LIBYAN JOURNAL OF MEDICINE
2018, VOL. 13, 1512330
https://doi.org/10.1080/19932820.2018.1512330

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A cross sectional study of bone and cartilage biomarkers: correlation with structural damage in rheumatoid arthritis

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ABSTRACT

The aim of our study was to assess the relationship between bone and cartilage remodeling biomarkers and joint damage in Rheumatoid Arthritis (RA), and to detect whether they have the capacity to predict the progression of joint disease assessment by computed tomography (CT) erosion score. We analyzed 65 female patients with established RA in our Rheumatology Department. Serum levels of bone and cartilage markers were measured: osteocalcin (OC), N-propeptide of type I collagen (PINP), collagen type I and II, C-telopeptide (CTX I, CTX-II) and cartilage oligomeric matrix protein (COMP). Radiography of both wrist and MCP joints were available. Two expert-readers independently scored articular damage and progression using the High-resolution low dose CT scan in a blinded fashion. 65 female patients with established RA with a median age of 44 years were included. The median disease-duration was two years and the median (Disease activity score) DAS 28 score at 4.46 [2.65–7.36]. The percentage of patient with low disease activity was 13.8%, while 55.4 and 30.8% for those with moderate and high disease activity respectively. The resorption bone markers were high in active versus non-active RA. Wrist and MCP erosion scores were also associated with RA activity. Our study shows that biomarkers of bone and cartilage collagen breakdown were related to specific joint erosion in RA and could predict subsequent radiographic damage in RA. Further larger scale longitudinal studies maybe needed to confirm our data.

ARTICLE HISTORY
Received 21 May 2018
Accepted 9 August 2018

KEYWORDS
RA, biomarkers, CT

1. Background

Rheumatoid arthritis (RA) is a chronic connective tissue disease with a worldwide prevalence around 1% [1]. It is associated with progressive disability, systemic complications, early death, and heavy socioeconomic costs [2]. It is characterized by a polyarticular inflammation affecting large and small joints, especially those of the hands. This inflammatory process caused by the synovitis leads to swollen and painful joints and then potential articular destruction, mostly with production of autoantibodies: rheumatoid factor (RF) and anti-citrullinated protein antibody (antiCCP). Consequently, alteration of articular cartilage and bone erosions induce impaired joint function which occurs mainly in the first two years of disease evolution [3–5].

Conventional radiographs (CR) and ultrasound (US) are widely performed for assessing structural joint damage associated with (RA). However, these methods are less sensitive – especially for the wrist evaluation- due to inter-reader variability [6]. For this reason, the computed tomography (CT) has become the most considered and sophisticated method based on its three-dimensional (3D) visualization of calcified tissue [7]. It allows acquiring high-resolution volume data in few seconds and providing detailed anatomical information, such as bone erosion, which can be assessed in frontal, sagittal and transversal planes [8].

Assessing the RA disease activity in clinical practice is mainly based on the evaluation of the DAS28 score, commonly used in daily practice and in studies related to RA evolution and therapeutic efficacy [9]. New biomarkers of bone and cartilage remodeling process have been discovered. They are molecular indicator of quantitative change in bone mineral status whether detecting formation, such as osteocalcin (OC), alkaline phosphatase bone isoenzyme (BALP) and C- and N-propeptide of type I collagen (PICP and PINP), or degradation with the collagen type I releases the N and C-terminal cross-linked telopeptide of type I collagen (NTX, CTX I) [10,11].

Likewise, several cartilage degradation fragments, such as collagen type II C-telopeptide (CTX II) and cartilage oligomeric matrix protein (COMP) [12,13], have been identified and can be measured.

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Therefore, our study aimed to assess the variation of bone and cartilage biomarker levels (CTX I, OC, PINP, CTX II and COMP) in RA patients and their correlation with disease duration and activity firstly and bone CT joint destruction secondarily.

2. Methods

2.1. Patients and protocol

Sixty-five RA female patients were recruited from outpatient clinics or hospitalized ones, during a period of 2 years at the Rheumatology department of two main university hospitals. All patients fulfilled the (ACR) classification criteria for RA [14]. There was no significant difference in biomarkers levels between pre- and post-menopausal women. All patients were DMARD (disease modifying anti-rheumatic drugs) naïve.

The exclusion criteria in our cohort study were: osteoporosis, osteoarthritis or any other disease affecting bone or cartilage remodeling.

The study protocol was approved by our institutional ethics committee. All patients gave written informed consent according to the Declaration of Helsinki before entering the trial.

2.2. Clinical assessment

All patients were subjected to detailed medical history. A thorough clinical examination was performed and the disease activity score 28-C-reactive protein (DAS28-CRP) assessed.

Patients were subdivided according to their DAS score into:

- Low disease activity: DAS28 ≤ 3.2
- Moderate disease activity: 3.2< DAS28 ≤ 5.1
- High disease activity: DAS28 > 5.1

To optimize statistical results, we further compared patients with very active RA (DAS 28 > 5.1) to the rest of the patients (DAS 28 < 5.1).

2.3. Laboratory examinations

Fasting blood samples were collected from all patients. Standard measure of CRP was performed the same day using architect ci 8200 automate. Serum samples for quantification of bone and cartilage remodeling markers were aliquoted, and frozen at −80°C until being processed.

Bone biomarkers including (OC), (PINP and CTXI) were assayed using a chemiluminescence method (ECLIA) on Cobas E411 PLC (from Roche Diagnostic). The intra-individual variance was CV %< 20%.

Cartilage biomarkers including: (CTXII) and COMP were quantified by a quantitative sandwich immunoassay technique (ELISA) assay kit (CUSABIO), according to the manufacturer protocol. The intra- and inter-assay coefficients of variation (CVs) were < 8 and < 10%, respectively.

2.4. CT assessment

All patients underwent a low dose high-resolution CT scan of both wrists and metacarpophalangeal joints using a Philips Brillance 6-slice scanner (Philips Medical Systems, Cleveland, OH, USA). Axial, coronal and sagittal CT images with a slice thickness of 0.6 mm were taken. Radiation dose was determined using DLP (Dose Length Product). The mean DLP was 695.4 mGy*cm. CT images were separately evaluated for detecting bone erosions by two experienced musculoskeletal radiologists (6 and 14 years' experience in musculoskeletal imaging), and blinded to clinical and other imaging data. The position and volume of erosions of the dominant wrist bones, scaphoid, lunate, triquetrum, pisiform, trapezium, trapezoid, capitate, hamate, distal ulna, distal radius and metacarpal bases, were estimated using OSIRIX imaging software version 7.0 (from Pixmeo SARL company, Switzerland) . The erosion scores were assigned considering the percentage of involved bone volume (score 0–10, by 10% volume increments), leading to a total score ranging from 0 to 150 on the basis of the OMERACT RAMRIS scoring method [15].

The score used in our statistical analysis is the mean score value obtained from the two observers' readings with an inter-observer variation coefficient < 5%.

2.5. Statistical analysis

Due to the non-Gaussian character of some variables, non-parametric tests were used in this statistical analysis. Therefore, we thought it was better to report the statistical results as median, minimum and maximum rather than as a mean ± standard deviation (SD).

The Kruskall-Wallis test was used to compare quantitative variables between the three RA subgroups. $p < 0.05$ was considered statistically significant.

However, to compare quantitative variables between subgroups if the overall comparison was significant, we use the Mann-Whitney test with a significant p value = 0.017 in the first way of subdivision (three groups to compare), and a $p < 0.05$ in the second way of subdivision (one single comparison).

A Spearman correlation coefficients were calculated for correlation analysis between radiographic erosion scores and demographic, clinical and biochemical markers. All statistical analyses were carried out using SPSS version 16.0. (SPSS Inc, Chicago, IL, USA).

3. Results

3.1. Demographic, clinical and biologic characteristics

Sixty-five female patients followed-up for RA with disease duration of 2 years [0–15] were included in this study (Table 1). There was no significant difference in menopausal status. Their median age was 44 years [21–59]. The median numbers of painful and swollen joints were 6 [1–28] and 3 [0–13], respectively. The median value of visual analogue scale for pain (VAS) was 60 [10–100]. The median CRP level was at 13 mg/L [0.3–88] and consequently the median DAS 28-CRP value was 4.46 [2.65–7.36]. Only 13.8% of RA patients were in low disease activity, while 55.4% and 30.8% were in moderate and high disease activity, respectively.

Regarding to bone and cartilage biomarkers, we noticed an increase in the resorption process in favor to the formation one by comparing the levels of biomarkers in RA patients to their normal control range.

Table 1. Baseline characteristic of the all RA cohort.

	Female patients (%)	100
Demographic	Age (years)	44 [21–59]
Clinical parameters	Disease duration (years)	2 [0.08–15]
	Tender joint	6 [1–28]
	Swollen joint	3 [0–13]
	VAS	60 [10–100]
	DAS 28	4.46 [2.65–7.36]
Biological parameters	CRP (mg/L)	13 [0.3–88]
	CTX I (ng/mL)	0.48 [0.3–1.04]
	OC (ng/mL)	14.99 [6.33–34.92]
	PINP (ng/mL)	37.9 [12.6–72.2]
	COMP (ng/mL)	10.6 [3.04–19.6]
	CTXII (ng/mL)	0.64 [023–1.25]
Radiological parameters	Erosion noted in MCP	0.5 [0–21]
	Erosion noted in Wrist	3.5 [0–30]
Treatment modalities	Methotrexate N (%)	45 (69.2%)
	Combination therapy N (%)	5 (7.69%)
	Sulfasalazine, N (%)	9 (13.84%)
	Leflunomide, N (%)	6 (9.23%)

Values expressed as median [Minimum-Maximum] or absolute value and percentage; **RA**: Rheumatoid arthritis; **VAS**: visual analogue scale for pain; **CRP**: C-reactive protein; **DAS28**: Disease activity score; **CTX I**: C-terminal telopeptide of type I collagen; **OC**: osteocalcin; **PINP**: N-terminal propeptide of collagen type I; **COMP**: Cartilage oligomeric matrix protein3; **CTX II**: C-telopeptide fragment of collagen II; **MCP**: metacarpo-phalangeal joint; **N**: number of patients.

3.2. CT scan results

The median erosion scores noted in wrist and MCP joints were 3.5 [0–30] and 0.5 [0–21], respectively.

3.3. Comparison of the different parameters according DAS28 results

We compared demographic, clinical and inflammatory parameters, bone and cartilage markers and CT erosion scores in the three subgroups of patients according to the RA activity (Table 2).

All our patients were treated with DMARD. Most of them were on methotrexate (69%) a common RA treatment, (7.6%) were under combined therapy and the rest were on sulfasalazine or leflunomide.

We noticed that the high disease activity cohort had the longest RA duration. This may be due to the low response to therapy. A significant correlation with RA activity was observed in bone markers levels (CTXI, OC and PINP) and CT erosion scores but not in the cartilage marker COMP.

In the multiple comparisons between RA subgroups (Table 3), there were no significant differences between RA in low or moderate disease activity. Whereas, these two subgroups were significantly different from the higher RA activity group in terms of bone markers levels (CTX I, OC and PINP) and CT erosion scores.

These results were more evident when we compared the group of high activity RA (DAS28 > 5.1) to the other patients (Table 4).

The study of correlation between CT erosions scores and the other parameters showed a strong positive correlation between structural damage and the other parameters, such as the DAS28 index, the CRP level and the bone resorption marker value CTXI, whereas a negative correlation was found with bone formation markers levels (OC and PINP). No correlation was established between erosion scores and cartilage degradation biomarkers. (Table 5).

When correlating between DAS 28 score and the other parameters, we found that disease severity correlated

Table 2. Comparison of demographic, clinical and biological characteristics of the different sub-groups of patients.

Baseline demographics, clinical and biological characteristics	Group I DAS28 ≤ 3.2	Group II 3.2< DAS28 ≤ 5.1	Group III DAS28 > 5.1	*p* value*
Number (%)	**9** [13.8]	**36** [55.4]	**20** [30.8]	NS
Age (years) (median)	**48** [32–54]	**42.5** [21–59]	**44** [31–54]	NS
Disease duration (years)	**1** [0.08–7]	**2.5** [0.08–10]	**6** [0.08–15]	**< 0.05**
CRP (mg/L)	**1.2** [0.3–13]	**7.9** [0.5–49]	**36** [5.2–88.5]	**< 0.001**
CTX I (ng/mL)	**0.37** [0.29–0.62]	**0.45** [0.3–0.83]	**0.58** [0.3–1.04]	**< 0.01**
OC (ng/mL)	**17.3** [12–34.9]	**17.2** [6.9–34.5]	**12.5** [6.3–29.9]	**< 0.01**
PINP (ng/mL)	**51.4** [31.5–69.5]	**41.6** [12.6–72.2]	**31.6** [12.8–56]	**< 0.01**
COMP (ng/mL)	**13** [5.1–15.3]	**9.89** [3.04–19.6]	**10.9** [5.1–16.5]	NS
CTX II (ng/mL)	**0.63** [0.48–1.03]	**0.62** [0.23–19.6]	**0.65** [0.38–1.21]	NS
MCP erosion score	**0** [0–3.5]	**0.25** [0–6]	**4.5** [0–21]	**< 0.01**
Wrist erosion score	**0** [0–8]	**3** [0–18]	**14** [0–30]	**< 0.01**

* Kruskall-Wallis test.

Values expressed as median [Minimum-Maximum]; **RA**: Rheumatoid arthritis; **CRP**: C-reactive protein; **DAS28**: Disease activity score; **CTX I**: C-terminal telopeptide of type I collagen; **OC**: osteocalcin; **PIPN**: N-terminal propeptide of collagen type I; **COMP**: Cartilage oligomeric matrix protein 3; **CTX II**: C-telopeptide fragment of collagen II; **MCP**: metacarpo-phalangeal joint; **NS**: no significant.

Table 3. Multiple comparison of clinical, radiological and biological characteristics between RA subgroups.

Clinical, biological and radiological parameters	Multiple comparisons inter RA subgroups		
	Group I vs group II	Group I vs Group III	Group II vs Group III
Disease duration (years)	NS	**< 0.01**	NS
CRP (mg/L)	**< 0.01**	**< 0.001**	**< 0.001**
CTX I (ng/mL)	NS	**< 0.01**	**< 0.01**
OC (ng/mL)	NS	**< 0.01**	**< 0.01**
PINP (ng/mL)	NS	**< 0.01**	**< 0.01**
COMP (ng/mL)	NS	NS	NS
CTX II (ng/mL)	NS	NS	NS
MCP erosion score	NS	NS	**< 0.01**
Wrist erosion score	NS	**< 0.01**	**< 0.01**

Mann-Whitney test.

Numbers indicate *p* values; **CRP**: C-reactive protein; **MCP**: metacarpo-phalangeal joint**; CTX I**: C-terminal telopeptide of type I collagen; **OC**: osteocalcin; **PINP**: N-terminal propeptide of collagen type I; **COMP**: Cartilage oligomeric matrix protein 3; **CTX II**: C-telopeptide fragment of collagen II; **Group I**: DAS28 ≤ 3.2, **Group II**: 3.2< DAS28 ≤ 5.1, **Group III**: DAS28 > 5.1; **NS**: no significant.

with disease duration, erosion score and bone markers but did not correlate with cartilage biomarkers. (Table 6).

4. Discussion

Bone erosions are major characteristics of RA and a part of its classification criteria. It occurs rapidly affecting 80% of patients within the 1st year of the disease [4]. Therefore, it is important to have a tight disease control to identify patients with rapid joint destruction. The CT scan represents a perfect method for the assessment of bone abnormalities, due to its high spacial resolution. It is sensitive for detecting bone erosions in MCP joints in the early stage of RA [16,17]. Otherwise, bone and cartilage biomarkers values can detect metabolism abnormalities observed during the remodeling process.

Our study showed a significant difference in levels of bone markers with a high level of resorption markers CTX I in patients with higher activity unlike bone formation ones, such as OC and PINP, which were higher in low active RA. These results were confirmed when we compared the group of very active RA to the others, with a statistically significant difference ($p < 0.01$). This has not been the case with cartilage biomarker.

The CTX I seems to be the best predictor of RA disease activity. In fact, any increase exceeding the normal range values may reflect an active RA and is manifested by rapid joint destruction.

Table 5. Correlation values between CT erosion scores and others parameters.

Variables	*r* values between CT scores and other parameters			
	Wrist erosion CT score		MCP erosion CT score	
Age	0.064	NS	0.173	NS
Disease duration (Years?)	0.228	NS	0.214	NS
DAS 28	**0.41**	***p* < 0.01**	**0.38**	***p* < 0.01**
CRP	**0.35**	**P < 0.01**	**0.37**	**P < 0.01**
CTX I	**0.43**	**P < 0.001**	**0.42**	**P < 0.001**
OC	**−0.39**	**P < 0.01**	**−0.38**	**P < 0.01**
PINP	**−0.32**	**P < 0.01**	**−026**	**P < 0.05**
COMP	0.196	NS	0.202	NS
CTXI I	0.061	NS	0.050	NS

r: Spearman correlation value; **NS**: non-significant; **CRP**: C-reactive protein; **DAS28**: Disease activity score; **CTX I**: C-terminal telopeptide of type I collagen; **OC**: osteocalcin; **PINP**: N-terminal propeptide of collagen type I; **COMP**: Cartilage oligomeric matrix protein3; **CTX II**: C-telopeptide fragment of collagen II.

Table 6. Correlation values between DAS28 score and others parameters.

Variables	*r* values between DAS28 scores and other parameters	
	DAS 28	*p*
Age	0.048	NS
Disease duration	**0.27**	**< 0.05**
CRP	**0.73**	**< 0.001**
CTX I	**0.46**	**< 0.001**
OC	**−0.40**	**< 0.01**
PINP	**−0.46**	**< 0.001**
COMP	0.17	NS
CTX II	0.03	NS
MCP erosion score	**0.38**	**< 0.01**
Wrist erosion score	**0.41**	**< 0.01**

r: Spearman correlation value; **NS**: no significant; **CRP**: C-reactive protein; **DAS28**: Disease activity score; **CTX I**: C-terminal telopeptide of type I collagen; **OC**: osteocalcin; **PINP**: N-terminal propeptide of collagen type I; **COMP**: Cartilage oligomeric matrix protein3; **CTX II**: C-telopeptide fragment of collagen II; **MCP**: metacarpo-phalangeal joint.

Table 4. Comparison of demographic, clinical, biological and radiological characteristics between very active RA group and the other sub group of patients.

Demographic, clinical, biological and radiological parameters	Group I (*N* = 45) Das28 ≤ 5.1	Group II (*N* = 20) Das28> Das 28 > 5.1	*p* value **
Age (years)	**43** [21–59]	**44** [31–54]	NS
RA duration (years)	**2** [0–10]	**6** [0–15]	NS
CRP (mg/L)	**7** [3–49]	**36** [5.2–88.5]	**< 0.001**
CTX I (ng/mL)	**0.44** [0.29–0.83]	**0.58** [0.3–1]	**< 0.01**
OC (ng/mL)	**17.3** [6.9–34.9]	**12.5** [6.3–29.9]	**< 0.01**
PINP (ng/mL)	**43.3** [12.6–72.2]	**31.6** [12.8–56)	**< 0.01**
COMP (ng/mL)	**10.2** [3–19.6]	**10.9** [5.1–16.5]	NS
CTX II (ng/mL)	**0.63** [0.23–1.25]	**0.65** [0.38–1.21]	NS
MCP erosion score	**0** [0–6]	**4.5** [0–21]	**< 0.01**
Wrist erosion score	**2** [0–18]	**14** [0–30]	**< 0.01**

** Mann-Whitney test.

Values as median [Minimum-Maximum]; **RA**: Rheumatoid arthritis; **CRP**: C-reactive protein, **DAS28**: Disease activity score; **CTX I**: C-terminal telopeptide of type I collagen; **OC**: Osteocalcin; **PINP**: N-terminal propeptide of collagen type I; **COMP**: Cartilage oligomeric matrix protein 3; **CTX II**: C-telopeptide fragment of collagen II; **NS**: no significant; **Group I**: DAS 28 ≤ 5.1; **Group II**: DAS 28 > 5.1.

These results were similar to those found by Zhu L et al. (2014) through a study conducted on 51 RA patients. Serum biochemical markers of bone formation (PINP, OC) and bone resorption (CTX I) were detected by chemiluminescence, in addition to other clinical and serological parameters. Serum CTX I level was significantly higher in RA patients than in healthy controls Serum PINP and OC levels of RA patients were correlated negatively with morning stiffness ($p < 0.05$) and pain VAS score ($p < 0.05$) [18].

These results were consistent with those found by Garnero P and et al. (1999); the CTX I levels were high in patients with destructive arthritis compared to controls (+ 35%, $p < 0.001$), but no difference between those with non-destructive RA and controls. However levels of OC were significantly lower in both destructive (−17%) and non-destructive (−22%) groups compared to control subjects ($p < 0.001$ for both groups) [19].

Several correlations have been assessed between CT erosions scores noted in both wrist and MCP with the other clinical and biological parameters. A significant correlation between erosion score and RA activity was shown. Concerning biomarkers, we found a strong positive correlation between score erosion and bone resorption CTX I. However, inverse correlation was found between CT score and bone formation markers such as OC and PINP. There was no correlation between CT score and disease duration or cartilage biomarkers.

Some studies evaluated the level of bone metabolism markers in RA patients. Some of them reported that patients who developed bone erosions had higher level of resorption markers and lower rate of bone formation markers. Aschenberg S et al. (2013) showed that erosions, evaluated by CT scan, correlated with age and disease activity, and strongly with disease duration. Indeed, regarding bone markers, only TRAP5b was correlated to bone erosion, while CTX I did not [20]. Thus the structural bone changes, assessed by CT, were associated with a variation in biomarkers levels. The bone erosions in RA patients depend on disease duration as noted in our cohort.

Another study, reported by Jansen et al. (2004), has shown that CTX I and OC levels were significantly higher ($p < 0.05$) in erosive disease group and that the levels of CTX I significantly correlated with radiographic damage, while OC did not [21]. Therefore, the bone turnover marker CTX I was associated with radiographic damage at baseline and after 2 years.

Furthermore, in longitudinal studies, catabolic bone markers (CTX I or pyridinoline (PYD)) were also considered as good predictors for radiologic progression in RA. In fact, Loët et al. (2010) showed that IgA-Rheumatoid factors and pyridinoline, were risk factors for erosions when their levels were simultaneously elevated [22]. The same results were reported by Krabben et al. (2013) which found that increased pyridinoline serum levels, both at baseline and during the disease course, were associated with more severe joint damage during the following years [23].

A recent study developed by Gao et al. (2016) showed a positive correlation between quantitative values of joint bone scan assessed by the single photon emission computed tomography (SPECT) and serum markers levels of CTX I and PINP in patients with RA. Thus, SPECT imaging alone or combined with bone markers are helpful for diagnosing an active RA [24].

Regarding cartilage biomarkers assessed in our study, we noticed a correlation between CTX II/COMP ($r = 0.53$ $p < 0.001$), however, there was no correlation with CT erosion.

Garnero et al. (2002) have proved that patients with high CTX II level had a higher progression of joint damage over one year, regardless of the baseline extent of joint destruction and clinical indexes of disease activity [25,26]. Baseline CTX II was increased more than two-fold and remained high after a year in patients with early RA compared to controls. Similarly, CTX II was higher in RA patients with long-standing disease compared to control subjects [27].

Andersson et al. (2013) reported that serum COMP was reduced in RA patients in remission. In early stage RA, early changes in serum COMP levels were related to radiological progression over the first 5 years. This biomarker wasn't yet studied in inactive RA on biologic therapy [13].In conclusion, COMP represents a new indicator tool for an activated destructive process in the joint.

The originality of our study is among the strength points. In fact, the variation of the bone and cartilaginous markers in correlation with RA activity and articular destruction identified by CT has not been overly discussed.

However, this study has some limitations, particularly the small number of patients and its cross-sectional aspect. The use of CT may not be considered as a limitation because we combined high-resolution images with low radiation dose delivered to each patient.

In conclusion, our evaluation pertaining to bone and cartilage markers in RA, showed an increase of resorption parameters comparing to those of formation. Our results confirmed these previous observations and suggested a positive correlation between CT erosion score, clinical data and resorption biomarkers. A follow-up of this cohort of patients is interesting in order to confirm the previous result obtained and to explore new markers like (Carboxy terminal type I collagen telopeptide) ICTP [28], which seems to be a sensitive marker of periarticular bone resorption, that we will consider in the near future.

Acknowledgments

This work was supported by a grant from "The Ministry of Higher Education, Scientific Research and Technologies.

Disclosure statement

No potential conflict of interest was reported by the authors.

Funding

This work was supported by a grant from The Ministry of Higher Education, Scientific Research and Technologies.

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