Phenotypes of osteoarthritis: current state and future implications

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ABSTRACT

In the most recent years, an extraordinary research effort has emerged to disentangle osteoarthritis heterogeneity, opening new avenues for progressing with therapeutic development and unravelling the pathogenesis of this complex condition. Several phenotypes and endotypes have been proposed albeit none has been sufficiently validated for clinical or research use as yet. This review discusses the latest advances in OA phenotyping including how new modern statistical strategies based on machine learning and big data can help advance this field of research.

Introduction

Osteoarthritis (OA) is among the most prevalent and debilitating chronic diseases worldwide, affecting predominantly older adults (1, 2). There has been significant effort to develop therapies to improve care for OA patients both from the symptomatic perspective and from the point of view of structure modification. Despite that, no therapies have been proven to modify disease progression or proven to be highly effective for symptomatic relief, other than joint replacement for advanced disease, leading to profound disappointment among researchers, patients and clinicians.

The contemporaneous evidence-based management of OA is based on non-pharmacological and pharmacological therapies, with surgical intervention reserved for patients with severe disabling symptoms who have not improved with non-surgical interventions (3). However, despite numerous treatment options being available, outcomes for patients with OA are usually suboptimal and patients remain vulnerable to the clinical consequences of the disease on pain and physical function (4). An important aspect of OA is its extraordinary interpatient variability in clinical and structural manifestations (5, 6). This heterogeneity may be one of the major factors associated with the complexity of OA and with the difficulties to identify one-size. fits-all therapeutic strategies.

Major advances in the physiopathology and manifestations of OA have occurred in the last decade, revealing the variety of potential molecular and cellular changes that can be involved in the joint destruction process. It has been demonstrated that all joint tissues can be affected (7), which occurs in different extents across patients and results in an array of possible structural OA manifestations (*e.g.* variable degrees of inflammation, meniscal lesions, bone damage, etc.). In addition, the pain experience can be caused by different factors including the peripheral joint pathology and extra-articular sources of pain such as psychosocial factors and neural mechanisms (8). New therapies have been developed that target pain but not structure including inhibitors of nerve growth factor (NGF) such as the anti-NGF monoclonal antibody tanezumab (9, 10). Interventions targeting many of these structural pathologies and pain mechanisms have been tested in trials but none to date have been approved as structural or disease modifying therapies.

One reason for the failure of clinical trials testing therapeutics intended for structure modification in OA is that it is unclear at present which patients would be most suitable for a specific therapy. For example, the failure of bisphosphonates to slow OA progression might have been due to enrolling any patient with symptomatic OA rather than selecting patients with greater subchondral bone turnover (11). In order to address the heterogeneity of OA to improve clinical research and trials, a new model of understanding OA based on a phenotype-guided approach is needed. Recently, a significant research effort

has emerged aimed to define a classification of OA phenotypes for the purpose of better identifying individuals at higher risk of progression and to better delineate OA subpopulations caused by distinct risk factors and disease mechanisms that would be suitable for targeted treatment and prevention strategies.

Other medical fields are more advanced than OA when it comes to disease phenotyping such as chronic obstructive pulmonary disease (12) and heart failure (13). A classification of phenotypes has been achieved in these fields, defining disease subtypes within the spectrum of the condition. In this regard, such classifications are only relevant and clinically useful if they can inform on differences in underlying pathophysiology, clinical outcomes or management. For example, heart failure is recognised as being divided into two main types according to a patient's left ventricle ejection fraction (*i.e.* percentage of blood that comes out of the heart with each contraction), which can be reduced or preserved and is associated with differences in systemic and local mechanisms, risk factors, natural history and treatment options (14). Another example is the field of oncology. Diseases such as breast cancer used to be seen as the same condition across different patient groups. It is now known that breast cancer is a heterogeneous condition with varied molecular pathophysiology, such as the presence/absence of biomarkers including hormone-receptors and the HER2 protein (15). Patients are now treated and have their prognosis estimated according to these biomarkers which delineate disease subtypes with particular behaviors. In knee OA, for example, clinically distinct subtypes exist such as medial and lateral tibiofemoral OA and patellofemoral knee OA, and potentially many others. However, the understanding of how this affects treatment decisions and prevention strategies is still in its infancy. Identifying specific OA phenotypes and endotypes can inform both prognosis and guide therapeutic development for this prevalent disease, with the potential of positively impacting patient care. This review summarises the latest progress on phenotyping/endotyping OA research and includes a discussion on novel methodologies for phenotyping based on machine learning and big data.

Approaches for OA phenotyping

A phenotype can be understood as the composite observable characteristics of an individual that result from genetic combined with environmental factors. Subgroups of patients that have similar clinically observable characteristics are considered to represent a phenotype. Division of patients into discrete subgroups or subtypes is sometimes referred to as stratification. Prognostic phenotyping is the identification of subgroups that are more likely, within a specified period of time, to reach a specific outcome of interest (*e.g.* disease progression defined by deterioration in joint structural features and worsening pain) (Fig. 1). Prescriptive phenotyping aims to define subgroups more likely to respond to a specific intervention with an outcome of interest (*e.g.* improved pain or function). Identifying subgroups by prognostic and prescriptive phenotyping (*e.g.* using prediction models) is necessary to meet the goals of precision medicine, defined as "treatments targeted to the needs of individual patients on the basis of genetic, biomarker, phenotypic, or psychosocial characteristics that distinguish a given patient from other patients with similar clinical presentations" (16).

Another concept that has emerged from phenotyping studies in chronic conditions such as asthma is the term "endotype" (17). Unlike phenotypes, which are based on clinical characteristics that are not necessarily connected to an established pathophysiologic mechanism of disease, an endotype "is a subtype of disease defined functionally and pathologically by a molecular mechanism" (17). It is important to note that a given OA phenotype (*e.g.* medial tibiofemoral OA) may be common to multiple endotypes (*i.e.* different mechanisms leading to the same manifestation). The importance of identifying endotypes for targeted treatment has gained much attention particularly from the point of view of drug discovery, where identifying the right target is key for success.

How to best subset OA into phenotypes and endotypes and whether certain subsets are of any clinical value is an important issue that has not yet been fully addressed but is under active investigation. A commentary was written in 2009 (18) by three notable figures in OA research in response to an article suggesting that "primary" or idiopathic OA could be divided into subsets consisting of genetic defects, menopause-associated estrogen deficiency, and aging (19). The authors of the commentary, Ken Brandt, Paul Dieppe, and Eric Radin, eloquently argued that dividing OA into primary and secondary subsets is not useful since "all OA is secondary" and that any attempt to subset OA had to take into account the fact that OA is largely a condition driven by the response to mechanical stress on the joint. They suggested that subsetting OA should be done on the basis of the mechanical abnormalities responsible for OA in a group of individuals that could include joint trauma, neuromuscular factors that affect the ability to absorb loading, congenital or developmental anatomic abnormalities causing joint incongruities or postinfectious. They also noted that it will be important to consider the large number of confounding variables involved.

Like other chronic heterogeneous conditions, there are multiple genetic and environmental factors that increase the risk of developing the joint changes characteristic of OA, clinical manifestations of pain and loss of function, and progression to end-stage disease (20, 21). There is a critical need to accurately define the various factors that could contribute to phenotypes and subgroups of OA from a large number of potentially important variables (Fig. 2). It is becoming clear that simply defining OA phenotypes based on risk factors (for example posttraumatic OA, obesity-related OA, age-related OA, postmenopausal OA, genetic OA, mechanical OA) is far too simplistic. Many individuals have more than one risk factor and, as already noted in the case of mechanics, there are shared mechanisms among risk factors with mechanical factors likely contributing to all OA. For phenotyping to be suc-

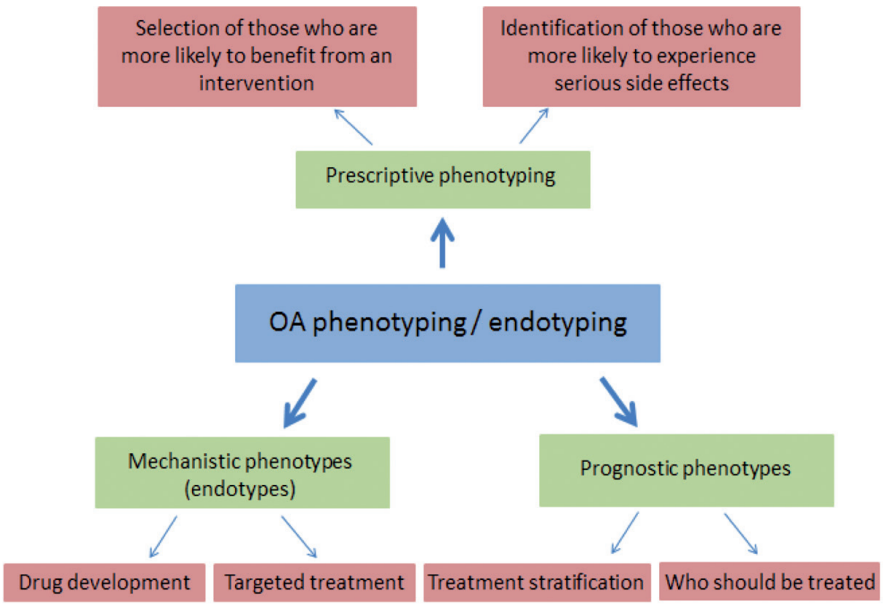

Fig. 1. Examples of different types of phenotypes and endotypes and their potential uses.

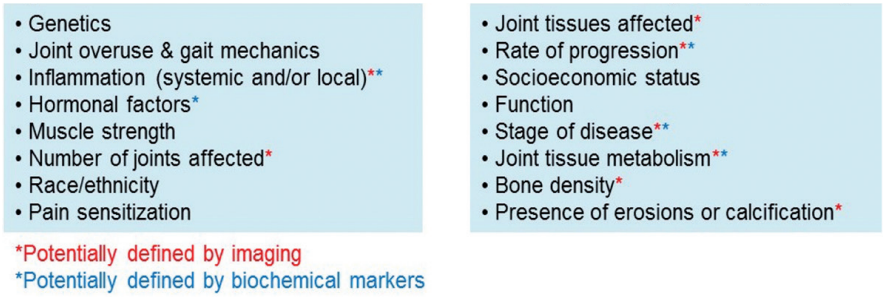

Fig. 2. Factors and manifestations that could contribute to OA phenotypes/subgroups.

cessful, datasets with a diverse set of variables and well-defined outcomes are needed. This may include various socio-demographic factors and clinical, imaging, and biochemical marker measurements in addition to mechanical measures. In some cases, genetic and "omic" data (transcriptomic, proteomic, metabolomic, microbiomic), or data from histologic analysis of tissue samples may be needed that will allow for more precise phenotyping.

Various types of analysis can be used to define phenotypes using clinical and biological data, which are discussed below in the "*Big data/ machine learning for OA phenotyping*" section. Latent class analysis was used to cluster clinical and imaging data from the Osteoarthritis Initiative (OAI) database and four clusters were identified that represented mild OA, mild OA with areas of denuded bone that the authors called "classical OA", and two severe OA groups of "aggressive OA" with larger areas of denuded bone and a high prevalence of progression with one of the two latter groups exhibiting more lateral involvement (22). Variables that were significantly different among clusters included BMI, alignment, and history of trauma which again emphasises the importance of mechanics in OA.

A recent systematic review of OA phenotypes published in 2016 examined the current evidence for groups of variables that would distinguish OA phenotypes (23). This review identified six phenotypes from 24 published studies that included: 1) chronic pain phenotype with central sensitisation; 2) inflammatory phenotype; 3) metabolic syndrome phenotype; 4) bone and cartilage metabolism phenotype; 5) mechanical (malalignment) phenotype; and 6) minimal joint disease phenotype. It is not clear how meaningful these phenotypes might be clinically or if they could be used for attempts at stratifying patients for clinical trials. A "metabolic syndrome phenotype" may simply represent individuals with obesity and OA. The association between metabolic syndrome and OA has not been well established and, after controlling for BMI, the correlations between OA and features of the metabolic syndrome are not significant (24). As mentioned above, all OA has a mechanical component and so it is unlikely to represent a distinct phenotype and all OA has involvement of bone and cartilage also making it unlikely to represent a distinct phenotype.

There has been much interest in defining an inflammatory phenotype or endotype in OA as well as a bone phenotype. Methodologies that can be used to better define an inflammatory phenotype include imaging (*e.g.* ultrasound or MRI) to detect synovitis (25, 26), blood levels of high sensitivity CRP and IL-6 (27-29), soluble macrophage markers (CD14 and CD163 in the synovial fluid and CD163 in serum) (30) and transcriptome data from peripheral blood leukocytes (31). Defining a bone phenotype would likely include imaging of osteophytes and subchondral sclerosis using radiographs and bone marrow lesions detected by MRI. However, since these are common features of OA, it is difficult to envision how they would define a distinct bone phenotype. Biomarkers of bone turnover such as urinary CTX-1, urinary NTX-1, serum PINP, and serum osteocalcin could be used to provide additional data on bone turnover (32, 33). Attempts to utilise inflammatory and bone phenotypes for targeted therapy, as well as the use of additional biomarkers, will be discussed below.

Current state of OA phenotyping

Endotypes/mechanistic subgroups

As discussed above, endotypes are disease subtypes resulting from differences in specific pathobiological mechanisms. Research so far has suggested the existence of a few possible endotypes that will be discussed in this review. However, there may be many others that are not included herewith. In this regard, pre-clinical studies are key

to understand how different etiologies such as post-traumatic and age-related OA may be associated with differences in disease pathophysiology and expression.

A structural endotype related to ageing or cell senescence has been suggested by a few studies, primarily in pre-clinical models (34, 35). Not only greater OA severity but differences in gene expression and pathways represented by these genes have been observed in older mice compared to younger mice in an injury-induced OA model (36), suggesting that the same OA model may result in different phenotypes depending on age. Defining a senescence endotype in human OA may be important as drugs for treatment of OA called senolytics are being developed that target and kill senescent cells in the joint (37).

There is an active interest in defining an inflammatory endotype that would have a shared mechanism related to a specific cytokine that could be targeted for therapy. Given the role for cytokines in OA this could be of value in advancing OA treatment as well. Supporting the existence of an endotype with increased inflammatory characteristics, Attur *et al*. showed the existence of two subgroups of knee OA patients with different gene expression profiles in peripheral blood leukocytes. In this study, clinical and structural outcomes were worse in the subgroup with higher production of IL-1β compared to the subgroup with lower levels (31). However, whether targeting specific anti-cytokine therapies to an inflammatory OA phenotype would be useful remains unproven. A recent phase 2 trial of an anti-IL1α/β antibody lutikizumab in patients with knee OA and synovitis detected by MRI showed limited improvement in pain scores and no change in synovitis in the treated group compared to placebo controls (38). This does not necessarily mean that targeting the inflammatory phenotype will not be successful but rather that inhibition of IL-1 may not be the right target. Other potential endotypes include ones associated with metabolic factors (39, 40) and hormonal dysregulation (41, 42).

Pain endotypes have also been investigated. Individuals with or at risk of knee OA who displayed greater features of sensitisation such as pressure pain sensitivity and temporal summation experienced worse clinical outcomes in cross-sectional studies (43-45) and were more likely to develop incident persistent pain after two years in a recent longitudinal analysis (46, 47). Presence of psychological characteristics such as pain catastrophising has additionally been shown to negatively influence pain outcomes (48). Identifying individuals with those characteristics and tailoring pain therapies to each patient's needs may be vital to achieve better clinical outcomes.

Prognostic subgroups

Heterogeneity in long-term OA outcomes has been highlighted by a number of recent studies using trajectory analysis. This statistical methodology uses a data-driven approach to identify clusters of people following different trajectories in a given outcome over time. Using trajectory analysis, we have recently shown that a minority of knee OA individuals (around 1 in 10) experience medial cartilage thickness loss assessed on MRI over 2 years (49), which is consistent with other studies using radiographs for outcome assessment (50, 51). This subgroup had greater odds of experiencing concurrent pain progression and requiring total knee replacement. Importantly, this subgroup could be identified with relatively good accuracy by a set of baseline clinical and disease characteristics. Other studies have also defined prediction models to identify knee OA progression (52-54) and incident knee OA with fast progression (55); however, there were different definitions of progression in these studies, such as an increase in Kellgren Lawrence grade (KLG) (52) and a reduction in medial joint space on radiographs (54). It should be highlighted that prediction models in most of these studies used characteristics that can be easily obtained through the clinical history, physical examination or radiographic assessment to facilitate their use in clinical practice or research using clinical datasets.

Other subgroups have been defined according to trajectories of clinical progression (56-59). Clear differences in prognosis have been shown, with the majority of individuals following a stable course over several years with mild to moderate symptoms, while others experience a more severe disease course with persistent intense pain and disability or significant decline over a few years. We have previously summarised these studies as well as the baseline characteristics that more frequently predicted worse trajectory outcomes (60). These included high BMI, lower education, more severe symptoms and radiographic disease at baseline, psychological factors (use of passive coping strategies and depression) and presence of other comorbidities including concomitant hip pain (60).

Defining individuals most likely to develop OA and the subgroup of individuals with OA most likely to exhibit structural progression within a selected time frame (rapid progressors) for both observational studies and clinical trials is extremely important. Latent class analysis of MRI variables collected at baseline from individuals without radiographic OA in the Multicenter Osteoarthritis Study, including cartilage damage, bone marrow lesions, meniscal tears, meniscal extrusion, synovitis, and effusion, was used to determine the odds of developing incident radiographic OA in 4 subgroups (61). As might be expected, those in the subgroups with more severe lesions were at greater risk than those with mild lesions. Radiographic criteria for progressor *versus* non-progressors by measurement of change in joint space width on plain films includes the OARSI-OMERACT criteria (62). These criteria were used to select progressors and non-progressors for a urine metabolomics study of participants in the Intensive Diet and Exercise for Arthritis (IDEA) trial that analysed the metabolomics data using OPLS-DA, a commonly employed method for analysis of such high dimensional multicollinear data (63). OPLS-DA distinguished the metabolite profile of radiographic progressors from non-progressors and found a panel of metabolites that associated with radiographic progression (63).

Biochemical markers, measured in serum, plasma, urine or synovial fluid, represent measures that can provide important information for phenotyping. To date no single marker has been found to be sufficient for diagnosis or prognosis in OA. A study from the Foundation for the NIH (FNIH) OA biomarkers Consortium, examined 18 biomarkers measured at baseline, 12 and 24 months in 194 participants from the OAI study (64). Eight catabolic biomarkers (urine (u) c-terminal crosslinked telopeptide type II collagen (uCTXII), uC2C-Human Urine Sandwich Assay (HUSA), type I collagen cross-linked N-telopeptide (uNTXI), c-terminal crosslinked telopeptide of type I collagen α and β (uCTX1α and uCTXIβ, respectively), serum (s) hyaluronic acid (sHA) and c-terminal crosslinked telopeptide type II collagen (sCTXI)) and one anabolic marker, N-terminal pro-peptide of collagen IIA (sPIIANP), were shown to be the best predictors of pain and radiographic progression over 48 months. These and newer biomarkers under development may be useful to define phenotypes most likely when used in combination with other data such as imaging and clinical data.

Treatment response subgroups / prescriptive phenotyping

There is an increasing understanding and awareness that optimal effects of OA treatments might be attained by personalising care according to clinically relevant characteristics, which is a goal of precision medicine. Clinical trials can be used to investigate variations in the extent patients improve or fail to improve with a given treatment, while observational studies cannot differentiate the effect of the intervention from the disease natural history without an appropriate control. Most analyses investigating subgroup effects of interventions in OA have been post-hoc and exploratory. For example, there is a great interest to identify subgroups of patients in whom biomechanical interventions may be more effective, which has been highlighted as a research priority by the National Institute for Health Care and Excellence (65). It has been shown, in an underpowered analysis from a clinical trial, that unloading shoes alleviate knee pain in a significantly greater extent in patients with more severe structural disease (KLG 3 or 4) than those with milder disease (KLG 2) compared to conventional shoes, and that this may be mediated by a decrease in peak knee adduction moment (66). Baseline disease severity, represented by higher baseline knee pain scores (at least 70 in a 0–100 scale), was also significantly associated with a greater response to intra-articular glucocorticoid injection after up to 4 weeks compared to placebo injection (67).

There is also interest in determining if a bone phenotype exists in OA that might be responsive to agents that act on bone such as the antiresorptive bisphosphonates. Selecting OA patients with bone marrow lesions in a clinical trial of the bisphosphonate zoledronic acid resulted in reduction in pain and the size of the bone marrow lesions in the treatment group compared to the placebo group over 6 months but not over 3 or 12 months (68). An individual patient data meta-analysis is underway to investigate whether particular patient subgroups are more likely to benefit from bisphosphonates than others (69).

Trajectory analysis has been used to investigate heterogeneous response following exposure to interventions (70). Lee *et al*. found four patterns of response to exercise over 12 weeks among knee OA patients, with over 70% of patients displaying early improvement while a minority experienced delayed improvement (15%) or no improvement (10%). Individuals with poorer physical and psychosocial status at baseline were more likely to follow an unfavourable trajectory. These findings highlight that early treatment is vital to reduce pain and disability and suggest that appropriate patient stratification may be needed to triage patients according to their likelihood of improvement with a given intervention. In other words, it would be helpful for clinicians to be able to differentiate patients who are likely to improve with safer and cheaper interventions, such as exercise and diet, from those who may need additional interventions (likely more complex and expensive) or a higher level of care. Currently, new OA models of care, characterised by a multi-disciplinary and holistic approach to personalise the therapeutic plan, have been implemented in several countries (71). At present, a decision support tool to identify persons with OA who would benefit the most from those programmes and who would be best targeted by specific interventions is lacking.

Prescriptive phenotyping can also be used to identify individuals more likely to experience serious side effects from interventions. A subgroup of patients receiving anti-NGF experience more rapid progression of their structural changes which is a serious concern that could limit its use unless those at higher risk of this adverse effect can be identified before treatment is initiated (72). A recent exploratory study attempted to do just that using a panel of serum biomarkers in an attempt to phenotype participants in the tanezumab trials who were most at risk of developing a rapidly progressive OA phenotype (73).

Big data / machine learning for OA phenotyping

Data sets in medicine are becoming ever larger, and in order to utilise these vast amounts of data, researchers need to look beyond traditional statistical methodology. Enter machine learning, where a computer learns from a variety of examples, eventually "learning" to classify new information based on these inputs (74). There are many names for machine learning methodologies, including artificial intelligence, artificial neural networks, deep learning, support vector machines, decision trees, etc. Machine learning algorithms can be supervised, unsupervised, or somewhere in between.

Only recently have these methodologies begun to impact the world of OA research (75). A variety of machine learning methodologies initially utilised primarily for image analysis in OA (76-78), are being increasingly applied to large datasets, often including detailed imaging, biochemical biomarker, and genetic/genomic information, for the purpose of identifying important OA subgroups (79-82). Of course, no meth-

od is a panacea, and analysis of large datasets can also generate seemingly meaningful results which are, in fact, spurious artifacts. As datasets become ever larger, and incorporate more complex objects, it becomes increasingly important to link confirmatory analysis with the scientific discovery process, while incorporating study design and subject area expertise.

Unsupervised learning

There are many alternative approaches to the validation and discovery of novel phenotypes (*e.g.* latent class methods, Bayesian approaches, factor analysis, etc.). A variety of tools are available for exploring clusters within data, all of which have positive and negative aspects, particularly in the high dimension and relatively low sample size setting (83). For example, cluster analysis (*i.e.* data segmentation) attempts to group items into clusters, such that items within a cluster are more closely related than those in different clusters. Once identified, these clusters are frequently arranged into a hierarchy to represent similarity among clusters. Principal components analysis and related methods attempt to reduce dimensionality in a dataset, thus providing more interpretable clusters, similar to the goals of latent class analysis (a subset of structural equation modelling) and factor analysis. Regardless of methods used, clusters can be readily identified in large datasets; the central challenge is to determine whether identified clusters are actually important in such unsupervised analyses. SigClust is an example of a novel method for hypothesis testing of clusters in high dimensions (84, 85), which can be used in conjunction with subject area expertise to determine whether identified clusters are likely important.

Supervised learning

In contrast to data-driven clustering, supervised machine learning methods are based in hypotheses, but take advantage of the computer's ability to utilise high dimensional data, beyond what is often possible using traditional statistical methods. One approach, described by Marron *et al*., is Object Oriented Data Analysis (OODA (86, 87)). OODA attempts to understand the data structure, determine appropriate data objects, and choose an appropriate analysis for the situation. Whereas in a typical analysis, the experimental unit may be a number or a set of numbers (*i.e.* a vector), OODA allows assessment of more complicated data objects, such as images or large multivariable datasets with repeated observations. Through consideration of all of the variables related to a given observation as a single data object, potential biases related to variable selection are alleviated, while providing a more complete picture using all available data.

Some of the OODA methods developed by Marron and colleagues include Distance Weighted Discrimination (DWD) and the Direction-Projection-Permutation (DiProPerm) test, which can be utilised in the setting where the classes are known, for example when validating previously hypothesised phenotypes, or comparing progressors and non-progressors. DWD is a linear discriminant analysis method allowing maximal separation of data points by class (88), which has been utilised in OA (78, 81), and is particularly suited to cases where the dimension of the data vector exceeds the number of samples (*i.e.* a large number of measurements relative to the sample size). The difference between two distributions obtained using DWD can then be tested for statistical significance using the DiProPerm test (89). DiProPerm ensures statistical specificity of the hypothesis test for two previously defined populations by first finding a separating direction (*e.g.* DWD), then projecting the data and using a one dimensional summary of the separation (*e.g.* the difference of the means. Statistical significance is obtained by a permutation approach, where the class labels are randomly shuffled and the DWD direction and projections are recomputed, giving a null distribution whose quantiles are used to compute *p*-values. This powerful machine learning method treats the overall vector of features as a single data object, so there is no requirement for adjustment for multiple comparisons.

Examples of applied machine learning in OA

Our group has applied DWD and DiProPerm to the publicly available OA Initiative FNIH Biomarkers Consortium dataset to assess differences between non-progressors and progressors by both radiographic (rKOA) and pain criteria (81). We found that, among 597 observations and 73 variables, the grouped baseline MRI variables contributed more (z score range 10.28–11.62) to the difference between progressors and non-progressors than did demographic and clinical variables (z score =1.47) or biochemical markers (z score =2.43). In addition, specific baseline variables (Western Ontario and McMaster Universities Osteoarthritis Index [WOMAC] pain, sPIIANP, and lateral meniscal extrusion) were higher among non-progressors, while uCTX-II, bone marrow lesions, and osteophyte number were higher among progressors; features that might inform phenotypes. In support of the validity of our methods, the published FNIH biomarkers study (64) also found sPIIANP was higher in non-progressors and uCTX-II was the strongest biomarker predictor of progression in the same dataset. The consistency of the results is reassuring, but notably, we were able to identify all of these associations in a single machine learning based analysis, rather than numerous studies focused on one or only a few features.

Strengths and limitations

Machine learning methodologies provide several advantages, including the ability to treat all available data as a single data object in high dimensional space, thereby obviating the need to adjust for multiple comparisons in some cases. All variables, even when there are hundreds or thousands of variables, can be considered together, reducing bias related to variable selection. A single analytic model can simultaneously identify a number of key variables or contributors to outcomes of interest. Limitations include the inherent limitations of the dataset (the analysis is limited to what is available), issues of generalisability, which requires both internal and external validation, and the

need for further analyses to determine the importance of the associated variables. These approaches, as currently described, are akin to genome-wide association study (GWAS) in that they provide several variables (*i.e.* single-nucleotide polymorphisms (SNPs)) of interest, but further "functional" assessments are needed to confirm and characterise the importance of those variables to the disease process both in the discovery cohort and in external populations.

Future directions

The field of OA phenotyping has evolved significantly, with multiple studies aiming to identify phenotypes based on different OA aspects (*e.g.* clinical, structural, laboratory and aetiologic phenotypes) and employing different methodologies. A framework to guide future research is underway and will hopefully help to optimise efforts in this field. As highlighted in this review, efforts in OA phenotype research should focus on one or more of three main goals: identify those individuals at higher risk of progression; identify those more likely to benefit from a given existing treatment; and identify specific pathological processes (*i.e.* disease mechanisms representing specific endotypes) for targeted treatment, potentially with new agents/treatment strategies. Ultimately, all approaches aim to achieve improved clinical outcomes for individual OA patients. In addition, there is a widely recognised discordance between structural involvement and symptomatic disease in OA, and phenotypes are likely to be more helpful if defined according to a specific perspective (*i.e.* structural damage and pain mechanisms) to inform treatment strategies. There is a need to identify those individuals in whom structural and clinical progression are coupled and those in whom they are dissociated. Research investigating phenotypes in other joints such as the hip, hand, foot and spine has lagged far behind that of knee OA and should also be the focus of future studies. Different OA phenotypes are likely to exist in joints with different pathophysiological drivers (knee *vs.* thumb base *vs.* hip), although risk factors that are common to more than one joint may be implicated in a phenotype of multiple joint OA (90).

Most evidence on the presence of phenotypes/endotypes so far come from single or few studies and lack validation. Further research is needed to validate previous findings and to assess their implications for clinically important outcomes and clinical trial design. In this regard, the availability of high-quality data, ideally longitudinal and from different populations, is key for OA phenotyping research. Efforts to combine datasets from existing OA cohorts/previous clinical trials are likely to be helpful by providing larger datasets for the identification and validation of phenotypes. In addition, imaging and/or laboratory biomarkers may be useful to define clinically relevant phenotypes. Nonetheless, to increase the uptake of proposed phenotypes and translation into practice, phenotypes should be recognisable using easy to obtain patient data (either clinical, imaging or laboratory).

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