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LETTER TO THE EDITOR

Letter to the Editor: Circulating Adult Stem and Progenitor Cells After Roux-en-Y Gastric Bypass Surgery in Myotonic Dystrophy

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In healthy subjects, homeostasis and repair of skeletal muscle rely on muscle-resident and circulating stem and progenitor cells, i.e., satellite cells and bone marrow–derived hematopoietic and endothelial (CPCs) or mesenchymal stem and progenitor cells (MPCs). Mature endothelial cells (ECs) support myogenesis by growth factor secretion [1]. Myotonic dystrophy type 1 (MD1) is a multisystem disorder of genetic origin that causes muscle wasting and impaired muscle regeneration. Furthermore, patients with MD1 are more prone to become adipose [2]. Muscle regeneration in obese MD1 patients by circulating precursor and supporting cells might be hampered since obesity suppresses the number and function of circulating precursor cells, as already shown for endothelial progenitor cells (EPCs) [3]. Weight loss management by bariatric surgery in obese patients without MD1 elevated the number of EPCs [4]. In MD1, however, bariatric surgery–induced CPC, MPC, and EC number increases could be attenuated due to disease-related degenerative effects.

In order to refine the understanding of the biological principles underpinning the cellular regenerative capacity in MD1, we introduce an exemplary case of an obese MD1 patient and describe the baseline circulating progenitor cell profile and the change in cell numbers after weight loss induced by Roux-en-Y gastric bypass (RYGB) surgery. A 34-year-old female patient suffering from MD1 and obesity with a body mass index (BMI) of 46 kg/m^2, that underwent RYGB surgery for weight reduction, was investigated and full informed consent was obtained. All procedures were in accordance with institutional and national ethical standards and with the 1964 Declaration of Helsinki and its later amendments.

Physical examinations included yearly medical assessment for MD1 status by an external specialist, venous blood analysis for whole blood cell counting and subgroup determination of circulating stem and progenitor cells [5], C-reactive protein (CRP) determination, and bioelectrical impedance analysis (BIA) before 3, 6, 21 months and 2 years (25 months) after RYGB surgery, sleep apnea evaluation at baseline and 6 months after surgery, and self-reported sleep questionnaires at all time points except 21 months after surgery.

Individual values and/or mean (standard deviation) from repeated samples are presented for each time point. Progenitor cell results are given in percentage of the mononuclear cell count. A CRP value < 10 mg/l was considered healthy. Spearman's Rho was used as correlation coefficient. A p value < 0.05 was considered significant.

At baseline, the patient was diagnosed with daily sleepiness and obstructive sleep apnea syndrome where non-invasive ventilation per mask failed in an ambulant and a stationary setting. In addition, hyperthyroidism (substituted), cataract (operated), hysterectomy, appendectomy, and mild reflux esophagitis were reported.

Bariatric surgery was successful; there were no problems of anesthesia, dysphagia, or perioperative complications—although MD1 patients are at higher risk [6–8]. The effectiveness of weight management was shown by a decrease in BMI (− 12 kg/m^2, − 25%, Fig. 1a), total muscle mass (TMM, − 5 kg, − 21%), fat mass (FM, − 23 kg, − 33%), and fat free mass (FFM, − 6 kg, − 13%) (Table 1). Secondary disease symptoms like mild sleep apnea improved over time characterized by a decreased apnea-hypopnea index, respiratory disturbance, and oxygen desaturation (− 38%, − 40%, and − 29%, respectively). Also, the patient reported reduced sleepiness during the day (− 46%, Table 1) 2 years after surgery. However, myotonic weakness increased over time.

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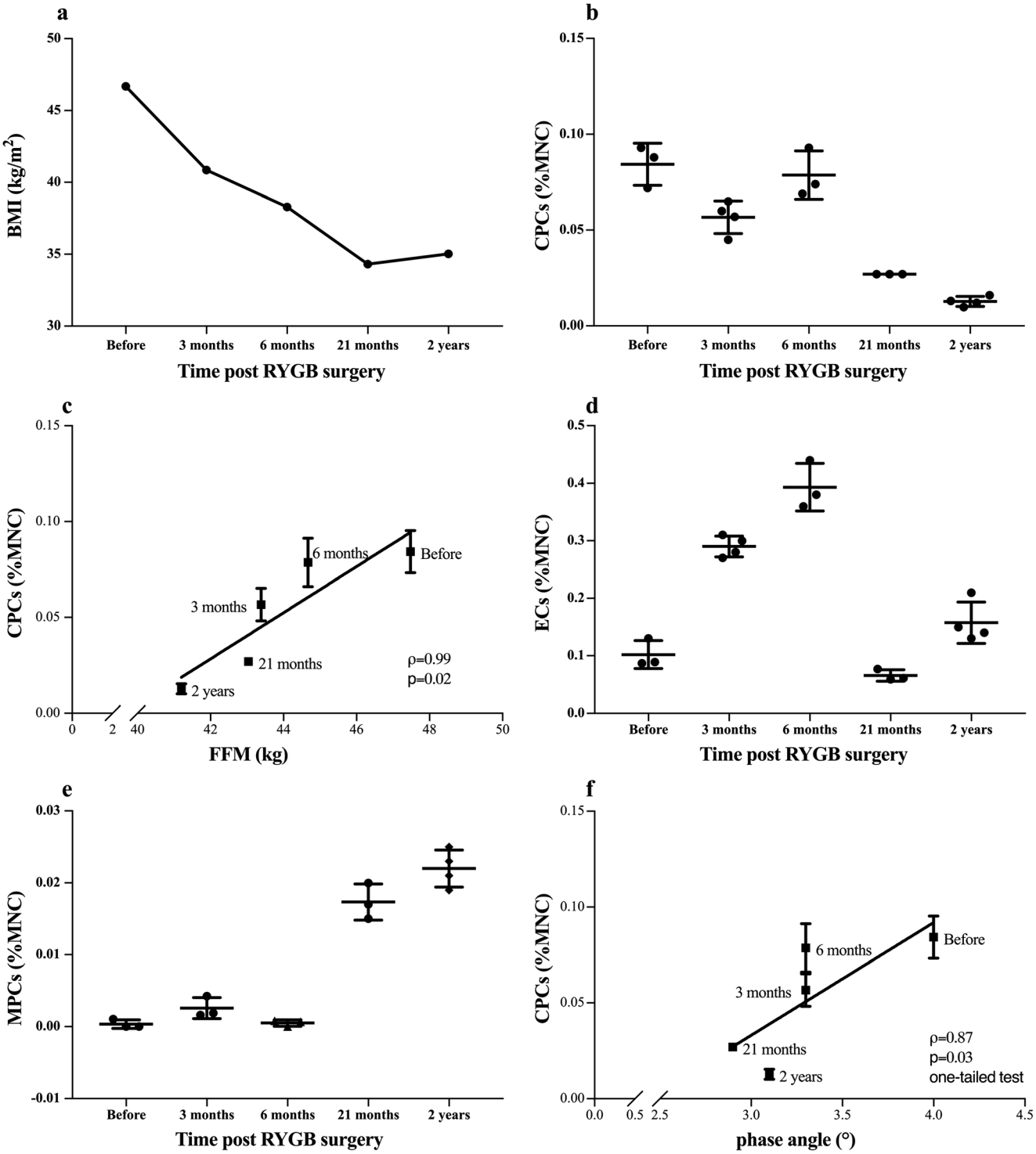

Fig. 1 Development of body mass index (BMI, **a**), relative circulating hematopoietic and endothelial stem and progenitor cell number (CPC, **b**), relationship between CPCs and fat free mass (FFM, **c**), relative mature endothelial cell number (EC, **d**), relative mesenchymal stem and progenitor cell number (MPC, **e**), and relationship between CPCs and phase angle of bioelectrical impedance analysis (**f**). *%MNC* percentage of the mononuclear cell count, *RYGB* Roux-en-Y gastric bypass

Postoperative protein supplementation of > 60 g/day ensures no loss of fat-free mass instead of fat mass after bariatric surgery [9, 10]. One month after surgery, the patient already showed sufficient protein intake (Table 2) and FFM reduction after 2 years was even less than in another case of a MD1 patient undergoing bariatric surgery [11].

Table 1 Weight, body composition, measures of sleep and sleep apnea, and blood parameters in a female MD1 patient before and up to 2 years after bariatric surgery

Anthropometry	Before	3 months	6 months	21 months	2 years
Weight (kg)	*116.6*	102.0	95.6	85.7	*87.5*
BIA	**Before**	**3 months**	**6 months**	**21 months**	**2 years**
FM (kg)	*69.1*	58.6	50.9	42.6	*46.3*
visceral fat (l)	4.24	2.82	2.49	1.87	2.01
FFM (kg)	*47.5*	43.4	44.7	43.0	*41.2*
Total MM (kg)	*21.6*	17.9	18.6	16.6	*17.0*
Resistance (Ω)	611.7	657.1	583.5	583.9	629.5
Reactance (Ω)	42.3	38.3	33.2	29.6	33.9
Phase angle (°)	4.0	3.3	3.3	2.9	3.1
Sleep questionnnaires	**Before**	**3 months**	**6 months**	**21 months**	**2 years**
Pittsburgh sleep quality index (score)	6	4	5	NA	13
Epworth Sleepiness Scale (score)	*13*	11	10	NA	*7*
Apnea indices	**Before**	**3 months**	**6 months**	**21 months**	**2 years**
Apnea-hypopnea index (events/h)	*13*	NA	*8*	NA	NA
Respiratory disturbance index (events)	*15*	NA	*9*	NA	NA
Apnoe Index (events/h)	0	NA	0	NA	NA
Hypopnoeindex (events/h)	13	NA	8	NA	NA
Oxygen desaturation index (events/h)	*21*	NA	*15*	NA	NA
Mean saturation (%)	90	NA	89	NA	NA
Lowest saturation (%)	71	NA	66	NA	NA
Mean heart rate (beats/min)	70	NA	61	NA	NA
Blood parameters	**Before**	**3 months**	**6 months**	**21 months**	**2 years**
WBC (10^9/l)	8.0	6.2	6.0	5.4	6.4
RBC (10^{12}/l)	4.00	4.06	3.57	3.71	4.01
Hct (%)	38.5	40.3	35.6	36.9	39.5
Hgb (g/dl)	13.2	13.1	11.6	12.0	12.9
RDW-CV (%)	15.4	15.9	15.3	15.1	15.3
Lymphocytes (10^3/μl)	2.9	2.1	2.0	2.3	2.9
Monocytes (10^3/μl)	0.4	0.3	0.3	0.2	0.3
Granulocytes (10^3/μl)	4.7	3.8	3.7	2.9	3.2
CRP (mg/l)	*30.4 (+)*	9.5	13.0(+)	0.5	*3.1*

Data are given as individual values

BIA bioelectric impedance analysis, *FM* fat mass, *FFM* fat free mass, *MM* muscle mass, *WBC* white blood cell count, *RBC* red blood cell count, *Hct* hematocrit, *Hgb* hemoglobin, *RDW-CV* red blood cell distribution width coefficient of variation, *CRP* C-reactive protein, *NA* not available

(+) indicates values elevated above reference values; important changes/information are indicated in italics

Mature blood cell counts were normal over the study period, except of increased CRP values before and 6 months after surgery (Table 1). Baseline CPC and EC numbers were in the expected range for a patient with BMI > 30 kg/m^2 [5]. Circulating MPCs, however, were atypically low [5] at baseline with values comparable to subjects with normal BMI—likely a disease indication of MD1 possibly resulting in impaired skeletal muscle regeneration by MPCs.

Vitamin B12 and iron values (Table 2) were also in a normal range, but folic acid dropped below reference values 2 years post-RYGB. In addition, there was a significant positive correlation between relative CPC count and vitamin B12 concentrations ($\rho = 0.90$, $p = 0.04$, one-tailed test).

CPCs decreased by 85% up to 2 years after the intervention (Fig. 1b) along with a 25% decrease in BMI. A decrease in EPCs after weight loss was already reported [12], and the respective authors found that the reduction in EPC number was linked to markers of adiposity (weight, BMI, waist circumference). Interestingly, the suppression of CPCs in our study was only significantly positively related to TMM ($\rho = 0.90$, $p = 0.04$, one-tailed test) and FFM ($\rho = 0.99$, $p = 0.02$, Fig. 1c), but not to FM or visceral fat mass, while ECs or MPCs did not correlate with these parameters. This highlights the importance of TMM- and FFM-mediated CPC-attracting chemotactic gradients stimulating cell mobilization. However, also the loss of FM might play a role, since decreasing FM-mediated inflammation by serum CRP values supported the decrease of CPCs during the study period. It could also be a hint for disease-related degenerative effects such as increased cell apoptosis [13] possibly mediated by vitamin B12 reduction over time [14], since—among others—vitamin B12 is very important for normal hematopoiesis in bone marrow [15]. A constant withdrawal of CPCs to sites of muscle regeneration could also be a possibility [1].

The number of myogenesis-supporting ECs increased by 285% 6 months after surgery and dropped again to 54% above

Table 2 Micronutrients in a female MD1 patient before and up to 2 years after bariatric surgery as well as nutritional assessment before and up to the first month post-RYGB

Micronutrients	Before	3 months	6 months	21 months	2 years
Calcium (mmol/l)	2.38	2.39	2.34	2.29	2.25
Creatinine (μmol/l)	78	71	68	66	62
Glucose (mmol/l)	4.4	5.0	4.7	4.6	4.8
Magnesium (mmol/l)	0.93	NA	NA	NA	0.85
Phosphor (mmol/l)	0.90	0.93	0.93	0.82	0.86
Protein (g/l)	74	66	69	73	66
Total cholesterol (mmol/l)	4.88	NA	3.64	NA	3.71
LDL cholesterol (mmol/l)	2.95 (+)	NA	1.92	NA	1.46
HDL cholesterol (mmol/l)	1.19	NA	1.30	NA	1.86 (+)
Triglycerides (mmol/l)	1.63	NA	0.92	NA	0.86
Vitamin B12 (pmol/l)	*531*	*504*	*477*	*444*	*325*
Iron (μmol/l)	11.9	9.7	7.2	23.8	14.8
Ferritin (ng/ml)	83.2	62.7	70.2	35.2	36.5
Folic acid (nmol/l)	8.1	10.7	9.6	5.6	5.4 (−)
TSH (mU/l)	7.16 (+)	5.60 (+)	3.85	NA	5.62 (+)
Parathyroid hormone (pmol/l)	7.40	6.00	8.20	4.93	6.51
Zinc (μmol/l)	10.8	9.5 (−)	8.8 (−)	NA	9.7 (−)
25-OH Vitamin D3 (μg/l)	12.0 (−)	14.0 (−)	8.9 (−)	NA	26.7 (−)
Perioperative assessment	Before	0.5 month	1 month		
Protein intake (g/day)	NA	*40–60*	*> 60*		
Fluid intake (l/day)	< 1	< 1	1–1.5		
Vomiting (events/day)	NA	No	No		
Bowel movement (events/day)	variable	1–3	< 1		
Bowel movement pain	NA	No	No		

Data are given as individual values

RYGB Roux-en-Y gastric bypass, *LDL* low-density lipoprotein, *HDL* high-density lipoprotein, *TSH* thyroid stimulating hormone, *NA* not available

(+) or (−) indicate values above or below reference values; important changes/information are indicated in italics

baseline after 2 years (Fig. 1d). After bariatric surgery, kinetics of ECs showed a different pattern than in patients without MD1 [16]. In our study, relative EC number dropped to baseline 21 months to 2 years after surgery while literature showed a further EC increase to 667% from baseline [16]. Our results could be a sign for decreased cell growth and tube formation.

The number of MPCs did not change within the first 6 months but was increased by 6186% (Fig. 1e) after 2 years. This might be explained by a higher MPC number and function being related to a healthier body weight, which was already reported for EPCs in healthy compared to obese mice [3], and would imply an increased ability of MPCs to support skeletal myoblast proliferation through the paracrine release of vascular endothelial growth factor [17].

The use of raw impedance parameters in disease progression, like a decrease in BIA phase angle (phA), provides information on decreasing cell membrane integrity and worse cell function. Baseline phA (4.0°) decreased by 0.9° (− 23%) 2 years after surgery (Table 1) and was positively related to CPC number ($\rho = 0.87$, $p = 0.03$, one-tailed test, Fig. 1f), while no relationship was found with ECs or MPCs. The presented phA-reduction of approximately 1° at 21 months after RYGB surgery is consistent with previous data assessed at 12 months after weight management surgery [18]. However, baseline phA in the presented MD1 patient was already 2.4° lower than the average of the described obese cohort without MD1 [18], possibly indicating MD1-related fatty muscle infiltrations increasing BIA resistance, decreasing BIA reactance and therefore lowering phA. Furthermore, the association between phA and CPC number suggests CPCs as a simple and cost-efficient health indicator after bariatric surgery.

One limitation of the study is the small number of follow-up measurements. Therefore correlation analysis must be interpreted with caution.

To conclude, the circulating progenitor cell profile of an obese MD1 patient is different from normal obese and

substantially changed by bariatric surgery which improves our understanding of the biological principles underpinning the cellular regenerative capacity in MD1.

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Compliance with Ethical Standards

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

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