Artículo Original

Association of musculoskeletal pain with type 2 diabetes mellitus among postmenopausal women aged 40 to 59 years in a rural Maya community of Quintana Roo, Yucatan

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RESUMEN

Introducción: Las mujeres enfrentan cambios físicos y metabólicos durante la menopausia con aumento de los niveles de lípidos y glucosa, peso corporal y obesidad que en conjunto pueden causar dolor leve a severo en múltiples articulaciones. **Objetivo:** Evaluar los niveles de dolor musculoesquelético y su asociación con la diabetes mellitus tipo 2 (DM2) en mujeres posmenopáusicas de Quintana Roo, Yucatán, México. **Materiales y métodos.** Se realizó un estudio transversal en Quintana Roo, una comunidad rural maya de Yucatán, México. Las participantes fueron 50 mujeres posmenopáusicas de 40 a 59 años. Se registraron los datos de la edad de la menarquia y la menopausia, reportado por las participantes. Se estimó el nivel de glucosa plasmática en ayunas (GPA) y se utilizó la Escala Visual Analógica (EVA) para evaluar los niveles de dolor en las articulaciones (hombro, rodilla, columna vertebral, parte inferior de la espalda y las piernas). **Resultados.** El promedio de edad de las mujeres fue de 53.28 años y de la menopausia de 46.04 años. Las mujeres diabéticas de la muestra (44%) tuvieron niveles más altos de dolor musculoesquelético en comparación con sus pares no diabéticas. La puntuación EVA tuvo una correlación positiva y negativa significativa ($p<0.05$) con el nivel de GPA y la edad de la menopausia, respectivamente. **Conclusión.** El dolor musculoesquelético en las mujeres posmenopáusicas aumentó cuando había mayor nivel de GPA, y la edad de menopausia relativamente temprana.
Palabras clave: Menopausia; Diabetes mellitus tipo 2; Dolor musculoesquelético; EVA.

SUMMARY

Introduction: Women experience physical and metabolic changes during menopause with increased lipid and glucose levels, body weight, and obesity that altogether can cause mild to severe pain in multiple joints. **Objective:** To evaluate levels of musculoskeletal pain and its association with type 2 diabetes mellitus (T2DM) in postmenopausal women at Quintana Roo, Yucatan, Mexico. **Materials and methods.** A cross-sectional study was carried out in Quintana Roo, a rural Maya community in Yucatan, and 50 postmenopausal women aged 40 to 59 years were the participants. Reported data of age at menarche and menopause were recorded. Fasting plasma glucose (FPG) level was estimated among women and Visual Analogue Scale (VAS) was used to evaluate levels of joint pain (shoulder, knee, vertebral column, lower back, and lower limb). **Results.** Mean value of age of women was 53.28 years and age at menopause was 46.04 years. Diabetic women in the sample (44%) had higher levels of musculoskeletal pain compared to the non-diabetic peers. VAS score had significant ($p<0.05$) positive and negative correlation with FPG level and age at menopause, respectively. **Conclusions.** Musculoskeletal pain among postmenopausal women increased with rise of FPG level, and relatively earlier age at menopause.
Keywords: Menopause; Type 2 diabetes mellitus; Joint pain; VAS.

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Introduction

Menopause is defined as the end of menstruation among women, and it is associated with the decrease of estrogen levels due to loss of follicular function; most women experience menopause between 40 and 58 years of age (1). Early menopause is considered ≤40 years, and ≥52 years is considered late menopause (2). Menopause is characterized by the end of a woman's reproductive phase and is due to the absence of ovarian hormones that affect bones, muscular, cardiovascular, and urogenital systems (3).

Estrogens play an important role in the metabolic process, one of its main functions is to regulate cholesterol levels and fluid retention in the body. Estrogens induce and facilitate high-density lipoprotein productivity and lower circulating levels of triglycerides and total cholesterol (4). When there is an alteration in hormonal changes, the lipid system is affected, causing an alteration in lipoproteins, having a direct effect on glucose tolerance (5). Estrogens secrete and regulate a protein called leptin in the adipose tissue; leptin has the function of sending receptor signals to the brain about the amount of energy reserves, plays a vital role in the regulation of body weight; it is one of the main reasons why women tend to gain weight.

Type 2 diabetes mellitus (T2DM) is a chronic-degenerative disease and is defined as an increase in blood glucose level causing an alteration in insulin secretion (6). Insulin is a hormone that is synthesized in the pancreas and its function is to transform foods rich in carbohydrates into energy for the body (7). Increased glucose concentrations will cause a decrease in insulin concentrations due to the effects of chronic hyperglycemia (8). Adipose tissue (AT) produces an enzyme called lipoprotein lipase that secretes and metabolizes sex hormones and estrogen receptors, its function is to control the intracellular amount of triglycerides and is stimulated in the adipocytes of the femoral gluteus favoring the development of resistance to insulin, obesity, hypertension and T2DM (9). Adipocytes are cells found in the AT and that accumulate fatty acids in the form of triglycerides, have a limited storage capacity and, therefore, travel to other organs such as the liver or skeletal muscle through adipokines (10). In a cohort study, an association was observed between the risk of developing T2DM with decreased ovarian function and impaired functionality of pancreatic β cells (11). Hyperglycemia contributes to the development of advanced glycation end products (AGE), which are proteins derived from the exposure of sugars that, when stored in the articular cartilage during menopause, cause an increase in stiffness and joint pain; AGE components bind to highly mobile receptor for AGE (RAGE) proteins (receptors for advanced glycosylation compounds), they promote the release of proinflammatory factors such as tumor necrosis factor (TNF-α), which is a protein from the group of cytokines that cause inflammation and joint destruction by promoting cartilage degradation (12, 13). Diabetes is one of the major health problems and the Mexican National Survey of Nutrition (ENSANUT 2022) reported a prevalence of T2DM of 13.6% in women and 11.3% in men (14).

Excessive concentration of AGE affects nociceptive and proprioceptive receptors (15). Nociceptors are a group of sensory receptors and peripheral endings of the primary sensory afferent fibers from which they receive and transform local stimuli such as pain, which are sent to the central nervous system (CNS), the joints are innervated by nociceptors of fine A-δ fibers that are located in the joint capsule, periosteum, and ligaments. Nociceptive responses vary in intensity and duration, and in the presence of very intense, repetitive or prolonged painful stimuli, they can lose their balance (16).

Metabolic alterations in postmenopausal women cause musculoskeletal pains due to the breakdown of cartilage; there is a decrease in the range of movement, causing functional limitations in the daily life activities. Visual Analogue Scale (VAS) is widely used to understand the functional and global status of the level of joint pain (17). Estrogen receptors are synthesized by aromatase, an enzyme found in the hypothalamus and in the joints (18). Articular

cartilage, articular chondrocytes, muscle, and ligament have estrogen receptors, which means that unbearable joint pain occurs during menopause (19).

In this background, objective of the present study was to evaluate levels of musculoskeletal pain and its association with T2DM in postmenopausal women at Quintana Roo, Yucatan, Mexico.

Material and Methods

A cross-sectional study was carried out in Quintana Roo, a rural Maya community in Yucatan during January to March 2020. The project was part of the "Integral Community Food and Nutrition Project in Yucatan" that has been approved by the Bioethics Committee on Human Health of Cinvestav-IPN. A household survey carried out in 2018–19 (20) recorded 780 individuals (385 males, 395 females) living in the community; 67 women were identified in the age-group of 40 to 59 years and 58 of them reported menopause. Finally, 50 women agreed to participate in the present study. Fasting plasma glucose (FPG) level was estimated, and diabetes was diagnosed following international criteria (FPG≥126.0 mg/dL) (21, 22). Blood sample (10 ml) was collected from the women participants (n=50) after 10 to 12-hours of overnight fasting; Cobas Integra 400 Plus automated analyzer was used to estimate FPG level.

The VAS was applied to evaluate levels of musculoskeletal pain in shoulder, knee, vertebral column, lower back (sacroiliac joint) and lower limb (lower leg, ankle, foot) (23). The scale was used to estimate the perceived intensity of pain in each joint, which was represented by a 10 cm line. The results obtained in this scale are the intensities: ≤4 means mild to moderate pain, between 4 and 6 means moderate to severe pain, and ≥6 means severe pain (24). Average score of perceived musculoskeletal pain in the individual regions were calculated and finally the overall score was estimated. Participant women reported their age at menarche (onset of sexual maturity), age at menopause and their date of birth was verified from an official record (birth certificate or national identification number). An approximate estimate of span of reproductive years was calculated (age at menopause – age at menarche). Maya ancestry was identified by the presence of both paternal and maternal Maya surnames; the women participants had at least one surname of Maya origin. The surnames were identified by an expert (see Acknowledgements). SPSS statistical package (version 19.00) was used for data analysis. Normality test for the variables followed the principle of Shapiro-Wilk test; VAS scores and FPG values were not observed to have normal distribution. Descriptive statistics (mean and standard deviation values) of age, age at menopause, age at menarche, span of reproductive years, and FPG in postmenopausal women were calculated. Significant differences of mean and Z values between two independent groups (diabetic and non-diabetic women) were estimated using Student's t-test and Mann-Whitney U, respectively. Parametric and non-parametric correlation coefficients (Pearson's r and Spearman's rho, respectively) and linear regression model were used to observe association between variables. Distribution of log transformed average score of VAS was normal (Shapiro-Wilk test, $p>0.05$) that was used as dependent variable in the regression model. Statistical significance was set a priori at $\alpha=0.05$.

Results

Mean value of age of the participant women (n=50) was 53.28 years, showing no significant difference of mean values between 28 non-diabetic (52.48 years) and 22 diabetic (54.29 years) women (Table 1). However, mean age at menopause was significantly different ($p<0.01$) in two groups (non-diabetic 47.46 years, diabetic 44.23 years). Reported age at menarche of women (10.94 years) was not different in two groups (non-diabetic versus diabetic) but estimated span of reproductive years (35.10 years) was significantly different ($p<0.01$) (non-diabetic 36.61 years, diabetic 33.18 years). Mean values of VAS scores for joint pain (shoulder joints, knee joints, vertebral column, lower back, and lower limb) were significantly different ($p<0.05$) except for lower limb ($p=0.33$) in non-

Table 1. Descriptive statistics of variables among postmenopausal women (n=50).

Variables	Total (n=50) Mean (SD)	Non-diabetic (n=28) Mean (SD)	Diabetic (n=22) Mean (SD)	t/z	p-value
Age (years)	53.28 (5.29)	52.48 (5.41)	54.29 (5.07)	-1.21	0.23
Age at menopause (years)	46.04 (4.48)	47.46 (4.51)	44.23 (3.80)	2.70	0.01
Age at menarche (years)	10.94 (1.72)	10.86 (1.86)	11.05 (1.56)	-0.38	0.70
Span of reproductive years	35.10 (4.45)	36.61 (4.12)	33.18 (4.17)	2.90	<0.01
VAS score (shoulder joints)	3.48 (4.00)	2.00 (3.08)	5.36 (4.29)	-2.79*	<0.01
VAS score (knee joints)	3.66 (4.24)	1.29 (2.19)	6.68 (4.31)	-4.10*	<0.0001
VAS score (vertebral column)	5.14 (4.10)	3.32 (3.46)	7.45 (3.71)	-3.69*	<0.0001
VAS score (lower back)	2.08 (3.66)	0.79 (1.91)	3.73 (4.63)	-2.26*	<0.02
VAS score (lower limb)	1.02 (2.56)	1.14 (2.40)	0.86 (2.80)	-0.98*	0.33
VAS (average score)	6.50 (3.14)	4.54 (2.83)	9.00 (1.02)	-5.39*	<0.0001
FPG (mg/dL)	148.85 (70.45)	89.16 (5.70)	206.84 (69.35)	-8.92*	<0.0001

SD: Standard deviation; VAS: Visual Analogue Scale; *Z values of Mann-Whitney U; PFG: Fasting plasma glucose

diabetic and diabetic women. Average VAS score (6.50 in 50 women) also showed significant difference in two groups (non-diabetic 4.54, diabetic 9.0). Fasting plasma glucose (FPG) was 144.85 mg/dL among women (n=50) that was significantly different in non-diabetic (89.16 mg/dL) and diabetic (206.84 mg/dL) participants (Table 1).

Correlation analysis showed T2DM was positively associated with average VAS score (Spearman's rho = 0.77, p<0.0001); age at menarche and menopause had negative correlation with average VAS score (Spearman's rho = -0.55, p<0.05). However, correlation between FPG level (mg/dL) and age at menopause was not significant (Spearman's rho = -0.09, p=0.68). These results raised our interest to use age at menopause and T2DM (1= diabetic, 0= non-diabetic) as the predictors while average VAS score as outcome variable in the linear regression model to understand the association between variables. Log transformed average VAS score was used since its distribution was not normal (Shapiro-Wilk test, p<0.05).

Parameter estimates of the outcome variable within 95% confidence interval for B, the regression coefficient showed significant interrelationships between dependent and explanatory variables that was estimated by ANOVA (p<0.05). Linear regression model accounted for 47% of total variability explained by adjusted R-square. There was no collinearity among the variables (variance inflation factor=1.11). The results showed significant association (p<0.05) between the predictors and outcome variable. For every one-unit (year) decrease in the age at menopause, average VAS score increased by about 1%. For every one-unit increase in the diabetes status (0 to 1), average VAS score increased, after adjusting for other predictor in the model (Table 2).

Table 2. Linear regression analysis for VAS scores (log transformed) predicted by age at menopause and T2DM among postmenopausal women (n=50).

Predictors	B	SE	t	p-value	95% C.I. for B Lower bound	Upper bound
Intercept	1.26	0.26	4.86	<0.0001	0.74	1.78
Age at menopause (years)	-0.01	0.01	-2.26	0.03	-0.02	0.00
T2DM	0.24	0.05	5.00	<0.0001	0.14	0.34

B: Regression coefficient; SE: standard error; CI: confidence interval; T2DM: Type 2 diabetes mellitus (categorical variable, diabetic= 1, non-diabetic= 0)

Discussion

Type 2 diabetes mellitus (T2DM) was observed to have significant association with the development of musculoskeletal pain among postmenopausal women in the age range of 40 to 59 years in the rural community of Quintana Roo, Yucatan. The women participants in the present study with earlier age at menarche and menopause had higher joint pain (significant correlation) and FPG level (though correlation coefficient was not significant). Previous studies also reported that earlier age at menopause could be a risk factor for the onset of chronic diseases including T2DM (25, 26). The results in the present study were found to be similar that were reported in a cohort-based study among adult women (33.5 to 49.5 years) in China, which demonstrated a significant association between the early menopause and a high prevalence of T2DM (27). A meta-analysis on the association between age at menopause and risk of T2DM, based on the review of literature using PubMed, Embase, and Web of Science, showed association of later age at menopause with lower risk of T2DM (11). A study in the University of Baltimore showed that menopausal women (42 to 55 years) who developed T2DM had high BMI (body mass index), waist circumference, fasting glucose, elevated triglycerides, and low HDL-C cholesterol; obesity was related to early menopause and increased prevalence of diabetes (28).

A critical review of literature showed that T2DM was a risk factor for the progression of joint pain, which demonstrated that the joints developed insulin resistance in obese patients, there was a higher level of pain in the synovial joint of knee in diabetic patients than among non-diabetics, showing that T2DM and joint pain frequently coincide with obesity/overweight in menopausal women aged 45 to 58 years (29). A study conducted among women aged between 30 and 75 years in Southern India reported menopausal women had high prevalence of T2DM (28). Another study from India demonstrated a positive association between earlier menopause and T2DM (31). In that study, average age of menopause among diabetic women was 44.65 years that was earlier than age at menopause in non-diabetic women (48.2 years). In our present study, age at menopause of diabetic women was earlier (44 years) than non-diabetic peers (47 years).

Another cohort-based study in Slovakia showed that central obesity in the stage of menopause caused joint pain, highlighting the lumbosacral joint as the most predominant one (32). However, in the present study, anthropometric parameters to evaluate nutritional status (BMI-based overweight and obesity, waist circumference-based central obesity, etc.) were not considered to observe such association. The present study was part of a thesis of one of the co-authors (MPT) that demonstrated women with high BMI and central obesity tended to suffer from higher levels of joint pain, predominantly in the lumbosacral and patellofemoral joints (33). The menopausal women with T2DM in the present study had a higher level of joint pain compared to non-diabetic women that was more intense when menopause occurred at an earlier age. Women in India with early menopause (40 years) had higher pain in the knee joint; changes in the levels of sex hormones influenced the risk of joint diseases (34).

It is worthy to mention some limitations of the present study that was cross-sectional in nature, which limited the temporal association of musculoskeletal pain with elevated T2DM and earlier age at menopause. The results need further verification in longitudinal studies, representing different groups (rural and urban, socioeconomic status, etc.) on the association of joint pains in pre- peri- and postmenopausal women with dietary habits, activity patterns, T2DM, body fat, central obesity, BMI, and other metabolic disorders (elevated levels of triglycerides and LDL cholesterol).

Conclusion

The present study carried out in a rural Maya community of Quintana Roo in Yucatan,
confirmed that the earlier age at menopause and T2DM are the risk factors for elevated joint pain.

VAS scale was found to be an effective tool to evaluate musculoskeletal pain.

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