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Gas exchange and breathing pattern in women with postmenopausal bone fragility

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ABSTRACT

Background: Little is known about the relationship between bone fragility and respiratory function. We hypothesized that women with osteoporosis or osteopenia, without cardio-pulmonary disease, have perturbations in the pattern of breathing and gas exchange.

Methods: In 44 women with bone fragility (BF, T score: < -1), and 20 anthropomorphically-matched control women (T score > -1) we compared pulmonary function tests, central respiratory drive (mouth occlusion pressure or P 0.1), pattern of breathing using optoelectronic plethysmograph and arterial blood gases at rest.

Results: Static pulmonary function was similar in BF subjects and controls. However, the arterial blood gas measurements differed significantly. The arterial pH was significantly higher in BF subjects than in controls ($P < 0.001$). The partial pressure of carbon dioxide ($PaCO_2$) and oxygen (PaO_2) in arterial blood were significantly lower in BF subjects than controls ($P < 0.001$ and $P = 0.009$, respectively). The BF subjects had a shorter inspiratory fraction compared with controls ($P = 0.036$). Moreover, T-scores were significantly inversely correlated with the alveolar–arterial gradient of oxygen ($r = -0.5$; $P = 0.0003$) and the arterial pH ($r = -0.4$; $P = 0.002$), and positively correlated with arterial PaO_2 ($r = 0.3$; $P = 0.01$) and $PaCO_2$ ($r = 0.4$; $P = 0.002$) among all subjects.

Conclusion: In the absence of known cardio-pulmonary disease, BF is associated with statistically significant perturbations in gas exchange and alterations in the pattern of breathing including shortening of the inspiratory time.

1. Introduction

Osteoporosis is a skeletal disorder characterized by a systemic impairment of the mass, strength, and microarchitecture of bone. Osteoporosis may also occur in a number of diseases including malnutrition, hormonal diseases, and chronic renal diseases especially in individuals with a sedentary life-style, or as part of a systemic comorbidity such as COPD [1]. Moreover, many drugs decrease bone density, including corticosteroids (CS) which are often used to treat several chronic respiratory conditions.

Osteoporosis leads to an increased risk of spontaneous and traumatic fractures [2,3], and is the most common cause of bone fracture in the elderly and also in post-menopausal women secondary to their lower levels of estrogen. These fractures, in addition to causing chronic pain and disability, can lead to thoracic kyphosis [4] when they affect the thoracic vertebrae. Thoracic kyphosis is associated with higher hospitalization rates and a poor prognosis [5]. Furthermore, each vertebral fracture reduces the forced vital capacity (FVC) by 9% [6]. Women with osteoporosis have an increased rate of thoracic kyphosis (19%) even in absence of vertebral fractures [5].

Most of the prior studies focusing on the relationship between respiratory function and osteoporosis were performed on patients having chronic respiratory pathologies as the primary diagnosis [7,8], or on those having osteoporosis or thoracic kyphosis as consequence of the respiratory disease itself, or as a consequence of chronic CS administration [9]. However, the results of these latter studies are difficult to

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interpret due to important biases, such as selection of patients with vertebral fractures [10], or subjects not matched for current hormonal therapies, cigarette smoking history, current smoker status, or corticosteroid use [11], and methodological biases [12]. Very few studies have evaluated pulmonary function in women with osteoporosis without physician-diagnosed chronic respiratory diseases [4,10–12].

The clinical observation that women with osteoporosis frequently complain about shortness of breath prompted us to conduct this study. We hypothesized that a fragile rib cage due to osteopenia or osteoporosis impairs respiratory function by reducing the systemic responses to respiratory stimuli, thus affecting the arterial acid-base balance. To test this hypothesis we measured lung function, central respiratory drive, breathing pattern and arterial blood gases in women with bone fragility (BF) who did not have physician-diagnosed cardio-respiratory disease, chronic renal disease, anemia, and were not taking drugs that are known to alter pH (e.g., diuretics, laxatives or aspirin) and compared the results with those of matched women without BF.

2. Methods

The study was approved by the local Ethics Committee "*ASL Napoli 3 Sud*" which reviewed the study design (34879/SCCE, April 19, 2016) and approved it with resolution n° 43/r.p.s.o., May 11, 2016, notified to the Authors (n° 62) on May 16, 2016.

2.1. Patient selection

From a total of 3678 post-menopausal women undergoing screening for osteoporosis between 2013 and 2015 in the pulmonary department of Salerno Province Healthcare, Italy, we identified 628 women who were never–smokers, had no known occupational exposures, and did not have physician-diagnosed cardio-pulmonary diseases, kypho-scoliosis, or bone fractures. From these 628 women, we selected 64 who had pulmonary function tests performed for screening and routine preoperative evaluations for minor and elective surgery (such as orthopedic disorders, or surgery for inguinal hernias, or eye and ear diseases, or hemorrhoids), and who had never taken hormone replacement therapy (Fig. 1). All the subjects were screened for chronic kidney disease and poorly-controlled diabetes as causes of metabolic acidosis. Among these 64 women, 44 were defined as belonging to the "bone-fragile" (BF) group, based upon Bone Mineral Density (BMD) evaluation and 20, without BF, as controls. The anthropometric data of the female study population are shown in Table 1.

A small cohort of males (11 with osteoporosis and 8 controls) was selected prospectively with the same criteria as used for the female cohort in order to validate the findings in males and assess the reproducibility of the findings in a prospective cohort.

2.2. Bone fragility diagnosis

A BMD evaluation with heel ultrasound scanner was performed as a screening tool for osteoporosis [13]. The results were expressed as T-score (percentage or standard deviation [SD] of a subject compared with a reference sex- and race-matched population at the peak of bone density) and Z-score (percentage or standard deviation of the bone density of a subject compared with a sex-, race-, and age-matched population). According to the World Health Organization standards, BMD values were divided into two groups: 1) normal: bone density within 1 SD (± 1 or −1 SD) of the young adult mean value; 2) subjects with BF, which included subjects with osteopenia (bone density is between 1 and 2.5 SD below the young adult mean value [−1 to −2.5 SD]) and subjects with osteoporosis (bone density of 2.5 SD or more below the young adult mean value [−2.5 SD or lower]).

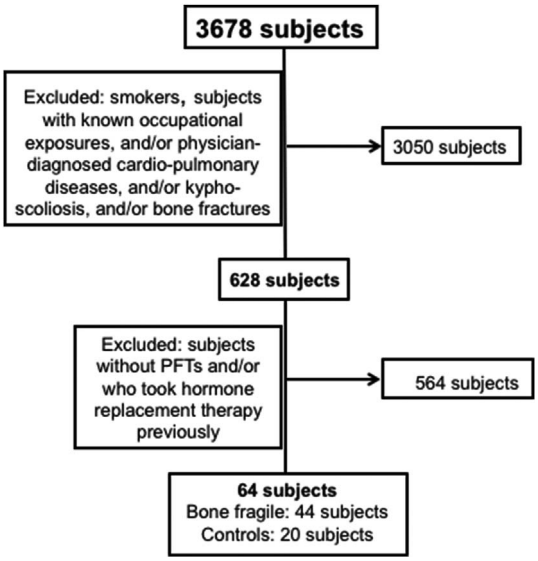

Fig. 1. Consort figure showing the process used to select the female subjects who were included in the study. From 3678 subjects that underwent screening for osteoporosis between 2013 and 2015, 3050 women who did not meet the following inclusion criteria were excluded: were never–smokers, had no known occupational exposures, and did not have physician-diagnosed cardio-pulmonary diseases, kypho-scoliosis, or bone fractures. From the remaining 628 women, 64 who had pulmonary function tests performed for screening and routine preoperative evaluations for minor and elective surgery (such as orthopedic disorders, or surgery for inguinal hernias, or eye and ear diseases, or hemorrhoids), and who had never taken hormone replacement therapy were further selected. All the subjects were screened for chronic kidney disease and poorly-controlled diabetes as causes of metabolic acidosis. Among these 64 women, 44 were defined as belonging to the "bone-fragile" (BF) group, based upon Bone Mineral Density (BMD) evaluation and 20, without BF, as controls.

Table 1
Anthropometric data of the female study population, bone health and C Reactive Protein values.

	BF (n = 44) Mean (± SEM) or Median (IQR)	Controls (n = 20) Mean (± SEM) or Median (IQR)	P values
Age (years)	63 ± 1	63 ± 2	NS
Weight (Kg)	70 (67–80)	70 (61.5–75)	NS
Height (cm)	154 ± 1	155 ± 1	NS
T-score	−2.3 (−3.2–−1.7)	0.2 (−0.1–0.3)	**P < 0.001**
Z-score	−0.6 (−1.5–0.1)	1.7 (1–2.1)	**P < 0.001**
CRP (mg/L)	2.3 (0.9–2.6)	1.2 (0.7–2.1)	**0.047**

BF: Women with Bone Fragility; NS: non-significant; SD: standard deviation; T-score and Z-score: Bone mineral density scores (see Methods); CRP: C Reactive Protein.
NS; not significant.
BOLD numbers indicates the P results that are significant (P < 0.05).

2.3. Respiratory function

Pulmonary function tests were performed following the ATS/ERS standards [14]. Measurements included spirometry, arterial blood gas analysis in the sitting position, and pattern of breathing (tidal volume [V_T], inspiratory time [T_I], expiratory time [T_E], total breath durations [T_{TOT}], V_T/T_I, and alveolar-arterial gradient of oxygen [A-aO_2]). Lung volumes were measured by plethysmography.

The breathing pattern was measured using an optoelectronic plethysmograph [15,16] (OEP, Optoelectronic Plethysmography, BTS Bioengineering Corp., Brooklyn, USA). The following variables were measured via a computed acquisition system on a breath-by-breath basis: V_T, respiratory rate (RR), minute ventilation (MV), T_I, T_E, and other breathing parameters which were computed including inspiratory duty cycle (T_I/T_{TOT}) and mean inspiratory flow (MIF: V_T/T_I).

Arterial gases (PaO_2 and $PaCO_2$) and pH (corrected for body