Comorbidities in generalized osteoarthritis

Ph.D. thesis

Eszter Kővári MD

Semmelweis University
Clinical Medicine Doctoral School

Supervisor:
Peter Vince Balint MD, Ph.D.
Official reviewers:
Zoltan Bejek, MD, Ph.D.
Anna Polgar, MD, Ph.D.
Head of the Final Examination Committee:
Csaba Horváth MD, D.Sc.
Members of the Final Examination Committee:
Márta Péntek MD, Ph.D.
Szilvia Mészáros, MD, Ph.D.

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1. Introduction

Osteoarthritis (OA) is the most common disease involving joints, which can affect all joints of the body, especially small joints in the hands, knees and hips. The socioeconomic burden of OA is significant worldwide: 10% of men and 18 % of women above 60 years of age are affected by symptomatic OA. The clinical picture is dominated by pain, joint disability and functional deficiency. OA is a heterogeneous disease: monoarticular, bilateral and generalized forms have been described. Many factors are involved in the development of OA: in addition to genetics, environmental, biomechanical factors, metabolism and inflammatory processes play a role. The multimorbid condition, coexisting non-musculoskeletal diseases of OA patients may influence treatment strategy, mortality outcomes, health care costs, surgery outcomes and also impact quality of life results.

2. Objectives

The purpose of our study was to investigate non-musculoskeletal comorbid conditions in GOA patients

compared to an age- and sex-matched control group. We measured the impact of comorbidity count on functional and quality of life outcomes. In addition, we investigated the relationship between multimorbidity (as summarized by the comorbidity count), age and body mass index (BMI).

Hypotheses:

a, The GOA group has a higher incidence of comorbidities compared to the control group.

b, Association between age, BMI and different comorbidities is stronger than the GOA group as compared to the control group.

c, A characteristic comorbidity pattern can be established based on the confirmed diseases. The verified clusters are different in the GOA and control groups.

d, The overall quality of life outcomes in the control group are better as compared to the GOA group.

e, Increasing comorbidity count is correlated with worse quality of life outcomes. This relationship can be detected in both study groups.

f, In both study groups older age and higher BMI are associated with a higher comorbidity count.
g, Functional tests in the GOA group show impaired functional capacity with increasing comorbidity count.

3. Methods

3.1. Study design and patient population

An observational, cross-sectional study was conducted. According to the American College of Rheumatology (ACR) classification criteria consecutive female patients with hand and knee osteoarthritis (classified in the study as GOA) were invited to participate in the study.
Volunteer participants without any musculoskeletal symptoms, history or evidence of OA or other rheumatic diseases were included in the control group. The control group was matched to the GOA group by age and sex. All study participants were ≥18 years old and a signed informed consent was required. The study was approved by the Medical Research Council of the Hungarian Ministry of Health (registration number 4/2015/EKU),

which ensured the observance of ethical and research requirements.

3.2. General demographics and investigated comorbidities

During an interview conducted by the study investigator medical history was recorded and all medical records were reviewed in both study groups. A routine physical examination and BMI calculation was also performed on all study participants.

We investigated the prevalence of 37 comorbidities. For cluster analysis 14 comorbidity groups were created (Table 1.).

Table 1.: Investigated comorbidities

Investigated comorbidities	**Comorbidity groups for cluster analysis**
1. Hypertension 2. Ischemic heart disease 3. Acute coronary syndrome (with coronary intervention)	1. Cardiovascular diseases

Investigated comorbidities	**Comorbidity groups for cluster analysis**
4. Hyperlipidaemia	2. Hyperlipidaemia
5. Pulmonary embolism 6. Deep vein thrombosis 7. Lower extremity varicectomy (treated by surgical procedure)	3. Venous diseases
8. Transient ischemic attack 9. Stroke	4. Cerebrovascular diseases
10. Diabetes mellitus type I. 11. Diabetes mellitus type II.	5. Diabetes mellitus
12. Euthyroid goiter 13. Hyperthyroidism 14. Hypothyroidism	6. Thyroid diseases

Investigated comorbidities	**Comorbidity groups for cluster analysis**
15. Asthma 16. Chronic obstructive pulmonary disease (COPD)	7. Obstructive pulmonary diseases
17. Malignant melanoma	
18. Cervical cancer 19. Malignant breast cancer	8. Gynaecological malignancies
20. Uterine leiomyoma 21. Benign breast tumour	9. Benign gynaecologic conditions
22. Colorectal carcinoma 23. Gastroesophageal reflux (GERD) 24. Diverticulosis 25. Gastric ulcer 26. Duodenal ulcer	10. Gastrointestinal diseases
27. Treated by psychiatrist 28. Regular anxiolytic intake (described by general practitioner)	11. Depression

Investigated comorbidities	**Comorbidity groups for cluster analysis**
29. Primary headache 30. Polyneuropathy 31. VBI (vertebrobasilar insufficiency 32. BPPV (benign paroxysmal positional vertigo) 33. Essential tremor 34. Parkinson's disease	12. Neurological comorbidities
35. Nephrolithiasis	
36. Otosclerosis surgery	13. Otosclerosis
37. Sleep apnoe syndrome	
	14. Obesity

Only comorbidities diagnosed by specialists (according to national and international protocols) were listed. A summarized comorbidity count (minimal count: 0 maximal count: 37) was calculated for each study participant.

3.3. Assessment of QoL and functional tests

Quality of life was assessed using the EuroQol-5D (EQ-5D-3L) test in both groups, while the subjective overall health was measured with visual analogue scale (VAS). Functional outcome of the knee was measured with The Western Ontario and McMaster Universities Arthritis Index (WOMAC) and The Knee injury and Osteoarthritis Outcome Score (KOOS), while hand function was evaluated with the Cochin Hand Functional Scale (Cochin test) questionnaire. Quality of life was evaluated with the disability index of the Health Assessment Questionnaire questionnaire (HAQ) in the GOA group and subjective pain intensity was recorded by the visual analogue scale.

3.4. Statistical analysis

Comorbidity data were measured as a binary variable (existing/non-existing disease). Descriptive statistics were applied to evaluate the differences between comorbidity counts in the GOA and control groups. The normal distribution of age and BMI were checked in both study groups using Q-Q plot (normal quantile-quantile plot).

The two-sample t-test was used to compare age and BMI between the study groups. Multivariate logistic regression was used to compare the prevalence of comorbidities between the two study groups and analyse the relationship between age, BMI and different comorbidities. A key question, whether odds ratios (ORs) per unit exposure (in case of age: one life year; in case of BMI: one BMI unit) differs in the GOA and control group was examined in connection with age and BMI calculation. The results were compared using chi-squared test and OR of the major parameters with 95% confidence intervals. The significance of the p value was assessed both at conventional ($p<0,05$) and by Bonferroni adjustment at 0,0014 (0,05/37 considering the 37 examined comorbidities). For cluster identification hierarchical agglomerative cluster analysis was utilized with Ward's minimum variance linkage method and Gower dissimilarity scoring.

The following dependent variables were used in the analysis of quality of life and functional outcome: age, BMI, VAS score for health assessment and pain, EQ-5D indices, HAQ, WOMAC, KOOS, and Cochin score. The

relationship between comorbidity count and dependent variables was determined separately in the two groups using Pearson's correlation test. Results were considered significant at the level of $p<0,05$.

The statistical analysis was performed using R (version 3.3.3) and STATA© software (Version 15).

4. Results

The study population included 200 GOA and 200 control female participants. The average age was similar in both groups: 65,47 ± 9,85. The mean BMI index was significantly higher in the GOA group (GOA: 29,13 ± 5,41, control group 26,80 ± 4,73, $p= 6,457 * 10^{-06}$). Similarly, the prevalence of obesity was also higher in the GOA group (42 %) as compared to the control group (29,5 %) (p=0,012). In the GOA group all examined comorbidities were more common. We found a significant difference in the summarized comorbidity count between the two groups: patients in the GOA group suffered from almost twice as many comorbidities than the control subjects (mean comorbidity count: 5,52 ± 2,55 and 2,80 ±

2,51 in the GOA and control group respectively, p= 8,886 *10^{-25}). Utilizing Bonferroni correction, the following comorbidities were observed with a significantly higher prevalence among individuals with GOA: hypertension, uterine leiomyoma, gastroesophageal reflux disease (GERD), diverticulosis, upper gastrointestinal tract (gastric and duodenal) ulcers, depression, diseases with vertigo (vertebrobasilar insufficiency, benign paroxysmal positional vertigo) and surgery due to otosclerosis. A significant relation was found in the case of hypertension, asthma and GERD, where age indicated a higher risk in the GOA group compared to the control group. In case of hypertension, ischemic heart disease and upper gastrointestinal tract ulcers BMI had a significantly higher impact in the control group than in the GOA group. In the cases of hyperlipidemia, hyperthyroidism and benign breast tumour similar effects were observed, which were also significant. Five comorbidity clusters could be identified through cluster analysis in the GOA group. In cluster 1 (G1, n=35) cardiovascular comorbidities (66%) and benign gynaecologic conditions (40%) were identified as

common coexisting diseases. In cluster 2. (G2, n=24) all patients suffered from cardiovascular comorbidity (100%). Hyperlipidaemia (92%) and neurological disorders (83%) were also identified as common coexisting diseases in this cluster. In cluster 3. (G3, n=28) obesity (86%), cardiovascular comorbidities (79%) and gynaecological malignancies (25%) were seen with a relatively high prevalence. In cluster 4. (G4, n=43) benign (72%) and malignant (23%) gynaecological conditions, hyperlipidaemia (95%), gastrointestinal disorders (72%) and also thyroid diseases (49%) were noted. In cluster 5. (G5, n=70) gastrointestinal (94%), neurological (79%) and cardiovascular comorbidities were the dominant diseases. In the control group cardiovascular comorbidities were seen with relatively high prevalence in three (G2, G3, G5) out of five cluster groups. In cluster 3. (G3 n=38) cardiovascular comorbidities were registered at all participants, hyperlipidaemia (89%) and obesity (68%) were identified as common diseases too. In cluster 4. (G4 n=29) gastrointestinal comorbidities (90%) and depression (52%) were the most common coexisting disorders. In cluster 5. (G5 n=27) cardiovascular

comorbidities (96%) were combined with obesity (67%) and endocrine disorders. Quality of life tests were significantly worse in the GOA group. As compared to the control group (0,80 ± 0,22), the EQ-5D-3L index indicated significantly poorer health status in the GOA group (0,42 ± 0,35). Patients' self-reported global subjective health assessment was also significantly lower in patients with GOA (mean VAS score for health assessment: 59,85 ± 20,97 and 73,78 ± 17,10 in the GOA and control group respectively, $p= 8,623 * 10^{-11}$). Subjects with a higher comorbidity number in both groups were characterized by poorer subjective health assessment outcome: correlation coefficient (r): -0,535, $p= 3,034 * 10^{-16}$ and -0,324, $p= 2,721 * 10^{-06}$ in the GOA and control group respectively. With increasing number of comorbidities, we also measured a lower quality of life as indicated by the EQ-5D-3L scale in both groups. Older age (r: 0,371, $p= 5,959 * 10^{-08}$ and r: 0,237, $p= 7,241* 10^{-04}$ in the GOA and control group respectively) and higher BMI (r: 0,182, $p= 9,676* 10^{-03}$ and r: 0,453, $p= 1,551 * 10^{-11}$ in the GOA and control group respectively) correlated with a higher comorbidity count in both groups. Interestingly,

correlation with BMI was more significant in the control group. In the GOA group we could demonstrate a strong correlation between comorbidity count and functional outcomes in particular for the knee. The KOOS score showed (r: -0,488) a slightly stronger correlation than the WOMAC score (r: 0,336) with multimorbidity, but both results were significant (for KOOS p= 2,095 * 10^{-13}, for WOMAC test p= 1,142 * 10^{-06}). A higher comorbidity count showed a numerically weaker relationship with hand function as compared to that of knee function (r: 0,287, p= 3,346 * 10^{-05}). Finally, HAQ values showed a very strong association with multimorbidity (r: 0,470, p= 2,176 * 10^{-12}) in the GOA group. We found a weaker correlation (r: 0,203, p= 3,846 * 10^{-03}) between self-reported pain intensity outcomes and a higher comorbidity count.

5. Conclusions

▪ Patients in the GOA group suffered from almost twice as many comorbidities as the control subjects. All of the investigated comorbidities were measured with higher prevalence in the GOA group. The following

comorbidities adjusted to Bonferroni correction were observed with a significantly higher prevalence among individuals with GOA: hypertension, uterine leiomyoma, GERD, diverticulosis, upper gastrointestinal tract ulcers, depression, diseases with vertigo (vertebrobasilar insufficiency, benign paroxysmal positional vertigo) and otosclerosis.

▪ In the case of hypertension, asthma and GERD, age had a significantly higher impact in the GOA group compared to the control group. In case of hypertension, ischemic heart disease and upper gastrointestinal tract ulcers, BMI had a significantly higher impact in the control group than in the GOA group. In case of hyperlipidemia, hyperthyroidism or benign breast tumour similar effects were observed, which were also significant.

▪ Five comorbidity clusters could be identified through cluster analysis in the GOA group. Cluster analysis allowed us to identify different comorbidity subsets for vascular, gastrointestinal and malignant gynaecological disorders. Cardiovascular comorbidities were notable in each GOA cluster, while gynaecological malignancies were linked only to a single GOA cluster. In the control

group cardiovascular comorbidities were also seen in three out of five cluster groups with relatively high prevalence.

▪ The most important novelty of our results is that GOA is a serious disease associated with serious comorbidities.

▪ The other most important novelty of our research is the examination of the comorbidity clusters. To the best of our knowledge it was not used before in previous studies in GOA. The identification of comorbidity clusters may be useful for the identification of different clinical subgroups and OA phenotypes. All this may facilitate the development of clinical treatment strategies for individual OA subtype, which may also provide new information on the pathophysiology of OA.

▪ In the GOA group general health tests (EQ-5D and also subjective health assessment outcomes) were significantly worse than in the control group, reflecting the burden of OA.

▪ Subjects with a higher comorbidity number in both groups were characterized by poorer subjective health assessment outcomes measured by the EQ-5D-3L scale and also with VAS score according to subjective health assessment.

▪ Both in GOA and the control group older age and higher BMI correlated with a higher comorbidity count. Correlation with BMI was more significant in the control group. Our results indicate a complex relationship between OA, comorbidities, and body weight, probably due to common pathophysiological processes.

▪ In the GOA group we were able to demonstrate a strong correlation between comorbidity count and functional outcomes in particular for the knee. A higher comorbidity count showed a numerically weaker relationship with hand function as compared to that of knee function. HAQ values showed a very strong association with multimorbidity in the GOA group, while correlation was weaker with self-reported pain intensity.

6. Bibliography of the candidate's publications

6.1. Publications related to the thesis

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