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RHEUMATOID ARTHRITIS PER SE IS NOT RISK FACTOR FOR CLINICAL FRACTURES: NINE-YEAR FINDINGS OF THE TOMORROW STUDY

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Background: Patients with rheumatoid arthritis (RA) who have sarcopenia and stiff or painful joints might be at increased risk of falls and fractures.

Objectives: The present study aimed to prospectively identify the incidence of clinical fractures and associated risk factors in patients with RA in a cohort study named the TOMORROW (UMIN00003876) that started in 2010.

Methods: We evaluated anthropometric parameters, bone mineral density (BMD), disease activity, RA medication at baseline and observed the incidence of clinical fractures during nine years in 202 patients with RA (mean age, 58.6 y; medication with biological agents, 54.9%) and 202 age- and sex-matched non-RA volunteers (mean age, 57.4 y). We compared the incidence of clinical fractures between patients with RA and controls for nine years, and analyzed the risk factors for fractures using Cox proportional hazard model.

Results: The incidence of clinical fractures in RA patients was significantly higher compared to controls (27.5 vs 18.3%, $p=0.04$). However, Cox proportional hazard model, adjusted by age, sex, smoking and body mass index, revealed that low BMD at thoracic vertebrae ($< 0.7 \text{ g/cm}^2$) significantly associated to the incidence of clinical fractures (hazard ratio [HR], 1.86, $p=0.02$), but not RA morbidity (HR 1.47, $p=0.10$) (Table 1). Among patients with RA, low BMD at the thoracic vertebrae ($< 0.7 \text{ g/cm}^2$) was the most prominent risk factor for clinical fractures (HR, 2.66, $p=0.02$) (Table 1). Although the use of glucocorticoid (GC) at baseline (HR, 1.68, $p=0.09$) was not a significant risk factor for fractures, a mean GC dose ($\geq 2 \text{ mg/day}$) at entry increased risk for clinical fractures in the patients (HR, 1.91, $p=0.04$) (Table 1).

Table 1. Cox proportional hazard model (adjusted for fracture risk factors including age, sex, smoking, and body mass) of risk factors for clinical fractures.

		hazard ratio	95% CI	p
All participants N=404	History of fractures	0.24	0.77-1.98	0.38
	Morbidity of RA	1.47	0.92-2.34	0.10
	Low BMD at thoracic vertebrae ($< 0.7 \text{ g/cm}^2$)	1.86	1.09-3.17	0.02
RA patients N=202	History of fractures	1.27	0.70-2.29	0.43
	GC medication	1.68	0.92-3.06	0.09
	A mean GC dose $\geq 2 \text{ mg/day}$ at entry	1.91	1.05-3.49	0.04
	Low BMD at thoracic vertebrae ($< 0.7 \text{ g/cm}^2$)	2.66	1.20-5.89	0.02

CI, confidence interval; RA, rheumatoid arthritis; GC, glucocorticoid; BMD, bone mineral density.

Conclusion: RA per se was not a risk factor for clinical fractures in this cohort. Low BMD at the thoracic vertebrae and the use of GC with even low dose at entry were apparently significant risk factors for the incidence of clinical fractures among patients with RA.

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STUDY OF METHOTREXATE METABOLITES CONCENTRATIONS IN RED BLOOD CELLS AND MONONUCLEAR CELLS IN RHEUMATOID ARTHRITIS

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Background: Studying the dynamics of the methotrexate metabolites concentration in cells will help to predict the therapeutic effect and assess patient compliance. We suggest that studying the dynamics of changes in the concentration of methotrexate metabolites in mononuclear cells (MO) may be a more accurate method than measuring in red blood cells (RBC).

Objectives: To study the dynamics of changes in the concentration of MTX and its metabolites in RBC and MO in methotrexate-naïve patients with RA.

Methods: 33 patients (26 women, 7 men) aged 53.2 ± 11.7 years with a diagnosis of rheumatoid arthritis, according to the ACR / EULAR 2010 criteria, were included. All patients had GFR $>60 \text{ ml/min}$. Patients were monitored after 4, 12, 24 and 36 weeks from the start of MTX. Mean Cell Volume (MCV) of RBC was measured by standard methods. Samples of RBC and MO were collected separately to determine the concentrations of MTX (basic monoglutamate form), total concentration of MTPG2, MTPG3 and MTPG4 (MTPG2-4), 7-hydroxymethotrexate (7-OH-MTX) by tandem mass spectrometry.

RESULTS:

A pairwise comparison of MTX, MTPG2-4 and 7-OH-MTX concentrations, according to the Wilcoxon method did not reveal statistically significant differences at weeks 4, 12 and 24. The concentration of the studied substances did not correlate with the value of the body mass index, taking statins, glucocorticoids, a cumulative dose of MTX, and the frequency of adverse reactions. At the week 4, of therapy, the level of MTPG4 in MO was inversely correlated with the duration of the disease (correlation coefficient - 0.58, $p 0.05$) The concentration of MTX and its metabolites in MO was lower in smokers (MTX 11.2 [2.6;21.9], 7-OH-MTX 2.1 [0.5; 10.4], MTPG2 0.5 [0.1;1.3]) than in non-smokers (MTX 46.5 [25.3;97.5], 7-OH-MTX 28.2 [7.1; 64.7], MTPG2 8.2 [4.1;32.9]), $p = 0.02$, 0.01 and 0.003, respectively. At week 24 of therapy, a negative correlation was found between age and MTPG4 level (correlation coefficient 0.51, $p <0.05$).

Table 1. Total concentration of MTPG2, MTPG3 and MTPG4 (MTPG2-4), nmol/l

		Me	[25;75]	Min	Max
Week 4	RBC	42.8	19.0;155.0	3	987.7
	MO	6.2	5.3;11.9	1.6	147.2
Week 12	RBC	48.1	17.1;89.0	0.1	519.9
	MO	10.9	3.9;31.0	0.9	147.6
Week 24	RBC	39.4	17.2;70.6	2.7	191.8
	MO	8.3	2.7;14.0	0.4	72.4

Conclusion: The inadequate response to MT therapy in smokers, described in many previous studies, may be associated with a low concentration of the MTX metabolites in mononuclear cells.

The level of MTPG4 in mononuclear cells increases more slowly in patients with a longer duration of the disease.

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PREDICTION OF RHEUMATOID ARTHRITIS DISEASE ACTIVITY BY AN ADAPTIVE DEEP NEURAL NETWORK: BETTER RESULTS IN SEROPOSITIVE PATIENTS WITH LONGER DISEASE DURATION

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Background: Deep neural networks learn from former experiences on a large scale and can be used to predict future disease activity as potential clinical decision support. AdaptiveNet is a novel adaptive recurrent neural network optimized to deal with missing clinical data. In rheumatoid arthritis (RA) it is unknown how disease characteristics influence the predictability by deep learning in terms of classification (e.g. active disease yes/no) or regression (numeric values such as DAS28).

Objectives: To investigate in which clinical RA subtypes AdaptiveNet achieves the best results for the prediction of individual disease activity

Methods: Demographic and disease characteristics from over 9500 patients and 65,000 visits from the Swiss Quality Management (SCQM) database were used to train and evaluate the network. Patient characteristics, clinical and patient reported outcomes, laboratory values and medication were used as input features. DAS28-BSR served as a target to predict active RA and future numeric individual disease activity by classification and regression. Feature importance