Multivariate diagnostic model for osteoarthritis highlights the importance of osteoclastogenesis and expression of interleukin 1 receptors

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Introduction

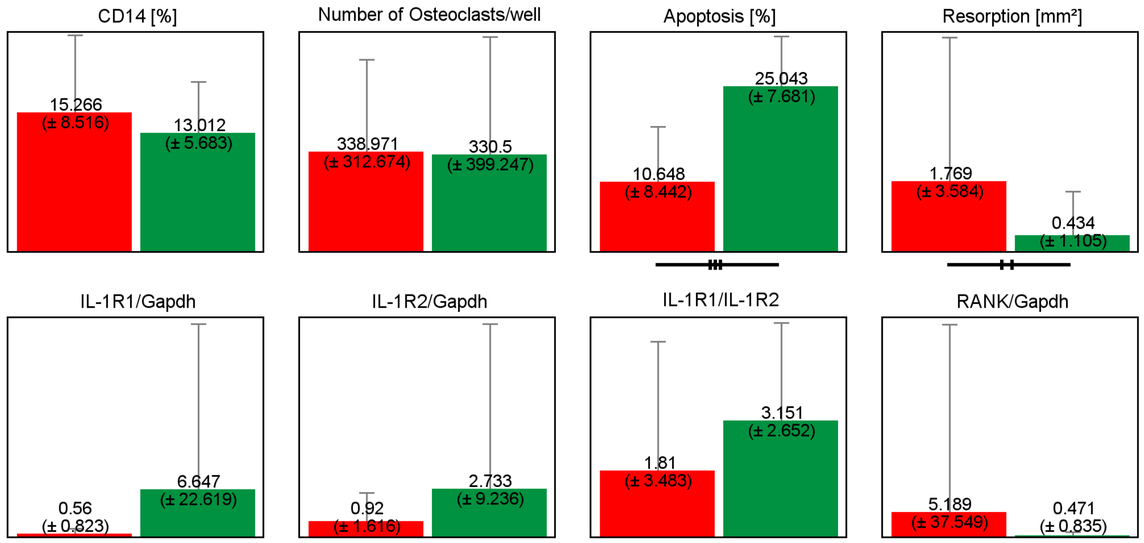
Bone is a central element in the pathophysiology of degenerative and inflammatory arthropathies. Subchondral bone sclerosis, bone cysts and osteophytes are hallmarks of the osteoarthritis (OA). There is indirect evidence implicating osteoclasts (OCs) in the pathogenesis of OA. The involvement of OCs in bone and joint destruction has been confirmed, yet their role in disease onset and progression has not been previously addressed. We have observed that the capacity for in vitro osteoclastogenesis varies widely in a normal human population, distinguishing two subgroups, high and low differentiators, regardless of age, gender, weight, or other demographic variables. We hypothesize that variations in osteoclastogenic capacity in OA population could underlie variation in predisposition for this disease and its severity.

Aim of study

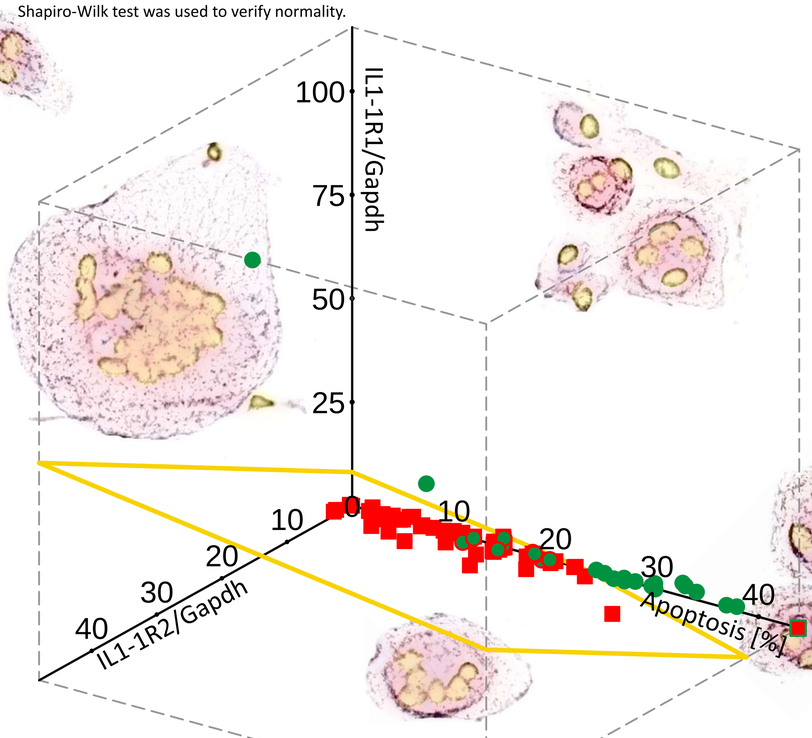
In this study we explore the hypothesis that the osteoclastogenic phenotype and expression of interleukin 1 receptors could be associated with the presence of OA. Our aim is to investigate, using modern data mining techniques, the possible multivariate relationships between osteoclastogenic characteristics and protein expression in OA patients compared to a cohort of self-reported normal individuals to develop a well-performing diagnostic model.

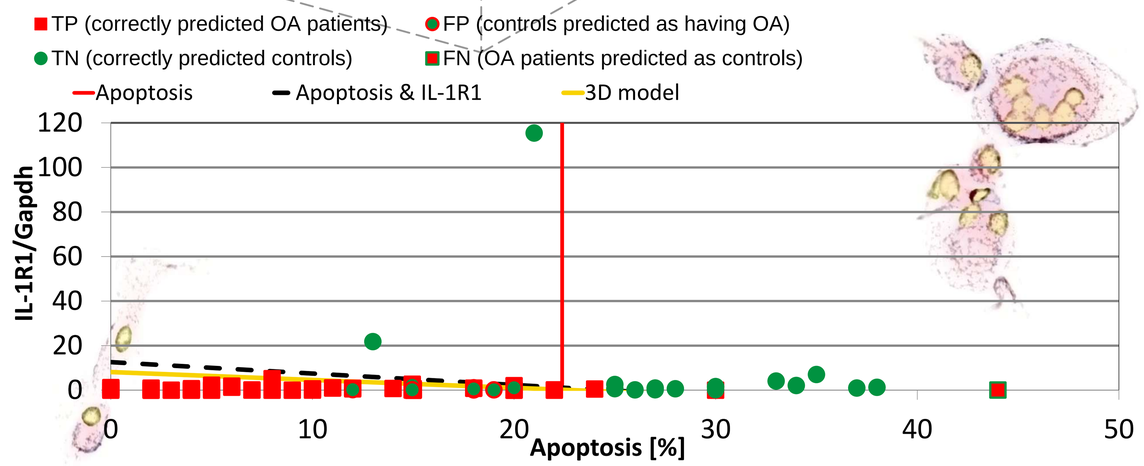
Demographics

	OAs	Controls
Gender (F/M)	48/20	16/10
Age	68 ± 9 years	65 ± 6 years
Height	164 ± 8.5 cm	164 ± 9.6 cm
Weight	82 ± 20 kg	74 ± 18 kg



Statistical analysis showing the difference in mean values between the OA (red) and control (green) groups for the statistically significant markers. * P value < 0.05, ** P value < 0.01, *** P value < 0.001; T-test was used for normal variables, otherwise the non-parametric Mann-Whitney test was used; Shapiro-Wilk test was used to verify normality.





Methods

Cohorts of 68 patients with OA and 26 self-reported healthy donors were investigated for OA markers. Peripheral blood mononuclear cells were assayed for CD14 expression and induced to differentiate into osteoclasts *in vitro*. We assessed the number of the osteoclasts (OCs), OC resorptive activity and apoptosis, and expression of RANK, IL-1R1 and IL-1R2 proteins. A *ridge logistic regression* classifier capable of discriminating between OA patients and controls was developed and evaluated. To ensure statistical validity, we imposed repeated 10-fold cross validation test protocols, and we measured the accuracy, sensitivity and specificity of the model. We also performed classical statistical analysis to validate the significance of the univariate markers.

Results

We found that OC parameters (in particular OC apoptosis) and expression of IL-1R1 and IL-1R2 can be used to build a well-performing multivariate diagnostic model for OA. Our regression model provides strong diagnostic input, with cross validation-based accuracy of about 87%. The multivariate model provides a significant improvement ($p < 0.001$) compared to the best-performing univariate model, indicating that OC parameters and expression of interleukin 1 receptors provide complementary diagnostic information.

	100 x 10 cv			Self check		
Inputs	Accuracy	Sensitivity	Specificity	Accuracy	Sensitivity	Specificity
Apoptosis	83.8% (±0.7)	95.4% (±0.8)	53.4% (±1.6)	84.0%	95.6%	53.8%
+ IL-1R1	85.5% (±0.9)	94.9% (±1.1)	61.0% (±1.8)	86.2%	95.6%	61.5%
+ IL-1R2	86.8% (±1.0)	96.5% (±1.4)	61.5% (±0.9)	88.3%	98.5%	61.5%

Conclusions

Our study not only demonstrates the feasibility of building an accurate diagnostic model, but also suggests underlying relationships. Our modelling indicates that patients with OA have an enhanced capacity to generate OCs from peripheral blood mononuclear cells *in vitro*. These results can be explained by the reduced apoptotic potential of the mature osteoclasts, and may relate to alterations in the expression of IL-1R1.

IODA - In vitro Osteoclast Differentiation in Arthritis

The work is a part of a large, multi-institution, and multi-year project called IODA. Our long-term goals are:

- establish osteoclastic parameters strongly related to presence and severity of bone and joint destruction
- determine whether these biomarkers could be used as predictors of patient progression and responsiveness to different treatment regimens
- identify new targets for development of antiresorptive therapies specifically aimed at arresting inflammation-induced bone loss.

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