"SARCOPENIA E OBESITÀ NEL PAZIENTE DIABETICO"

Giuseppe Paolisso

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Il Prof. Giuseppe Paolisso dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- MSD
- NOVO
- NOVARTIS
- LILLY

The Role of Inflammation in Age-Related Sarcopenia

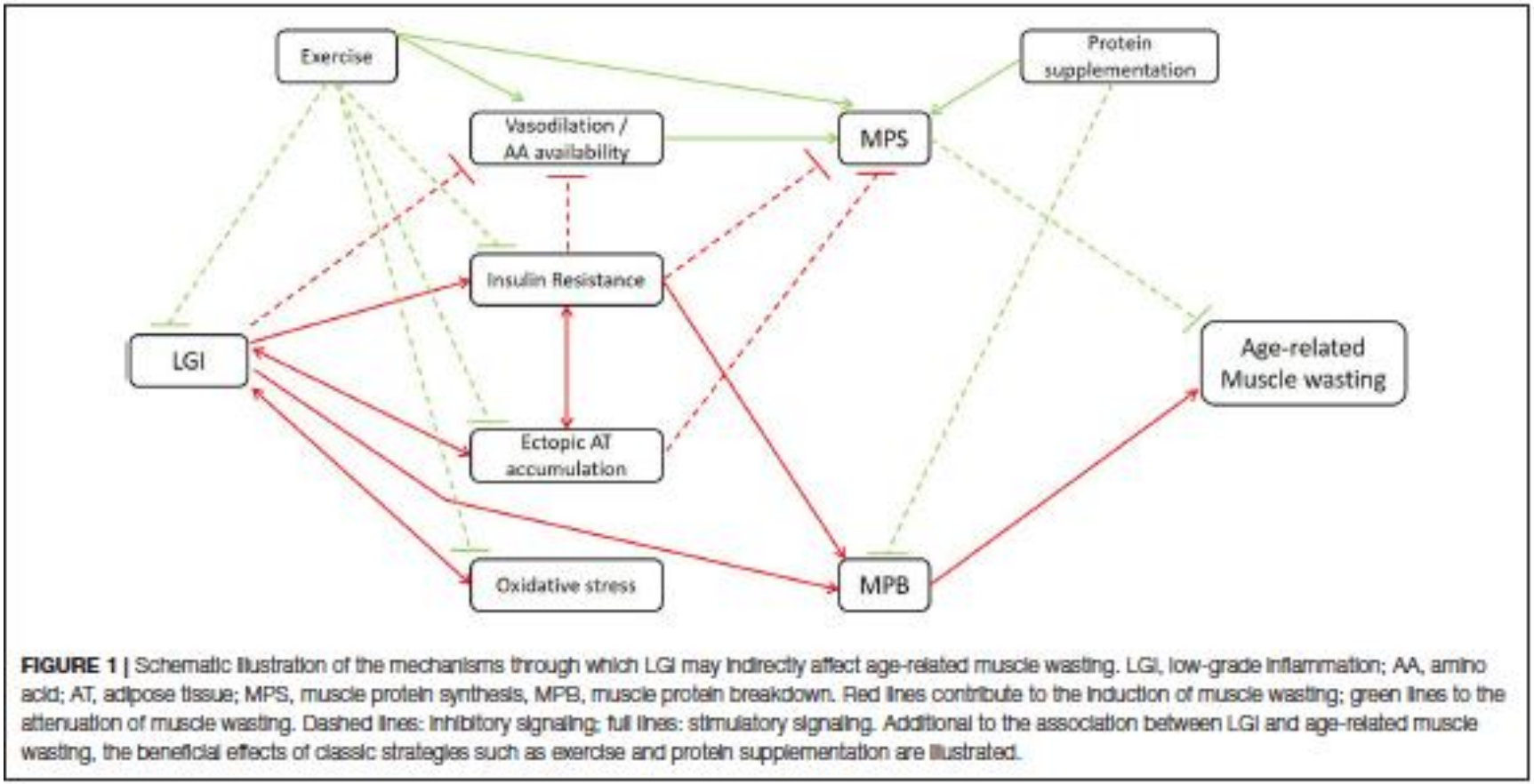
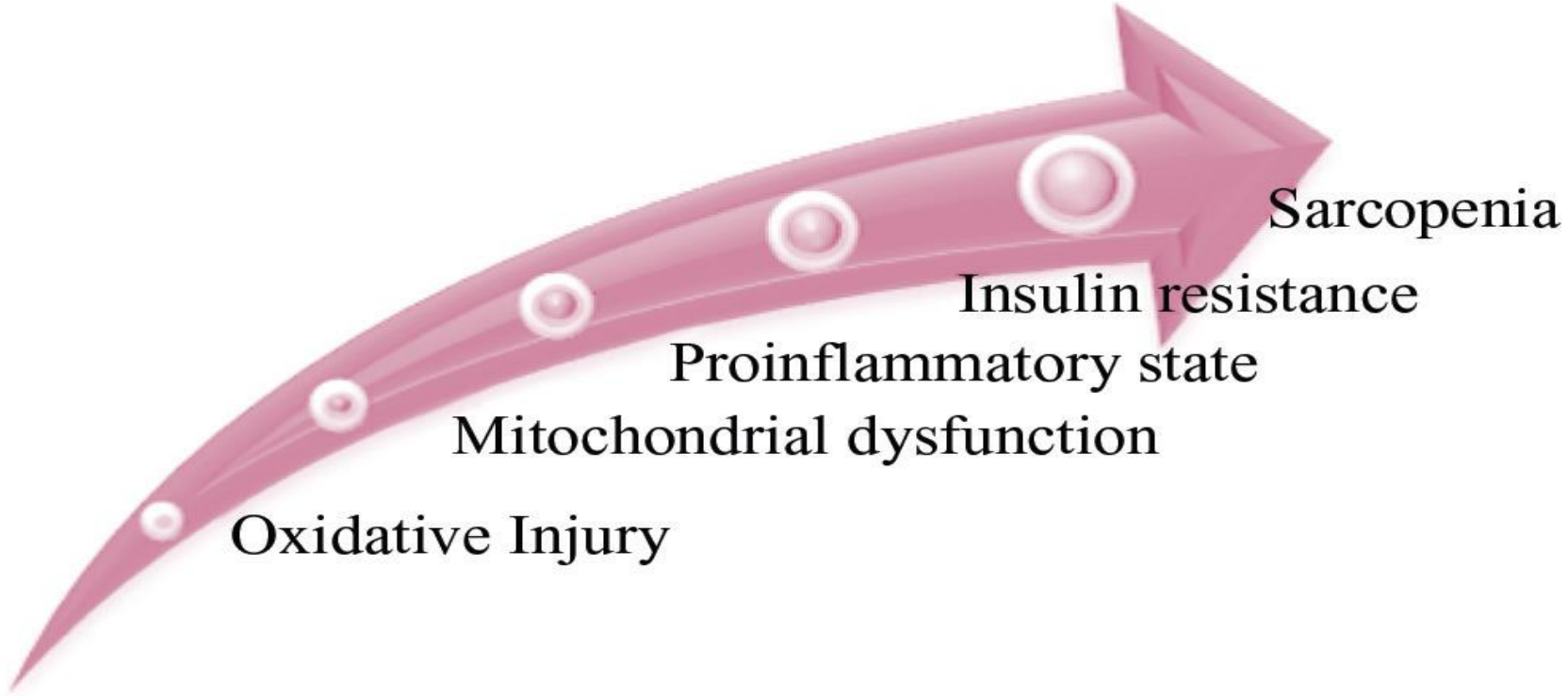


FIGURE 1 | Schematic illustration of the mechanisms through which LGI may indirectly affect age-related muscle wasting. LGI, low-grade inflammation; AA, amino acid; AT, adipose tissue; MPS, muscle protein synthesis, MPB, muscle protein breakdown. Red lines contribute to the induction of muscle wasting; green lines to the attenuation of muscle wasting. Dashed lines: inhibitory signaling; full lines: stimulatory signaling. Additional to the association between LGI and age-related muscle wasting, the beneficial effects of classic strategies such as exercise and protein supplementation are illustrated.

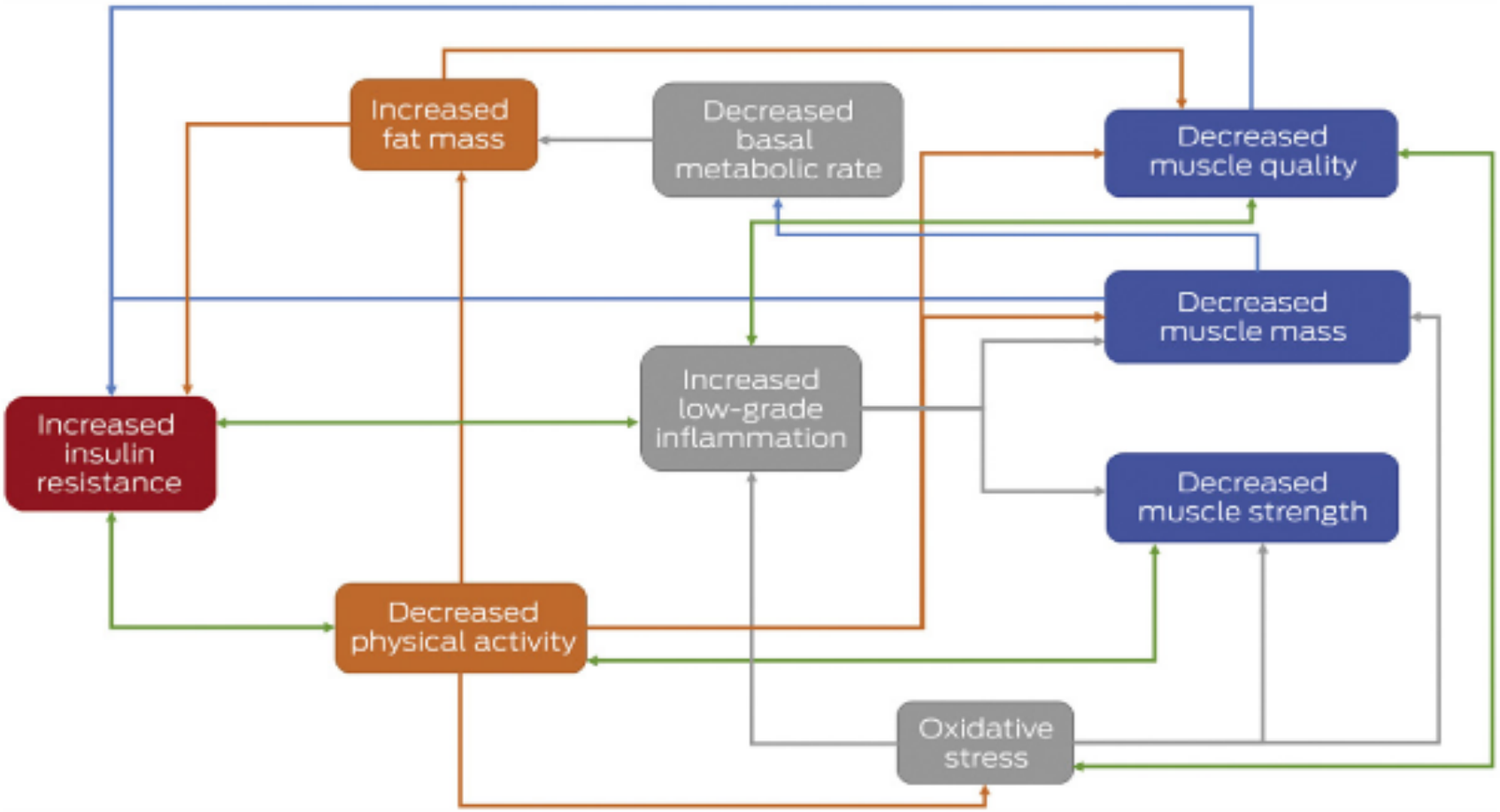
Dalle et al Frontiers in Physiology Dec 2017

Multiple mechanisms have been proposed to be involved in acceleration of sarcopenia in diabetic patients



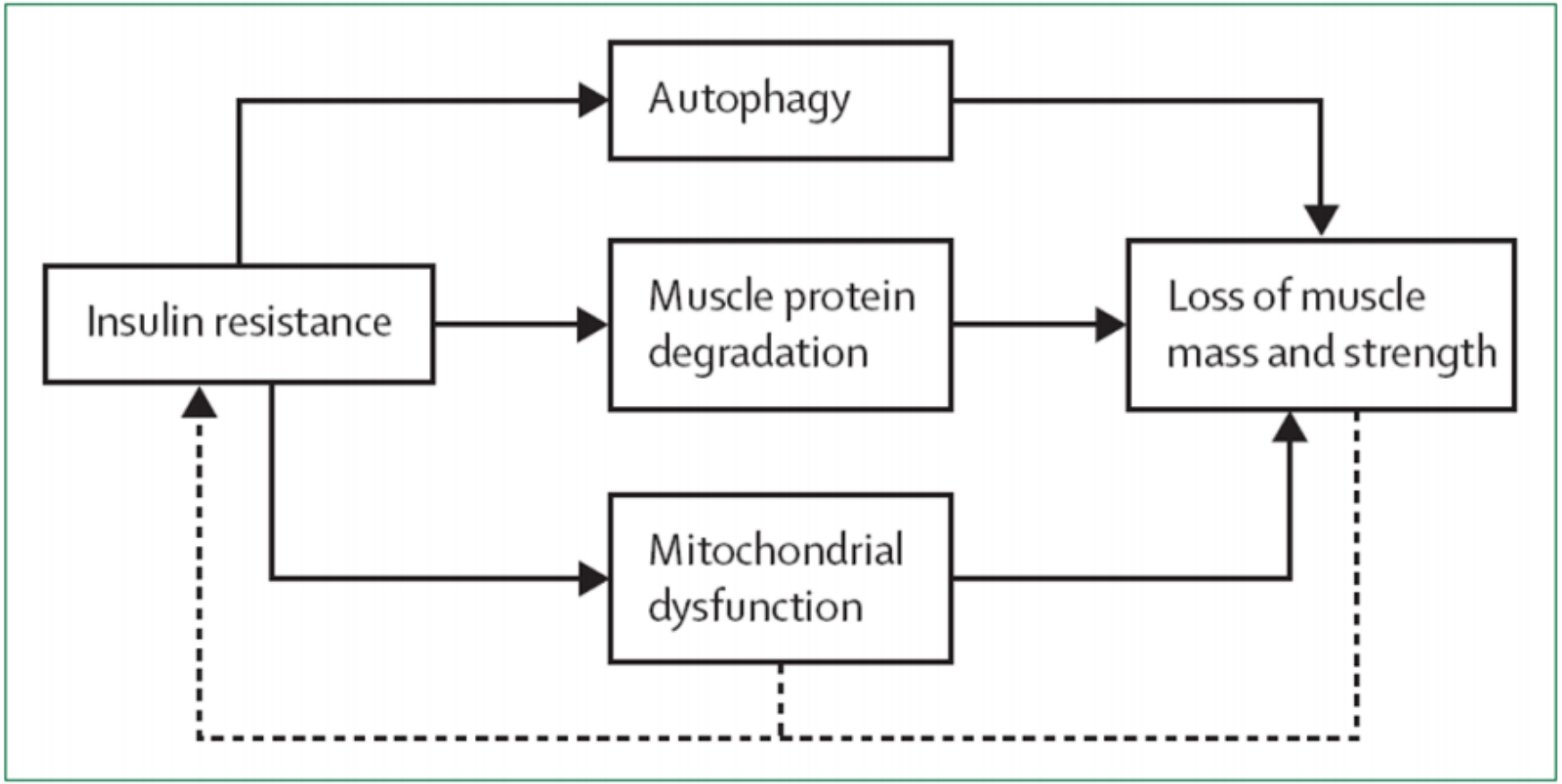
Br J Diabetes Vasc Dis 2011;11:230-234

Potential pathways by which sarcopenia contributes to insulin resistance in ageing*

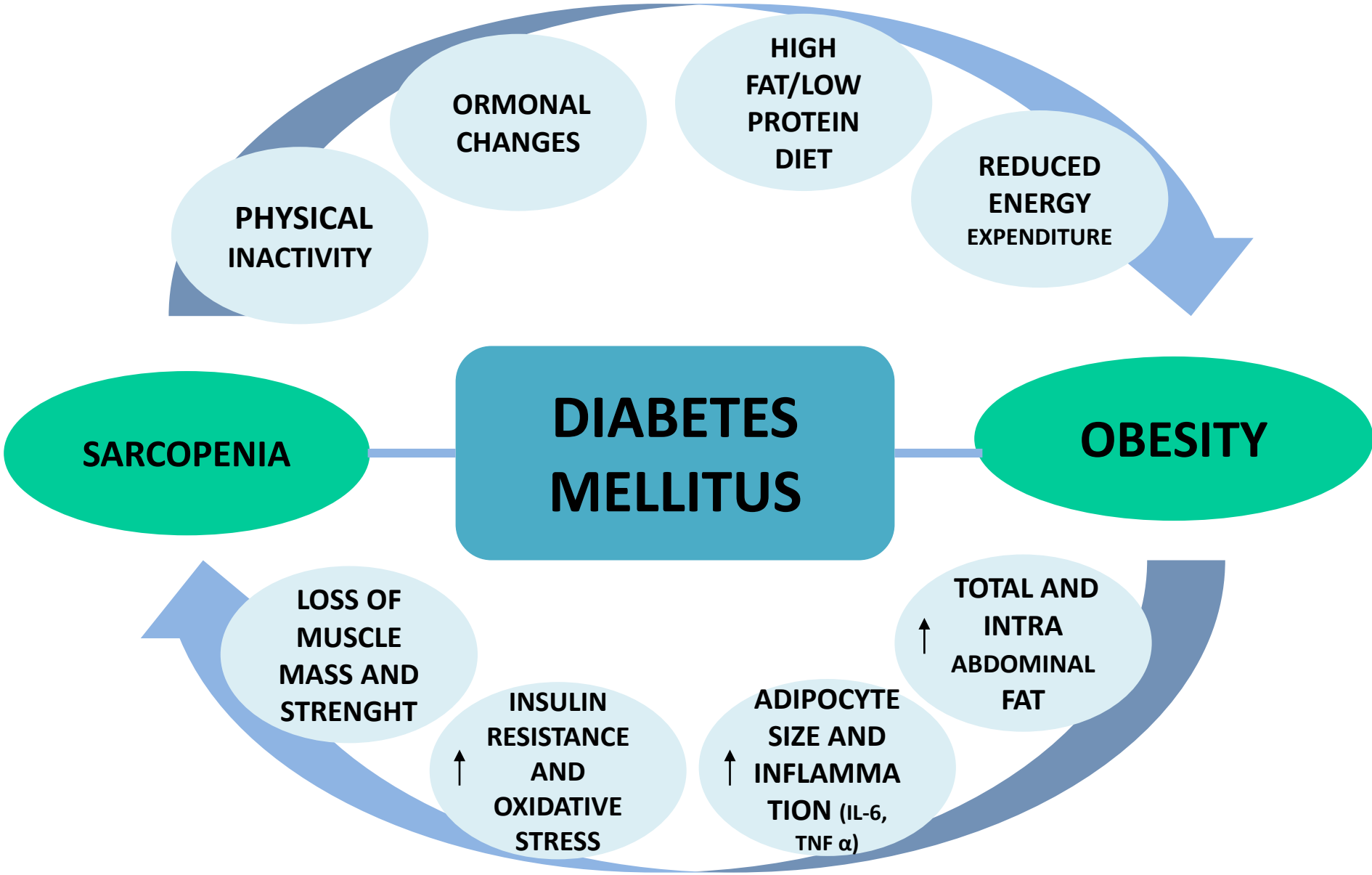


*Components of sarcopenia are shown in the blue boxes.
Green arrows indicate possible bidirectional relationships, illustrating mechanisms by which sarcopenia may be accelerated in people with type 2 diabetes.

PATHWAYS OF ACCELERATED MUSCLE LOSS IN TYPE 2 DIABETES



Rita Rastogi Kalyani et al. Lancet Diabetes Endocrinol. 2014



Adattato da The Lancet Diabetes & Endocrinology, Vol. 2, Issue 10, p819–829 2014

SARCOPENIA AND DIABETES

Decreased Muscle Strength and Quality in Older Adults With Type 2 Diabetes

The Health, Aging, and Body Composition Study

Seok Won Park,[1,2] Bret H. Goodpaster,[3] Elsa S. Strotmeyer,[2] Nathalie de Rekeneire,[4] Tamara B. Harris,[5] Ann V. Schwartz,[6] Frances A. Tylavsky,[7] and Anne B. Newman[2]

N= 485 with type 2 diabetes
N=2,133 without diabetes
Aged 70–79 years

- ✓ muscle strength test
- ✓ DEXA measurements

of body composition

Comparison of arm and leg muscle strength, regional muscle mass, and muscle quality by diabetes status, stratified by sex

	Men			Women		
	No diabetes (n = 1,004)	Diabetes (n = 273)	P value	No diabetes (n = 1,129)	Diabetes (n = 212)	P value
Leg strength (Nm)	133.0 ± 32.4	128.5 ± 34.6	0.046	81.1 ± 22.0	83.8 ± 21.4	0.096
Leg muscle mass (kg)	8.7 ± 1.3	9.1 ± 1.4	<0.001	6.3 ± 1.2	7.0 ± 1.2	<0.001
Leg muscle quality (Nm/kg)	15.3 ± 3.2	14.2 ± 3.3	<0.001	13.0 ± 3.1	12.1 ± 3.2	<0.001
Hand grip strength (kg)	40.0 ± 8.9	38.7 ± 8.8	0.037	24.3 ± 6.4	25.1 ± 5.9	0.098
Arm muscle mass (kg)	3.4 ± 0.6	3.6 ± 0.6	<0.001	2.1 ± 0.4	2.3 ± 0.4	<0.001
Arm muscle quality (kg/kg)	11.7 ± 2.4	10.8 ± 2.3	<0.001	12.0 ± 2.9	11.0 ± 2.9	<0.001

Data are means ± SD. Nm, Newton meters.

	β for diabetes	SE	P value	β for diabetes	SE	P value
Arm muscle quality (kg/kg)						
Unadjusted	−0.89	0.16	<0.001	−1.05	0.22	<0.001
Model 1	−0.84	0.16	<0.001	−0.85	0.22	<0.001
Model 2= model 1+ BMI	−0.53	0.16	0.001	−0.43	0.21	0.043
Model 3	−0.50	0.16	0.002	−0.34	0.22	0.111
Leg muscle quality (Nm/kg)						
Unadjusted	−1.10	0.22	<0.001	−0.87	0.24	<0.001
Model 1	−1.01	0.22	<0.001	−0.61	0.24	0.011
Model 2= model 1+ BMI	−0.84	0.22	<0.001	−0.19	0.23	0.404
Model 3	−0.80	0.22	<0.001	−0.15	0.24	0.524

Adjustments of covariates were performed using multiple regression analyses by cumulatively adding the following covariates into the model. Model 1, race, age, clinic site, and physical activity; model 2, model 1 + BMI; model 3, model 2 + smoking, drinking, comorbidity score, impaired vision, and renal insufficiency. Nm, Newton meters.

Diabetes, vol. 55, june 2006

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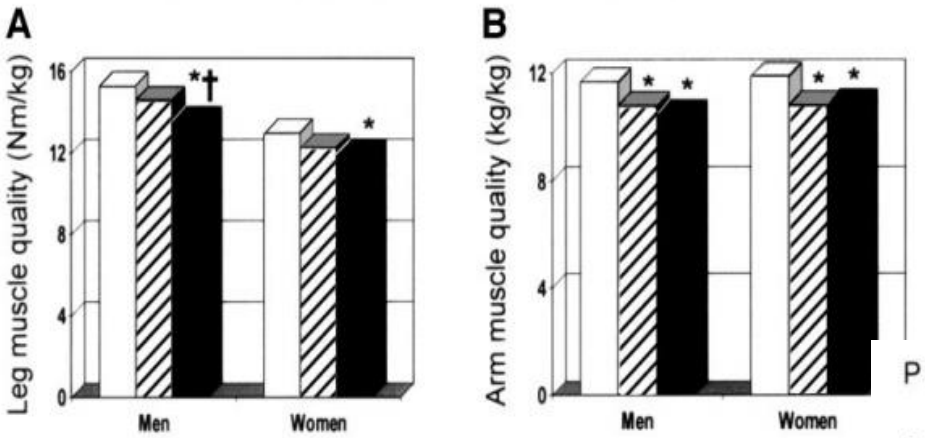
N= 485 with type 2 diabetes
N=2,133 without diabetes
Aged 70–79 years

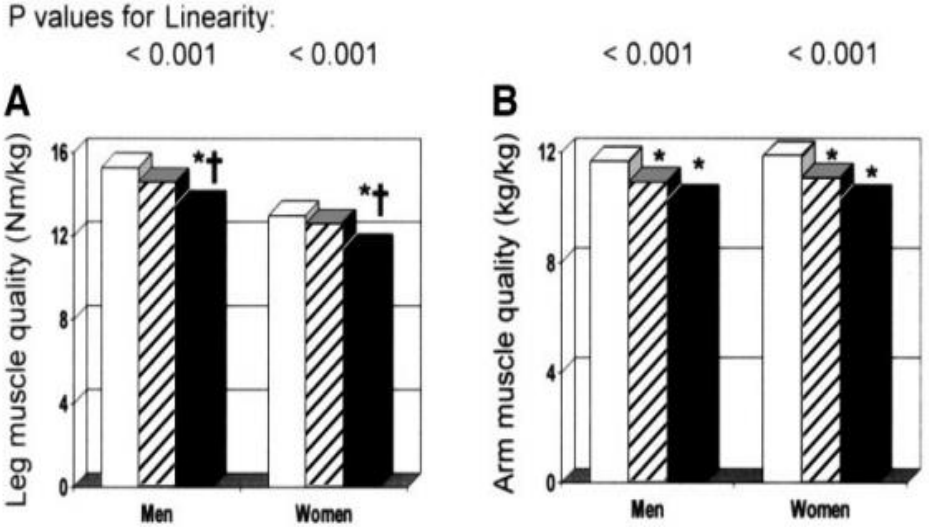
- ✓ muscle strength test
- ✓ DEXA measurements

of body composition

*P < 0.05 compared with subjects without diabetes.
†P < 0.05 compared with diabetic subjects with duration <6 years.



subjects without diabetes
diabetic subjects with duration <6 years
diabetic subjects with duration >6 years



subjects without diabetes
diabetic subjects with A1C <8.0%
diabetic subjects with with A1C >8.0%

*P < 0.05 compared with subjects without diabetes.
†P < 0.05 compared with diabetic subjects with A1C <8.0%.

Diabetes, vol. 55, june 2006

SARCOPENIA AND DIABETES

Prevalence and Determinant Factors of Sarcopenia in Patients With Type 2 Diabetes

Diabetes Care 33:1497–1499, 2010

The Korean Sarcopenic Obesity Study (KSOS)

N= 414 with type 2 diabetes
N= 396 without diabetes
Age= 58 ± 10 years old

- ✓ BMI
- ✓ DEXA measurements

of body composition

Indices of Sarcopenia	ASM/height^2 below 2 SD (Baumgartner et al.)			SMI below 2 SD (Janssen et al.)		
	With diabetes	Without diabetes	*P*-value	With diabetes	Without diabetes	*P*-value
Total (n = 810)	5.3	2.0	0.010	15.7	6.9	<0.001
Men (n = 370)	10.1	4.6	0.039	10.1	3.3	0.010
40-59 years (n = 191)	2.5	2.7	0.634	2.5	1.4	0.505
≥ 60 years (n = 179)	19.0	6.3	0.011	19.0	5.1	0.005
Women (n = 440)	0	0.4	0.555	21.9	9.0	<0.001
40-59 years (n = 219)	0	0	-	16.7	4.1	0.002
≥ 60 years (n = 221)	0	0.8				

ASM, appendicular skeletal muscle; SMI, skeletal muscl
P-values represent overall differences across groups, as

In subjects older than 60 years, prevalence of sarcopenia was greater in both men and women with diabetes.

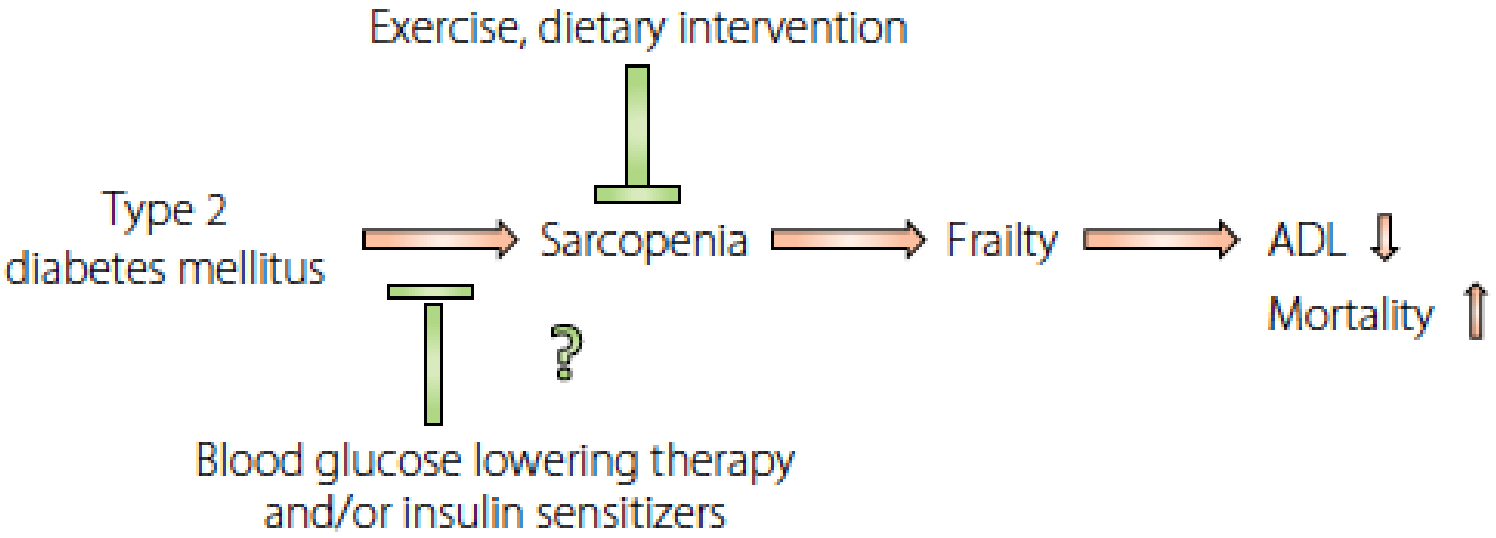
Independent variable: Type 2 diabetes	OR (95% CI)	*P*-value
Unadjusted	2.538 (1.583 – 4.070)	<0.001
Model 1	2.976 (1.816 – 4.879)	<0.001
Model 2	3.200 (1.834 – 5.583)	<0.001
Model 3	3.199 (1.822 – 5.615)	<0.001
Model 4	3.069 (1.422 – 6.621)	0.004

Data are odds ratio (OR) (95% confidence interval (CI)).
Model 1: adjustment for age and gender. Model 2: Model 1 + adjustments for BMI. Model 3: Model 2 + adjustment for smoking, alcohol drinking, and physical activity. Model 4: Model 3 + adjustment for antihypertensive agent, lipid lowering agent, systolic and diastolic blood pressure, total cholesterol, triglyceride, and HDL-cholesterol.
*Sarcopenia was defined using SMI below 2SD of young reference group.

Patients with diabetes had three times higher risk of sarcopenia than subjects without diabetes

Diabetes Care. 2010 Jul;33(7):1497-9.

SARCOPENIA AND DIABETES: HYPERGLYCEMIA IS A RISK FACTOR FOR AGE-ASSOCIATED MUSCLE MASS AND FUNCTIONAL REDUCTION

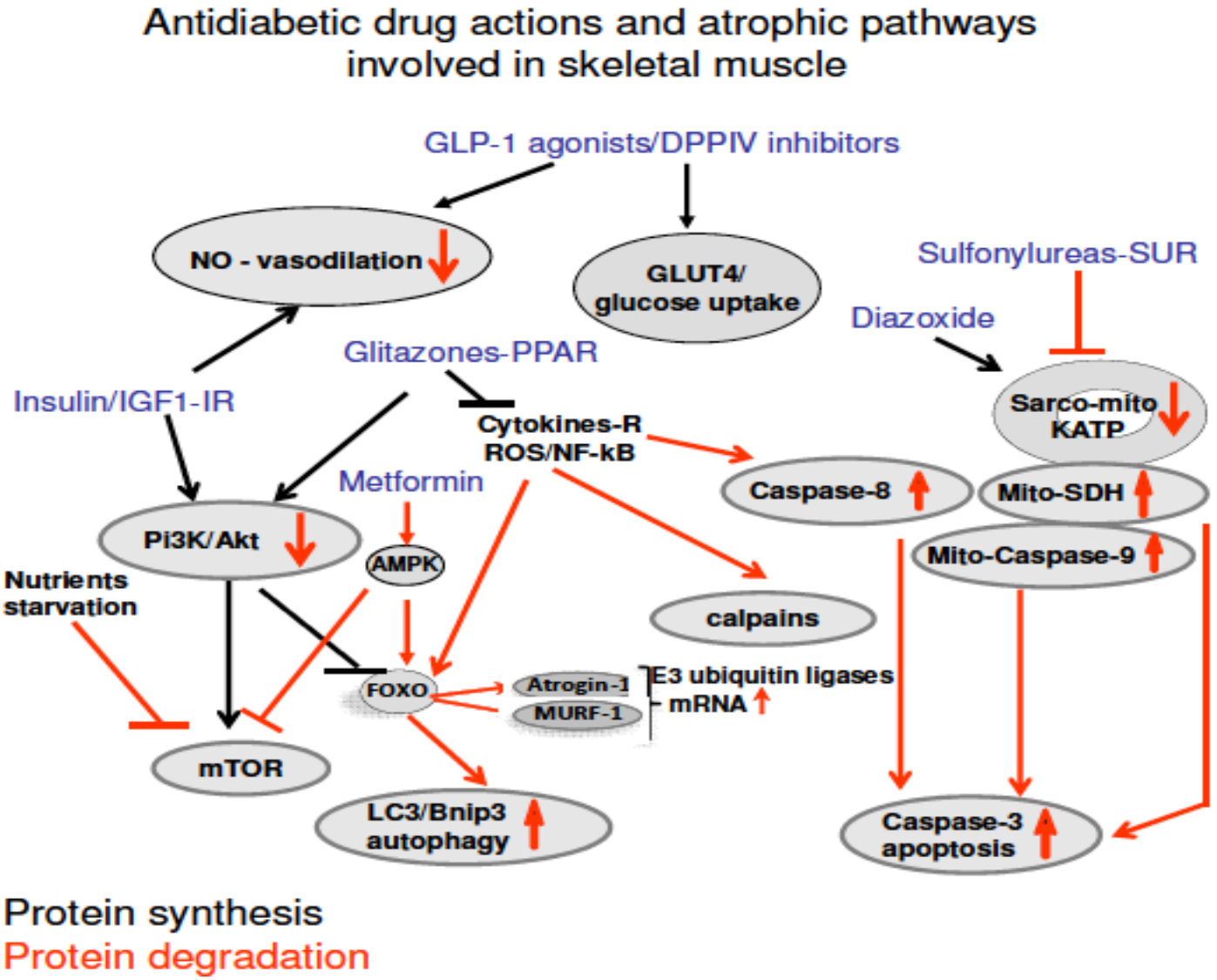


Exercise and/or dietary intervention prevent the progress of sarcopenia. Blood glucose-lowering therapy might also prevent the progression.

J Diabetes Investig Vol. 6 No. 6 November 2015

Effects of the Antidiabetic Drugs on the Age-Related Atrophy and Sarcopenia Associated with Diabetes Type II.

Current Diabetes Reviews, 2014, *10*, 231-237



Journal of the American Medical Directors Association

Volume 17, Issue 10, 1 October 2016, Pages 896–901

Original Study

Sarcopenia in Elderly Diabetic Patients: Role of Dipeptidyl Peptidase 4 Inhibitors

Maria Rosaria Rizzo, MD, Michelangela Barbieri, MD, Ilaria Fava, MD, Manuela Desiderio, MD, Carla Coppola, MD, Raffaele Marfella, MD, Giuseppe Paolisso, MD

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Study population

Original Study

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Inclusion criteria :

Patients aged 65 years or older with diagnosis of diabetes over a minimum 5-year period with HbA1c levels ≤8% (30-31), treated with oral glucose lowering drugs *(metformin in add-on to sulfonylureas or metformin in add-on to dipeptidyl peptidase-4 inhibitors)* for at least 24 months before enrollment.

135 elderly type 2 diabetic patients were screened

80 elderly type 2 diabetic patients (42 males and 38 females)

DPP4-I Group

DPP4-I
(vildagliptin 50 mg bid
o sitagliptin 100 mg/die
o saxagliptin 5 mg/die)
+
METFORMINA (1000 mg)

Sulfonylureas Group

(glimepiride 2 mg/die
o gliburide 15 mg/die
o glipizide 10 mg/die)
+
METFORMINA (1000 mg)

Exclusion criteria

Patients treated with insulin or glucagon-like peptide-1 analogue (GLP-1) or any medications influencing glycaemic function (i.e.corticosteroid), with clinically significant or unstable medical illnesses or severe diabetes complications, or any other disorders affecting glucose metabolism and/or anemia and/or pulmonary disease and/or cancer, or recent acute illness were excluded from the study. They were also excluded from the study all patients with severe cognitive decline and/or Alzheimer dementia, or depression history, drugs or alcohol abuse or dependence in the last two years, or patients affected by malnutrition or who modified the diet, drug treatment or life style within the 3 months before the study.

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Clinical, metabolic and inflammatory characteristics of the study participants, according to antidiabetic therapy

	All patients n=80	Sulfonylureas Group n= 43	p	DPP4-I Group n=37
Antropometric variables				
Age (years)	76.2 ± 5.4	77.1 ± 5.3	0.054	74.9 ± 4.8
Gender (M/F)	38/42	21/22	0.799	17/20
Weight (Kg)	71.5 ± 7.3	69.5 ± 6.9	0.006	73.9 ± 7.1
BMI (Kg/m^2)	26.4 ± 2.5	25.8 ± 2.5	0.02	27.1 ± 2.5
Systolic blood pressure (mmHg)	129 ± 15	128 ± 11	0.773	130 ± 10
Diastolic blood pressure (mmHg)	77 ± 10	78 ± 9	0.781	77 ± 11
Metabolic variables				
FPG (mg/dl)	120 ± 23	121 ± 18	0.767	119 ± 28
PPG (mg/dl)	174 ± 27	187 ± 25	0.001	159 ± 21
HbA1c (%)	7.4 ± 0.2	7.5 ± 0.3	0.03	7.3 ± 0.2
Cholesterol (mg/dl)	228 ± 18	230 ± 20	0.257	225 ± 17
Triglycerides (mg/dl)	162 ± 20	166 ± 21	0.084	158 ± 18
Glucagon (pmol/L)	10.5 ± 1.1	10.8 ± 0.8	0.007	10.2 ± 1.1
GLP-1 AUC (pmol x h x L)	2915 ± 346	2614 ± 346	0.001	3266 ± 100
Inflammatory variables				
TNF-a (pg/ml)	2.7 ± 0.8	3.1 ± 0.9	0.001	2.4 ± 0.6
PCR (mg/ml)	2.2 ± 0.7	2.4 ± 0.8	0.001	1.9 ± 0.3
IL6 (pg/ml)	2.4 ± 0.6	2.5 ± 0.7	0.02	2.2 ± 0.4
Diabetes duration (years)	7.8 ± 2.1			
Current smoking (%)	31 (n=25)			
Anti-hypertensive medication (%)	42 (n=37)			

Data are expressed as means ± DS or %. BMI= Body Mass Index; FPG=Fasting Plasma Glucose; PPG=Post Prandial Glucose; GPL1AUC =area under the curve of GLP1; TNF-a=Tumor Necrosis Factor a; PCR=C-reactive protein; IL6= Interleukin 6.

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Body composition and sarcopenic indices of the study participants, according to antidiabetic therapy

	All patient N=80	Sulfonylureas Group n= 43	p	DPP4-I Group n=37
FFM (Kg)	51.8 ± 7.1	49.4 ± 6.5	0.001	54.5 ± 6.8
FM (Kg)	19.7 ± 1.6	19.9 ± 1.7	0.186	19.4 ± 1.6
FFM/FM	2.6 ± 0.4	2.5 ± 0.3	0.001	2.8 ± 0.4
FFM index (Kg/m²)	19.1 ± 2.2	18.4 ± 2.1	0.001	19.9 ± 2.1
SMM (Kg)	22.4 ± 5.3	20.5 ± 4.7	0.001	24.7 ± 5.3
SMM index (Kg/m²)	8.2 ± 1.7	7.6 ± 1.5	0.001	9.0 ± 1.6
Handgrip strength (Kg)	23.5 ± 4.9	21.4 ± 4.2	0.001	26.1 ± 4.4
Gait speed 4m (m/s)*	3.5 ± 0.7	3.7 ± 0.7	0.001	3.1 ± 0.6

Data are expressed as means ± DS. FFM= Free Fat Mass; FM= Fat Mass; SMM= Skeletal Muscle Mass.
* The used unit, in meters/seconds (m/s), expresses the useful time to cover 4 meters distance (a fixed distance, 4 meters) in a time (s) varying from subject to subject

Based on the findings of other studies in the literature, the relative SMM index less than 8.87 kg/m² for men and 6.42 kg/m² for women was considered abnormal

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Cross Tab Correlations among metabolic and sarcopenic indices in all study population

Characteristics	Age	Diabetes duration	HbA1c	FFM	FFM Index	SMM	SMM Index	Handgrip strength	Gait speed	PCR
FFM	- 0.597**	-0.366**	- 0.396**							
FFM Index	- 0.598**	-0.428**	- 0.362**	0.828**						
SMM	- 0.261*	-0.162	- 0.255*	0.461**	0.182					
SMM Index	- 0.249*	-0.189	- 0.247*	0.346*	0.229*	0.951**				
Handgrip strength	-0.146	-0.046	-0.173	0.449**	0.159	0.558**	0.432**			
Gait speed	0.190	0.096	0.119	-0.279*	-0.277*	-0.032	-0.011	-0.176		
PCR	0.215*	0.072	0.062	-0.128	-0.171	-0.228*	- 0.273*	-0.260*	0.067	
GPL-1 AUC	-0.213*	0.137	-0.236*	0.382**	0.340**	0.373**	0.378**	0.449**	- 0.444**	-0.484**

FFM= Free Fat Mass; SMM= Skeletal Muscle Mass, PCR=C-reactive protein, IL6= Interleukin 6, GPL1AUC =area under the curve of GLP1.
*p< 0.05; **p < 0.01.

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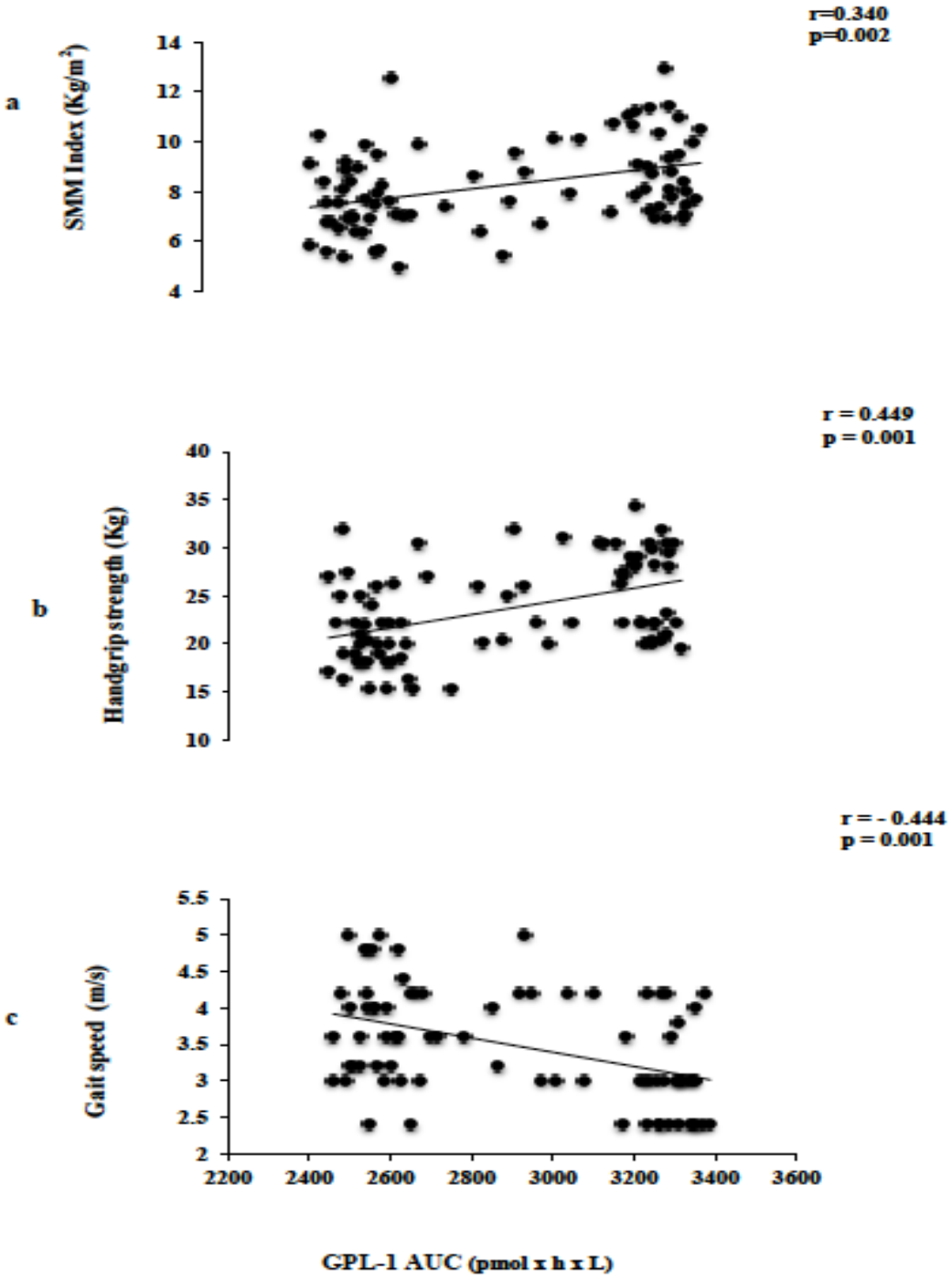
Correlations between GPL-1 AUC and
(a) SMM Index,
(b) Handgrip strength and
(c) Gait speed



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Linear multivariate analyses with SMMI, Handgrip strength and Gait speed as dependent variable

	SMM Index					Handgrip strength					Gaitspeed				
	B	SEM	Beta	t	p value	B	SEM	Beta	t	p value	B	SEM	Beta	t	p value
Age	-,067	,056	-,202	-1,191	,238	-,217	,147	-,233	-1,476	,145	,018	,022	,124	,793	,431
Diabetes duration	-,036	,245	-,023	-,147	,883	,241	,643	,055	,375	,709	,001	,097	,002	,013	,990
BMI	-,087	,087	-,131	-,992	,325	-,668	,230	-,356	-2,909	,055	-,031	,035	-,110	-,904	,369
PPG	,005	,008	,076	,578	,565	-,010	,022	-,053	-,436	,664	,008	,003	,303	2,502	,051
HbA1c	-1,439	,836	-,218	-1,721	,090	-1,671	2,198	-,089	-,760	,450	-,241	,333	-,084	-,726	,470
TNF-a	-,011	,283	-,006	-,041	,968	,207	,743	,036	,278	,782	,078	,112	,088	,692	,492
PCR	-,333	,352	-,135	-,945	,348	-1,014	,927	-,145	-1,094	,278	-,159	,140	-,149	-1,134	,261
IL-6	,032	,345	,012	,093	,926	1,169	,906	,155	1,290	,201	-,268	,137	-,233	-1,954	,055
Glucagon	,049	,209	,029	,233	,817	-,945	,550	-,196	-1,717	,090	-,034	,083	-,046	-,405	,687
GLP1AUC	**,001**	**,001**	**,293**	**2,075**	**,042**	**,006**	**,002**	**,390**	**2,976**	**,004**	**-,001**	**,000**	**-,388**	**-2,991**	**,004**

BMI = body mass index; PPG post prandial glucose; TNF-a=Tumor Necrosis Factor a; PCR=C-reactive protein; IL6= Interleukin 6;GPL1AUC =area under the curve of GLP1.
Bold values indicate results with statistical significance.

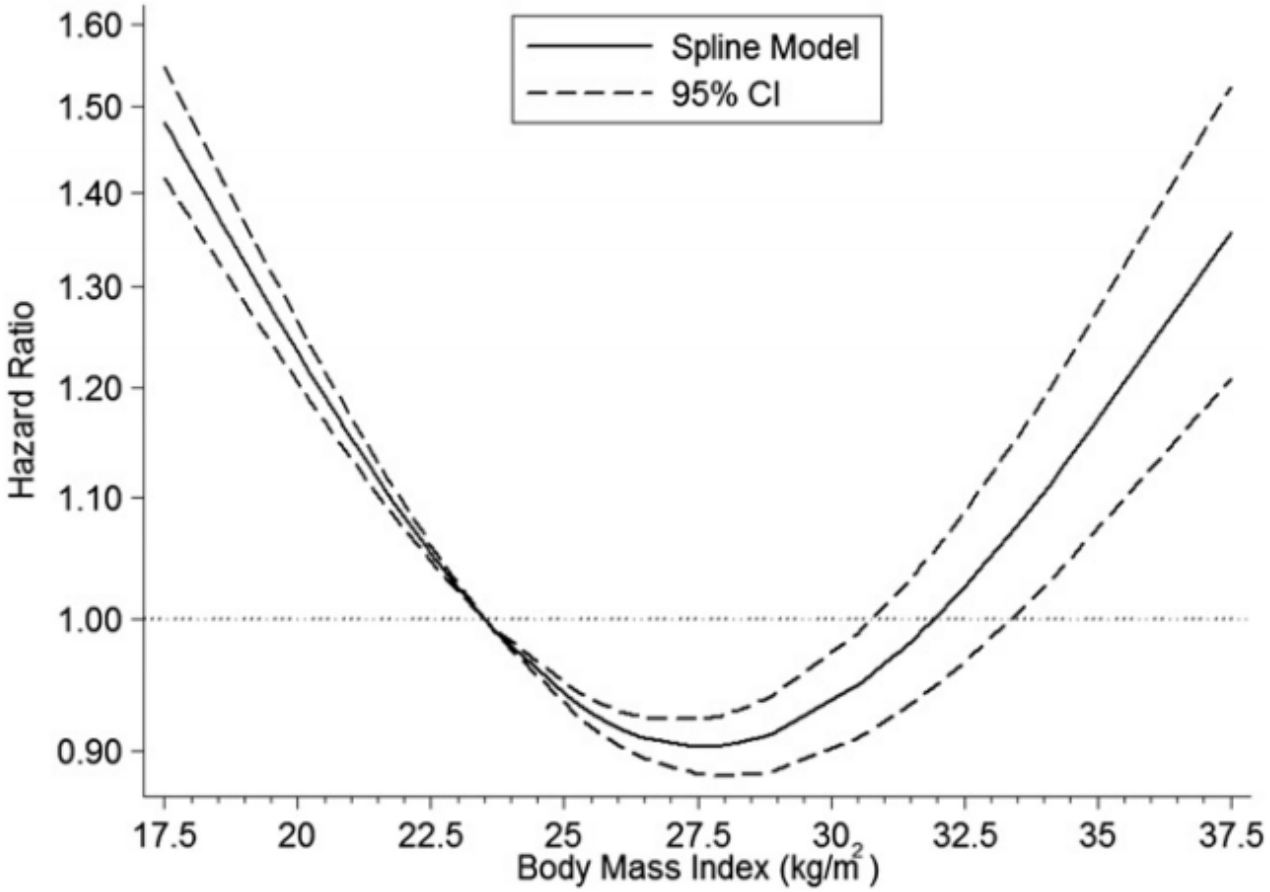
OBESITY AND OUTCOME

BMI and all-cause mortality in older adults: a meta-analysis[1–3]

Jane E Winter, Robert J MacInnis, Naiyana Wattanapenpaiboon, and Caryl A Nowson

N= 200.00 older people

HRs (95% CIs) of all-cause mortality according to BMI for men and women aged > 65 years



In elderly subjects BMI is not an useful parametes

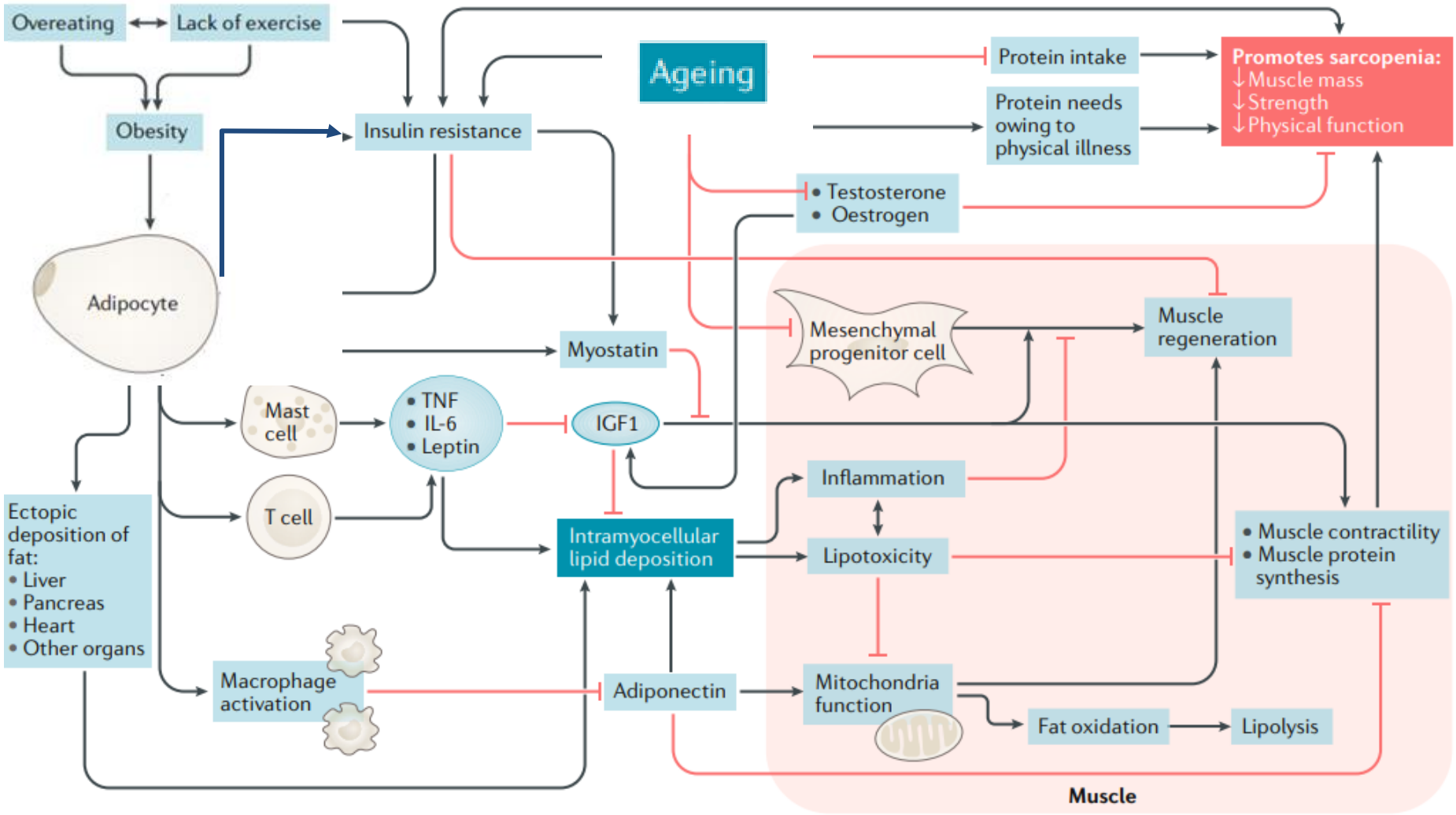
Jane E Winter et al. Am J Clin Nutr 2014;99:875-890

SARCOPENIC OBESITY: A NEW PROBLEM IN ELDERLY

Body Composition Phenotype Characteristics

Characteristic	Sarcopenic	Obese	Sarcopenic obese
Weight	Low	High	Normal/*high*
Fat mass	Low/normal	High	High
Appendicular lean mass	Low	Normal/high	Low
Body mass index (kg/m^2)	Low	High	Normal/*high*
Waist circumference	Low/normal	High	Normal/high

SARCOPENIC OBESITY



Batsis, J. A., & Villareal, D. T. Nature Reviews Endocrinology, 14(9), 513–537.2018

SARCOPENIC OBESITY AND OUTCOME

Clinical Interventions in Aging

Dovepress
open access to scientific and medical research

Open Access Full Text Article

ORIGINAL RESEARCH

Sarcopenic obesity and cognitive performance

N= 353

Age mean 69 years

- ✓ Cognitive test
- ✓ body composition measurements.

Characteristics	Controls	Obesity	Sarcopenia	Sarcopenic obesity
Age, years	**65.87±0.89**	66.98±1.02	73.02±0.90	71.17±2.21
Female, %	76 (68.5)	61 (71.8)	73 (67.0)	15 (83.3)
White race, %	66 (66.0)	43 (54.4)	73 (69.5)	9 (50.0)
BMI	**25.37±0.30**	**35.09±0.35**	**24.92±0.31**	32.16±0.76
Body fat, %	**30.70±0.74**	41.83±0.83	**32.51±0.75**	42.48±1.92
Muscle strength, lb	**63.74±1.82**	**56.62±2.08**	42.81±1.87	35.23±4.53
Muscle mass, lb	98.59±2.10	**108.17±2.39**	93.97±2.15	95.53±5.50
MoCA	**23.86±0.50**	22.51±0.58	21.67±0.51	20.83±1.25
Charlson index	4.89±0.19	5.22±0.22	5.83±0.19	5.33±0.50
Depression	4.56±0.37	5.90±0.43	5.77±0.39	5.20±1.01

Bold values indicate significant difference from the sarcopenic obesity group at p,0.05.

Cognitive domains	Definition 1				Definition 3			
	None	Obesity	Sarcopenia	Sarcopenic obesity	None	Obesity	Sarcopenia	Sarcopenic obesity
Executive function	0	**−0.52±0.27**	**−0.76±0.26**	**−1.22±0.46**	0	**−0.55±0.27**	**−0.65±0.28**	**−1.16±0.35**
Language	0	−0.11±0.20	−0.38±0.19	0.47±0.35	0	0.02±0.20	−0.26±0.21	−0.38±0.25
Attention	0	**−0.58±0.24**	−0.38±0.24	−0.33±0.41	0	**−0.71±0.23**	−0.26±0.25	**−0.83±0.30**
Delayed memory	0	−0.11±0.27	−0.30±0.26	−0.68±0.46	0	−0.49±0.26	−0.47±0.28	**−0.74±0.33**
Orientation	0	−0.29±0.15	**−0.36±0.15**	**−0.59±0.26**	0	**−0.34±0.15**	**−0.40±0.15**	**−0.45±0.19**

Notes: Bold values indicate significant difference from the control group; models are adjusted for age and race.
Abbreviation: BMI, body mass index.

SARCOPENIC OBESITY AND OUTCOME

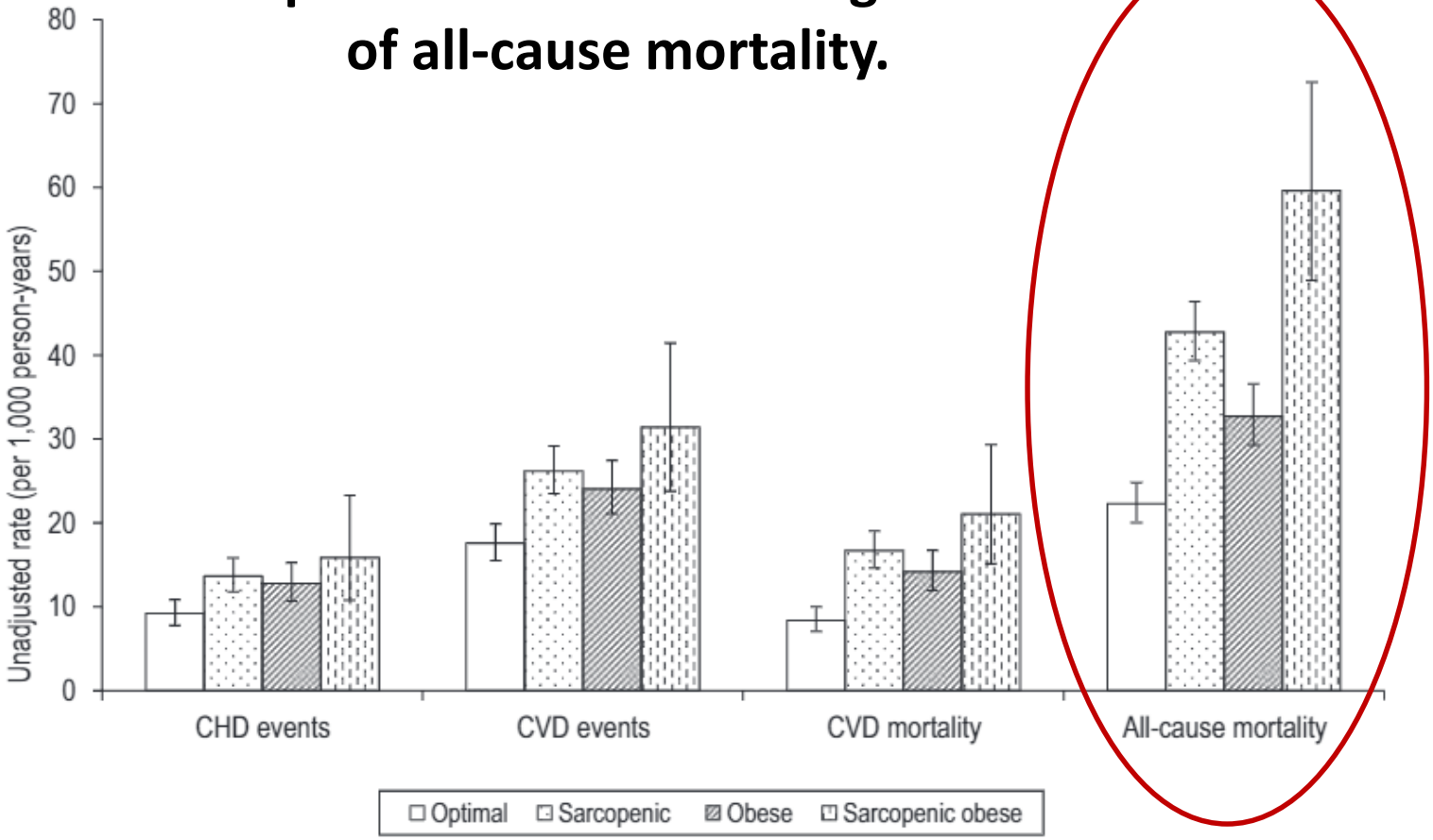
Sarcopenic Obesity and Risk of Cardiovascular Disease and Mortality: A Population-Based Cohort Study of Older Men

Janice L. Atkins, MSc, Peter H. Whincup, PhD,† Richard W. Morris, PhD,* Lucy T. Lennon, MSc,* Olia Papacosta, MSc,* and S. Goya Wannamethee, PhD**

N= 4,252
Aged 60–79 years
Follow-up: 11.3 years

✓ Anthropometric measurements

Sarcopenic obese had the highest risk of all-cause mortality.



JAGS 62:253–260, 2014

SARCOPENIA AND OUTCOME

Sarcopenia Is Independently Associated with Cardiovascular Disease in Older Korean Adults: The Korea National Health and Nutrition Examination Survey (KNHANES) from 2009

Sang Ouk Chin[1], Sang Youl Rhee[1], Suk Chon[1], You-Cheol Hwang[2]*, In-Kyung Jeong[2], Seungjoon Oh[1], Kyu Jeung Ahn[2], Ho
Hong-Yup Ahn[3]

PLOS | ONE

N= 1,578 of 4,888,503 older people

- ✓ BMI
- ✓ DEXA measurements

of body composition

Sarcopenia was associated with CVD independent of other well-documented cardiovascular risk factors.

age (years)						
male (%)						
ASM (kg)						
ASM/weight (%)						
BMI (kg/m^2)	21.8±0.1	22.9±0.2	<0.001	26.7±0.1	27.6±0.1	<0.001
				93.3±0.4	93.7±0.6	<0.001
				104.5±1.3	111.9±2.0	0.002
				7.0±0.1	7.2±0.2	0.176
				1.85±0.05	1.9±0.06	<0.001

CVD PREVALENCE ACCORDING TO THE PRESENCE OF METABOLIC SYNDROME (M) AND SARCOPENIA (S).

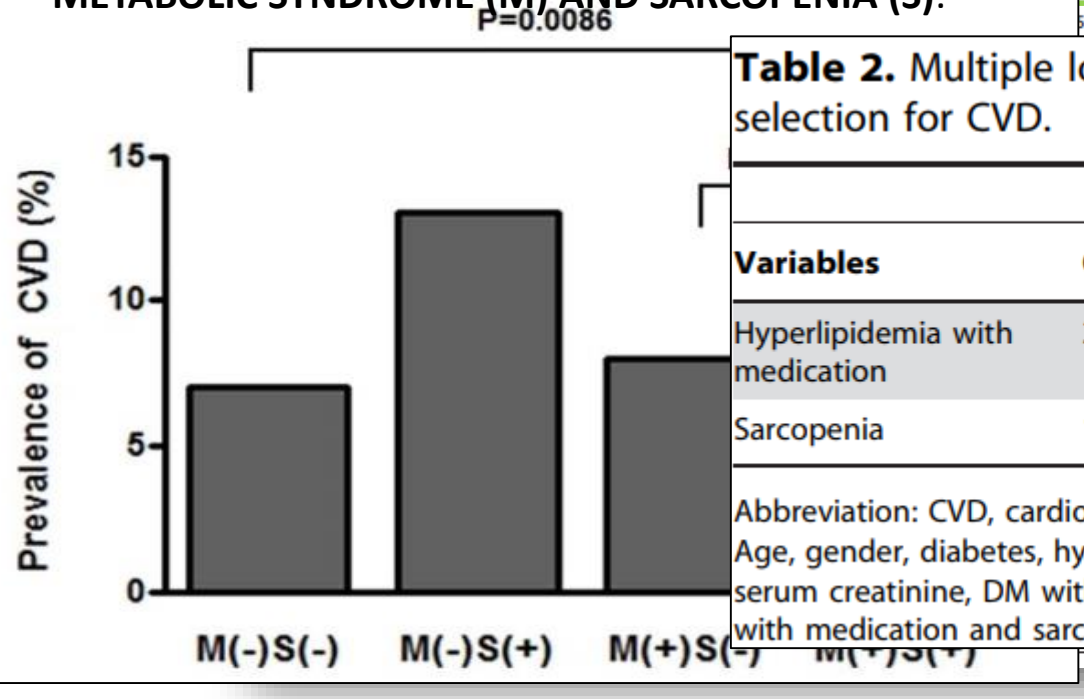


Table 2. Multiple logistic regression analysis and backward selection for CVD.

Variables	OR (95% CI)	*P*
Hyperlipidemia with medication	3.026 (1.509–6.067)	0.002
Sarcopenia	1.768 (1.075–2.909)	0.025

Abbreviation: CVD, cardiovascular diseases.
Age, gender, diabetes, hypertension, hyperlipidemia, current smoking, obesity, serum creatinine, DM with medications, HTN with medication, hyperlidemia with medication and sarcopenia were included as dependent variables.

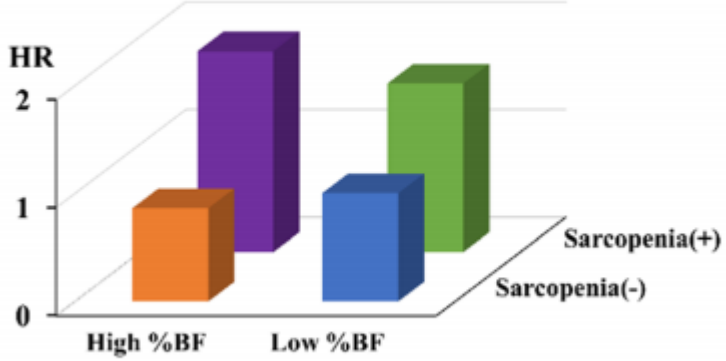
PLoS One. 2013;8(3):e60119.

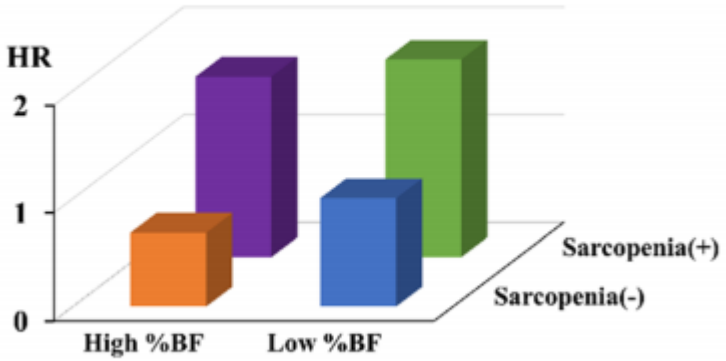
SARCOPENIC OBESITY AND OUTCOME

Sarcopenic obesity assessed using dual energy X-ray absorptiometry (DXA) can predict cardiovascular disease in patients with type 2 diabetes: a retrospective observational study

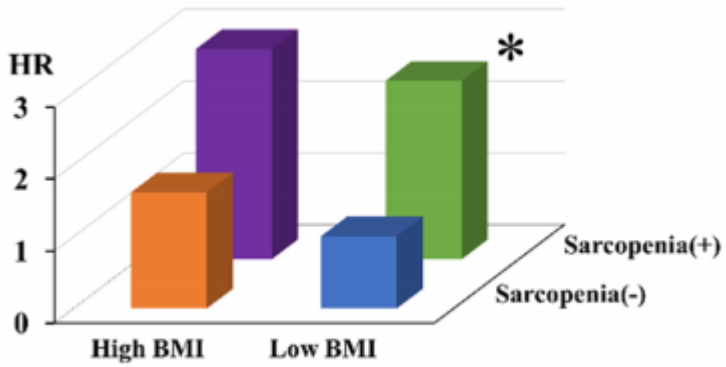
N= 716 patients with diabetes
Mean age: 65±13 years
Follow up of 2.6 years
✓ DEXA measurements of body composition
✓ BMI

e **UNIVARIATE MODEL** *p<0.05 f **MULTIVARIATE MODEL**





g



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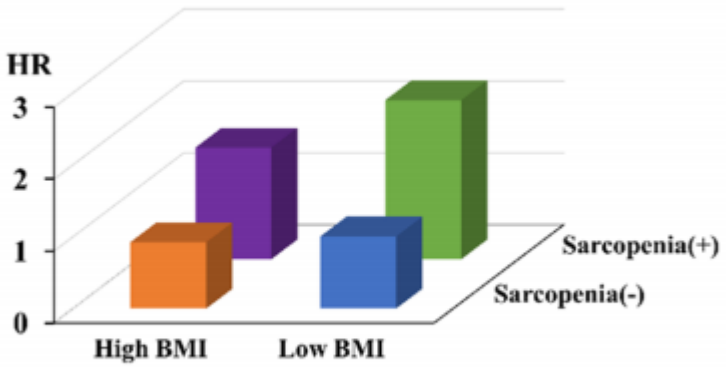


The multivariate models included included HDL cholesterol,HbA1c, eGFR, ACEIs or ARBs, DPP4 inhibitors and history of CVD as covariates

Hazard ratio (95% CI)

Fukuda et al. Cardiovasc Diabetol (2018) 17:55

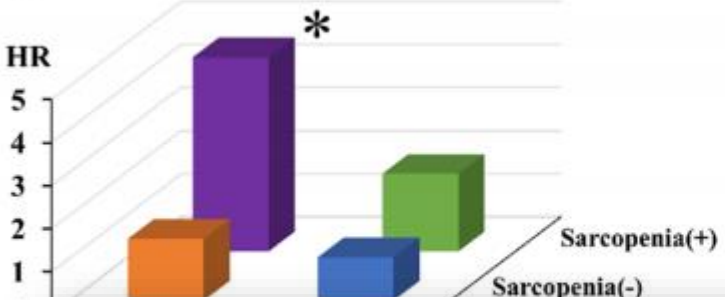
SARCOPENIC OBESITY AND OUTCOME

Sarcopenic obesity assessed using dual energy X-ray absorptiometry (DXA) can predict cardiovascular disease in patients with type 2 diabetes: a retrospective observational study

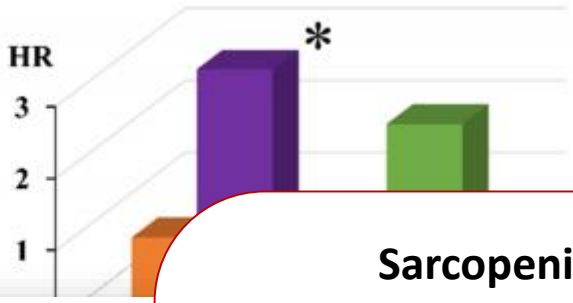
N= 716 patients with diabetes
Mean age: 65±13 years
Follow up of 2.6 years
✓ DEXA measurements of body composition
✓ BMI

*p<0.05

a UNIVARIATE MODEL



b MULTIVARIATE MODEL



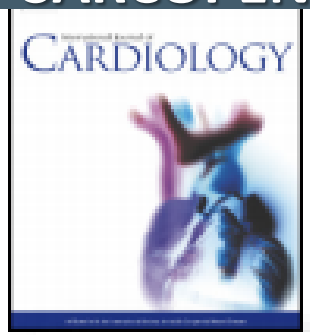
The multivariate models included included HDL cholesterol,HbA1c, eGFR, ACEIs or ARBs, DPP4 inhibitors and history of CVD as

	Hazard ra	
	A/G ratio	Android fat mass
Univariate model		
Normal	1.00(reference)	1.00(reference)
Sarcopenia	1.43(0.58-3.52)	1.87(0.77-4.51)
Obesity	1.56(0.71-3.43)	1.59 (0.71-3.60)
Sarcopenic Obesity	4.50(1.93-10.46)	3.84(1.54-9.58)
Multivariate model		
Normal	1.00(reference)	1.00(reference)
Sarcopenia	1.88(0.75-4.74)	2.42(0.99-5.93)
Obesity	0.98(0.44-2.21)	1.19(0.52-2.68)
Sarcopenic Obesity	2.63(1.10-6.28)	2.57(1.01-6.54)

Sarcopenic obesity is an independent risk factor for CVD event in patients with type 2 diabetes, when using A/G ratio or android fat mass to determine obesity and remained statistically significant after addition of well-known cardiovascular risk factors.

Fukuda et al. Cardiovasc Diabetol (2018) 17:55

SARCOPENIA AND OUTCOME

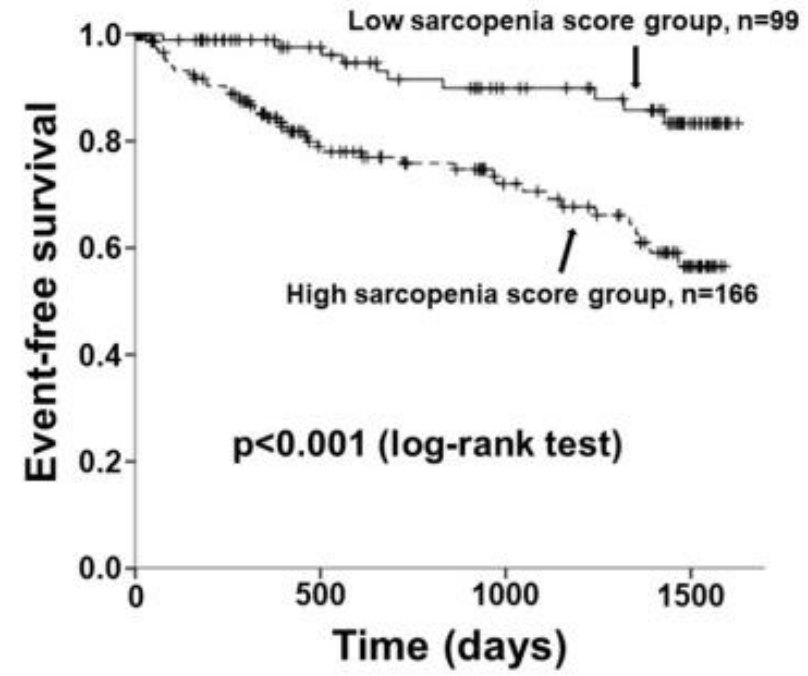


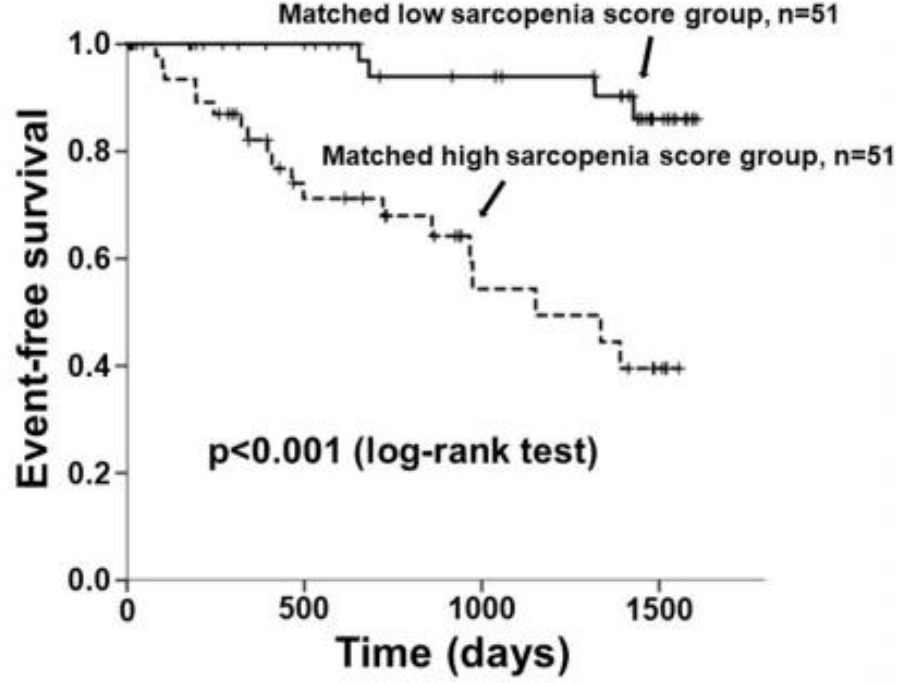
Non-invasive testing for sarcopenia predicts future cardiovascular events in patients with chronic kidney disease

Shinsuke Hanatani, Yasuhiro Izumiya *, Yoshiro Onoue, Tomoko Tanaka, Masahiro Yamamoto, Toshifumi Ishida, Satoru Yamamura, Yuichi Kimura, Satoshi Araki, Yuichiro Arima, Taishi Nakamura, Koichiro Fujisue, Seiji Takashio, Daisuke Sueta, Kenji Sakamoto, Eiichiro Yamamoto, Sunao Kojima, Koichi Kaikita, Kenichi Tsujita

Department of Cardiovascular Medicine, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan

N= 265 pazienti con IRC





A significantly higher probability of death or cardiovascular events in the high than low sarcopenia score group. Kaplan–Meier analysis after propensity score matching also showed that patients with CKD with a high sarcopenia score had a higher probability of adverse events than those with a low sarcopenia score.

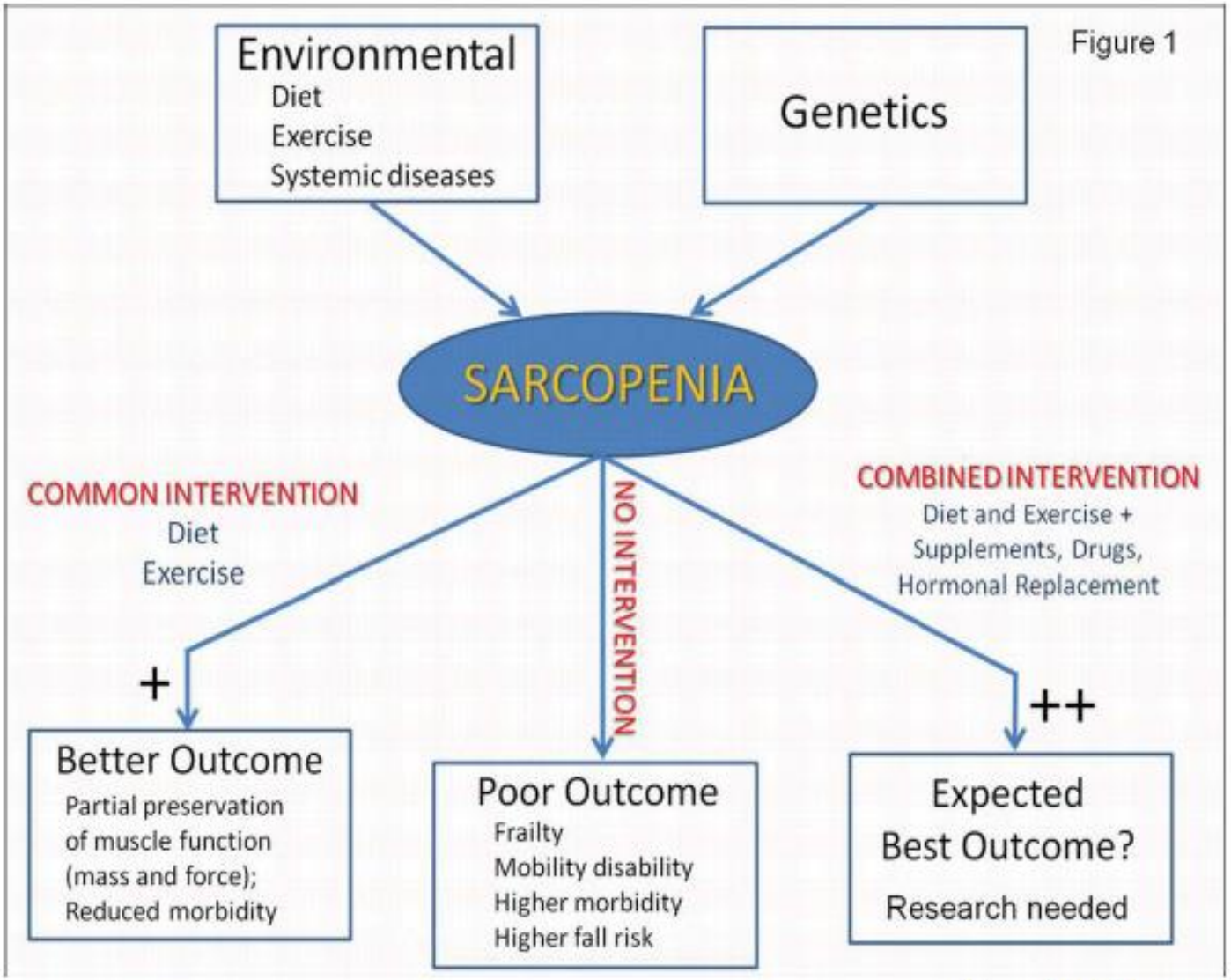
POTENTIAL APPROVED THERAPIES IN SARCOPENIC OBESITY

Component	Goal	Suggested approach
Calorie restriction	Lose body fat and improve physical function	500–1,000 kcal per day
		~0.5 kg per week aiming for 8–10% weight loss at 6 months followed by weight loss maintenance
		No specific diets are proven in this population
Aerobic exercises	Improve cardiorespiratory fitness	150 min per week of moderate to vigorous aerobic exercise
Resistance exercises	Improve muscle strength and mass; attenuate loss of muscle and bone during weight loss efforts	60–75 min of resistance training 3 times weekly, separated by one day focusing on strength, balance and flexibility
Protein supplementation	Mitigate loss of muscle mass and strength	1.0–1.2 g/kg per day of protein in divided doses (25–30 g daily)
		2.5–2.8 g leucine daily
Calcium supplementation	Prevent potential disturbances in bone metabolism	1,200 mg per day of supplemental calcium, preferably through dietary measures
Vitamin D supplementation	Prevent potential disturbances in bone metabolism	1,000 IU vitamin D per day, ideally maintaining blood levels ≥30 ng/ml

IU, international units.

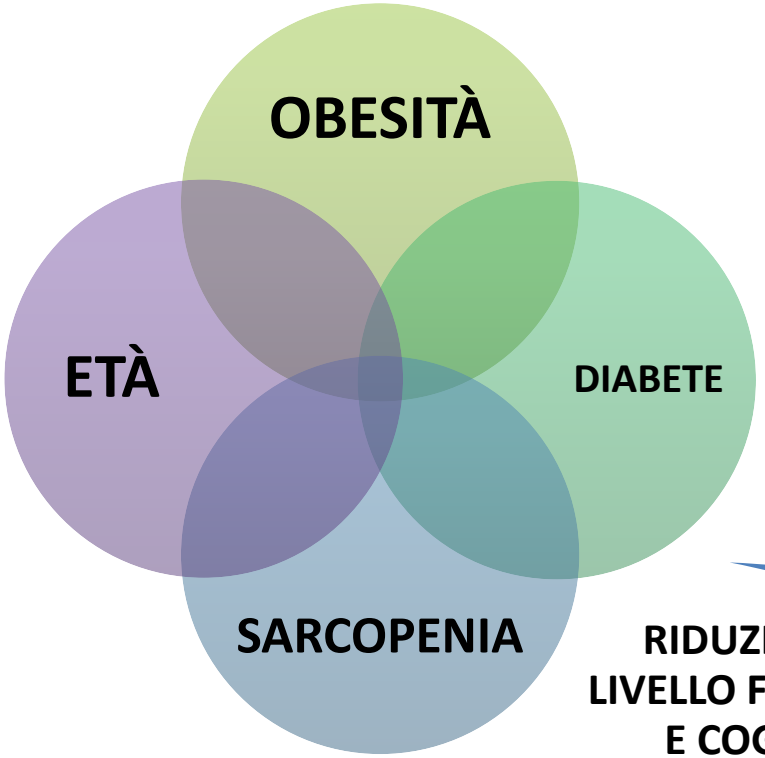
Batsis, J. A., & Villareal, D. T. Nature Reviews Endocrinology, 14(9), 513–537.2018

Consequences of treating and not treating



Brotto MP J Pharmacol Exp Ther 2012

DEADLY QUARTET BAND



RIDUZIONE DEL LIVELLO FUNZIONALE E COGNITIVO

AUMENTATO RISCHIO DI CADUTE

AUMENTATO RISCHIO DI MALATTIA CARDIOVASCOLARE

FRAGILITÀ

AUMENTATO BISOGNO DI SALUTE

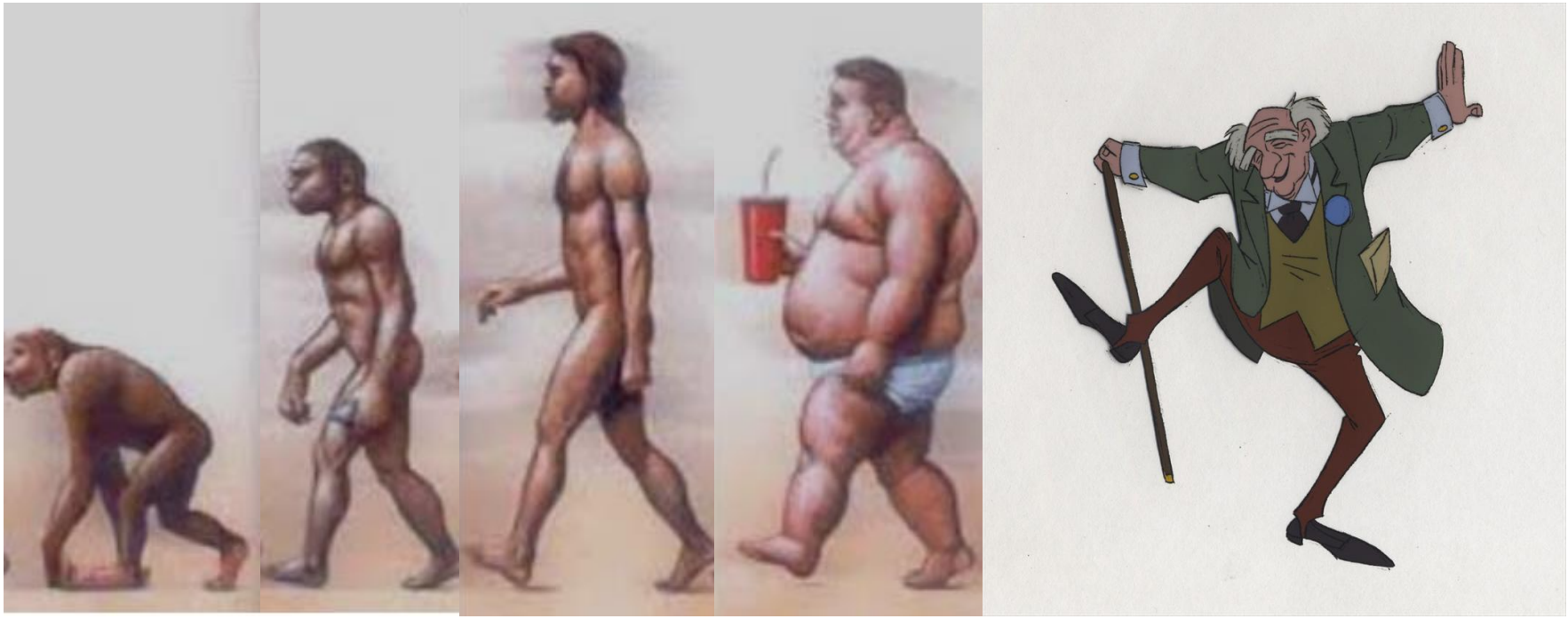
PEGGIORAMENTO DELL' ASPETTATIVA E QUALITÀ DI VITA

TAKE HOME MESSAGGES

- ✓ Finora il trattamento del diabete nel paziente anziano si è concentrato sulla prevenzione delle complicanze croniche dovute a microangiopatia ed eventi cardiovascolari.

- ✓ La coesistenza di sarcopenia, e/o obesità sarcopenica nei pazienti anziani con diabete, sinergicamente peggiora gli outcome e la prognosi.

- ✓ Mantenere un normale peso corporeo nell'età geriatrica, preservando la massa magra ed evitando anche il sottopeso.



GRAZIE PER L'ATTENZIONE

Diabetes related fatigue sarcopenia, frailty

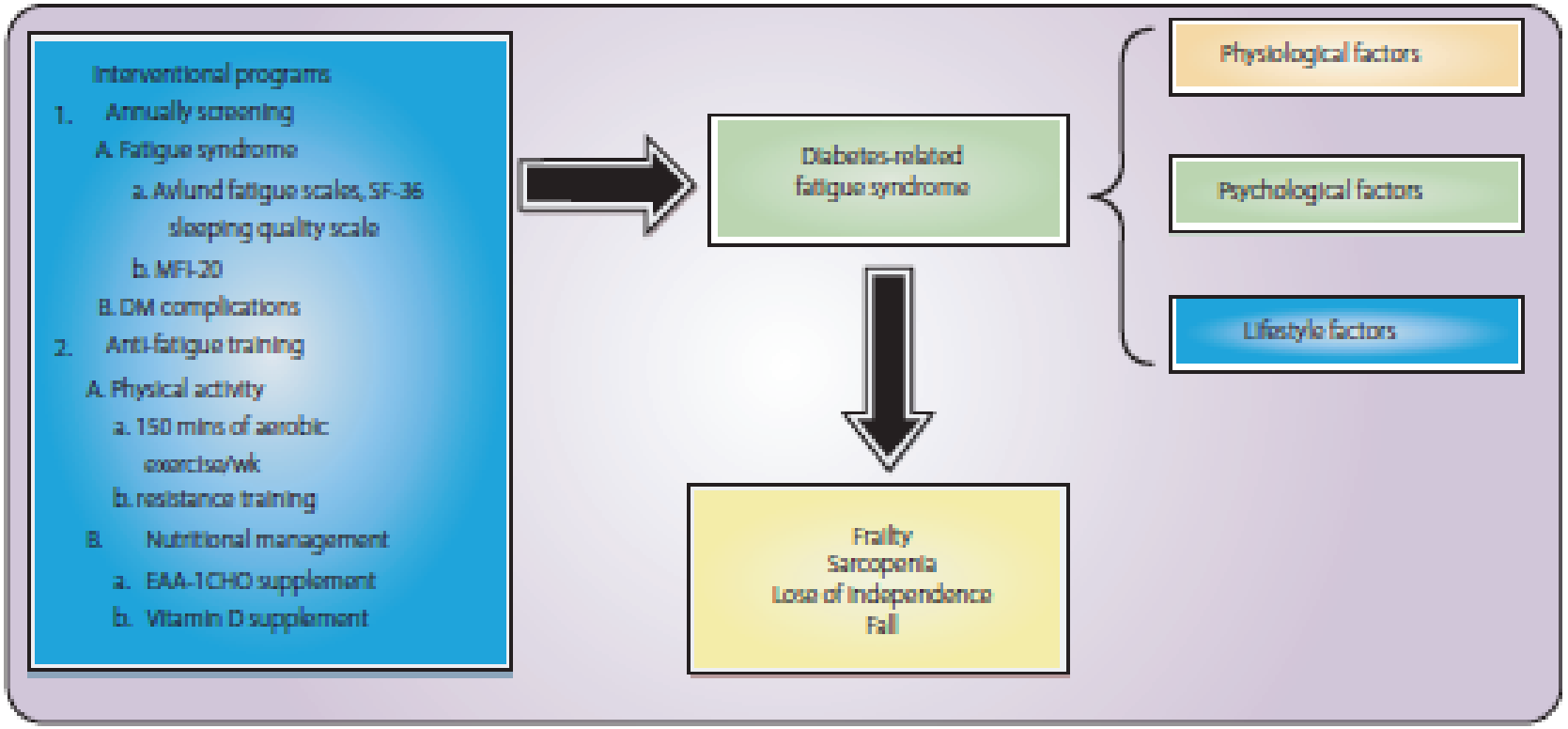
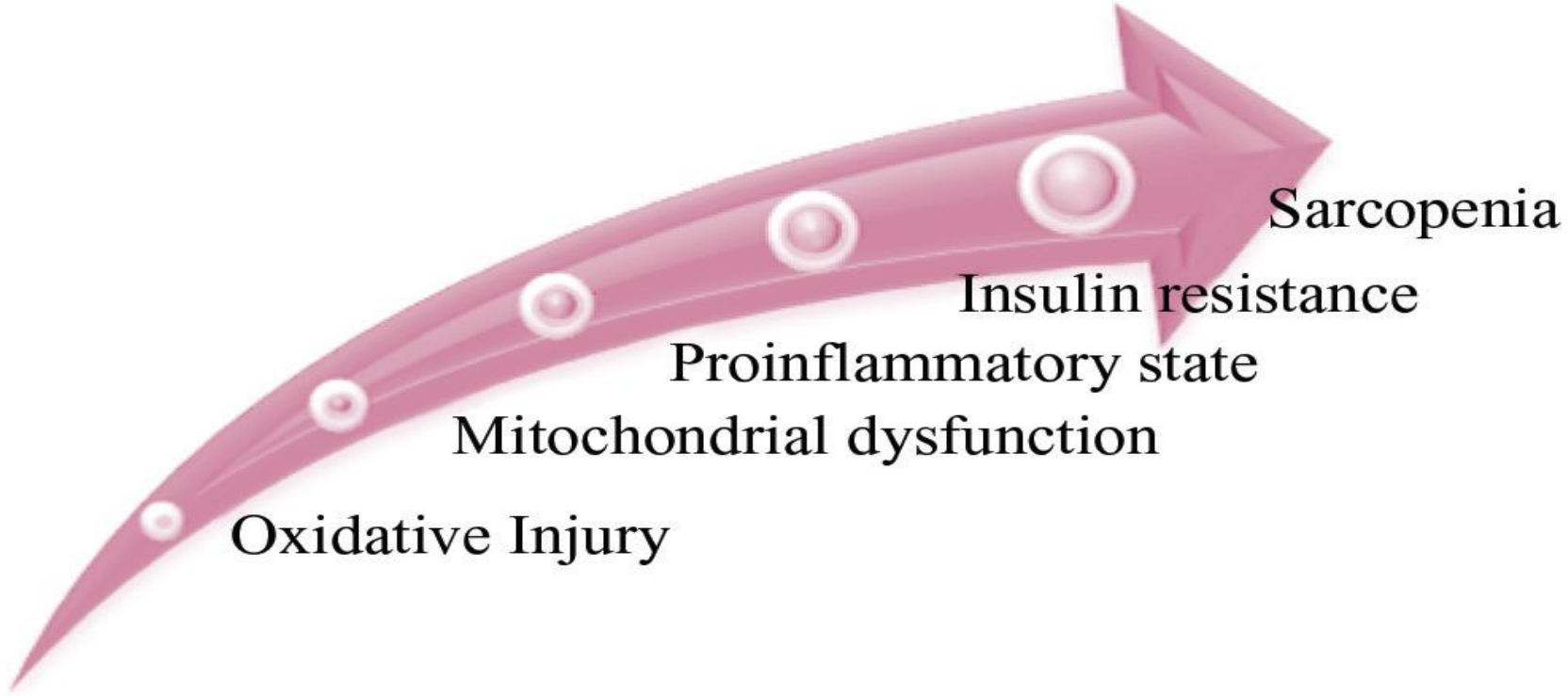


Figure 1 | The rationale of diabetes-related fatigue syndrome and interventions. Fatigue caused by physiological, psychological or lifestyle factors will lead to frailty, sarcopenia and falls. Annual screening and anti-fatigue training can be introduced in the early stage. DM, diabetes mellitus; EAA-1CHO, essential amino acids and carbohydrate; MFI-20, Multidimensional Fatigue Inventory; SF-36, 36-Item Short Form Health Survey.

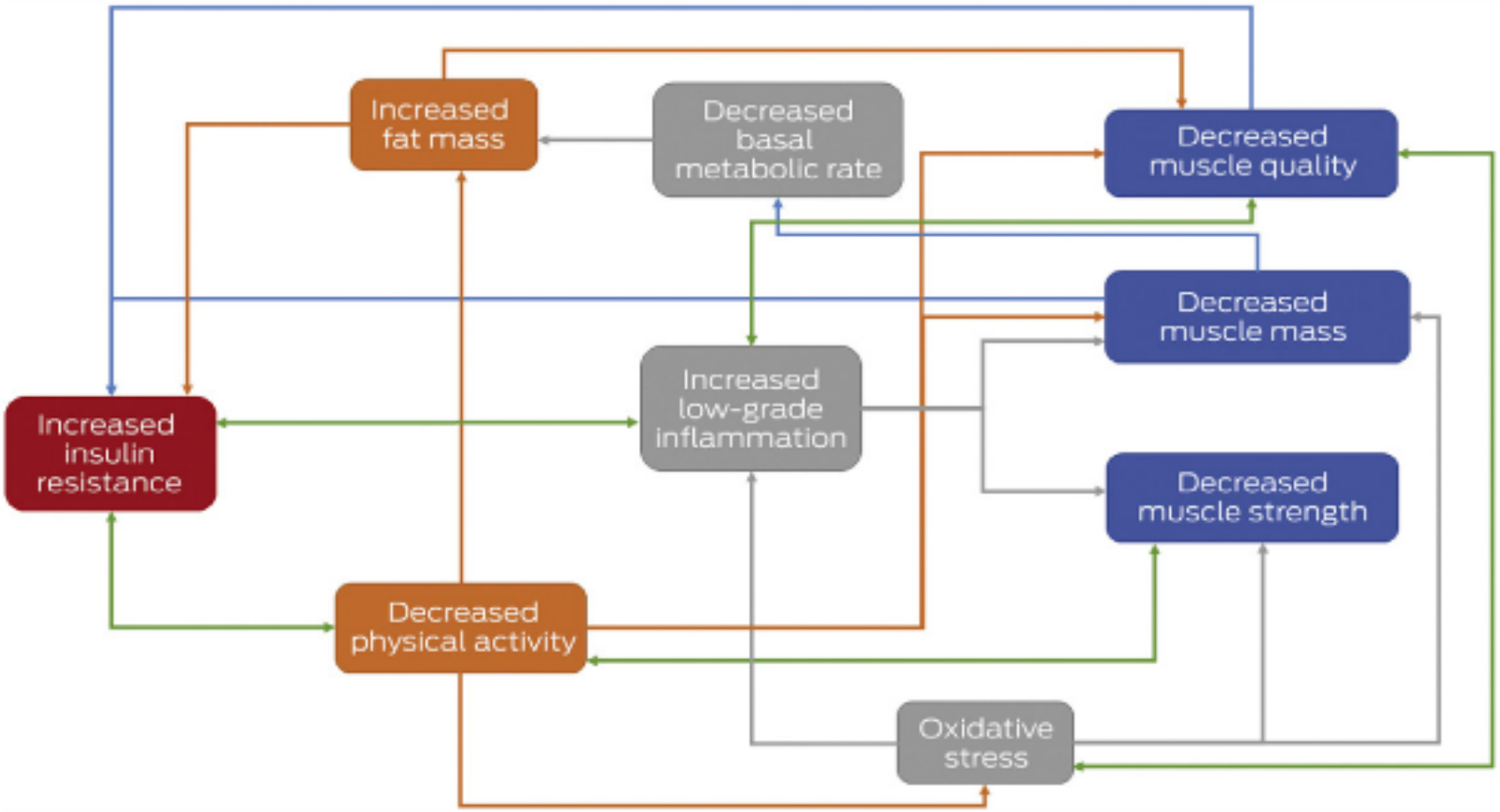
Shin Yu Liun et al Journal Diabetes Investigation 2018

Multiple mechanisms have been proposed to be involved in acceleration of sarcopenia in diabetic patients



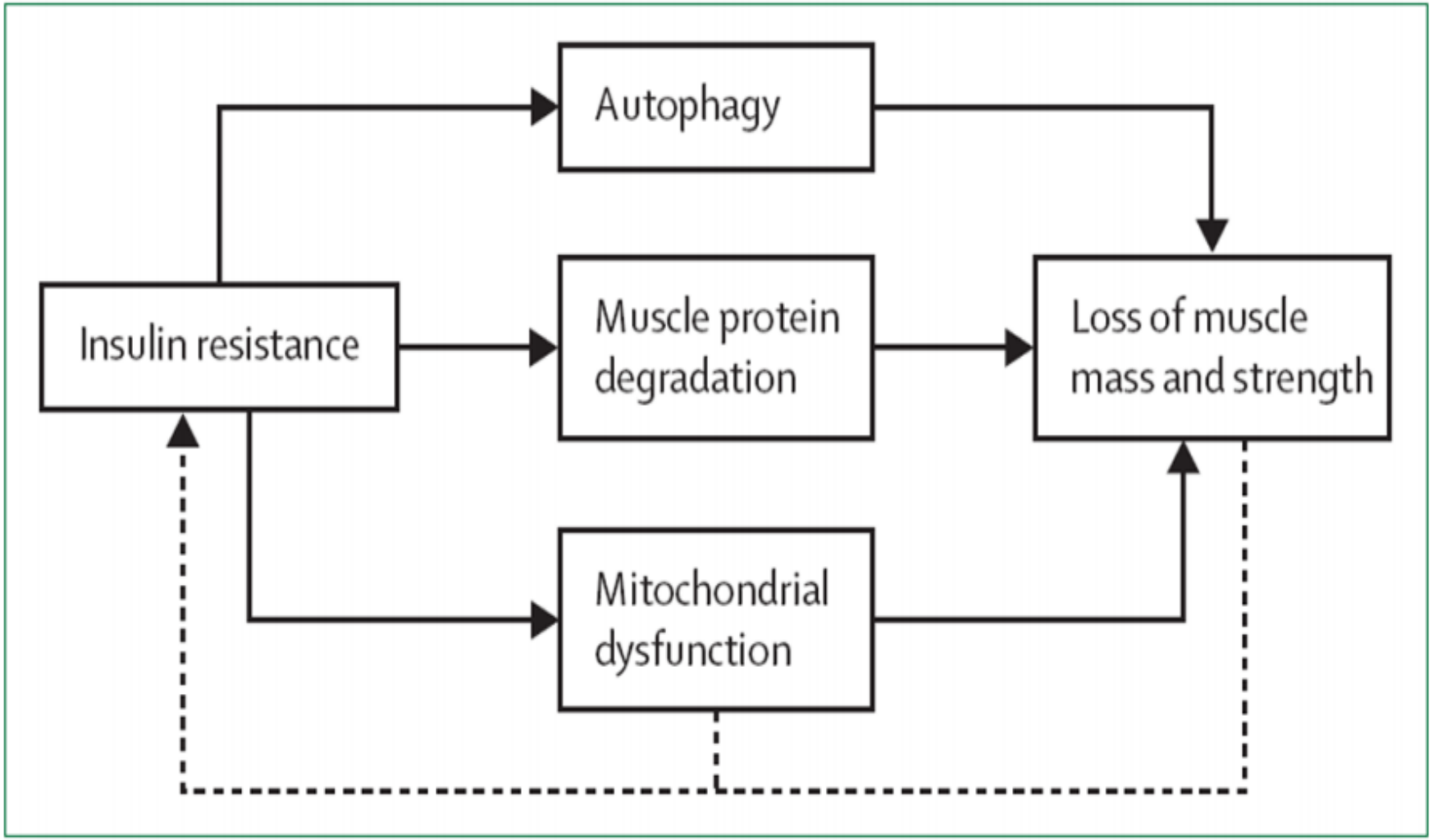
Br J Diabetes Vasc Dis 2011;11:230-234

Potential pathways by which sarcopenia contributes to insulin resistance in ageing*



*Components of sarcopenia are shown in the blue boxes.
Green arrows indicate possible bidirectional relationships, illustrating mechanisms by which sarcopenia may be accelerated in people with type 2 diabetes.

PATHWAYS OF ACCELERATED MUSCLE LOSS IN TYPE 2 DIABETES

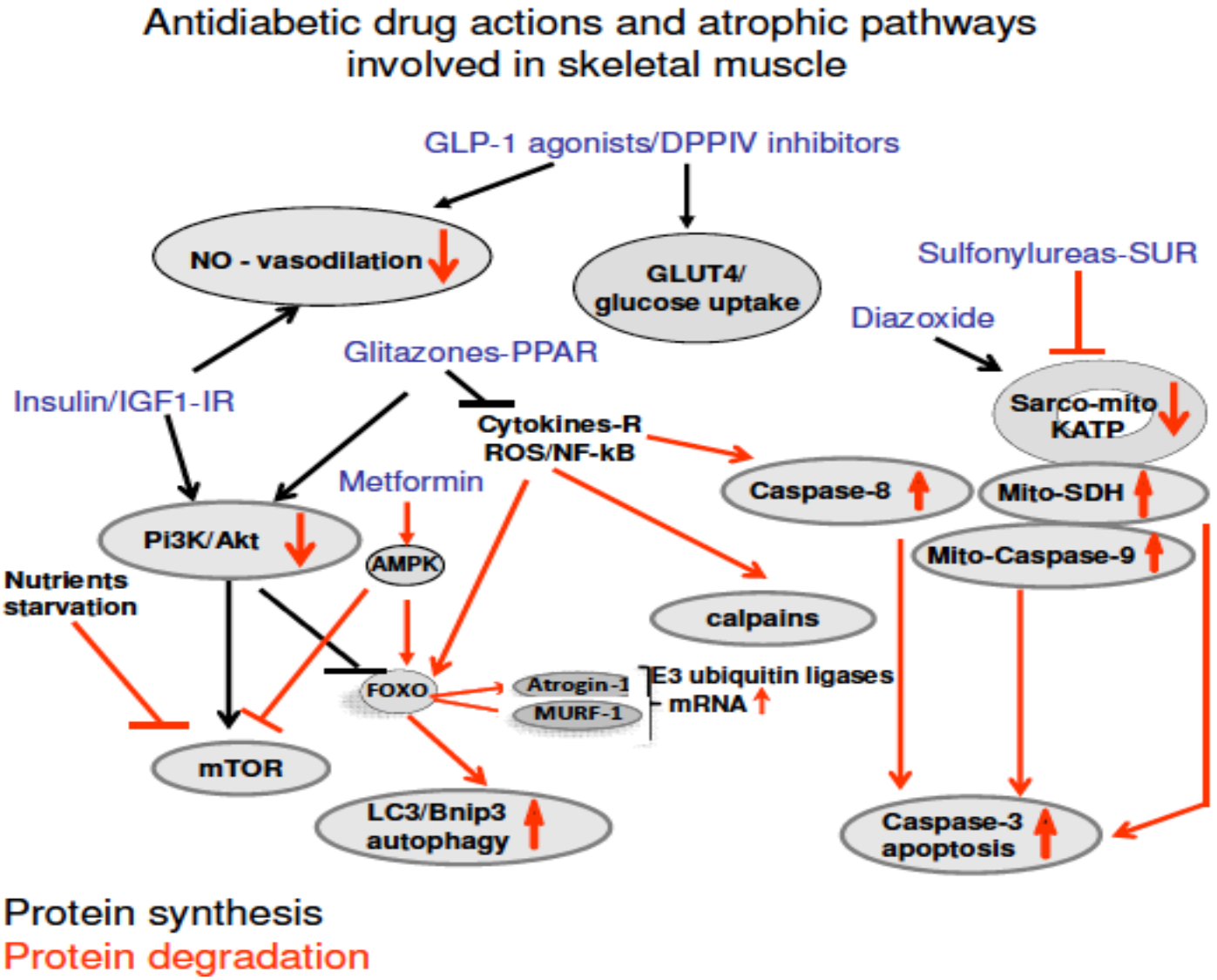


Rita Rastogi Kalyani et al. Lancet Diabetes Endocrinol. 2014

Concurrent therapies for type 2 diabete and sarcopenia

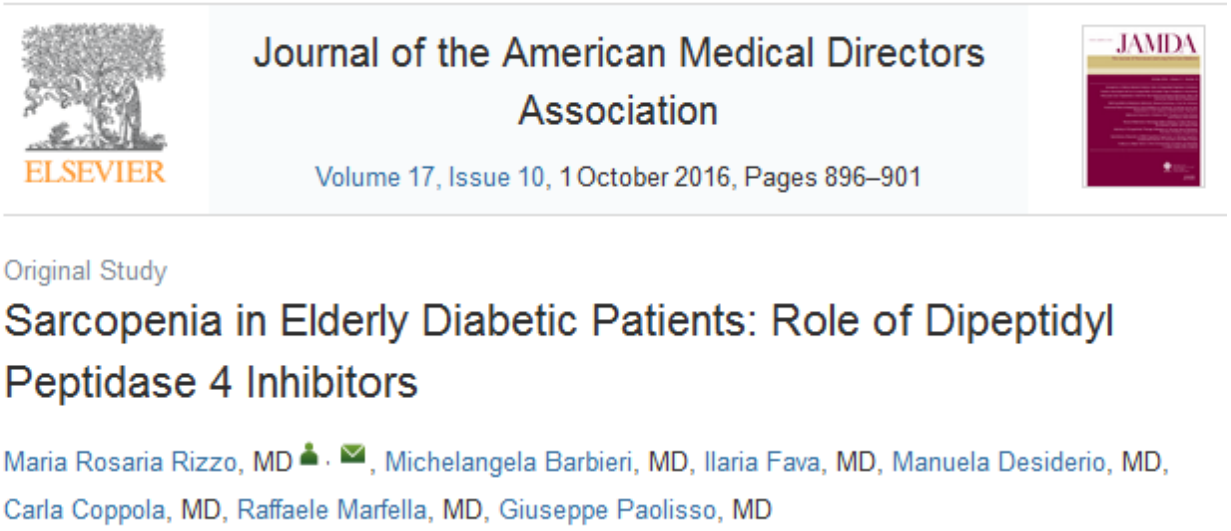
Effects of the Antidiabetic Drugs on the Age-Related Atrophy and Sarcopenia Associated with Diabetes Type II.

Current Diabetes Reviews, 2014, *10*, 231-237



Studies, investigating the clinical effects of DPP4-I on sarcopenic parameters in elderly diabetics patients, are thus far lacking.

Thus, our study aimed at investigating the DPP4-I effect on sarcopenic parameters in elderly type 2 diabetic patients.


ELSEVIER

Journal of the American Medical Directors Association

Volume 17, Issue 10, 1 October 2016, Pages 896–901

Original Study

Sarcopenia in Elderly Diabetic Patients: Role of Dipeptidyl Peptidase 4 Inhibitors

Maria Rosaria Rizzo, MD, Michelangela Barbieri, MD, Ilaria Fava, MD, Manuela Desiderio, MD, Carla Coppola, MD, Raffaele Marfella, MD, Giuseppe Paolisso, MD

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Study population

Original Study

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Inclusion criteria :

Patients aged 65 years or older with diagnosis of diabetes over a minimum 5-year period with HbA1c levels ≤8% (30-31), treated with oral glucose lowering drugs *(metformin in add-on to sulfonylureas or metformin in add-on to dipeptidyl peptidase-4 inhibitors)* for at least 24 months before enrollment.

135 elderly type 2 diabetic patients were screened

80 elderly type 2 diabetic patients (42 males and 38 females)

DPP4-I Group

DPP4-I
(vildagliptin 50 mg bid
o sitagliptin 100 mg/die
o saxagliptin 5 mg/die)
+
METFORMINA (1000 mg)

Sulfonylureas Group

(glimepiride 2 mg/die
o gliburide 15 mg/die
o glipizide 10 mg/die)
+
METFORMINA (1000 mg)

Exclusion criteria

Patients treated with insulin or glucagon-like peptide-1 analogue (GLP-1) or any medications influencing glycaemic function (i.e.corticosteroid), with clinically significant or unstable medical illnesses or severe diabetes complications, or any other disorders affecting glucose metabolism and/or anemia and/or pulmonary disease and/or cancer, or recent acute illness were excluded from the study. They were also excluded from the study all patients with severe cognitive decline and/or Alzheimer dementia, or depression history, drugs or alcohol abuse or dependence in the last two years, or patients affected by malnutrition or who modified the diet, drug treatment or life style within the 3 months before the study.

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Methods

Original Study

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Clinical examination

***Laboratory measurements* (fasting plasma glucose, HbA1c, glucagon, GLP1, IL-6, TNF-a and PCR; meal test)**

Body composition evaluation *

BIA

Muscle strength evaluation

Kern dynamometer

Physical performance

4-m gait speed test

FFM index (FFMI), Skeletal muscle mass (SMM), and SMM index (SMMI).

FFMIwas calculated as FFM divided by body height squared (kg/m^2).
MM was calculated using the BIAequation:
SMM(kg)=[0.401 x (height^2/resistance) + (3.825 x gender) - (0.071 x age) + 5.102

Absolute SMM was converted to an SMM index (SMMI) based on the equation established by Janssen et al. (SMMI = 100 × skeletal muscle mass/h^2) (Kg/m^2)

Based on the findings of other studies in the literature, the relative SMM index less than 8.87 kg/m^2 for men and 6.42 kg/m^2 for women was considered abnormal

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Clinical, metabolic and inflammatory characteristics of the study participants, according to antidiabetic therapy

	All patients n=80	Sulfonylureas Group n= 43	p	DPP4-I Group n=37
Antropometric variables				
Age (years)	76.2 ± 5.4	77.1 ± 5.3	0.054	74.9 ± 4.8
Gender (M/F)	38/42	21/22	0.799	17/20
Weight (Kg)	71.5 ± 7.3	69.5 ± 6.9	0.006	73.9 ± 7.1
BMI (Kg/m^2)	26.4 ± 2.5	25.8 ± 2.5	0.02	27.1 ± 2.5
Systolic blood pressure (mmHg)	129 ± 15	128 ± 11	0.773	130 ± 10
Diastolic blood pressure (mmHg)	77 ± 10	78 ± 9	0.781	77 ± 11
Metabolic variables				
FPG (mg/dl)	120 ± 23	121 ± 18	0.767	119 ± 28
PPG (mg/dl)	174 ± 27	187 ± 25	0.001	159 ± 21
HbA1c (%)	7.4 ± 0.2	7.5 ± 0.3	0.03	7.3 ± 0.2
Cholesterol (mg/dl)	228 ± 18	230 ± 20	0.257	225 ± 17
Triglycerides (mg/dl)	162 ± 20	166 ± 21	0.084	158 ± 18
Glucagon (pmol/L)	10.5 ± 1.1	10.8 ± 0.8	0.007	10.2 ± 1.1
GLP-1 AUC (pmol x h x L)	2915 ± 346	2614 ± 346	0.001	3266 ± 100
Inflammatory variables				
TNF-a (pg/ml)	2.7 ± 0.8	3.1 ± 0.9	0.001	2.4 ± 0.6
PCR (mg/ml)	2.2 ± 0.7	2.4 ± 0.8	0.001	1.9 ± 0.3
IL6 (pg/ml)	2.4 ± 0.6	2.5 ± 0.7	0.02	2.2 ± 0.4
Diabetes duration (years)	7.8 ± 2.1			
Current smoking (%)	31 (n=25)			
Anti-hypertensive medication (%)	42 (n=37)			

Data are expressed as means ± DS or %. BMI= Body Mass Index; FPG=Fasting Plasma Glucose; PPG=Post Prandial Glucose; GPL1AUC =area under the curve of GLP1; TNF-a=Tumor Necrosis Factor a; PCR=C-reactive protein; IL6= Interleukin 6.

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Original Study

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Body composition and sarcopenic indices of the study participants, according to antidiabetic therapy

	All patient N=80	Sulfonylureas Group n= 43	p	DPP4-I Group n=37
FFM (Kg)	51.8 ± 7.1	49.4 ± 6.5	0.001	54.5 ± 6.8
FM (Kg)	19.7 ± 1.6	19.9 ± 1.7	0.186	19.4 ± 1.6
FFM/FM	2.6 ± 0.4	2.5 ± 0.3	0.001	2.8 ± 0.4
FFM index (Kg/m²)	19.1 ± 2.2	18.4 ± 2.1	0.001	19.9 ± 2.1
SMM (Kg)	22.4 ± 5.3	20.5 ± 4.7	0.001	24.7 ± 5.3
SMM index (Kg/m²)	8.2 ± 1.7	7.6 ± 1.5	0.001	9.0 ± 1.6
Handgrip strength (Kg)	23.5 ± 4.9	21.4 ± 4.2	0.001	26.1 ± 4.4
Gait speed 4m (m/s)*	3.5 ± 0.7	3.7 ± 0.7	0.001	3.1 ± 0.6

Data are expressed as means ± DS. FFM= Free Fat Mass; FM= Fat Mass; SMM= Skeletal Muscle Mass.
* The used unit, in meters/seconds (m/s), expresses the useful time to cover 4 meters distance (a fixed distance, 4 meters) in a time (s) varying from subject to subject

Based on the findings of other studies in the literature, the relative SMM index less than 8.87 kg/m² for men and 6.42 kg/m² for women was considered abnormal

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Original Study

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Cross Tab Correlations among metabolic, sarcopenic indices in all patients

Characteristics	Age	Diabetes duration	HbA1c	FFM	FFM Index	SMM	SMM Index	Handgrip strength	Gait speed	PCR
FFM	- 0.597**	-0.366**	- 0.396**							
FFM Index	- 0.598**	-0.428**	- 0.362**	0.828**						
SMM	- 0.261*	-0.162	- 0.255*	0.461**	0.182					
SMM Index	- 0.249*	-0.189	- 0.247*	0.346*	0.229*	0.951**				
Handgrip strength	-0.146	-0.046	-0.173	0.449**	0.159	0.558**	0.432**			
Gait speed	0.190	0.096	0.119	-0.279*	-0.277*	-0.032	-0.011	-0.176		
PCR	0.215*	0.072	0.062	-0.128	-0.171	-0.228*	- 0.273*	-0.260*	0.067	
GPL-1 AUC	-0.213*	0.137	-0.236*	0.382**	0.340**	0.373**	0.378**	0.449**	- 0.444**	-0.484**

FFM= Free Fat Mass; SMM= Skeletal Muscle Mass, PCR=C-reactive protein, IL6= Interleukin 6, GPL1AUC =area under the curve of GLP1.
*p< 0.05; **p < 0.01.

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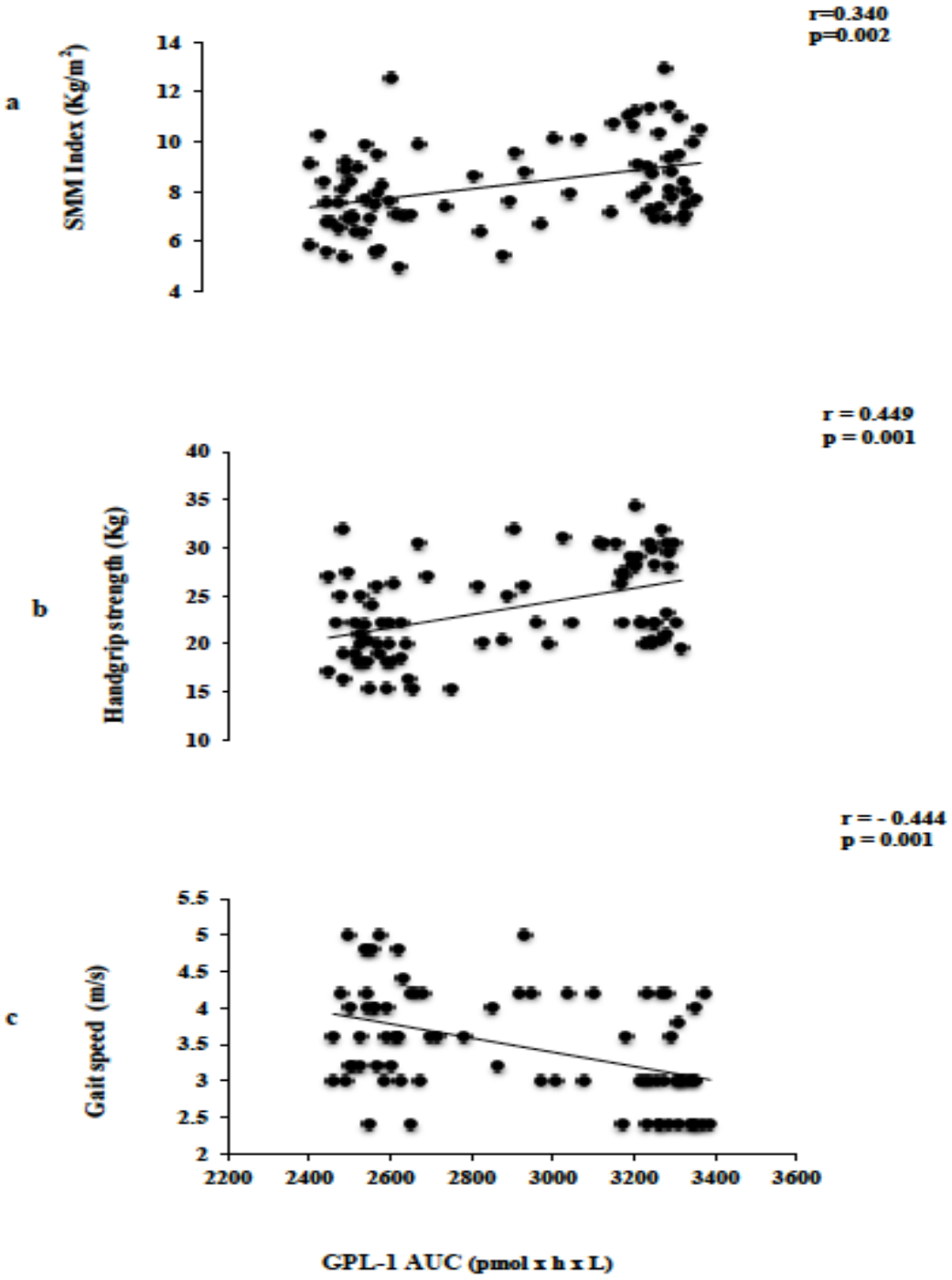
Correlations between GPL-1 AUC and
(a) SMM Index,
(b) Handgrip strength and
(c) Gait speed



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Linear multivariate analyses with SMMI, Handgrip strength and Gait speed as dependent variable

	SMM Index					Handgrip strength					Gaitspeed				
	B	SEM	Beta	t	p value	B	SEM	Beta	t	p value	B	SEM	Beta	t	p value
Age	-,067	,056	-,202	-1,191	,238	-,217	,147	-,233	-1,476	,145	,018	,022	,124	,793	,431
Diabetes duration	-,036	,245	-,023	-,147	,883	,241	,643	,055	,375	,709	,001	,097	,002	,013	,990
BMI	-,087	,087	-,131	-,992	,325	-,668	,230	-,356	-2,909	,055	-,031	,035	-,110	-,904	,369
PPG	,005	,008	,076	,578	,565	-,010	,022	-,053	-,436	,664	,008	,003	,303	2,502	,051
HbA1c	-1,439	,836	-,218	-1,721	,090	-1,671	2,198	-,089	-,760	,450	-,241	,333	-,084	-,726	,470
TNF-a	-,011	,283	-,006	-,041	,968	,207	,743	,036	,278	,782	,078	,112	,088	,692	,492
PCR	-,333	,352	-,135	-,945	,348	-1,014	,927	-,145	-1,094	,278	-,159	,140	-,149	-1,134	,261
IL-6	,032	,345	,012	,093	,926	1,169	,906	,155	1,290	,201	-,268	,137	-,233	-1,954	,055
Glucagon	,049	,209	,029	,233	,817	-,945	,550	-,196	-1,717	,090	-,034	,083	-,046	-,405	,687
GLP1AUC	**,001**	**,001**	**,293**	**2,075**	**,042**	**,006**	**,002**	**,390**	**2,976**	**,004**	**-,001**	**,000**	**-,388**	**-2,991**	**,004**

BMI = body mass index; PPG post prandial glucose; TNF-a=Tumor Necrosis Factor a; PCR=C-reactive protein; IL6= Interleukin 6;GPL1AUC =area under the curve of GLP1.
Bold values indicate results with statistical significance.

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CONCLUSION

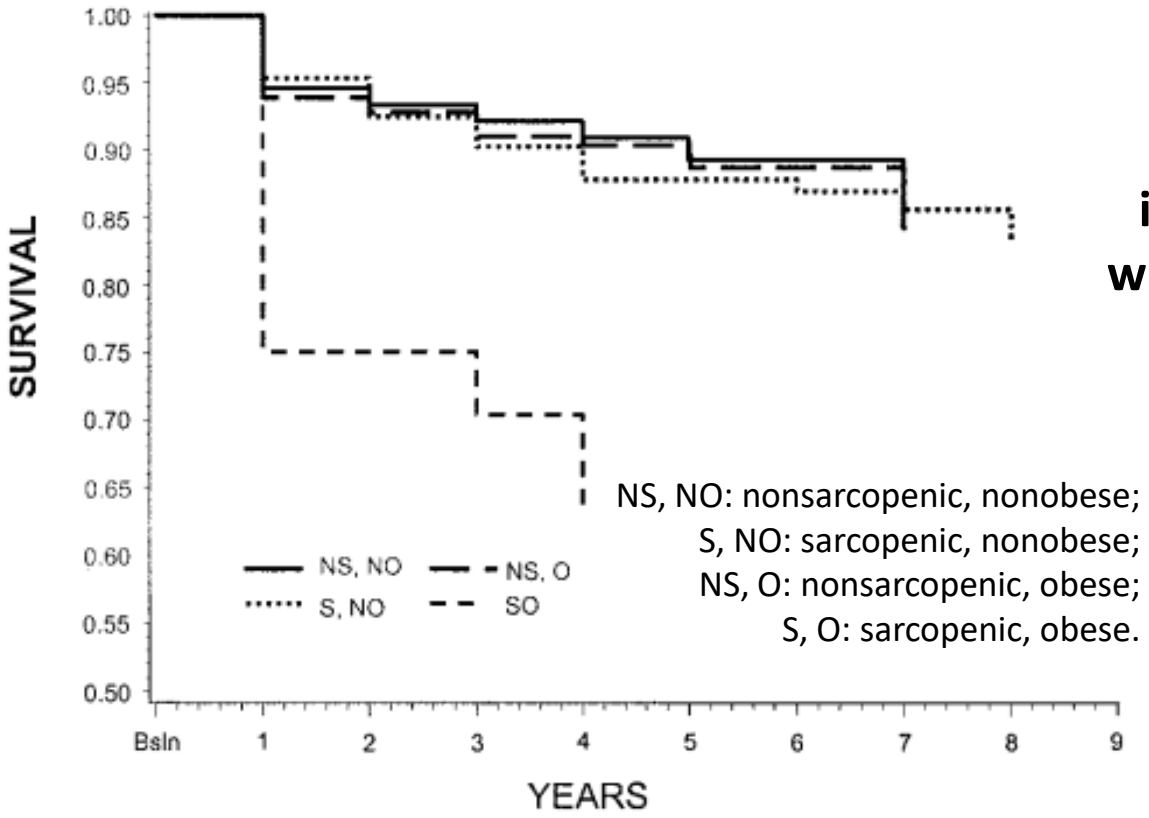
The results are consistent with the hypothesis that DPP4-I use might have a positive effect against the loss of muscle mass and its function.

SARCOPENIC OBESITY AND OUTCOME

Sarcopenic Obesity Predicts Instrumental Activities of Daily Living Disability in the Elderly

Richard N. Baumgartner, Sharon J. Wayne,* Debra L. Waters,* Ian Janssen,† Dympna Gallagher,‡ and John E. Morley§*

Kaplan-Meier survival curve for time to drop in IADL by body composition type



NS, NO: nonsarcopenic, nonobese;
S, NO: sarcopenic, nonobese;
NS, O: nonsarcopenic, obese;
S, O: sarcopenic, obese.

Sarcopenic obesity is independently associated with and precedes the onset of IADL disability in the Community-dwelling elderly.

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