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The need of a treat to target strategy in OA

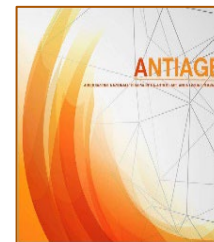


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It Is the Time to Think About a Treat-to-Target Strategy for Knee Osteoarthritis


This article was published in the following Dove Press journal:
Therapeutics and Clinical Risk Management

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- ✓ In the literature, several evidence-based guidelines and recommendations for the management OA are available.
- ✓ These recommendations list the different therapeutic options rather than addressing a hierarchy between the treatments and defining the real target.
- ✓ We suggest a change in our therapeutic strategies.
- ✓ In this editorial, we address this challenge by suggesting that it is time to develop a “treat to target strategy” for KOA.

What have we learned from the management of chronic diseases?

- For many chronic diseases, there are specific targets useful for monitoring disease evolution over time and driving the treatment.
- In diabetes it is crucial to keep within specific limits of blood glucose level or glycated hemoglobin serum level to better control the disease and to prevent complications.
- In osteoporosis the evaluation of BMD and prevalent vertebral fractures drive the treatment target to prevent new osteoporotic fractures.
- In cardiovascular disease, the targets are to maintain normal blood pressure values and normal serum lipid levels as well as to normalize weight
- In RA, the treat-to-target strategy, based on the definition of a specific target, remission or low disease activity, has been successfully developed

The need of a T2T strategy in OA

- The main goals in OA need to be defined.
- Many therapies are now available for OA
- However there is still an urgent need for diagnosis and target biomarkers leading to more concrete treat-to-target strategy.
- This approach could help us to surpass the limits of the international recommendations that are a list of interventions
- A treat-to-target strategy should aim at improving joint pain and quality of life specially in elderly population.
- A T2T strategy may help to find the best combination/sequence of the most appropriate treatments to reach this target for any patient.

The challenge of T2T in OA: what is the ideal target in OA?

- It is not yet clearly defined and standardized
- In clinical trials, usual endpoints are:
 - ✓ pain,
 - ✓ function,
 - ✓ range of motion,
 - ✓ quality of life,
 - ✓ structural evolution progression
 - ✓ even hard outcomes such as delay to TKR

The challenge of T2T in OA: what is the ideal target in OA?

- It is difficult to identify a single target from a structural prospective because the whole joint:
 - ✓ bone,
 - ✓ muscle,
 - ✓ cartilage,
 - ✓ synovia
 - ✓ joint capsule)

This multiple involvement leads to several phenotypes the disease

The challenge of T2T in OA: what is the ideal target in OA?

- Actually no clinical biomarkers are available.
- Regarding imaging:
 - ✓ only radiographic parameters are currently well standardized to evaluate the structural progression
 - ✓ MRI , despite interesting results, does not provide well-standardized assessment tools or parameters

What is the clinical target for knee osteoarthritis therapy?

The use for rheumatoid arthritis of the treat to target strategy has improved the pathology management, so the purpose of the ISIAT expert panel was to introduce the treat to target strategy for osteoarthritis as well.





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Good clinical practice on treat to target strategy in OA

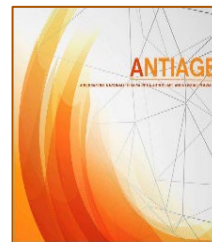


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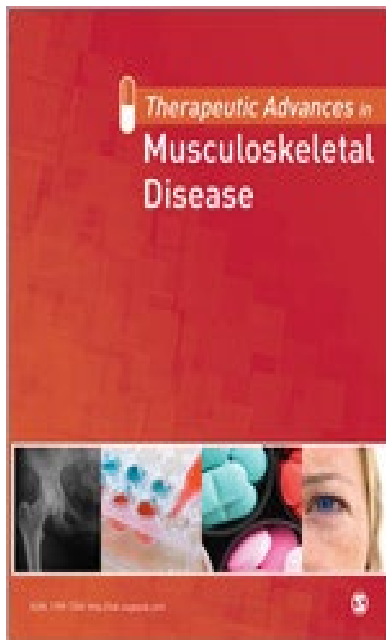


Treat-to-target strategy for knee osteoarthritis. International technical expert panel consensus and good clinical practice statements

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Treat-to-target strategy for knee osteoarthritis. International technical expert panel consensus and good clinical practice statements



RESEARCH QUESTIONS (PICOs)

- Is it reported a strategy to treat to target for knee OA?
NO
- In patients with knee OA which are the most commonly used outcome measures of efficacy/effectiveness, safety and adherence in clinical trials and cohort observational studies? **WOMAC complete score, VAS pain**
- Which are the cut off of level of pain, function and quality of life or combined indexes used at the entry in clinical trials on knee OA? **VAS pain ≥ 4 , WOMAC pain scale ≥ 4 , WOMAC total score ≥ 25**

... it is necessary a common consensus and an addition of cut off levels!

SEARCH STRATEGY (DB)

Patients population:

patients with Knee OA

Inclusion criteria

- Knee OA, RCT, cohort

Search strategy (DB)

P	Knee Osteoarthritis
I	Pharmacological and non-pharmacological interventions
C	-
O	efficacy/effectiveness, safety and adherence
s	RCT, cohort

Literature research
over the last 15 years
170 ARTICLES

MAIN AREAS

>>>>

P > patients

I > intervention

C > control

O > outcome

s > study design

Treat-to-target strategy for knee osteoarthritis. International technical expert panel consensus and good clinical practice statements

Two Overarching principles and 10 recommendations were formulated by the TEP



OVERARCHING PRINCIPLES

1) *The treatment of knee OA must be based on a shared decision between patient and physician;*

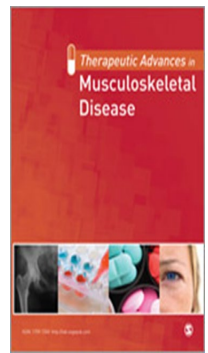
2) *The primary goal of treating the patient with KOA is to maximize long-term health-related quality of life through :control of symptoms, prevention of evolution of structural damage, improvement of mobility and self-management*

Treat-to-target strategy for knee osteoarthritis. International technical expert panel consensus and good clinical practice statements

- ✓ The patient should be encouraged to acquire self-management techniques, and these should include adoption of a healthy lifestyle, cognitive and behaviour skills.
- ✓ The treating team of health practitioners (HPs) should work in cooperation with the patient to foster his/her well-being.

Treatment should control:

- symptoms,
- disease flares/relapses,
- Maximize function,
- improvement of mobility and self-management
- avoid long-term structural damage and disabilities



Treat-to-target strategy for knee osteoarthritis. International technical expert panel consensus and good clinical practice statements

GPC STATEMENTS

LEVEL OF CONSENSUS

(1) The primary target for treatment of knee OA should be a clinical improvement, bringing the patient to the PASS

Strongly in favour

(2) Treatment should begin as early as possible with the diagnosis of symptomatic OA, and include pharmacological and nonpharmacological treatment

Unanimously in favour

(3) All patients should be encouraged to maintain a healthy weight and adopt regular and appropriate physical activity

Unanimously in favour

(4) The management should be evaluated every 3–6 months (depending on the patient symptoms) until the desired target is reached and continued thereafter

Unanimously in favour

(5) Documenting measures of pain, function, physical and mental state, and consumption of painkillers (analgesics, NSAIDs, etc.) regularly, to monitor clinical improvement, adherence, tolerability and safety is recommended

Strongly in favour

Treat-to-target strategy for knee osteoarthritis. International technical expert panel consensus and good clinical practice statements

GPC STATEMENTS	LEVEL OF CONSENSUS
(6) The patient has to be appropriately informed about the treatment options and a shared decision should be made	Unanimously in favour
(7) Modifiable risk factors of OA progression should be identified and managed with patients at the beginning of the treatment and monitored regularly	Unanimously in favour
(8) Comorbidities and concomitant treatments should be systematically screened and managed	Unanimously in favour
(9) The treatment should be adapted according to patient phenotype and disease severity	Strongly in favour
(10) Surgical options should be considered for the appropriate patients	Strongly in favour

(1) The primary target for treatment of knee OA should be a clinical improvement, bringing the patient to the PASS

- The PASS is a clinically relevant cut-off that allows assessment of clinical status of an individual patient, at a given time, by classifying the patient as being in 'an acceptable state' (score \leq PASS threshold) or not (score $>$ the PASS).
- In other words, PASS can be defined as the highest level of different symptoms e.g. pain, PGA, functional improvements beyond which patients consider themselves well
- Thus, it can be considered a clinically relevant treatment target
- the definition of the PASS is anchored to the personal experience of the patient (satisfaction and adaptation to symptoms).

2) Treatment should begin as early as possible with the diagnosis of symptomatic OA and include pharmacological and non-pharmacological treatment

- Early management of KOA is recommended by several guidelines.
- The rationale for this approach is that early interventions could modify the course of the disease, including the pathological anatomy and clinical features of KOA.
- Although pharmacological agents play a key role in symptom relief, there is a growing interest in disease-modifying agents in KOA that could delay disease progression

(3) All patients should be encouraged to maintain a healthy weight and adopt regular and appropriate physical activity

- Therapeutic exercises, particularly low-impact aerobic training, aquatic exercise and strengthening are recommended by several guidelines.
- They are both core treatment and first-line conservative approach for KOA-related pain and disability.
- Pain must be controlled to encourage regular physical activity.
- Changes of appropriate lifestyle should be encouraged as soon as possible, and regular weight control should be included through the introduction of a balanced diet that needs to consider existing comorbidities (e.g. DM, hypercholesterolaemia, hypertension)

(4) The management should be evaluated every 3–6 months (depending on the patient symptoms) until the desired target is reached and continued thereafter

- It has been demonstrated that close monitoring of patient compliance is an important strategy in patient management.
- In particular, pharmacological and nonpharmacological treatments should be scrupulously followed.
- Symptom control can be fast acting (NSAIDs or analgesics) or slow acting (SYSADOAs, exercise or weight loss) agents
- The suggested 3–6 month period to achieve the therapeutic target **OA is a chronic disease**
- Even if the use of SYSADOAs is not recommended practice in North America and the UK, and by OARSI, without doubt, it is supported by various clinical trials and positive experiences in clinical practice.
- The periodic assessment of the disease status allows an effective evaluation of both compliance and effectiveness of the therapeutic strategies.

5) Documenting measures of pain, function, physical and mental state, and consumption of painkillers (analgesics, NSAIDs, etc.) regularly, to monitor clinical improvement, adherence, tolerability and safety is recommended

- The complexity of KOA requires a regular follow up which should be part of the treat-to-target strategy
- Along with painkillers, a multimodal approach should be chosen, including:
 - ✓ early use of nonpharmacological and pharmacological treatments,
 - ✓ targeting inflammation,
 - ✓ preventing sensitization and transition to chronic pain.
- The aim is: to maximize beneficial effects and to delay disease progression.
- Awareness of treatment potential side effects is mandatory
- NSAIDs are associated with risk of GI and CV AEs. For a short-term use, opioids such as tramadol may be considered for severely symptomatic KOA patients.
- The appropriate selection of the patient is crucial

(6) The patient has to be appropriately informed about the treatment options and a shared decision should be made

- The physician and the patient should discuss the condition of the disease
- the physician should explain in detail the benefits of the chosen treatment and its possible side effects.
- The doctor must listen to the concerns and worries of the patient and address him/her in lay language.
- By this method, the patient and his doctor can co-decide on the most appropriate treatment.
- A scrupulous information will raise patient's awareness and aid him in early recognition of side effects.

(7) Modifiable risk factors of OA progression should be identified and managed with patients at the beginning of the treatment and monitored regularly

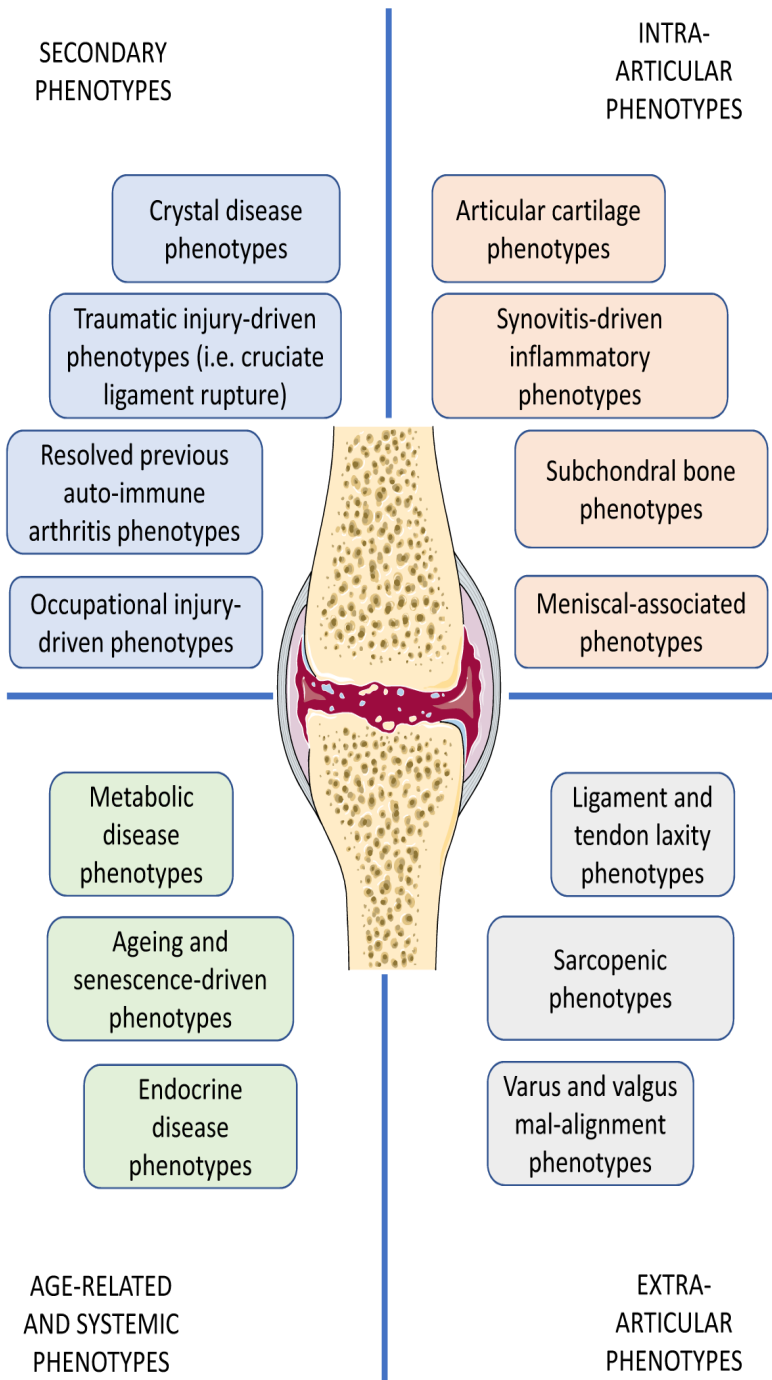
- The management of modifiable OA risk factors (e.g. weight loss) and regular resistance-training exercises is crucial in patient's management
- Among the OA initiative patient population, overweight was identified as a risk factor for developing bone-marrow lesions and joint effusions
- The data from CHECK also suggest that BMI may play a role in the reduction of range of movement and in overall activities
- A weight loss over 5% may improve symptoms and function, even in advanced stage of the disease.
- Low-energy diet may be helpful to maintain weight loss
- Obesity is also associated with sleep apnoea and steatohepatitis, which might complicate surgery options in these patients

(8) Comorbidities and concomitant treatments should be systematically screened and managed

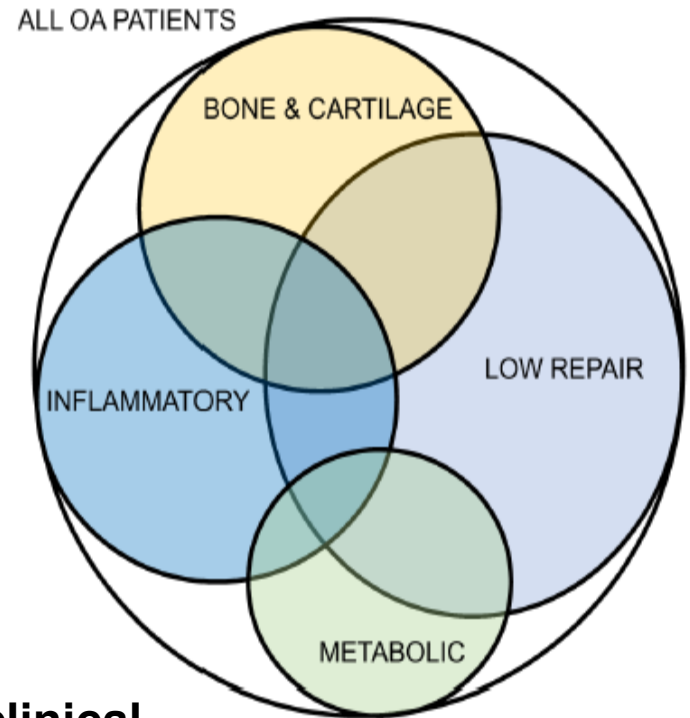
- The presence of metabolic diseases seems to have a cumulative and negative effect on the incidence and the progression of KOA
- Age, physical inactivity, low-grade inflammation, MetS contribute to increase CV disease and CV-related mortality.
- The association between type 2 DM and KOA is controversial
- In the elderly and overweight populations with KOA, concomitant treatment should be carefully monitored.
- Several drugs used in KOA can induce side effects that might be more severe due to associated comorbidities
- Given the different safety profiles, the choice of NSAIDs, traditional or coxibs, should be based on individual patient risk factors.
- Longterm safety of acetaminophen is controversial

9) The treatment should be adapted according to patient phenotype and disease severity

- The complexity of factors involved in OA makes it impossible to offer a standardized treatment for all individuals.
- There is a great heterogeneity between patients, due to mechanical, inflammatory, metabolic, post-traumatic, molecular, genetic, epigenetic and psychological alterations
- In addition each factor is acting alone or in combination.
- Similarly, there is great variation among individuals regarding disease trajectory, (fast o slow progressors)
- Several authors have proposed different OA phenotypes based on clinical or imaging findings
- Therefore, adapting the treatment according to patient phenotype and disease severity is essential to adequately treat OA patients



Venn diagram illustrating diverse overlapping molecular endotypes of OA



Diverse clinical osteoarthritis phenotypes

FICCOResearch

F1000Research 2019, 8:F1000 Faculty Rev:2091 Last updated: 12 DEC 2019



REVIEW

Recent advances in understanding the phenotypes of osteoarthritis [version 1; peer review: 2 approved]

Ali Mobasher¹⁻⁴, Simo Saarakkala², Mikko Finnilä², Morten A. Karsdal⁴, Anne-Christine Bay-Jensen⁴, Willem Evert van Spijl^{5,6}

(10) Surgical options should be considered for the appropriate patients

- Knee arthroplasty should be considered when both pharmacological and nonpharmacological treatments have failed.
- Arthroscopic lavage is not recommended for patients with OA
- TKR is a valid option in patients who have advanced degenerative knee OA and are symptomatically severe.
- Such patients must be medically screened to assess their fitness for surgery before arthroplasty is offered.
- Osteotomy and realignment procedures, may also be considered in appropriate patients after discussing the risks, rewards and longevity of these procedures.

Conclusions

- ✓ Treatment should achieve clinical improvement bringing the patient at the **Patient Acceptable Symptom State (PASS)**;
- ✓ pharmacological and non-pharmacological treatment should begin as early as possible with an early diagnosis of symptomatic KOA;
- ✓ the patient should be evaluated periodically;
- ✓ risk factors of KOA progression should be identified and managed with patients at the beginning of the treatment and monitored regularly;
- ✓ the treatment should be adapted according to patient phenotype and disease severity



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