



Original/Síndrome metabólico

## Overweight obesity and cardiovascular risk in menopausal transition

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### Abstract

**Introduction:** the hormonal decline that is characteristic of the menopause, in conjunction with the associated weight gain, is considered a determinant factor of cardiovascular risk.

**Objective:** to examine weight status in relation to clinical symptoms during the menopausal transition, in women referred from primary care to an endocrinology specialist, to determine potential cardiovascular risk profiles.

**Method:** observational analytic cross-sectional study, conducted with data from medical records created at time of referral. Study population: 805 women aged 40 years or older, a sufficient number of subjects and medical records for cardiovascular risk to be estimated.

**Results:** hierarchic cluster analysis distinguished four clusters. The prevalence of obesity in each one exceeded 60%. The highest mean cardiovascular risk was observed in women who were older and presented obesity and hypertension. In younger age groups, the risk was low, rising to levels similar to those of the older women by the age of 65 years.

**Conclusion:** these results suggest that preventive and therapeutic monitoring of obesity and modifiable risk factors should be conducted during the menopausal transition, to reduce the risk attributable to these factors, a risk that increases with time.

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Key words: *Overweight. Obesity. Menopause. Cardiovascular diseases.*

### SOBREPESO, OBESIDAD Y RIESGO CARDIOVASCULAR EN LA TRANSICIÓN MENOPÁUSICA

### Resumen

**Introducción:** el declive hormonal característico de la menopausia, junto al aumento ponderal añadido, está considerado como un factor determinante de riesgo cardiovascular.

**Propósito:** examinar la situación ponderal en relación con la sintomatología clínica, durante la transición menopáusica, en mujeres derivadas desde atención primaria a la especialidad de endocrinología, para describir los posibles perfiles de riesgo cardiovascular.

**Método:** se realizó un diseño observacional, analítico, de corte transversal, con los datos registrados en las historias clínicas en el momento de la derivación. 805 mujeres con 40 y más años de edad disponían de los registros necesarios para la estimación del riesgo cardiovascular.

**Resultados:** la agrupación jerárquica distingue cuatro grupos. La frecuencia de obesidad en todos ellos superó el 60%, observándose los mayores promedios de riesgo cardiovascular en las mujeres de mayor edad y elevada frecuencia de obesidad e hipertensión arterial. En los grupos de menor edad, la estimación del riesgo fue baja, incrementándose hasta niveles similares a los de mayor edad, al proyectarlo a 65 años.

**Conclusión:** estos resultados sugieren la necesidad de un seguimiento preventivo y terapéutico de la obesidad y los factores de riesgo modificables durante la transición menopáusica, para reducir el riesgo atribuible a dichos factores con el paso de los años.

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Palabras clave: *Sobrepeso. Obesidad. Menopausia. Riesgo cardiovascular.*

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## Introduction

Population aging has a particular impact on women, whose life expectancy exceeds that of men by almost a decade. A distinguishing feature of female aging is the menopause, or cessation of ovarian function, which gives rise to important physical, psychological and social changes<sup>1,2</sup>. The menopause is one of the critical stages in a woman's life, a time of hormonal changes that take place throughout the menopausal transition, during which the prevalence of obesity is higher and mood changes greater than at any other stage of life<sup>3,4</sup>.

Obesity provokes a unique burden of disease in women, in response to diverse biological, hormonal, environmental and cultural factors. Reproductive transitions such as pregnancy and menopause increase the risk of obesity<sup>5</sup>. Today it is considered a chronic disease, the prevalence of which (defined as BMI >30 kg/m<sup>2</sup>) increases progressively. It is most commonly found in the USA, followed by the UK and Central Europe. The global incidence exceeds 50% of the population, which has led to it being termed the epidemic of the twenty-first century<sup>6</sup>.

According to the latest National Health Survey, obesity in Spain has increased by 17% in recent years, and overweight by 37%<sup>7</sup>. The regions of Murcia, Andalusia, Extremadura and the Canary Islands have the highest prevalence of obesity, and it is more common among women than among men in all regions<sup>8,9</sup>.

Among the determinant factors of obesity are the existence of an energy imbalance between intake and expenditure, and situations of stress and anxiety, which directly affect nutritional behaviour<sup>10</sup>. These factors are notably present in women during the perimenopause, due to the physiological, emotional and psychosocial consequences suffered by many women, which thus contribute to weight gains<sup>11-13</sup>.

Life expectancy at birth for women is 83 years, and so one third of a woman's life will be lived in the postmenopausal period. One characteristic of this period is the presence of hypo-oestrogenism, which, together with the increased body weight, is a risk factor for cardiovascular disease<sup>14-17</sup>.

The aim of this study is to assess cardiovascular risk in relation to weight status, among female subjects whose age range includes the menopausal transition and who are referred from primary care to endocrinology consultation, within the public health system of Granada (southern Spain).

## Method

An observational, analytic, cross-section study was performed, based on data obtained from patients' medical records. The study population was composed of 3,187 patients who were referred from primary care to endocrinology consultation, over a period of four years. The sample included all women aged 40 years or more

for whom the necessary records to estimate cardiovascular risk were available. The final sample contained 805 women, with the characteristics shown in table I.

## Procedure

Body Mass Index (BMI) is a parameter that is simple to calculate and extremely useful for classifying subjects according to weight status. Moreover, it enables comparisons to be made between individuals with different characteristics and even from different sample populations. According to the Expert Panel on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults<sup>18</sup>, BMI is considered normal in the range 18.5-25 kg/m<sup>2</sup>, while >25-29 kg/m<sup>2</sup> represents overweight, and  $\geq 30$  kg/m<sup>2</sup> represents obesity. In addition to sex and age, we also considered clinical variables such as blood pressure (according to SEH-SEC criteria)<sup>19</sup>, total and HDL cholesterol (according to ATP III criteria)<sup>20</sup>, glycaemia, diabetes (if present, and according to the criteria of the Expert Committee on Diagnosis and Classification of Diabetes Mellitus)<sup>21</sup> and tobacco consumption.

Ten-year cardiovascular risk (CVR) was calculated by the Framingham equation adapted to the Spanish population, with data from the DORICA study<sup>22</sup>, and applying the procedure described by Ramírez<sup>23</sup>. Results are expressed as Low-Moderate risk (CVR <10%) and High-Very high risk (CVR >40%).

Algorithms for CVR prediction are an important tool to establish therapeutic criteria aimed at reducing the incidence of cardiovascular disease, which is the leading cause of death in developed societies. The first references in this respect concern the Framingham equation<sup>24</sup>. Different models are now being used to estimate the absolute risk (usually with respect to the next 10 years) of suffering a cardiovascular event, according to the conjunction of a number of risk factors (RF) that accumulate within a given period, such as sex, age, blood pressure, lipid profile, smoking and diabetes<sup>25</sup>. This absolute risk (AR) value can then be used to calculate other forms, such as comparative risk (CR), i.e., the risk at the same age without the modifiable RF, marginal risk (MR), i.e., the difference between AR and CR, and projected risk at 65 years of age (PR).

Although BMI as such is not used in any of the standard prediction equations, there is evidence of its relationship with sex, age, lipid profile, blood pressure, etc., and so we consider it of interest to determine the relationship between BMI and CVR in women during the menopausal transition [26-29] in order to establish possible risk profiles based on clinical history and treatment.

## Statistical analysis

Statistical analysis was performed with SPSS for Windows 17.0. The comparison of the means was determi-

ned using the Kruskal-Wallis test, and subsequent analysis of multiple comparisons was carried out using the Mann-Whitney test. On the basis of the CVR factors examined, an initial two-stage cluster analysis of CVR was conducted, in two phases, in accordance with the Bayesian criterion described by Schwarz, and then the k-means method, which was complemented with a confirmatory principal components analysis with varimax rotation. In all cases, results were considered significant at  $p < 0.05$ .

## Results

The women in the study had a mean age of  $52.4 \pm 13.6$  years. Given the importance of age in relation to the menopause, the sample was stratified into four

subgroups: <50 years ( $n=311$ ); 50-59 years ( $n=210$ ); 60-69 years ( $n=195$ ) and 70 or more years ( $n=89$ ). The incidence of obesity exceeded 70% in all groups, reaching 82% in the women aged 60-69 years. The incidence of subjects with overweight was 10-20% and was highest in those older than 70 years, while the highest incidence (18%) of normal weight was among the women aged under 50 years (Table I).

The variables used in estimating CVR presented significantly higher values between obese ( $BMI \geq 30$ ) and non-obese women, except for glycaemia and total cholesterol (Table II).

Levels of cardiovascular risk, shows differences by weight status (Table III).

The exploratory cluster analysis conducted on the CVR factors present in the sample revealed four clus-

| Age years       | Normal weight<br>n(%) | Overweight<br>n(%) | Obesity<br>n(%) | Total<br>N(100%) |
|-----------------|-----------------------|--------------------|-----------------|------------------|
| < 50            | 56 (18%)              | 33 (10.6%)         | 222 (71.4%)     | 311              |
| 50 - 59         | 18 (8.6%)             | 26 (12.4%)         | 166 (79%)       | 210              |
| 60 - 69         | 8 (4.1%)              | 27 (13.8%)         | 160 (82.1%)     | 195              |
| $\geq 70$       | 5 (5.6%)              | 18 (20.2%)         | 66 (74.2%)      | 89               |
| $52.4 \pm 13.6$ | 87 (10.8%)            | 104 (12.9%)        | 614 (76.3%)     | 805              |

|           | <i>BMI 37.1 <math>\pm</math> 5.8<br/>(n=614)</i> | <i>BMI 25.1 <math>\pm</math> 3.2<br/>(n=191)</i> | <i>p-value</i>    |
|-----------|--|--|-------------------|
| AGE       | $53.3 \pm 13.0$                                  | $49.7 \pm 10.0$                                  | <b>&lt; 0.003</b> |
| SBP       | $144.4 \pm 21.8$                                 | $131.1 \pm 23.6$                                 | <b>&lt; 0.001</b> |
| DBP       | $89.1 \pm 12.3$                                  | $81.0 \pm 13.1$                                  | <b>&lt; 0.001</b> |
| GLYCAEMIA | $169.2 \pm 60.4$                                 | $156.0 \pm 76.5$                                 | 0.175             |
| cTotal    | $205.4 \pm 28.5$                                 | $199.6 \pm 39.9$                                 | 0.063             |
| cHDL      | $54.6 \pm 7.3$                                   | $52.4 \pm 9.6$                                   | <b>&lt; 0.003</b> |

SBP: Systolic blood pressure; DBP: Diastolic blood pressure; cTotal: Total cholesterol; cHDL: Cholesterol in high density lipoprotein

| Weight status | Absolute          | Comparative       | Relative          | Attributable      | Projected         |
|---------------|-------------------|-------------------|-------------------|-------------------|-------------------|
| Normal        | $4.4 \pm 5.3$     | $1.6 \pm 1.4$     | $2.6 \pm 1.4$     | $3.1 \pm 4.4$     | $9.9 \pm 4.1$     |
| Overweight    | $9.1 \pm 8.4$     | $2.6 \pm 1.3$     | $3.2 \pm 2.0$     | $6.7 \pm 7.7$     | $12.3 \pm 7.7$    |
| Obesity       | $9.2 \pm 7.1$     | $2.6 \pm 1.3$     | $3.3 \pm 1.7$     | $6.6 \pm 6.2$     | $12.3 \pm 6.0$    |
| Total         | $8.7 \pm 7.2$     | $2.5 \pm 1.4$     | $3.2 \pm 1.7$     | $6.3 \pm 6.4$     | $12.0 \pm 6.1$    |
| p-value       | <b>&lt; 0.001</b> |

**Table IV**  
*Differential characteristics of the four clusters*

|           | Age       | BMI      | SBP        | DBP       | Glucose    | cTotal     | cHDL      | CVR-AR   | CVR-65    |
|-----------|-----------|----------|------------|-----------|------------|------------|-----------|----------|-----------|
| 1 (n=159) | 45.7±6.2  | 28.5±7.2 | 122.7±15.1 | 77.4±10.7 | 146.1±54.5 | 170.9±11.9 | 47.9±4.4  | 4.9±5.5  | 9.3±3.5   |
| 2 (n=284) | 49.1±10.1 | 35.5±6.0 | 129.4±11.7 | 82.7±9.3  | 183.4±82.5 | 204.5±8.7  | 55.5±5.6  | 6.5±5.6  | 10.0±4.0  |
| 3 (n=118) | 56.5±11.9 | 32.1±6.1 | 144.9±21.1 | 88.1±12.2 | 161.0±69.7 | 264.4±26.3 | 59.0±13.6 | 11.2±9.8 | 14.4±10.1 |
| 4 (n=244) | 58.7±10.6 | 37.6±6.9 | 165.4±15.5 | 98.2±10.1 | 167.5±54.3 | 195.7±15.5 | 54.0±5.6  | 12.4±6.3 | 15.0±5.3  |
| p-value   | < 0.001   | < 0.001  | < 0.001    | < 0.001   | > 0.05     | < 0.001    | < 0.001   | < 0.001  | < 0.001   |

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; cTotal: Total cholesterol; cHDL: Cholesterol in high density lipoprotein; CVR-AR: Cardiovascular risk-Absolute risk; CVR-65: Cardiovascular risk at age 65 years.

**Table V**  
*Factorial analysis*  
*(Variance explained by the model: 78.9%)*

|                   | Factor       |              |              |              |
|-------------------|--------------|--------------|--------------|--------------|
|                   | 1            | 2            | 3            | 4            |
| Age               | 0.022        | 0.102        | <b>0.869</b> | 0.127        |
| BMI               | <b>0.839</b> | 0.075        | -0.214       | 0.009        |
| SBP               | <b>0.690</b> | 0.019        | <b>0.595</b> | 0.070        |
| DBP               | <b>0.746</b> | 0.041        | <b>0.437</b> | -0.013       |
| Glucose           | 0.019        | -0.003       | 0.126        | <b>0.976</b> |
| Total cholesterol | 0.050        | <b>0.826</b> | 0.063        | 0.155        |
| cHDL              | 0.045        | <b>0.831</b> | 0.052        | -0.156       |

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; cHDL: Cholesterol in high density lipoprotein.

ters; table IV shows the main characteristics of these clusters, the number of women in each and the statistical significance of the comparison of the means test performed.

The subsequent factor analysis confirmed the 4-factor model accounting for 78.9% of the variance (Table V).

## Discussion

In our sample, the distribution of women by body composition revealed a high proportion of obesity (>70%) in all age groups and a small proportion of women with normal weight (10.8%), of whom over 50% were less than 50 years of age, which explains the large standard deviation values obtained.

These data reflect the composition of the sample (women referred from primary health care to endocrinology) and do not reflect the reported prevalence of obesity and overweight in Spain. The sample was not one of the general population<sup>7-9</sup>, but of women of a particular age range, with characteristic pathological features. Nevertheless, the high prevalence of obesity

recorded is indicative of the magnitude of the problem for many women at this stage of life<sup>5</sup>, and suggests there is a need for better management of body weight in the context of primary and secondary health care<sup>26-29</sup>.

The analysis of CVR in relation to BMI in the menopausal transition requires the use of clinical parameters; however, these are not always available, and are often unknown by the women concerned. This is an area of interest, because consideration of these data could reveal an otherwise imperceptible pathology or one that is poorly controlled<sup>27-30</sup>. Our analysis of the variables involved in determining CVR in obese and non-obese women shows that age was significantly greater in the obese subjects, as were systolic and diastolic levels. These circumstances are compatible with a situation in which blood pressure is inadequately controlled. Total cholesterol levels were also higher in obese women, but did not reach statistical significance (Table II). On the other hand, HDL cholesterol did not fit the expected pattern, with the lowest levels being found among the non-obese women, which suggests a good response was obtained to the lipid-lowering treatment that many of these women had been prescribed. Mean blood glucose levels exceeded the limit established for the diagnosis of diabetes<sup>20</sup> in both groups, between which there were no significant differences.

The 10-year absolute risk for the different weight-status groups was significant in all cases (Table III). In the women with normal weight, mostly aged under 50 years and in the premenopausal stage, the probability of suffering a cardiovascular event within 10 years is low (<5%) and corresponds to the attributable risk (3.1%). The estimated projected risk at 65 years is double the AR if the factors remain unchanged, which corroborates the importance of age and the protective role of oestrogen in this group<sup>16</sup>.

The risk attributable to modifiable factors is an important indicator of the need for intervention and control of these factors, in order to prevent their cumulative effects over time<sup>27-28</sup>. The menopausal transition progressively increases the risk of stroke in women, exceeding that faced by men<sup>7-15,31</sup>. The AR values obtained highlight the importance of controlling these factors for primary prevention<sup>26,28,32</sup>, as reflected in

the PR at 65 years (only calculated at ages below 65 years), which is significantly higher in situations of overweight and obesity, although there were no significant differences between these two situations and therefore the risk of suffering a cardiovascular event in similar in each case.

To derive a clinical profile of these menopausal transition women, a hierarchic cluster analysis was performed, revealing four clusters from the following prognostic outcome variables: age, BMI, systolic and diastolic blood pressure, total and HDL cholesterol. The analysis of variance, for the four clusters, shows the central values for the variables considered, which differed significantly among the groups, except glucose, the levels of which revealed poorly-controlled hyperglycaemia and were similar in all cases. The factorial analysis confirmed a 4-factor pattern that explained 78.9% of the variance (Tables IV and V).

The following distinctive features were observed: cluster 1 presented the lowest mean age, with 62% of the women being aged under 50 years; 38% were of normal weight, 72% had normal blood pressure, 100% had normal levels of cholesterol and 79% had no diabetes. In cluster 2, 48% of the women were aged under 50 years; 91% had obesity, 16% had diabetes, 57% had normal blood pressure and 96% had cholesterol in the normal-high range; 6.5% presented a moderate 10-year absolute risk. In cluster 3, 62% of the women were aged 50-69 years, 63% were obese, 69% had hypertension, 93% had normal-high cholesterol and 37% had diabetes. Finally, in cluster 4, 81% of the women were aged over 50 years, 91% had obesity, 100% suffered hypertension, 73% had normal-high cholesterol and 34% had diabetes.

The highest mean risk values were obtained for cluster 3 (11.2%) and cluster 4 (12.4%). The groups of older women presented the highest levels of AR and PR to 65 years, with values of 14.4 and 15% in clusters 3 and 4, respectively, if modifiable factors remained unchanged until that age, which underlines the importance of controlling these factors<sup>33</sup>.

## Conclusions

The results obtained support an explanatory model with four profiles: 1) Obesity-Hypertension; 2) Dyslipidaemia; 3) Age-Hypertension; 4) Diabetes. Each profile has a different effect on CVR, and so our study sample can be classified into four risk groups, each with a specific necessity as to the type of imminent control required for the primary prevention of cardiovascular disease. Groups 3 and 4 contain the women at highest risk, with a profile of greater age and a high prevalence of obesity, hypertension, hypercholesterolaemia and diabetes. At the other extreme are Groups 1 and 2, with a lower average age and at less risk. In all groups, the excess risk attributable to the factors considered was higher among those aged 60-69 years,

which emphasises the need for special preventive and therapeutic monitoring of this age group.

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