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The endocrine manifestations of adults with spinal muscular atrophy

Matej Rakusa MD, PhD[1,2] | Blaž Koritnik MD, PhD[3,4] | Lea Leonardis MD, PhD[3,4] | Katja Goricar MD, PhD[5] | Tjasa Rudolf MD[2] | Dejan Firbas MD[2] | Žiga Snoj MD, PhD[6] | Mojca Jensterle MD, PhD[1,2]

[1]Department of Endocrinology, Diabetes and Metabolic Disease, University Medical Centre Ljubljana, Ljubljana, Slovenia

[2]Department of Internal Medicine, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[3]Institute of Clinical Neurophysiology, University Medical Centre Ljubljana, Ljubljana, Slovenia

[4]Department of Neurology, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[5]Pharmacogenetics Laboratory, Institute of Biochemistry, Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia

[6]Radiology Institute, University Medical Centre Ljubljana, Ljubljana, Slovenia

Correspondence
Mojca Jensterle, Department of Endocrinology, Diabetes and Metabolic Disease, University Medical Centre Ljubljana, Zaloska cesta 7, 1000 Ljubljana, Slovenija.
Email: mojcajensterle@yahoo.com

Abstract

Introduction/Aims: Changes in body composition in patients with spinal muscular atrophy (SMA) can cause endocrine abnormalities that are insufficiently studied in adults. We aimed to assess the endocrine profile in a cohort of adults with SMA. Second, we compared body composition and endocrine profiles between nonambulatory and ambulatory patients and between different types of SMA.

Methods: The cross-sectional study included 29 SMA patients (18 [62.1%] males and 11 [37.9%] females) of median age 44 (IQR 30–51.5) years with type 2, 3, or 4. Body composition was measured by bioimpedance. Morning blood samples were drawn for glycated hemoglobin (HbA1c), lipid profile, testosterone, cortisol, and insulin-like growth factor-1 (IGF-1). Blood glucose, insulin, and beta-hydroxybutyrate (BHB) were measured during a 75 g oral glucose tolerance test. The homeostatic model assessment for insulin resistance index was calculated.

Results: In total, 75.9% of patients had increased fat mass (FM), with 51.7% having an increase despite normal body mass index. Ambulation was the most important discriminating factor of body composition. 93.1% of patients had metabolic abnormalities, including hyperglycemia, insulin resistance, and dyslipidemia. Increased BHB, a marker of ketosis, was present in more than a third of patients. Functional

Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BHB, beta-hydroxybutyrate; BIA, bioelectrical impedance analysis; BMI, body mass index; CGM, continuous glucose monitoring; DM, diabetes mellitus; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; GH, growth hormone; HDL, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment for insulin resistance; OGTT, oral glucose tolerance test; IGF-1, insulin-like growth factor-1; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IR, insulin resistance; LDL, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); RHS, Revised Hammersmith Scale; RULM, revised upper limb module; SDS, SD score; SMA, spinal muscular atrophy; T, testosterone; TC, total cholesterol; TG, triglycerides.

hypogonadism was present in half of male patients. Testosterone and IGF-1 negatively correlated with FM.

Discussion: Adult patients with SMA had abnormal body composition and highly prevalent metabolic disturbances that might increase cardiometabolic risk. Because treatments have modified the course of SMA, it is important to investigate whether these observations translate into clinically relevant outcomes.

KEYWORDS
beta-hydroxybutyrate, body composition, glucose metabolism, hypogonadism, lipid profile

1 | INTRODUCTION

Changes in body composition in patients with spinal muscular atrophy (SMA) can cause a wide range of endocrine abnormalities. Fasting hyperglycemia, glucose intolerance, hyperglucagonemia, and abnormal fatty acid metabolism with dyslipidemia were confirmed in animal models of SMA.[1,2] In clinical settings, most studies on endocrinological abnormalities have been conducted in pediatric or mixed pediatric–adult populations with SMA. Studies in the pediatric population showed a high prevalence of hyperglycemia and dyslipidemia and an increased risk of hypoglycemia.[2–4] Disturbances in glucose and fatty acid metabolism led to ketoacidosis with an elevated anion gap.[5] Other reported endocrine abnormalities were insulin resistance (IR), early puberty, and hypogonadism due to cryptorchism.[3,4,6] IR had a bimodal distribution and was increased in obese as well as in severely underweight patients.[7] The associations between IR, testosterone, and cortisol confirmed in the general population[8] have not yet been explored in the SMA population. The current approach to care, with new therapeutic options for SMA patients, increasingly focuses on assessing multiorgan system involvement to further improve quality of life and extend life expectancy. Data on the broader spectrum of endocrinologic disturbances in an adult population of SMA patients are largely insufficient. Comparisons of the endocrinologic profiles of ambulatory versus nonambulatory adults with SMA are lacking. The primary aim of our study was to comprehensively evaluate the endocrine profile of adults with SMA. Secondarily, we aimed to compare body composition and endocrine profiles between nonambulatory and ambulatory patients and among different types of SMA.

2 | METHODS

2.1 | Population

We conducted a cross-sectional study on SMA patients who were referred from the National Referral Centre for SMA patients at the Institute of Clinical Neurophysiology, University Medical Centre Ljubljana, to the Endocrinology Outpatient Clinics in 2022 for endocrinological and metabolic screening. All adult patients with SMA who met inclusion and exclusion criteria were referred and invited to participate in a study at the Endocrinology Outpatient Clinics for endocrinological and metabolic screening. Inclusion criteria were a genetically confirmed diagnosis of SMA, age >18 years, and the capability to understand the aims and goals of the research. Exclusion criteria were an implanted pacemaker, inflammatory bowel disease, past treatment with glucocorticoids, valproate, or antiresorptive medication.

We recorded the type of SMA, anthropometric data, data on symptoms of hypoglycemia, testicular retention in childhood (in male patients), and medical therapies. We acquired anthropometric measurement data and assessed functional capability. Body composition was measured by bioelectrical impedance analysis (BIA). We assessed glucose metabolism, ketosis, insulin secretion and resistance, lipid metabolism, hypogonadism (in male patients), insulin-like growth factor-1 (IGF-1), and cortisol levels with laboratory evaluations. The study was approved by the Slovenian National Medical Ethics Committee (approval number 0120-292/2022/3) in accordance with the Helsinki Declaration. All study participants provided informed consent.

2.2 | Anthropometric measurements and functional capability

Standing height was measured using a wall-mounted stadiometer. If patients had contractures or were unable to stand, a segmental length in the recumbent position was measured. Using a non-stretchable measuring tape, the following segments were measured: from the top of the head to the right greater trochanter of the hip, the hip to the right femoral epicondyle of the knee, and from the knee to the distal point of the calcaneus. Body mass index (BMI) was calculated as the weight in kilograms divided by the height in meters squared. We recorded each patient's ambulatory status. Functional capability was measured with the Revised Hammersmith Scale (RHS)[9] and revised upper limb module (RULM).[10]

2.3 | Bioelectrical impedance analysis

Body composition was measured using a Quadscan 4000 TS bioimpedance analyzer (Bodystat Ltd., Douglas, Isle of Man, UK). Measurements were performed in the morning before 10 a.m., after 8 h of

fasting, with an empty bladder. Increased fat mass (FM) was defined as FM (%) >35% in females and >25% in males. Fat mass index (FMI) and fat-free mass index (FFMI) were compared with the median and 90th percentiles of the general population.[11]

2.4 | Assessment of glucose metabolism

We assessed glucose and beta-hydroxybutyrate (BHB) at 0- and 120-min post-75 g of glucose (oral glucose tolerance test [OGTT]), HbA1c, C-peptide, and calculated homeostatic model assessment for IR index (HOMA-IR). Glucose was measured using the standard oxidase method (Beckman Coulter Glucose Analyzer, Beckman Coulter Inc., CA, USA). Impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes mellitus (DM) were defined according to American Diabetes Association guidelines.[12] BHB was measured using the enzymatic kinetic method with reagent D-3-Hydroxybutyrate RANBUT (Alinity C, Abbott, USA). HbA1c was measured with capillary electrophoresis (Capillarys 2 FLEX-PIERCING, Sebia, Lisses, France). Serum fasting insulin was measured by the two-site sandwich chemiluminescent immunoassay, and the Atellica IM Insulin (IRI) kit (Atellica IM 1600 analyzer, Minaris Medical Co for Siemens Healthcare Diagnostics, USA). HOMA-IR was calculated as HOMA-IR = [insulin (mU/L) × glucose (mmol/L)] / 22.5. HOMA-IR 1.0 (0.5–1.4) was defined as the healthy range IR, >1.9 as early IR, and >2.9 significantly increased IR. C-peptide was measured by two-site sandwich, chemiluminescent immunoassay using the Atellica IM C-peptide (CpS) kit and Atellica IM 1600 analyzer (Minaris Medical Co for Siemens Healthcare Diagnostics, USA).

2.5 | Assessment of lipid abnormalities

Total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), lipoprotein (a) (Lp(a)), apolipoprotein B (ApoB), and apolipoprotein A1 (ApoA1) were measured in the fasting state. TC and TG were measured with the enzyme method, LDL, and HDL with method elimination/catalysis (ADVIA® Chemistry systems, Siemens Healthcare, Erlangen, Germany). Lp(a), ApoB, and ApoA1 were measured with the nephelometry immune method (Nephelometer Analyzer Atellica Neph 630, Siemens Healthcare, Erlangen, Germany).

2.6 | Assessment of hypogonadism in men

Testosterone (T) was measured using the radioimmunoassay method (Dia-Sorin S. p. A., Sallugia, Italy in Diagnostic Products Corporation, LA). Serum LH and FSH were measured by two-site sandwich, chemiluminescent immunoassay using the Atellica IM Luteinizing Hormone (LH) kit, Atellica IM Follicle Stimulating Hormone (FSH) kit and Atellica IM 1600 analyzer (Minaris Medical Co for Siemens Healthcare Diagnostics, USA). Hypogonadism was defined according to Endocrine Society Guidelines.[13]

2.7 | Assessment of IGF-1 and cortisol

IGF-1 was measured by chemiluminescence using an SYS analyzer (IDS-iSYS Insulin-like Growth Factor-I Immunodiagnostic Systems Limited, Boldon, UK). Serum cortisol was determined by the commercially available solid-phase, competitive chemiluminescent enzyme immunoassay, using the Immulite2000 Cortisol kit and Immulite2000 XPI analyzer (Siemens Healthcare Diagnostics Products Ltd., UK).

2.8 | Statistics

Continuous variables were described using median and interquartile or 5%–95% range. Categorical variables were described using frequencies. As several variables were not normally distributed, nonparametric tests were used for statistical analyses. The Mann–Whitney test was used to compare the distribution of continuous variables between different groups. Spearman's rho was used to evaluate correlations between continuous variables. The *p*-values below .05 were considered statistically significant. Statistical analysis was performed using SPSS Statistics, version 27.0 (IBM, Armonk, NY, USA).

3 | RESULTS

Of 61 patients who were referred for endocrine evaluation, 29 responded. The study cohort constituted 18 males, 13 SMA type 2 (SMA2, 6 males), 14 SMA type 3 (SMA3, 10 males), and 2 SMA type 4 (SMA4, 2 males). At the time of endocrine assessment, 16 patients were being treated with nusinersen, 6 patients had previously been treated with nusinersen and changed to risdiplam, 5 patients were being treated with risdiplam, and 2 patients had declined disease-modifying treatment for SMA. Duration of treatment for nusinersen group was 790 days (IQR 719–917), for the group treated with risdiplam 45 days (IQR 30–57), and for the group switched from nusinersen 718 days (IQR 590–782) to risdiplam 110 days (IQR 105–125).

For analytical purposes, we pooled the data for SMA3 and SMA4. SMA2 and nonambulatory patients had lower FFM parameters, higher FM (%), more disrupted glucose metabolism, and higher BHB than SMA3 + 4 and ambulatory patients. In addition, the nonambulatory group had increased FMI, lower IGF-1 levels, and IGF-1 SD score (SDS) compared with the ambulatory group. The comparison of demographic, anthropometric, and functional characteristics between SMA 2 versus combined group SMA3 and SMA4 are presented in Table 1, and the comparison of metabolic and endocrine parameters between these two groups in Table 2. The comparison of demographic,

TABLE 1 Comparison of demographic, anthropometric and functional parameters between SMA2 and combined group SMA3 and SMA4.

	Total	SMA2 ($N = 13$)	SMA3 + 4 ($N = 16$)	p
Age (years)	44 (32.0–51.0)	34 (24.5–48.5)	46 (40–54)	.110
BMI (kg/m^2)	24.6 (22.0–28.4)	22.9 (16.5–27.5)	25.7 (22.6–29.2)	.199
FMI (kg/m^2)	8.4 (6.2–10.7)	9.5 (7.9–11.3)	7.4 (5.8–10.8)	.170
FFMI (kg/m^2)	17.2 (12.7–18.6)	13.4 (10.2–18.2)	18.4 (14.7–19.7)	.040*
FM (kg)	23 (19.5–29.2)	22.7 (17.3–28.9)	23.1 (19.8–31.9)	.682
FM (%)	35.7 (29.7–41.8)	40 (36–47)	30 (23–37)	.007*
FFM (kg)	46.6 (32.8–61.7)	32.8 (26.3–47)	57.4 (41.2–68)	.001*
FFM (%)	64.3 (58.2–70.3)	60 (54–64)	70 (63–77)	.007*
RHS	6 (3–46)	4 (2–4)	41 (7–52)	.006*
RULM—Part 1	3 (3–6)	3 (3–3)	6 (3–6)	.007*
RULM—Total	22 (13–37)	13 (11–17)	35 (20–37)	<.001*
FM/FFM	0.56 (0.42–0.72)	0.67 (0.56–0.87)	0.43 (0.30–0.59)	.007*

Note: *p-Significance <.05.
Abbreviations: BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; RHS, Revised Hammersmith Scale; RULM, revised upper limb module; SMA, spinal muscular atrophy.

TABLE 2 Comparison of metabolic and endocrine parameters between SMA2 and combined group SMA3 and SMA4.

	Total	SMA2 ($N = 13$)	SMA3 + 4 ($N = 16$)	p	Normal range
HbA1c (%)	4.8 (4.6–5.1)	4.7 (4.4–5.2)	4.9 (4.7–5.2)	.144	<6.5
C-peptide (nmol/L)	0.62 (0.38–0.75)	0.62 (0.31–0.8)	0.65 (0.39–0.8)	.650	0.27–1.27
Glucose 0 min (mmol/L)	5.2 (4.6–5.7)	4.7 (4.3–5.3)	5.5 (4.7–6.2)	.025*	<6.1
Glucose 120 min (mmol/L)	9.2 (6.3–11.7)	10.7 (9.2–13.2)	8.0 (4.7–9.6)	.010*	<7.8
BHB 0 min (µmol/L)	214.5 (78.3–511)	522 (285–1668)	95 (59–230)	<.001*	<400
BHB 120 min (µmol/L)	40.5 (30–55.8)	50 (37–73.8)	33 (28.3–43.3)	.017*	<400
HOMA-IR	2.74 (1.36–3.49)	1.92 (1.3–3.38)	3.04 (1.7–5.5)	.268	<1.9
Insulin (mE/L)	12.1 (7.1–15.2)	9.2 (5.9–15)	12.4 (7.93–19.83)	.503	3–25
IGF-1 (µg/L)	120 (87–163)	118 (68.5–164.5)	122 (88.8–168.8)	.682	Age and sex dependent
IGF-1 SDS	−0.468 (−1.324 to 0.468)	−0.632 (−1.522 to 0.334)	−0.349 (−1.131 to 0.866)	.215	−2.0 to 2.0
Cortisol (nmol/L)	471 (402–611.3)	471 (318.8–701.8)	477 (421.3–591.8)	.767	>140
TC (mmol/L)	5.4 (4.7–5.9)	5.2 (4.3–5.6)	5.5 (4.8–6)	.184	<5
LDL (mmol/L)	3.8 (3.2–4.3)	3.5 (3.1–4.2)	3.9 (3.3–4.6)	.351	<3
HDL (mmol/L)	1.1 (0.9–1.3)	1.1 (1–1.3)	1.1 (0.8–1.3)	.531	Women >1.15 Men >1.0
TG (mmol/L)	1.3 (0.9–2.2)	1.3 (0.8–2.5)	1.3 (0.9–2.6)	.589	<1.7
Lp(a) (mg/L)[a]	557 (154–829)	655 (173–1050)	203 (110.3–807)	.336	<300
ApoAI	1.44 (1.27–1.60)	1.45 (1.34–1.58)	1.38 (1.26–1.66)	.856	Women 1.25–2.15 Men 1.10–2.05
ApoB (g/L)	1.01 (0.89–1.12)	1 (0.79–1.11)	1.01 (0.94–1.16)	.387	Women <1.25 Men <1.4

Note: *p-Significance <.05.
Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BHB, beta-hydroxybutyrate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); SDS, SD score; SMA, spinal muscular atrophy; TC, total cholesterol; TG, triglycerides.
[a]Determined in 14 patients (7 SMA 2, 7 SMA 3) with values above 80 mg/L.

anthropometric, and functional parameters between the ambulatory and nonambulatory groups is presented in Table 3, and the comparison of the metabolic and endocrine parameters between the ambulatory and nonambulatory patients is presented in Table 4.

3.1 | Assessment of body composition

Body composition was assessed in 29 patients. Data on BMI, FM (%), and FFMI are presented in Table 5. Increased FM (%) was present in

	Ambulatory ($N = 10$)	Nonambulatory ($N = 19$)	p
Age (years)	43 (32–52)	45 (30–51)	1.000
BMI (kg/m^2)	25.7 (24.3–28.7)	23.3 (20.2–28.0)	.353
FMI (kg/m^2)	6.5 (5.6–7.8)	9.5 (7.9–10.9)	.040*
FFMI (kg/m^2)	19.0 (16.9–19.9)	14.6 (12.1–18.1)	.011*
FM (kg)	21.0 (17.5–26.2)	24.2 (22.1–29.8)	.377
FM (%)	24.0 (21.9–34.3)	39.7 (34.8–44.5)	.001*
FFM (kg)	62.7 (46.6–70.7)	38.7 (31.1–51.3)	.001*
FFM (%)	76.0 (65.7–78.1)	60.3 (55.6–65.2)	.001*
RHS	50 (44–54)	4 (2–6)	<.001*
RULM—Part 1	6 (6–6)	3 (3–3)	<.001*
RULM—Total	37 (37–37)	15 (12–20)	<.001*

TABLE 3 Comparison of demographic, anthropometric and functional parameters between ambulatory and nonambulatory patients.

Note: *p-significance <.05.
Abbreviations: BMI, body mass index; FFM, fat-free mass; FFMI, fat-free mass index; FM, fat mass; FMI, fat mass index; RHS, Revised Hammersmith Scale; RULM, revised upper limb module.

TABLE 4 Comparison of metabolic and endocrine parameters between ambulatory and nonambulatory patients.

	Ambulatory ($N = 10$)	Nonambulatory ($N = 19$)	p	Normal range
HbA1c (%)	4.8 (4.7–5.6)	4.8 (4.6–5.1)	.286	<6.5
C-peptide (nmol/L)	0.65 (0.43–0.73)	0.62 (0.34–0.80)	.735	0.27–1.27
Glucose 0 min (µmol/L)	5.6 (5.2–6.2)	4.7 (4.4–5.4)	.050*	<6.1
Glucose 120 min (mmol/L)	5.3 (4.6–8.9)	9.8 (9.0–12.8)	.003*	<7.8
BHB 0 min (µmol/L)	89 (58–210)	493 (116–1203)	.007*	<400
BHB 120 min (µmol/L)	30 (28–37)	45 (35–73)	.003*	<400
HOMA-IR	3.04 (1.85–4.21)	1.92 (1.30–3.47)	.308	<1.9
Insulin (mE/L)	12.45 (8.4–16.9)	9.20 (6.35–15.00)	.484	3–25
IGF-1 (µg/L)	155 (122–203)	96 (72–136)	.040*	Age and sex dependent
IGF-1 SDS	0.510 (−0.463–1.028)	−1.002 (−1.416 to −0.328)	.009*	−2.0-2.0
Cortisol (nmol/L)	538 (459–608)	451 (302–631)	.208	>140
TC (mmol/L)	5.3 (4.7–6.0)	5.4 (4.4–5.8)	.804	<5
LDL (mmol/L)	3.9 (3.1–4.3)	3.6 (3.2–4.2)	.875	<3
HDL (mmol/L)	1.0 (0.8–1.3)	1.1 (1.0–1.3)	.211	Women >1.15 Men >1.0
TG (mmol/L)	1.2 (0.9–2.7)	1.3 (0.9–2.2)	.875	<1.7
Lp(a) (mg/L)[a]	80 (80–203)	95 (80–655)	.468	<300
ApoAI (g/L)	1.34 (1.26–1.51)	1.46 (1.40–1.61)	.142	Women 1.25–2.15 Men 1.10–2.05
ApoB (g/L)	1.01 (0.94–1.11)	1.02 (0.85–1.12)	.809	Women <1.25 Men <1.4

Note: *p-Significance <.05.
Abbreviations: ApoA1, apolipoprotein A1; ApoB, apolipoprotein B; BHB, beta-hydroxybutyrate; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein cholesterol; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; IGF-1, insulin-like growth factor-1; LDL, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); SDS, SD score; SMA, spinal muscular atrophy; TC, total cholesterol; TG, triglycerides.
[a]Determined in 14 patients (7 SMA 2, 7 SMA 3) with values above 80 mg/L.

11 (73.3%) patients with BMI <25 kg/m^2, 7 (70.0%) with BMI 25–30 kg/m^2, and all 4 (100.0%) with BMI > 30 kg/m^2. FFM (kg) and FFM (%) were significantly lower in the SMA 2 group compared with the SMA3 + 4 group. Similarly, nonambulatory patients had lower FFM (kg), FFM (%), and FFMI than ambulatory patients. The majority (75.9%) of patients had increased FM (%) above the median to normal healthy reference range measurement, despite half of them having normal weight as assessed by BMI <25 kg/m^2.

TABLE 5 Prevalences of metabolic and endocrine disorders in adult patients with SMA.

Endocrine abnormality	Number of patients (%)
BMI (kg/m^2)	
<25	15 (51.7)
25–30	10 (34.5)
>30	4 (13.8)
Body composition (FM %)	
Normal	7 (24.1)
Increased	22 (75.9)
Body composition (FMI)	
Normal	10 (34.5)
Increased above median	13 (44.8)
Increased above 90th percentile	6 (20.7)
Body composition (FFMI)	
Normal	3 (10.3)
Reduced below median	10 (34.5)
Reduced below 90th percentile	16 (55.2)
Glucose metabolism[a]	
Normal	8 (28.6)
IFG	0 (0)
IGT	9 (32.1)
IFG + IGT	2 (7.2)
DM	9 (32.1)
Insulin resistance	
Normal	13 (44.8)
Early	3 (10.3)
Significant	13 (44.8)
Beta-hydroxybutyrate	
Normal	18 (62.1)
Increased	11 (37.9)
Lipid metabolism	
Increased TC	20 (69.0)
Increased LDL	24 (82.8)
Increased TG	10 (34.5)
Decreased HDL	12 (41.4)
Increased Lp(a)[a]	8 (28.6)
Increased ApoAI[a]	0 (0)
Increased ApoB[a]	3 (10.7)
Increased ApoB/ApoAI[a]	3 (10.7)
Hypogonadism[b]	
Normal gonadal function	9 (50.0)
Primary hypogonadism	2 (11.1)
Functional hypogonadism	7 (38.9)

Abbreviations: ApoAI, apoliprotein AI, ApoB, apolipoprotein B; BMI, body mass index; DM, diabetes mellitus; FFMI, fat free mass index; FM %, fat mass %; FMI, fat mass index; HDL, high density lipoprotein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; LDL, low density lipoprotein; Lp(a), lipoprotein a; SMA, spinal muscular atrophy; TC, total cholesterol; TG, triglycerides.

[a]Test performed in 28 patients.

[b]Evaluation in male patients.

3.2 | Assessment of glucose metabolism

OGTT was done in 28 patients. Prevalence of diabetes, IR, and increased HbA1c is presented in Table 5. Other measurements of glucose metabolism were done in all 29 patients. Prevalence of IR and glucose metabolism impairment are presented in Table 5. We measured higher post-OGTT glucose in SMA2 compared with the SMA3 + 4 group and in the nonambulatory compared with the ambulatory group. Only one patient had HbA1c >6.5%. IGT was present in more than two-thirds of our cohort. Almost half of them had glucose in the range of DM. Only 4 (13.8%) patients (3 SMA2 and 1 SMA3) had c-peptide below the reference range. Patients with HOMA-IR >1.9, compared with HOMA-IR <1.9, differed significantly in FFMI (14.5 kg/m^2 [10.5–18.5] vs. 18.2 kg/m^2 (14.9–19.7), $p = .032$). Fasting glucose, FFM (kg), FFM (%), and FFMI were significantly lower in the SMA 2 group compared to the SMA3 + 4 group as well as in nonambulatory patients compared with ambulatory.

3.3 | Assessment of hyperlipidemia

TC, LDL, TG, and HDL were assessed in 29 patients. ApoA1, ApoB, and Lp(a) were assessed in 28. At least 1 lipid abnormality was present in 26 (89.7%). More than two thirds of our patients had either 2 or 3 lipid abnormalities. When evaluating TC, LDL, TG, and HDL, 3 (10.3%) patients had 1 lipid abnormality, 10 (34.5%) had 2, 10 (34.5%) had 3, and 3 (10.3%) had all 4 lipid abnormalities. The prevalence of increased Lp(a) in our cohort is 28.6%. Only 10.7% of our participants had increased ApoB and ApoB/ApoA1. A summarized prevalence of lipid abnormalities is presented in Table 5.

3.4 | Assessment of hypogonadism in males

Hypogonadism was assessed in all 18 male patients. The prevalence of hypogonadism is present in Table 5. T for the entire cohort was 11.95 nmol/L (IQR 6.55–17.28), in a group of normal T 17.30 nmol/L (IQR 12.80–21.10) nmol/L, and in the hypogonadal group 6.50 nmol/L (IQR 5.10–8.90). There was no history of cryptorchism in childhood.

3.5 | Assessment of cortisol and IGF-1

There was no significant difference between SMA groups or ambulatory and nonambulatory groups in cortisol and IGF-1.

3.6 | Correlations between body composition, metabolic, and endocrine parameters

There were statistically significant, moderate correlations between BHB 0 min and glucose 0 min, FFM (kg), FFM (%), FFMI, between T

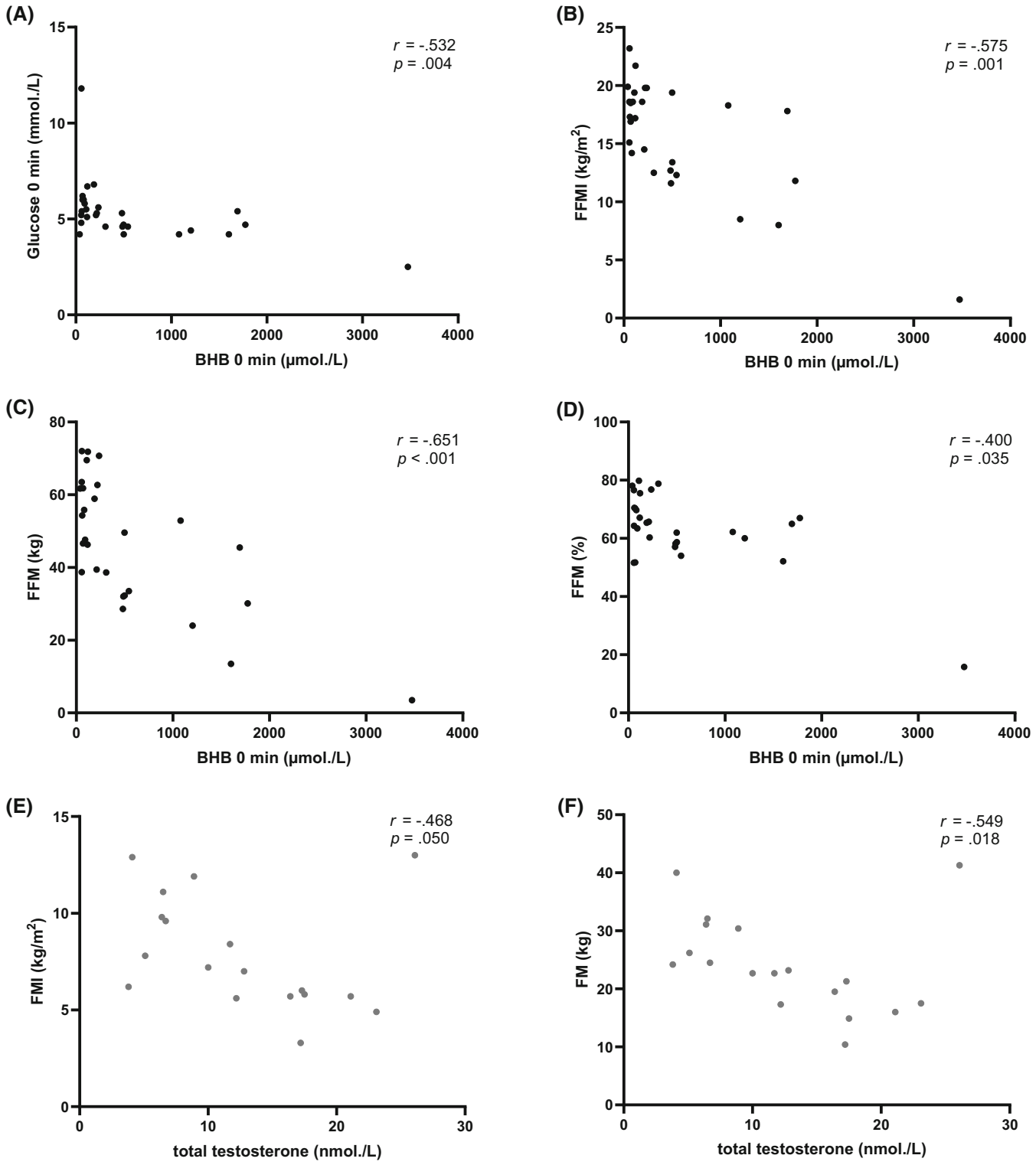

FIGURE 1 Correlation between body composition, metabolic, and endocrine parameters. Correlation between BHB at 0 min and glucose at 0 min (A), FFMI (B), FFM (kg) (C), FFM (%) (D), between T and FMI (E), FM (kg) (F), between FM (%) and IGF-1 (G), IGF-1 SDS (H) and between FMI and IGF-1 (I), IGF-1 SDS (J). BHB, beta-hydroxybutyrate; FFM, fat free mass; FFMI, fat free mass index; FM, fat mass; FMI, fat mass index; IGF-1, insulin like growth factor-1; SDS, SD score; *p*-significance <.05.

and FMI (kg/m^2), FM (kg), between IGF-1 and FM (%), FFMI, and between IGF-1 SDS and FM (%), FFMI. Correlations between body composition and metabolic and endocrine parameters are shown in Figure 1.

4 | DISCUSSION

Our main findings demonstrated that the majority (75.9%) of adult patients with SMA had increased FM (%) above the median to normal

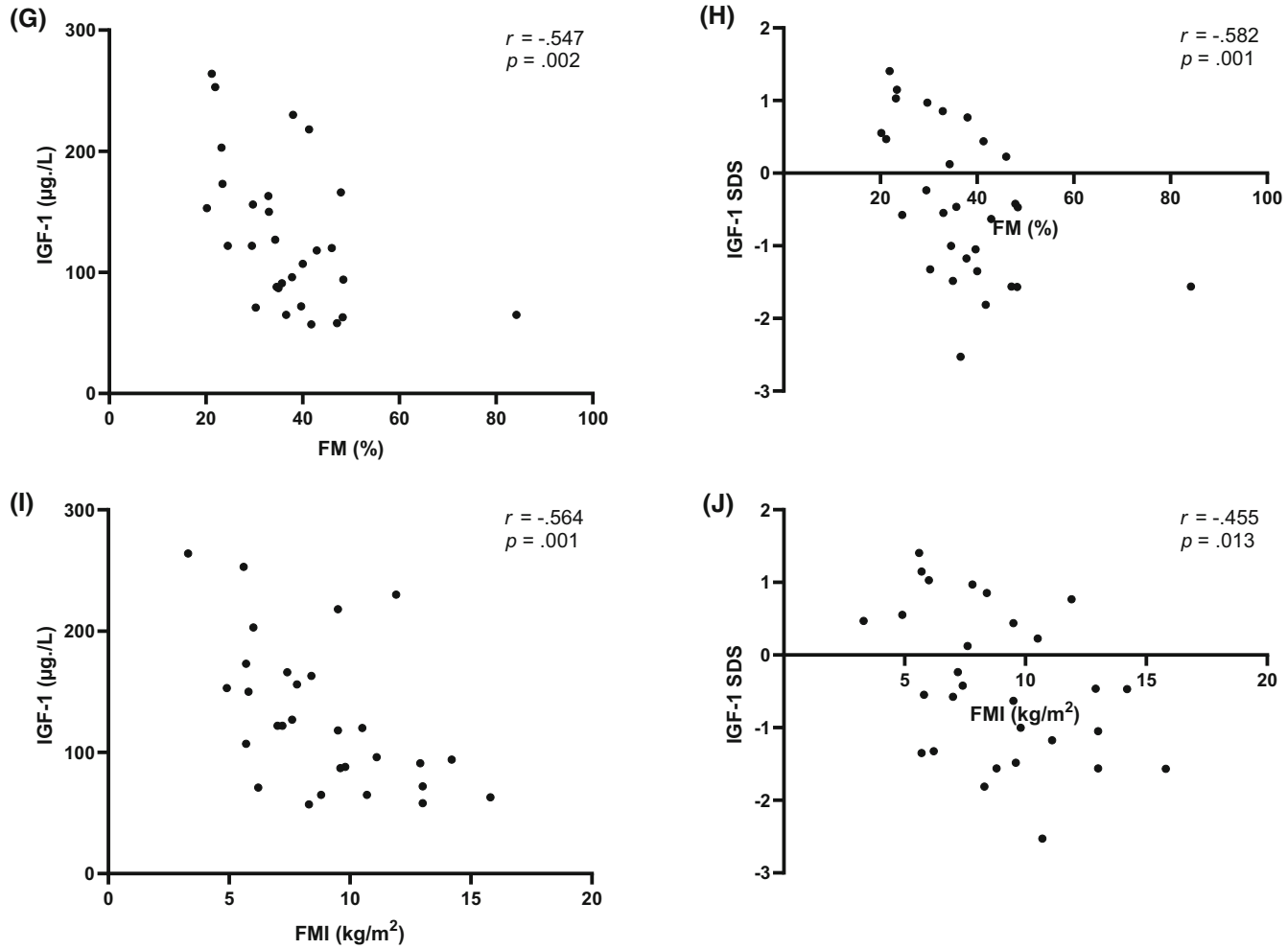

FIGURE 1 (Continued)

healthy reference range and that half of these patients had normal body weight as assessed by BMI <25 kg/m^2. The most important discriminating factor of unfavorable changes in body composition was the loss of ambulation. 93.1% of patients had metabolic abnormalities, including hyperglycemia, IR, and dyslipidemia. Increased BHB as a marker of ketosis was present in more than a third of patients. Functional hypogonadism was presented in half of the male patients. Metabolic and endocrine abnormalities were associated with changes in body composition.

Data on body composition for adults with SMA is lacking. Increased FM (%) has been described in children with SMA.[14–16] The age differences could explain differences in FM between our cohort and pediatric populations, as healthy children have higher FM (%) than adults.[11] Body composition was less favorable in SMA2 and nonambulatory patients. FM (%) was increased in SMA2 compared with SMA3 + 4 group. The nonambulatory group had increased FM (%) and FMI compared with the ambulatory group. No differences existed in BMI, confirming this parameter's low utility in the adult SMA population.

Compared with the pediatric population,[3,4] impaired glucose metabolism was twice as common in our adult cohort. One possible mechanism would be hypoinsulinemia and hyperglucagonemia because of reduced pancreatic β-cell and increased α-cell number.[11] We could not confirm this, as four patients with low C-peptide had low insulin requirements in the presence of low IR assessed with HOMA-IR. In pediatric SMA studies, hyperglycemia was associated with increased IR, body fat, and BMI.[3,4] More than half of our population had increased IR, similar to the mixed pediatric and young adult population of SMA patients.[7] However, there were no significant differences in IR between groups with different SMA types and different levels of ambulation. It has been previously demonstrated that HbA1c is not a good marker for the assessment of chronic hyperglycemia in the SMA population,[3,4] and low sensitivity of HbA1c was also suggested by our results. A greater prevalence of hypoglycemia than in our population was described in the SMA1 population, with lower BMI, particularly during acute illness.[17] Probably the most important factor for hypoglycemia is low muscle mass. To elaborate, with ~40%–50% of body weight, skeletal muscle is the primary glycogen storage site, storing around 80% of total glycogen,[18] and accounting for 70%–75% of insulin-stimulated glucose disposal.[19] Muscle glycogen is primarily a local energy source but also contributes to

euglycemia through the Cori cycle. In this process, glycogen is broken down into lactate and transported to the liver for gluconeogenesis.[18] Endurance training increases muscle glycogen.[20] In contrast, IR impairs glycogen storage and reduces insulin-stimulated glycogen synthesis and nonoxidative glucose metabolism.[18]

BHB is the most abundant ketone body and an important source of energy. It is predominantly produced in the mitochondria of the liver in states of fasting, starvation, low carbohydrate diet, and post-exercise.[21] Fasting BHB was increased in more than a third of our population and more than two-thirds of SMA2 patients. In another study, all fasted adolescent and adult SMA2 patients had ketosis, with low skeletal mass, impaired mitochondrial biogenesis, and oxidation identified as the most important causes of ketosis.[22] In our cohort, BHB was significantly higher, and FFM (kg), FFM (%), and FFMI were significantly lower in SMA2 and nonambulatory patients.

Standard lipid tests showed a high prevalence of lipid abnormalities in our cohort, whereas the additional assessment of Lp(a), ApoA1, and ApoB did not contribute any additional benefit to the cardiovascular risk assessment. In pediatric SMA patients, about one third of children had at least one abnormality in their lipid profile; most of them had SMA1 or SMA2 and were overweight.[2,3] We did not find any differences in lipid parameters between different SMA types in our cohort.

Moreover, we diagnosed hypogonadism in half of the male participants. Contrary to previously published data,[6] there was no history of cryptorchism in our cohort. The most probable cause of hypogonadism in our cohort was functional adiposity-related hypogonadism.[23] We found a significant negative correlation between T and FM (kg) as well as FMI.

IGF-1, which is predominantly synthesized in the liver upon growth hormone (GH) stimulation, is crucial for the development of muscle and bone in childhood and maintenance in later life. Prior studies in SMA populations showed discrepant results on IGF-1, with either normal within the population range[7] or decreased compared with healthy controls.[24] Levels of IGF-1 were dependent on the presence of IR.[7] In our cohort, all patients had normal IGF-1. Contrary to the prior study, we did not find a correlation with IR, but we determined a significant negative correlation between parameters of the GH axis and body composition.

Placing our results in the context of other neuromuscular diseases, the endocrine and metabolic changes present in Duchenne muscular atrophy are mainly due to treatment with corticosteroids. They can be prevented or ameliorated with lower glucocorticoid doses, non-pharmacological intervention, or medical treatment.[25,26] Endocrine changes in myotonic dystrophy type 1 are intrinsic, as they are caused by CTG expansion in the *DPMK* gene. These patients have an increased risk of primary testicular failure, IR, DM, thyroid nodules, bone fractures, and hyperparathyroidism.[27–29] Endocrine changes in amyotrophic lateral sclerosis encompass reduced GH secretion and primary hyperparathyroidism. Interestingly, the onset of DM, dyslipidemia, and higher BMI improved survival.[30]

There are some limitations to our study. The cross-sectional study design makes associations difficult to interpret, is not suitable for investigating the temporal relation between outcome and risk, and makes the study susceptible to nonresponse and recall bias. The small sample size limits the strength of the conclusions and reinforces the need for larger validation studies. Our data was incomplete as our sample presents approximately half of the patients of genetically confirmed patients in our tertiary national referral center. FM (%) is calculated from total body mass and FFM.[31] Intramuscular fat cannot be evaluated by BIA. Moreover, as reported previously in children with SMA, BIA could underestimate FM and overestimate muscle mass compared with dual-energy x-ray absorptiometry.[32] Differences between methods, with high bias, were also reported in a study in a group of SMA children and adults.[33] In contrast, another study on SMA patients reported an excellent correlation of 0.92 between DXA and BIA measurement for the Cordain equation.[34]

In conclusion, our results suggest that multiple endocrine abnormalities are prevalent in adults with SMA. Active screening and treatment of endocrine abnormalities in SMA patients should be considered to prevent potential cardiometabolic complications. The role of protective measures against cardiometabolic complications needs to be further investigated. The highest priority should be given to preserving ambulation as this is a significant factor in lowering the risk of endocrine disturbances.

AUTHOR CONTRIBUTIONS

Matej Rakusa: Conceptualization; investigation; writing—original draft. **Blaž Koritnik:** Investigation; writing—review and editing. **Lea Leonardis:** Investigation; writing—review and editing. **Katja Goricar:** Writing—review and editing; formal analysis. **Tjasa Rudolf:** Investigation; writing—review and editing. **Dejan Firbas:** Investigation; writing—review and editing. **Žiga Snoj:** Writing—review and editing. **Mojca Jensterle:** Conceptualization; writing—review and editing; supervision.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

We confirm that we have read the journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

ORCID

Matej Rakusa https://orcid.org/0000-0002-8044-3527
Blaž Koritnik https://orcid.org/0000-0002-5083-8261
Žiga Snoj https://orcid.org/0000-0001-6864-8880

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