The role of bone mineral density and cartilage volume to predict knee cartilage degeneration

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Abstract

Knee Osteoarthritis (OA) is a highly prevalent condition affecting knee joint that causes loss of physical function and pain. Clinical treatments are mainly focused on pain relief and limitation of disabilities; therefore, it is crucial to find new paradigms assessing cartilage conditions for detecting and monitoring the progression of OA. The goal of this paper is to highlight the predictive power of several features, such as cartilage density, volume and surface. These features were extracted from the 3D reconstruction of knee joint of forty-seven different patients, subdivided into two categories: degenerative and non-degenerative. The most influent parameters for the degeneration of the knee cartilage were determined using two machine learning classification algorithms (logistic regression and support vector machine); later, box plots, which depicted differences between the classes by gender, were presented to analyze several of the key features' trend. This work is part of a strategy that aims to find a new solution to assess cartilage condition based on new-investigated features.

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Osteoarthritis (OA) occurs when protective cartilage between bones breaks down because of injuries or diseases. This condition also involves changes to the bone underneath the cartilage and can affect nearby soft tissues. Knee OA affects the three compartments of the knee joint (medial, lateral, and patellofemoral) and usually develops slowly over 10 to 15 years.[1] OA is a highly prevalent condition worldwide, that can result in disabling pain and loss of physical function. This pathology is still under investigation; however, there exist common risk factors, including advancing age, family history, obesity, joint trauma.[2] As potential consequences, weakness, damages, healing of cartilages due to OA can further lead to a limitation in the range of motion up to the loss of physical function. Moreover, a damaged cartilage causes friction between bones and changes to bone tissue, which can cause pain. To date, several strategies to address knee OA have been proposed. Usually, treatments for knee OA are more focused on improving patients' quality of life: the attention is on pain relief and limitation of disabilities. Even if surgical operation is needed in patients with advanced stages of OA, non-surgical treatments, like hyaluronic acid and stem cell injections, can be used in patients in early stages of the disease. However, in final stages, the only available treatment option is total knee replacement surgery, which is highly invasive and affects patients' living state. For this reason, it is really

important to detect knee OA on time. Assessment of cartilage condition is therefore crucial for both detecting and monitoring the progression of OA, and in recent years several novel strategies (also based on artificial intelligence)[3] have been proposed to this aim. In this context, starting from the approach presented in the previous paper,[4] the purpose of this work is to remark the predictive power of several of the features already presented, but investigating their straightness considering simpler Machine Learning (ML) models and setting up a binary classification study (considering both the controls and traumatic patients in the same groups since the non-crucial differences in the statistical analyses in the previous paper).[4]

The findings suggest the overall workflow (presented in this and the previous paper)[4] may represent in the future a potential advanced platform for cartilage diagnosis.

Materials and Methods

Study population

This study is part of the European project RESTORE (https://restoreproject.eu/), whose aim is to develop and validate solutions for personalised knee cartilage regeneration. A database containing knee radiographical images and anatomical 3D reconstruction of all the patients was developed and is available at https://restore-project.ru.is.

The subjects enrolled for this study and the recruitment process were the same described in the previous paper,[4] with slight modifications. Specifically, while the considered Degenerative (D) group (24 subjects, mean age = 64 years, std age = 12 years) was considered as-is, as anticipated the traumatic + control groups – herein labeled as "Non Degenerative" (ND) – were considered as a unique group (23 patients, mean age = 35 years, std age = 12 years).

Scanning process

Each of the 47 patients underwent both a CT and an MRI acquisition. A standardized protocol was defined

and followed for each person, using the exact same knee positioning for all the patients. As already described in the previous paper,[4] the CT acquisition was performed by a Toshiba Aquillion One scanner (320 slice) capable to cover a 16 cm area of interest in a single gantry rotation. The acquisition covered about 15 cm of area (axial plane) centered at the knee joint with small variations according to patient size. The MRI acquisition was performed by a 3T Siemens Healthcare Prisma scanner. The acquired areas of interest were the cartilage-covered areas around the knee (14 cm centered at the knee joint). The results of the acquisitions were volumetric 3D sequences (with isotropic voxels of 0.6 mm) acquired in the axial plane

Data Processing

As already described in our previous paper,[4] the medical 3D modeling software Materialise MIMICS (Materialise Interactive Medical Image Control System, Materialise, Belgium) was used to segment the acquired images – the same protocols for bones and cartilages, respectively taken from CT scan and MRI, was followed – of each acquisition and to extract 24 parameters per patient. The considered bones are femur, tibia and patella, while the cartilages are femoral, lateral and medial tibial and patellar. The overall workflow is summarized in Figure 1. Firstly, a mask for each entity by setting a density threshold interval was created. These masks were further converted into 3D objects: a new CT image was created combining together bones and cartilage objects in the process of image registration. The creation of a 3D object from CT has already been proposed in Esposito L. et al. (2018)[5] for similar aims and in Latessa I. et al. (2021)[6] for the extraction of the BMD. Some refinements were applied to have a model as accurate as possible. From this model, the following features were extracted:

- Average Bone Mineral Density (BMD) of all considered bones,
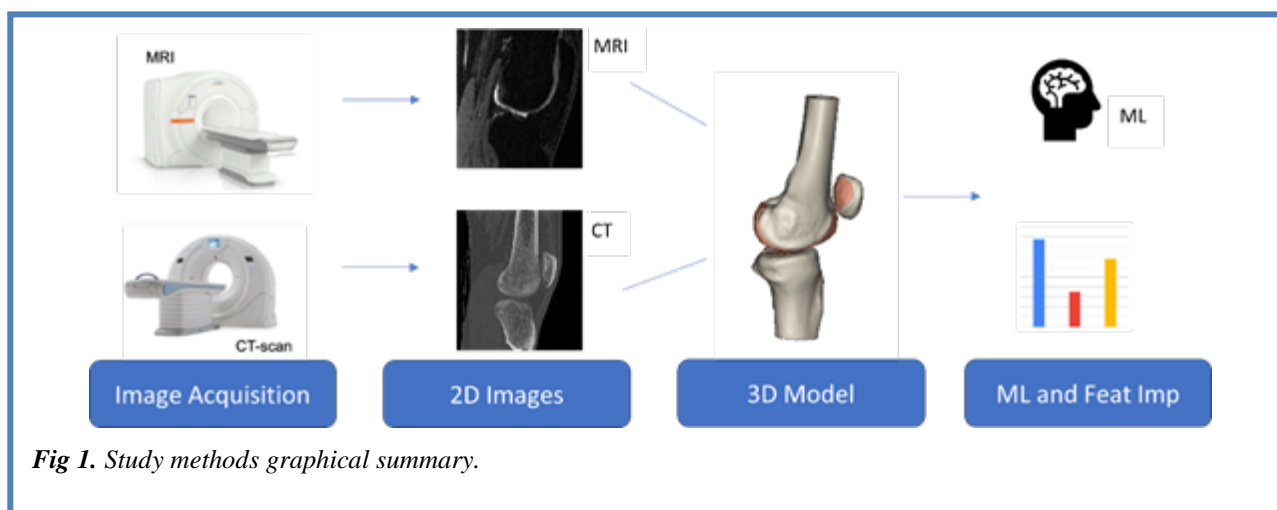- STandard Deviation (STD) of BMD of all considered bones,

Fig 1. *Study methods graphical summary.*

- Average radiodensity – in Hounsfield units (HU) – of all considered cartilages,
- STD of radiodensity of all considered cartilages,
- Volumes of all the considered cartilages,
- Surfaces of all the considered cartilages,
- Volume and surface of patella bone.

Since the relevance was on the part of bone near the cartilages and bone segments resulted in different sizes due to the acquisition process, it was decided to consider only a selected region of interest for bones, specifically the one closer to the bone. For each patient, the tibia and femur masks were cropped according to different landmarks: in the sagittal view for the tibial part, a line was drawn between the tubercular zone and the two opposite parts and the region between 5 mm under this line was selected; for the femoral part in coronal projection, the region was cut starting from 10 mm above the lateral condyle. The patella is always acquired in its entirety.

MIMICS allows the calculation of volume and surfaces of created objects and the computation of radiodensity in HU directly from a region of interest on CT scans, as e.g. described previously.[7] To this aim, cartilage masks were filtered from 0-300 HU, a good range for visualization of soft tissue pixel intensities (cartilage being soft tissue), before HU was computed. Simultaneously, bone mineral density was computed from the radiodensity (in HU) using a linear formula that was determined empirically based on a phantom, as further described in previous research.[8,9]

Machine learning and tools

ML tools were used to assess the capability of the extracted features to distinguish the two classes – D versus ND, with D positive and ND negative class. The analyses were performed in Scikit-Learn, a widely used open-source tool for ML in Python.[10] Support Vector Machine (SVM) and Logistic Regression (LR) were used to this aim. SVM in a binary classification, as in

the case under study, creates a hyperplane that separates data from two different classes. The largest possible distance is established between the separating hyperplane by maximizing the margin, thus creating the separation.[11] The kernel choice determines the separation boundary of the classes. In this study, SVM with a linear kernel was used. LR is an efficient and powerful way to analyse the effect of several independent variables on a binary outcome, as in the case under study, and allows quantifying the contribution of each feature. LR iteratively identifies the strongest linear combination of variables with the highest probability to detect the observed outcome.[12] Before the model training, a feature selection stage through Least Absolute Shrinkage and Selection Operator (LASSO) regularization was performed to have an automatic selection of the most significant features.[13] It completely eliminates the weights of the least important features, setting them to zero. K-fold cross-validation (CV) is one of the most widely used approaches for estimating classifiers error and was employed in our study as five- and ten-fold cross-validation to validate the predictive models described above and provide more robust evidence on the proposed workflow, based on features extracted from the region of interest analysed. Concurrently, Leave-One-Out (LOO) CV was also used; this is a special case of CV where the number of folds equals the number of instances in the dataset. Thus, the learning algorithm is applied once for each instance, using all other instances as a training set and using the selected instance as a single-item test-set. Different classification metrics – namely, accuracy, sensitivity and specificity – were used to analyse more in deep the results of classes separability.[14] Finally, a feature importance stage was performed in order to find out how (and whether) each feature affects the prediction of the degeneration of the knee cartilages. A feature importance refers to several techniques for assigning scores to input features to a

Table 1. ML algorithm scores.

Algorithm	Validation	Accuracy			Sensitivity			Specificity		
		Mean	±	STD	Mean	±	STD	Mean	±	STD
LR	K-fold (k=5)	0.85	±	0.10	0.87	±	0.11	0.85	±	0.13
	K-fold (k=10)	0.84	±	0.19	0.88	±	0.18	0.82	±	0.24
	LOO	0.81	±	0.40	0.75	±	0.49	0.87	±	0.50
SVM	K-fold (k=5)	0.92	±	0.04	0.89	±	0.09	0.97	±	0.07
	K-fold (k=10)	0.83	±	0.18	0.86	±	0.18	0.83	±	0.31
	LOO	0.83	±	0.38	0.83	±	0.49	0.83	±	0.49

LOO: leave-one-out; LR: Logistic Regression; STD: Standard Deviation

***Table 2**. Feature Importance (top 5 features) for Logistic Regression (k=5).*

Feature	Importance (%)
FemCartVOL	24.22
StdDensTibCartMed	15.90
AvDensTibCartLat	14.29
AvBMDTibia	10.25
AvBMDPatella	10.16

AvBMDPatella: Average BMD of patella bone; AvBMDTibia: Average BMD of tibia bone; AvDensTibCartLat: Average density of lateral tibial cartilage; FemCartVOL: Volume of femoral cartilage; StdDensTibCartMed: Standard Deviation of density distribution of medial tibial cartilage.

predictive model that indicates the relative importance of each feature when making a prediction.

Results and Discussion

The ML algorithm scores – following the different validation steps pursued – are reported in Table 1. In addition, Tables 2 and 3 show, respectively, the feature importance (in terms of percentage) computed for the best configuration of both the ML algorithms. Finally, Figure 2 shows the boxplots which depicts the distribution of several of the top five features found for both the different validation steps. The best results in terms of accuracy, sensitivity and specificity are obtained using SVM with k=5. In any case, the best results also for LR are obtained with a 5-fold cross validation. These findings show that both the models present a high percentage of both properly predict the D class (sensitivity) and a fairly high percentage of properly predict the ND class (specificity).
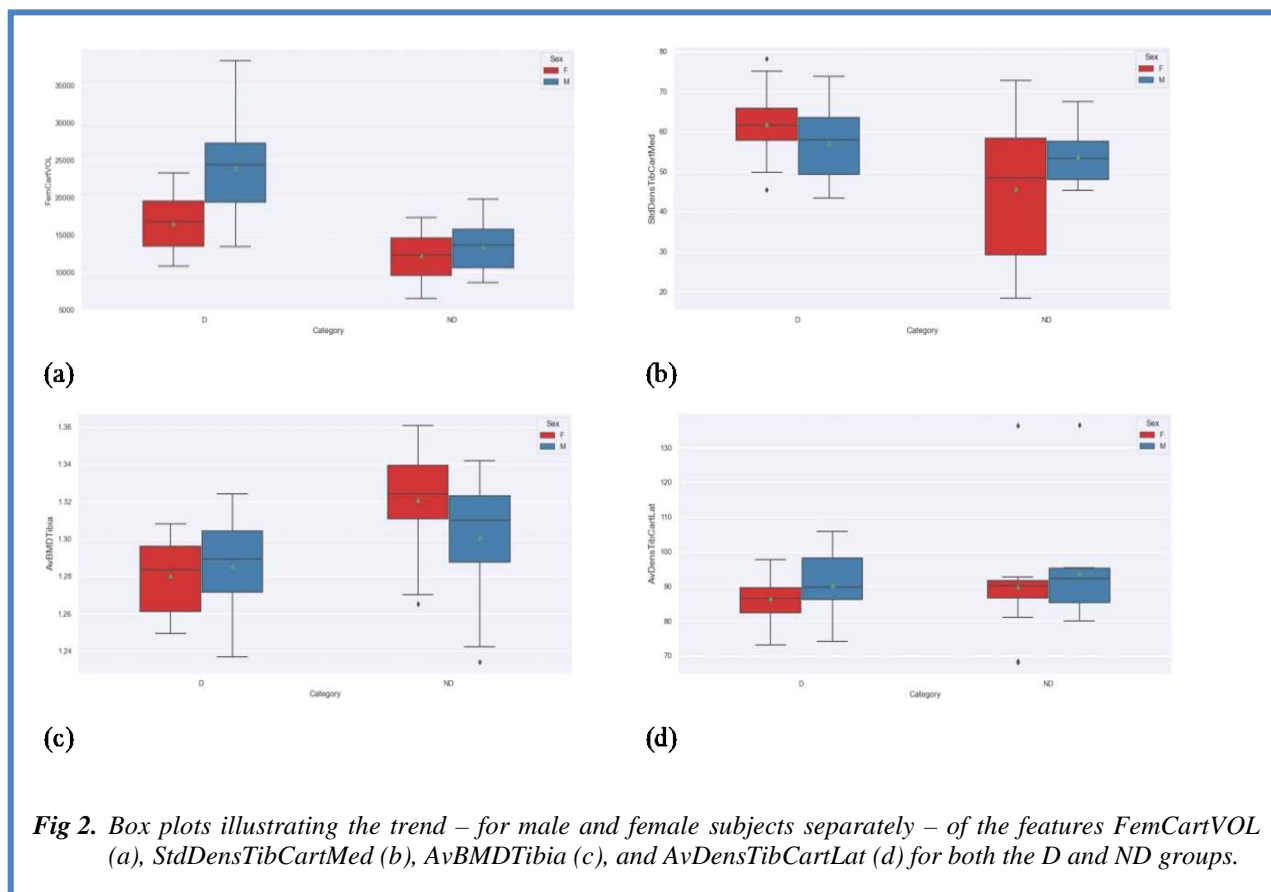
From these results, it has been found volumes and densities values result good discriminants in separating the two classes, with enough accuracy, sensitivity, and specificity. The features that result to be the most influent are almost the same among the two algorithms.

Specifically, the feature importance step showed the volume of the femoral cartilage resulted the most influent between the features when using LR and the second most influent using SVM. This results in agreement with the feature importance study we yet presented,[4] confirming the inference of cartilage swelling due to the increasing water content. Surprisingly, at the state-of-the-art, even if changes on the volumes in cases of cartilage degeneration are well-known, to the best of the authors' knowledge no one have ever used cartilages volumes as an evaluable feature in a ML model for the prediction of OA. STD of the densities of medial and lateral tibial cartilages also demonstrated influent – medial tibial results even the most informative one using SVM – similarly to what we already reported using RF.[4] Moreover, since BMD also has an impact in discriminating D and ND classes, similarly to what showed in our previous research,[4] it is possible to claim again changes in cartilage composition affect the surrounding bones and, therefore, BMD can be confidently used as control parameter to distinguish a healthy cartilage from a damaged one. Degenerated cartilages usually present a greater amount of water with respect to healthy ones, because of the tears of the

***Table 3**. Feature Importance (top 5 features) for Support Vector Machine (k=5).*

Feature	Importance (%)
StdDensTibCartMed	8.80
FemCartVOL	8.46
AvDensPatCart	8.41
AvBMDTibia	8.11
AvDensTibCartLat	8.09

AvBMDTibia: Average BMD of tibia bone; AvDensPatCart: Average density of patellar cartilage; AvDensTibCartLat: Average density of lateral tibial cartilage; FemCartVOL: Volume of femoral cartilage; StdDensTibCartMed: Standard Deviation of density distribution of medial tibial cartilage.

Fig 2. *Box plots illustrating the trend – for male and female subjects separately – of the features FemCartVOL (a), StdDensTibCartMed (b), AvBMDTibia (c), and AvDensTibCartLat (d) for both the D and ND groups.*

collagen matrix tissue cartilage is composed of.[15] This could explain both the relevance of cartilage volume and density in the presented study: the presence of water leads to a change in density and to a swelling increasing the volume.[16,17] Looking at the boxplot (Figure 2), it is possible to notice that femoral cartilage volume seems to present higher values in degenerative patients, with particular enhancement on male subjects, pinpointing the idea of cartilage swelling due to water content. In fact, males generally present larger cartilage volumes with respect to females, and Cicuttini F. et al. (1999)[18] remarked this difference showing the femoral cartilage volume increased in males subject together with their age, subjects who, therefore, seem more prone to develop a degeneration.[18]

Regarding cartilage density, instead, the STD of medial tibial cartilage appears higher in D patients, while the average of lateral tibial seems to present slight differences between the two classes and between males and females. In addition, Figure 2 suggest that the average BMD of tibia is lower in patients with a degenerated cartilage. BMD at both medial and lateral compartment is affected by the presence of cysts and lower joint space narrowing between bones.[19,20] However, according to the literature, this case should lead to higher BMD values which conflicts with the presented findings. Yet, the relationship between BMD and cartilage defects is still under investigation and, in fact, there are studies such as e.g. Abdin-Mohamed M.

et al.,(2009)[21] proving that BMD of tibia do not increase in presence of knee OA; this result is in line with another recent study which illustrated that BMD was lower in moderate-to-severe OA states.[22] As already pointed out in a previous paper, it is possible to claim confidently the ensemble of purpose, experimental strategy (mainly, signal acquisition and processing workflows), and the promising findings obtained represent, to the best of the authors' knowledge, a partially unexplored strategy in this field, which sets this study apart from others. Moreover, as already we claimed,[4] there were no studies which presented and evaluated the predictive power of similar 3D features extracted on MRI and CT data of the knee joint. This particular case is confirmed even by several recent reviews which proved evidence these types of features were not found in previous screenings.[23,24]

Consequently, we will briefly discuss, in the following of this section, papers in the fields with a similar objective, still focusing on the predictive power of features for effective/potential classification studies.

For instance, in 2020 Jafarzadeh and co-workers presented a preliminary study whose aim was to assess if both clinical and imaging features of OA could help to predict knee replacement over a 7-year period, including knees with and without radiographic OA.[25] The authors combined multiple ML algorithms to develop a predictive model able to provide the highest predictive accuracy; the developed model demonstrated

MRI features (such as cartilage morphology, presence of bone marrow lesions) improved prediction of knee replacement in knees without radiographic OA.[25] Later, the authors investigated in a further paper if a similar group of MRI-defined OA features could explain anterior knee pain (AKP) in individuals with, or at risk for, knee OA; in particular, the focus was on the relation between AKP and MRI-based patellofemoral and tibiofemoral OA-related features. From the outcomes of the investigation, it appeared (after a regression analysis) that patellofemoral OA-features, but not tibiofemoral OA-features, were associated with AKP (in particular, lateral and medial full-thickness patellofemoral cartilage damage, and lateral bone marrow lesions).[26] Other studies have investigated additional parameters, such as raw radiographic data, physical examination, patients' medical history, anthropometric data and, only optionally, a radiologist's statement (Kellgren-Lawrence grade), to predict the progression of OA disease, jointly with the current OA severity, using deep convolutional neural networks and gradient boosting.[27]

Another study used LR to predict risk and time to total knee replacement of an osteoarthritic knee, identifying which features are most related in accelerated knee OA within a dataset with several features coming from the OsteoArthritis Initiative (OAI) cohort, which include imaging, biochemical, genetic and risk markers of knee OA. The results of this study showed that the most involved features included radiographs, bone marrow lesions of the medial condyle on MRI, hyaluronic acid injection, performance measure, medical history and knee-related symptoms.[28] A similar study also used a subset of the OAI cohort database to develop ML prediction models and to identify important risk factors which contribute to the prediction of knee OA. A robust feature selection was provided and SVM, K-Nearest Neighbor, eXtreme Gradient Boosting, LR, Decision Tree and Random Forest algorithms were applied on this set of chosen features (that include patient symptoms, medical history and medical imaging outcome like the presence of osteophytes and joint space narrowing). Final results indicate LR and SVM as the best performing models, due to their high suitability on small datasets.[29] The same authors in a more recent study extended the knowledge investigating a novel fuzzy feature selection methodology.[30] They analyzed the data (among which, as anticipated, there are no 3D features similar to those object of this paper) of 3872 subjects extracted from a public database demonstrating a larger amount of the most informative features belongs to three categories (namely, subject characteristics, symptoms and physical exam). When fed to several ML algorithm (the feature selection results were tuned for each algorithm), the authors found promising scores (however, considering SVM, one of the best ones, the scores demonstrated less promising than those showed in this paper or

comparable to the best one achieved in the previous paper,[4] suggesting this methodology could represent a promising example of increasing the understanding of the rationale behind the decision-making mechanism of the selected ML model and the impact of the used risk factors on the prediction output.

Although this paper presented several promising findings, these results are not conclusive, since few limitations must be considered. Firstly, the main limitation consists in the restricted number of patients considered: ML models will be more accurate and reliable with an increased number of samples, and this also would allow the use of more complex models. Moreover, some inaccuracies due to the manual process of segmentation and to personal (subjective) decisions could be present. Image quality also affects the extracted data and therefore the final results.

In conclusion, the presented findings have shown volumes and densities of cartilages can be relevant to predict cartilage degeneration with good performances results; therefore, these features can be part of a set of new 3D features to which look deeply into in case of suspected cases OA or knee related problems.

List of acronyms

AKP - anterior knee pain
BMD - bone mineral density
CV - cross validation
D - Degenerative
HU - Hounsfield unit
LASSO - least absolute shrinkage selection operator
LOO - Leave-One-Out
LR - logistic regression
ML - machine learning
ND - non-degenerative
OA - osteoarthritis
OAI - osteoarthritis initiative
STD - standard deviation
SVM - support vector machine

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