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Original Article

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The influence of auxology and long-term glycemic control on muscle function in children and adolescents with type 1 diabetes mellitus

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Abstract

We intended to investigate in this pilot-study if long-term glycemic control stands in close relationship with muscle function in children and adolescents with type 1 diabetes mellitus (T1DM). Muscle function (MIGF, maximal isometric grip force; PJF, peak jump force; PJP, peak jump power) was investigated in 40 children and adolescents (males 20, females 20; age 13.5±2.5 yr) affected with T1DM. Muscular parameters were correlated with anthropometric parameters (age, height, weight) and with glycosylated hemoglobin (HbA1c) of the presence and the past. Standard deviation scores (SDSs) of weight and MIGF indicated significantly higher weight (mean 0.75±1.83 (SD)) and lower MIGF (mean -1.06±1.76 (SD)) in individuals with T1DM. When the study group was divided into two groups by the criteria that the actual HbA1c ($HbA1c_0$) was lower (N=25) or higher (N=15) than 8.5%, the comparison showed significantly higher muscular parameters (PJF-SDS, PJP-SDS and MIGF-SDS) in individuals with higher $HbA1c_0$. Multiple regression analyses demonstrated that body weight and height primarily predicted muscle force (MIGF, PJF) in T1DM. In conclusion, skeletal growth is an important determinant for the development of muscle function in children and adolescents with T1DM.

Keywords: Peak Jump Force, Peak Jump Power, Maximal Isometric Grip Force, Glycosylated Hemoglobin

Introduction

Chronic diseases are often associated with reduced physical activity and impaired muscular function. Rauch et al. reported reduced maximal isometric grip force (MIGF) in children and adolescents with kidney transplantation, cystic fibrosis and anticonvulsant therapy[1]. Limited knowledge is currently available on the development of muscle function in children and adolescents affected with type 1 diabetes mellitus (T1DM)[2]. Hypothetically, poor long-term glycemic control influences the development of muscle function in two different ways: 1) Reference data on muscle function revealed a strong relationship between muscular parameters (maximal muscle force and power) and anthropometric parameters (weight, height) in children and adolescents[1,3]. This aspect is theoretically underlined by the linear relationship between logarithmic parameters of muscle function and body size, because this association is based on allometric scaling laws describing the relationship between body size and metabolic rate[4,5]. Because individuals with insufficient insulin therapy have a lower growth rate, a delay in pubertal development and lower final body height[6], these factors could influence the development of muscle function in individuals with T1DM. 2) On the other hand, glycemic control stands with muscle metabolism in a direct relationship and could be an important determinant of muscle force and power in T1DM[7,8].

The present study was designed as a pilot-study to investigate if children and adolescents with T1DM are characterized by impaired muscle function. Especially, the present study intended to elucidate if long-term glycemic control primarily influences muscular function indirectly by direct effects on body size development.

The authors have no conflict of interest.

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Subjects and methods

Subjects

Forty children and adolescents (males 20, females 20) affected with T1DM took part in this study. Individuals were patients of the outpatient clinic of the Children's Hospital of the University of Cologne. The mean age ±SD was 13.0±2.5 years and the range comprised 6.3 to 18.4 years. An obvious musculoskeletal disease was excluded in all individuals by physical examination. The mean time period ±SD was 4.9±2.7 years with a median of 4.3 years (range from 0.2 to 11.3 years) since the occurrence of T1DM. Informed consent was obtained from all individuals and their parents. All investigations were in consent with the Ethical Committee of the University.

Assessment of MIGF

MIGF of the non-dominant hand was measured by the use of a Jamar dynamometer (Preston, Jackson, MI, U.S.A.) as previously described[1].

Assessment of PJF and PJP (mechanographic analyses)

Jumping forces were measured by use of the Leonardo Jumping Platform (Novotec GmbH, Pforzheim, Germany) as also formerly described[3]. This device measures forces applied to the plate over time. Therefore, stationary forces as well as the variation of forces over time (ground reaction forces) can be investigated.

The applied forces are recognized by 8 sensors of the plate. The distribution of forces to the different sensors is dependent on the area where the forces are applied, whereas the detected sum of forces is not dependent on the location of application. Each sensor is able to record up to 900 N. Software for the detection, storage and calculation of data was also manufactured by Novotec GmbH (Pforzheim, Germany).

Individuals stood on the plate and each foot was placed on one section of the jumping platform. The jump was performed as a counter movement jump with freely moving arms, and the subjects were instructed to jump as high as possible with the head and chest in a stretched position. The weight force of the individual was measured in order to calculate body weight (weight force/acceleration of gravity= body weight) before the first jump. The maximum of force of the ascending part of the jump was used for further calculations and is defined as the peak jump force (PJF). The peak of the calculated power (product of force and velocity) is called peak jump power (PJP). The subjects performed three jumps and the highest peak of the three recordings was selected for further calculations.

Assessment of anthropometric parameters

Weight was measured to the nearest 0.1 kg. Body height was determined to the next succeeding 1 mm using a Harpenden stadiometer. The measurement of parameters describing body size and muscular parameters were performed on the same day.

Abbreviations
T1DM: type 1 diabetes mellitus
HbA1c: glycosylated hemoglobin
BMI: body mass index
PJF: peak jump force
PJP: peak jump power
MIGF: maximal isometric grip force

HbA1c	**Mean±SD**	**Median**
$HbA1c_{12}$, N=39	4.4±1.9 /yr	4.0/yr
$HbA1c_{24}$, N=40	8.0±3.3 /2yr	7.5/2yr
$HbA1c_{36}$, N=40	10.9±5.6 /3yr	10.0/3yr
$HbA1c_{13\text{-}24}$, N=32	3.6±2.4 /yr	4.0/yr
$HbA1c_{25\text{-}36}$, N=25	3.0±3.0 /yr	3.0/yr

Table 1. Frequency of HbA1c measurements for different time periods.

Measurement of HbA1c

HbA1c was determined by Diabetes Control Assay (DCA) 2000 (Bayer HealthCare LCC, Elkhart, IN, U.S.A.), which is based on a latex immunoagglutination methodology. This instrument was commercially available.

HbA1c was measured at preceding points of time. The time interval and the number of HbA1c measurements differed between individuals, because the evaluation of HbA1c was performed retrospectively. Means of HbA1c values were calculated for different time periods and are indicated following the annotation:

$HbA1c_x$=: mean of HbA1c values in the last x months before assessment of muscle function.

Moreover, the following point of time and time periods were used for analyses:

1) $HbA1c_0$=: HbA1c value with the closest time relation to the assessment of muscle function. Thereby, determinations of $HbA1c_0$ and muscular parameters were performed at the same day for a subgroup of 31 individuals. The mean time period was 1.2 (range 0.1 to 3.0) months between measurement of $HbA1c_0$ and muscular performance for all other individuals.

2) Time periods x= 12, 24, 13-24 and 25-36 months before investigation of muscular parameters were used to calculate means of HbA1c values. The frequencies of HbA1c measurements are displayed in Table 1.

Parameter	Mean + SD			Median			P	
Sex	M+F (N=40)	M (N=20)	F (N=20)	M+F	M	F	P^a	P^b
Age [yr]	13.0±0.5	13.5±2.9	12.6±2.6	13.3	13.1	13.4		0.3
Height [cm]	158.8±2.8	162.3±17.9	155.3±14.8	158.9	167.5	157.4		0.18
Height-SDS	0.21±0.94	0.07±1.06	0.36±0.81	0.3	0.14	0.33	0.17	0.34
Weight [kg]	52.7±16.5	54.8±18.0	50.6±15.1	54.0	54.2	54.0		0.43
Weight-SDS*	0.75±1.83	0.49±1.74	1.02±1.94	0.29	0.06	0.47	0.01	0.37
BMI [kg/m²]	20.0±3.2	19.6±3.0	20.3±3.5	19.6	19.1	20.9		0.5
PJF [N]	1344±486	1377±559	1312±411	1336	1344	1336		0.68
PJF-SDS	0.15±1.07	0.10±1.30	0.2±0.82	0.33	0.42	0.23	0.38	0.77
PJP [W]	2222±887	2442±984	2001±739	2066	2222	2031		0.12
PJP-SDS	-0.11±1.21	-0.26±1.08	0.05±1.33	-0.15	-0.05	-0.21	0.57	0.42
MIGF [N]	228±113	259±124	197±93	206	280	196		0.08
MIGF-SDS*	-1.06±1.76	-1.1±1.47	-1.02±2.04	-0.88	-0.88	-1.09	<0.001	0.89
$HbA1c_0$%	8.32±1.47	8.17±1.54	8.48±1.41	8.10	7.80	8.10		0.51
$HbA1c_{12}$%	8.34±1.34 (N=39)	8.23±1.35	8.45±1.35 (N=19)	7.95	7.95	8.10		0.61
$HbA1c_{24}$%	8.30±1.27	8.15±1.26	8.44±1.30	7.65	7.95	8.00		0.48
$HbA1c_{36}$%	8.41±1.24	8.32±1.26	8.49±1.26	7.75	8.05	8.10		0.67
$HbA1c_{13-24}$%	8.17±1.41 (N=32)	8.12±1.44 (N=16)	8.23±1.43 (N=16)	7.50	7.55	7.60		0.83
$HbA1c_{25-36}$%	8.39±1.73 (N=25)	8.63±1.67 (N=13)	8.12±1.83 (N=12)	8.00	8.30	8.00		0.47

M indicates males, F indicates females. P reflects p-values of comparisons between means of SDS and reference individuals (P^a) and between means of males and females (P^b) by two-tailed t-tests. Significant differences are indicated by an asterisk. When the number of individuals was different from the group size indicated in the second row of the table, the number of individuals was displayed for the specific parameter.

Table 2. Anthropometric characteristics and muscular parameters of the entire study population.

Statistical analyses

Descriptive statistical parameters were calculated for the entire study population and individuals with $HbA1c_0$> and <8.5% (Tables 2 and 3). Muscular parameters were transformed into height- and gender-dependent standard deviation scores (SDS) using reference populations previously described by the formula[7,15]:

SDS= (rough value – mean of reference population)/SD of reference population. SDS for height and weight were calculated with reference to age and gender and derived from a previously described reference group[1]. SDSs were compared to each other and to the reference population by paired t-tests. Subgroups (e.g., gender) were compared by two-tailed and unpaired t-tests for homo- or heterogeneous variances after variances were compared by F-tests. Multiple regression analyses were performed for the prediction of muscle force and power. Thereby, beta weights indicated how strong HbA1c values and anthropometric parameters contributed to the prediction of muscular parameters. Partial correlations were calculated to reveal significant relationships between HbA1c values, anthropometric and muscular parameters. Simple linear correlations were calculated between logarithmic anthropometric parameters (height, weight) and muscular parameters. Statistical differences were ascribed to be significant at $p<0.05$. All statistical procedures were performed by the use of PC Statistics 4.0 (Hoffmann-Software, Gießen).

Parameter	Mean±SD		
	$HbA1c_0$<8.5% (N=25)	$HbA1c_0$>8.5% (N=15)	P
Age*	12.4±3.1	14.1±1.7	0.02
Weight-SDS	0.39±1.73	1.35±1.90	0.11
Height-SDS	0.25±1.07	0.16±0.71	0.77
MIGF-SDS*	-1.74±1.54	0.08±1.51	<0.001
PJF-SDS*	-0.19±1.02	0.72±0.93	0.008
PJP-SDS*	-0.42±0.93	0.41±1.44	0.03

Significant differences between groups are indicated by an asterisk (two-tailed unpaired t-tests).

Table 3. Characteristics of individuals with higher or lower $HbA1c_0$ than 8.5%.

Results

Anthropometric characteristics of the entire study population are listed in Table 2 and the relationship of muscular parameters to weight, height and age is displayed in Figures 1-3. Means of weight-SDS and MIGF-SDS significantly differed from zero. In contrast, means of SDSs of height, PJF and PJP did not significantly differ from zero. Moreover,

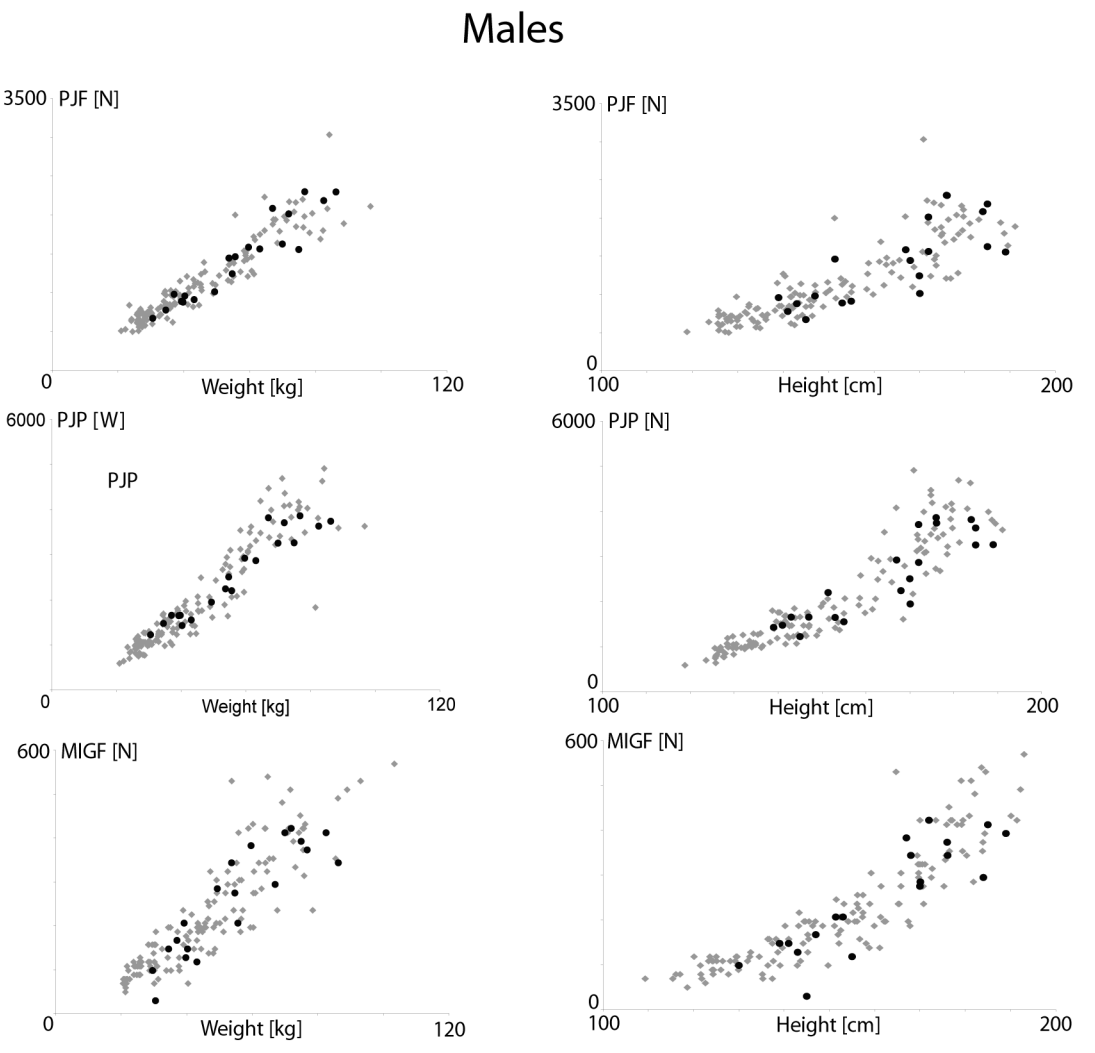

Figure 1. Muscular parameters in diabetic males. Muscular parameters of 20 diabetic males (black dots) are displayed in front of reference males (gray dots, see reference (1) for MIGF and reference (3) for PJF and PJP).

means of SDSs did not significantly differ between genders (Figures 1 and 2).

When the study group was divided into two groups by the criteria that the actual HbA1c ($HbA1c_0$) was lower (N=25) or higher (N=15) than 8.5%, the comparison of anthropometric and muscular parameters showed significant differences for muscular parameters (means of PJF-SDS, PJP-SDS and MIGF-SDS). Individuals with higher $HbA1c_0$ values were characterized by higher values of muscular parameters (Table 3).

Multiple regression analyses (four-variate) were calculated to investigate the interaction of HbA1c values and anthropometric parameters (age, height, weight) for the prediction of PJF, PJP and MIGF. Table 4 displays to what extent anthropometric parameters and HbA1c values contributed to the prediction of muscle force. Thereby, HbA1c values comprised a range of beta weights from -0.07 to 0.27. Weight possessed the highest predictive power with a range of beta weights between 0.25 and 1.04. Partial correlations indicated strong correlations of muscular parameters with parameters describing body size (Table 5). According to allometric scaling, those correlations got partially closer when logarithmic parameters were correlated by simple linear regression models. The logarithm of weight significantly correlated with ln(PJF) (r=0.93), ln(PJP) (r=0.91) and with ln(MIGF) (r=0.80). The logarithm of height was significantly correlated with ln(PJF) (r=0.85), ln(PJP) (r=0.83) and with ln(MIGF) (r=0.75).

Discussion

The present collective of individuals with T1DM was characterized by decreased MIGF-SDS and increased weight-SDS. Therefore, individuals with T1DM developed signifi-

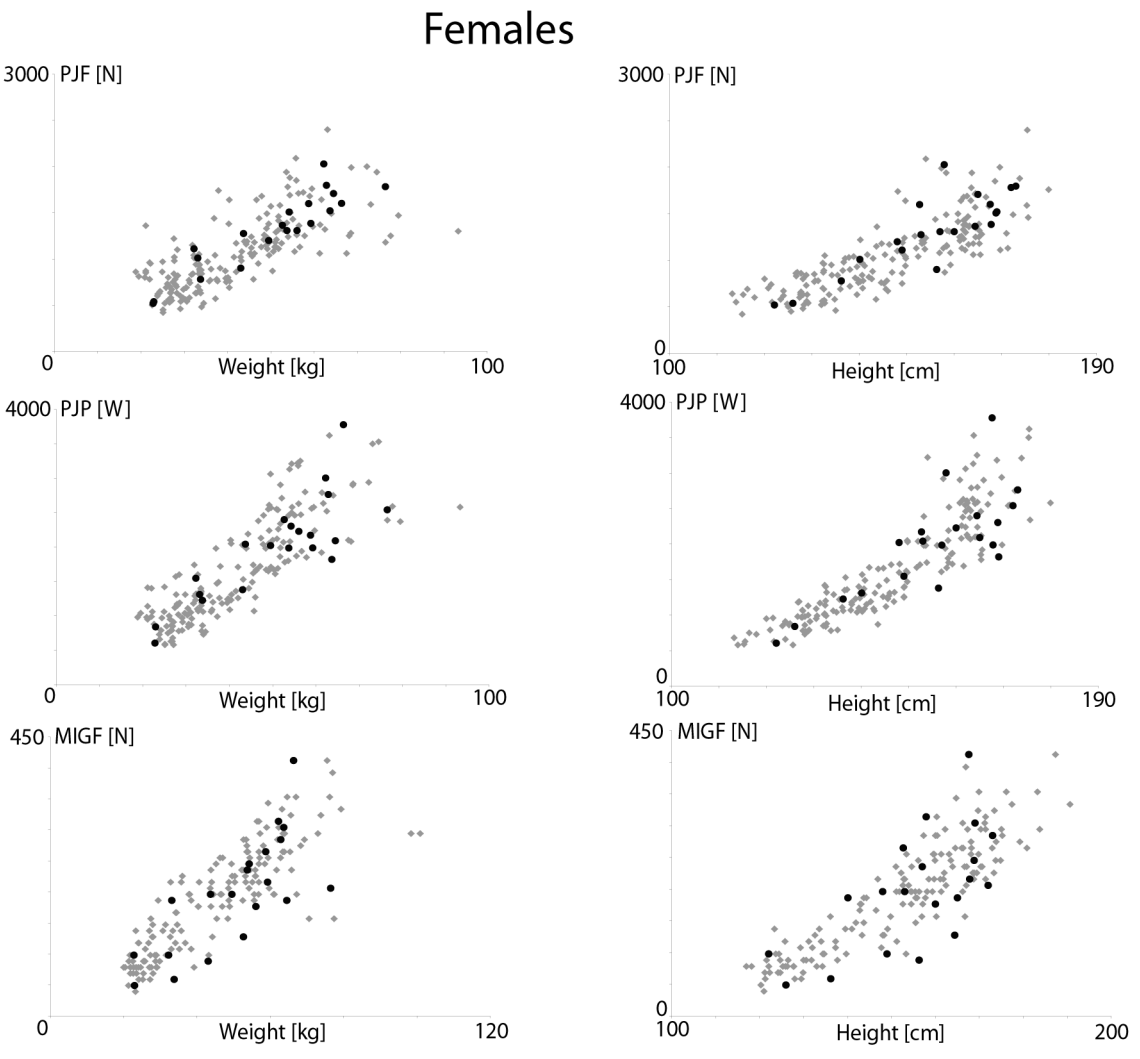

Figure 2. Muscular parameters in diabetic females. Muscular parameters of 20 diabetic females (black dots) are displayed in front of reference females (gray dots, see reference (1) for MIGF and reference (3) for PJF and PJP).

Parameter	Time period of HbA1c measurements	beta weight				R
		Age [yr]	Weight [kg]	Height [cm]	HbA1c %	
PJF [N]	$HbA1c_0$	0.46	0.96	-0.47	0.02	0.95
	$HbA1c_{36}$	0.48	0.96	-0.49	0.04	0.96
	$HbA1c_{13-24}$	0.54	1.04	-0.61	-0.07	0.96
MIGF [N]	$HbA1c_0$	0.15	0.25	0.43	0.16	0.86
	$HbA1c_{12}$	0.19	0.46	0.19	0.19	0.87
	$HbA1c_{24}$	0.25	0.48	0.12	0.11	0.85
	$HbA1c_{36}$	0.26	0.46	0.11	0.17	0.86
	$HbA1c_{13-24}$	0.27	0.49	0.06	0.08	0.82
	$HbA1c_{25-36}$	0.08	0.64	0.06	0.27	0.88
PJP [W]	NS					
'R' indicates the regression coefficient. All displayed regressions are significant with $p<0.0001$. 'NS' indicates not significant regression models.						

Table 4. Multiple regressions (four-variate models) for the prediction of muscle force and power.

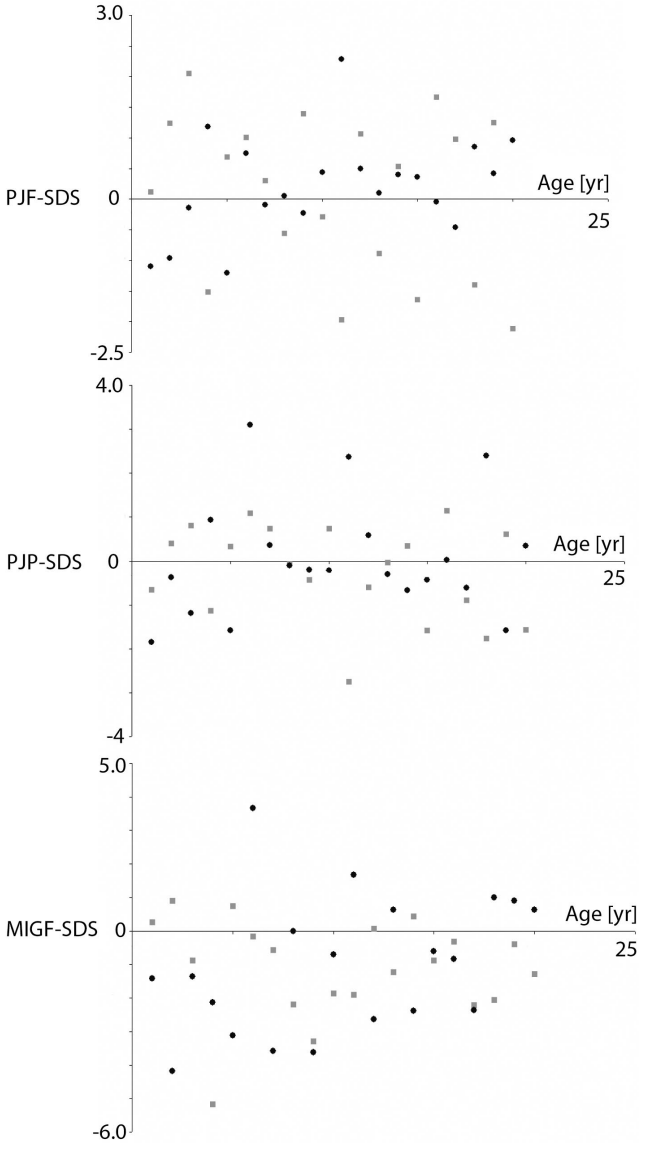

Figure 3. The relationship of muscular parameters to age in diabetic individuals. SD-scores of muscular parameters (PJF, PJP and MIGF) are displayed in their relationship to age. Black dots indicate girls, grey squares indicate boys.

cantly less maximal isometric force than reference individuals with the same height and were characterized by significantly higher weight than reference individuals with the same age. This result is partly consistent with Bechtold et al. who recently described that children with T1DM are characterized by higher weight-SDS and reduced muscle cross-sectional area at the forearm when the manifestation of T1DM had been in early childhood[9].

When the study group was divided into individuals with $HbA1c_0$ higher or lower than 8.5%, individuals with higher $HbA1c_0$ were characterized by higher age and higher MIGF-SDS, PJF-SDS and PJP-SDS than individuals with lower $HbA1c_0$. Because glycemic control is regarded to be an important determinant of normal skeletal growth in the recent literature[10], the present result was not expected that higher HbA1c was associated with higher muscle force and power. Partial correlations revealed that body weight was the strongest predictor of maximal muscle force in the most four-variate models using age, height, weight and HbA1c for the prediction. Moreover, weight was significantly partial correlated with HbA1c in the prediction of MIGF. Therefore, weight is suggested to be the decisive physiological link between HbA1c and muscular performance in individuals with T1DM. This present association between muscle force and body weight was also previously described by allometric scaling laws in normal individuals and represents the physiological adaptation of muscle force on body weight. When this result is discussed on a metabolic level, the application of higher insulin doses can be suggested in individuals with higher weight. Thereby, individuals with poor glycemic control often use higher insulin doses and are typically characterized by higher HbA1c[11]. Insulin is suggested to have anabolic effects on muscle metabolism in diabetic individuals[12]. Therefore, higher insulin doses might be responsible for the development of increased muscle force in the present study collective of individuals with T1DM.

Moreover, older individuals were characterized by higher HbA1c in the present study. This result could reflect that puberty-associated effects were responsible for insufficient glycemic control in older individuals[13-16]. Recently published data support the theory that this deterioration is partly effected by physiological processes (e.g., insulin resistance mediated by increased growth hormone in puberty) and also partly effected by worsening of adherence behaviors in puberty[2,4]. Because pubertal stages were not assessed in the present study, we are limited to deliver any significant proof if puberty was the suggested determinant factor that older individuals were characterized by higher HbA1c.

Interestingly, PJP could not be predicted by four-variate regression models and was not partial correlated with HbA1c in the present study. Power is suggested to be also dependent on the current glycemic control and will be probably strongly predicted by the actual glucose serum level in individuals with T1DM. Because actual glucose levels during mechanographic analyses were not included into the present analyses, the variance was probably insufficiently explained by the used independent parameters height, weight and HbA1c in the multiple regression models predicting PJP.

In conclusion, the present pilot-study gives an overview on the development of muscular function in children and adolescents with T1DM treated in a German pediatric outpatient clinic. Therefore, the results reflect the typical collective of patients with T1DM, but the data are not based on a representative drawn sample of individuals with T1DM. Nevertheless, the present results represent some important aspects of the association between long-term glycemic control and muscle function in children and adolescents with T1DM. The development of muscle force was primarily asso-

	PJF	Age	Weight	Height	HbA1c
PJF		0.52-0.61	0.81-0.85	-0.60-0.44	NS
Age	0.52-0.61		-0.49- -0.37	0.74-0.79	NS
Weight	0.81-0.85	-0.49- -0.37		0.66-0.73	NS
Height	-0.60- -0.44	0.74-0.79	0.66-0.73		NS
HbA1c	NS	NS	NS	NS	
The range of significant partial correlations is displayed. When correlations were not significant, they are indicated by 'NS'.					

5.1. Range of correlation coefficients in partial correlations between variables for the prediction of PJF in multiple regressions.

	PJP	Age	Weight	Height	HbA1c
PJP		NS	0.58-0.65	NS	NS
Age	Ns		Ns	0.63-0.68	NS
Weight	0.58-0.65	Ns		0.46-0.49	NS
Height	Ns	0.63-0.68	0.46-0.49		NS
HbA1c	NS	NS	NS	NS	
The range of significant partial correlations is displayed. When correlations were not significant, they are indicated by 'NS'.					

5.2. Range of correlation coefficients in partial correlations between variables for the prediction of PJP in multiple regressions.

	MIGF	Age	Weight	Height	HbA1c
MIGF		NS	0.34-0.51	NS	0.35($HbA1c_{12}$), 0.47($HbA1c_{25-36}$)
Age	NS		NS	0.63- 0.67	NS
Weight	0.34-0.51	NS		0.48- 0.51	NS
Height	NS	0.63- 0.67	0.48- 0.51		NS
HbA1c	0.35($HbA1c_{12}$), 0.47($HbA1c_{25-36}$)	NS	NS	NS	
The range of significant partial correlations is displayed. When correlations were not significant, they are indicated by 'NS'.					

5.3. Range of correlation coefficients in partial correlations between variables for the prediction of MIGF in multiple regressions.

Table 5. Range of correlation coefficients in partial correlations between variables for the prediction of muscular parameters in multiple regressions.

ciated with body weight development and less associated with long-term glycemic control indicated by HbA1c. Moreover, PJP could not be sufficiently predicted by anthropometric parameters in combintation with HbA1c. Therefore, actual glucose levels are suggested to be a stronger predictor of muscular power than HbA1c in individuals with T1DM. Finally, children and adolescents with T1DM are characterized by the tendency to develop lower isometric grip force than normal individuals reflecting the importance to follow up the development of muscular function in T1DM.

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