

Influence of Body Fat and Lean Mass on HbA1c and Apolipoprotein in Children and Adolescents With Type 1 Diabetes Mellitus

Thais Menegucci , [Eduardo Federighi Baisi Chagas](#) , Barbara De Oliveira Zanuso , Karina Quesada , Jesselina Francisco Dos Santos Haber , Tereza Laís Menegucci Zutin , Luis Felipe Pimenta , Adriano Cressoni Araújo , Elen Landgraf Guiguer , Claudia Rucco P. Detregiachi , Marcia Gabaldi Rocha , Patrícia Cincotto dos Santos Bueno , [Lucas Fornari Laurindo](#) ^{*} , [Sandra M. Barbalho](#)

Posted Date: 10 August 2023

doi: 10.20944/preprints202308.0831.v1

Keywords: Type 1 Diabetes Mellitus; body fat; lean mass; glycated hemoglobin; apolipoprotein.



Preprints.org is a free multidiscipline platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This is an open access article distributed under the Creative Commons Attribution License which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Article

Influence of Body Fat and Lean Mass on HbA1c and Apolipoprotein in Children and Adolescents With Type 1 Diabetes Mellitus

Thais Menegucci ¹, Eduardo F. B. Chagas ^{1,2,3}, Barbara de Oliveira Zanuso ⁴, Karina Quesada ^{4,5}, Jesselina Francisco dos Santos Haber ^{3,4}, Tereza Laís Menegucci Zutin ^{1,4}, Luis Felipe Pimenta ¹, Adriano Cressoni Araújo ^{1,4}, Elen L. Guiguer ^{1,4,5}, Claudia Rucco P. Detregiachi ^{1,4}, Marcia Gabaldi Rocha ⁴, Patrícia Cincotto dos Santos Bueno ⁶, Lucas Fornari Laurindo ^{4,7} and Sandra M. Barbalho ^{1,4,5,*}

¹ Postgraduate Program in Structural and Functional Interactions in Rehabilitation, School of Medicine, Universidade de Marília (UNIMAR), Marília 17525-902, São Paulo, Brazil

² Postgraduate Program of Health and Aging, School of Medicine, Faculdade de Medicina de Marília (FAMEMA), Marília 17519-030, São Paulo, Brazil

³ Interdisciplinary Center on Diabetes (CENID), Universidade de Marília (UNIMAR), Marília 17525-902, São Paulo, Brazil

⁴ Department of Biochemistry and Pharmacology, School of Medicine, Universidade de Marília (UNIMAR), Marília 17525-902, São Paulo, Brazil

⁵ Department of Biochemistry and Nutrition, School of Food and Technology of Marília (FATEC), Marília 17500-000, São Paulo, Brazil

⁶ Department of Animal Sciences, School of Veterinary Medicine, Universidade de Marília (UNIMAR), Marília 17525-902, São Paulo, Brazil

⁷ Department of Biochemistry and Pharmacology, School of Medicine, Faculdade de Medicina de Marília (FAMEMA), Marília 17519-030, São Paulo, Brazil

* Correspondence: smbarbalho@gmail.com

Abstract: Glycated hemoglobin (HbA1c) is used to assess glycemic control in Type 1 diabetes (DM1) patients. Apolipoproteins play an essential role in DM1 pathophysiology and may be associated with complications, as well as HbA1c. This cross-sectional observational study consisting of 81 children and adolescents of both sexes diagnosed with DM1 investigated the relationship between body fat distribution and lean mass with HbA1C and apolipoprotein values analyzing biochemical and body composition measurements. Shapiro-Wilk test with Lilliefors correction, non-parametric Mann-Whitney test, and others were used with a significance level of 5%. The sample had a diagnosis time of 4.32 years and high blood glucose levels (mean 178.19 mg/dL) and HbA1c (mean 8.57%). Subjects also had a moderate level of adiposity, as indicated by arm and thigh fat areas. The study also found significant differences in the distribution of patients concerning levels of apolipoproteins A and B, with a smaller proportion of patients having undesirable levels. Finally, the study found a significant difference in the distribution of patients with estimated cardiovascular risk based on the ApoB/ApoA-1 ratio. Conclusively, visceral fat in children and adolescents with DM1 may increase the risk of DM1 long-term complications owing to its association with elevated HbA1C and apolipoprotein values.

Keywords: Type 1 diabetes mellitus; body fat; lean mass; glycated hemoglobin; apolipoprotein

1. Introduction

Type 1 diabetes (DM1) is one of the common chronic diseases in childhood and adolescence. It is characterized by the autoimmune destruction of pancreatic β cells, causing partial or total deficiency in insulin production, which can lead to serious complications in the short and long term if not treated correctly [1-3]. This condition has a significant economic and social impact in Brazil and in the world. The losses are immeasurable and the onset of the disease leads to loss of quality of life

and the change in social commitments brings negative results to the lives of children, adolescents and their families [4,5].

DM1 involves a complex interaction between genetic and environmental factors and with the participation of adaptive immunity. The initial phase of the disease is characterized by chronic inflammation that involves degeneration of the pancreatic islets and reduced insulin synthesis. Inflammation also contributes to T1D complications such as diabetic retinopathy and nephropathy [6-9].

Although DM1 patients traditionally tend to be underweight, the increase in sedentary lifestyle and exacerbated consumption of foods high in sugar and fat has contributed to weight gain in this population. It is known that an increase in the proportion of fat, especially visceral fat, and a reduction in lean mass worsen glycemic control and plasma lipid levels. [10-12]. In addition, the increase in visceral adipose tissue to the detriment of the reduction in lean mass has direct implications for the installation of a pro-inflammatory scenario and oxidative stress that will strongly contribute to the micro and macro-vascular complications of DM1 [13-16].

Although intensive insulin therapy is crucial for glycemic control, it can also contribute to weight gain, especially if performed improperly and with excessive calorie intake [17,18].

Glycated hemoglobin (HbA1c) is one of the main indicators of glycemic control and is strongly correlated with risks of long-term complications [17,19-21].

In addition to HbA1C, apolipoproteins (apo) A1, A2 and the Apo A2/Apo A1 ratio play an important role in the pathological process of DM1, playing a fundamental role in glucose metabolism and cardiovascular complications. Thus, alterations in these molecules are related to glycemic control in DM1 as well as in the proportion of adipose tissue. Studies show that lower levels of apo A or higher levels of apo B are correlated with signs of microvascular dysfunction, which plays a crucial role in DM-related complications, such as the pathogenesis of diabetic retinopathy [22-25].

Although increased body fat is associated with worse metabolic control, there is evidence that different regions of fat deposition are associated with different metabolic consequences in terms of insulin sensitivity, serum lipids, adipokines, and inflammatory factors [26].

Therefore, assessing the distribution of lean mass and adipose tissue is important to help control blood glucose, contributing to the prevention of future complications in DM1 patients. In view of the above, this study aimed to investigate the relationship between body fat and lean mass distribution on HbA1C, lipid profile and Apo A/B values in children with DM1.

2. Materials and Methods

2.1. General Data

The sample size was calculated using the G*Power software, version 3.1.9.2 (Franz Faul, Universität Kiel, Germany) to analyze the association between overweight/obesity and apolipoprotein values in children and adolescents with DM1. Considering an expected proportion of 10% (0.10), a degree of freedom and a large effect size (0.50), a minimum sample of 72 sample elements was estimated for a type I margin of error (α) of 1% and a study power of 95% [27].

The sample consisted of 81 children and adolescents of both sexes (59.3% male / 40.7% female) diagnosed with DM1 for at least 1 and a maximum of 14 years and aged between 4 and 19 years. Data were obtained from medical records filed in the database of the Medical Specialty Ambulatory (AME) of the Associação Beneficente Hospital Universitário (ABHU) of the University of Marília (UNIMAR) in the activities of the extension program of the Centro Interdisciplinar em Diabetes (CENID) between the years 2019 to 2020. Patients were referred by the Regional Health Department of Marília-DRS IX via the Health Service Supply Regulation Center (CROSS). The general project was approved by the Ethics and Research Committee of UNIMAR (opinion: 3,606,397/2019).

Patients who did not authorize access to the medical records by signing the Term of Assent (TA) and Term of Free and Informed Consent (TCLE) were not included in the study; had a diagnosis of Autistic Spectrum Disorder; presented physical disability with malfunction or paralysis of upper and/or lower limbs.

Patient data in this cross-sectional observational study were obtained by accessing clinical data filed in the CENID database. Data were collected on the patient's clinical history (age, sex, time since diagnosis, therapeutic strategy, history of diseases and complications), pattern of habitual physical activity, body composition, lipid profile, fasting glucose, glycated hemoglobin (HbA1c) and apolipoproteins A and B. Body composition was analyzed using anthropometric measurements of body mass, height, circumferences and skinfolds, as well as bioimpedance tests to estimate lean mass, percentage of fat and muscle mass. The biochemical tests used in the clinical routine of patients consist of: complete blood count; fasting blood glucose (GLj), casual blood glucose (GLc), glycated hemoglobin (HbA1c), total cholesterol (TC), LDL-cholesterol (LDL), HDL-cholesterol (HDL), triglycerides (TG), VLDL-cholesterol (VLDL) and apolipoproteins "A" (ApoA) and "B" (ApoB).

2.2. Study Variables

The prevalence of chronic diseases in the population was obtained through a questionnaire of reported morbidities and confirmed by clinical diagnosis present in the medical referral and complemented with information about the time of diagnosis of the disease and information about the use of medications.

The analysis methods for the biochemical measurements were Glycemia, Total cholesterol, HDL-c, triglycerides and LDL-c by the enzymatic colorimetric method; HbA1c by high performance liquid chromatography (HPLC); and ApoA and ApoB were performed by nephelometry or immunoturbidimetry. For the population of children and adolescents, apo A-I values below 120 (mg/dL) and for ApoB values above 90 (mg/dL) are undesirable. The following cutoff points were considered for stratifying the risk of acute myocardial infarction (AMI) based on the values of the apo B/apoA index for men and women respectively: low risk 0.40-0.69/ 0.30-0.59; moderate risk 0.70-0.79/ 0.60-0.79; high risk 0.90-1.10/ 0.80-1.00 [28,29].

For the analysis of body composition, anthropometric measures of body mass (BM), height (EST), skinfolds and circumferences were used, as well as body fat and lean mass data referring to the bioimpedance test. From the anthropometric measurements, body composition indicators were calculated.

Circumference, body weight and height measurements were used to calculate the conicity index to analyze visceral fat [30]. For the estimation of lean mass and body fat through bioimpedance, specific equations for age and gender were used [31,32]. Arm circumference (AC) and triceps skinfold (TCF) measurements were used to calculate arm fat area (AGB), arm muscle circumference (AMC), arm muscle area (AMB) and arm muscle area, corrected arm (AMBc) [33,34]. Thigh circumference and thigh skinfold measurements were used to estimate thigh muscle area (AMC) and thigh fat area (AGC) [35].

2.3. Data Analysis Methodology

Quantitative variables are described by mean, standard deviation (SD) and range (minimum and maximum value). Qualitative variables are described by absolute and relative frequency distribution. Differences in the proportion distribution of qualitative variables were analyzed using Fisher's exact test. The normal distribution was verified using the Shapiro-Wilk test with Lilliefors correction. To analyze the relationship between the ordinal quantitative and qualitative variables, Spearman's non-parametric correlation test was performed.

The multiple linear regression model was used to analyze the effect of body composition variables on the values of HbA1c, ApoA, ApoB and ApoB/ApoA coefficient controlling the effect of sex, time of diagnosis and pubertal stage by the Enter method. The R² was analyzed to verify the determination coefficient of the variation percentage explained by the model. For all analyses, the SPSS software version 19.0 for Windows was used, with a significance level of 5%.

3. Results

Table 1 presents the mean, standard deviation, minimum and maximum values of several clinical and anthropometric variables in a sample of individuals with DM1. In general, the mean values of the sample indicate that individuals have a relatively long time since diagnosis (4.32 years), with high levels of blood glucose (mean of 178.19 mg/dL) and HbA1c (mean of 8.57%). In addition, the average Apolipoprotein B / Apolipoprotein A-I ratio is greater than the value considered ideal for individuals at increased risk of cardiovascular disease. Furthermore, arm and thigh fat areas also indicate a moderate level of adiposity in the sample.

Table 1. Descriptive statistics of the sample's quantitative variables.

	Averag e	SD	Mínim um	Maxim um
Age (years)	12.60	3.58	4.00	19.00
Diagnostic time (years)	4.32	2.99	1.00	14.00
Glycemia (mg/dL)	178.19	69.14	73.00	429.00
Total cholesterol (mg/dL)	165.27	33.80	87.00	246.00
Triglycerides (mg/dL)	82.55	52.52	21.72	343.00
LDL (mg/dL)	89.37	27.41	24.00	171.00
HDL (mg/dL)	55.07	10.66	23.00	76.00
Non HDL cholesterol	110.20	34.43	37.00	201.00
HbA1c (%)	8.57	2.27	4.91	15.30
ApoA	149.00	17.89	95.00	213.00
ApoB	77.20	18.61	31.00	126.00
Apolipoprotein B / Apolipoprotein A-I coefficient	0.28	0.85	0.52	0.12
Taper index	1.14	0.08	0.79	1.36
BMI z-score	0.25	1.23	-3.01	3.30
Arm muscle area (cm2)	20.93	3.15	15.37	28.72
Arm area (cm2)	59.75	11.09	40.75	95.00
Arm fat area (cm2)	12.36	2.84	7.87	22.98
% Arm fat	20.55	1.12	19.16	24.44
Thigh muscle area (cm2)	106.21	38.58	43.53	208.58
Thigh area (cm2)	157.18	58.38	66.96	336.39
Thigh fat area (cm2)	50.97	27.79	7.60	132.58
% Thigh fat area (cm2)	31.65	9.82	4.14	55.37
% Fat bioimpedance	21.73	7.63	9.60	40.00
Fat (kg) bioimpedance	10.93	6.01	2.42	28.20

Note: standard deviation.

Table 2 presents an analysis of variables that include: sex, time of diagnosis, insulin administration, presence of associated morbidities, level of physical activity, level of glycated hemoglobin (HbA1c), levels of apolipoproteins A and B, cardiovascular risk and index of body mass (BMI).

Regarding insulin administration, there was a significant difference ($p < 0.001$) in the proportion of patients using an insulin pump compared to those using a pen.

A significant difference was also found in the distribution of patients in the different HbA1c classes, considering that the proportion of patients with HbA1c above 8% was significantly higher compared to the other classes ($p < 0.001$).

There was a significant difference in the distribution of patients into ApoA and ApoB classes, as the proportion of patients with undesirable levels of these proteins was significantly lower compared to desirable levels ($p < 0.001$).

The table also shows that there was a significant difference in the distribution of patients in relation to the cardiovascular risk estimated by the ApoB/ApoA-1 coefficient. Most patients were at low risk ($p < 0.001$). Finally, there was a significant difference in the distribution of patients in the different classes of BMIz. The proportion of thin/thin patients was significantly lower compared to the other classes ($p < 0.001$).

The other variables did not show statistically significant differences.

Table 2. Absolute (f) and relative (%) frequency distribution of the qualitative variables that characterize the sample.

		<i>f</i>	%	p- value
Gender	Male	48	59.3	0.119
	Female	33	40.7	
Diagnostic time class	< 5 years	46	56.8	0.226
	> 5 years	35	43.2	
Insulin Administration	Bomb	22	27.2	<0.001*
	Pen	59	72.8	
Associated morbidities	Yes	5	6.2	<0.001*
	No	76	93.8	
LFA	Sedentary	47	58.0	0.182
	Little active	34	42.0	
Class HbA1c	<7%	20	24.7	<0.001*
	7 a 8%	17	21.0	
	>8%	44	54.3	
Class ApoA	Desirable	79	97.5	<0.001*
	Undesirable	2	2.5	
Class ApoB	Desirable	65	80.2	<0.001*
	Undesirable	16	19.8	
Cardiovascular risk ApoB/ApoA-1 coefficient	Low	71	87.7	<0.001*
	Moderate	9	11.1	
	High	1	1.2	
BMI class	Thinness/skinny	9	11.1	<0.001*
	Eutrophic	52	64.2	
	Overweight	18	22.2	
	Obese	2	2.5	

Note: * indicates significant difference in the proportion distribution of response categories by Fisher's exact test for $p\text{-value} \leq 0.050$.

Table 3 presents a correlation analysis between various anthropometric and biochemical parameters with respect to levels of HbA1c, ApoA, ApoB and ApoB/ApoA-I coefficient. Correlation analysis was performed using Pearson's correlation coefficient (r) and p-value.

The results show that the conicity index had a significant correlation with the ApoB level ($r = 0.227$, $p\text{-value} = 0.042^*$) and the ApoB/ApoA-I coefficient ($r = 0.119$, $p\text{-value} = 0.289$). Arm muscle area showed a significant negative correlation with ApoB ($r = -0.298$, $p\text{-value} = 0.007^*$) and with the ApoB/ApoA-I coefficient ($r = -0.269$, $p\text{-value} = 0.015^*$).

The percentage of body fat measured by bioimpedance (Bio) showed a significant positive correlation with the level of ApoA ($r = 0.141$, $p\text{-value} = 0.210$). Body fat (kg) measured by bioimpedance showed a significant positive correlation with HbA1c ($r = 0.272$, $p\text{-value} = 0.014^*$). Lean mass (%) measured by bioimpedance showed a significant negative correlation with HbA1c ($r = -0.275$, $p\text{-value} = 0.013^*$) and with the ApoB/ApoA-I coefficient ($r = -0.104$, $p\text{-value} = 0.357$).

In addition, some parameters, such as the BMI z-score, thigh muscle area, thigh area, thigh fat area, % arm fat and arm fat area did not show a significant correlation with any of the four parameters analyzed (HbA1c, ApoA, ApoB and ApoB/ApoA-I coefficient).

Table 3. Correlation analysis of HbA1c, ApoA-I, ApoB and ApoB/ApoA-I coefficient with body composition variables.

	HbA1c (%)		ApoA		ApoB		ApoB / ApoA-I coefficient	
	r	p-value	r	p-value	r	p-value	r	p-value
Taper index	-0.086	0.447	0.039	0.730	0.227	0.042 *	0.119	0.289
z-score BMI	0.041	0.717	0.083	0.461	0.018	0.874	-0.085	0.449
Arm muscle area (cm2)	0.034	0.765	-0.172	0.126	-0.298	0.007 *	-0.269	0.015 *
Arm area (cm2)	0.034	0.761	-0.087	0.440	-0.148	0.186	-0.177	0.113
Arm fat area (cm2)	0.059	0.603	-0.066	0.561	-0.113	0.316	-0.152	0.175
% arm fat	0.116	0.303	0.059	0.602	0.140	0.213	0.071	0.531
Thigh muscle area (cm2)	0.098	0.383	-0.069	0.540	-0.195	0.081	-0.210	0.060
Thigh area (cm2)	0.137	0.224	-0.032	0.774	-0.118	0.296	-0.155	0.167
Thigh fat area (cm2)	0.170	0.129	0.010	0.928	0.071	0.527	0.010	0.926
% Thigh fat area (cm2)	0.111	0.325	0.033	0.770	0.199	0.075	0.182	0.104
% Fat bioimpedance	0.252	0.023 *	0.141	0.210	0.181	0.106	0.076	0.499
Fat bioimpedance (kg)	0.272	0.014 *	0.088	0.435	0.091	0.417	-0.003	0.979

Lean mass (kg)	0.134	0.235	-	0.351	-	0.073	-	0.090
bioimpedance			0.105		0.201		0.190	
Lean mass (%)	-	0.013	-	0.135	-	0.059	-	0.357
bioimpedance	0.275	*	0.167		0.211		0.104	

Note: regression coefficient (r); * indicates significant correlation by Spearman's test for p-value ≤ 0.050.

In Table 4, a multiple linear regression analysis was performed to verify the effect of the body composition variables on HbA1c, ApoA, ApoB and ApoB/ApoA coefficient, controlling for the variables sex, time of diagnosis and pubertal stage. There was a significant effect of percentage of fat and lean mass by bioimpedance on HbA1c values. The increase in the percentage of fat and the reduction in lean mass are related to the increase in HbA1c. For the percentage of fat and lean mass, the model did not show a significant effect. When analyzing the R2 value, it was verified that the percentage of fat and lean mass explain, respectively, 6.4% and 8.4% of the HbA1c variation.

It was observed that the increase in AMB (cm²), controlling for the effect of gender, time of diagnosis and pubertal stage, is related to the reduction of ApoB and significantly this model explains 13.0% (R²) of the ApoB variation. The increase in AMB (cm²) is also related to the reduction in the ApoB/ApoA coefficient and although the model did not show a significant effect, R² points out that the variation in AMB (cm²), controlling for the effect of gender, time of diagnosis and pubertal stage explains 10% of the variation in the ApoB/ApoA coefficient.

Table 4. Multiple linear regression analysis for the effect of body composition variables on HbA1c, ApoA, ApoB and ApoB/ApoA coefficient controlling for gender, time of diagnosis and pubertal stage.

Variables			CI 95%			Model	
Dependent	Independent	B	IL	UL	p-value	p-value	R2
HbA1c (%)	(Constant)	7.636	5.687	9.586	<0.001*	0.274	0.064
	Gender	-0.539	-1.718	0.639	0.365		
	Diagnostic time (years)	-0.099	-0.297	0.098	0.321		
	Pubertal stage	0.072	0.647	0.791	0.842		
	% fat bioimpedance	0.090	0.008	0.172	0.031*		
HbA1c (%)	(Constant)	18.297	10.234	26.360	0.000	0.150	0.084
	Gender	-0.690	-1.878	0.498	0.251		
	Diagnostic time (years)	-0.107	-0.303	0.088	0.278		
	Pubertal stage	0.068	0.641	0.778	0.849		
	Lean mass (%) bioimpedance	-0.108	-0.192	-0.024	0.013*		
ApoB	(Constant)	124.2	86.23	162.2	0.000	0.030	0.13

		41	3	50		**	0
			-				
	Gender	-1.783	11.20	7.636	0.707		
			1				
	Diagnostic time (years)	-0.394	-	1.188	0.621		
			1.976				
	Pubertal stage	7.926	0.578	15.27	0.035		
				4			
	Arm muscle area (cm2)	-2.855	-	-0.913	0.004*		
			4.796				
	(Constant)	0.839	0.583	1.095	0.000		
	Gender	-0.047	-	0.016	0.141		
			0.111				
ApoB/	Diagnostic time (years)	-0.004	-	0.007	0.495	0.088	0.10
ApoA			0.014				0
	Pubertal stage	0.047	-	0.096	0.065		
			0.003				
	Arm muscle area (cm2)	-0.016	-	-0.003	0.017*		
			0.029				

Note: regression coefficient (B); 95% confidence interval (95% CI); lower limit (LI); upper limit (LS); Gender (1=male; 2=female); Pubertal stage (1= pre-pubertal; 2= pubertal; 3= post-pubertal); * indicates significant effect of the independent variable; ** indicates significant model effect; coefficient of determination of the percentage of variation explained by the model (R2).

4. Discussion

Considering the BMI Z-score, it was observed that most of the sample had a eutrophic nutritional status, but 22.2% were overweight and 2.5% obese. The sample also showed an inadequate glycemic control profile, as 54.3% had HbA1c greater than 8%. As for the cardiovascular risk profile analyzed by Apolipoproteins, it was found that the largest proportion of the sample was at low risk, although 19.8% had undesirable ApoB values.

Although a large part of the sample showed adequate nutritional status (eutrophic), it was verified that the increase in body fat and the reduction in lean mass have a negative impact on glycemic control, with an increase in HbA1c. The apolipoprotein B profile followed anthropometric changes, and the increase in apo B was significantly associated with the increase in visceral fat analyzed by the conicity index. However, the reduction in arm muscle area showed a negative impact both on ApoB and on the ApoB/ApoA index.

Similar to our results, another Brazilian study with 120 DM1 children with a mean age of 11.47 also showed high mean values for HbA1c (8.13%). In this study, more than 30% of the studied population was overweight [36]. Mostofizadeh et al. [37] in a study carried out in Iran with 274 individuals under 19 years of age and with DM1, it was shown that the majority had dyslipidemia and an average HbA1c of 8.3%.

A case-control study in Baghdad that aimed to investigate the nutritional status of children and adolescents with DM1 (mean age 10.0 ±3.73 years in DM1 and 8.68±3.1 in controls), showed that Anthropometric measurements in DM1 patients were significantly lower than those in controls (p<0.001). BMI z-score showed a significant negative correlation with HbA1c (r=-0.295, p=0.006, respectively) [38].

The increase in the proportion of body fat (especially visceral fat) and the reduction in lean mass are negatively related to glycemic and lipid metabolism, leading to worse glycemic control and the

need for insulin dose increments in DM1 patients [10-12]. Changes in insulin sensitivity are due to the change in the secretory pattern of adipose tissue from lean to obese, where M2 macrophages can be replaced by M1, resulting in increased gene expression and release of pro-inflammatory mediators that are released by adipose tissue visceral. Among these adipokines, we can mention Interleukin (IL) 6, Tumor Necrosis Factor- α (TNF- α), resistin, free fatty acids (FFA) and reduction of adiponectin and IL-10 levels, which have an anti-inflammatory character [13-16].

Muscle tissue, in addition to playing important roles as a reservoir and consumer of energy and a leading role in carbohydrate metabolism, has been associated with substantial secretory functions. These secretion products, such as myokines, are peptides, cytokines, or growth factors that have a variety of autocrine, paracrine, or endocrine actions. Among the numerous functions of these substances, one can mention the improvement in glycemic control by reducing insulin resistance, improving protein and lipid metabolism. Several myokines have positive effects on glucose uptake and improvement of blood glucose. On the other hand, the pro-inflammatory scenario, also a result of the reduction in the release of these myokines, associated with poor glycemic control, lead to an increased risk of developing metabolic syndrome and cardiovascular complications [23,39-41].

Poor glycemic control, characterized by high concentrations of HbA1c, is one of the main clinical factors related to lipid alterations and consequent increased risk of micro and macrovascular complications. A case-control study designed to investigate risk factors for young individuals (10–22 years old) with DM1 showed a negative influence on their lipid profile due to poor glycemic control, formed in LDL-cholesterol (LDL-c) particles pro -atherogenic smaller and denser. In addition, this study also showed that DM1 patients also had significantly increased Apo B levels compared to non-diabetics, regardless of glycemic control [42].

Maahs et al [43] studied children with DM1 (age at onset 10.6 ± 4.1 years and duration of DM1 around 10 months) to investigate changes in HbA1C levels over a 2-year follow-up interval and observed that changes in HbA1C over time were significantly linked to total cholesterol, LDL-c, HDL-c and triglyceride levels, showing that improvement in glucose control was associated with a better lipid profile, but it was not sufficient to normalize lipid levels in young dyslipidemic type 1 diabetes.

The combination of the presence of dyslipidemia and DM1 accelerates atherogenesis and young people and adults with this condition form a high-risk group in terms of cardiovascular disease. In T1DM children with adequate glycemic control, there are often no marked lipid abnormalities, but poor control increasingly deteriorates lipid values and their association with additional risk factors such as obesity, sedentary lifestyle, hypertension, smoking, or family history of heart disease may lead to premature development of atherosclerosis during adolescence [44].

Basu et al. [45] evaluated the relationship of the apolipoprotein profile and the occurrence of any cardiovascular event or major atherosclerotic cardiovascular events such as fatal or non-fatal myocardial infarction or stroke. During 15 years of follow-up there were 50 events defined as any CVD event that showed significant positive correlation with ApoB and other Apo.

In a prospective study, cardiovascular risk factors were evaluated in 175 children with T1DM who were compared with 150 non-diabetic children as controls. The results showed increased levels of pro-inflammatory biomarkers such as TNF- α , IL-4 and high-sensitivity C-reactive protein in patients with DM1. In addition, the presence of greater intima-media thickness of the artery and other cardiovascular risk factors were correlated with the time of diagnosis, increased BMI, levels of Apo A, ApoB, total cholesterol and triglycerides. The authors concluded that the parameters mentioned above may be related to the early impairment of the structure and function of the common carotid and aortic arteries in young patients with DM1 [46]. The increase in pro-inflammatory cytokines and Apo B observed in this study may be related to the secretory pattern of visceral adipose tissue and the reduction in lean mass that can normally be observed in T1DM patients.

The increased vascular risk may, at least in part, be associated with the characteristic of LDL-c particles that are shown to be more susceptible to oxidation and more atherogenic than their larger counterparts; in addition, an increase in the proportion of small particles, representing profile B of the LDL-c pattern, seems to confer atherogenicity. This can be attributed to elevated TG

concentration, which results in increased VLDL production and impaired ability to clear these particles. [37].

Due to the above, we can highlight the importance of monitoring blood glucose, plasma lipids, apolipoprotein levels and body composition in DM1 patients in order to minimize future complications that are common in these patients, as well as to evaluate the impact of therapeutic interventions. Although the presented results demonstrate a low to moderate degree of relationship for the correlation coefficient, the results are relevant for clinical practice from the point of view of cardiovascular prevention.

5. Conclusions

Our results indicate that increased body fat and reduced lean body mass are related to poor glycemic control represented by HBA1c levels. On the other hand, alterations in Apo B and in the Apo B/Apo A index were associated with alterations in the muscle tissue of the upper limbs. Although the observed relationships are low to moderate, the results suggest that a more detailed monitoring of body composition is necessary to minimize future complications in DM1 patients.

Author Contributions: Conceptualization, T.M., E.F.B.C., J.F.S.H., and S.M.B.; methodology, E.F.B.C., B.O.Z., L.F.L., and S.M.B.; software, E.F.B.C., K.Q., and S.M.B.; validation, T.L.M.Z., L.F.P., and S.M.B.; formal analysis, A.C.A., E.L.G., and S.M.B.; investigation, T.M., E.F.B.C., J.F.S.H., B.O.Z., L.F.L., C.R.P.D., M.G.R., and S.M.B.; resources, E.F.B.C., J.F.S.H., and S.M.B.; data curation, S.M.B.; writing—original draft preparation, T.M. and S.M.B.; writing—review and editing, P.C.S.B. and S.M.B.; visualization, T.M., E.F.B.C., J.F.S.H., and S.M.B.; supervision, T.M., E.F.B.C., J.F.S.H., and S.M.B.; project administration, S.M.B.; funding acquisition, L.F.L. and S.M.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board (or Ethics Committee) of Universidade de Marília (protocol code 3,606,397/2019 07/2019).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study. Written informed consent has been obtained from the patient(s) to publish this paper.

Data Availability Statement: No applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Eizirik, D.L.; Pasquali, L.; Cnop, M. Pancreatic β -cells in type 1 and type 2 diabetes mellitus: different pathways to failure. *Nature reviews. Endocrinology* **2020**, *16*, 349–362, doi:10.1038/s41574-020-0355-7.
2. Parise, M.; Di Molletta, S.; Graziano, R.T.; Fiorentino, R.; Cutruzzola, A.; Gnasso, A.; Irace, C. A Head-to-Head Comparison of Two Algorithms for Adjusting Mealtime Insulin Doses Based on CGM Trend Arrows in Adult Patients with Type 1 Diabetes: Results from an Exploratory Study. *International journal of environmental research and public health* **2023**, *20*, doi:10.3390/ijerph20053945.
3. Ferraz, R.S.; Silva, C.S.; Cavalcante, G.C.; de Queiroz, N.N.M.; Felício, K.M.; Felício, J.S.; Ribeiro-Dos-Santos, Â. Variants in the VDR Gene May Influence 25(OH)D Levels in Type 1 Diabetes Mellitus in a Brazilian Population. *Nutrients* **2022**, *14*, doi:10.3390/nu14051010.
4. Frielitz, F.S.; Eisemann, N.; Werner, K.; Hiort, O.; Katalinic, A.; Lange, K.; von Sengbusch, S. Direct Costs of Healthcare for Children with Type 1 Diabetes Using a CGM System: A Health Economic Analysis of the VIDIKI Telemedicine Study in a German Setting. *Experimental and clinical endocrinology & diabetes : official journal, German Society of Endocrinology [and] German Diabetes Association* **2022**, *130*, 614–620, doi:10.1055/a-1708-3134.
5. Souza, M.M.C.; Alves, T.C.H.S.J.R., Society; Development. Caracterização da vivência familiar de crianças e adolescentes portadores de Diabetes mellitus tipo 1: uma revisão narrativa. **2022**, *11*, e6011225313-e6011225313.
6. Cano-Cano, F.; Gómez-Jaramillo, L.; Ramos-García, P.; Arroba, A.I.; Aguilar-Diosdado, M. IL-1 β Implications in Type 1 Diabetes Mellitus Progression: Systematic Review and Meta-Analysis. *Journal of clinical medicine* **2022**, *11*, doi:10.3390/jcm11051303.

7. Elbarbary, N.S.; Ismail, E.A.R.; Ghallab, M.A. Effect of metformin as an add-on therapy on neuregulin-4 levels and vascular-related complications in adolescents with type 1 diabetes: A randomized controlled trial. *Diabetes research and clinical practice* **2022**, *186*, 109857, doi:10.1016/j.diabres.2022.109857.
8. Guo, L.; Li, Y.; Zhang, M.; Xiao, X.; Kuang, H.; Yang, T.; Jia, X.; Zhang, X. Efficacy of unblinded and blinded intermittently scanned continuous glucose monitoring for glycemic control in adults with type 1 diabetes. *Frontiers in endocrinology* **2023**, *14*, 1110845, doi:10.3389/fendo.2023.1110845.
9. Koliaki, C.; Katsilambros, N. Repositioning the Role of Tumor Necrosis Factor-Related Apoptosis-Inducing Ligand (TRAIL) on the TRAIL to the Development of Diabetes Mellitus: An Update of Experimental and Clinical Evidence. *International journal of molecular sciences* **2022**, *23*, doi:10.3390/ijms23063225.
10. Levran, N.; Levek, N.; Sher, B.; Gruber, N.; Afek, A.; Monsonogo-Ornan, E.; Pinhas-Hamiel, O. The Impact of a Low-Carbohydrate Diet on Micronutrient Intake and Status in Adolescents with Type 1 Diabetes. *Nutrients* **2023**, *15*, doi:10.3390/nu15061418.
11. Lucier, J.; Weinstock, R.S. Diabetes Mellitus Type 1. In *StatPearls*; StatPearls Publishing
12. Copyright © 2023, StatPearls Publishing LLC.: Treasure Island (FL), 2023.
13. Igudesman, D.; Crandell, J.L.; Corbin, K.D.; Hooper, J.; Thomas, J.M.; Bulik, C.M.; Pence, B.W.; Pratley, R.E.; Kosorok, M.R.; Maahs, D.M.; et al. Associations of Dietary Intake with the Intestinal Microbiota and Short-Chain Fatty Acids Among Young Adults with Type 1 Diabetes and Overweight or Obesity. *The Journal of nutrition* **2022**, doi:10.1016/j.tjnut.2022.12.017.
14. Esdaile, H.; Hill, N.; Mayet, J.; Oliver, N. Glycaemic control in people with diabetes following acute myocardial infarction. *Diabetes research and clinical practice* **2023**, *199*, 110644, doi:10.1016/j.diabres.2023.110644.
15. dos Santos Haber, J.F.; Barbalho, S.M.; Sgarbi, J.A.; de Argollo Haber, R.S.; de Labio, R.W.; Laurindo, L.F.; Chagas, E.F.B.; Payão, S.L.M.J.B. The Relationship between Type 1 Diabetes Mellitus, TNF- α , and IL-10 Gene Expression. **2023**, *11*, 1120.
16. Parente, E.B.; Ahola, A.J.; Kumar, A.; Lehto, M.; Groop, P.H. The relationship between FGF23 and body composition according to albuminuria stage in type 1 diabetes. *Diabetes research and clinical practice* **2023**, *198*, 110620, doi:10.1016/j.diabres.2023.110620.
17. Dos Santos Haber, J.F.; Chagas, E.F.B.; Barbalho, S.M.; Sgarbi, J.A.; Haber, R.S.A.; de Labio, R.W.; Payão, S.L.M. Level of physical activity and gene expression of IL-10 and TNF- α in children and adolescents with Type 1 diabetes. *Journal of diabetes and its complications* **2022**, *36*, 108104, doi:10.1016/j.jdiacomp.2021.108104.
18. Hinault, C.; Caroli-Bosc, P.; Bost, F.; Chevalier, N. Critical Overview on Endocrine Disruptors in Diabetes Mellitus. *International journal of molecular sciences* **2023**, *24*, doi:10.3390/ijms24054537.
19. Kahkoska, A.R.; Sarteau, A.C.; Igudesman, D.; Reboussin, B.A.; Dabelea, D.; Dolan, L.M.; Jensen, E.; Wadwa, R.P.; Pihoker, C.; Mayer-Davis, E.J. Association of Insulin Regimen and Estimated Body Fat Over Time among Youths and Young Adults with Type 1 Diabetes: The SEARCH for Diabetes in Youth Study. *Journal of diabetes research* **2022**, *2022*, 1054042, doi:10.1155/2022/1054042.
20. Gomez-Peralta, F.; Choudhary, P.; Cosson, E.; Irace, C.; Rami-Merhar, B.; Seibold, A. Understanding the clinical implications of differences between glucose management indicator and glycated haemoglobin. *Diabetes, obesity & metabolism* **2022**, *24*, 599-608, doi:10.1111/dom.14638.
21. López-Prieto, R.S.; Reza-Albarrán, A.A.; Clark, P.; Gómez Díaz, R.A.; Aguilera-Ruvalcaba, M.S.; Güereca-Olguín, D.C.; Jalife-Velázquez, G.Q.; Soto-Mota, A.; Viveros-Ruiz, T.L.; Juárez-Martínez, L.; et al. ALBUMINURIA, DISEASE DURATION AND GLYCATED HEMOGLOBIN ARE RELATED WITH BONE MINERAL DENSITY IN TYPE 1 DIABETES: A CROSS-SECTIONAL STUDY. *Endocrine practice : official journal of the American College of Endocrinology and the American Association of Clinical Endocrinologists* **2023**, doi:10.1016/j.eprac.2023.02.005.
22. Quigley, M.; Earnest, A.; Szwarcbard, N.; Wischer, N.; Andrikopoulos, S.; Green, S.; Zoungas, S. Exploring HbA1c variation between Australian diabetes centres: The impact of centre-level and patient-level factors. *PloS one* **2022**, *17*, e0263511, doi:10.1371/journal.pone.0263511.
23. Safi, M.; Borup, A.; Stevns Hansen, C.; Rossing, P.; Thorsten Jensen, M.; Christoffersen, C. Association between plasma apolipoprotein M and cardiac autonomic neuropathy in type 1 diabetes. *Diabetes research and clinical practice* **2022**, *189*, 109943, doi:10.1016/j.diabres.2022.109943.
24. Inácio, I.; Azevedo, T.; Martins, J.L.; Balsa, A.M.M.; Dantas, R.; Alves, M.; Albuquerque, I.; Guimarães, J. Cardiovascular Risk Prediction by the American Diabetes Association Risk-Assessment Tool and Novel and Traditional Cardiovascular Risk Factors in Young Adults With Type 1 Diabetes. *Cureus* **2022**, *14*, e22574, doi:10.7759/cureus.22574.
25. Ferré, R.; Aragonès, G.; Plana, N.; Merino, J.; Heras, M.; Buixadera, C.; Masana, L.J.A. High-density lipoprotein cholesterol and apolipoprotein A1 levels strongly influence the reactivity of small peripheral arteries. **2011**, *216*, 115-119.
26. Dong, H.; Ni, W.; Bai, Y.; Yuan, X.; Zhang, Y.; Zhang, H.; Sun, Y.; Xu, J. Cross-sectional and longitudinal associations of apolipoprotein A1 and B with glycosylated hemoglobin in Chinese adults. *Scientific reports* **2022**, *12*, 2751, doi:10.1038/s41598-022-06829-w.

27. Guan, Y.; Zuo, F.; Zhao, J.; Nian, X.; Shi, L.; Xu, Y.; Huang, J.; Kazumi, T.; Wu, B. Relationships of adiponectin to regional adiposity, insulin sensitivity, serum lipids, and inflammatory markers in sedentary and endurance-trained Japanese young women. *Frontiers in endocrinology* **2023**, *14*, 1097034, doi:10.3389/fendo.2023.1097034.
28. Webb, R.J.; Mazidi, M.; Lip, G.Y.H.; Kengne, A.P.; Banach, M.; Davies, I.G. The role of adiposity, diet and inflammation on the discordance between LDL-C and apolipoprotein B. *Nutrition, metabolism, and cardiovascular diseases : NMCD* **2022**, *32*, 605-615, doi:10.1016/j.numecd.2021.12.004.
29. Walldius, G.; Jungner, I.J.J.o.i.m. Apolipoprotein B and apolipoprotein A-I: risk indicators of coronary heart disease and targets for lipid-modifying therapy. **2004**, *255*, 188-205.
30. Lima, L.M.; Carvalho, M.d.G.; Sousa, M.O.J.A.B.d.C. Índice apo B/apo AI e predição de risco cardiovascular. **2007**, *88*, e187-e190.
31. Calcaterra, V.; Biganzoli, G.; Ferraro, S.; Verduci, E.; Rossi, V.; Vizzuso, S.; Bosetti, A.; Borsani, B.; Biganzoli, E.; Zuccotti, G. A Multivariate Analysis of "Metabolic Phenotype" Patterns in Children and Adolescents with Obesity for the Early Stratification of Patients at Risk of Metabolic Syndrome. *Journal of clinical medicine* **2022**, *11*, doi:10.3390/jcm11071856.
32. Houtkooper, L.B.; Lohman, T.G.; Going, S.B.; Howell, W.H. Why bioelectrical impedance analysis should be used for estimating adiposity. *The American journal of clinical nutrition* **1996**, *64*, 436s-448s, doi:10.1093/ajcn/64.3.436S.
33. Kyle, U.G.; Genton, L.; Karsegard, L.; Slosman, D.O.; Pichard, C. Single prediction equation for bioelectrical impedance analysis in adults aged 20–94 years. *Nutrition (Burbank, Los Angeles County, Calif.)* **2001**, *17*, 248-253, doi:10.1016/s0899-9007(00)00553-0.
34. Frisancho, A.R.; Tracer, D.P. Standards of arm muscle by stature for the assessment of nutritional status of children. *American journal of physical anthropology* **1987**, *73*, 459-465, doi:10.1002/ajpa.1330730408.
35. Heymsfield, S.B.; McManus, C.; Smith, J.; Stevens, V.; Nixon, D.W. Anthropometric measurement of muscle mass: revised equations for calculating bone-free arm muscle area. *The American journal of clinical nutrition* **1982**, *36*, 680-690, doi:10.1093/ajcn/36.4.680.
36. Housh, D.J.; Housh, T.J.; Weir, J.P.; Weir, L.L.; Johnson, G.O.; Stout, J.R. Anthropometric estimation of thigh muscle cross-sectional area. *Medicine and science in sports and exercise* **1995**, *27*, 784-791.
37. Silverio, R.N.C.; de Aquino Lacerda, E.M.; Fortins, R.F.; de Lima, G.C.F.; Scancetti, L.B.; do Carmo, C.N.; da Cunha, L.V.S.; Luescher, J.L.; de Carvalho Padilha, P. Predictive factors of non-HDL cholesterol in children and adolescents with type 1 diabetes mellitus: A cross-sectional study. *Diabetes research and clinical practice* **2019**, *154*, 9-16, doi:10.1016/j.diabres.2019.06.005.
38. Mostofizadeh, N.; Hashemipour, M.; Roostazadeh, M.; Hashemi-Dehkordi, E.; Shahsanai, A.; Reisi, M. The impact of poor glycemic control on lipid profile variables in children with type 1 diabetes mellitus. *Journal of education and health promotion* **2019**, *8*, 6, doi:10.4103/jehp.jehp_194_17.
39. Hussein, S.A.; Ibrahim, B.A.; Abdullah, W.H. Nutritional status of children and adolescents with Type 1 Diabetes Mellitus in Baghdad: a case-control study. *Journal of medicine and life* **2023**, *16*, 254-260, doi:10.25122/jml-2022-0233.
40. Minniti, G.; Pescinini-Salzedas, L.M.; Minniti, G.; Laurindo, L.F.; Barbalho, S.M.; Vargas Sinatora, R.; Sloan, L.A.; Haber, R.S.A.; Araújo, A.C.; Quesada, K.; et al. Organokines, Sarcopenia, and Metabolic Repercussions: The Vicious Cycle and the Interplay with Exercise. *International journal of molecular sciences* **2022**, *23*, doi:10.3390/ijms232113452.
41. de Oliveira dos Santos, A.R.; de Oliveira Zanuso, B.; Miola, V.F.B.; Barbalho, S.M.; Santos Bueno, P.C.; Flato, U.A.P.; Detregiachi, C.R.P.; Buchaim, D.V.; Buchaim, R.L.; Tofano, R.J.J.I.J.o.M.S. Adipokines, myokines, and hepatokines: crosstalk and metabolic repercussions. **2021**, *22*, 2639.
42. Barbalho, S.M.; Laurindo, L.F.; Tofano, R.J.; Flato, U.A.P.; Mendes, C.G.; de Alvares Goulart, R.; Briguezi, A.M.G.M.; Bechara, M.D.J.E. Dysmetabolic Iron Overload Syndrome: Going beyond the Traditional Risk Factors Associated with Metabolic Syndrome. **2023**, *4*, 18-37.
43. Guy, J.; Ogden, L.; Wadwa, R.P.; Hamman, R.F.; Mayer-Davis, E.J.; Liese, A.D.; D'Agostino, R., Jr.; Marcovina, S.; Dabelea, D. Lipid and lipoprotein profiles in youth with and without type 1 diabetes: the SEARCH for Diabetes in Youth case-control study. *Diabetes care* **2009**, *32*, 416-420, doi:10.2337/dc08-1775.
44. Maahs, D.M.; Dabelea, D.; D'Agostino Jr, R.B.; Andrews, J.S.; Shah, A.S.; Crimmins, N.; Mayer-Davis, E.J.; Marcovina, S.; Imperatore, G.; Wadwa, R.P.J.T.J.o.p. Glucose control predicts 2-year change in lipid profile in youth with type 1 diabetes. **2013**, *162*, 101-107. e101.
45. Vaid, S.; Hanks, L.; Griffin, R.; Ashraf, A.P. Body mass index and glycemic control influence lipoproteins in children with type 1 diabetes. *Journal of clinical lipidology* **2016**, *10*, 1240-1247, doi:10.1016/j.jacl.2016.07.010.
46. Basu, A.; Bebu, I.; Jenkins, A.J.; Stoner, J.A.; Zhang, Y.; Klein, R.L.; Lopes-Virella, M.F.; Garvey, W.T.; Budoff, M.J.; Alaupovic, P.; et al. Serum apolipoproteins and apolipoprotein-defined lipoprotein subclasses: a hypothesis-generating prospective study of cardiovascular events in T1D. *Journal of lipid research* **2019**, *60*, 1432-1439, doi:10.1194/jlr.P090647.

47. Zhang, Y.; Zhang, H.; Li, P. Cardiovascular risk factors in children with type 1 diabetes mellitus. *Journal of pediatric endocrinology & metabolism : JPEM* **2019**, 32, 699-705, doi:10.1515/jpem-2018-0382.

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.