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1 **Deltoid muscle morphometry as an index of impaired skeletal muscularity in neonatal**
2 **intensive care**

3

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28

29 **ABSTRACT**

30 We hypothesised that extremely premature infants would have decreased muscle mass at
31 term-corrected age compared to term-born infants and that the degree of reduced muscle
32 mass acquisition would correlate with the duration of invasive mechanical ventilation. The
33 MRI brain scans of infants admitted in the neonatal unit at King's College Hospital between
34 1/1/2010 and 1/6/2016 were retrospectively reviewed. The coronal cross-sectional area of
35 the left deltoid muscle (DCSA) was measured in 17 infants born <28 weeks of gestation and
36 in 20 infants born at term. The prematurely born infants had a median(IQR) gestation age of
37 25(24-27) weeks and the term infants 40(38-41) weeks. The duration of invasive mechanical
38 ventilation for the prematurely born infants was 39(14-62) days and for the term infants for
39 4(2-5) days, $p<0.001$. DCSA was smaller in prematurely-born infants (median 189, IQR:176-
40 223mm²) compared to term-born infants (median 302, IQR 236-389mm²), $p<0.001$. DCSA
41 was related to gestation age ($r=0.545$, $p=0.001$), weight z-score at MRI ($r=0.658$, $p<0.001$)
42 and days of invasive mechanical ventilation ($r=-0.583$, $p<0.001$). In conclusion, extremely
43 premature infants studied at term had a lower muscle mass compared to term-born infants.

44 *Conclusion:* Our results suggest prolonged mechanical ventilation in infants admitted in
45 neonatal intensive care is associated with reduced skeletal muscle mass acquisition.

46 **KEY WORDS:** Deltoid muscle morphometry, impaired skeletal muscularity, neonatal
47 intensive care

48

49 **ABBREVIATIONS**

50 DCSA Deltoid cross-sectional area

51 IQR Interquartile range

52 MRI Magnetic Resonance Imaging

53

54 **AUTHORS SUMMARY**

55

56 **What is known:**

- 57 • Prolonged mechanical ventilation in adult intensive care patients has been
58 associated with skeletal muscle dysfunction and atrophy.
- 59 • The cross-sectional area of the deltoid muscle has been used to evaluate muscle
60 atrophy in infants with a previous brachial plexus birth injury.

61

62

63 **What is new:**

- 64 • Premature infants studied at term exhibit lower cross-sectional area of the deltoid
65 muscle than their term counterparts.
- 66 • Prolonged mechanical ventilation could be associated with skeletal muscle
67 impairment.

68

69 **INTRODUCTION**

70

71 Following birth, prematurely-born infants commonly spend a long period in neonatal
72 intensive care where they often undergo invasive mechanical ventilation. The effect of critical
73 illness on the skeletal muscles, commonly referred to as “critical illness myopathy”, has been
74 well-described in adults. The most common predisposing conditions in adult intensive care
75 patients are acute respiratory disorders such as acute respiratory distress syndrome,
76 pneumonia and severe asthma [6, 13]. In addition, use of high-dose steroids, non-
77 depolarizing blocking agents [2], aminoglycosides [19] and acidosis [14] may also
78 predispose to critical illness myopathy.

79

80 In prematurely born neonates, the postnatal nutritional target is the accretion of body weight
81 at a rate similar to that achieved during intrauterine development [1]; that gold standard,
82 however, is infrequently achieved [4, 5] especially in the sickest infants who rely for long
83 periods on parenteral nutrition. The “weight-targeted” nutritional approach fails to detect
84 qualitative differences in body composition and weight accretion, predominantly in the form
85 of adipose tissue, does not necessarily translate to better outcomes [9]. This is particularly
86 relevant in the prematurely born population whose adult-life adiposity profile might place
87 them at an increased risk for cardiovascular and metabolic disease [15].

88

89 Few studies have reported data on qualitative body composition in prematurely born
90 compared to term-born infants [16] and to our knowledge none has specifically investigated
91 skeletal muscle mass. The magnetic resonance imaging (MRI) appearance of the deltoid
92 muscle has been used to evaluate muscle atrophy in infants with a previous brachial plexus
93 birth injury [10, 17]. The cross-sectional area of the deltoid muscle (DCSA) on the affected

94 side has been shown to be significantly decreased compared to the unaffected size with a
95 mean affected to normal ratio of 76% [17]. The deltoid muscle is often included in the
96 coronal images of MRI-brain scans that prematurely born infants have to assess ventricular
97 dilatation and periventricular leukomalacia and term infants for evidence of white matter
98 injury secondary to hypoxic ischemic encephalopathy (HIE).

99

100 We hypothesised that DCSA would be smaller in prematurely born infants studied at term
101 compared to term born infants and that the DCSA would correlate with body weight and
102 gestational age. We also hypothesised that DCSA would correlate with days of ventilation
103 and days of parenteral nutrition. Our aims were to test those hypotheses.

104

105 **METHODOLOGY**

106

107 **Subjects**

108 The MRI brain scans of infants that were admitted to the neonatal unit at King's College
109 Hospital NHS Foundation Trust, London, UK and underwent a scan between 1 January 2010
110 and 1 June 2016 were retrospectively reviewed. Two groups of infants were assessed: term-
111 born infants with HIE and extremely prematurely born infants (<28 weeks of gestation at
112 birth) scanned at term that had periventricular leucomalacia or ventricular dilatation
113 diagnosed and sequentially assessed by cranial ultrasonography. The Research and
114 Development department confirmed that the data collection was consistent with a service
115 evaluation/audit, and as such did not require research ethics approval. The study was
116 registered with the Clinical Governance Department of King's College Hospital NHS
117 Foundation Trust.

118 **Calculation of DCSA**

119 Infants were scanned on a 1.5 T MR imager (Siemens, Erlanger, Germany). After localizer
120 sequences, T1-weighted in axial, oblique coronal (angled to the temporal lobe) and oblique
121 sagittal planes were obtained (TR/TE 4000/126 msec: base resolution: 256 mm). T2-
122 weighted images in axial, oblique coronal (angled to the temporal lobe) were obtained
123 (TR/TE 4000/126 msec: base resolution: 256 mm. The slice thickness was 4 mm for all
124 sequences. The field of view was 200x200 mm for T1-weighted images and 220x220 mm for
125 T2-weighted images).

126

127 The deltoid muscle was visualised on the oblique coronal plane at the level where the head
128 of the humerus had the maximum diameter at which level the area of the deltoid is maximal
129 [17]. Free-hand tracing of the perimeter of the left deltoid muscle was undertaken by a
130 consultant radiologist (MK) and the DCSA was calculated in mm² by the Sectra PACS
131 software (Sectra AB, Linköping, Sweden) (Figure 1). The radiologist performing the DCSA
132 measurement was unaware of the infant's clinical condition and demographics.

133

134 **Information from the medical records**

135 Gender, gestation age at birth, birth weight and postmenstrual age, postnatal age and weight
136 at the time of MRI were recorded. Data also recorded were whether the infant had had
137 postnatal steroids or confirmed necrotising enterocolitis, the days of invasive mechanical
138 ventilation and parenteral nutrition prior to the MRI and the use of non-depolarising muscle
139 relaxing agents.

140

141

142 **Statistical analysis**

143 Data were tested for normality with the Kolmogorov–Smirnov test and found to be non-
144 normally distributed. Continuous data are presented as median and interquartile range
145 (IQR). Differences between term and premature infants were tested for significance using
146 the Mann-Witney rank sum test. Multiple linear regression was used to adjust for
147 confounders in differences of DCSA between term and prematurely born infants. Variables
148 without normal distribution were logarithmically transformed. Multi-collinearity among the
149 independent variables in the multiple regression analysis was assessed by calculation of the
150 tolerance for the independent variables. Kendall’s tau rank correlation coefficient (τ) was
151 used to examine the relationship of DCSA with gestational age, age at MRI, birth weight,
152 weight at measurement, days of ventilation and days of parenteral nutrition. Multiple
153 regression analysis was used to examine the independent effect on DCSA of the parameters
154 that were significantly related to DCSA in the bivariate analysis. Parameters with a variance
155 inflation factor (VIF) of more than three were considered collinear.

156 Linear regression analysis was used to examine the relationship of DCSA to weight at MRI.
157 The type of non-linearity was tested by visual inspection of the residuals. Statistical analysis
158 was performed using IBM SPSS Software (IBM, Chicago IL).

159

160 **RESULTS**

161

162 Between 1 January 2010 and 1 June 2016, 291 infants were admitted to the neonatal unit
163 with a gestational age of less than 28 weeks; 17 had an MRI brain scan to assess the extent
164 of periventricular leukomalacia or ventricular dilatation. Twenty-one term infants underwent
165 an MRI brain scan for HIE. One term infant was excluded from the study because the
166 coronal views did not fully include the left deltoid muscle. Premature infants did not differ

167 from term infants in terms of gender, birth weight z-score, weight at MRI and administration
168 of postnatal steroids. Prematurely born infants had longer durations of mechanical ventilation
169 and parenteral nutrition and lower weight z-score at MRI than the term infants (table 1).
170 Premature infants had lower DCSA compared to term infants (table 1) and lower DCSA
171 compared to term infants after adjusting for weight at MRI ($p=0.021$, 95% Confidence
172 Intervals: 9.628 – 111.843, Odds ratio: 0.343). DCSA was significantly related to gestational
173 age ($\tau=0.545$, $p=0.001$), birth weight z-score ($\tau=0.547$, $p=0.001$), age at MRI ($\tau=-0.590$,
174 $p<0.001$), weight z-score at MRI ($\tau=0.658$, $p<0.001$), days of mechanical ventilation ($\tau=-$
175 0.583 , $p<0.001$), and days of parenteral nutrition ($\tau=-0.617$, $p<0.001$). Following multiple
176 regression analysis with DCSA as the outcome variable, corrected GA was excluded from
177 the model due to collinearity with GA (VIF: 3.29) and days of parenteral nutrition were
178 excluded from the model due to collinearity with days of mechanical ventilation (VIF: 4.32).
179 DCSA remained significantly related to GA (adjusted $p=0.003$) and days of mechanical
180 ventilation (adjusted $p=0.008$).

181 The linear regression analysis of DCSA against weight z-score at MRI is presented in figure
182 2. The quadratic model was found to accommodate the best non-linear fit (r^2 quadratic =
183 0.576).

184

185 **DISCUSSION**

186

187 We have demonstrated that DCSA is smaller in prematurely-born infants studied at term
188 compared to term-born infants and that the DCSA is related to gestation, weight, duration of
189 mechanical ventilation and duration of parenteral nutrition. Our results are in agreement
190 with previous studies that have described that respiratory muscle strength in prematurely-
191 born infants increases with increasing maturity [3]. Furthermore, the deleterious effect of
192 prolonged mechanical ventilation on skeletal muscle function has been reported in adult

193 intensive care studies [6, 13]. In this paper we further highlight that prematurity, prolonged
194 mechanical ventilation and parenteral nutrition (PN) are associated with reduced skeletal
195 muscle mass acquisition. The importance of our study is that it is the first study to highlight
196 that extremely premature infants exhibit postnatal skeletal muscle growth impairment which
197 is related to prolonged mechanical ventilation. The duration of PN might directly represent a
198 nutritional deficit or it might indirectly describe the cumulative severity of the intensive care
199 stay as sicker infants will fail to advance on enteral nutrition and will require longer courses
200 of PN.

201 Muscle atrophy and prolonged mechanical ventilation have an adverse synergistic
202 relationship. Prolonged mechanical ventilation is associated with a release of pro-
203 inflammatory cytokines [11] and the use of non-depolarizing muscle relaxants [2]. Inversely,
204 sepsis [12] and disuse atrophy [18] directly impact on respiratory muscle function and lead to
205 inability to wean off respiratory support. A plausible pathophysiological mechanism that
206 explains our findings is that prolonged intensive care leads to a generalised skeletal
207 myopathy with atrophy and necrosis of the muscle fibres and loss of myelinated nerve fibres
208 [7, 8].

209

210 One implication of our study is that weight accretion alone might not be an adequate
211 nutritional target in neonatal intensive care and that other anthropometric parameters should
212 be taken into account in evaluating postnatal growth. These could include body composition
213 analysis either by dual-energy X-ray absorptiometry, whole body MRI or bioelectrical
214 impedance analysis. Those methods, however, have their own disadvantages such as high
215 cost, non-availability and technical difficulties of performing serial measurements. The DCSA
216 was indeed significantly related to weight at MRI however, given that they are both
217 anthropometric indices, one might expect a stronger correlation. This relatively weak
218 correlation would support the conclusion that body weight might not be the most appropriate

219 variable to reflect the nutritional status of these infants. Possibly, indices that incorporate
220 information on height such as the ponderal index or the body mass index might be more
221 appropriate.

222

223 The strengths of our study include that the radiologist who performed the DCSA
224 measurements was blinded to the demographic and clinical details and hence was not
225 biased in estimating the DCSA. We should acknowledge as a limitation the retrospective
226 nature of our study and that we evaluated a selected subpopulation of premature infants that
227 had significant intracranial pathology detected on cranial ultrasound. As such, these infants
228 might have had a relatively more severe intensive care course. It is plausible that equally
229 premature infants without intracranial pathology might have exhibited less prominent muscle
230 atrophy. Our positive results emphasize the interest to study a "well" preterm population to
231 demonstrate the independent impact of prolonged mechanical ventilation on these infants.
232 We should also note as a limitation that the radiologist that evaluated the MRIs had access
233 to the full images including the brain appearances. We should also note as a limitation that
234 the radiologist that evaluated the MRIs had access to the full images including the brain
235 appearances. The appearances of PVL or ventricular dilatation, therefore, might have had
236 an impact on the blinding process. We thus suggest that future studies could eliminate this
237 bias by excluding the brain from the reviewed images.

238 In conclusion, we have demonstrated that extremely premature infants do not
239 accumulate/accrete muscle mass at a rate similar to their term counterparts and that
240 prolonged ventilation in these infants is related to reduced skeletal muscle mass acquisition.

241

242

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244 **Compliance with ethical standards**

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248 those of the NHS, the NIHR or the Department of Health.

249

250 **Compliance and ethical standards:** The Research and Development department
251 confirmed that the data collection was consistent with a service evaluation/audit, and as
252 such did not require research ethics approval. The study was registered with the Clinical
253 Governance Department of King's College Hospital NHS Foundation Trust.

254

255 **Conflict of interest:** The authors have no financial relationship relevant to this article to
256 disclose.

257 **Informed consent:** Not required.

258 **Contributors' statement:**

259 T.D. conceived the study, participated in the analysis of the data, and drafted the first version
260 of the article.

261 O.K. collected the data and participated in the analysis of the data.

262 M.K. independently reviewed the MRI scans and critically reviewed the manuscript.

263 A.H. contributed to study design, writing of the manuscript and interpretation of the results.

264 A.G. supervised the project, contributed to the study design and interpretation of the results,
265 and critically revised the manuscript.

266 All authors were involved in the preparation of the manuscript and approved the final
267 manuscript as submitted.

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- 330
331

332 **Table 1: Demographics, clinical parameters and DCSA in prematurely born and term infants**

333 **Data are presented as median (IQR) or N (%)**

	Premature	Term	p-value
	N=17	N=20	
Male gender	11 (65)	9 (45)	0.325*
Gestation age (weeks)	25 (24-27)	40 (38 – 41)	<0.001
CGA (weeks)	42 (40 – 48)	41 (40 – 41)	0.005
Age (days)	113 (98 – 172)	6 (4 – 8)	<0.001
Birth weight (kg)	0.76 (0.64 – 0.93)	3.56 (3.15 – 3.87)	<0.001
Birth weight z-score	-0.47 (-1.15-0.23)	0.15 (-0.81 – 0.95)	0.065
Weight at MRI (kg)	2.98 (2.59 – 4.25)	3.65 (3.20 – 4.16)	0.185
Weight at MRI z-score	-1.61 (-3.01 - -1.08)	0.14 (-1.05 – 0.79)	<0.001
Days of invasive MV	39 (14 – 62)	4 (2 – 5)	<0.001
Days of PN	34 (19 – 52)	2 (1 – 4)	<0.001
Muscle relaxing agents	3 (18)	4 (20)	0.587
Postnatal steroids	5 (27)	2 (10)	0.212*
NEC	11 (65)	0 (0)	<0.001*
DCSA (mm ²)	189 (176 – 223)	302 (236 – 389)	<0.001

334

335 Mann-Whitney U test

336 *Chi square

337 IQR: interquartile range, CGA: corrected gestation age, MRI: Magnetic resonance imaging, MV:
 338 invasive mechanical ventilation, PN: parenteral nutrition, NEC: necrotising enterocolitis, DCSA:
 339 deltoid cross sectional area.

340

341

342

343

344 **FIGURE LEGENDS**

345

346

347 **Figure 1:** Method of free hand tracing of the perimeter of the DCSA

348 **Figure 2:** Regression analysis of DCSA with weight z-score. The regression line and 95%

349 confidence intervals are presented.

350 ▲ male infants

351 ○ female infants

352

353