

## Supplementary material

**Supplementary table 1. Glucose-lowering medication in type 2 diabetes at baseline and 5-year follow-up.**

Glucose-lowering medication		Type 2 diabetes (n=39)	
		Baseline	Follow up
<b>Yes</b>		28 (72%)	33 (85%)
	Metformin	26 (67%)	29 (74%)
	Insulin	4 (10%)	7 (18%)
	DPP4 inhibitors	2 (5%)	2 (5%)
	Sulfonylurea drugs	3 (8%)	2 (5%)
	GLP-1 receptor agonists	4 (10%)	9 (23%)
	SGLT-2 inhibitors	0	10 (26%)
<b>No</b>		11 (28%)	6 (15%)

% refers to the whole type 2 diabetes group.

**Supplementary table 2. Detailed protocol for the acquisition of  $^1\text{H}$  magnetic resonance spectroscopy (1H-MRS) data.**

1. Hardware	
a. Field strength [T]	3T
b. Manufacturer	Philips
c. Model (software version if available)	Achieva dStream 3T
d. RF coils: nuclei (transmit/ receive), number of channels, type, body part	$^1\text{H}$ , dStream Torso coil, 32 channels
e. Additional hardware	no
2. Acquisition	
a. Pulse sequence	Point resolve spectroscopy (PRESS)
b. Volume of Interest (VOI) locations	Tibialis anterior (Supplementary Figure 1)
c. Nominal VOI size [ $\text{cm}^3$ , $\text{mm}^3$ ]	$10 \times 10 \times 20 \text{ mm}^3$
d. Repetition Time (TR), Echo Time (TE) [ms, s]	TR/TE=2000/29 ms
e. Total number of Excitations or acquisitions per spectrum	16 averages in non-water suppressed spectra with 2 startup acquisitions, 96 averages in water suppressed spectra with 2 startup acquisitions
f. Additional sequence parameters (spectral width in Hz, number of spectral points, frequency offsets)	Bandwidth 2000 Hz, 2048 spectral points
g. Water Suppression Method	Chemical Shift Selective (CHESS) suppression
h. Shimming Method, reference peak, and thresholds for “acceptance of shim” chosen	PB-volume shim, second order, typical linewidth (full width at half maximum, FWHM) of water resonance: 20-25 Hz
i. Triggering or motion correction method (respiratory, peripheral, cardiac triggering, incl. device used and delays)	None
3. Data analysis methods and outputs	
a. Analysis software	jMRUI
b. Processing steps deviating from quoted reference or product	Spectra without water suppression were phase-corrected (zero order phase) and then fitted with AMARES in jMRUI (Gaussian lineshape). Water-suppressed spectra were apodized with 4Hz, phased-corrected (zero order phase), and then fitted with AMARES in JMRUI (Gaussian lineshape).
c. Output measure (e.g. absolute concentration, institutional units, ratio) Processing steps deviating from quoted reference or product	Intramyocellular lipid content (IMCL), calculated from the peak areas of IMCL- $\text{CH}_2$ resonance at 1.3 ppm with respect to the water resonance after correction for T1 and T2 relaxation effects.
d. Quantification references and assumptions, fitting model assumptions	Prior knowledge about relative chemical shifts and relative ratios of linewidth was

	applied for the lipid resonances (EMCL-CH <sub>2</sub> , IMCL-CH <sub>2</sub> , EMCL-CH <sub>3</sub> , and IMCL-CH <sub>3</sub> ). All resonances were fitted with AMARES, using a Gaussian lineshapes and the unsuppressed water resonance was used as reference.
4. Data Quality	
a. Reported variables (SNR, Linewidth (with reference peaks))	SNR and FWHM not reported
b. Data exclusion criteria	Only spectra with clearly visible separation of EMCL and IMCL peaks were taken into the analysis
c. Quality measures of postprocessing Model fitting (e.g. CRLB, goodness of fit, SD of residual)	No quality measures described
d. Sample Spectrum	Supplementary Figure 1

**Supplementary table 3. Correlations between intramuscular triglyceride content and selected metabolic parameters across different glycemic groups at baseline and 5-year follow up.**

	Glucose-tolerant controls		Type 1 diabetes		Type 2 diabetes	
	Baseline (n=128)	Follow up (n=20)	Baseline (n=132)	Follow up (n=27)	Baseline (n=139)	Follow up (n=38)
Blood glucose (mg/dl)	r=-0.03, p=0.705	r=-0.26, p=0.324	r=0.09, p=0.319	r=0.23, p=0.252	<b>r=0.21, p=0.012</b>	r=0.03, p=0.892
HbA1c (NGSP, %)	r=0.04, p=0.429	r=-0.24, p=0.302	r=0.24, p=0.118	r=-0.11, p=0.780	r=0.25, p=0.087	r=0.15, p=0.578
Total cholesterol (mg/dl)	r=0.13, p=0.159	r=-0.09, p=0.699	<b>r=0.19, p=0.032</b>	r=0.19, p=0.331	r=0.09, p=0.289	r=0.30, p=0.112
FFA ( $\mu\text{mol/l}$ )	r=-0.11, p=0.213	r=-0.47, p=0.043	r=0.06, p=0.558	r=-0.06, p=0.775	r=0.09, p=0.319	r=-0.19, p=0.318
Insulin sensitivity ( $\text{mg} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ )	r=-0.06, p=0.350	r=-0.13, p=0.611	<b>r=-0.21, p=0.003</b>	r=-0.03, p=0.894	<b>r=-0.32, p&lt;0.001</b>	r=-0.06, p=0.552
ADIPO-IR (a.u.)	r=0.06, p=0.701	r=-0.17, p=0.791	r=0.28, p=0.122	r=-0.92, p=0.080	<b>r=0.49, p=0.001</b>	r=0.07, p=0.825
Whole body adipose tissue volume ( $\text{cm}^3$ )	r=0.15, p=0.113	r=0.27, p=0.333	r=0.20, p=0.092	r=0.08, p=0.698	<b>r=0.24, p=0.041</b>	r=0.14, p=0.543
Subcutaneous adipose tissue volume ( $\text{cm}^3$ )	r=0.13, p=0.174	r=0.23, p=0.408	r=0.19, p=0.110	r=0.09, p=0.689	r=0.22, p=0.053	r=-0.07, p=0.764
Visceral adipose tissue volume ( $\text{cm}^3$ )	r=0.16, p=0.089	r=0.46, p=0.086	r=0.01, p=0.913	r=0.04, p=0.858	r=0.11, p=0.353	<b>r=0.62, p=0.003</b>
Skeletal muscle volume ( $\text{cm}^3$ )	r=0.14, p=0.165	r=0.36, p=0.183	r=0.05, p=0.601	r=-0.14, p=0.592	r=-0.08, p=0.469	r=0.08, p=0.716
RQbasal (a.u.)	r=-0.03, p=0.748	r=0.06, p=0.817	r=0.14, p=0.137	r=0.38, p=0.066	r=0.02, p=0.775	r=0.05, p=0.811
RQclamp (a.u.)	r=-0.08, p=0.368	r=-0.18, p=0.528	<b>r=-0.24, p=0.008</b>	r=-0.10, p=0.670	r=-0.07, p=0.402	r=0.08, p=0.710
REEbasal (kcal/day)	r=0.17, p=0.054	r=0.45, p=0.083	r=0.05, p=0.574	r=0.13, p=0.557	r=0.02, p=0.820	r=0.21, p=0.314
REEclamp (kcal/day)	r=0.11, p=0.214	<b>r=0.59, p=0.027</b>	r=-0.03, p=0.730	r=0.21, p=0.347	r=-0.04, p=0.620	r=0.09, p=0.653

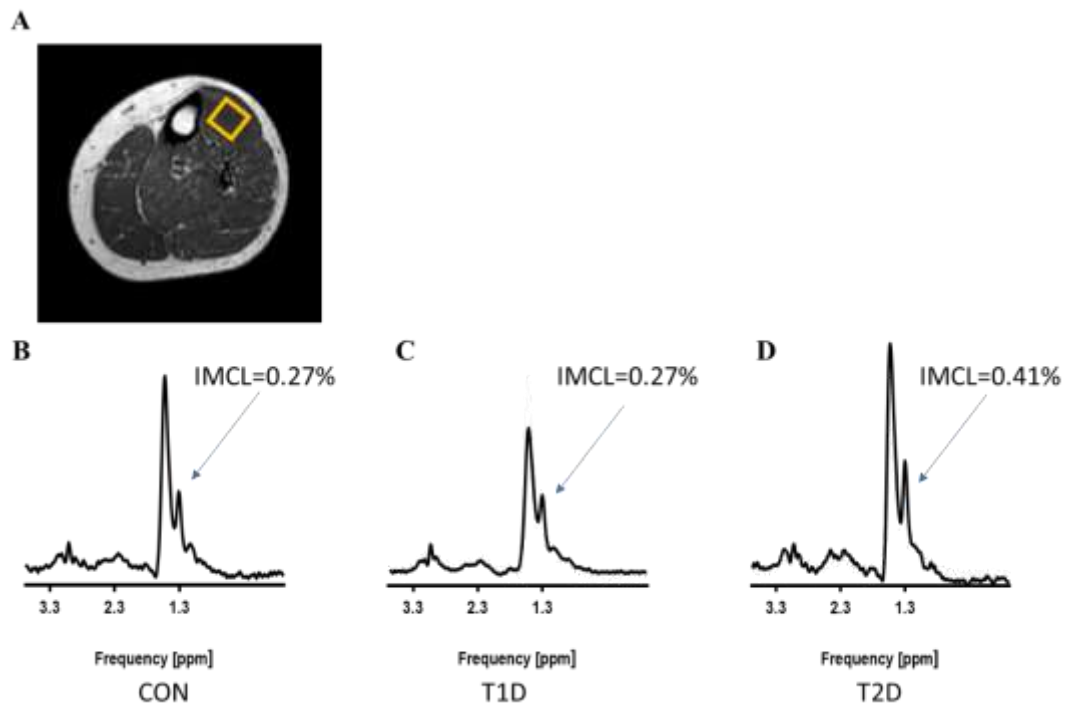
Blood sampling was done in overnight fasted participants. Data are shown as correlation coefficient and p value. ADIPO-IR, fasting adipose tissue insulin resistance; FFA, free fatty acids; HbA1c, glycated hemoglobin A1c; RQbasal, respiratory quotient in fasting conditions; RQclamp, respiratory quotient during clamp; REEbasal, resting energy expenditure in fasting conditions; REEclamp, resting energy expenditure during clamp.

**Supplementary table 4. Tridimensional relationship between physical fitness (VO<sub>2</sub>max), intramyocellular lipid content (IMCL), and whole-body insulin sensitivity (M-value) in glucose-tolerant controls and adults with type 1 and type 2 diabetes at baseline.**

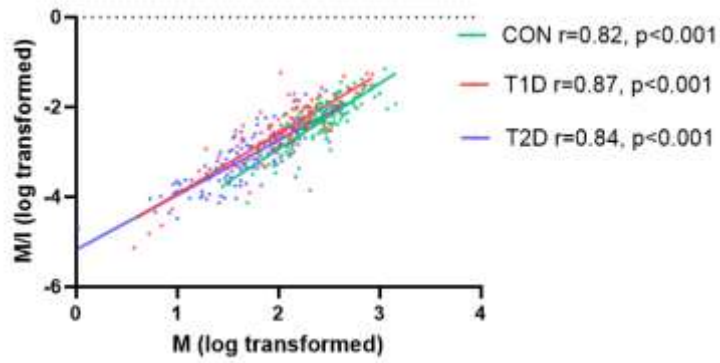
	<b>Glucose-tolerant controls</b> (n=128)			<b>Type 1 diabetes</b> (n=132)			<b>Type 2 diabetes</b> (n=139)		
	r	SE	p	r	SE	p	r	SE	p
M value	-0.10	3.64	0.978	-2.20	2.59	0.782	<b>-6.54</b>	<b>2.66</b>	<b>0.015</b>
VO <sub>2</sub> max	0.11	1.15	0.925	-0.27	0.73	0.709	<b>-1.27</b>	<b>0.61</b>	<b>0.040</b>
M value * VO <sub>2</sub> max	<0.01	0.47	0.999	0.24	0.34	0.486	<b>0.81</b>	<b>0.35</b>	<b>0.022</b>

p based on multiple linear regression. VO<sub>2</sub>max, maximal aerobic capacity.

**Supplementary figure 1. Representative voxel location from tibialis anterior muscle (A) and representative spectra of intramyocellular lipid content (IMCL) from glucose-tolerant person (B), individual with type 1 (C) and type 2 (D) diabetes. CON, glucose tolerant controls; IMCL, intramyocellular lipid content; T1D, type 1 diabetes; T2D, type 2 diabetes.**



**Supplementary figure 2. Correlation between whole-body insulin sensitivity expressed as M value and when adjusted for plasma insulin levels during clamp steady state (M/I).**



CON, glucose tolerant controls; T1D, type 1 diabetes; T2D, type 2 diabetes.