

Distinct periarticular muscle transcriptomes: inflammation in rheumatoid arthritis *versus* metabolic dysregulation in osteoarthritis

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Abstract

Objective

Periarticular skeletal muscle abnormalities are recognised in rheumatoid arthritis (RA) and osteoarthritis (OA), but their divergent molecular pathologies are poorly defined. This study aimed to elucidate and directly compare the transcriptomic profiles of periarticular muscle in patients with RA and OA.

Methods

We performed bulk RNA sequencing of periarticular skeletal muscle samples collected during total joint arthroplasty from RA (n=6) and OA (n=4) patients. Differential gene expression analysis, weighted gene co-expression network analysis (WGCNA), pathway enrichment, and gene set variation analyses were conducted to identify disease-specific molecular features and their clinical associations.

Results

The two conditions showed fundamentally distinct profiles. RA muscle exhibited a pronounced inflammatory signature, characterised by upregulation of cytokine-responsive genes including *FOS*, *EGR1*, and *CXCL2*, and enrichment of tumour necrosis factor- α and interleukin-6 (IL-6)/JAK-STAT3 signalling. In contrast, OA muscle was characterised by metabolic dysregulation, with upregulation of genes linked to adipogenesis (*PCK1*, *SFRP4*) and significant enrichment of epithelial-to-mesenchymal transition (EMT) signalling. These divergent profiles were further supported by WGCNA, which identified distinct modules reflecting heightened innate immune and complement activation in RA, and disrupted metabolic processes in OA. Notably, in RA, the IL-2–STAT5 signalling pathway was unique among those tested in showing a strong positive correlation with DAS28-ESR ($r=0.94$, $p=0.019$).

Conclusion

This study reveals distinct molecular pathologies in the periarticular muscle of RA and OA. RA muscle shows an intense inflammatory profile potentially linked to cachexia, whereas OA muscle displays features of metabolic disease and pro-fibrotic remodelling.

Key words

rheumatoid arthritis, osteoarthritis, muscle, transcriptome, metabolic dysregulation

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Received on October 25, 2025; accepted
 in revised form on January 30, 2026.

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 EXPERIMENTAL RHEUMATOLOGY 2026.

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Funding: this research was supported by
 the Japan Agency for Medical Research
 and Development (AMED) under grant
 no. 19ek0410047 and by JSPS KAKENHI
 Grant-in-Aid for Research Activity Start-up
 (grant no. 25K23897 to S.I.).

Competing interests: see page 1765.

Introduction

Rheumatoid arthritis (RA) is a multi-factorial autoimmune disease shaped by interacting genetic, environmental, and immune mechanisms, with both innate and adaptive immune pathways contributing to joint pathology and systemic manifestations (1). Skeletal muscle is increasingly recognised not merely as a tissue secondarily affected by joint disease but as an organ directly implicated in the pathophysiology of both RA and osteoarthritis (OA). In RA, this is exemplified by rheumatoid cachexia – loss of muscle mass and function – that adds substantially to disability, morbidity, and premature mortality (2, 3). This debilitating muscle wasting is driven by a systemic inflammatory milieu, wherein pro-inflammatory cytokines such as tumour necrosis factor- α (TNF- α) and interleukin-6 (IL-6) exert direct catabolic effects on muscle tissue by activating proteolytic pathways and disrupting metabolic homeostasis (3). Furthermore, quantitative imaging shows that muscle inflammation and fatty infiltration arise early in RA and persist despite clinical remission, underscoring muscle involvement as a core disease feature (4). Moreover, evidence from animal models, histopathology, and positron emission tomography (PET) suggests that synovial inflammation can extend into adjacent periarticular muscle (5).

In contrast, the muscle pathology in OA, while also characterised by periarticular atrophy and fatty infiltration that compromise joint stability and function (6, 7), is thought to be driven by more localised mechanisms. This includes low-grade inflammation and altered molecular signalling, with elevated levels of proteins such as p65 NF- κ B, STAT-3, and JNK observed in the muscle of OA patients, distinguishing it from simple disuse atrophy (8). Despite phenotypic overlap, the molecular distinctions between RA- and OA-associated muscle pathology remain unclear. We therefore performed a comparative transcriptomic analysis of periarticular muscle from RA and OA to define disease-specific programmes.

Methods

Study design and participants

Muscle biopsy samples and clinical data

were collected from patients with RA and OA. All patients provided written informed consent, and the study was approved by the Ethics Committee of the University of Tokyo (approval no. G10137).

Muscle biopsy and

RNA-sequencing library preparation

Muscle biopsies were obtained during arthroplasty procedures, with detailed methods having been described previously (9). Following the careful dissection and removal of adjacent non-muscle tissues (*e.g.* ligaments, synovium, adipose tissue), the remaining muscle was sectioned into ~3-mm cubes and immediately preserved in RNAlater (Qiagen). For RNA extraction, tissues were homogenised and lysed in QIAzol Lysis Reagent (Qiagen) using a Tissue-Lyser LT (Qiagen) at 50 Hz for 2 minutes. Total RNA was subsequently isolated using the RNeasy Universal Mini Kit (Qiagen). Complementary DNA (cDNA) was synthesised from the extracted RNA with the SMART-Seq HT Kit (Takara Bio). Finally, sequencing libraries were prepared using the Nextera XT DNA Library Preparation Kit (Illumina) and purified with AMPure XP beads (Beckman Coulter). The resulting libraries were sequenced on an Illumina NovaSeq 6000 platform to generate 150-bp paired-end reads.

RNA-sequencing data

mapping and quality control

Raw reads were aligned to the human reference genome (GRCh38) with STAR (v. 2.5.3) using GENCODE v. 27 annotations; non-canonical haplotypes were excluded. Only reads that were uniquely mapped and properly paired were retained. Gene-level counts were generated with HTSeq-count (v. 0.6.0), and transcript-level estimates with RSEM (v. 1.3.0). Genes were filtered to remove low-expression features. Specifically, genes were excluded if they had fewer than 10 raw counts in more than 85% of samples and/or had CPM <1 in more than 85% of samples. Filtered count matrices were normalised using the trimmed mean of M-values (TMM) method implemented in edgeR (v. 4.3).

Table I. Baseline patient characteristics.

	Disease	Sex	Age	Operation	PSL	MTX	bDMARDs	RF	CCP	CRP	PhGA	PtGA	DAS28-CRP	DAS28-ESR	SDAI	CDAI
1	RA	M	81	THA	+	+	-	-	-	0.18	10	78	2.7	3.65	9.98	9.8
2	RA	M	70	TKA	+	-	-	+	+	1.57	20	50	2.67	3.32	8.57	7
3	RA	F	71	THA	+	+	TCZ	-	+	0	20	30	1.24	1.25	4	4
4	RA	F	74	THA	+	+	ETN	+	-	2.03	50	50	3.72	4.88	15.03	13
5	RA	F	71	TKA	+	+	-	-	+	0.14	45	52	2.49	4.24	12.84	12.7
6	RA	F	60	TKA	-	+	-	+	-	0.05	0	0	1.95	2.38	2.05	2
7	OA	F	45	THA	-	-	-	-	-	0.5	0	0				
8	OA	F	63	THA	-	-	-	-	-	0.34	50	50				
9	OA	F	65	THA	-	-	-	-	-	0.04	80	80				
10	OA	F	68	THA	-	-	-	-	-	0.14	80	84				

RA: rheumatoid arthritis; OA: osteoarthritis; M: male; F: female; THA: total hip arthroplasty; TKA: total knee arthroplasty; PSL: prednisolone; MTX: methotrexate; bDMARDs: biologic disease-modifying anti-rheumatic drugs; TCZ: tocilizumab; ETN: etanercept; RF: rheumatoid factor; CCP: anti-cyclic citrullinated peptide antibody; CRP: C-reactive protein; PhGA: physician's global assessment of disease activity; PtGA: patient's global assessment of disease activity; DAS28-CRP: Disease Activity Score 28 using C-reactive protein; DAS28-ESR: Disease Activity Score 28 using erythrocyte sedimentation rate; SDAI: Simplified Disease Activity Index; CDAI: Clinical Disease Activity Index.

Differential expression and enrichment analysis and weighted gene co-expression network analysis

Differential expression analysis between RA and OA was performed using edgeR's negative binomial generalised linear model framework, with adjustment for age and sex. Weighted gene co-expression network analysis (WGCNA) (v. 1.72-5) identified modules linked to clinical traits. A soft-thresholding power of 20 (selected by scale-free topology fit) produced a signed adjacency matrix that was transformed into a Topological Overlap Matrix (TOM). Hierarchical clustering of 1 – TOM defined gene modules, and their eigengenes were correlated with clinical variables to highlight biologically relevant modules. Gene ontology (GO) biological process (BP) enrichment was then performed for each module to infer putative functions.

Gene set enrichment and variation analysis

A ranked gene list from the differential gene expression (DEG) analysis (using log₂ fold change in descending order) was used to conduct gene set enrichment analysis (GSEA) with the clusterProfiler package, applying a *p*-value cut-off of 0.05 to identify significantly enriched gene sets. Additionally, gene set variation analysis (GSVA) was performed using GSVA software (v. 3.18) to calculate enrichment scores and *p*-values were adjusted using the Benjamini-Hochberg method, applying a cut-off of 0.05 to identify significantly enriched

gene sets. Gene sets were selected from the Molecular Signature Database (MSigDB) hallmarks collection, including pathways such as the complement system, interleukin-2 (IL-2)/STAT5 signalling, IL-6/JAK-STAT3 signalling, interferon- α response, oxidative phosphorylation, TNF- α signalling via NF- κ B, and hypoxia.

Exploratory within-RA transcriptional profiling by biologic therapy

To explore treatment-associated transcriptional patterns in RA periarticular muscle, we performed an exploratory comparison between RA samples from patients receiving biologic therapies (etanercept or tocilizumab; *n*=2 total) and RA samples from patients not receiving biologics. Given the very small number of biologic-treated samples, we did not perform conventional gene-level differential expression testing and instead focused on covariate-adjusted effect sizes and pathway-level ranking. Raw read counts were TMM-normalised, lowly expressed genes were filtered using filterByExpr, and expression values were transformed to voom log₂ counts per million (logCPM). We fit a linear model to voom-transformed expression with biologic exposure as the primary variable of interest and age, sex, and DAS28-ESR as covariates to account for demographic differences and disease activity. The covariate-adjusted coefficient for biologic exposure was used as an effect-size metric to rank genes. Preranked GSEA was

performed using fgsea (multilevel implementation; v. 1.36.2). All genes were ranked by the covariate-adjusted biologic exposure coefficient, and enrichment was assessed against MSigDB Hallmark gene sets and GO BP gene sets. Gene sets were filtered by size (min 15, max 500). Results are reported as normalised enrichment scores (NES) and fgsea-adjusted *p*-values (*padj*) and were interpreted as pathway-level summaries of the ranked list (hypothesis-generating), rather than as gene-level statistical significance.

Statistical analysis

Differential expression was assessed using edgeR with a negative binomial generalised linear model including disease status and adjustment for age and sex, and differential expression was tested using a likelihood ratio test. *p*-values were adjusted for multiple testing using the Benjamini-Hochberg method, and genes with FDR <0.05 were considered significant. GSVA enrichment scores were compared between groups using the Mann-Whitney U-test with Benjamini-Hochberg correction across the tested gene sets (adjusted *p*<0.05). Associations between pathway scores and clinical parameters were evaluated using Spearman's rank correlation. All analyses were performed in R (v. 4.3.2).

Results

Patient characteristics

We analysed periarticular muscle from ten patients who underwent total knee

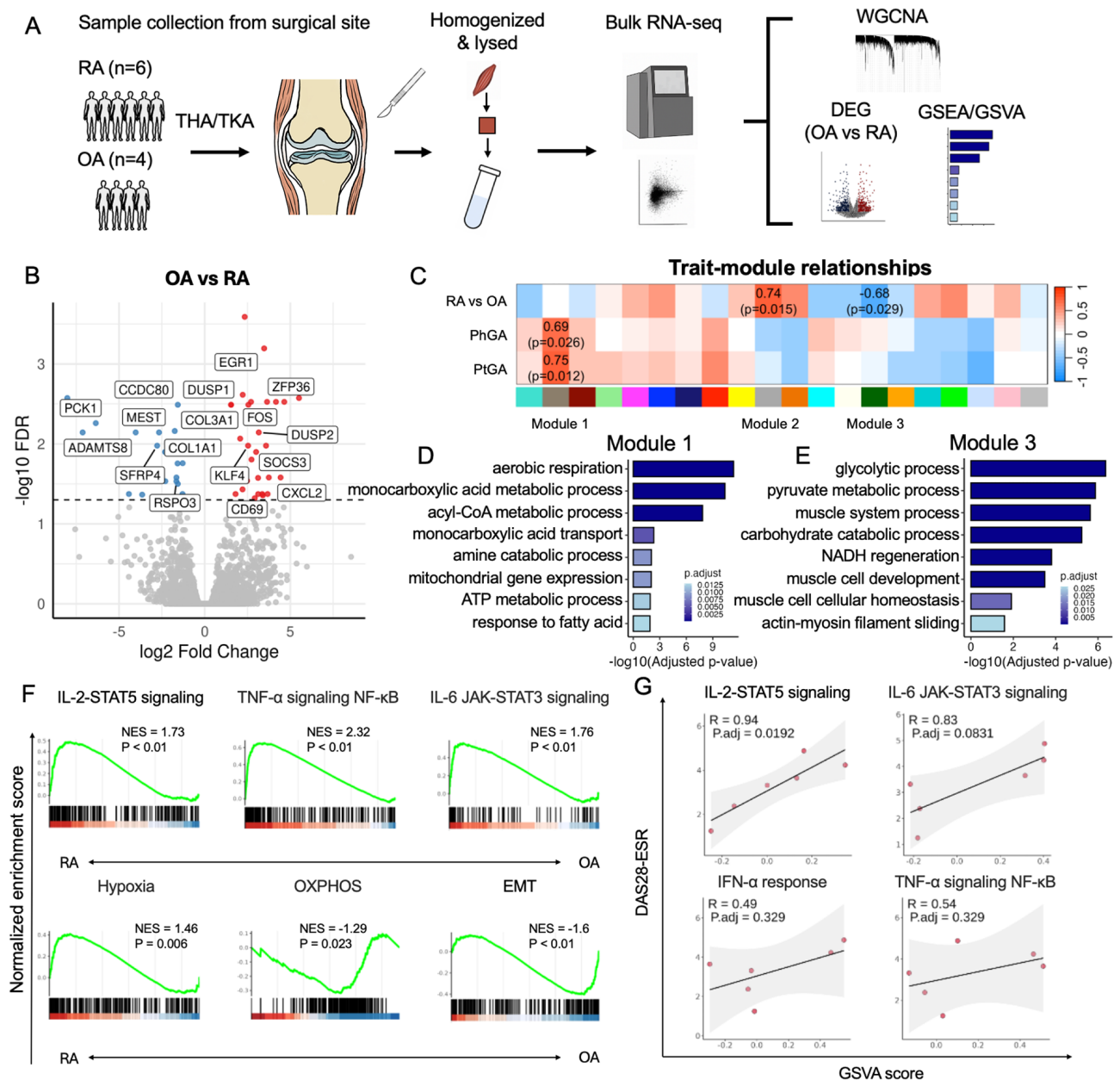


Fig. 1. Distinct periarticular muscle transcriptomic signatures in RA and OA.

A: Study workflow. Periarticular skeletal muscle was collected from patients with rheumatoid arthritis (RA; $n=6$) or osteoarthritis (OA; $n=4$) undergoing TKA or THA. Samples were homogenised and subjected to bulk RNA sequencing followed by WGCNA, DEG, GSEA, and GSVA.

B: DEGs comparing OA vs. RA.

C: Heatmap of WGCNA module-trait correlations, showing associations of gene co-expression modules with disease, PhGA and PtGA.

D-E: Top enriched gene ontology terms in modules 1 and 3, respectively.

F: GSEA results for hallmark gene sets in RA vs. OA muscle. Pathways such as IL-2-STAT5, TNF- α -NF- κ B, IL-6-JAK-STAT3 signalling, and hypoxia are enriched in RA, whereas oxidative phosphorylation and epithelial-mesenchymal transition are enriched in OA.

G: Scatter plots showing GSVA scores of inflammatory pathways in RA muscle correlated with DAS28-ESR.

TKA: total knee arthroplasty; THA: total hip arthroplasty; RA: rheumatoid arthritis; OA: osteoarthritis; FDR: false discovery rate; GSEA: gene set enrichment analysis; GSVA: gene set variation analysis; WGCNA: weighted gene co-expression network analysis; DEGs: differentially expressed genes; PhGA: physician's global assessment of disease activity; PtGA: patient's global assessment of disease activity; DAS28-ESR: Disease Activity Score 28 using erythrocyte sedimentation rate.

or hip arthroplasty at our institution (Table I, Fig. 1A). Six fulfilled the 2010 ACR/EULAR criteria for RA (10); the remaining four had radiographically confirmed OA. The RA group (median age, 71 years) comprised four women

and two men; three underwent THA and three TKA. Five of the six RA patients were receiving low-dose prednisolone, four were on methotrexate, and two were treated with biologics (one etanercept, one tocilizumab). Their median

DAS28-ESR was 3.49 (interquartile range, 2.38–4.88), reflecting low-to-moderate disease activity. In contrast, the OA patients (all women; median age, 64 years) underwent THA exclusively, received no immunosuppression.

Transcriptomic overview and weighted gene co-expression network analysis

Bulk RNA-seq revealed strikingly different transcriptomic profiles in RA and OA muscle. DEG analysis revealed upregulation of cytokine-responsive genes in RA muscle (e.g. *CXCL2*, *FOS*, *EGR1*), whereas OA muscle showed increased expression of adipogenesis and metabolism-related genes (e.g. *PCK1*, *SFRP4*, *MEST*) (Fig. 1B).

WGCNA identified several gene co-expression modules associated with disease type and clinical parameters. Module 1 was correlated with physician's and patient's global assessment (Fig. 1C-D). This module was associated with mitochondrial and fatty acid metabolism pathways. RA-associated module 2 is enriched for innate immune (e.g. *NLRP3*), complement (e.g. *SERPING1*, *CFI*, *CFB*), and extracellular-matrix genes (e.g. *PLOD1*, *ECM1*, *COL28A1*), indicating heightened innate immunity and fibrotic remodelling in RA muscle (5). OA-associated module 3 demonstrated enrichment for glycolytic/pyruvate metabolic processes and muscle cellular homeostasis (Fig. 1C and E), suggesting dysregulated muscle metabolic processes may substantially affect OA pathology.

Gene set enrichment analysis and gene set variation analysis

GSEA confirmed the significant divergence in molecular pathology between RA and OA muscle. RA muscle was significantly enriched for hallmark inflammatory pathways, including, IL-2-STAT5, TNF- α /NF- κ B, IL-6/JAK-STAT3 signalling, hypoxia (Fig. 1F). OA muscle showed enrichment for oxidative phosphorylation and, notably, epithelial-to-mesenchymal transition (EMT) signalling (Fig. 1F). Lastly, to connect these muscle-specific molecular changes to articular inflammation, we performed GSVA in the RA cohort. Among the tested inflammatory pathways, only the activity of the IL-2-STAT5 signalling pathway in muscle showed a significant positive correlation with the DAS28-ESR ($r=0.94$, $p=0.019$), suggesting inflammatory mechanisms distinct from those in the synovium (Fig. 1G).

Biologic therapy is associated with attenuation of inflammatory transcriptional programmes in RA periarticular muscle

Because only two patients with RA were receiving biologic therapies (etanercept or tocilizumab), we performed an exploratory within-RA analysis to characterise treatment-associated transcriptional patterns without relying on gene-level statistical significance. Effect-size ranking from covariate-adjusted models suggested that biologic exposure was associated with lower expression of cytokine-responsive immediate-early and inflammatory genes in periarticular muscle, including *IL6*, *CXCL2*, *CCL2*, *FOS*, *JUNB*, and *ICAM1*. In contrast, immunoglobulin-associated transcripts tended to remain detectable and appeared relatively preserved compared with the broader attenuation of immediate-early cytokine response programmes (Supplementary Fig. S1A). Consistent with the gene-level ranking, preranked pathway analyses indicated reduced enrichment of pro-inflammatory and tissue remodelling programmes in biologic-treated samples, including TNF- α signalling via NF- κ B, inflammatory response (Suppl. Fig. S1B). In contrast, several adaptive immune response-related pathways showed comparatively smaller shifts, suggesting that biologic therapy in these samples may preferentially dampen cytokine-associated signalling modules rather than uniformly suppressing adaptive immune signatures in muscle. These findings should be interpreted as hypothesis-generating due to the limited sample size and heterogeneity of biologic mechanisms.

Discussion

This study provides the first direct transcriptomic comparison of periarticular muscle in RA and OA, revealing fundamentally divergent molecular pathologies that mirror and extend the known clinical phenotypes of muscle involvement in these diseases.

Upregulation of *EGR1* in RA periarticular muscle – together with increased *FOS* and prior evidence of *JUN* – points to monocyte/macrophage involvement and systemic AP-1 activation, consistent

with single-cell data in high-activity RA (11). The crucial role of these myeloid cells in causing muscle damage is further underscored by our own prior work in idiopathic inflammatory myopathies, which provided direct evidence linking monocyte infiltration with the severity of muscle damage (9). This intense, monocyte-driven local inflammation, fueled by TNF- α and IL-6 signalling pathways, not only aligns with the known drivers of rheumatoid cachexia (12) but also directly reflects the systemic inflammatory burden of RA. This systemic burden manifests in various tissues, as demonstrated by Dijkshoorn *et al.*, who linked systemic inflammatory markers to endothelial dysfunction and vascular inflammation (13).

OA muscle exhibits metabolic dysregulation and fatty infiltration, often accompanied by impaired mitochondrial function (7, 14). Our key finding of upregulated EMT signalling indicates a pro-fibrotic shift in OA muscle, a process also seen in synovial fibroblasts (15). One compelling explanation for this pro-fibrotic shift is paracrine signalling from the adjacent synovium. Recent work by van Kooten *et al.* revealed that the OA synovium is dominated by M2-like macrophages that secrete pro-fibrotic mediators, most notably TGF- β , a canonical inducer of EMT (16).

Clinically, these distinct muscle signatures provide a potential explanation for differences in functional impairment across arthritis phenotypes. In RA, the cytokine-responsive transcriptional programme observed in periarticular muscle is consistent with systemic inflammatory burden and may contribute to muscle wasting, weakness, and reduced physical function, hallmarks of rheumatoid cachexia. The exploratory within-RA analysis suggests that these cytokine-associated muscle programmes are modulated by biologic therapy, indicating that inflammatory control may influence muscle pathology beyond the joint. In contrast, OA muscle was characterised by metabolic dysregulation and EMT-associated remodelling, consistent with a muscle phenotype shaped by metabolic dysfunction and pro-fibrotic processes. Together, these findings highlight the

potential relevance of targeting muscle metabolism, adipose infiltration, and tissue remodelling, in addition to structured exercise therapy, to improve functional outcomes in OA.

This pilot study is limited by small sample size and sampling of periarticular rather than large muscle groups; thus, generalisation requires caution. Nonetheless, it provides the first comparative view of periarticular muscle transcriptomes in RA *versus* OA. In summary, our study demonstrates distinct molecular alterations in skeletal muscle between RA and OA. The pronounced inflammatory environment in RA may contribute to rheumatoid cachexia, whereas the metabolic alterations observed in OA are indicative of fatty infiltration and muscle dysfunction.

Acknowledgments

We would like to express gratitude toward the patients, medical staff, technicians, and many others who helped with this study.

Competing interests

T. Komai has received grants or contracts and speaking fees/honoraria from GlaxoSmithKline K.K.; and speaking fees/honoraria from Mitsubishi Tanabe Pharma Corporation, Pfizer Japan Inc., AbbVie GK, Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., Eli Lilly Japan K.K., Eisai Co., Ltd., Novartis Pharma K.K., Taisho Pharmaceutical Co., Ltd., Janssen Pharmaceutical K.K., and AstraZeneca K.K.

S. Yamada has received grants or contracts from the Japan College of Rheumatology; and speaking fees/honoraria from Pfizer, Asahi Kasei, BMS, AstraZeneca, Taisho Pharmaceutical Co., Ltd., Eli Lilly, and Eisai.

M. Ota has received grants from Astellas Foundation for Research on Metabolic Disorder, Chugai foundation for innovative drug discovery science.

H. Tsuchiya has received grants or contracts and speaking fees/honoraria from AbbVie GK; grants or contracts from Mochida Pharmaceutical Co., Ltd. and Takeda Pharmaceutical Co., Ltd.; and speaking fees/honoraria from Amgen K.K., Asahi Kasei Pharma Co., Ltd., Astellas Pharma Inc., Bristol Myers

Squibb K.K., Chugai Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., Eisai Co., Ltd., Eli Lilly Japan K.K., Gilead Sciences K.K., Janssen Pharmaceutical K.K., Novartis Pharma K.K., Sanofi K.K., Mitsubishi Tanabe Pharma Corporation, and UCB Japan Co., Ltd.

T. Okamura belonged to the Social Cooperation Program, Department of Functional Genomics and Immunological Diseases, supported by Chugai Pharmaceutical; and speaking fees/honoraria from Asahi Kasei Pharma Corporation, Bristol-Myers Squibb, and EpiVax. KF has received grants or contracts, consulting fees, speaking fees/honoraria, and/or fees for advisory board participation from Asahi Kasei Pharma Co., Ltd.; grants or contracts and speaking fees/honoraria from AbbVie GK, AstraZeneca K.K., Bristol Myers Squibb K.K., Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., and Taisho Pharmaceutical Co., Ltd.; grants or contracts from Tsumura Co., Ltd.; and speaking fees/honoraria from Alexion Pharma GK, Astellas Pharma Inc., Daiichi-Sankyo Co., Ltd., Eli Lilly Japan K.K., Gilead Sciences K.K., GlaxoSmithKline K.K., Mitsubishi Tanabe Pharma Corporation, Novartis Pharma K.K., and Pfizer Japan Inc.

The other authors have declared no competing interests.

References

1. NOTO G, SALVETTI F, DEMAJ A *et al.*: Pathogenesis of rheumatoid arthritis: one year in review 2025. *Clin Exp Rheumatol* 2025; 43(9): 1533-40. <https://doi.org/10.55563/clinexp Rheumatol/53rkan>
2. JIN H, WANG G, LU Q *et al.*: Pathophysiology of myopenia in rheumatoid arthritis. *Bone Res* 2025; 13(1): 64. <https://doi.org/10.1038/s41413-025-00438-9>
3. RALL LC, ROUBENOFF R: Rheumatoid cachexia: metabolic abnormalities, mechanisms and interventions. *Rheumatology* (Oxford) 2004; 43(10): 1219-23. <https://doi.org/10.1093/rheumatology/keh321>
4. FARROW M, BIGLANDS J, TANNER S *et al.*: Muscle deterioration due to rheumatoid arthritis: assessment by quantitative MRI and strength testing. *Rheumatology* (Oxford) 2021; 60(3): 1216-25. <https://doi.org/10.1093/rheumatology/keaa364>
5. DAY J, LOUIS C, SWIDERSKI K *et al.*: Periarticular myositis and muscle fibrosis are cytokine-dependent complications of inflammatory arthritis. *JCI Insight* 2025; 10(7). <https://doi.org/10.1172/jci.insight.179928>
6. SHORTER E, SANNICANDRO AJ, POULET B, GOLJANEK-WHYSALL K: Skeletal muscle wasting and its relationship with osteoarthritis: A mini-review of mechanisms and current interventions. *Curr Rheumatol Rep* 2019; 21(8): 40. <https://doi.org/10.1007/s11926-019-0839-4>
7. WENG Q, JIANG T, YANG T *et al.*: Association of thigh intramuscular fat infiltration with incident knee and hip osteoarthritis: a longitudinal cohort study. *Arthritis Rheumatol* 2025; 77(9): 1205-15. <https://doi.org/10.1002/art.43159>
8. LEVINGER P, CALDOW MK, FELLER JA *et al.*: Association between skeletal muscle inflammatory markers and walking pattern in people with knee osteoarthritis. *Arthritis Care Res* (Hoboken) 2011; 63(12): 1715-21. <https://doi.org/10.1002/acr.20625>
9. IZUKA S, UMEZAWA N, KOMAI T *et al.*: Muscle tissue transcriptome of idiopathic inflammatory myopathy reflects the muscle damage process by monocytes and presence of skin lesions. *Arthritis Rheumatol* 2025; 77(1): 99-106. <https://doi.org/10.1002/art.42972>
10. ALETAHA D, NEOGI T, SILMAN AJ *et al.*: 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Arthritis Rheum* 2010; 62(9): 2569-81. <https://doi.org/10.1002/art.27584>
11. BINVIGNAT M, MIAO BY, WIBRAND C *et al.*: Single-cell RNA-Seq analysis reveals cell subsets and gene signatures associated with rheumatoid arthritis disease activity. *JCI Insight* 2024; 9(16). <https://doi.org/10.1172/jci.insight.178499>
12. SANTO RCE, FERNANDES KZ, LORA PS, FILIPPINI LI, XAVIER RM: Prevalence of rheumatoid cachexia in rheumatoid arthritis: a systematic review and meta-analysis: systematic review of RA cachexia prevalence. *J Cachexia Sarcopenia Muscle* 2018; 9(5): 816-25. <https://doi.org/10.1002/jcsm.12320>
13. DIJKSHOORN B, MOOIJ GW DE, BLANKEN AB, POPA CD, NURMOHAMED MT: Endothelial cell dysfunction in RA: biomarkers IL-8, E-selectin, VCAM-1 and MCP-1 correlated with PET/CT. *Rheumatology* (Oxford) 2025; 64(9): 4968-75. <https://doi.org/10.1093/rheumatology/keaf208>
14. DISTEFANO G, HARRISON S, LYNCH J *et al.*: Skeletal muscle composition, power, and mitochondrial energetics in older men and women with knee osteoarthritis. *Arthritis Rheumatol* 2024; 76(12): 1764-74. <https://doi.org/10.1002/art.42953>
15. CAO X, WU S, WANG X, HUANG J, ZHANG W, LIANG C: Receptor tyrosine kinase C-kit promotes a destructive phenotype of FLS in osteoarthritis via intracellular EMT signaling. *Mol Med* 2023; 29(1): 38. <https://doi.org/10.1186/s10020-023-00633-6>
16. VAN KOOTEN NJT, BLOM AB, TEUNISSEN VAN MANEN JJ *et al.*: S100A8/A9 drives monocytes towards M2-like macrophage differentiation and associates with M2-like macrophages in osteoarthritic synovium. *Rheumatology* (Oxford) 2025; 64(1): 332-43. <https://doi.org/10.1093/rheumatology/keae020>