Longitudinal association of type 2 diabetes and insulin therapy with muscle parameters in the KORA-Age study

Uta Ferrari, Cornelia Then, Marietta Rottenkolber, Canan Selte, Jochen Seissler, Romy Conzade, Birgit Linkohr, Annette Peters, et al.

Acta Diabetologica

ISSN 0940-5429

Acta Diabetol
DOI 10.1007/s00592-020-01523-7

Springer

Acta Diabetologica
https://doi.org/10.1007/s00592-020-01523-7

ORIGINAL ARTICLE

Longitudinal association of type 2 diabetes and insulin therapy with muscle parameters in the KORA-Age study

Uta Ferrari[1] · Cornelia Then[1] · Marietta Rottenkolber[1] · Canan Selte[1] · Jochen Seissler[1] · Romy Conzade[2] · Birgit Linkohr[2] · Annette Peters[2,3] · Michael Drey[1] · Barbara Thorand[2,3]

Received: 10 February 2020 / Accepted: 19 March 2020

Abstract

Aims The aim of the current study was to investigate the association of type 2 diabetes (T2D) and insulin treatment with changes in muscle mass, muscle strength, and physical performance in older adults.

Methods In 731 participants of the population-based KORA-Age study aged 74.6 ± 6.2 years (T2D: $n = 118$; insulin treatment: $n = 20$), skeletal muscle index (SMI [kg/m^2]), hand grip strength (GS [kg]), and a timed up and go test (TUG [s]) were performed at baseline and after a follow-up time of 3 years. The association of T2D and insulin therapy with changes in muscle parameters was analyzed using linear regression models.

Results After adjustment for sex, age, BMI, physical activity, smoking, and multimorbidity, T2D was associated with the change in SMI during follow-up (β −0.1 (95% CI −0.3 to −0.02) kg/m^2; $p = 0.02$), but not with a change in GS (β −0.9 (95% CI −1.9 to 0.04) kg) or TUG (β −0.1 (95% CI −0.7 to 0.5) s). Insulin therapy was positively associated with change in SMI (β 0.6 (95% CI 0.3–0.9) kg/m^2; $p = 0.001$), but not in GS (β −1.6 (95% CI −4.1 to 0.8) kg) or TUG (β 1.6 (95% CI −0.2–3.4) s) in comparison with treatment with oral anti-diabetic medication alone.

Conclusions Participants with T2D showed an accelerated decline in muscle mass compared to non-diabetic participants. Insulin therapy was associated with preserved muscle mass, but not muscle function parameters, indicating a discrepancy between muscle mass and function in this high-risk population.

Keywords Muscle function · Muscle mass · Diabetes · KORA-Age · Sarcopenia · Insulin

Introduction

Older adults are at high risk for frailty, immobility and loss of independence. One of the factors most strongly associated with mobility limitation and the risk for future disability in older adults is type 2 diabetes (T2D) [1]. The remarkable link between T2D and frailty indicates that T2D might be a driving force of muscle dysfunction. Mechanisms potentially explaining diabetes-related muscle dysfunction are hyperglycemia-associated oxidative stress and mitochondrial dysfunction [2], decreased macro- and microvascular muscle reserves, dysfunction of muscle innervation [3], insulin resistance and/or depletion, and possibly negative effects of anti-diabetic drugs [4]. Moreover, T2D and sarcopenia share several common risk factors, such as obesity, physical inactivity and chronic low-grade inflammation [5]. Skeletal muscle both takes part in and is influenced by chronic inflammation. The muscle is an endocrine organ secreting myokines, one of which is interleukin 6, a pro-inflammatory cytokine

Managed by Massimo Porta.

Uta Ferrari and Cornelia Then contributed equally.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00592-020-01523-7) contains supplementary material, which is available to authorized users.

✉ Uta Ferrari
uta.ferrari@med.uni-muenchen.de

[1] Geriatrie, Department of Medicine IV, University Hospital, LMU Munich, Ziemssenstraße 1, 80336 Munich, Germany

[2] Institute of Epidemiology, Helmholtz Zentrum München - German Research Center for Environmental Health (GmbH), Neuherberg, Germany

[3] German Center for Diabetes Research (DZD), Munich-Neuherberg, Germany

Published online: 04 April 2020

involved in the low-grade inflammatory status promoting the development of the metabolic syndrome and T2D [6]. Elevated interleukin 6 and tumor necrosis factor-α levels in serum and muscle result in loss of muscle fibers [1]. Muscle biopsies from diabetic participants show reduced numbers of the predominantly oxidative type I fibers in relation to the primarily glycolytic type II fibers (16). This shifted relation of muscle fiber types may contribute to insulin resistance (17). In turn, insulin resistance is an independent risk factor for a decreased skeletal muscle mass [7–9].

Treatment of T2D does not necessarily improve muscle integrity, and the best anti-diabetic therapy strategy regarding muscle function remains to be determined. Commonly used oral anti-diabetic drugs, such as biguanides and sulfonylureas, may even promote muscle atrophy. Potentially muscle-protective agents, such as glitazones, have a limited range of indications due to an overall unfavorable benefit/risk profile, and data on incretins are insufficient [10, 11]. Insulin is an anabolic hormone that increases muscle protein synthesis and limits degradation [12], thus making insulin a candidate for treating both T2D and muscle dysfunction. In fact, insulin therapy was shown to stimulate protein anabolism in younger patients with T2D [13]. However, in the same study, older participants with T2D did not benefit from the insulin therapy in terms of muscle mass and function [13].

Longitudinal population-based associations of T2D and insulin treatment with changes in muscle mass, strength, or function are lacking. In the current study, we investigated the association between T2D and changes in muscle mass, strength, and physical performance in participants of the KORA-Age study aged ≥ 65 years. Furthermore, we analyzed the effect of insulin treatment on changes of these muscle parameters.

Methods

Study population

The population-based KORA (Cooperative Health Research in the Region of Augsburg)-Age cohort study included 1079 participants born before 1944 (i.e., aged ≥ 65 years at the first visit in 2009). All participants gave written informed consent. The study was approved by the Ethics Committee of the Bavarian Medical Association (reference number: 08064). All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national, Ethics Committee of the Bavarian Medical Association) and with the Helsinki Declaration of 1975, as revised in 2008. Study design, sampling, and data collection methods have been published previously [14]. After exclusion of 257 participants without follow-up data and 91 participants with missing information on muscle parameters at baseline and/or follow-up examination or with missing covariables, 731 participants were included the present analysis.

Diabetes mellitus was defined as self-reported physician-diagnosed diabetes and/or treatment with anti-diabetic medication and/or an HbA1c value ≥ 6.5% (48 mmol/mol). Participants were considered to have T2D if they reported having the diagnosis after the age of 25 years. Participants with diabetes other than type 2 were excluded from the analyses. Insulin treatment was defined as use of insulin only or of insulin plus further anti-diabetic medication.

Physical activity scores were calculated as total score of the physical activity scale for the elderly (PASE) and further covariates assessed as described before [15, 16]. Smoking was divided into three groups (never, former, and current).

Muscle parameters

Skeletal muscle mass was estimated using bioelectrical impedance analysis (BIA 2000-S; Data Input GmbH, Frankfurt, Germany) and the equation of Janssen et al. [17]. The skeletal muscle index (SMI) was calculated as skeletal muscle mass divided by height squared [kg/m^2]. Handgrip strength was assessed by the JAMAR (SAEHAN Corp., Masan, Korea) handheld dynamometer. Grip strength (kg) of the dominant hand was taken three times. The mean score was used for calculations. The time to complete the timed up and go test (TUG) was measured in seconds (s) as the time required to stand up from a chair, walk three meters, turn, walk back to the chair, and sit down.

Statistical analyses

Baseline characteristics of the study participants were compared between participants with and without T2D using the Mann–Whitney *U* test. The Chi-square test was used to compare binomial proportions. Delta of muscle parameters was calculated by subtracting the values of the follow-up visit (visit 2) from the values of the baseline visit (visit 1). In addition to analyses in the total study sample, calculations were also stratified by sex as indicated in the tables, and an interaction test for sex was included as indicated in the results section. Associations between diabetes status and change in muscle parameters were assessed using multivariable linear regression models. Data were adjusted for clinical relevant confounders as indicated in the tables for each analysis. Analyses were performed using the SAS version 9.2 (SAS institute, Cary, NC, USA). The level of statistical significance was set at 5% (two-sided).

Results

Baseline characteristics of the study participants

Among the 731 participants with a mean age of 74.6 ± 6.2 years, 49.3% ($n = 360$) were female, 16.1% ($n = 118$) suffered from T2D (mean diabetes duration 10.1 ± 9.9 years) and 16.9% of the diabetic participants ($n = 20$) were treated with insulin alone or in combination with other anti-diabetic medications (Table 1). Participants with T2D were slightly older, had a higher BMI, a lower level of physical activity, and more chronic diseases than non-diabetic participants. SMI was higher in participants with T2D compared to participants without T2D at baseline. GS was similar in diabetic and non-diabetic participants, whereas the time needed to complete the TUG was significantly higher in participants with T2D compared to non-diabetic participants.

Changes of muscle parameters over time

After 3 years of follow-up in unadjusted analyses, study participants with T2D showed a greater albeit not statistically significant decrease in GS (women: − 0.7 (95% CI − 3.3 to 2.0) kg, men: − 1.3 (95% CI − 4.0 to 1.7) kg) and SMI (women: − 0.2 (95% CI − 0.6 to 0.2) kg/m^2, men: − 0.2 (95% CI − 0.5 to 0.2) kg/m^2) than participants without T2D (GS: women: 0.0 (95% CI − 2.7 to 2.0) kg, men: − 0.7 (95% CI − 3.3 to 2.7) kg; SMI: women: − 0.0 (95% CI − 0.3 to 0.3) kg/m^2; men: 0.0 (95% CI − 0.4 to 0.3) kg/m^2). The time needed to complete the TUG increased more strongly in women with T2D compared to women without T2D (0.7 (95% CI − 0.5 to 2.6) s vs. − 0.0 (95% CI − 1.1 to 1.2) s; $p = 0.006$). In men, the time needed for the TUG decreased in those with and without T2D without significant differences between diabetic and non-diabetic men (− 0.9 (95% CI − 2.4 to 0.4) s vs. − 0.6 (95% CI − 1.8 to 0.8); Online Resource 1).

After adjustment for age and sex, T2D was significantly associated with the change in GS ($p = 0.045$) and SMI ($p = 0.006$) in the total cohort (Table 2). The association with SMI remained significant after further adjustment for BMI,

Table 1 Baseline characteristics of the study participants stratified by diabetes status

	Total [a] ($n = 731$)		Diabetes[a] ($n = 118$ (16.1%))		No diabetes[a] ($n = 613$ (83.9%))		p value[b]
	Women	Men	Women	Men	Women	Men	Women/men
n (%)	360 (49.3)	371 (50.8)	58 (16.1)	60 (16.2)	311 (83.8)	302 (83.9)	0.9820[x]
Age (years)	74.5 ± 6.2	74.7 ± 6.2	76.4 ± 5.8	75.4 ± 6.3	74.1 ± 6.3	74.5 ± 6.1	0.006/0.255
BMI (kg/m^2)	28.3 ± 4.5	28.4 ± 3.9	31.0 ± 4.0	29.9 ± 4.4	27.7 ± 4.4	28.1 ± 3.7	< 0.001/0.007
GS (kg)	20.7 ± 5.3	34.3 ± 7.6	20.2 ± 5.9	34.4 ± 7.5	20.7 ± 5.1	34.3 ± 7.7	0.409/0.602
SMI (kg/m^2)	7.4 ± 0.9	10.1 ± 1.0	8.0 ± 1.0	10.5 ± 1.0	7.3 ± 0.9	10.0 ± 1.0	< 0.001/< 0.001
TUG (s)	10.5 ± 3.2	10.3 ± 2.9	11.8 ± 3.3	10.9 ± 2.6	10.3 ± 3.1	10.2 ± 3.0	< 0.001/0.018
PASE: Total Score	119.1 ± 48.9	131.1 ± 59.7	112.7 ± 53.1	110.4 ± 57.6	120.3 ± 48.1	135.1 ± 59.4	0.173/0.002
HbA1c (%) (mmol/mol)	5.7 ± 0.5 (39)	5.7 ± 0.6 (39)	6.5 ± 0.7 (48)	6.5 ± 0.6 (48)	5.6 ± 0.3 (38)	5.6 ± 0.5 (38)	< 0.001/< 0.001
Insulin therapy only			4 (6.9%)	5 (8.3%)			
Oral anti-diabetics only			33 (56.9%)	38 (63.3%)			
Combination therapy[y]			7 (12.1%)	4 (6.7%)			
No anti-diabetic treatment			14 (24.1%)	13 (21.7%)			
Current smoker n (%)	16 (4.4)	21 (5.7)	2 (3.5)	4 (6.7)	14 (4.6)	17 (5.5)	0.624/0.925
Ex-Smoker n (%)	71 (19.7)	197 (53.1)	14 (24.1)	32 (53.3)	57 (18.9)	165 (54.6)	
Non-Smoker n (%)	273 (75.8)	153 (41.2)	42 (72.4)	24 (40.0)	231 (76.5)	129 (42.7)	
No chronic disease n (%)	33 (9.2)	54 (14.6)	3 (5.2)	5 (8.3)	30 (10.0)	49 (15.8)	0.017/0.006
1 chronic disease n (%)	107 (29.9)	115 (31.0)	10 (17.2)	11 (18.3)	97 (32.3)	104 (33.4)	
≥ 2 chronic diseases n (%)	218 (60.9)	202 (54.5)	45 (77.6)	44 (73.3)	173 (57.7)	158 (50.8)	

Mann–Whitney U test was used for continuous variables, Chi-square test for categorical variables

[a]Mean ± standard deviation, or proportion (%)

[b]The p value is related to the null hypothesis of no differences between those with and without T2D

[x]For sex [female]

[y]Insulin and oral anti-diabetics

Abbreviations: PASE: Physical Activity Scale for the Elderly; GS: Hand grip strength; SMI: Skeletal muscle index; TUG: Timed up and go test

Table 2 Prospective association between T2D and change in muscle parameters over 3 years of follow-up: Results of linear regression models, dependent variable Δ calculated by value of follow-up visit (2012)—baseline visit (2009) and diabetes status at baseline

		Model 1		Model 2	
		Regression coefficient (95% CI)	*p* value	Regression coefficient (95% CI)	*p* value
Δ GS	Total $n=728$	−1.0 (−1.9 to −0.0)	**0.045**	−0.9 (−1.9 to 0.04)*	0.061
	Men $n=370$	−1.3 (−2.8 to 0.2)	0.090	−1.3 (−2.9 to 0.2)	0.097
	Women $n=358$	−0.7 (−1.8 to 0.4)	0.233	−0.6 (−1.8 to 0.6)*	0.343
Δ SMI	Total $n=712$	−0.2 (−0.3 to −0.04)	**0.006**	−0.1 (−0.2 to −0.02)*	**0.024**
	Men $n=356$	−0.2 (−0.3 to −0.01)	**0.033**	−0.2 (−0.3 to −0.004)	0.057
	Women $n=356$	−0.1 (−0.3 to 0.02)	0.090	−0.1 (−0.3 to 0.05)*	0.169
Δ TUG	Total $n=649$	0.2 (−0.4 to 0.7)	0.607	−0.1 (−0.7 to 0.5)*	0.839
	Men $n=336$	−0.6 (−1.5 to 0.3)	0.181	−0.8 (−1.7 to 0.1)	0.099
	Women $n=313$	1.0 (0.2 to 1.7)	**0.012**	0.7 (−0.1 to 1.5)*	0.075

Bold values indicate significant *p* value (< 0.05)

Model 1: adjusted for sex in the total cohort (ref.: women) and age [years]

Model 2: additionally adjusted for BMI [kg/m^2], physical activity [score per unit], multimorbidity (ref: 0; 1, ≥ 2)-diabetes and smoking;

*Missing $n=1$

Abbreviations: GS: Hand grip strength; SMI: Skeletal muscle index; TUG: Timed up and go test

physical activity, multimorbidity, and smoking ($p=0.024$). T2D was not significantly associated with the change in time needed to complete the TUG test in any of the models in the total cohort. In women, T2D was associated with delta TUG after adjustment for age ($p=0.012$), but no longer after multivariable adjustment. In men, T2D was not associated with a change in TUG (*p* value for sex interaction in a model adjusted for sex and T2D = 0.033). T2D was not associated with change in GS in any of the models. The interaction tests displayed no significant differences in the association of the change in GS and SMI with T2D by sex.

Impact of insulin treatment on muscle parameters

Absolute changes of muscle parameters over time in participants with pharmacologically treated T2D stratified for insulin treatment are shown in Online Resource 2. Women with insulin therapy displayed a significantly stronger increase in time needed to complete the TUG (2.6 (95% CI 2.0–3.5) s) than women treated with oral anti-diabetic medication only (0.7 (95% CI −0.8–1.6) s; $p=0.015$), despite more favorable albeit not statistically significantly different changes in SMI over time (0.1 (95% CI −0.5 to 0.6) kg/m^2) compared to those treated with oral anti-diabetic medication only (−0.3 (95% CI −0.8 to 0.2) kg/m^2; $p=0.064$).

In men, the change in SMI differed significantly between participants with and without insulin therapy with an increase of 0.2 (95% CI 0.1 to 0.5) kg/m^2 in those treated with insulin versus a decrease of −0.3 (95% CI −0.6 to 0.2) kg/m^2 in participants with oral anti-diabetic medication only ($p=0.017$), whereas changes in TUG were not different in men with or without insulin therapy.

Changes in GS were not significantly different in women or men with and without insulin therapy (Online Resource 2).

Table 3 displays the results of the linear regression models investigating the associations of treatment type with deltas of GS, SMI and TUG. In men, insulin therapy was inversely associated with delta GS, but just missed significance in the fully adjusted model (β: −3.4 (95% CI −6.7 to 0.02) kg; $p=0.051$). In women, no respective associations were observed (β: 0.4 (95% CI −3.3–4.1) kg; $p=0.830$ in the fully adjusted model).

The crude linear regression model revealed a positive association of insulin treatment with SMI (β: 0.5 (95% CI 0.2–0.9) kg/m^2; $p=0.005$). This effect was even more pronounced after multivariable adjustment (β: 0.6 (95% CI 0.3–0.9) kg/m^2; $p=0.001$) and was stronger in women (β: 0.8 (95% CI 0.2–1.4) kg/m^2; $p=0.009$) than in men (β: 0.5 (95% CI 0.1–0.9) kg/m^2; $p=0.021$). However, the interaction test displayed no significant differences in the association of insulin therapy with change in SMI between women and men (p-value for sex interaction in the model adjusted for sex and T2D = 0.452).

The time needed to complete the TUG increased more strongly in women treated with insulin versus women treated with oral anti-diabetic medication only (β: 4.3 (95% CI 1.1–7.5) s; $p=0.010$ in the fully adjusted model), but changes in TUG were not different in men with or without insulin treatment. In the total cohort, the time for the TUG increased more strongly in participants treated with insulin, but the results were not statistically significant (β: 1.6 (95% CI −0.2 to 3.4) s; $p=0.086$ in the fully adjusted model). The interaction test displayed a significantly stronger association

Table 3 Prospective association between type of treatment (insulin versus oral anti-diabetic medication only) and change in muscle parameters over 3 years of follow-up

		Model 1		Model 2	
		Regression coefficient (95% CI)	*p* value	Regression coefficient (95% CI)	*p* value
Δ GS	Total *n* = 90	− 1.2 (− 3.6 to 1.1)	0.294	− 1.6 (− 4.1 to 0.8)	0.190
	Men *n* = 47	− 3.0 (− 6.3 to 0.4)	0.081	− 3.4 (− 6.7 to 0.02)	0.051
	Women n = 43	0.1 (− 3.1 to 3.3)	0.927	0.4 (− 3.3 to 4.1)	0.830
Δ SMI	Total *n* = 88	0.5 (0.2–0.9)	**0.005**	0.6 (0.3–0.9)	**0.001**
	Men *n* = 45	0.5 (0.02–1.0)	**0.041**	0.5 (0.1–0.9)	**0.021**
	Women *n* = 43	0.5 (− 0.02 to 1.1)	0.060	0.8 (0.2–1.4)	**0.009**
Δ TUG	Total *n* = 79	1.4 (− 0.3 to 3.0)	0.096	1.6 (− 0.2 to 3.4)	0.086
	Men *n* = 43	0.1 (− 2.0 to 2.2)	0.946	0.4 (− 2.0 to 2.7)	0.758
	Women *n* = 36	2.7 (0.1–5.4)	**0.041**	4.3 (1.1–7.5)	**0.010**

Results of linear regression models, dependent variable Δ calculated by value of follow-up visit (2012)—baseline visit (2009) of participants with diabetes and treatment (insulin versus non-insulin anti-diabetic therapy only)

Bold values indicate significant *p* value (< 0.05)

Model 1: adjusted for sex (ref.: women) and age (years)

Model 2: additionally adjusted for BMI (kg/m^2), physical activity (score per unit), HbA1c (%), multimorbidity (ref: 0; 1, ≥ 2)-diabetes, smoking and duration of diabetes (categories: < 6 years; ≥ 6 years)

Abbreviations: GS: Hand grip strength; SMI: Skeletal muscle index; TUG: Timed up and go test

of insulin therapy with the change in TUG in women than in men (p-value for sex interaction in the model adjusted for sex and T2D = 0.002). The association of insulin therapy with delta TUG in the total cohort remained statistically not significant after inclusion of the sex interaction term (data not shown).

Discussion

In our population-based cohort aged ≥ 65 years, SMI was higher at baseline but decreased more strongly in participants with T2D during 3 years of follow-up compared to participants without T2D. The association between T2D and changes in SMI was independent of relevant confounders (sex, age, BMI, physical activity, smoking, and multimorbidity). At baseline, time needed to complete the TUG was higher in diabetic participants, whereas GS did not differ between participants with and without T2D. These data are in line with previous studies showing a decreased muscle mass and strength predominantly in the lower extremities with subsequent walking impairments, but a preserved muscle function of the upper extremities in diabetic individuals [18, 19]. A reduction in numbers of the predominantly oxidative type I fibers in relation to the primarily glycolytic type II fibers [20] is a possible explanation for this finding. The present data indicate, unlike a previous study describing lower leg muscle quality and physical performance status only in participants with poor glycemic control as indicated by HbA1c values ≥ 8.5% (69 mmol/mol) [21], that even mild disturbances of glycemic control are associated with changes of muscle parameters. The KORA-Age participants with T2D had only mild hyperglycemia and/or were well-treated with a mean HbA1c of 6.5% (48 mmol/mol), but still displayed differences in TUG and in the decline of muscle mass compared with non-diabetic participants. The fact that neither change in TUG nor in GS differed significantly between participants with or without T2D in the longitudinal analysis after multivariable adjustment might be attributable to the short follow-up time of three years.

Insulin treatment was associated with preservation of SMI, despite higher HbA1c values (6.9 ± 0.7%; 52 mmol/mol) in participants receiving insulin. During follow-up, the SMI decline was significantly stronger in diabetic participants treated with oral anti-diabetic therapy, suggesting a positive effect of insulin treatment on muscle mass. In a previous retrospective observational study, insulin treatment prevented the decline of SMI in the lower, but not the upper extremities [22]. However, in contrast to the preserved or even improved SMI, muscle function was not ameliorated in participants with insulin treatment in our study. GS decreased more strongly in men with insulin therapy compared to diabetic men without insulin therapy, an observation that just missed significance in the fully adjusted model. TUG increased significantly stronger in women treated with insulin. These data indicate a discrepancy between muscle mass and muscle function especially in insulin-treated women who also displayed a stronger favorable difference in delta SMI than men. This interesting finding may indicate that the elevation of muscle mass might be mainly due

to an increase in intramuscular adipose tissue and not to an increase in functional muscle fibers. This finding is in line with previous data showing a decreased muscle quality despite an equal lean body mass in diabetic participants with increasing HbA1c values [23]. A possible explanation may be a differential insulin resistance, in which the sensitivity to insulin-mediated glucose uptake is partially preserved, and thus promotes the possibility to an increased generation of intramuscular fat in case of insulin therapy, but the insulin-mediated protein synthesis is blunted [24]. In turn, accumulation of intramuscular adipose tissue seems to contribute to insulin resistance [25] and to mobility limitations [26]. In fact, anabolic resistance—a reduced muscle protein synthesis in response to nutrients [27] or insulin [28, 29] accompanied by a diminished insulin-mediated suppression of proteolysis [30]—may develop previous to glucose intolerance as the most widely recognized form of insulin resistance. Particularly, older people with T2D may be affected by a differential insulin resistance [28]. Thus, in older people, supra-physiological insulin doses may be necessary to stimulate protein synthesis and muscle anabolism [28]. However, permanent hyper-insulinemia has acknowledged negative effects. Altogether, beneficial effects of insulin on muscle function and mass in elderly remain questionable and are no justification for the initiation of an insulin therapy.

Study strengths and limitations

Strengths of our study are the population-based longitudinal design and the detailed examination of muscle mass and function. Limitations are the relatively short follow-up time of 3 years, the lack of data on fasting plasma glucose and insulin sensitivity, and the relatively low number of participants treated with insulin. Muscle mass was measured using BIA and not with dual energy X-ray absorptiometry in order to avoid radiation exposure, and we did not obtain muscle biopsies.

Conclusions

The present study demonstrates that the decline of muscle function and muscle mass is accelerated in individuals with T2D and that insulin therapy is associated with preservation of muscle mass. However, insulin treatment did not improve muscle function in the current cohort. Therefore, these data do not implicate that an early insulin treatment in elderly may be favorable regarding muscle integrity. Prospective studies including muscle biopsies are required to assess the effect of insulin treatment on muscle quality. Since other pharmaceutical approaches also did not succeed so far in improving muscle function in T2D [13] and yet no strategy exists for reversing muscle losses, the current data stress the necessity of a timely detection of low muscle quality, which may be present in patients with even mild T2D, and an early combined intervention including physiotherapy, dietary modifications and, possibly, adapted anti-diabetic therapy with the goal of preventing loss of muscle mass and function.

Acknowledgments We gratefully acknowledge the contribution of all members of field staffs conducting the KORA-Age study and thank all study participants.

Author contributions Conceptualization was carried out by Barbara Thorand, Annette Peters, Birgit Linkohr, Jochen Seissler, and Michael Drey; Methodology was carried out by Barbara Thorand, Jochen Seissler, Michael Drey, Marietta Rottenkolber, Uta Ferrari, Cornelia Then, and Romy Conzade; Formal analysis and investigation was carried out by Marietta Rottenkolber, Canan Selte, and Romy Conzade; Writing–original draft preparation were carried out by Uta Ferrari and Cornelia Then; Writing–review and editing were carried out by all authors; Funding acquisition was done by Barbara Thorand and Annette Peters; Resources were done by Barbara Thorand, Annette Peters, and Birgit Linkohr; Supervision was done by Barbara Thorand and Michael Drey.

Funding The KORA research platform studies were initiated and financed by the Helmholtz Zentrum München—German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. The KORA-Age project was financed by the German Federal Ministry of Education and Research (BMBF FKZ 01ET0713 and 01ET1003A) as part of the 'Health in old age' program.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical standards The study was approved by the Ethics Committee of the Bavarian Medical Association (reference number: 08064). All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national, Ethics Committee of the Bavarian Medical Association) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent All participants gave written informed consent.

References

1. Bianchi L, Volpato S (2016) Muscle dysfunction in type 2 diabetes: a major threat to patient's mobility and independence. Acta Diabetol 53:879–889. https://doi.org/10.1007/s00592-016-0880-y

2. Phielix E, Schrauwen-Hinderling VB, Mensink M et al (2008) Lower intrinsic ADP-stimulated mitochondrial respiration underlies in vivo mitochondrial dysfunction in muscle of male type 2 diabetic patients. Diabetes 57:2943–2949. https://doi.org/10.2337/db08-0391
3. Andreassen CS, Jakobsen J, Andersen H (2006) Muscle weakness: a progressive late complication in diabetic distal symmetric polyneuropathy. Diabetes 55:806–812. https://doi.org/10.2337/diabetes.55.03.06.db05-1237
4. Scott D, de Courten B, Ebeling PR (2016) Sarcopenia: a potential cause and consequence of type 2 diabetes in Australia's ageing population? Med J Aust 205:329–333
5. Kang S, Lim GE, Kim YK, et al (2017) Association between Sarcopenic Obesity and Metabolic Syndrome in Postmenopausal Women : A Cross-sectional Study Based on the Korean National Health and Nutritional Examination Surveys from 2008 to 2011. 9–14
6. Herder C, Karakas M, Koenig W (2011) Biomarkers for the prediction of type 2 diabetes and cardiovascular disease. Clin Pharmacol Ther 90:52–66. https://doi.org/10.1038/clpt.2011.93
7. Mavros Y, Kay S, Anderberg KA et al (2013) Changes in insulin resistance and HbA1c Are related to exercise-mediated changes in body composition in older adults with Type 2 diabetes: interim outcomes from the GREAT2DO trial. Diabetes Care 36:2372–2379. https://doi.org/10.2337/dc12-2196
8. Kalyani RR, Metter EJ, Ramachandran R et al (2012) Glucose and insulin measurements from the oral glucose tolerance test and relationship to muscle mass. J Gerontol A Biol Sci Med Sci 67:74–81. https://doi.org/10.1093/gerona/glr022
9. Koo BK, Roh E, Yang YS, Moon MK (2016) Difference between old and young adults in contribution of β-cell function and sarcopenia in developing diabetes mellitus. J Diabetes Investig 7:233–240. https://doi.org/10.1111/jdi.12392
10. Stangl MK, Böcker W, Chubanov V et al (2019) Sarcopenia - endocrinological and neurological aspects. Exp Clin Endocrinol Diabetes 127:8–22. https://doi.org/10.1055/a-0672-1007
11. Mesinovic J, Zengin A, De Courten B et al (2019) Sarcopenia and type 2 diabetes mellitus: a bidirectional relationship. Diabetes Metab Syndr Obes Targets Ther 12:1057–1072. https://doi.org/10.2147/dmso.s186600
12. Dimitriadis G, Mitrou P, Lambadiari V et al (2011) Insulin effects in muscle and adipose tissue. Diabetes Res Clin Pract 93:S52–S59. https://doi.org/10.1016/S0168-8227(11)70014-6
13. Cetrone M, Mele A, Tricarico D (2014) Effects of the antidiabetic drugs on the age-related atrophy and sarcopenia associated with diabetes type II. Curr Diabetes Rev 10:231–237. https://doi.org/10.2174/1573399810666140918121022
14. Peters A, Döring A, Ladwig K-H et al (2011) Multimorbidity and successful aging: the population-based KORA-Age study. Z Gerontol Geriatr 44(Suppl 2):41–54. https://doi.org/10.1007/s00391-011-0245-7
15. Washburn RA, Zhu W, McAuley E et al (2002) The physical activity scale for individuals with physical disabilities: development and evaluation. Arch Phys Med Rehabil 83:193–200. https://doi.org/10.1053/apmr.2002.27467
16. Autenrieth CS, Kirchberger I, Heier M et al (2013) Physical activity is inversely associated with multimorbidity in elderly men: results from the KORA-Age Augsburg Study. Prev Med (Baltim) 57:17–19. https://doi.org/10.1016/j.ypmed.2013.02.014
17. Janssen I, Heymsfield SB, Baumgartner RN, Ross R (2000) Estimation of skeletal muscle mass by bioelectrical impedance analysis. J Appl Physiol 89:465–471. https://doi.org/10.3945/ajcn.115.119925
18. Kalyani RR, Tra Y, Yeh H-C et al (2013) Quadriceps Strength, Quadriceps Power, and Gait Speed in Older U.S. Adults with Diabetes Mellitus: results from the National Health and Nutrition Examination Survey, 1999-2002. J Am Geriatr Soc 61:769–775. https://doi.org/10.1111/jgs.12204
19. Volpato S, Bianchi L, Lauretani F et al (2012) Role of muscle mass and muscle quality in the association between diabetes and gait speed. Diabetes Care 35:1672–1679. https://doi.org/10.2337/dc11-2202
20. Oberbach A, Bossenz Y, Lehmann S et al (2006) Altered Fiber Distribution and Fiber- Specific Glycolytic and Oxidative Enzyme Activity in Skeletal Muscle of Patients With Type 2 Diabetes. Diabetes Care 29:895–900. https://doi.org/10.2337/diacare.29.04.06.dc05-1854
21. Yoon JW, Ha YC, Kim KM et al (2016) Hyperglycemia is associated with impaired muscle quality in older men with diabetes: the Korean Longitudinal Study on Health and Aging. Diabetes Metab J 40:140–146. https://doi.org/10.4093/dmj.2016.40.2.140
22. Bouchi R, Fukuda T, Takeuchi T et al (2017) Insulin treatment attenuates decline of muscle mass in Japanese patients with Type 2 diabetes. Calcif Tissue Int. https://doi.org/10.1007/s00223-017-0251-x
23. Kalyani RR, Metter EJ, Egan J et al (2015) Hyperglycemia predicts persistently lower muscle strength with aging. Diabetes Care 38:82–90. https://doi.org/10.2337/dc14-1166
24. Rasmussen BB, Fujita S, Wolfe RR et al (2006) Insulin resistance of muscle protein metabolism in aging. FASEB J 20:768–769. https://doi.org/10.1096/fj.05-4607fje
25. Boettcher M, Machann J, Stefan N et al (2009) Intermuscular adipose tissue (IMAT): association with other adipose tissue compartments and insulin sensitivity. J Magn Reson Imaging 29:1340–1345. https://doi.org/10.1002/jmri.21754
26. Marcus RL, Addison O, Dibble LE et al (2012) Intramuscular adipose tissue, sarcopenia, and mobility function in older individuals. J Aging Res. https://doi.org/10.1155/2012/629637
27. Cuthbertson D (2004) Anabolic signaling deficits underlie amino acid resistance of wasting, aging muscle. FASEB J. https://doi.org/10.1096/fj.04-2640fje
28. Fujita S, Glynn EL, Timmerman KL et al (2009) Supraphysiological hyperinsulinaemia is necessary to stimulate skeletal muscle protein anabolism in older adults: evidence of a true age-related insulin resistance of muscle protein metabolism. Diabetologia 52:1889–1898. https://doi.org/10.1007/s00125-009-1430-8
29. Pereira S, Marliss EB, Morais JA et al (2008) Insulin resistance of protein metabolism in type 2 diabetes. Diabetes 57:56–63. https://doi.org/10.2337/db07-0887
30. Wilkes EA, Selby AL, Atherton PJ et al (2009) Blunting of insulin inhibition of proteolysis in legs of older subjects may contribute to age-related sarcopenia. Am J Clin Nutr 90:1343–1350. https://doi.org/10.3945/ajcn.2009.27543