

Extended data 1. Median (interquartile range) serum concentrations for all time points.

<i>Time point</i>	<i>Pre-stress (-0.5h; T0)</i>	<i>0h (T1)</i>	<i>0.5h (T2)</i>	<i>1.5h (T3)</i>	<i>3.5h (T4)</i>	<i>5.5h (T5)</i>
COMP (ng/ml)	708.0 (553.9–918.5)	725.1 (584.4–939.3)	685.3 (544.3–881.5)	640.2 (502.1–764.4)	565.1 (463.1–696.0)	555.8 (438.9–688.8)
MMP-1 (ng/ml)	28.9 (9.1–137.3)	32.3 (8.2–130.1)	31.5 (8.1–126.2)	28.2 (7.9–122.6)	30.1 (7.3–127.6)	31.9 (7.6–141.8)
MMP-3 (ng/ml)	20.0 (15.2–28.1)	22.8 (16.7–31.9)	21.7 (16.7–27.3)	18.7 (13.8–23.4)	13.5 (10.7–19.7)	12.3 (9.7–17.3)
MMP-9 (ng/ml)	692.6 (611.5–1000.7)	705.8 (567.6–1079.3)	648.5 (555.7–880.0)	621.1 (530.4–809.4)	730.8 (570.9–917.8)	564.3 (392.6–716.6)
C2C (ng/ml)	228.8 (215.8–293.5)	230.3 (213.3–277.1)	249.6 (208.9–288.2)	249.3 (229.4–277.0)	242.4 (211.1–310.5)	262.0 (200.4–314.5)
CPII (ng/ml)	3213.6 (2638.2–4106.0)	3212.1 (2712.7–4286.6)	3133.6 (2444.0–3797.6)	3273.0 (2896.5–3985.8)	3231.5 (2726.4–3589.7)	3603.3 (2678.7–4018.6)
C2C/CPII	0.072 (0.058–0.099)	0.074 (0.056–0.093)	0.085 (0.059–0.100)	0.080 (0.062–0.102)	0.083 (0.066–0.111)	0.073 (0.056–0.096)
log ADAMTS-4	-1.2 (-5.1–1.5)	-0.9 (-5.1–1.5)	-1.4 (-5.1–1.5)	-2.0 (-5.1–1.4)	-1.3 (-5.1–1.4)	-2.0 (-5.1–1.3)
IL-6 (pg/ml)	1.453 (1.177–2.945)	1.501 (1.169–2.770)	1.375 (1.180–2.610)	1.511 (1.155–2.288)	2.328 (1.597–4.372)	2.237 (1.395–3.667)
PRG-4 (ng/ml)	191.8 (91.0–265.7)	154.8 (70.9–269.6)	85.5 (56.7–249.8)	103.7 (61.7–248.0)	124.9 (61.1–238.8)	81.3 (57.6–265.0)
Resistin (ng/ml)	6.8 (6.4–8.0)	6.7 (6.2–8.0)	6.6 (5.7–7.6)	6.3 (5.2–7.8)	6.8 (5.4–8.5)	6.5 (4.6–7.8)

COMP—cartilage oligomeric matrix protein; MMP—matrix metalloproteinases; C2C—COL2-3/4Clong mono epitope; CPII—rate of type II procollagen synthesis; ADAMTS—A disintegrin and metalloproteinase with thrombospondin motifs; IL—interleukin; PRG—proteoglycan.

Extended data 2. Cross-correlations between baseline blood marker levels and patient reported outcome measures. Spearman's rho and corresponding P-values are shown. Significant correlations are shown in bold font.

		KOOS					SF36		
		Symptoms	Pain	ADL	Rec/Sport	QOL	Total	Phys Funct	Pain
<i>hCOMP(T0)</i>	<i>rho</i>	-0.200	-0.213	-0.077	-0.106	0.025	0.093	0.065	0.063
	<i>P-value</i>	0.209	0.181	0.633	0.516	0.877	0.562	0.687	0.699
<i>hIL-6(T0)</i>	<i>rho</i>	-0.188	-0.173	-0.105	0.004	-0.132	-0.102	-0.049	-0.072
	<i>P-value</i>	0.239	0.280	0.512	0.980	0.410	0.527	0.760	0.660
<i>C2C(T0)</i>	<i>rho</i>	-0.369*	-0.450**	-0.415**	-0.443**	-0.270	-0.278	-0.289	-0.206
	<i>P-value</i>	0.018	0.003	0.007	0.004	0.088	0.079	0.067	0.202
<i>CPII(T0)</i>	<i>rho</i>	-0.189	-0.150	-0.096	-0.088	-0.095	-0.136	-0.063	-0.033
	<i>P-value</i>	0.237	0.350	0.549	0.591	0.554	0.398	0.695	0.841
<i>C2C/CPII(T0)</i>	<i>rho</i>	0.110	-0.010	-0.068	-0.073	0.030	0.076	-0.015	-0.027
	<i>P-value</i>	0.492	0.949	0.673	0.653	0.850	0.635	0.927	0.868
<i>MMP-1(T0)</i>	<i>rho</i>	-0.145	-0.222	-0.241	-0.090	-0.160	-0.314*	-0.254	-0.233
	<i>P-value</i>	0.365	0.163	0.129	0.579	0.318	0.046	0.109	0.148
<i>MMP-3(T0)</i>	<i>rho</i>	0.007	0.147	0.128	0.234	0.159	0.217	0.301	0.240
	<i>P-value</i>	0.967	0.359	0.424	0.146	0.319	0.172	0.056	0.137
<i>MMP-9(T0)</i>	<i>rho</i>	-0.226	-0.024	-0.008	0.021	-0.250	0.112	0.061	0.036
	<i>P-value</i>	0.156	0.883	0.962	0.895	0.116	0.488	0.704	0.828
<i>PRG-4(T0)</i>	<i>rho</i>	-0.149	-0.275	-0.213	-0.142	-0.321*	-0.243	-0.097	-0.258
	<i>P-value</i>	0.352	0.082	0.181	0.383	0.041	0.126	0.548	0.108
<i>ADAMTS-4(T0)</i>	<i>rho</i>	0.007	-0.074	0.029	0.045	-0.069	-0.071	0.086	-0.028
	<i>P-value</i>	0.966	0.644	0.855	0.785	0.670	0.658	0.595	0.866
<i>Resistin(T0)</i>	<i>rho</i>	0.077	0.178	0.188	0.267	-0.041	0.131	0.179	0.142
	<i>P-value</i>	0.632	0.266	0.239	0.096	0.797	0.414	0.263	0.381

COMP—cartilage oligomeric matrix protein; MMP—matrix metalloproteinases; C2C—COL2-3/4Clong mono epitope; CPII—rate of type II procollagen synthesis; ADAMTS—A disintegrin and metalloproteinase with thrombospondin motifs; IL—interleukin; PRG—proteoglycan; KOOS—Knee Injury and Osteoarthritis Score; SF36—Short Form 36 (SF36) quality of life; ADL—activities of daily living; Rec/Sport—recreation and sport; QOL—quality of life; Phys Funct—physical function. **. Correlation is significant at the 0.01 level (2-tailed); *. Correlation is significant at the 0.05 level (2-tailed). Note: We only interpreted associations between blood marker levels and their load-induced changes with patient reported osteoarthritis outcome and QoL if at significant correlations were observed with at least two KOOS or SF36 subscores to account for the possibility of detecting correlations by chance.

Extended data 3. Cross-correlations between load-induced change in blood marker levels and patient reported outcome measures. Spearman's rho and corresponding P-values are shown. Significant correlations are shown in bold font.

		KOOS					SF36		
		Symptoms	Pain	ADL	Rec/Sport	QOL	Total	Phys Funct	Pain
<i>hCOMP(T1-T0)</i>	<i>rho</i>	0.195	0.129	0.096	0.083	0.192	0.082	-0.081	0.117
	<i>P-value</i>	0.362	0.547	0.655	0.708	0.368	0.703	0.708	0.586
<i>hIL-6(T1-T0)</i>	<i>rho</i>	0.033	0.047	0.154	0.050	0.355	0.430*	0.467*	0.208
	<i>P-value</i>	0.878	0.829	0.474	0.822	0.088	0.036	0.022	0.330
<i>C2C(T1-T0)</i>	<i>rho</i>	0.204	0.304	0.224	0.464*	0.100	0.023	0.054	-0.041
	<i>P-value</i>	0.339	0.148	0.293	0.026	0.644	0.915	0.801	0.848
<i>CPII(T1-T0)</i>	<i>rho</i>	0.297	0.363	0.259	0.399	0.284	-0.039	-0.037	0.055
	<i>P-value</i>	0.159	0.081	0.221	0.059	0.178	0.858	0.863	0.797
<i>C2C/CPII(T1-T0)</i>	<i>rho</i>	-0.065	-0.141	-0.057	-0.062	-0.198	0.048	0.135	-0.009
	<i>P-value</i>	0.762	0.512	0.791	0.778	0.354	0.824	0.528	0.966
<i>MMP-1(T1-T0)</i>	<i>rho</i>	-0.291	-0.456	-0.305	-0.442	-0.326	-0.001	0.076	-0.133
	<i>P-value</i>	0.168	0.025	0.147	0.035	0.120	0.997	0.723	0.536
<i>MMP-3(T1-T0)</i>	<i>rho</i>	0.227	0.398	0.363	0.340	0.429*	0.366	0.273	0.444*
	<i>P-value</i>	0.285	0.054	0.081	0.112	0.036	0.079	0.196	0.030
<i>MMP-9(T1-T0)</i>	<i>rho</i>	-0.220	-0.075	-0.031	-0.153	-0.070	0.067	-0.014	0.030
	<i>P-value</i>	0.303	0.726	0.884	0.486	0.744	0.754	0.948	0.888
<i>PRG-4(T1-T0)</i>	<i>rho</i>	0.012	0.091	-0.285	-0.002	0.118	-0.131	-0.209	-0.324
	<i>P-value</i>	0.960	0.702	0.223	0.992	0.621	0.582	0.378	0.163
<i>ADAMTS-4(T1-T0)</i>	<i>rho</i>	0.011	-0.240	-0.036	-0.313	0.077	0.055	-0.004	-0.169
	<i>P-value</i>	0.970	0.389	0.899	0.256	0.786	0.845	0.990	0.547
<i>Resistin(T1-T0)</i>	<i>rho</i>	-0.415	-0.319	-0.239	-0.335	-0.182	0.156	0.246	0.026
	<i>P-value</i>	0.044	0.128	0.261	0.118	0.394	0.468	0.247	0.903

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