Heterogeneity of lipid and protein cartilage profiles associated with human osteoarthritis with or without type 2 diabetes mellitus

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Supporting information

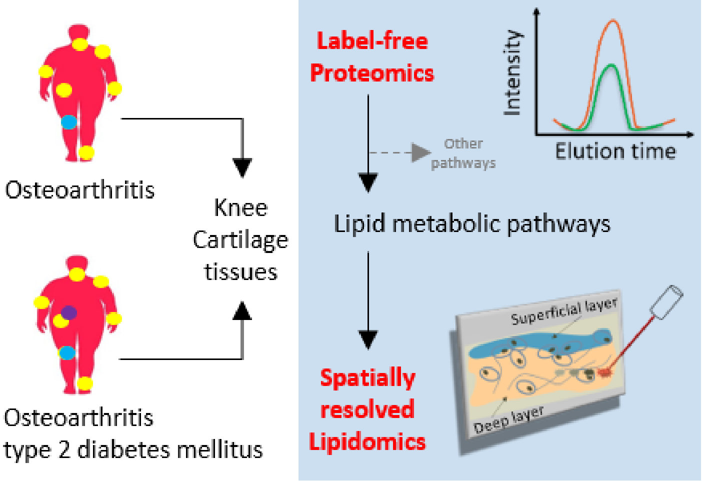

Table S1. Patient information.

Table S2. Significantly up and down-regulated proteins found in OA/T2DM$^-$ compared to OA/T2DM$^+$.

Table S3. Top 10 enriched pathways associated to the significant up and down-regulated proteins found in OA/T2DM$^-$ compared to OA/T2DM$^+$.

Table S4. Assignments of 15 lipid species based on targeted MS/MS experiments performed at high-mass resolution.

Figure S1. Sample collection and processing.

Figure S2. Example of the spatial distribution of SM and LPC species in OA/T2DM$^-$ and OA/T2DM$^+$ patients.

Figure S3. Linear discriminant analysis of superficial and deep layers of both groups independently.

Table S1. Patient information. The (*) displayed the samples used for the comparative MALDI-MSI experiments. (BMI: Body mass index; KL: Kellgren-Lawrence).

	Sample number	**Age**	**Gender**	**Affected knee**	**BMI**	**KL score**
OA/T2DM$^-$ patients (n=10)	1*	78	Male	Left	25.0	2
	2*	61	Male	Left	32.0	3
	3*	80	Female	Left	30.5	4
	4*	82	Male	Left	24.3	4
	5*	59	Female	Right	25.7	3
	6*	71	Male	Left	26.9	3
	7	67	Female	Left	24.0	3
	8	77	Female	Left	Not specified	Not specified
	9	75	Male	Left	28.0	4
	10	66	Female	Right	27.0	4
OA/T2DM$^+$ patients (n=10)	1*	86	Male	Left	24.9	4
	2*	70	Female	Right	34.9	3
	3*	72	Male	Right	32.4	4
	4*	78	Male	Left	35.6	4
	5*	81	Male	Right	24.9	3
	6*	75	Male	Left	27.7	3
	7	75	Female	Left	33.3	2
	8	56	Female	Left	37.2	Not specified
	9	73	Male	Right	28.4	4
	10	58	Male	Right	23.9	4

Table S2. Significantly up and down-regulated proteins found in OA/T2DM$^-$ compared to OA/T2DM$^+$. The FC cut-off is at 1.5-fold and adjusted p-value is ≤ 0.05. 75 proteins were more abundant in OA/T2DM$^-$ samples whereas 40 were more abundant in OA/T2DM$^+$. References of relevant proteins in the context of OA or T2DM have been included.

Protein Name	Fold change	p-value
Carbonyl reductase [NADPH] 3	0.01	1.99E-16
Plastin-2	0.01	1.99E-16
C-X-C motif chemokine 10	0.01	1.99E-16
Cell surface glycoprotein MUC18	0.01	1.99E-16
Aminopeptidase N	0.01	1.99E-16
Band 3 anion transport protein	0.01	1.99E-16
Glutathione hydrolase 5 proenzyme [62]	0.01	1.99E-16
Calponin-2	0.01	1.99E-16
Olfactomedin-like protein 1 [61]	0.01	1.99E-16
Neural cell adhesion molecule 1	0.01	1.99E-16
Catenin beta-1	0.01	1.99E-16
Serum amyloid A-4 protein	0.01	1.99E-16
Tartrate-resistant acid phosphatase type 5	0.01	1.99E-16
Properdin [61]	0.01	1.99E-16
Lysyl oxidase homolog 1	0.01	1.99E-16
Cadherin-13	0.01	1.99E-16
Protein-glutamine gamma-glutamyltransferase E	0.01	1.99E-16
U6 snRNA-associated Sm-like protein LSm2	0.01	1.99E-16
Endoplasmic reticulum aminopeptidase 1	0.01	1.99E-16
Peptidyl-prolyl cis-trans isomerase FKBP5 [62]	0.01	1.99E-16
Cytochrome b-c1 complex subunit Rieske, mitochondrial [62]	0.01	1.99E-16
NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial	0.01	1.99E-16
Osteopontin [61]	0.08	1.99E-16
Peroxiredoxin-like 2A	0.11	1.99E-16
Keratocan	0.24	2.71E-05
Microsomal glutathione S-transferase 1	0.24	3.72E-08
Carbonic anhydrase 1 [61, 62]	0.24	7.42E-13
Casein kinase II subunit alpha	0.28	4.49E-06
Prostacyclin synthase	0.29	1.13E-03
Dipeptidyl peptidase 4 [62]	0.30	2.93E-03
Collagen alpha-1(I) chain [61, 62]	0.30	4.33E-09
Fibronectin type III domain-containing protein 1 [62]	0.31	1.79E-03
Apolipoprotein A-I [42, 43, 44, 61]	0.31	1.35E-08
Ras-related protein Rap-1A [62]	0.31	1.41E-06
Ubiquitin-conjugating enzyme E2 K	0.32	6.00E-04

MAM domain-containing protein 2 [61]	0.32	2.17E-03
Short-chain specific acyl-CoA dehydrogenase, mitochondrial	0.32	4.33E-03
Apolipoprotein A-II	0.34	4.50E-03
Histidine triad nucleotide-binding protein 2, mitochondrial	0.35	2.21E-02
Collagen alpha-2(IV) chain [62]	0.35	6.38E-03
NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12	0.36	3.06E-02
ATP synthase subunit e, mitochondrial [62]	0.36	9.09E-03
Sushi repeat-containing protein SRPX [61, 62]	0.37	8.86E-03
Fatty acid synthase [62]	0.40	4.01E-02
Liver carboxylesterase 1	0.41	4.77E-02
Secreted phosphoprotein 24 [61, 62]	0.42	1.74E-02
Pigment epithelium-derived factor [61]	0.43	2.53E-04
Insulin-like growth factor-binding protein 6 [62]	0.44	4.16E-02
Leucine-rich alpha-2-glycoprotein	0.44	8.81E-03
5'-nucleotidase	0.44	5.68E-04
Small ubiquitin-related modifier 3	0.44	2.46E-03
SPARC [61]	0.45	1.13E-04
Superoxide dismutase [Mn], mitochondrial [61]	0.47	2.32E-03
BTB/POZ domain-containing protein KCTD12	0.47	3.10E-02
Collagen alpha-2(I) chain [61, 62]	0.48	3.19E-03
Dermatopontin [61, 62]	0.49	5.12E-03
Tetranectin [61]	0.49	5.41E-03
Vitrin [61, 62]	0.49	5.51E-03
Protein-glutamine gamma-glutamyltransferase 2	0.49	5.72E-03
60S ribosomal protein L23a [61]	0.49	3.39E-02
60S ribosomal protein L7a [61, 62]	0.50	7.94E-03
ATP synthase subunit gamma, mitochondrial	0.50	1.53E-02
Collagen triple helix repeat-containing protein 1 [61, 62]	0.50	9.20E-03
Extracellular superoxide dismutase [Cu-Zn] [61, 62]	0.51	1.08E-02
Guanine nucleotide-binding protein G(I)/G(S)/G(O) subunit gamma-12	0.51	1.73E-02
Histone H2A type 2-B	0.51	3.67E-02
Keratinocyte proline-rich protein	0.52	5.82E-03
60S ribosomal protein L13a	0.53	3.33E-02
Cytochrome b reductase 1 [62]	0.54	3.47E-02
Rho GDP-dissociation inhibitor 2	0.54	3.99E-02
Collagen alpha-1(XII) chain [61, 62]	0.54	3.39E-02
Asporin [61]	0.54	3.75E-02
Histone H2B type 1-K [61]	0.54	4.01E-02
Hemopexin [61, 62]	0.55	2.46E-02
CCN family member 2	0.57	4.41E-02
Cartilage intermediate layer protein 1	1.51	8.64E-03
Serine protease HTRA3	1.52	6.97E-03
Ribonuclease 4	1.55	4.77E-03
Angiogenin	1.57	4.09E-03

Apolipoprotein A-IV [63]	1.59	2.83E-03
Platelet-derived growth factor C	1.63	2.50E-03
Serine protease HTRA1 [64]	1.63	1.64E-03
Lysozyme C	1.71	5.68E-04
Metalloproteinase inhibitor 3	1.73	4.28E-04
Nucleobindin-1	1.78	2.17E-02
Alpha-crystallin A chain	1.79	1.80E-04
Matrilin-3	1.81	1.34E-04
Enolase-phosphatase E1	1.83	8.52E-03
Phospholipase A2, membrane associated [46, 47, 48, 49, 61, 81]	1.90	3.30E-05
Metalloreductase STEAP4	1.94	5.97E-06
40S ribosomal protein S21	1.94	2.20E-05
Retinal dehydrogenase 1	2.42	9.10E-07
Transthyretin	2.95	4.90E-12
Calcium-activated chloride channel regulator 1	3.00	6.17E-09
Protein ABHD13	3.85	1.99E-16
Gamma-crystallin B	4.96	1.99E-16
Gamma-crystallin C	5.05	1.99E-16
Gamma-crystallin A	5.43	1.99E-16
Beta-crystallin A3	6.35	1.99E-16
Regenerating islet-derived protein 3-alpha	10.72	1.99E-16
Desmin	100.00	1.99E-16
Glutathione S-transferase Mu 4	100.00	1.99E-16
Defensin-6	100.00	1.99E-16
Fatty acid-binding protein, liver	100.00	1.99E-16
High mobility group protein HMG-I/HMG-Y	100.00	1.99E-16
Beta-crystallin A2	100.00	1.99E-16
Glycine amidinotransferase, mitochondrial	100.00	1.99E-16
Transmembrane glycoprotein NMB	100.00	1.99E-16
E3 ubiquitin/ISG15 ligase TRIM25	100.00	1.99E-16
Dihydropyrimidinase	100.00	1.99E-16
Neutrophil elastase	100.00	1.99E-16
Beta-crystallin B1	100.00	1.99E-16
C-C motif chemokine 24	100.00	1.99E-16
Neprilysin	100.00	1.99E-16
Leucine-rich repeat-containing protein 15	100.00	1.99E-16

Table S3. Top 10 enriched pathways associated to the significant up and down-regulated proteins found in OA/T2DM$^-$ compared to OA/T2DM$^+$. (**A**) Top 10 enriched pathways in the OA/T2DM$^-$ group from WikiPathways database**.** (**B**) Top 10 enriched pathways in the OA/T2DM$^-$ group from KEGG database. (**C**) Top 10 enriched pathways in the OA/T2DM$^+$ group from WikiPathways database**.** (**D**) Top 10 enriched pathways in the OA/T2DM$^+$ group from KEGG database. The (*) displays the pathways related to lipid regulation.

A WikiPathways database (Human) - OA/T2DM$^-$ group

			OA/T2DM$^+$ vs OA/T2DM$^-$	
Pathway description	Protein ID	Protein name	Fold change	P-value
WP3601 - composition of lipid particles*	P02647	Apolipoprotein A-I	0.31	1.35E-08
	P02652	Apolipoprotein A-II	0.34	4.50E-03
WP1533 - vitamin B12 metabolism*	P35542	Serum amyloid A-4 protein	0.01	1.99E-16
	P02647	Apolipoprotein A-I	0.31	1.35E-08
	P04179	Superoxide dismutase [Mn], mitochondrial	0.47	2.32E-03
	P08294	Extracellular superoxide dismutase [Cu-Zn]	0.51	1.08E-02
WP4522 - metabolic pathway of LDL, HDL and TG*	P02647	Apolipoprotein A-I	0.31	1.35E-08
	P02652	Apolipoprotein A-II	0.34	4.50E-03
WP12 - osteoclast signaling	P10451	Osteopontin	0.08	1.99E-16
	P13686	Tartrate-resistant acid phosphatase type 5	0.01	1.99E-16
WP408 - oxidative stress	P10620	Microsomal glutathione S-transferase 1	0.24	3.72E-08
	P04179	Superoxide dismutase [Mn], mitochondrial	0.47	2.32E-03
	P08294	Extracellular superoxide dismutase [Cu-Zn]	0.51	1.08E-02
WP3967 - miR-509-3p alteration of YAP1/ECM axis	P02452	Collagen alpha-1(I) chain	0.30	4.33E-09
	P09486	SPARC	0.45	1.13E-04
WP176 - folate metabolism*	P35542	Serum amyloid A-4 protein	0.01	1.99E-16
	P02647	Apolipoprotein A-I	0.31	1.35E-08
	P04179	Superoxide dismutase [Mn], mitochondrial	0.47	2.32E-03
	P08294	Extracellular superoxide dismutase [Cu-Zn]	0.51	1.08E-02
WP2911 - miRNA targets in ECM and membrane receptors	P08123	Collagen alpha-2(I) chain	0.48	3.19E-03
	P08572	Collagen alpha-2(IV) chain	0.35	6.38E-03
WP100 - glutathione metabolism	P36269	Glutathione hydrolase 5 proenzyme	0.01	1.99E-16
	P15144	Aminopeptidase N	0.01	1.99E-16
WP111 - electron transport chain (OXPHOS system in mitochondria)	Q9UI09	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12	0.36	3.06E-02
	P47985	Cytochrome b-c1 complex subunit Rieske, mitochondrial	0.01	1.99E-16
	P36542	ATP synthase subunit gamma, mitochondrial	0.50	1.53E-02
	P49821	NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial	0.01	1.99E-16
	P56385	ATP synthase subunit e, mitochondrial	0.36	9.09E-03

B KEGG database (Human) - OA/T2DM$^-$ group

			OA/T2DM$^+$ vs OA/T2DM$^-$	
Pathway description	Protein ID	Protein name	Fold change	P-value
protein digestion and absorption	P02452	Collagen alpha-1(I) chain	0.30	4.33E-09
	P27487	Dipeptidyl peptidase 4	0.30	2.93E-03
	P08123	Collagen alpha-2(I) chain	0.48	3.19E-03
	P08572	Collagen alpha-2(IV) chain	0.35	6.38E-03
	Q99715	Collagen alpha-1(XII) chain	0.54	3.39E-02
riboflavin metabolism*	P13686	Tartrate-resistant acid phosphatase type 5	0.01	1.99E-16
ECM-receptor interaction	P02452	Collagen alpha-1(I) chain	0.30	4.33E-09
	P08123	Collagen alpha-2(I) chain	0.48	3.19E-03
	P08572	Collagen alpha-2(IV) chain	0.35	6.38E-03
	P10451	Osteopontin	0.08	1.99E-16
glutathione metabolism	P36269	Glutathione hydrolase 5 proenzyme	0.01	1.99E-16
	P15144	Aminopeptidase N	0.01	1.99E-16
	P10620	Microsomal glutathione S-transferase 1	0.24	3.72E-08
oxidative phosphorylation	Q9UI09	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12	0.36	3.06E-02
	P47985	Cytochrome b-c1 complex subunit Rieske, mitochondrial	0.01	1.99E-16
	P36542	ATP synthase subunit gamma, mitochondrial	0.50	1.53E-02
	P49821	NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial	0.01	1.99E-16
	P56385	ATP synthase subunit e, mitochondrial	0.36	9.09E-03
arachidonic acid metabolism*	P36269	Glutathione hydrolase 5 proenzyme	0.01	1.99E-16
	Q16647	Prostacyclin synthase	0.29	1.13E-03
	O75828	Carbonyl reductase [NADPH] 3	0.01	1.99E-16
taurine and hypotaurine metabolism	P36269	Glutathione hydrolase 5 proenzyme	0.01	1.99E-16
huntington disease	Q9UI09	NADH dehydrogenase [ubiquinone] 1 alpha subcomplex subunit 12	0.36	3.06E-02
	P47985	Cytochrome b-c1 complex subunit Rieske, mitochondrial	0.01	1.99E-16
	P04179	Superoxide dismutase [Mn], mitochondrial	0.47	2.32E-03
	P36542	ATP synthase subunit gamma, mitochondrial	0.50	1.53E-02
	P49821	NADH dehydrogenase [ubiquinone] flavoprotein 1, mitochondrial	0.01	1.99E-16
	P21980	Protein-glutamine gamma-glutamyltransferase 2	0.49	5.72E-03
focal adhesion	P02452	Collagen alpha-1(I) chain	0.30	4.33E-09
	P08123	Collagen alpha-2(I) chain	0.48	3.19E-03
	P62834	Ras-related protein Rap-1A	0.31	1.41E-06
	P08572	Collagen alpha-2(IV) chain	0.35	6.38E-03
	P10451	Osteopontin	0.08	1.99E-16
	P35222	Catenin beta-1	0.01	1.99E-16
fatty acid biosynthesis*	P49327	Fatty acid synthase	0.40	4.01E-02

C WikiPathways database (Human) - OA/T2DM$^+$ group

			OA/T2DM$^+$ vs OA/T2DM$^-$	
Pathway description	Protein ID	Protein name	Fold change	P-value
WP1589 - folate-alcohol and cancer pathway hypotheses	P00352	Retinal dehydrogenase 1	2.42	9.10E-07
WP4225 - pyrimidine metabolism and related diseases	Q14117	Dihydropyrimidinase	100.00	1.99E-16
WP4146 - macrophage markers	P61626	Lysozyme C	1.71	5.68E-04
WP206 - fatty acid omega oxidation*	P00352	Retinal dehydrogenase 1	2.42	9.10E-07
WP497 - urea cycle and metabolism of amino groups	P50440	Glycine amidinotransferase, mitochondrial	100.00	1.99E-16
WP2533 - glycerophospholipid biosynthetic pathway*	P14555	Phospholipase A2, membrane associated	1.90	3.30E-05
WP3580 - methionine de novo and salvage pathway	Q9UHY7	Enolase-phosphatase E1	1.83	8.52E-03
WP1539 - angiogenesis	P35625	Metalloproteinase inhibitor 3	1.73	4.28E-04
WP2878 - PPAR alpha pathway*	P07148	Fatty acid-binding protein, liver	100.00	1.99E-16
WP167 - eicosanoid synthesis*	P14555	Phospholipase A2, membrane associated	1.90	3.30E-05

D KEGG database (Human) - OA/T2DM^{+} group

			OA/T2DM^{+} vs OA/T2DM^{-}	
Pathway description	Protein ID	Protein name	Fold change	P-value
fat digestion and absorption*	P07148	Fatty acid-binding protein, liver	100.00	1.99E-16
	P14555	Phospholipase A2, membrane associated	1.90	3.30E-05
	P06727	Apolipoprotein A-IV	1.59	2.83E-03
pantothenate and CoA biosynthesis*	Q14117	Dihydropyrimidinase	100.00	1.99E-16
renin-angiotensin system	P08473	Neprilysin	100.00	1.99E-16
vitamin digestion and absorption*	P06727	Apolipoprotein A-IV	1.59	2.83E-03
alpha-linolenic acid metabolism*	P14555	Phospholipase A2, membrane associated	1.90	3.30E-05
linoleic acid metabolism*	P14555	Phospholipase A2, membrane associated	1.90	3.30E-05
beta-alanine metabolism	Q14117	Dihydropyrimidinase	100.00	1.99E-16
pancreatic secretion	P14555	Phospholipase A2, membrane associated	1.90	3.30E-05
	A8K7I4	Calcium-activated chloride channel regulator 1	3.00	6.17E-09
drug metabolism	Q03013	Glutathione S-transferase Mu 4	100.00	1.99E-16
	Q14117	Dihydropyrimidinase	100.00	1.99E-16
glycine, serine and threonine metabolism	P50440	Glycine amidinotransferase, mitochondrial	100.00	1.99E-16

Table S4. Assignments of 15 lipid species based on targeted MS/MS experiments performed at high-mass resolution. (*) 3 lipids were tentatively assigned.

Precursor *m/z*	MS/MS fragments	Assignment	Δppm error	Characteristic of
732.55406	714.59 (H_2O loss) 673.34 ($N(CH_3)_3$ neutral loss) 184.00 (Phosphocholine)	$[PC\ 32{:}1+H]^+$	0.1	Superficial layer
734.56996	716.50 (H_2O loss) 675.34 ($N(CH_3)_3$ neutral loss) 184.00 (Phosphocholine)	$[PC\ 32{:}0+H]^+$	0.8	Superficial layer
756.55189	697.42 ($N(CH_3)_3$ neutral loss) 573.50 (Headgroup neutral loss) 184.00 (Phosphocholine) 146.83 (Cyclophosphane + Na)	$[PC\ 32{:}0+Na]^+$	0.8	Superficial layer
758.57007	740.42 (H_2O loss) 699.42 ($N(CH_3)_3$ neutral loss) 575.50 (Headgroup neutral loss) 184.00 (Phosphocholine)	$[PC\ 34{:}2+H]^+$	0.9	Superficial layer
760.58559	742.59 (H_2O loss) 701.42 ($N(CH_3)_3$ neutral loss) 577.42 (Headgroup neutral loss) 184.00 (Phosphocholine)	$[PC\ 34{:}1+H]^+$	0.7	Superficial layer
780.55218 *	721.50 ($N(CH_3)_3$ neutral loss) 597.50 (Headgroup neutral loss) 184.00 (Phosphocholine)	$[PC\ 34{:}2+Na]^+$	0.3	Superficial layer
782.56773	723.50 ($N(CH_3)_3$ neutral loss) 599.50 (Headgroup neutral loss) 577.33 (Headgroup Na neutral loss) 184.00 (Phosphocholine)	$[PC\ 34{:}1+Na]^+$	0.9	Superficial layer
785.65389	767.59 (H_2O loss) 726.50 ($N(CH_3)_3$ neutral loss) 602.50 (Headgroup neutral loss) 184.00 (Phosphocholine)	$[SM\ 40{:}2;2+H]^+$	1.0	Superficial layer
786.60121	768.59 (H_2O loss) 727.50 ($N(CH_3)_3$ neutral loss) 184.00 (Phosphocholine)	$[PC\ 36{:}2+H]^+$	0.6	Superficial layer

787.66935	769.67 (H_2O loss) 728.42 ($N(CH_3)_3$ neutral loss) 604.33 (Headgroup neutral loss) 184.00 (Phosphocholine)	$[SM 40:1;2+H]^+$	0.8	Superficial layer
788.61708	770.67 (H_2O loss) 729.42 ($N(CH_3)_3$ neutral loss) 605.42 (Headgroup neutral loss) 184.00 (Phosphocholine)	$[PC 36:1+H]^+$	0.9	Superficial layer
806.56757 *	747.50 ($N(CH_3)_3$ neutral loss) 623.50 (Headgroup neutral loss) 184.00 (Phosphocholine)	$[PC 36:3+Na]^+$	0.4	Superficial layer
703.57548	685.50 (H_2O loss) 644.42 ($N(CH_3)_3$ neutral loss) 184.00 (Phosphocholine)	$[SM 34:1;2+H]^+$	0.8	OA/T2DM$^-$ patients
725.55744	707.42 (H_2O loss) 666.42 ($N(CH_3)_3$ neutral loss) 542.42 (Headgroup neutral loss) 184.00 (Phosphocholine)	$[SM 34:1;2+Na]^+$	0.8	OA/T2DM$^-$ patients
731.60674	713.59 (H_2O loss) 672.42 ($N(CH_3)_3$ neutral loss) 184.00 (Phosphocholine)	$[SM 36:1;2+H]^+$	0.7	OA/T2DM$^-$ patients
753.58865 *	694.50 ($N(CH_3)_3$ neutral loss) 570.25 (Headgroup neutral loss) 184.08 (Phosphocholine)	$[SM 36:1;2+Na]^+$	0.7	OA/T2DM$^-$ patients
552.33050	492.31 ($C_2H_4O_2$ loss) 267.23 (FA 17:1(+O)) 153.00 (Lysophosphocholine)	$[LPC 17:1+HCOO]^-$	0.4	OA/T2DM$^+$ patients & Deep layer
554.34672	494.32 ($C_2H_4O_2$ loss) 269.25 (FA 17:0(+O)) 153.00 (Lysophosphocholine)	$[LPC 17:0+HCOO]^-$	0.7	OA/T2DM$^+$ patients

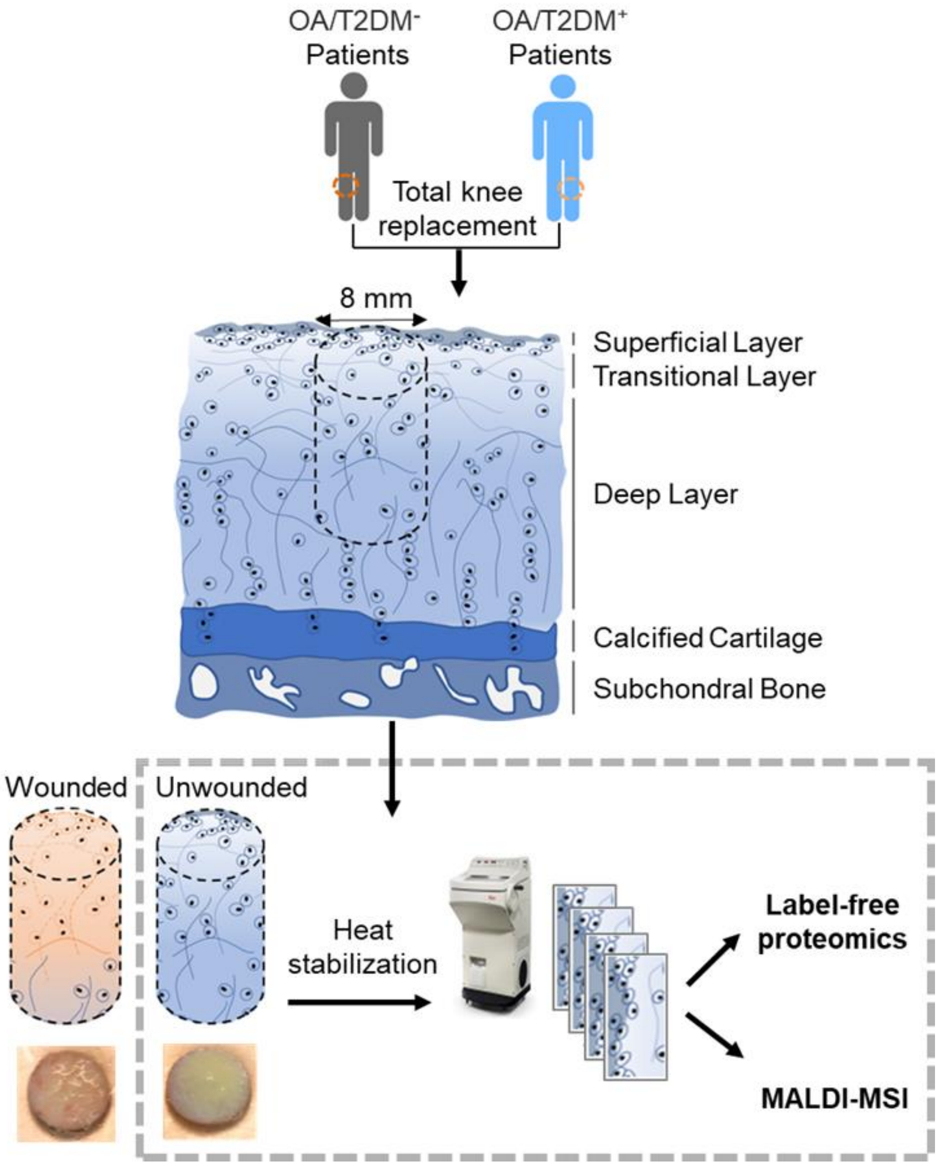

Figure S1. Sample collection and processing. Human cartilage was obtained from patients undergoing total knee replacement. The tissues were cut into punches of 8 mm. Unwounded cartilage punches were isolated from the wounded tissue macroscopically. The unwounded cartilage punches were heat stabilized to avoid molecular degradation before being snap-frozen in liquid nitrogen. Finally, 12 μm thick sections were prepared for either label-free proteomics or MALDI-MSI experiments.

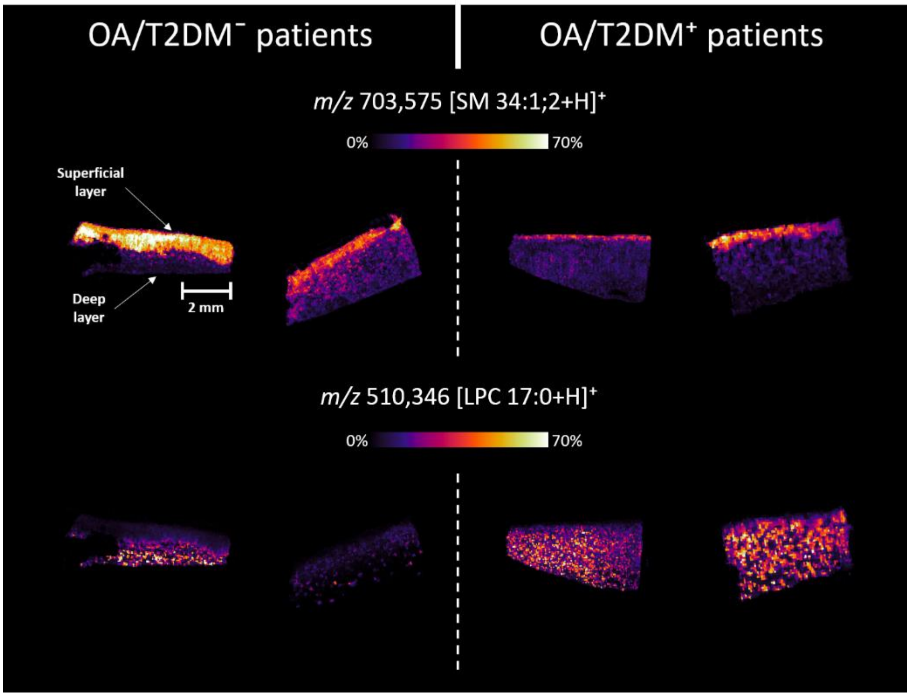

Figure S2. Example of the spatial distribution of SM and LPC species in OA/T2DM$^-$ and OA/T2DM$^+$ patients.

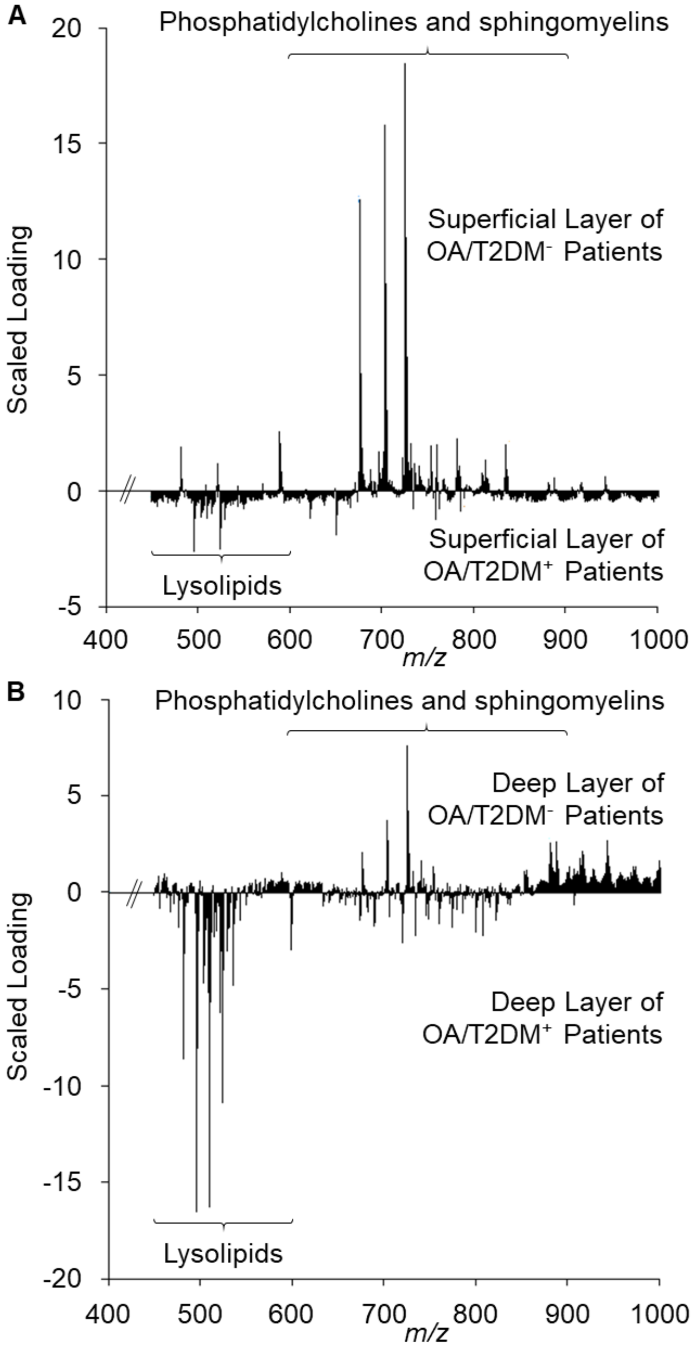

Figure S3. Linear discriminant analysis of superficial and deep layers of both groups independently. Discriminant function 1 scaled loading spectrum of (**A**) OA/T2DM$^-$ and OA/T2DM$^+$ superficial layers and (**B**) OA/T2DM$^-$ and OA/T2DM$^+$ deep layers.