The DIGICOD cohort: a hospital-based observational prospective cohort of patients with hand osteoarthritis - methodology and baseline characteristics of the population

Jérémie Sellam, Emmanuel Maheu, Michel D Crema, Amel Touati, Alice Courties, Sophie Tuffet, Alexandra Rousseau, Xavier Chevalier, Bernard Combe, Maxime Dougados, et al.

The DIGICOD cohort: a hospital-based observational prospective cohort of patients with hand osteoarthritis - methodology and baseline characteristics of the population

Jérémie SELLAM (1,2), Emmanuel MAHEU (1), Michel D. CREMA (3), Amel TOUATI (4), Alice COURTIES (1,2), Sophie TUFFET (4), Alexandra ROUSSEAU (4), Xavier CHEVALIER (5), Bernard COMBE (6), Maxime DOUGADOS (7), Bruno FAUTREL (8), Margreet KLOPPENBURG (9), Jean-Denis LAREDO (10), Damien LOEUILLE (11), Anne MIQUEL (12), François RANNOU (13), Pascal RICHETTE (14), Tabassome SIMON (4), Francis BERENBAUM (1,2)

1. Assistance Publique – Hôpitaux de Paris (AP-HP), Sorbonne Université, Service de rhumatologie, Hôpital Saint-Antoine, Paris, France
2. Centre de Recherche Saint-Antoine, Inserm URMS_938, Paris, France
3. Institut d'Imagerie du Sport, Institut National du Sport, de l'Expertise et de la Performance (INSEP), Paris, France
4. AP-HP, Sorbonne-Université, Service de Pharmacologie Clinique et Plateforme de Recherche Clinique de l'Est Parisien (URCEST, CRB, CRC), Hôpital Saint-Antoine, Paris, France
5. AP-HP, UPEC, Service de rhumatologie, Hôpital Henri Mondor, Paris, France
6. Département de rhumatologie, CHU et Université de Montpellier, Montpellier, France
7. AP-HP, Service de rhumatologie, Université de Paris, Service de rhumatologie, Hôpital Cochin, Paris, France
8. AP-HP, Sorbonne Université, Service de rhumatologie, Hôpital Pitié Salpêtrière, Paris, France
9. Departments of Rheumatology and Clinical Epidemiology, Leiden University Medical Center, Leiden, Netherlands
10. Service de radiologie, Université de Paris, Hôpital Lariboisière, Paris, France
11. Service de rhumatologie, CHU de Nancy, Nancy, France
12. AP-HP, Sorbonne Université, Service de radiologie, Hôpital Saint-Antoine, Paris, France
13. Service de Rééducation et de Réadaptation de l'Appareil Locomoteur et des Pathologies du Rachis, AP-HP, Centre-Université de Paris, Hôpital Cochin,

Paris, France; Université de Paris, Faculté de Santé, UFR de Médecine de l'Université de Paris, 75006 Paris, France; INSERM UMRS-1124, Toxicité Environnementale, Cibles Thérapeutiques, Signalisation Cellulaire et Biomarqueurs (T3S), Campus Saint-Germain-des-Prés, Paris, France.

14. AP-HP, Université de Paris, Service de rhumatologie, Hôpital Lariboisière, Paris, France

Correspondance: Prof. Francis Berenbaum
Saint-Antoine Hospital, Department of Rheumatology
184 rue du Faubourg Saint-Antoine, 75012 Paris, France
e-mail : francis.berenbaum@aphp.fr
tel : + 33 1 49 28 25 20
fax : + 33 1 49 28 25 13

Key words: hand, osteoarthritis, cohort, erosive hand osteoarthritis

Abstract

Objective. Despite its prevalence, there are few worldwide hand osteoarthritis (HOA) cohorts. The main objective of DIGItal COhort Design (DIGICOD) cohort is to investigate prognostic clinical, biological, genetic and imaging factors of clinical worsening after 6 years follow-up.

Methods. DIGICOD is a hospital-based prospective cohort including patients >35 years-old with symptomatic HOA fulfilling: i) ACR criteria for HOA with ≥2 symptomatic joints among proximal/distal interphalangeal joints or 1st interphalangeal joint with Kellgren-Lawrence (KL) ≥2; or ii) symptomatic thumb base OA with KL≥2. Main exclusion criteria were inflammatory arthritis and crystal arthropathies. Annual clinical evaluations were scheduled with imaging (X-rays of the hands and of other OA symptomatic joints) and biological sampling every 3 years. Hand radiographs are scored using KL and anatomical Verbruggen-Veys scores. Follow-up visits are ongoing. Cohort methodology and baseline characteristics are presented.

Results. Between April 2013 and June 2017, from the 436 HOA included patients, 426 have been analysed of whom 357 (84%) are women. Mean age ± standard deviation was 66.7 ±7.3 years and mean disease duration was 12.6 ±9.6 years. Metabolic syndrome affected 151 (36.5%) patients. Mean visual analog scale (VAS) hand pain (0-100 mm) was 44.4 ±26.7 mm at activity. Mean FIHOA (0-100) was 19.9 ±18.6. Elevated serum CRP level (≥5 mg/L) involved 10% patients. Mean KL score (0-128) was 46.7 ±18 and the mean number of joint with KL ≥2 was 15.1 ±6.3. Erosive HOA (defined as ≥1 Erosive or Remodeling phase joint according to Verbruggen-Veys score) involved 195/426 (45.8%) patients and the median number (interquartile range) of erosive joints in erosive patients was 3.0 (1.0-5.0).

Conclusion DIGICOD is a unique prospective HOA cohort with a long-term 6 years standardized assessment and has included severe radiologically HOA patients with a high prevalence of erosive disease.

Introduction

Osteoarthritis (OA) is a highly prevalent musculoskeletal disorder involving all components of the joint with cartilage degradation, subchondral bone remodeling and synovial inflammation. All joints can be affected by OA: the first symptomatic predilection site is the knee (10.2% prevalence), but the hand is also a frequent one (6.2%) [1]. HOA is associated with hand pain, stiffness, functional limitation, decreased grip strength, aesthetic discomfort and reduced quality of life [2–4]. Clinical hallmarks of the disease include bony enlargement and deformities of the hand joints, with or without soft tissue swelling corresponding to capsule-synovial enlargement [5]. Its prevalence increasing with age, the associated health-care costs for treating hand OA (HOA) are expected to increase in the coming decades as the ageing population continues to grow. However, HOA also may affect younger population [6]. Despite its high prevalence, HOA has long been neglected conversely to hip or knee OA for which several cohorts exist [7]. Interestingly, several studies have shown that the burden related to HOA is similar to rheumatoid arthritis [8].

In the past few years, this “forgotten disease” has attracted increasing attention because of the unmet therapeutic needs [9]. Unfortunately, several randomized controlled trials gave disappointing results except oral low-dose corticosteroids, chondroitin sulfate and base thumb splinting [10–15]. From a pathophysiological point of view, non-weighted bearing joints of hand are localizations that accurately illustrates the role of hormones (i.e., occurrence in post-menopausal women), of genetic susceptibility (i.e., HOA familial history) as well as the systemic nature of OA. Such a systemic component is illustrated by the association between HOA and metabolic syndrome or atherosclerosis, in relation with meta-inflammation [16,17].

Clinical presentation of HOA is heterogeneous with variable involvement of thumb-base, distal and/or proximal inter-phalangeal joints. In addition to hand joints involvement, HOA is frequently associated with OA at other sites such as knees and hips delineating the generalized OA phenotype [18]. For some years, attention has been given to the most severe HOA subtype, namely erosive HOA (EHOA), which is defined by the presence of radiographic erosion(s) or severe subchondral bone remodeling on standard radiographs and characterized by more systemic and joint synovial inflammation according to biological and imaging data, as well as more pain, more disability and more aesthetic discomfort than its non-erosive counterpart [19-21].

Beyond its heterogeneous clinical presentation and its well-known risk factors, HOA has a variable disease course. The natural history of HOA and its determinants associated with clinical or radiographic evolution have been poorly investigated in prospective cohorts [22–25]. In the largest one that included 289 HOA patients, radiographic progression involved 52.5% of patients and these progressors were associated with higher baseline levels of pain, nodes, osteophytes and erosions after 6 years of follow up [24]. However, such data about HOA evolution are scarce while they are critical to better identify patients susceptible to a worse evolution. Such patients could indeed represent the appropriate target population that would be more responsive to any novel symptomatic or structural treatments, as in knee OA [26].

We launched a hand OA cohort, of which the main objective is to investigate clinical, biological, genetic and imaging prognostic factors for severity after a 6-year follow-up. Here, we present the design of the protocol and the description of this ongoing cohort at baseline.

Methods

Design and setting

DIGItal COhort Design (DIGICOD) study is a monocentric university hospital-based prospective cohort including patients with symptomatic HOA. This study fulfills the current Good Clinical Practices guidelines and has been approved by the appropriate ethics committee (Paris Ile de France IV). It has been registered on www.clinicaltrial.gov as n°NCT01831570.

The study has been proposed to all patients viewed at the out-patient clinic specifically dedicated to HOA taking place in the Rheumatology Department of Saint-Antoine Hospital, Assistance Publique – Hôpitaux de Paris (AP-HP) since 2004. Patients also came from other AP-HP hospitals (Cochin, Pitié Salpêtrière, and Henri Mondor hospitals), private practice (general practitioners or rheumatologists) or were recruited via public conferences or media advertisements.

HOA patients undergo 1 annual visit per year for 6 years (i.e., 7 visits). At each visit, a standardized clinical assessment of hands and a general examination are performed. Radiographs and blood sampling are performed at baseline, 3- and 6-year visits. Since DIGICOD is a routine care observational cohort, the management of patients remained under the supervision of his/her treating doctor. Thus, participation to the DIGICOD cohort did not interfere with patient management, which was yearly recorded in the Case Report Form.

Patients

Inclusion criteria are as follows:

- Patients ≥35 years-old
- Symptomatic HOA according to one of these definitions: American College of Rheumatology (ACR) criteria [27] for HOA with ≥2 symptomatic joints among

proximal/distal interphalangeal joints or 1st interphalangeal joint at radiographic Kellgren-Lawrence (KL) stage ≥2 or symptomatic thumb base OA at KL≥2

- Able to understand the questions and complete the questionnaires in French
- Beneficiary of a social security scheme.

Exclusion criteria are:

- Inflammatory destructive arthritis (such as rheumatoid arthritis, or psoriatic arthritis),
- Gout or chondrocalcinosis involving hands,
- Tophaceous gouty arthritis,
- HOA secondary due to infection or acute trauma or rare genetic OA,
- Current pregnancy
- Breast feeding
- Legal protection measure or patient unable to express consent.

All participants gave their written informed consent before entering the cohort.

Sample size

According to Bijsterbosch et al. [24] in which mean ± standard deviation AUSCAN functional score at inclusion was 11.8 ± 8.9, the inclusion of 500 patients in the DIGICOD study were needed to achieve a 80% power to detect a mean difference in the AUSCAN total functional score of 1.2 points between inclusion and 6 years of follow-up (end of study) considering a two sided alpha of 5% and an expected dropout rate of 15% [24].

Follow up

All patients are followed every year for 6 years. To avoid as much as possible loss of follow up, each patient is contacted by phone 1 month before each annual visit in order to confirm the appointment and to complete auto-questionnaires. If the patient

does not attend the visit, a special letter is sent and he/she is then contacted again by phone to schedule a new appointment. In case of impossibility to come to the hospital, questionnaires are sent by mail and completed by the patient. A missing visit at any time does not exclude the patient for the following visit.

Demographic and clinical data collection

These parameters are collected in the Case Report Form, at the baseline visit and, if appropriate, at each visit:

- Age, sex, weight at 20 years, height at 20 years, birth country, marital status, current employment status,
- Usual follow-up in rheumatology (private or hospital practice)
- Current or previous occupations were classified using the INSEE (Institut national de la statistique et des études économiques) classification.
- General physical examination (e.g., height, weight, blood pressure, waist circumference, hip circumference)
- Hand Solicitation in current or past primary employment
- Familial history of HOA, HOA disease duration, continuous chronic hand joint pain or evolution by flare, main expectation for the treatment of HOA (pain, function, aesthetic)
- Examination of hands including spontaneous painful joints, painful joint at palpation, joint soft tissue swelling (i.e., capsulo-synovial enlargment) of hand joints
- Pinch strength and grip strength of each hand using a digital pressure gauge and a Jamar hydraulic hand dynamometer, respectively. We recorded the best result of 3 tests for each hand.

- Total Doyle index, which consists to score 48 joints for tenderness on pressure or movement on a 4-point scale (i.e., equivalent for HOA of Ritchie index used in rheumatoid arthritis) [28].
- Other hand joints disorders (i.e., carpal tunnel syndrome, Dupuytren's disease)

Comorbidities in a pre-established list (cancer, cardiovascular diseases, digestive diseases, diabetes mellitus, neurological diseases except ischemic, depression, visual disturbances such as cataract, glaucoma, age-related macular degeneration, hearing disorders and osteoporosis,

- Questionnaires self-assessed by the patient including several visual analog scales (VAS) for hand pain at rest, pain at activity, patient global assessment of HOA, of perceived aesthetic discomfort, Australian/Canadian Hand Osteoarthritis Index AUSCAN VA3.0 [29], and Functional Index for HOA (FIHOA) [30], short form score for the assessment and quantification of chronic rheumatic affections of the hands (SF-SACRAH)[31], Cochin hand functional disability scale [32], Hospital Anxiety and Depression Scale (HAD) [33], short form of the Arthritis Impact Measurement Scales 2 (AIMS-2) [34], Disabilities of the Arm, Shoulder and Hand (DASH) questionnaire [35]
- Other symptomatic articular localizations suggestive of OA (among forefeet, shoulders, cervical and lumbar spine, hips and knees) leading to the realization of standard radiographs of these joints
- Fulfillment or not to ACR clinical criteria for knee OA recorded in 209 consecutive patients as of January 2015 [36,37].
- Previous treatments for HOA including previous hand surgery

- Ongoing OA treatments were recorded by class of drugs (paracetamol, NSAIDs, opioids, SYSADOA, orthosis,…) (dropdown menu) and then each molecule and its dosage were detailed (free text)
- For disorders other than OA (i.e., cardiovascular, diabetes mellitus, dyslipidemia, depression, osteoporosis, hypo or hyperthyroidism, menopause), we recorded treatments by class of drugs (dropdown menu) and then by noting each molecule and its dosage (free text).

Consolidation of variables

Diabetes diagnosis is retained in case of declared diabetes, and/or biological diabetes (fasting blood glucose > 6.9 mmol/L or HBA1c ≥ 6.5%) and/or anti-diabetic treatment (insulin or oral antidiabetic drugs) prescription.

Dyslipidemia diagnosis is retained in case of declared dyslipidemia or hypolipemic drugs prescription.

Hypertension diagnosis is retained in case of declared hypertension, clinical arterial hypertension during a visit (systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg) and/or antihypertensive drugs prescription.

Cardiovascular diseases (CVDs) diagnosis (excluding hypertension) is retained in case of declared heart failure, declared history of myocardial infarction or ischemic heart disease, declared history of stroke/transient ischemic stroke, or declared peripheral vascular pathology.

Metabolic syndrome was defined according to the criteria of the Adult Treatment Panel III [38], based on the presence of at least three of the following criteria:

- High waist circumference (≥102 cm in men, ≥88 cm in women),
- High triglycerides (≥1.5 g/L or drug treatment for high triglycerides),

- Reduction of HDL cholesterol (<0.4 mg/dL in men, <0.5 mg/L in women or drug treatment to reduce HDL cholesterol),
- High blood pressure (systolic blood pressure ≥130 mm Hg, diastolic blood pressure ≥85 mm Hg or antihypertensive),
- Elevation of fasting blood glucose (≥5.6 mmol/L or blood glucose lowering medication).

Biological assessment

A blood sample was performed at baseline, 3- and 6-year visits, preferentially at a fasted-state (fasted/unfasted state at the time of sampling mentioned in the Case Report Form).

Routine laboratory exploration is systematically performed at baseline visit, 3 and 6 years including hemogram, erythrocyte sedimentation rate, C-reactive protein (threshold 0,5 mg/dL), creatininemia, total cholesterol, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol, triglycerides, glycaemia, glycated haemoglobin (HbA1c), ferritinemia, transferrin saturation coefficient, calcemia, phosphatemia, albuminemia, vitamin D, parathyroid hormone, rheumatoid factor (Latex - Waaler Rose test). A serum sample is kept for subsequent biomarker studies at inclusion, at 3- and 6-year visits. A whole-blood DNA sample is also sampled at the baseline visit.

Serum and DNA are stored in the Centre des Ressources Biologiques (CRB) of Saint-Antoine hospital, following the good practice guidelines for biological samples storage.

Radiographic data

Hand radiographs are systematically performed at baseline, 3- and 6-year visits.

Both hands are on a single 18 x 24 cassette. Bilateral frontal images of the hands are obtained with a posterior–anterior view. The patient sits with both hands pronated and the palmar surfaces placed on the detector. These radiographs allow visualization of wrists, carpometacarpal joints (CMC), metacarpophalangeal (MCP), proximal inter-phalangeal (PUP), distal inter-phalangeal (DIP) joints and have a medial centering, between the MCPs. The focal-film distance is 1m. Indicated technical parameters were 40 to 65 kV, 5-10 mAs. To ensure reproducibility of hand radiograph procedures from one year to another we created at the first visit a positioning model that is reused for each subsequent visit. Hand radiographs are scored for HOA using the Kellgren-Lawrence score and the Verbruggen-Veys scores by an experimented musculoskeletal radiologist (MDC) [39–41].

If other OA sites were symptomatic, patients underwent a standard radiograph: feet (bilateral antero-posterior view), knees (bilateral antero-posterior view and Schuss incidence), frontal pelvis radiograph, lumbar spine (antero-posterior and profile views), cervical spine (antero-posterior and profile views)

Objectives

The primary objective of DIGICOD is to determine the baseline clinical, biological, genetic and imaging factors associated with the evolution of the AUSCAN VA3.0 function subscore over a 6 year period.

The main secondary objectives and outcomes are:

- to determine the baseline clinical, biological, genetic and imaging factors associated with HOA clinical evolution at 3 or 6 years using as a secondary

outcome the mean difference of AUSCAN VA3.0 pain or stiffness subscores between inclusion and 3-year visit and or 6-year visit.

- to determine the baseline clinical, biological, genetic and imaging factors associated with HOA clinical change at 3 or 6 years assessed using as secondary outcomes the mean difference of FIHOA between baseline visit and 3 year or 6 year visit
- to determine the baseline factors associated with HOA radiographic progression between baseline and 3 years or between baseline and 6 years using as secondary outcomes: mean changes between baseline and 3 or 6 years of the sum of the Kellgren Lawrence score of hands, or of the number of joints with Kellgren Lawrence score ≥ 2 of hands, or of the number of erosive joints (phase E or R according the Verbruggen Veys score)
- to identify the baseline clinical, demographic, biological factors associated with EHOA (at least 1 erosive joint according to phase E or R according the Verbruggen Veys score) versus non EHOA at baseline
- to determine the baseline clinical, demographic, biological factors associated with the development of an EHOA at 3 or 6 years in patients having no radiographic erosion at baseline

Furthermore, DIGICOD can serve as a research platform database for various clinical, radiographic and/or biological studies (biomarkers, genetic, patient reported outcome, pathophysiology, imaging, prognosis, safety).

Monitoring

The clinical Research Unit of East Paris (URCEST) is in charge of the monitoring of the study via clinical research assistants in charge of annual visits and managements of potential queries.

Organization and committee

The cohort is monocentric but the steering committee is multicentric and composed of rheumatologists, methodologists and musculoskeletal radiologists. Patients with HOA gave their input for the finalization of the case report form.

The steering committee is in charge of organizational, administrative and financial coordination of the cohort. The scientific committee includes steering committee members or individuals proposed by the members of the steering committee. The scientific committee is in charge of evaluating and validating scientific projects using the cohort database.

A request for proposals is sent bi-annually to all steering and scientific committee members and also the investigators using a specific form. Each application is reviewed by 2 internal reviewers. This procedure is restricted to the participants of the steering or scientific committee for 2 years following the lock of the baseline database.

Funding sources

DIGICOD is sponsored by the AP-HP and an unrestricted grant form TRB Chemedica which did not take part in the study design, collection, analysis and interpretation of data, writing of the report or the decision to submit the article for publication.

Statistical analysis

Baseline characteristics of the patients were expressed as frequencies and percentages for categorical variables and as means ± standard deviation (SD) or median and interquartile ranges (IQRs) for continuous variables, depending on their distribution.

AUSCAN VA3.0 subscores have been normalized to a 0-100 scale, as well as the FIHOA score. When one pain or 1-2 physical function items of the AUSCAN were missing, we substituted the average value of the subscale score for each missing item value(s), as recommended by the AUSCAN developers [42]. If less than two FIHOA items were missing, the sum of the available responses has been reported on 0-100 scale. Otherwise, missing values were not replaced and the score was considered as invalid.

All analyses were performed with SAS version 9·4 statistical software (SAS Institute Inc).

Results

Patient's disposition

A total of 436 patients with HOA have been included between April 2013 and June 2017. Ten patients were not analyzed due to consent withdrew (n=1), not meeting inclusion criteria (n=6) or unavailability of hand radiographs (n=3). Likewise, 426 patients have been analyzed at baseline (**Figure 1)**.

Description of the population

The demographic characteristics of the patients are summarized in **Table 1**. The majority were referred by hospital practitioner rheumatologists (57.1%). Mean age ± SD at inclusion was 66.7 ± 7.3 years, there was a predominance of women (83.8%) and 45.3% patients were obese or overweight.

Menopause involved 244/357 (68.3%) women, of whom 57 received hormone-replacement therapy.

CVDs and hypertension were the main co-morbidities (56.8% and 55.9%, respectively). Interestingly, 144/422 (34.1%) patients reported knee pain suggestive of OA.

The HOA features are in the **Table 2**. Mean disease duration was 12.9 ± 9.6 years. Patients were mildly to moderately symptomatic at the time of the baseline visit as illustrated by VAS (0-100 mm) hand pain intensity (median (IQR): 16.0 (0.0-35.0) mm and 45.0 (22.0-67.0) mm, at rest and at activity respectively).

Functional impairment was also mild to moderate since the median FIHOA (0-100) was 16.7 (3.3-33.3). However, 43.5% patients displayed at least 1 capsulo-synovial swelling and the median number of nodes was 8.0 (4.0-12.0).

Biological data are reported in the **Table 3**. Few patients had elevated level of CRP (10.3%). Serum samples at baseline and DNA samples are available for nearly all patients (98.6% and 97.7%, respectively).

Current treatment or treatments stopped during the last year treatment for HOA of the patients analyzed at the baseline visit are reported in **Table 4.** Prior hand joint orthopedic surgery involved 41 patients and included thumb base OA surgery or surgery of osteophytes, arthroplasty, arthrodesis and synovial cyst.

Radiographic data

Radiographic scorings are reported in **Table 5**. Mean KL score (0-128) was 46.7 ± 18 and the mean number of joint with KL ≥ 2 was 15.1 ± 6.3. Erosive HOA, defined as ≥ 1 erosive joint (E or R phase of Verbruggen-Veys score), involves 195/426 (45.8%) patients of whom 145 (74.4%) had ≥ 2 erosive joints. The median number (interquartile range) of erosive joints in erosive patients with ≥ 1 erosive joint was 3.0 (1.0-5.0).

Discussion

This manuscript summarizes the methodology and baseline characteristics of the HOA patients included in the first French hospital-based observational prospective DIGICOD cohort. The main objective of DIGICOD is to determine the factors associated with HOA clinical evolution at 6 years, but above all to recruit a large number of HOA patients to create a clinical, biological and radiographic database in order to develop clinical and basic scientific projects open to the scientific community.

It is noteworthy that the patients recruited in DIGICOD were mainly referred by university hospital rheumatologists (57.1%) and private rheumatologists (18.1%). Such recruitment modalities may enhance the proportion of severe HOA patients in terms of symptoms or structural severity and deformations, while in France patients with mild HOA are mainly managed by general practitioners or even by themselves using over the counter auto-medication or “alternative” therapies. Such recruitment explains the particular structural severity of included patients since almost half of the DIGICOD population (45.8%) has an erosive disease with a median number of erosive joints at 3.0 (1.0-5.0) among the EHOA patients. Such a frequency fits with our previous work coming from the same department finding 46% erosive disease on 172 consecutive HOA patients [3] but is higher than the prevalence observed in other cohorts [24,43]. This high proportion of EHOA in DIGICOD should give the opportunity to specifically investigate such a severe subtype of HOA. This is of particular interest since the high unmet need in innovative therapy especially involves this particular severe form of HOA. So, specific studies on erosive HOA patients will

help to better understand the natural course, the risk factors and biomarkers of this severe HOA.

Another valuable characteristic of the included population is the frequency of comorbidities, and especially CVDs (56.8%), hypertension (55.9%) and other cardio-metabolic comorbidities that will allow studying the reciprocal influence between cardio-metabolic diseases and HOA. To ensure the reliability of these variables, we have performed a validation process using declarative data from the patients, current drug prescription and results of biological investigations performed at the baseline visit. Such a similar process will be done at the 3- and 6-year visits.

The rheumatology department of Saint-Antoine hospital has established since 2004 an out-patient clinic dedicated to HOA management in routine care. Considering such an active file of patients in one single site, the frequency of established HOA and cost constraint, we have chosen a monocentric design, but gathered a multicentric steering committee.

Beyond the pre-specified main objective of the cohort, the quality of the clinical, radiological and biological database should allow the development of multiple researches in various fields such as prognosis, epidemiology, pathogenesis, biomarkers and therapeutics. Moreover, baseline hand radiographs have been all read by an experimented musculoskeletal radiologist who has 13 years' experience in imaging analyses from large OA cohorts (MDC).

One limitation of this cohort is the monocentric design. This choice was made mainly to limit costs, as funding to support cohorts in this field is particularly challenging. Nevertheless, in order to limit as much as possible, the inconveniences due to monocentric recruitment, we have set up a steering committee of rheumatologists from different hospitals throughout the country and from a foreign country (the

Netherland), involving them not only in the establishment of the CRF but also in the recruitment, inviting them to refer their patients meeting the inclusion criteria. Another limitation is the clinical assessment of the joint swelling (i.e., capsulo-synovial enlargement) by different investigators, similarly to what happen in rheumatoid arthritis prospective cohort. However, since DIGICOD is a 6 year prospective cohort, it is unrealistic to have only one clinician assessing all the patients at baseline and during the follow up. However, such an assessment by different investigators may reflect what happens in the routine clinical care. An ancillary study combining clinical hand examination and hand joint ultrasound is planned in a subset of patients.

In conclusion, DIGICOD cohort is the first French hospital-based observational prospective of HOA patients with a high proportion of erosive HOA patients and a high frequency of comorbidities allowing for developing a multifaceted research program to help understand the natural course of HOA, its determinants and validation of potential new biomarkers or therapeutic targets, in order to answer unresolved questions.

Acknowledgements

All the patients who have accepted to participate to the DIGICOD cohort.

All the investigators who manage or have managed patients' recruitments, and the monitoring the clinical visits (Dr Camille DEPROUW, Dr Sandra DESOUCHES, Dr Ariane DO, Dr Emeline GAIGNEUX, Dr Camille GLANOWSKI, Dr Karine LOUATI, Dr Stéphanie MALBOS, Dr Sabine TRELLU, Dr Houda AJLANI, Dr Juliette Louis PETIT and Dr Clémence GORLIER all from the Rheumatology Department of AP-HP Saint-Antoine Hospital), the staff members of the URCEST and of the Centre des Ressources Biologiques from AP-HP Saint-Antoine Hospital.

Sponsor: DIGICOD is sponsored by AP-HP

Grant research: unrestricted grant from TRB Chemedica, which did not take part in the study design, collection, analysis and interpretation of data, writing of the report or the decision to submit the article for publication.

Disclosures of interest :

JS reports fees from MSD, Pfizer, Abbvie, Fresenius Kabi, BMS, Roche Chugai, Sandoz, Lilly, Gilead, Novartis, Janssen outside of this work and unrelated to osteoarthritis treatment, grant research from Schwa Medico, MSD and Roche. EM reports disclosures of interest with TRB Chemedica, during the conduct of the study; personal fees from Expanscience, personal fees from Sublimed, personal fees from Fidia France, personal fees from Meda-Mylan, outside the submitted work. MDC is shareholder of Boston Imaging Core Lab, LLC. AC reports fees from Meda pharma, UCB outside of this study. XC reports fees from Pfizer, Ibsa, Macopharma, Sanofi. MK reports consultancy (Abbvie, Pfizer, Levicept, GlaxoSmithKline, Merck-Serono, Kiniksa, Flexion, Galapagos, CHDR) and local investigator of industry-driven trial

(Abbvie), from Wolters Kluwer (UptoDate), Springer Verlag (Reumatologie en klinische immunologie), grants from Pfizer, grants from IMI-APPROACH, grants from Dutch Arthritis Association, outside the submitted work. FR reports personal fees for lecture or advisory boards from Pierre Fabre, Expanscience, Thuasne, Genevrier, Sanofi Aventis Genzyme. Grunenthal, Bayer. PR reports personal fees from Pierre Fabre and Labhra, outside the submitted work. TS reports personal fees from Astra Zeneca, Astellas, bayer, MSD, Novartis, Sanofi, grants from Astra Zeneca, Bayer, Boehringer, Daiichi-Sankyo, Eli Lilly, GSK, Novartis, and Sanofi, outside the submitted work. FB reports grants from TRB Chemedica, during the conduct of the study; personal fees from 4P Pharma, AbbVie, Boehringer, Bone Therapeutics, Eli Lilly, Expanscience, Flexion, Galapagos, Gilead, GSK, Janssen, Medivir, Merck, Merck Serono, Nordic Pharma, Novartis, Peptinov, Pfizer, Regeneron, Regulaxis, Roche, Sandoz, Sanofi, Servier,TRB Chemedica, UCB outside the submitted work. AT, AR, ST, BC, MD, BF, J-DL, DL and AM have nothing to disclose.

Table 1. Demographic characteristics of the 426 patients analyzed at baseline visit of DIGICOD.

	Number of data available	Results, No. (%)*
Sex	426	
Men		69 (16.2)
Women		357 (83.8)
Age (year), mean±sd	426	66.7 ± 7.3
Patients referred by:	420	
General practioner		23 (5.5)
Private rheumatologist		76 (18.1)
Hospital rheumatologist		240 (57.1)
Other (including social media)		81 (19.3)
Socio-educational level	426	
Primary or secondary (college)		58 (13.6)
Secondary (high school)		117 (27.5)
University		251 (58.9)
Marital Status	424	
Single		63 (14.9)
Married or cohabiting		239 (56.4)
Divorced		77 (18.2)
Widow (widower)		45 (10.6)
Menopause	357	244 (68.3)
Number of child(ren), median (IQR)	426	2.0 (1.0-2.0)
Current professional situation	426	
Active		95 (22.3)
Retired		311 (73.0)
Inactive and ever worked (other than retired)		12 (2.8)
Inactive and never worked		8 (1.9)
Main occupation (past or current)	418	
Farmers, craftsmen, traders and workers		27 (6.5)
Intermediate professions and employees		170 (40.7)
Intellectual professions		221 (52.9)
Solicitation of hands in current or past main job	412	297 (72.1)
Smoking	420	
Never		236 (56.2)
Past, stop > 3 years		145 (34.5)
Past, stop < 3 years		10 (2.4)
Current		29 (6.9)
Number of pack-year, mean±SD		17.0 ±15.1
Current alcohol consumption	420	
No		95 (22.6)
Yes, less than 40g per day		314 (74.8)
Yes, more than 40g/day		11 (2.6)
Body mass index, mean±SD	419	25.1 ± 4.3
OMS Weight status (kg/m^2)	419	
Underweight (<18.5)		15 (3.6)
Normal weight (18.5-24.99)		214 (51.1)
Overweight (25-29.99)		140 (33.4)
Obese (≥30)		50 (11.9)
Comorbidities		
- CVDs	426	242 (56.8)
- Metabolic syndrome (ATP III criteria)	414	151 (36.5)
- Hypertension	426	238 (55.9)
- Dyslipidemia	426	149 (35)
- Diabetes	426	33 (7.7)
- Neurological disease (excluding stroke/TIA) (e.g. MS, Parkinson's...)	426	14 (3.3)
- Cancer	426	52 (12.2)
- Digestive diseases**	426	57 (13.4)
- Depression	426	41 (9.6)
- Vision disorders (cataract, glaucoma, macular degeneration)	426	40 (9.4)
- Hearing problems (severe hearing loss despite a hearing aid)	426	7 (1.6)
- Pulmonary diseases***	426	42 (9.9)
- Thyroid abnormality	426	86 (20.2)
- Osteoporosis	426	53 (12.4)
- Menopause	357	244 (68.3)
- Chronic low back pain or lumbago	425	46 (10.8)
Presence of		
- Knee pain	422	144 (34.1)
- Hip pain	422	67 (15.9)
- Forefoot	422	142 (33.6)
- Low back pain	422	171 (40.5)
- Cervical pain	417	118 (28.3)
Fulfillment of ACR clinical criteria for knee OA	209	54 (25.8)

*Except if mean ± SD or median (IQR) is mentioned
**Diverticulitis, digestive ulcer, gastroduodenal reflux, hernia, B or C viral hepatitis, inflammatory bowel disease or other
***Chronic obstructive pulmonary disease, asthma or other
Abbreviations: OA: osteoarthritis; MS: multiple sclerosis; VAS: visual analog scale, ATPIII: Adult Treatment Panel III

Table 2. Variables related to hand osteoarthritis of the 426 patients analyzed at baseline visit of DIGICOD

	Number of data available	Results, No. (%)*
Familial history of HOA**	412	285 (69.2)
HOA disease duration (year), mean ± sd	422	12.9 ± 9.6
Hand pain profile		
- Continuous pain	424	186 (43.9)
- Evolution by flares	424	359 (84.7)
Hand pain		
- Hand pain intensity at rest (0-100 mm VAS), median (IQR)	423	16.0 (0.0-35.0)
- Hand pain intensity at activity (0-100 mm VAS), median (IQR)	423	45.0 (22.0-67.0)
Esthetic discomfort score (0-100 mm VAS), median (IQR)	423	27.0 (0.0-64.0)
Main expectation regarding HOA treatment	425	
Pain relief		172 (40.5)
Functional improvement		220 (51.8)
Aesthetic consideration		33 (7.8)
Number of painful joints at palpation (range 0-30) , median (IQR)	425	3.0 (2.0-7.0)
Number of patients with		
- ≥1 painful joint pain at palpation	426	371 (87.1)
- ≥2 painful joints at palpation	426	321 (75.4)
Doyle index (range 0-144) , mean ± sd	408	6.0 (3.0-12.0)
Number of joint soft tissue swelling (range 0-30) , median (IQR)	424	0.0 (0.0-2.0)
Number of patients with		
- ≥1 joint soft tissue swelling	425	185 (43.5)
- ≥2 joint soft tissue swelling	424	116 (27.4)
Number of nodes (range 0-30) , median (IQR)	424	8.0 (4.0-12.0)
Number of patients with		
- ≥1 node	425	404 (95.1)
- ≥2 nodes	425	392 (92.2)
AUSCAN (ranges 0-100)		
- Pain subscore, median (IQR)	396	19.8 (7.9-38.8)
- Stiffness subscore, median (IQR)	395	23.0 (8.0-53.0)
- Function subcore, median (IQR)	400	34.2 (13.3-55.3)
FIHOA (range 0-100) , median (IQR)	405	16.7 (3.3-33.3)
Grip strength*** (kg) , mean ± SD	424	26.2 ± 12.5
Pinch strength*** (kg), mean ± SD	411	5.6 ± 1.8

*Except if mean ± SD or median (IQR) is mentioned

**mother, father or siblings

***dominant hand

Abbreviations: HOA: hand osteoarthritis, AUSCAN: Australian/Canadian Hand Osteoarthritis Index VA3.0; FIHOA: Functional Index for hand osteoarthritis; IQR: interquartile range; SD: standard deviation

Table 3. Biological data of the 426 patients analyzed at baseline visit of DIGICOD

	Number of data available	Results, n (%) or median (IQR)
Leucocytes count (/mm3)	419	5700.0 [4840.0 ; 6770.0]
Hemoglobin (g/dL)	419	13.7 [13.1 ; 14.5]
Erythrocyte sedimentation rate (mm)	178	13.0 [8.0 ; 18.0]
Thyroid-stimulating hormone (mU/L)	396	1.4 [1.0 ; 1.9]
Creatininemia (µmol/L)	418	76.5 [70.0 ; 85.0]
Total cholesterol level (g/L)	413	2.2 [2.0 ; 2.5]
LDL cholesterol level (g/L)	412	1.4 [1.1 ; 1.6]
HDL cholesterol level (g/L)	412	0.7 [0.6 ; 0.8]
Triglycerid level (g/L)	413	0.9 [0.7 ; 1.2]
Fasted glycemia (mmol/l)	410	5.2 [4.9 ; 5.6]
HbA1c (%)	413	5.6 [5.4 ; 5.9]
Ferritinemia (µg/l)	375	79.0 [48.0 ; 143.0]
Transferrin saturation coefficient (%)	412	27.1 [21.7 ; 32.9]
Calcemia (mmol/L)	415	2.4 [2.3 ; 2.4]
Phosphatemia (mmol/l)	415	1.1 [1.0 ; 1.2]
Albuminemia (g/L)	354	43.7 [42.0 ; 45.5]
Vitamin D (ng/mL)	405	29.2 [22.5 ; 39.1]
Parathormon (pg/mL)	402	46.0 [34.0 ; 61.0]
Positive rheumatoid factor	364	23 (6.3)
CRP level **Normal level (<5 mg/L)** **Elevated (≥5 mg/L)** **Level if ≥5 mg/L, median (IQR)**	350 36	 314 (89.7) 36 (10.3) 7.8 (6.4-14.0)
Serum samples available	426	420 (98.6)
Fasted state at the time of the sample	416	385 (92.5)
Whole blood DNA sample available	426	416 (97.7)

Abbreviations: CRP: C-reactive protein ; IQR: interquartile range; HbA1c: Glycated hemoglobin; HDL: High-density lipoprotein; LDL: low-density lipoprotein

Table 4. Current treatment or treatment stopped during the previous year for hand osteoarthritis of patients analyzed at baseline visit of DIGICOD

	Number of data available	Results, No. (%)
- Paracetamol	421	140 (33.3)
- Oral corticosteroid	421	6 (1.4)
- Immunomodulatory/immunosuppressive drugs*	421	14 (3.3)
- Oral NSAIDs	421	90 (21.4)
- Analgesics (eg opioids)	421	37 (8.8)
- Topical NSAIDs	421	114 (27.1)
- SYSADOA	421	159 (37.8)
- Intraarticular steroid hand joint injection	421	33 (7.8)
- Intraarticular HA hand joint injection	421	2 (0.5)
- Hand orthosis	421	105 (24.9)

Abbreviations: NSAIDs Nonsteroidal anti-inflammatory drugs; SYSADOA: symptomatic slow-acting drugs for osteoarthritis; HA: hyaluronic acid

*: hydroxychloroquine n=9; methotrexate; n=4

Table 5. Radiographic data of the 426 patients analyzed at baseline visit of DIGICOD

	Number of data available	Results mean ± SD or n(%)
Kellgren Lawrence score:		
- Kellgren Lawrence sum of hands (0-128), median [IQR]	410*	47.0 [34.0 ; 60.0]
- Number of hand joints with KL≥2 (0-32), median [IQR]	410*	16.0 [11.0 ; 20.0]
- IPD Kellgren Lawrence sum of hands (0-32), median [IQR]	410*	19.5 [15.0 ; 24.0]
- IPP Kellgren Lawrence sum of hands (0-40), median [IQR]	410*	17.0 [9.0 ; 24.0]
- MCP Kellgren Lawrence sum of hands (0-40), median [IQR]	410*	3.0 [1.0 ; 6.0]
- At least one TMC joint with KL≥2 (0-2), n (%)	410*	287 (70.0)
Verbruggen Veys score**:		
- EHOA defined as ≥ 1 erosive joint	426	195 (45.8)
- EHOA defined as ≥2 erosive joints	426	145 (34.0)
- Number of erosive joints in EHOA patients with ≥ 1 erosive joint (0-28), median (IQR)	195	3.0 (1.0-5.0)

*number of patients with available radiographic Kellgren Lawrence scoring for all digital joints
** Erosive joint is defined as phase “E” (erosion) or “R” (remodeling) in the Verbruggen Veys score
Abbreviations: SD: standard deviation, EHOA: erosive hand osteoarthritis, KL: Kellgren Lawrence, IQR: interquartile range

Figure 1. Study flow chart of the cohort at inclusion

References

[1] Carmona L, Ballina J, Gabriel R, Laffon A, EPISER Study Group. The burden of musculoskeletal diseases in the general population of Spain: results from a national survey. Ann Rheum Dis 2001;60:1040–5.
[2] Kloppenburg M, Kwok W-Y. Hand osteoarthritis--a heterogeneous disorder. Nat Rev Rheumatol 2011;8:22–31.
[3] Hodkinson B, Maheu E, Michon M, Carrat F, Berenbaum F. Assessment and determinants of aesthetic discomfort in hand osteoarthritis. Ann Rheum Dis 2012;71:45–9.
[4] Zhang Y, Niu J, Kelly-Hayes M, Chaisson CE, Aliabadi P, Felson DT. Prevalence of symptomatic hand osteoarthritis and its impact on functional status among the elderly: The Framingham Study. Am J Epidemiol 2002;156:1021–7.
[5] Zhang W, Doherty M, Leeb BF, Alekseeva L, Arden NK, Bijlsma JW, et al. EULAR evidence-based recommendations for the diagnosis of hand osteoarthritis: report of a task force of ESCISIT. Ann Rheum Dis 2009;68:8–17.
[6] Haugen IK, Englund M, Aliabadi P, Niu J, Clancy M, Kvien TK, et al. Prevalence, incidence and progression of hand osteoarthritis in the general population: the Framingham Osteoarthritis Study. Ann Rheum Dis 2011;70:1581–6.
[7] Wieczorek M, Rotonda C, Guillemin F, Rat A-C. What have we learned from trajectory analysis of clinical outcomes in knee and hip osteoarthritis before surgery? Arthritis Care Res (Hoboken) 2020;72:1693-1702
[8] Wittoek R, Cruyssen BV, Verbruggen G. Predictors of functional impairment and pain in erosive osteoarthritis of the interphalangeal joints: comparison with controlled inflammatory arthritis. Arthritis Rheum 2012;64:1430–6.
[9] Kloppenburg M, Stamm T, Watt I, Kainberger F, Cawston TE, Birrell FN, et al. Research in hand osteoarthritis: time for reappraisal and demand for new strategies. An opinion paper. Ann Rheum Dis 2007;66:1157–61.
[10] Kloppenburg M, Kroon FP, Blanco FJ, Doherty M, Dziedzic KS, Greibrokk E, et al. 2018 update of the EULAR recommendations for the management of hand osteoarthritis. Ann Rheum Dis 2019;78:16-24.
.
[11] Chevalier X, Ravaud P, Maheu E, Baron G, Rialland A, Vergnaud P, et al. Adalimumab in patients with hand osteoarthritis refractory to analgesics and NSAIDs: a randomised, multicentre, double-blind, placebo-controlled trial. Ann Rheum Dis 2015;74:1697–705.
[12] Kingsbury SR, Tharmanathan P, Keding A, Ronaldson SJ, Grainger A, Wakefield RJ, et al. Hydroxychloroquine Effectiveness in Reducing Symptoms of Hand Osteoarthritis: A Randomized Trial. Ann Intern Med 2018;168:385–95.
[13] Persson MSM, Sarmanova A, Doherty M, Zhang W. Conventional and biologic disease-modifying anti-rheumatic drugs for osteoarthritis: a meta-analysis of randomized controlled trials. Rheumatology (Oxford) 2018;57:1830-1837.
[14] Rannou F, Dimet J, Boutron I, Baron G, Fayad F, Macé Y, et al. Splint for base-of-thumb osteoarthritis: a randomized trial. Ann Intern Med 2009;150:661–9.
[15] Gabay C, Medinger-Sadowski C, Gascon D, Kolo F, Finckh A. Symptomatic effects of chondroitin 4 and chondroitin 6 sulfate on hand osteoarthritis: a randomized, double-blind, placebo-controlled clinical trial at a single center. Arthritis Rheum 2011;63:3383–91.
[16] Tomi A-L, Sellam J, Lacombe K, Fellahi S, Sebire M, Rey-Jouvin C, et al. Increased prevalence and severity of radiographic hand osteoarthritis in patients with

HIV-1 infection associated with metabolic syndrome: data from the cross-sectional METAFIB-OA study. Ann Rheum Dis 2016;75:2101–7.
[17] Visser AW, de Mutsert R, le Cessie S, den Heijer M, Rosendaal FR, Kloppenburg M, et al. The relative contribution of mechanical stress and systemic processes in different types of osteoarthritis: the NEO study. Ann Rheum Dis 2015;74:1842–7.
[18] Cicuttini FM, Baker J, Hart DJ, Spector TD. Relation between Heberden's nodes and distal interphalangeal joint osteophytes and their role as markers of generalised disease. Ann Rheum Dis 1998;57:246–8.
[19] Haugen IK, Mathiessen A, Slatkowsky-Christensen B, Magnusson K, Bøyesen P, Sesseng S, et al. Synovitis and radiographic progression in non-erosive and erosive hand osteoarthritis: is erosive hand osteoarthritis a separate inflammatory phenotype? Osteoarthr Cartilage 2016;24:647–54.
[20] Slatkowsky-Christensen B, Mowinckel P, Kvien TK. Health status and perception of pain: a comparative study between female patients with hand osteoarthritis and rheumatoid arthritis. Scand J Rheumatol 2009;38:342–8.
[21] Almeida D, Costa E, Guimarães F, Azevedo S, Rodrigues J, Silva J, Faria D, Teixeira F, Afonso C, Tavares-Costa J, NevesJ, Ribeiro AR, Cerqueira M. Are we overlooking osteoarthritis? A comparative study of pain, function and quality of life in patients with hand osetoarthritis and rheumatoid arthritis. Ann Rheum Dis 2020;79:787.
[22] Harris PA, Hart DJ, Dacre JE, Huskisson EC, Spector TD. The progression of radiological hand osteoarthritis over ten years: a clinical follow-up study. Osteoarthr Cartilage 1994;2:247–52.
[23] Balblanc JC, Mathieu P, Mathieu L, Tron AM, Conrozier T, Piperno M, et al. Progression of digital osteoarthritis: a sequential scintigraphic and radiographic study. Osteoarthr Cartiage 1995;3:181–6.
[24] Bijsterbosch J, Watt I, Meulenbelt I, Rosendaal FR, Huizinga TWJ, Kloppenburg M. Clinical and radiographic disease course of hand osteoarthritis and determinants of outcome after 6 years. Ann Rheum Dis 2011;70:68–73.
[25] Botha-Scheepers S, Riyazi N, Watt I, Rosendaal FR, Slagboom E, Bellamy N, et al. Progression of hand osteoarthritis over 2 years: a clinical and radiological follow-up study. Ann Rheum Dis 2009;68:1260–4.
[26] van Helvoort EM, van Spil WE, Jansen MP, Welsing PMJ, Kloppenburg M, Loef M, et al. Cohort profile: The Applied Public-Private Research enabling OsteoArthritis Clinical Headway (IMI-APPROACH) study: a 2-year, European, cohort study to describe, validate and predict phenotypes of osteoarthritis using clinical, imaging and biochemical markers. BMJ Open 2020;10:e035101.
[27] Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand. Arthritis Rheum 1990;33:1601–10.
[28] Doyle DV, Dieppe PA, Scott J, Huskisson EC. An articular index for the assessment of osteoarthritis. Ann Rheum Dis 1981;40:75–8.
[29] Bellamy N, Campbell J, Haraoui B, Buchbinder R, Hobby K, Roth JH, et al. Dimensionality and clinical importance of pain and disability in hand osteoarthritis: Development of the Australian/Canadian (AUSCAN) Osteoarthritis Hand Index. Osteoarthr Cartilage 2002;10:855–62.
[30] Dreiser RL, Maheu E, Guillou GB, Caspard H, Grouin JM. Validation of an algofunctional index for osteoarthritis of the hand. Rev Rhum Engl Ed 1995;62:43S-53S.

[31] Rintelen B, Haindl PM, Mai HTH, Sautner J, Maktari A, Leeb BF. A tool for the assessment of hand involvement in rheumatic disorders in daily routine--the SF-SACRAH (short form score for the assessment and quantification of chronic rheumatic affections of the hands). Osteoarthr Cartil 2009;17:59–63.
[32] Poiraudeau S, Chevalier X, Conrozier T, Flippo RM, Lioté F, Noël E, et al. Reliability, validity, and sensitivity to change of the Cochin hand functional disability scale in hand osteoarthritis. Osteoarthr Cartil 2001;9:570–7.
[33] Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand 1983;67:361–70.
[34] Pouchot J, Guillemin F, Coste J, Brégeon C, Sany J. Validation of the French version of the arthritis impact measurement scales 2 and comparison with the french version of the Nottingham Health Profile. “Quality of Life in Rheumatology” Task Force. Rev Rhum Engl Ed 1996;63:389–404.
[35] Hudak PL, Amadio PC, Bombardier C. Development of an upper extremity outcome measure: the DASH (disabilities of the arm, shoulder and hand) [corrected]. The Upper Extremity Collaborative Group (UECG). Am J Ind Med 1996;29:602–8.
[36] Altman R, Asch E, Bloch D, Bole G, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Diagnostic and Therapeutic Criteria Committee of the American Rheumatism Association. Arthritis Rheum 1986;29:1039–49.
[37] Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, et al. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505–14.
[38] Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001;285:2486–97.
[39] Verbruggen G, Veys EM. Numerical scoring systems for the anatomic evolution of osteoarthritis of the finger joints. Arthritis Rheum 1996;39:308–20.
[40] Verbruggen G, Goemaere S, Veys EM. Systems to assess the progression of finger joint osteoarthritis and the effects of disease modifying osteoarthritis drugs. Clin Rheumatol 2002;21:231–43.
[41] Kellgren JH, Lawrence JS. Radiological assessment of osteo-arthrosis. Ann Rheum Dis 1957;16:494–502.
[42] Bellamy N, Wilson C, Hendrikz J. Population-based normative values for the Australian/Canadian (AUSCAN) Hand Osteoarthritis Index: part 2. Semin Arthritis Rheum 2011;41:149–56.
[43] van Delft MAM, van Beest S, Kloppenburg M, Trouw LA, Ioan-Facsinay A. Presence of Autoantibodies in Erosive Hand Osteoarthritis and Association with Clinical Presentation. J Rheumatol 2019;46:101–5.