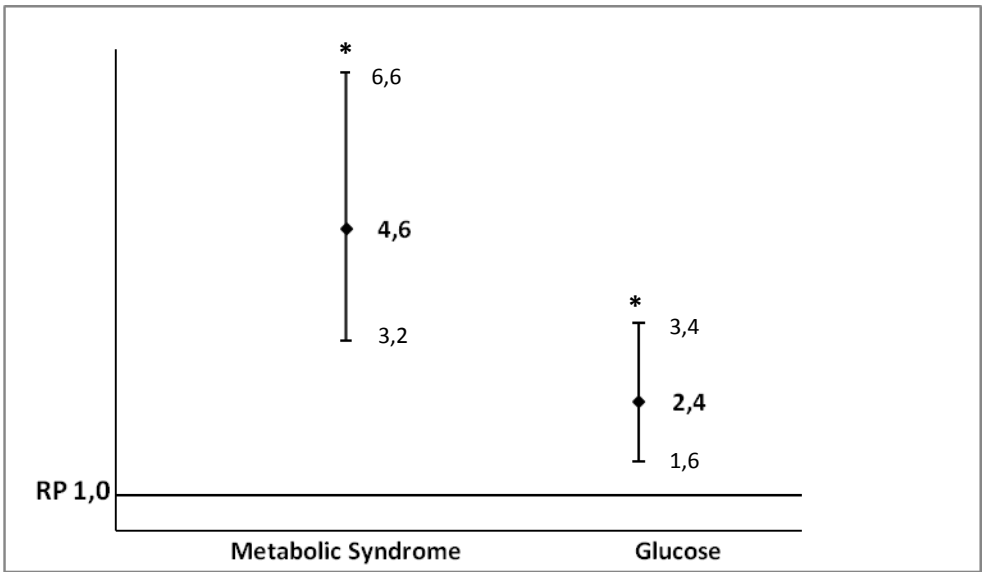
*linear trend
**t test
***Anova
LAP: Lipid Accumulation Product

Table 2. Analysis of simple and multiple linear regression of demographic, socioeconomic, reproductive, lifestyle and nutritional status characteristics on LAP (Lipid Accumulation Product)in women in climacteric period treated at a clinic in southern Brazil.

Variables	Linear Regression ß coefficient ($CI_{95\%}$)	Model I ß coefficient ($CI_{95\%}$)	Model II ß coefficient ($CI_{95\%}$)	Model III ß coefficient ($CI_{95\%}$)
Age (in years) quarters	<0.001	0.005	-	-
40 to 45	Ref.	Ref.		
46 to 50	0.82 (-8.90 to 10.55)	0.69 (-8.99 to 10.37)		
51 to 55	6.56 (-3.34 to 16.46)	4.83 (-5.13 to 14.79)		
56 a 65	15.24 (5.19 to 25.29)	13.18 (2.95 to 23.42)		
Skin color	0.87	-	-	-
White	Ref.			
Other	0.62 (-7.01 to 8.26)			
Marital Status	0.75	-	-	-
Without partner	Ref.			
With partner	- 1.18 (-8.39 to 6.02)			
Schooling (in years) quarters	0.03	0.14	-	-
0 to 4	Ref.	Ref.		
5 to 8	-11.94(-20.14 to -3.75)	-8.30 (-16.66 to 0.06)		
9 to 11	-9.79 (-19.38 to -0.19)	-6.77 (-16.52 to 2.97)		
≥ 12	-15.00 (-34.93 to 4.94)	-7.58 (-27.78 to 12.61)		
Family income (quarters)	0.007	0.08	-	-
0 to 2	Ref.	Ref.		
2,01 to 3,00	11.82 (1.99 to 21.64)	13.32 (3.52 to 23.11)		
3,01 to 5,00	5.71 (-14.82 to 3.40)	-2.90 (-12.20 to 6.41)		
5,01 or over	-9.13 (-18.58 to 0.33)	-4.95 (-14.80 to 4.88)		
Paid work	0.03	0.27	-	-
Yes	Ref.	Ref.		
No	-7.42 (-14.27 to -0.58)	-3.39 (-10.38 to 3.60)		
Physical Activity	0.17	-	0.19	-
Sedentary	Ref.		Ref.	
No sedentaty	5.18 (-2.15 to 12.51)		4.43 (-2.86 to 11.76)	
Smoking	0.02	-	0.05	-
Non-smoker	Ref.		Ref.	
Former smoker	10.00 (2.09 to 17.91)		9.07 (1.20 to 16.95)	
Smoker	-2.24(-11.42 to 6.94)		-1.33 (-10.67 to 8.01)	
Menarche (years)	0.08	-	0.06	-
≥ 14	Ref.		Ref.	
12 to 13	6.54 (-1.21 to 14.30)		4.83 (-2.83 to 12.49)	
≤ 11	7.83 (-1.66 to 17.32)		9.41 (0.01 to 18.81)	
Number of pregnacies	0.01	-	0.04	-
0 to 1	Ref.		Ref.	
2	5.29 (-6.50 to 17.08)		7.95 (-3.80 to 19.69)	
≥ 3	11.69 (1.32 to 22.06)		10.56 (0.19 to 20.94)	
Nutritional status (BMI)	<0.001	-	-	<0.001
Eutrophic (18,5 to 24,4)	Ref.			Ref.
Overweight (25 to 29,9)	20.71 (12.40 to 29.03)			20.55 (12.29 to 28.80)
Obese (≥ 30)	53.50 (45.57 to 61.41)			51.45 (43.34 to 59.56)
Menopausal Status	0.003	-	-	0.94
Premenopausal	Ref			Ref.
Perimenopausal	5.88 (-3.54 to 15.30)			-1.93 (-10.45 to 6.59)
Postmenopausal	13.77 (4.03 to 23.50)			-1.07 (-12.22 to 10.09)

Model II: variables of life style and reproductive, adjusted for age, schooling, family income and paid work.
Model III: nutritional status and menopausal status, adjusted for age, family income, paid work, leisure physical activity, smoking, menarche and number of pregnancies.

Figure 1. Prevalence ratios and confidence intervals (95%) of metabolic syndrome and fasting glucose above 100mg/dl and / or diabetes mellitus for the presence of high LAP (≥34.5 cm.mmol/L) in women in climacteric period (n = 551).



* P-value <0.001; adjusted to the age of women.
LAP: Lipid Accumulation Product
Metabolic Syndrome: NCEP-ATP III's criteria
Glucose: Fasting blood glucose ≥ 100mg/dl and / or presence of Diabetes Mellitus