SUPPLEMENTARY DATA

Supplementary Table S1. Case-control studies investigating the association between mitochondrial oxidative capacity and insulin resistance/types 2 diabetes (T2DM) in humans

Authors	Size	Covariates	Diagnosis	Mt capacity	Results
Petersen, *Science*, 2003	15 insulin-resistant elderly and 13 young controls	BMI and physical activity matched	Medical history and OGTT	13C/31P NMR spectroscopy	Reduced mitochondrial oxidative capacity
Schrauwen-Hinderling, *Diabetologia*, 2007	12 over weighted T2DM subjects and 9 controls	BMI matched	Medications	PCr recovery using MRS	Reduced mitochondrial oxidative capacity
Szendroedi, *Plos Med*, 2007	10 patients with T2DM, 10 older controls; and 11 younger controls	age-, sex- and body mass-matched (only older controls)	Medical history	ATP synthetic flux using MRS	Reduced mitochondrial oxidative capacity
Tranell, *Diabetes Care*, 2008	10 well-controlled T2D subjects and 10 controls	Age, sex, weight and physical activity matched	Medical history and medications	PCr recovery using MRS	No difference in mitochondrial oxidative capacity
De Fayter, *Eur J Endocrinol*., 2008	10 long-standing, insulin-treated T2DM patients (diabetes group), 11 subjects with impaired fasting glucose, impaired glucose tolerance and/or recently diagnosed T2DM (pre-diabetes group) , and 12 controls	Age, body mass and composition, physical activity	Fasting glucose and OGTT	PCr recovery using MRS	No difference in mitochondrial oxidative capacity
Phielix, *Diabetes*, 2008	10 overweight diabetic patients, 12 first-degree	Age and BMI matched	Medications	PCr recovery using MRS	Reduced mitochondrial oxidative capacity

	relatives, and 16 control subjects, all men				
Van Tienen, *J Clin Endocrinol Metab*, 2012	12 prediabetic, 11 longstanding T2DM male subjects and 12 male controls	Age and BMI matched	OGTT	PCr recovery using MRS	No difference in mitochondrial oxidative capacity
Tecilazich, *J Vasc Surg*, 2013	11 T2DM patients without complication, 12 T2DM patients with neuropathy, 7 T2DM patients with neuropathy-PAD and 14 controls		Medical history, physical examination, characterization of neuropathy , ABIs	PCr recovery using MRS	Reduced mitochondrial oxidative capacity only in T2DM patients with neuropathy
Van der Weijer, *Plos One*, 2013	30 obese sedentary male T2D patients and 31 obese sedentary male control subjects		Medications	PCr recovery using MRS	Reduced mitochondrial oxidative capacity

Notes:

References:

De Feyter HM, van den Broek NM, Praet SF, Nicolay K, van Loon LJ, Prompers JJ. Early or advanced stage type 2 diabetes is not accompanied by in vivo skeletal muscle mitochondrial dysfunction. Eur J Endocrinol. 2008 May;158(5):643-53. doi: 10.1530/EJE-07-0756.

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Phielix E, Schrauwen-Hinderling VB, Mensink M et al. Lower intrinsic ADP-stimulated mitochondrial respiration underlies in vivo mitochondrial dysfunction in muscle of male type 2 diabetic patients. Diabetes. 2008 Nov;57(11):2943-9. doi: 10.2337/db08-0391.

Schrauwen-Hinderling VB, Kooi ME, Hesselink MK et al. Impaired in vivo mitochondrial function but similar intramyocellular lipid content in patients with type 2 diabetes mellitus and BMI-matched control subjects. Diabetologia. 2007 Jan;50(1):113-20.

Szendroedi J, Schmid AI, Chmelik M et al. Muscle mitochondrial ATP synthesis and glucose transport/phosphorylation in type 2 diabetes. PLoS Med. 2007 May;4(5):e154.

Tecilazich F, Dinh T, Lyons TE et al. Postexercise phosphocreatine recovery, an index of mitochondrial

oxidative phosphorylation, is reduced in diabetic patients with lower extremity complications. J Vasc Surg. 2013 Apr;57(4):997-1005. doi: 10.1016/j.jvs.2012.10.011.
Trenell MI, Hollingsworth KG, Lim EL, Taylor R. Increased daily walking improves lipid oxidation without changes in mitochondrial function in type 2 diabetes. Diabetes Care. 2008 Aug;31(8):1644-9. doi: 10.2337/dc08-0303.
van de Weijer T, Sparks LM, Phielix E et al. Relationships between mitochondrial function and metabolic flexibility in type 2 diabetes mellitus. PLoS One. 2013;8(2):e51648. doi: 10.1371/journal.pone.0051648.

van Tienen FH, Praet SF, de Feyter HM et al. Physical activity is the key determinant of skeletal muscle mitochondrial function in type 2 diabetes. J Clin Endocrinol Metab. 2012 Sep;97(9):3261-9. doi: 10.1210/jc.2011-3454.

SUPPLEMENTARY DATA

Supplementary Table S2. Spearman correlations exploring the relationship between τ_{PCr} (sec) and prediabetes, HOMA index, Matsuda Index and Reduced Matsuda index:

	τ_{PCr} (sec)					
	Model I (age, sex and %PCr depletion adjusted) (N=248)		**Model II ¥ (N=248)**		**Model III § (N=248)**	
	R	**P value**	**R**	**P value**	**R**	**P value**
Prediabetes	0.26	<.001	0.21	.001	0.22	<.001
HOMA index	0.19	.002	0.16	.014	0.17	.009
Matsuda index	-0.22	<.001	-0.16	.012	-0.17	.009
Reduced Matsuda index	-0.27	<.001	-0.20	.002	-0.21	.001

	Model IV ∞ (N=247)		**Model V # (N=248)**		**Model VI ¤ (N=248)**		**Model VII ǂK (N=248)**	
	R	**P value**	**R**	**P value**	**R**	**P value**	**R**	**P value**
Prediabetes	0.25	<.001	0.22	<.001	0.22	<.001	0.23	<.001
HOMA index	0.21	<.001	0.17	.010	0.16	.013	0.19	.003
Matsuda index	-0.22	<.001	-0.17	.011	-0.17	.009	-0.20	.002
Reduced Matsuda index	-0.26	<.001	-0.19	.002	-0.21	.001	-0.24	<.001

¥ age, sex and %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured trunk fat mass.

§ age, sex and %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured trunk fat mass, plasma levels of IL6, CRP, leptin and adiponectin

∞ age, sex and %PCr depletion, race, education, smoking status, physical activity level, body height, body weight, waist circumference, plasma levels of IL6, CRP, leptin and adiponectin

age, sex and %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured total body fat mass, plasma levels of IL6, CRP, leptin and adiponectin

¤ age, sex and %PCr depletion, race, education, smoking status, physical activity level, body height,

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percentage of body fatness, plasma levels of IL6, CRP, leptin and adiponectin

ж age, sex and %PCr depletion, race, education, smoking status, physical activity level, BMI, plasma levels of IL6, CRP, leptin and adiponectin

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Supplementary Table S3. Results from multivariate logistic models testing the association between tertiles of τ_{PCr} (sec) and likelihood (OR) of having prediabetes or being in a higher tertile of HOMA Index, Matsuda Index and Reduced Matsuda Index:

	Likelihood of prediabetes							
	Model I (age, sex and %PCr depletion adjusted) (N=248)		**Model II ¥ (N=248)**		**Model III § (N=248)**			
Tertiles of τ_{PCr}	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**		
Second Vs First	4.21 (2.07-8.57)	<.001	3.57 (1.62-7.86)	.002	3.44 (1.54-7.68)	.003		
Third vs First	4.67 (2.19-9.96)	<.001	5.04 (2.13-11.91)	<.001	5.11 (2.14-12.18)	<.001		
	Model IV ∞ (N=247)		**Model V # (N=248)**		**Model VI ¤ (N=248)**		**Model VII ж (N=248)**	
Tertiles of τ_{PCr}	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Second Vs First	4.17 (1.94-8.96)	<.001	3.59 (1.64-7.84)	.001	3.58 (1.66-7.73)	.001	4.39 (2.07-9.30)	<.001
Third vs First	5.84 (2.51-13.62)	<.001	4.63 (1.98-10.83)	<.001	4.51 (1.95-10.44)	<.001	5.28 (2.32-12.03)	<.001
	Higher Tertile of HOMA Index (Insulin Resistance)							
	Model I (age, sex and %PCr depletion adjusted) (N=248)		**Model II ¥ (N=248)**		**Model III § (N=248)**			
Tertiles of τ_{PCr}	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**		
Second Vs First	1.47 (0.82-2.63)	.194	1.09 (0.57-2.11)	.777	1.07 (0.55-2.09)	.829		
Third vs First	2.94 (1.58-5.45)	<.001	2.95 (1.45-5.98)	.003	2.84 (1.39-5.80)	.004		
	Model IV ∞ (N=247)		**Model V # (N=248)**		**Model VI ¤ (N=248)**		**Model VII ж (N=248)**	
Tertiles of τ_{PCr}	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Second Vs First	1.26 (0.66-2.44)	.481	1.84 (0.61-2.28)	.614	1.03 (0.54-1.96)	.926	1.36 (0.72-2.57)	.347
Third vs First	3.46 (1.69-7.09)	<.001	2.79 (1.37-5.73)	.005	2.30 (1.16-4.59)	.018	3.16 (1.56-6.38)	.001
	Higher Tertile of Matsuda Index (Insulin Sensitivity)							
	Model I (age, sex and %PCr		**Model II ¥**		**Model III §**			

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	depletion adjusted) (N=248)		(N=248)		(N=248)	
Tertiles of τ_{PCr}	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Second Vs First	0.50 (0.28-0.90)	.021	0.59 (0.31-1.12)	.106	0.56 (0.29-1.09)	.087
Third vs First	0.32 (0.17-0.59)	<.001	0.33 (0.16-0.66)	.002	0.31 (0.15-0.63)	.001

	Model IV ∞ (N=247)		**Model V # (N=248)**		**Model VI ¤ (N=248)**		**Model VII ж (N=248)**	
Tertiles of τ_{PCr}	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Second Vs First	0.49 (0.25-0.95)	.034	0.53 (0.28-1.02)	.059	0.62 (0.33-1.18)	.148	0.5 (0.27-0.95)	.035
Third vs First	0.24 (0.12-0.50)	<.001	0.31 (0.15-0.63)	.001	0.38 (0.19-0.76)	.006	0.28 (0.14-0.57)	<.001

	Higher Tertile of Reduced Matsuda Index(Insulin Sensitivity)							
	Model I (age, sex and %PCr depletion adjusted) (N=248)		**Model II ¥ (N=248)**		**Model III § (N=248)**			
Tertiles of τ_{PCr}	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**		
Second Vs First	0.38 (0.21-0.69)	.001	0.46 (0.24-0.88)	.018	0.45 (0.24-0.87)	.018		
Third vs First	0.28 (0.15-0.53)	<.001	0.32 (0.16-0.63)	.001	0.31 (0.16-0.63)	.001		

	Model IV ∞ (N=247)		**Model V # (N=248)**		**Model VI ¤ (N=248)**		**Model VII ж (N=248)**	
Tertiles of τ_{PCr}	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**	**OR (95%CI)**	**P value**
Second Vs First	0.38 (0.19-0.73)	.004	0.44 (0.23-0.83)	.012	0.49 (0.26-0.92)	.027	0.41 (0.22-0.76)	.005
Third vs First	0.25 (0.12-0.49)	<.001	0.32 (0.16-0.64)	.003	0.36 (0.18-0.72)	.004	0.29 (0.14-0.57)	<.001

¥ age, sex and %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured trunk fat mass.

§ age, sex and %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured trunk fat mass, plasma levels of IL6, CRP, leptin and adiponectin

∞ age, sex and %PCr depletion, race, education, smoking status, physical activity level, body height, body weight, waist circumference, plasma levels of IL6, CRP, leptin and adiponectin

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age, sex and %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured total body fat mass, plasma levels of IL6, CRP, leptin and adiponectin

¤ age, sex and %PCr depletion, race, education, smoking status, physical activity level, body height, percentage of body fatness, plasma levels of IL6, CRP, leptin and adiponectin

Ж age, sex and %PCr depletion, race, education, smoking status, physical activity level, BMI, plasma levels of IL6, CRP, leptin and adiponectin

SUPPLEMENTARY DATA

Supplementary Table S4. Akaike Information Criterion (AIC) for linear, quadratic and cubic spline models testing the relationship between τ PCr and HOMA_IR/Matsuda Index/ Reduced Matsuda Index

	HOMA_IR	**Matsuda Index**	**Reduced Matsuda Index**
	AIC	AIC	AIC
Linear model	1894.014	1888.414	1881.302
Quadratic model	1895.991	1890.221	1881.582
Cubic spline model	1892.062	1892.220	1883.037

SUPPLEMENTARY DATA

Supplementary Table S5. Spearman correlations exploring the relationship between τ_{PCr} (sec) and hepatic insulin resistance/muscle insulin sensitivity indices:

	τ_{PCr} (sec)									
	Un-adjusted correlation		**Age, sex and %PCr depletion adjusted - correlation**		**Age, sex and %PCr depletion, race, education, weight, height, smoking status adjusted - correlation**		**Age, sex and %PCr depletion, race, education, weight, height, smoking status trunk fat mass, physical activity level adjusted – correlation**		**Fully*- adjusted correlation**	
	R	**P value**	**R**	**P value**	**R**	**P value**	**R**	**P value**	**R**	**P value**
Hepatic insulin resistance	0.06	.362	0.09	.151	0.08	.218	0.05	.467	0.03	.639
Skeletal muscle insulin sensitivity	-0.19	.003	-0.19	.004	-0.15	.021	-0.09	.159	-0.07	.288

*age, sex and %PCr depletion, race, education, smoking status, physical activity level, body weight, body height, DEXA-measured trunk fat mass, plasma levels of IL6, CRP, leptin and adiponectin

SUPPLEMENTARY DATA

Supplementary Figure S1. Crude plots exploring the relationship between τ PCr and HOMA_IR/Matsuda Index/ (reduced-) Matsuda Index (red line=linear regression line; blue line=lowess line).