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Clinical phenotypes and associated factors in knee osteoarthritis in an African black population

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ABSTRACT

Objective: Our objective was to study the clinical phenotypes of knee osteoarthritis in rheumatology in a black sub-Saharan African population.
Methods: This study took place from October 1, 2022, to September 30, 2023, in the rheumatology department. It involved adult patients with knee osteoarthritis. The researchers used K-means clustering analysis to identify different phenotypes and logistic regression to determine associated factors.
Results: A total of 321 patients were included in the study. The mean age was 58.7 years (ranging from 21 to 92 years), with a sex ratio of 0.23 (M/F). The study identified five clinical phenotypes through clustering: 152 patients (47.3 %) exhibited the "osteoporotic" phenotype, 113 patients (35.2 %) exhibited the "metabolic" phenotype, 17 patients (5.3 %) exhibited the "genetic" phenotype, 24 patients (7.4 %) exhibited the "biomechanical" phenotype, and 15 patients (4.6 %) exhibited the "post-traumatic" phenotype. The "osteoporotic" phenotype was significantly more frequent in patients aged 60 years or older (OR = 1.13 [1.10; 1.16], $p < 0.0001$) and in women (OR = 2.44 [1.20; 4.94], $p < 0.0001$). On the other hand, the "post-traumatic" phenotype was significantly more frequent in patients younger than 60 years (OR = 1.93 [1.91; 1.96], $p < 0.0001$) and in those with tibiofemoral osteoarthritis (OR = 0.44 [0.21; 0.94], $p = 0.034$).
Conclusion: The osteoporotic and metabolic phenotypes were the most frequently observed. The osteoporotic phenotype was more common in women and patients over 60 years while the post-traumatic phenotype was more prevalent in tibiofemoral osteoarthritis under 60 years.

1. Introduction

Knee osteoarthritis is a common condition in rheumatology and is the primary cause of disability in people over 50 years old [1]. Managing this condition poses a challenge due to the diverse nature of knee osteoarthritis, making it difficult to develop a single treatment for all patients [2]. Whether localized at the knee or elsewhere, recent data suggest that osteoarthritis is a heterogeneous and multifaceted disease that can be grouped according to molecular, biological, radiological or clinical phenotypes [2]. This highlights the importance of identifying patient subgroups with similar characteristics, known as clinical phenotypes, to tailor treatments accordingly. Distinct subtypes exist when patients can be grouped such that the variation in these phenotypic traits within a subtype is lower than the variation between subtypes. Clinical phenotypes are a set of observable traits resulting from the interaction of environmental and genetic factors [2]. Identifying clinical phenotypes of knee osteoarthritis is important, as it allows for categorizing patients into distinct groups and developing personalized treatments for each subgroup. While several phenotypes have been described in Western literature [3,4], there is a lack of African studies focusing on identifying clinical phenotypes of knee osteoarthritis. This gap prevents the implementation of specific and personalized treatment strategies for African

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patients and would there be different clinical phenotypes from Western populations. This study aimed to identify the different clinical phenotypes of knee osteoarthritis observed in rheumatology consultations in a black sub-Saharan African population.

2. Methods

This was a cross-sectional, retrospective, and analytical study conducted from October 1, 2022, to September 30, 2023, in a Rheumatology department in Burkina Faso. The study included patients who were seen in rheumatology consultations during this period with a clinical record completeness rate of at least 75 %. Also, these were patients diagnosed with knee osteoarthritis according to the American College of Rheumatology criteria [5]. Patients with a history of microcrystalline arthropathy, infectious arthritis, chronic inflammatory rheumatism, neoplasia, osteonecrosis, or those who had undergone total knee arthroplasty were excluded from the study. Participants missing data on variables used for phenotyping were excluded from the study. The source documents included consultation registers, medical records, and reports of imaging and laboratory results.

The variables of interest were:

1. Sociodemographic data: including age, sex, occupation, and residence.
2. Clinical data: encompassing history, comorbidities, intense sports activity, characteristics of knee osteoarthritis, and physical examination findings.
3. Biological data: fasting blood glucose, HDL cholesterol, LDL cholesterol, triglycerides, and total cholesterol.
4. Radiological data: detailing the topography of knee osteoarthritis, static disorders, knee deformities, radiological stage of knee osteoarthritis according to Kellgren and Lawrence, and bone densitometry.
5. Therapeutic data: covering pharmacological treatment, non-pharmacological treatment, and surgery.

Five main clinical phenotypic hypotheses of knee osteoarthritis were identified based on prior literature research [2–4]. The criteria for assigning each clinical phenotype are detailed in Table 1.

Table 1
Criteria for assigning different phenotypes.

Phenotypes	Criteria
Metabolic	• Body mass index ≥30 kg/m^2 • Presence of at least 3 out of the following 5 criteria [25]: - Abdominal obesity: Man ≥94 cm; Woman ≥80 cm - Elevated triglycerides ≥1.7 mmol/l (150 mg/dl) or treatment for dyslipidemia - Reduced HDL-c: Man <1.0 mmol/l (40 mg/dl); Woman <1.3 mmol/l (50 mg/dl) or treatment for dyslipidemia - Glucose intolerance: Fasting blood glucose ≥1 g/l or antidiabetic treatment - Hypertension ≥135/85 mm Hg or antihypertensive treatment
Biomechanical	• Presence of static disorders such as varus, valgus, flexum, or recurvatum • Leg length discrepancy • Ligamentous laxity • other congenital or acquired knee deformities
Osteoporotic	• Menopause • Bone mineral density (BMD) ≤ −2.5 SD
Post-traumatic	• History of severe knee trauma • History of meniscal or ligamentous injury and/or surgery • Intense sports activity
Genetic	• Family history of knee osteoarthritis in a first-degree relative • Absence of criteria supporting another phenotype

Data were entered into an Excel database, and all analyses were performed using Epi Info version 07 and R Studio software. Missing data were treated as such during analyses. K-means clustering was the type of clustering used to identify phenotypes. Clinical variables bringing together pathological and traumatic history, physical examination and disease history data, biological and radiological variables were used for K-means clustering. Additionally, we calculated the F-Beale ratio to assess the potential for an additional cluster beyond those already detected. Pearson's Chi-square test, or Fisher's Exact test, was used in univariate analysis to determine qualitative variables associated with clinical phenotypes. All variables with a p-value <0.2 in univariate analysis were included in a logistic regression model to determine the variables significantly associated with each clinical phenotype, with a statistical significance threshold set at 5 % ($p < 0.05$).

Anonymity and data confidentiality were maintained in accordance with the recommendations of the Declaration of Helsinki. Identifiers were assigned to each patient during data collection, ensuring that no names were included in our database, thereby preserving anonymity and confidentiality. Written informed consent obtained from all the participants. Ethical approval was obtained from the institutional ethics committee **(Approval number 2022-02-034).**

3. Results

3.1. General characteristics of the population

Out of 351 cases of knee osteoarthritis recorded in the Rheumatology department, 30 cases were excluded and 321 met the inclusion criteria. It was 62 males (19.3 %) and 259 females (80.7 %), with a male-to-female sex ratio of 0.23. The patient's average age was 58.7 years ± 17.8. The youngest was 21 years old and the oldest 92. Table 2 provides an overview of the general characteristics of the population.

Table 2
General characteristics of the study population.

	Variables	Counts (%)
Sociodemographic characteristics	Mean age (years)	58.7 ans ± 17.8
	Women	259 (80.7 %)
	Occupation	
	Informal sector	175 (54.51)
	Formal sector	146 (45.48)
	Residence	
	Rural	31 (9.65)
	Urban	290 (90.34)
Clinical characteristics	Pain	
	Pain intensity (VAS)	
	1-3	79 (24.61)
	4-6	166 (51.71)
	7-10	76 (23.68)
	Bilateral pain	46 (44.23)
	Mechanical pattern	282 (87.8)
	Comorbidities	
	Hypertension	106 (33)
	Diabetes mellitus	17 (5.3)
	Axial deviation	167 (52)
	Patellar shock	33 (3.86)
	BMI	
	<30	231 (71.96)
	≥30	90 (28.03)
Paraclinical characteristics	Topography of knee osteoarthritis	
	Medial tibiofemoral	302 (94.1)
	Lateral tibiofemoral	276 (85.9)
	Femoropatellar	217 (67.6)
	Radiological stage of knee osteoarthritis (Kellgren and Lawrence)	
	Stages 1 and 2	76 (23.67)
	Stages 3 and 4	245 (76.32)

3.2. Clinical phenotypes identification

The clustering analysis confirmed our phenotypic hypotheses and grouped the 321 patients into five subgroups, as shown in Fig. 1. The Beale's F-ratio did not support the idea of an additional phenotype. The most common cluster in the study was the osteoporotic phenotype, including 152 individuals, accounting for 47.3 % of the total. This was followed by the metabolic phenotype, which included 113 individuals (35.2 %). The genetic, biomechanical, and post-traumatic clusters contained 17 (5.3 %), 24 (7.4 %), and 15 (4.6 %) patients, respectively.

3.3. Factors linked with various phenotypes

The sociodemographic, clinical, and paraclinical parameters correlated with each clinical phenotype in univariate analysis are displayed in Table 3. In multivariate logistic regression analysis, age over 60 years was significantly associated with the osteoporotic phenotype ($p < 0.001$, OR = 1.13 [1.10; 1.16]). There was also a significant association between female gender and the osteoporotic phenotype ($p < 0.001$, OR = 2.44 [1.20; 4.94]). An age under 60 years was statistically associated with the post-traumatic phenotype ($p < 0.001$, OR = 1.93 [1.91; 1.96]), as was the tibiofemoral location of knee osteoarthritis (OR = 0.44 [0.21; 0.94], $p = 0.034$). The factors associated with the different phenotypes are summarized in Table 4.

4. Discussion

Our study aimed to identify the different clinical phenotypes of knee osteoarthritis observed in rheumatology consultations at a level-1 Teaching sub-Saharan Hospital. This is the first study to focus on identifying clinical phenotypes within a Black sub-Saharan African population. Over one year, we documented 351 patients with knee osteoarthritis and ultimately included 321 of them in the study.

We used the K-means clustering technique to group our patients into phenotypes. It's worth noting that other techniques, such as hierarchical clustering, density-based clustering, and Latent Class Analysis, are also available. However, K-means clustering is more sensitive as it partitions patients while minimizing variance within each subgroup [6]. This technique helped us identify five distinct clinical phenotypes: “osteoporotic,” “metabolic,” “genetic,” “biomechanical,” and “post-traumatic.”

The osteoporotic phenotype or postmenopausal phenotype was observed in 47.3 % of our female patients. In Europe, the EUGMS-ESCEO group found this phenotype in 32.6 % of cases, and it was also mentioned in a literature review by Nelson et al. [7,8]. This phenotype includes osteoarthritis secondary to osteoporosis. Oestrogen deficiency harms all joint tissues, especially the subchondral bone, where significant remodeling can lead to the development of osteoporotic osteoarthritis [9]. Age over 60 and female sex were significantly associated with the osteoporotic phenotype, with a p-value <0.001. These findings align with the literature, as osteoarthritis primarily affects the elderly and is more prevalent in females [8,9]. Recent studies have indicated that women taking oestrogen have a significantly lower prevalence of knee osteoarthritis, and oestrogen therapy reduces the need for knee arthroplasty by nearly 40 % [10]. Therefore, hormone replacement therapy, along with vitamin D and calcium supplementation, could play a critical role in the progression of osteoarthritis in this phenotypic population [11].

Post-traumatic phenotype was found in 4.6 % of patients. It was also more common in other European studies [12]. This phenotype is likely due to alterations in the articular cartilage following the initial trauma and subsequent local post-traumatic inflammation [13]. Our results showed that the post-traumatic phenotype was statistically more frequent in patients under 60 years of age. This could be explained by the more frequent exposure of younger individuals to trauma and intense sports activities [14]. Additionally, the tibiofemoral location was associated with this phenotype, likely due to the high incidence of meniscal injuries in traumatic events, which increase stress in the tibiofemoral compartments [15,16]. To prevent this subtype of osteoarthritis, early and surgical management of trauma is recommended [17–20].

Our study identified biomechanical phenotypes in 7.4 % of the patients. Our findings are similar to those of Lijima et al. [18] in Japan (9.7 %) but differ from European studies where this frequency was higher (15 %–20.6 %) [7,12]. This phenotype results from excessive stress on certain areas of the knee joint due to malalignment in static disorders [21]. According to recommendations, patients with this phenotype may benefit from knee braces or orthopedic insoles for symptomatic relief [22]. Surgical options include knee arthroplasty, realignment surgery, or joint stabilization procedures [22].

We observed the genetic phenotype in 5.3 % of our patients. This phenotype was found in patients with a first-degree family history of knee osteoarthritis and no other associated phenotypes, as genetic studies are not common in our African context. Similar findings have been reported in Western studies, confirming a genetic predisposition to osteoarthritis [23]. In addition to rare genetic disorders like collagen II or XI mutations, which cause severe and widespread osteoarthritis, there is a genetic susceptibility that is not yet fully understood and could explain over 40 % of osteoarthritis cases [24]. This susceptibility is not limited to the knee but also affects other joints [24].

Our study is not without limitations. We selected records with a clinical file completeness rate of at least 75 %, which may have introduced selection bias, as only 91.4 % of the records could be included. This is a common challenge in all retrospective hospital studies in our

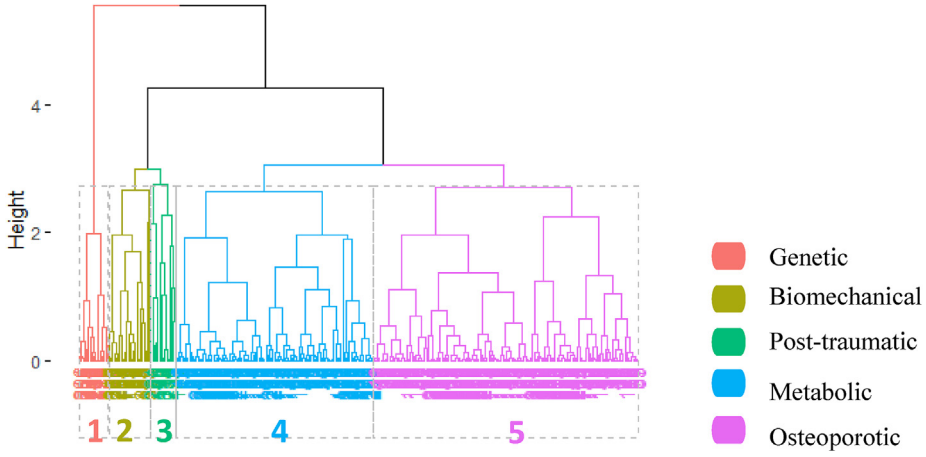

Fig. 1. Dendrogram of the different clinical phenotype clusters. Fig. 1 represents the different phenotypes found in our study. The X axis is the proportion of each phenotype according to color. The Y axis represents the weight or the linkage distance between the different phenotypes.

Table 3
Factors associated with different phenotypes in univariate analysis.

Cluster	Osteoporotic (n = 152)		Genetic (n = 17)		Metabolic (n = 113)		Post-traumatic (n = 15)		Biomechanical (n = 24)	
	% (n)	p	% (n)	p	% (n)	P	% (n)	p	% (n)	p
Age										
<60 years	10.2 (33)	<**0.001**	3.7 (12)	0.296	27.1 (87)	<**0.001**	3.1 (10)	<**0.001**	7.1 (23)	**0.134**
≥60 years	37 (119)		1.5 (5)		8 (26)		1.6 (5)		0.3 (1)	
Sex										
Men	0 (0)	<**0.001**	2.8 (9)	<**0.001**	12.7 (41)	0.313	3	**0.048**	2.8 (9)	**0.089**
Women	47.3 (152)		2.4 (8)		22.4 (72)		12		4.6 (15)	
Residence										
Urban	9.3 (30)	0.501	1.5 (5)	**0.126**	5.6 (18)	0.378	2	0.757	1.4 (4)	0.638
Rural	38 (122)		3.7 (12)		29.5 (95)		13		6.2 (20)	
Pain location										
Unilateral	17.4 (56)	0.457	1.2 (4)	0.206	8.7 (28)	**0.160**	3.1 (10)	**0.025**	3.1 (10)	**0.107**
Bilateral	32 (103)		4 (13)		19.3 (62)		5.9 (15)		4.3 (14)	

Cluster	Osteoporotic		Genetic		Metabolic		Post-traumatic		Biomechanical	
	% (n)	p	% (n)	p	% (n)	p	% (n)	p	% (n)	p
Pain type										
Mechanical	43.2 (139)	**0.118**	4.3 (14)	0.781	29.9 (96)	0.703	4 (13)	0.670	6.2 (20)	0.308
Inflammatory	3.1 (10)		0.6 (2)		2.8 (9)		0 (0)		0.6 (3)	
Mixed	0.9 (3)		0.3 (1)		2.4 (8)		0.62 (2)		0.3 (1)	
VAS										
0–3	14 (45)	**0.057**	0.9 (3)	0.738	6.5 (21)	**0.069**	1.5 (5)	0.416	1.5 (5)	0.960
4–6	25.5 (82)		2.8 (9)		18.6 (58)		1.8 (6)		3.4 (11)	
7–10	7.7 (25)		1.5 (5)		10.5 (34)		1.24 (4)		2.4 (8)	
Patellar shock										
Yes	4.7 (15)	0.378	1.5 (5)	**0.021**	3.4 (11)	0.786	0 (0)	0.203	0.6 (2)	**0.163**
No	42.6 (137)		3.7 (12)		31.7 (102)		4.6 (15)		6.8 (22)	
Kellgren and Lawrence stage										
Stages 1 and 2	7.7 (25)	<**0.001**	1.5 (5)	**0.089**	10.2 (33)	0.255	1.5 (5)	**0.177**	2.1 (9)	**0.087**
Stages 3 and 4	36.7 (118)		3.7 (12)		2.4 (80)		3 (10)		7.6 (25)	

Cluster	Osteoporotic		Genetic		Metabolic		Post-traumatic		Biomechanical	
	% (n)	p	% (n)	p	% (n)	p	% (n)	p	% (n)	p
Axial deviation										
Yes	29.5 (95)	**0.004**	0 (0)	**0.001**	13.3 (43)	0.206	4.6 (15)	0.050	7.4 (24)	<**0.001**
No	22.4 (72)		5.2 (17)		14.6 (47)		7.4 (24)		0 (0)	
Topography of knee osteoarthritis										
Femoropatellar	38 (122)	<**0.001**	3.7 (12)	0.509	20.2 (65)	0.291	5.2 (17)	<**0.001**	2.8 (9)	**0.090**
Tibiofemoral	11.5 (37)		1.5 (5)		7.7 (25)		6.8 (22)		4.6 (15)	

Table 4
Factors associated with different phenotypes in multivariate analysis after logistic regression.

Variable	Univariate analysis		Multivariate analysis		
	OR	P value	OR	[IC 95 %]	P value
Osteoporotic phenotype					
Age ≥60 years	1.13	<0.001	1.13	[1.10; 1.16]	<**0.001**
Women	2.03	<0.001	2.44	[1.20; 4.94]	<**0.001**
Post-traumatic phenotype					
Age < 60 years	1.93	<0.001	1.93	[1.91; 1.96]	<**0.001**
Tibiofemoral knee osteoarthritis	0.44	<0.001	0.44	[0.21; 0.94]	**0.034**

setting, due to the insufficient archiving of medical records. Additionally, other phenotypes have been reported in the literature, such as the "inflammatory," "depressive," or "aging" phenotypes. However, due to the unavailability of certain variables in patient records and the difficulty in assessing them in our clinical practice, these phenotypes were not part of our hypotheses. Nevertheless, our study stands out for its precise identification of clinical phenotypes of knee osteoarthritis using a highly sensitive statistical method, K-means clustering. Through this method, we were able to more reliably and comprehensively detect the different clinical phenotypes of knee osteoarthritis.

5. Conclusion

This study successfully identified the various clinical phenotypes of knee osteoarthritis in rheumatology consultations within an African black population. We conducted a clustering analysis based on hypothetical phenotypes that could be detected in our clinical practice. Consequently, we identified five clinical phenotypes of knee osteoarthritis: "osteoporotic," "metabolic," "biomechanical," "post-traumatic," and "genetic." These subgroups have significant implications for both research and clinical practice, as they could enhance patient stratification, osteoarthritis prevention, the development of personalized therapies, and the pursuit of novel treatments. These phenotypes associated with different risk factors. Current knowledge on personalized interventions remains limited, and further research is needed to compare sociodemographic, clinical, and paraclinical parameters among the five phenotypes, evaluate differences in response to interventions and diagnostic performance indicators.

Authors' contributions

CS, MD, YLTB conceptualized and designed the study and drafting/revisions of the manuscript. IAT, FK, WJSZT managed the data collected, analyzed and interpreted the data and drafted the manuscript. PWHD and D-DO contributed to the conception and design. All authors read and approved the final manuscript.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics approval and consent to participate

The Bogodogo University Hospital institutional ethics committee (Approval number 2022-02-034) approved the protocol for this study.

Consent for publication

Consent for publication is not applicable.

Clinical trial number

Not applicable.

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Declaration of competing interest

The authors declare that they have no competing interests.

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