

PhD Thesis: Sarcopenia and adipokines-implications for postmenopausal osteoporosis

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1. Translation, adaptation, and validation of the Sarcopenia related quality of life questionnaire (SarQoL) in Romanian

Introduction. Sarcopenia has been associated with a reduced quality of life (QoL) due to an increased risk for falls, fractures and impaired physical performance. Generic instruments do not accurately assess the impact of sarcopenia on QoL hence the need for a specific questionnaire. We recently have provided a translated and culturally adapted version of the original SarQoL questionnaire in the Romanian language.

Objective. This study addressed the need to evaluate the psychometric properties of the Romanian SarQoL in order to validate the questionnaire.

Material and Methods. The sample size included 100 volunteers aged ≥ 65 years. Generic questionnaires such as SF-36 and EuroQol-5D were completed besides SarQoL questionnaire, by 70 subjects. Muscle strength was evaluated using a hand dynamometer with the following cut off-values (for women < 20 kg and for men < 30 kg) and to estimate the muscle mass we used Lee equation (≤ 6.37 kg/m² for female patients and ≤ 8.90 kg/m² for male patients). Based upon low muscle mass and hand grip strength below the cut-off values, we stratified our population in sarcopenic and non-sarcopenic subjects. The following properties were tested: discriminative power (the ability of the questionnaire to distinguish between subjects with or without sarcopenia in terms of QoL scores), internal consistency (measures if items are consistent in measuring the same construct of interest), construct validity (is meant to assess the degree to which a questionnaire measures the trait that is intended to measure) and floor and ceiling effects (which reflects that items are missing in the lower or upper ends of the scale, thus limiting the reliability of the questionnaire).

Results. Among sarcopenic subjects (n=13), mean SarQoL scores were significantly lower compared with non-sarcopenic individuals (n=87) which shows a good discriminative power of the Romanian SarQoL questionnaire (54.92 $\pm$ 18.2 vs 68.64 $\pm$ 17.59, p=0.018). Sarcopenic individuals had significantly lower scores in almost all domains. The Cronbach's Alpha value of 0.946, indicates a high internal consistency. No floor or ceiling effects were found. Strong positive correlation was also found between similar domain scores from SF-36 and EQ-5D questionnaires with the total SarQoL score. Moreover, lower scores of QoL have been showed to be significantly associated with lower muscle strength, in univariate analyses and lower gait speed, both in univariate and multivariate analyses.

Conclusions. The Romanian version of the SarQoL questionnaire qualifies in terms of psychometric properties and is comparable regarding the content and accuracy with the original instrument.

2. Sarcopenia assessment in women with postmenopausal osteoporosis

Introduction. Sarcopenia and osteoporosis are age-related disorders that often coexist in a subset of elderly individuals. The term osteosarcopenia emphasizes the concept of combined weak bones and sarcopenia in frail individuals. Individuals with osteosarcopenia have a higher risk of falls and fracture compared to sarcopenia or osteoporosis alone, which makes this category of patients more vulnerable. Prior studies have shown that sarcopenia is frequent among patients with osteoporosis. In addition, low muscle strength defined as probable sarcopenia by the European Working Group On Sarcopenia In Older People (EWGSOP2), has also been shown to be more prevalent in osteoporosis.

Objectives. The aim of the study is to determine the prevalence of sarcopenia and probable sarcopenia in a cohort of Romanian women with postmenopausal osteoporosis. Our second objective was to assess the predictive factors for sarcopenia/probable sarcopenia in the same cohort. Lastly, we wanted to evaluate the need to screening for sarcopenia in women with postmenopausal osteoporosis.

Materials and methods. A number of 78 postmenopausal women (mean age 64 years $\pm$ 6.74 SD) were recruited from the Clinical County Hospital, Endocrinology Department, Targu Mures, Romania. Sarcopenia was diagnosed according to the algorithm proposed by the EWGSOP2. Muscle strength was measured with a hand dynamometer (low muscle strength was considered if the grip strength was < 16 kg), physical performance was assessed with gait speed test (a walking speed ≤ 0.8 m/s was considered as an indicator of severe sarcopenia) and skeletal muscle mass was estimated by using a Tanita body composition analyser, (MC-780 MA). Low muscle mass was considered if the sarcopenic index (derived automatically from the Tanita software as the ratio between the total skeletal muscle mass of the 4 limbs and height per square meter) was < 5.5 kg/m² according to the EWGSOP2 criteria. Probable sarcopenia was defined if a low muscle strength was detected in the absence of a low muscle mass. In addition, patients had to fill out the Romanian SarQoL questionnaire.

Results. The prevalence of sarcopenia in our cohort of women with postmenopausal osteoporosis was found to be 1% whereas probable sarcopenia was observed in 36% of the cases. The sole subject with sarcopenia was categorized as having severe sarcopenia. Within our groups, subjects with osteosarcopenia did not show a higher incidence of fractures (including vertebral fractures). However, when analysing predicting factors for probable sarcopenia, the presence of fractures was a significant risk factor for the condition (OR 3.66, 95% CI 1.03-12.93). In our subgroup analysis we observed that women with diminished muscle strength had a notably reduced QoL compared to those with a normal muscle strength.

Conclusions. Our study showed that probable sarcopenia was highly prevalent in our cohort of postmenopausal women with osteoporosis. In addition, we found that subjects with osteoporosis and probable sarcopenia, had poorer QoL. A history of fragility fracture was found to be a risk factor for probable sarcopenia in our cohort. Apart from its research applications, the rationale for osteosarcopenia screening in clinical practice is hindered by the lack of a specific pharmacological treatment. However, given the increasing interest in osteosarcopenia, changes in our practice could occur sooner than anticipated.

3. Associations between visfatin, RBP-4, insulin resistance and bone mineral density in women under treatment for postmenopausal osteoporosis

Introduction. The impact of the two adipokines visfatin and retinol-binding protein 4, on bone metabolism and bone mineral density (BMD) has been analysed in various studies with conflicting results.

Objectives. The aim of the study was to evaluate the relationship between serum concentrations of visfatin, RBP-4, markers of insulin resistance and current bone mineral density in postmenopausal treated osteoporosis.

Material and methods. A cross-sectional study was performed on 61 subjects with postmenopausal osteoporosis and at least a year of treatment, recruited from 2 centres in Romania (Clinical County Hospital's Endocrinology Department in Targu Mures, Romania, and the Medical Rehabilitation Hospital in Baile Felix, Romania). Subjects with secondary osteoporosis or unable/unwilling to give written consent

were excluded. Demographics, menopause age, age at osteoporosis diagnosis, previous treatment, metabolic status, anthropometry, visfatin, RBP-4, the HOMA index, and BMD were evaluated.

Results. In regression analysis, RBP-4, ALP, and treatment with strontium ranelate, denosumab and previous BMD were significant predictors for lumbar BMD ($r^2=0.712$, $p<0.001$). When introducing HOMA IR as an independent factor, the model explains 76.5% of the lumbar BMD variation with age, denosumab, ALP, previous BMD and HOMA index as significant predictors.

Conclusions. Our data indicate a positive relationship between BMD and RBP-4, an inverse relationship between markers of insulin resistance, and current BMD, while no significant effect of visfatin on BMD was observed in Romanian subjects with post-menopausal treated osteoporosis.

4. Associations between serum adipokines and osteoporosis in postmenopausal women: a systematic review

Introduction. Studies investigating the impact of adipokines on BMD have produced conflicting results, and a clear relationship has not been established so far. Nonetheless, there is a continuous effort to better characterize these adipokines because they hold the promise of potential biomarkers which makes this arduous process worthwhile.

Objectives. Our aim was to study the relationship between adipokines and bone mineral density in postmenopausal women. The following adipokines were considered: adiponectin, leptin, resistin, visfatin, vaspin, chemerin, omentin-1, retinol binding protein 4 (RBP-4), CTRP3.

Materials and methods. Postmenopausal women with DXA scans and at least one adipokine measurement were considered. A literature review was conducted from 1946 to 26 July 2019 initially, with 2 subsequent updates performed in November 2020 and July 2023. The research was conducted using Ovid MEDLINE(R) and Scopus electronic databases.

Results. After the initial research and 2 subsequent updates, we have identified 1273 records through database searching, of which 282 records were found to be duplicated. Duplicates were removed through manual identification and using Endnote reference manager tool. In total 75 studies were found to be eligible for full-text review of which 26 were included in the systematic review. Through manual research, 3 other additional articles were included. In total 29 studies were included in this analysis. The total sample size consists of 3237 postmenopausal women. Most of the studies were cross-sectional studies ($n=26$) and 3 were longitudinal in their study design. Included studies showed a wide heterogeneity with regards to adipokines, sample size, characteristics of subjects, and BMD site measurement. Leptin and adiponectin were the most frequently studied adipokines in postmenopausal women.

Leptin appears to be decreased in postmenopausal women with osteoporosis, whereas adiponectin, resistin, chemerin show the opposite. We found no significant data to support a discriminative capacity of osteoporotic status for serum omentin-1, vaspin, and RBP-4 levels, visfatin. Most of the studies included in our research showed a positive relationship between leptin and BMD. We found no convincing data to support connections between adiponectin, resistin, chemerin, visfatin, omentin-1, vaspin, RBP-4 with BMD in postmenopausal women.

Conclusions. This systematic review thoroughly summarizes the available literature regarding serum adipokine levels and its associations with BMD in postmenopausal women. While serum leptin, adiponectin, resistin and chemerin appear to exhibit a discriminative capacity of osteoporotic status, only leptin appears to be associated with BMD.