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Musculoskeletal Health of 40-65 Year Old Males and Females in Kosova and the Impact of N05B, A02B (PPI, H2RA), H02AB and Lifestyle Factors on It

Ermira Krasniqi^{1,4}, Mynyr Koni^{1,2}, Harald Tchan³, Blerim Krasniqi⁴, Antigona Kabashi¹, and Arben Boshnjaku³

¹Medical University of Tirana, Faculty of Medical Technical Sciences, Tirana, Albania

²University of Tirana, Faculty of Natural Sciences, Tirana, Albania

³University of Vienna, Faculty of Natural Sciences /Life Sciences, Vienna, Austria

⁴Medical Sciences College Rezonanca, Prishtinë, Kosova

Corresponding author: Ermira Krasniqi, Mati 1, 11/29, Prishtinë, Kosova, <http://orcid.org/0000-0002-2586-0934>, tel: 0037744639993. E-mail: ph.ermirakrasniqi@gmail.com

ABSTRACT

Background: This observational, cross-sectional study investigates the impact of medication usage, physical activity (PA) and nutritional status on musculoskeletal health (MSH) in males and females aged 40-65 in the population of a post conflict, developing country. **Methods:** Bone Mineral Density (BMD), T-score and Z-score at distal forearm regions (measured by DEXA scan), together with isometric hand grip strength (dynamometer) were evaluated in a total of 162 subjects (53 Males, average age 55.15±7.12 and 109 Females, 54.27±5.1). Additionally, bio-anthropometric assessments, medication usage, PA level and nutritional status were assessed. **Results:** Significant differences ($p<0.05$) were found in total subjects Body Mass Index (BMI), PA, BMD, T-score and Hand grip between genders. 42% of total participants met the diagnostic criteria of, out of which 6.8% with T-score below -2, while no cases of Osteoporosis was recorded. N05B Anxiolytics and A02B Drugs for peptic ulcer and gastro-oesophageal reflux disease medication groups consumption turned to have no significant differences ($p>0.05$) in BMD, T-score, and hand grip in total population, except for A02B where $p<0.05$ were found in Hand grip, as well as between female consumers and no consumers in all variables. Meanwhile, in total subjects consuming H02AB Glucocorticoids $p<0.05$ were observed in BMD and T-score, but not on hand grip. **Conclusions:** This study shows a low risk for MSH problems amongst the studied population in Kosova, while the consumption of H02AB medication group in both genders and A02B in females only for extended periods might effect MSH, therefore appropriate benefit/risk assessment should be made before prescribing these medications, notwithstanding age, gender, PA or nutritional status.

Key words: Bone; Hand grip Strength; Side Effects; N05B, H02AB; A02B.

1. BACKGROUND

The aging phenomenon of human beings, presents one great concern of modern science. The advancing age is associated with profound changes in body composition, including increased fat mass, decreased fat-free mass (particularly muscle), decreased total body water and decreased bone density (1). Bone itself presents an organ of particular interest in both medical and phar-

macological sciences. In medical sciences because of its unique physiology, since it undergoes remodeling throughout the lifespan with faster formation in the youth and faster resorption by growing older (2). Bone is important in pharmacological sciences since different medications can either improve or worsen bone health, with different studies having analyzed the link between drug use and adverse effects in MSH, some of

which even resulted in potentially serious consequences such as drug-induced osteoporosis (3, 4, 5). Corticosteroids seem to be the leading cause of secondary osteoporosis (5, 6), with many other medication groups seeming to increase the risk, such as thyroxine overdose, gonadotropin-releasing hormone (GnRH) agonists, aromatase inhibitors, thiazolidines, PPI (Proton Pump Inhibitors), loop diuretics, anticoagulant drugs, tricyclic antidepressants, anticonvulsant (7) which are still under scientific debates and investigations. While the regular controlled prescription presents a common standard in every developed country, in a developing, low income country such as Kosova (8), it is generally believed that there are major problems regarding self-medication and usage of different medicines without the professional prescription. These might result in higher risk of unsafe usage of medicines, declining the efficacy and increasing the overall price of treatment. Unfortunately, there are very few published studies carried out in Kosovo concerning drug use, side effects, drug - drug interactions (4, 9, 10, 11). This directly contributed to the main aims of this study, that are:

- Having an overview regarding the MSH status of mature adults (40-65 years old) in Kosovo,
- Finding out the impact of specific medications on adults MSH.

We hypothesized that our subjects should be physically active enough to fulfill the international recommendations, while some medication groups discussed for their possible (contradicting) effect on MSH such as N05B, A02B (PPI, H2RA), H02AB, might have an impact on their MSH, which could directly be affecting them. Especially since these medications are proved to be highly consumed within the studied group ages (40-65) (12, 13, 14), there is an increasing prevalence of poly-pharmacy by age (12), and the increasing risk of drug-drug interactions and adverse effects with the number of drugs used (12, 13).

2. METHODS

This is an observational, cross-sectional study, designed and implemented in accordance with the current version of the Declaration of Helsinki of ethical principles regarding human experimentation (14). This study was approved by the Committee of Ethical and Professional issues of University Clinical Center of Kosova (797-12/03/2015), while every participant was informed about procedures of this research and consciously signed a consent for participation and publication before the measurements. A total number of 162 subjects (53 or 32.7% males and 109 or 67.3% females) aged between 40 to 65 years old, residents of Kosova, were recruited. Participants were randomly selected after announcements in the local media (radio and TV stations) and social networks (Facebook and Twitter), and after fulfilling the inclusion criteria. Each subject's weight and height was measured with clinical scale and stadiometer (respectively), with a precision of 100g (weight) and 1 mm (height). Deriving from these data's BMI (Body Mass Index) was calculated. Inclusion criteria were males

and females aged 40-65, who have not been previously diagnosed with Osteoporosis or Osteopenia and (consequently) not being treated for that, patients with any conditions where X-ray radiation is counter-indicated and those with long term immobilizations. For analyzing medications effect on MSH, patient that have been using the chosen medications for at least 6 months within the last 2 years were recruited. A random General Healthcare Status Questionnaire provided by University Clinical Center of Kosova (UCCCK), was used for inclusion criteria.

BMQ1 (Brief Medication Questionnaire 1) combined with additional questions for adherence of medicines use (15, 16) were used to evaluate medicine usage, timeline frame of their usage and the origin of prescription/suggestion, in order to analyze reference and reliability of the subjects to information regarding medicines use. Medications in this study are grouped according to ATC code (Anatomical Therapeutic Chemical classification system).

International Physical Activity Questionnaire (17), translated and updated in Albanian from Boshnjaku A et al (18), was used to assess the participants physical activity level, calculated as Metabolic Equivalent for Task (MET)/hour. Self-administered Nutritional Standard Questionnaire (NSQ) (19), modified by members of the department of Health Sciences, University of Rome "Foro Italico", was used to assess nutritional intakes in our study subjects.

Bone density was measured on the distal radial bone of non-dominant arm by DXA scan (Dual Energy X-ray Absorptiometry), with a host software version 3.9.4. (NORLAND PDEXA bone densitometer device, Florida, USA). All measurements were performed by an experienced radiologist.

Isometric hand grip strength was measured with electronic dynamometer (SAEHAN Corporation, Masan, Korea), while in a sitting position when subjects squeezed for maximal isometric contraction in a duration of 4–5 seconds.

Statistical analysis

All statistical analyzes were applied using the program Graph Pad Prism 6 for statistical analysis and statistical significance set at $p < 0.05$. Differences between groups with continual data were performed using unpaired t test with Welch's correction (to compare two groups), one-way Anova (to compare three groups) and multi-way Anova (to compare more than three groups), whereas the differences between categorical variables were made by using χ^2 test.

3. RESULTS

Descriptive statistics for bio-anthropometric and physical activity (PA) level results are shown in Table 1. Male and female subjects enrolled in this study did not differ significantly in terms of age and weight ($p > 0.05$), which was not the case in height and BMI ($p < 0.05$). Interestingly, females were statistically more active than males ($p < 0.05$).

Surprisingly, there were no significant differences in terms of nutritional habits between genders, except for milk product consumption (males consuming on average 2.19±0.48 rations per day, comparing to females 1.91±0.7) (data not shown). Despite 41.5% of males and 22% of females reporting to be low alcohol consumers, since no differences in any parameter analyzed were detected, we decided to consider them as homogeneous

| | Male (n=53) | Female (n=109) | P-value | Total (n=162) |
|-------------------------------------|-------------|----------------|---------|---------------|
| Age, years | 55.15±7.12 | 54.27±5.1 | p>0.05 | 54.63±6.56 |
| Weight, kg | 78.21±13.25 | 75.52±11.01 | p>0.05 | 76.4±11.8 |
| Height, cm | 173.06±7.51 | 164.52±5.58 | P<0.05 | 167.3±7.45 |
| Body Mass Index, kg/m ² | 26.05±3.73 | 27.95±4.36 | P<0.05 | 27.3±4.26 |
| Physical Activity level (1, 2 or 3) | | | | |
| Physical Activity level | 1.9±0.83 | 2.4±0.68 | P<0.05 | 2.26±0.76 |

Table 1. Participants characteristics

groups.

When analyzing variables amongst our study participants (Table 2), significant differences (p<0.05) were

found in BMD and T-score but not on Z-score (p>0.05) between genders. Males presented a much higher BMD and better T-score results. Similar results were observed in Hand grip (Table 3), where males generated significantly higher force (p<0.05). 42% of total participants met the diagnostic criteria (20) of Osteopenia (18.8% of males and 51.3% of females), out of which (total subjects) 6.8% are on the verge of getting Osteoporosis (with T-score below -2) with menopausal woman being at the greatest risk (11.6%). No one met the diagnostic criteria of Osteoporosis. When comparing the possible differences in study subjects that consumed N05B (Anxiolytics) drugs comparing to those that don't (Table 3), no significant differences (p>0.05) in any variables were found in total, males and females except for Hand grip in females (p<0.05). In contrary to that, when analyzing H02AB medication group (Glucocorticoids) between consumers and non-consumers, significantly better results (p<0.05) were registered in all variables except Hand grip strength (p>0.05) in total subjects, in females and male consumers (Table 3). It was interesting to see that amongst the subjects consuming A02B drugs (drugs for peptic ulcer and gastro-oesophageal reflux disease-GORD) no sig-

| | Males (n=53) | Females (n=103) | P value | Total (n=162) | Pre-Menopausal (n=40) | Menopausal (p=69) | P value |
|--|--------------|-----------------|---------|---------------|-----------------------|-------------------|---------|
| BMD (g/cm ²) | 0.423±0.08 | 0.317±0.06 | P<0.05 | 0.365±0.09 | 0.334±0.06 | 0.307±0.06 | P<0.05 |
| T-score | -0.17±1.07 | -0.69±1.17 | P<0.05 | -0.25±1.38 | -0.31±1.25 | -0.91±1.05 | P<0.05 |
| Z-score | 0.10±1.01 | -0.07±0.92 | p>0.05 | 0.25±1.17 | 0.03±1.07 | -0.13±0.81 | P>0.05 |
| Handgrip (kg) | 35.74±9.56 | 24.59±1.47 | P<0.05 | 28.24±8.81 | 26.19±6.94 | 23.69±4.58 | P<0.05 |
| Diagnostic criteria according to WHO (%) | | | | | | | |
| Osteopenia | 18.8% | 51.3% | P<0.05 | 42% | 37.5% | 57.9% | P<0.05 |
| Osteoporosis | 0 | 0 | - | 0 | 0% | 0% | - |
| T-score below -2 | 1.9% | 9.2% | P<0.05 | 6.8% | 0.5% | 11.6% | P<0.05 |

Table 2. MSH in Males, Females and total

| | | | | |
|------------------|------------|------------|------------|-------------|
| P value | P<0.05 | P<0.05 | P<0.05 | P>0.05 |
| F-H02AB- (n=91) | 0.376±0.01 | -0.52±1.18 | 0.89±0.43 | 26.3±4.54 |
| F-H02AB+ (n=18) | 0.314±0.06 | 0.76±1.16 | -0.13±0.91 | 24.55±5.76 |
| P value | P<0.05 | P<0.05 | P>0.05 | P<0.05 |
| M-H02A-(n=39) | 0.428±0.01 | -0.33±0.16 | 0.01±0.23 | 44.6±2.76 |
| M-H02AB+ (n=14) | 0.413±0.09 | -0.11±1.14 | 0.15±1.08 | 34.71±9.14 |
| P value | P<0.05 | P<0.05 | P<0.05 | P>0.05 |
| T-H02AB- (n=130) | 0.402±0.03 | 0.09±0.46 | 0.45±0.56 | 34.97±10.33 |
| T-H02AB+ (n=32) | 0.348±0.09 | -0.57±1.19 | -0.05±0.97 | 27.68±8.41 |
| P value | p>0.05 | p>0.05 | p>0.05 | P<0.05 |
| F-N05B+ (n=34) | 0.317±0.06 | -0.68±1.29 | 0.01±0.92 | 21.49±4.14 |
| F-N05B- (n=75) | 0.318±0.06 | -0.69±1.11 | -0.11±0.92 | 26.01±5.76 |
| P value | p>0.05 | p>0.05 | p>0.05 | p>0.05 |
| M-N05B- (n=34) | 0.42±0.1 | -0.14±1.24 | 0.14±1.16 | 35.98±9.13 |
| M-N05B+ (n=18) | 0.429±0.05 | -0.23±0.68 | 0.03±0.67 | 35.60±9.36 |
| P value | P>0.05 | P>0.05 | P>0.05 | P>0.05 |
| T-N05B- (n=109) | 0.341±0.09 | -0.47±1.18 | -0.08±1.01 | 29.91±8.38 |
| T-N05B+ (n=53) | 0.356±0.08 | -0.54±1.13 | 0.01±0.84 | 26.48±9.24 |
| | BMD | T-score | Z-score | Handgrip |

Table 3. N05B and H02AB medication groups consumers. T-N05B+ Total consumers T-H02AB+ Total consumers, T-N05B- Total non-consumers T-H02AB- Total non-consumers, M-N05B+ Male consumers M-H02AB+ Male consumers, M-N05B- Male non-consumers M-H02AB- Male non-consumers, F-N05B+ Female consumers F-H02AB+ Female consumers, F-N05B- female non-consumers F-H02AB- Female non-consumers,

| | T-A02B+ (n=44) | T-A02B- (n=117) | P value | M-A02B+ (n=14) | M-A02B- (n=38) | P value | F-A02B- (n=79) | F-A02B+ (n=30) | P value | T-PPI+ (n=38) | T-H2RA+ (n=44) |
|----------|-------------------|--------------------|---------|-------------------|-------------------|---------|-------------------|-------------------|---------|------------------|-------------------|
| BMD | 0.341±0.07 | 0.356±0.09 | p>0.05 | 0.420±0.04 | 0.424±0.09 | p>0.05 | 0.338±0.06 | 0.304±0.05 | P<0.05 | 0.323±0.08 | 0.351±0.06 |
| T-score | -0.76±0.91 | -0.43±1.24 | p>0.05 | -0.45±0.55 | -0.06±1.20 | p>0.05 | -0.61±1.21 | -0.98±1.01 | P<0.05 | -1.19±0.99 | -0.51±0.76 |
| Z-score | -0.23±0.69 | 0.06±1.03 | p>0.05 | -0.18±0.26 | 0.20±1.16 | p>0.05 | 0±0.95 | -0.35±0.81 | P<0.05 | -0.35±0.85 | -0.16±0.56 |
| Handgrip | 29.05±9.42 | 27.91±8.51 | P<0.05 | 40.38±3.42 | 34.18±9.09 | P<0.05 | 26.95±5.53 | 23.76±6.05 | P<0.05 | 32.02±8.48 | 27.36±9.51 |

Table 4. A02B medication group consumers, T-A02B+ Total consumers- T-PPI+ Total consumers, T-A02B- Total non-consumers - T-H2RA+ Total consumers, M-A02B+ Male consumers - T-A02B+ Total consumers, M-A02B+ Male non-consumers, F-A02B+ Female consumers., F-A02B- Female non-consumers

nificant differences in BMD, T-score and Z-score were found ($p>0.05$) comparing to those that don't, whereas significantly better results ($p<0.05$) were registered in Hand grip isometric strength only (Table 4). The same situation was encountered within males (consumers versus non-consumers) in BMD, T-score, Z-score and Hand grip, whereas significantly better results were recorded in all variables in females. When dividing the A02B drug consumers into two subgroups: PPI and H2 Receptor Antagonists, significantly higher ($p<0.05$) impact on BMD, T-score, Z-score and Hand grip isometric strength had PPI usage comparing to H2RA, but nevertheless this wasn't the case when comparing each of these groups with the rest of this study subjects (non-consumers of A02B) (Table 4).

4. DISCUSSION

Our study shows that the prevalence of Osteoporosis (PO) and Osteopenia (POpen) in Kosovo seems to be lower than in several developed countries, such as Sweden-PO 6% in women and 2.5% men (aged >50) (21), UK-PO 24% and POpen 49% in women (7th decade, either hip, spine or both) (22), Korea-PO 30.6% (45-64years old in lumbar spine) (23), as well as in other developing countries, including here the Latin American countries - PO vertebral 12-18% and 8-22% proximal femur (aged >50) (24), as well as China-PO 6.6-19.3% (25).

From our total study sample, the gender distribution of Osteopenia was in line with the current world prevalence being much higher in females (51.3%) comparing to males (18.8%). Yet, the lower PO provides exceptional results for this population. In fact, a previous study of ours (18) raised concerns regarding the MSH of young females (aged 17-30 years old) in Kosova comparing to their counterparts in developing countries, but this was not the case in this study. Perhaps the higher levels of PA amongst our study participants (2.26±0.76 in total, 2.4±0.68 in females and 1.98±0.83 in males) comparing to young adult females from the other study (1.1±0.3) (18) might be playing a role in the general results.

Within the contradicting studies regarding the effect of N05B drugs (including benzodiazepines: Alprazolam, Diazepam, Bromazepam, Lorazepam, Midazolam) in MSH of consumers comparing to non-consumers, the comparison within our study was in line with other similar studies' results regarding the lack of association between benzodiazepines usage and reduce in bone mineral density (26, 27), as well as the association between benzodiazepines usage and the improve in hand grip strength (28). When comparing our study findings with other already published studies regarding the pos-

sible impact of the usage of H02AB drugs (Methylprednisolone, Dexamethasone) in their consumers MSH comparing to non-consumers, similar significant results ($p<0.05$) were found with the majority of the up to date published data, allowing us to stay in line with the known facts of the existing correlation between glucocorticoids usage and osteoporosis (5, 6, 29).

Interesting results were observed when analyzing the possible effects of A02B medication group (PPI inhibitors: Pantoprazole, Omeprazole, Lansoprazole, Esomeprazole and H2 antagonists: Ranitidine) in subjects that have been consuming them, where no significant differences ($p>0.05$) were found in all bone variables and significant differences ($p<0.05$) were found only in Hand grip isometric strength in total subjects and in males. Yet, significant differences ($p<0.05$) between female consumers and no consumers were found in all variables, supporting findings from van der Hoorn study (30), and suggesting that the prescription of A02B medication group should be especially careful when prescribing in middle aged or elderly females. We believe that significant differences ($p<0.05$) found in Hand grip isometric muscle strength in total and in gender based, could be linked to the possible association between PPI usage and hypomagnesemia which is related to muscle cramps, something that has been proofed previously by Furlanetto & Faulhaber and Matsuyama et al. (31, 32).

When investigating the effect of each of two subgroups of A02B (PPI and H2RA) on MSH, significantly higher ($p<0.05$) impact had PPI usage comparing to H2RA, supporting previous findings from Vestergaard (33).

Finally, this study has a couple of limitations, such as the measurement site (only on distal radial bone). While recommendations suggest to perform measurements in Hip and Lumbar Spine as well, due to the lack of accessibility to the device we had to use only distal forearm DXA. Another possible limitation could be the number of participants, but this was mainly due to the type of study, small population of Kosova, the small percentage of this age group within this country (23.1%) (34), and the difficulties in recruitment process (the radiological exposure was a big concern amongst our study subjects).

5. CONCLUSION

The PO and POpen amongst the mature adults in Kosovo seems to be quite low, and together with the relatively high levels of PA (amongst the study participants), allows us to believe that this population stands a solid position against age related MSH conditions such as Osteoporosis and Osteopenia. Nevertheless, future studies using other measurement sites (such as hip and vertebral region) should be

done in order to prove and establish these results. One important recommendation resulting from this study would be that the appropriate benefit/risk assessment should be always made before prescribing and ordering medication, while the therapy ordination must be prescribed by qualified health professionals. One field of particular carefulness should be especially the patients that take medications discussed to be affecting MSH for long periods of time, where precautions should always be considered. This includes recommendation of regular DEXA scans, prescription of additional protective therapy, including here bisphosphonates, calcitonin or supplements as calcium-Ca, Vitamin C or D analogues (35, 36, 37), as well as prescription of specific physical activity for improving bone health such as multi-component exercise with an emphasize on resistance exercise (38). It should also be invested in patients awareness raising and medical practitioners professional update, in order for them both to be informed about the positive and negative effects of medicines use and the steps that can be taken to minimize possible side effects.

- **Abbreviations:** MSH: Musculo-Skeletal Health; BMD: Bone Mineral Density; PO: Prevalence of Osteoporosis; POpen: Prevalence of Osteopenia; PA: Physical Activity; DXA: Dual Energy X-ray Absorptiometry; MET: Metabolic Energy Requirement; BMI: Body Mass Index; N05B: Anxiolytics; N02BE: Anilides; C09A: agents acting on the renin-angiotensin system; C07A: Beta blockers; GORD: gastro-oesophageal reflux disease; A02B: drugs for peptic ulcer and GORD; PPI: Proton Pump Inhibitors; H2RA: Histamine 2 Receptor Antagonists; H02AB: Glucocorticoids;

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