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ORIGINAL ARTICLE

Metformin use is associated with a lower risk of osteoporosis in adult women independent of type 2 diabetes mellitus and obesity. REDLINC IX study

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ABSTRACT

Metformin may decrease cell senescence, including bone; hence we aimed at evaluating the association between metformin use and osteoporosis. This was a cross-sectional study carried out in 1259 Latin American adult women aged 40 or more who were not on anti-osteoporotic drugs, were on metformin and had a bone densitometry performed. Of the whole sample, 40.3% reported being on metformin (at least 1 year), 30.2% had type 2 diabetes mellitus and 22.6% had osteoporosis. Median (interquartile range) body mass index (BMI) for the whole cohort was 27.7 (4.6) kg/m^2 and 30.2% had type 2 diabetes mellitus. Current use of hormone therapy, calcium, and vitamin D corresponded respectively to 10.7%, 47.7%, and 43.1% of all surveyed women. A logistic regression model was used to analyze the association of osteoporosis with various covariates incorporated into the model such as age (OR: 1.07, 95% CI: 1.05–1.09), BMI (OR: 0.92, 95% CI: 0.89–0.96) and metformin use (OR: 0.44, 95% CI: 0.32–0.59). Metformin use, regardless of the presence of type 2 diabetes or obesity, was associated with a lower risk of osteoporosis in adult women. We propose that one explanation for this observation could be the effect of the drug over cellular senescence.

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Introduction

Metformin, regardless of its antidiabetic action, affects a series of processes related to aging. It decreases cellular senescence, chronic inflammation, and stimulates autophagy [1]. In this sense, adenosine monophosphate-activated protein kinase (AMPK), a key molecule in the antidiabetic effect of metformin, also plays a central role in bone metabolism. Therefore, it is not of surprise that metformin decreases the risk of fractures in diabetics [2].

It has been observed that diabetics treated with metformin have a 20% lower risk of cardiovascular disease and 36% lower all-cause mortality when compared to patients managed with other diabetic treatments [3]. The HOME study reported a 40% reduction in cardiovascular events after 4 years when metformin was added to patients treated with insulin [4]. In the Singapore Longitudinal Aging Study, metformin showed an inverse association with cognitive impairment [5]. With this background, a randomized clinical trial was designed (the TAME study [Targeting Aging with Metformin]) to analyze the effects of metformin on molecular aging pathways involved at slowing the incidence of age-related multi-morbidity and functional decline [6].

Osteoporosis is among the diseases of old age. An increase of senescent cells in the bone tissue has been demonstrated with aging in both, animal and human experimental studies. In women, the loss of bone mineral density (BMD) begins before midlife and continues throughout life [7]. Therefore, bone could be an earlier marker of cellular senescence as compared to other tissues affected by chronic diseases. If metformin is able to modify the senescence of bone tissue, we, therefore, hypothesized that metformin users would have less osteoporosis. To test this hypothesis, this study aimed at evaluating the association between metformin use and the risk of osteoporosis in adult women.

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Methods

Study design and population

This was a cross sectional carried out from May 2018 to March 2019, the so-called '*REDLINC IX*', the ninth study of the Collaborative Group for Research of the Climacteric in Latin America. Osteoporosis and its association with metformin use and the clinical history of women were evaluated. The study was carried out in 15 healthcare centers of Latin American (Lima, Perú [3 centers]; Santiago de Chile, Chile; Rosario, Argentina; Ambato, Ecuador; Santa Cruz, Bolivia; Córdoba, Argentina [1 each, total 5 centers]; Cusco, Perú [1 center]; Buenos Aires, Argentina [2 centers]; Puebla, Mexico [1 center]; Asunción, Paraguay [1 center]; Porto Alegre, Brazil [1 center]; and, Panamá City, Panamá 1 center]). We included and surveyed women aged 40–89, who attended these centers for their annual gynecological checkup and had bone densitometry. Their general data were registered in a datasheet designed for the purpose. Those with at least a year of metformin use were defined as metformin users. The response rate was over 90% in all centers. Participants were excluded if they were on anti-osteoporotic drugs. Type 2 diabetics or participants taking calcium and/or vitamin D were not ruled out.

The study protocol was reviewed and approved by the local ethics committee of the Southern Metropolitan Health Service, Santiago de Chile, Chile (Memorandum N° 655/2018). All women were informed about the study (aims and survey) and requested to provide written consent of participation.

Calculation of the sample size

A minimum sample of 263 women was calculated by estimating a 20% prevalence of osteoporosis in this population [8] and considering a 5% error, a 95% confidence level, and assuming a 50% decrease in the risk of osteoporosis among metformin users.

General questionnaire

A registry data sheet was elaborated for the study in which personal and clinical information was recorded. Variables included: age (years), years of schooling, weight (kg), height (m), reproductive stage, presence of type 2 diabetes (yes/no), and current tobacco consumption. Current use of metformin, calcium, vitamin D, and menopausal hormone therapy (MHT), was also recorded.

Assessment of bone mineral density

BMD was assessed by dual-energy X-ray absorptiometry of the lumbar spine (from L1 to L4) and both hips (femoral neck) in antero-posterior projection. The average of both hips was considered and in those cases in which a hip was missing (i.e. prosthesis) the value of the evaluated hip was considered. All exams were performed in a standardized manner, according to the manufacturer's recommendations. Osteoporosis was defined according to the World Health Organization, as a T score of less than −2.5 [9].

Statistical analysis

Statistical analysis was performed with the Stata program (Stata/SE version 15.0 for Windows, Copyright 1985–2017, StataCorp LLC, College Station, TX). The Kolmogorov–Smirnov test was used to evaluate the normality of data. According to this, numeric data are presented as means, standard deviations or medians, and interquartile ranges (IQRs). Categorical data are presented as frequencies and proportions [10].

The presence of osteoporosis was compared according to age, body mass index (BMI), menopausal status, presence of the type of 2 diabetes mellitus, history of cigarette consumption, and the use of metformin, MHT, calcium, and vitamin D. Pearson's chi-squared test was used to compare frequencies. The Mann–Whitney U test was used for the case of non-normally distributed continuous data.

Spearman's correlation coefficients were determined between the pairs: the presence of osteoporosis *versus* age, BMI, menopausal status, presence of type 2 diabetes mellitus, cigarette consumption, and the use of metformin, MHT, calcium, and vitamin D.

Multivariate logistic regression analysis was performed to evaluate the association of osteoporosis with the included covariates. Prior to the construction of the logistic regression model, the continuous quantitative predictors were assessed for linearity to the logit by performing a linear trend test and LOESS plot [11]. A stepwise backward selection approach was used. The final logistic regression model was established with variables with coefficients that showed statistical significance (p value $< .05$) upon the Wald test. In the final model, adjust measures (log likelihood [LL], Akaike information Criterion [AIC], and Bayesian information criterion [BIC]) and standardized odds ratios (ORs) were determined. For the independent variables, a collinearity analysis was carried out, obtaining the number of the global condition, condition index, and the variance inflation factors centered. The adequate compliance of the following requirements was assessed: specification, calibration, and discrimination [12].

The appropriate specification of the final model was studied through the link test. The calibration aspect of the model was assessed using graphical methods, pseudo-r-squared and Hosmer and Lemeshow's goodness-of-fit test [13]. The receiver operating characteristics area was used to assess discrimination of the final regression model. All tests were two-tailed and for all calculations, a p value of $<.05$ was considered statistically significant.

Leverage estimation, Pearson delta chi-square ($\Delta\chi^2$), Delta deviation (ΔD) and Delta-Beta Pregibon statistics were also used to weigh the influence of certain individual cases over the fitness and parameters of the final model. In the event that type 2 diabetes did not appear to be significant in the logistic regression model; and considering that this condition is usually associated with metformin use, logistic regression was performed by subgroups, that is, considering those with and those without type 2 diabetes.

Results

A total of 1370 women were recruited of which 111 were excluded for analysis due to incomplete records. Thus, the studied cohort included 1259 women of which age and BMI were symmetrically distributed. Median (IRQ) age and BMI for the whole cohort was 61.5 (8.0) years and 27.7 (4.6) kg/m^2, respectively. About 22.6% of all women displayed osteoporosis; of these, 84.6% had osteoporosis in the vertebral spine, 37.9% in the hip, and 22.4% in both.

Overall, 9.8% of women had a history of cigarette consumption and 96.7% were postmenopausal. Age of menopause onset was asymmetrically distributed with a median of 49 years (IQR:

Table 1. Clinical findings according to the presence of osteoporosis in 1259 women.

Characteristic	Absence osteoporosis n= 974	Presence osteoporosis n= 285	Two tailed p Value
Age (years)[a]	60.0 (11.0)	64.0 (12.0)	<.001[c]
Body mass index (kg/m^2)[a]	26.8 (6.6)	25.9 (5.9)	<.001[c]
Years of education[a]	12.0 (6.0)	11.0 (7.0)	<.0001[c]
Postmenopausal status	941 (96.6)	276 (96.8)	.849[d]
Presence of diabetes mellitus type 2	315 (32.3)	65 (22.8)	.002[d]
History of cigarette consumption	101 (10.4)	22 (7.7)	.185[d]
Metformin use[b]	430 (44.2)	77 (27.0)	<.0001[d]
Hormonal therapy use[b]	107 (11.0)	28 (9.8)	.577[d]
Calcium use[b]	462 (47.4)	139 (48.8)	.691[d]
Vitamin D use[b]	414 (42.5)	129 (45.3)	.408[d]

Data are presented as medians [interquartile ranges] or frequency n (%); [a]The p values of the Kolmogorov–Smirnov test were <.01 for these numeric variables; [b]History of intake for at least one year; [c]Mann–Whitney U test assuming unequal variance and a non-normal distribution of data (Kolmogorov–Smirnov test p Value<.05); [d]Pearson's chi squared test.

Table 2. Spearman's correlation coefficients between osteoporosis and variable clinical.

Variable	Spearman's correlation	
	Coefficient value	p Value
Age	0.209	<.01
Body mass index	−0.132	<.01
Menopausal status	0.005	.849
Presence of diabetes mellitus type 2	−0.087	.002
Previous history of cigarette consumption	−0.037	.185
History of at least one year of metformin use	−0.146	<.01
Hormonal therapy for the menopause	−0.016	.578
Calcium use	0.011	.691
Vitamin D use	0.023	.409

6). About 30.2% of participants had type 2 diabetes mellitus and 40.3% reported having used metformin for at least 1 year. Of the 507 metformin users, 380 were diabetics and the rest were obese (Table 1). Current use of MHT (at least 1 year), calcium, and vitamin D were, respectively, reported in 10.7%, 47.7%, and 43.1% of all surveyed women.

The median age was significantly higher in subjects with osteoporosis. Contrary to this, median BMI was significantly higher in women without osteoporosis (Table 1). The frequencies of type 2 diabetes mellitus and history for at least one year of use metformin were significantly higher in women without osteoporosis (Table 1).

Spearman's correlation coefficient between osteoporosis and clinical variables are shown in Table 2. Age, BMI, and metformin use showed a significant correlation. The final logistic regression model for the risk of osteoporosis incorporated age (OR: 1.07; 95% CI 1.05–1.09), BMI (OR: 0.92; 95% CI: 0.89–0.96) and metformin use (OR: 0.44; 95% CI: 0.32–0.59). The logistic regression for osteoporosis that included predictors such as age, BMI and history for at least one year of metformin use was not modified upon subgroup analysis (diabetic *versus* non-diabetic participants).

Discussion

Metformin is a drug not only used to treat diabetes mellitus, but also used for other conditions such as insulin resistance and obesity [14]. Therefore, it is not of surprise that in this study we found that 27% of metformin users were not diabetic. We found a lower risk of osteoporosis among metformin users, an effect that was independent of type 2 diabetes, obesity, and age. To the best of our knowledge, we have not found studies evaluating such association (metformin use *versus* osteoporosis) in non-diabetic individuals; yet there is research among diabetics and experimental animals. A study that compared BMD in diabetics showed that metformin was able to block bone loss induced by rosiglitazone [15]. A model in rats suggests that metformin prevents glucocorticoid-induced bone loss by suppressing bone resorption and stimulating bone formation in the trabecular bone. Contrary to this, alendronate only suppresses bone resorption [16].

The positive effects of metformin on bone tissue observed in diabetics have made it plausible to suggest that this drug could reduce the risk of fractures in this population. In a case-control study conducted in Denmark it was observed that diabetes (types 1 and 2) was associated with an increased risk of fracture, especially of the hip; and, the use of metformin, but not insulin, decreased this risk [17]. In another study performed in the USA, fracture risk was increased in diabetics receiving insulin, but the risk was reduced among biguanide users (i.e. metformin) [18]. A recent meta-analysis, including six studies, showed a significant decrease in fracture risk among diabetic patients using metformin [19].

Patients with diabetes mellitus have worse bone quality in comparison to their non-diabetic counterparts mainly because of hyperglycemia, which is associated with the toxic bone effects of advanced glycosylated end-products (AGEs), and an impaired bone microvascular system [2]. High glucose levels down regulate the effects of autophagy on osteoclastogenesis *via* the AMPK/mTOR/ULK1 pathway, and these metabolic disorders may explain the greater risk of fractures observed in diabetics [20]. The positive effect of metformin at lowering the risk of osteoporotic fractures seen in diabetics could be explained by the fact that on the bone this drug exerts beneficial effects on the metabolic pathways that are altered by diabetes [21]. The presence of type 2 diabetes was indeed included in our model, but the step-by-step backward selection approach eliminated this variable. Diabetes is not associated with an increased risk of osteoporosis yet to an increased risk of fracture due to poor bone quality [22].

We found that metformin use, independent of the presence of type 2 diabetes, or obesity, was a protective factor for osteoporosis. Although obesity and insulin resistance could share some pathophysiological aspects of diabetes, they differ in terms of the magnitude of hyperglycemia and metabolic abnormalities. Therefore, the beneficial bone effect of metformin in obese or insulin-resistant subjects could have differences in the mechanisms described above among diabetics. AMPK, the key molecule in metformin's antidiabetic mechanism of action, is also effective in signaling pathways involved in cellular senescence. Senescent cells produce a pro-inflammatory secretome that leads to increased bone resorption and decreased bone formation. Treatment either eliminates senescent cells or impairs the production of their pro-inflammatory secretome; showing in mice preventive age-related bone loss [23]. We suggest that metformin may also be fulfilling this role in humans. However, since markers of cell senescence were not measured, we cannot confirm that the mechanism associated with a lower risk of osteoporosis observed among metformin users was in fact due to an anti-senescent action of this drug.

As previously stated, metformin is also used to treat obesity. In our regression model, BMI and age were associated with

osteoporosis; situation which was to be expected. Increased risk of osteoporosis with age is indisputable. On the other hand, greater weight can be associated with both, protection, as observed in our study, as well as paradoxically with an increased risk of osteoporosis and fractures [24]. To highlight this, one can mention an Asian study that showed a lower likelihood of osteoporosis among women older than 50 years with obesity (OR: 0.58; 95% CI 0.43–0.78), especially in those with normal muscular mass. Nevertheless, those that had obesity and sarcopenia displayed a higher risk of osteoporosis (OR: 2.93; IC 95%, 1.99–4.32) [25]. This dual effect of obesity over bone metabolism may probably be related to the existence of a chronic pro-inflammatory state that is observed among some obese individuals (perhaps more unhealthy) that leads to osteoporosis and simultaneous sarcopenia. Due to its action over AMPK, metformin may increase osteoblastic activity, decrease inflammation, and therefore reduce osteoporosis risk [26].

In relation to other studied risk factors, it was a surprise finding that MHT use was not associated with a lower risk of osteoporosis, given the fact that for years it has been known that it improves bone mass and decreases the risk of fractures [27]. A plausible explanation could be associated to the fact that the main indication for MHT is the management of vasomotor symptoms. Indeed, one study has reported that women with these symptoms are more likely to have osteopenia or osteoporosis [28]. It could be that although MHT improves symptoms and also BMD, its positive effects may have been exerted over a poorer baseline bone quality. We have previously observed the same situation in women with severe hot flashes managed with MHT; after weeks of use, although symptom intensity decreases these usually level to those found among women who are not receiving treatment [29]. Another explanation for the apparent null effect of MHT of bone is that women usually stop treatment early or use it irregularly [30]; hence avoiding us to observe a beneficial effect on BMD.

As for the limitations of this study, one can mention its cross-sectional design, which precludes conclusions regarding the direction of cause and effect. Likewise, we cannot attribute the observed effect to a decrease in cellular senescence, since we did not study the characteristic signs of this disorder in bone tissue. Despite this, there seems to be a biological plausibility to hypothesize that metformin could modify cellular senescence of the bone. Nevertheless, we must wait for new studies that enlighten us regarding cellular senescence. Another recognizable drawback for our study is the lack of measuring serum analytes related to glucose and bone metabolism (i.e. glucose, insulin, HOMA IR, vitamin D, calcium, and phosphorus). Regarding the strengths of this study, one can mention the large sample size, consequence of a multicentre network of outpatient clinics, which has allowed us to show a relationship between the use of metformin and a lower osteoporosis prevalence.

In conclusion, metformin use, independent of the presence of type 2 diabetes, or obesity, was associated with a lower risk of osteoporosis in adult women. One explanation for this observation could be the effect of metformin over cellular senescence.

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Disclosure statement

The authors report no potential conflicts of interest.

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