Evaluation of nutritional status in children with refractory epilepsy

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Short title: nutritional status in refractory epilepsy

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Abstract

Background: children affected by refractory epilepsy could be at risk of malnutrition because of feeding difficulties (anorexia, chewing, swallowing difficulties or vomiting) and chronic use of anticonvulsants, which may affect food intake and energy metabolism. Moreover, their energy requirement may be changed as their disabilities would impede normal daily activities. The aim of the present study was to evaluate nutritional status, energy metabolism and food intake in children with refractory epilepsy.

Methods: 17 children with refractory epilepsy (13 boys and 4 girls; mean age 9±3,2 years; Body Mass Index 15,7±3,6) underwent an anthropometric assessment, body composition evaluation by dual-energy X-ray absorptiometry, detailed dietetic survey and measurement of resting energy expenditure by indirect calorimetry. Weight-for-age, height-for-age (stunting) and weight-for-height (wasting) were estimated compared to those of a reference population of the same age.

Results: 40% of children were malnourished and 24% were wasted. The nutritional status was worse in the more disabled children. Dietary intake resulted unbalanced (18%, 39%, 43% of total daily energy intake derived respectively from protein, lipid and carbohydrate). Adequacy index [nutrient daily intake/recommended allowance (RDA) x 100] was < 60% for calcium iron and zinc.

Conclusions: many children with refractory epilepsy would benefit from individual nutritional assessment and management as part of their overall care.

Keywords: body composition, food intake, dxa, energy metabolism, refractory epilepsy

Background

Refractory epilepsy (RE) is a condition in which seizures do not respond to first and second-line anticonvulsant drug therapy. Despite the use of new antiepileptic drugs
1 (many antiepileptic drugs have been marketed in the last decade), refractory
2 epilepsy occurs in approximately 20-30% of patients with epilepsy probably due to
3 the multiple pathogenetic mechanisms underlying refractoriness [1].
4 Drug-resistant epilepsy is frequent in several disorders such as hereditary metabolic
5 or degenerative disorders, cerebral palsy, severe myoclonic epilepsy of infancy, brain
6 injuries/ malformations, Lennox-Gastaut syndrome [2]. Though epilepsy itself does
7 not cause neurological deterioration, the evolution of refractory epilepsy does, since
8 patients are submitted to multiple drug treatments which lead to neurological
9 deterioration in children affected by RE. This is characterised by cognitive decline,
10 motorial problems and behaviour disorders (attention reduction, problems of social
11 relationships and problems of conduct) and leads to disabled children [3,4].
12 Several authors showed that feeding difficulties and malnutrition are common in
13 disabled children: intake may be reduced because of anorexia, chewing and
14 swallowing difficulties, or vomiting [5]. Moreover, most of the commonly used
15 anticonvulsants influence nutritional status. In particular, some drugs affect the
16 regulation of energy balance and appetite with consequent loss (topiramate) or gain
17 (carbamazepina, valproate) of body weight [6,7,8]. Phenytoin, phenobarbitone, and
18 carbamazepine can interfere with vitamin D metabolism and increase the risk of
19 osteopenia and osteoporosis [9]. Dahl et al [10] found an altered nutritional status in
20 52 % of children with moderate or severe cerebral palsy: 43% were underweight
21 and 9% were overweight compared with reference values of healthy children.
22 Undernourished disabled children had significantly lower height for age, weight for

23 height, triceps skinfold thickness and upper-arm circumference than healthy children.
24 A Cross-sectional analyses in a large cohort of disabled children showed that their
25 energy and nutrient intake were lower in comparison with recommended values [11].
26 Since children with RE gradually become disabled it could be assumed that this state
27 is associated with malnutrition being linked to feeding difficulties, to the wrong
28 choice of foods and to changes in energy requirement due to physical inactivity and
29 drugs. This inadequate nutritional status would then worsen the children's health, in
30 particular their immunity status.
31 The aims of our study were to evaluate nutritional status, energy metabolism and
32 food intake in children affected by refractory epilepsy.
33

33

34 **Methods**

35 **Subjects**

36 All the children with RE treated at the Child Neuropsychiatry Department, Casimiro
37 Mondino Foundation (Pavia, Italy) (from 1995 to 2000) were invited to participate,
38 except for those affected by diseases causing significant nutritional status
39 impairment (neoplasia, chronic infections), or changes in energy metabolism (hyper-
40 hypothyroidism), or treated with special diets (diabetes, phenylketonuria). Patients
41 on enteral tube or parenteral feeding were also excluded. All children had to be free
42 from acute infections and were being treated only with antiepilectic drugs at the
43 time of the study.

44 Seventeen children with RE, (13 boys and 4 girls) mean age 9.06 ± 3.17, range 3-16
45 years were enrolled and studied. The Research ethics board approval was obtained
46 and a consent form was signed by all parents/ caregivers before the beginning of the
47 study.

48 **Experimental procedure**

49 The assessment of nutritional status and energy metabolism was conducted at the
50 International Centre for the assessment of Nutritional Status (ICANS), University of
51 Milan. On the same morning anthropometric measurements and resting energy
52 expenditure were evaluated. Dual-energy X-ray absorptiometry (DXA) was performed
53 on a sub sample of children. The evaluation of food intake was completed at the
54 Human Nutrition and Eating Disorders Research Centre, University of Pavia in all
55 children.

56 **Anthropometric measurements**

57 Anthropometric measurements were taken by the same operator, according to
58 conventional criteria and measuring procedures [12]. Body Weight (BW, Kg) and
59 Body Height (BH, cm) were measured to the nearest 100 g and 0.5 cm respectively.
60 When the child was not able to maintain the erect position the BW was assessed
61 measuring the parent's weight with the child in their arms and subtracting the weight
62 of parent and the BH was measured using supine length.
63 Body Mass Index (BMI) was calculated using the formula: BMI (Kg/m^2) = BW (Kg) /
64 BH^2 (m^2). Triceps and subscapular skinfold thickness measurements, were used to
65 provide an estimate of total body fat and were measured as proposed by Lohman
66 et al [12] by means of to Holtain LTD caliper. All the measurements were performed
67 on the non-dominant side of the body. They were made in triplicate for all sites and
68 the average of the three values was calculated for subsequent analysis.
69 The BW and BH were compared with the standards for linear growth derived from
70 the Tanner-Whitehouse growth charts [13] and the percentage of ideal BW
71 (%BW) and ideal BH (%BH) for sex and age at 50th percentile was calculated. Cut-
72 off point of malnutritional status was identified at 80% of the weight for age value.
73 According to Waterlow classification [14] children were defined as "stunted " when
74 their %BH was lower than 80% compared with the reference height for age. BW
75 was also espressed as a percentage of ideal weight for height, sex, and age (%IBW-
76 H) [15]. This index is used regularly as a measure of nutritional status in children
77 affected by several diseases such as cystic fibrosis [16], liver disease [17] and
78 tumors [18]. Ideal body weights for height was derived by comparing actual weight
79 with the 50th centile weight for a child of the same height who is on the 50th centile
80 for height [14]. Children were classified as "wasted" when their %IBW-H was lower
81 than 90% compared with reference values [14].

82 Skinfold thickness measurements, were compared with the reference standards
83 proposed by Rolland-Cachera [19] and were expressed as a percentage of ideal
84 value for sex and age at 50th percentile.

85 **Body composition assessment**

86 Measurements of fat mass (FM, Kg), fat free mass (FFM, Kg) and bone mineral
87 content (BMC, g) was performed with a Lunar DPX-IQ scanner (Lunar Corp, Madison,
88 WI) equipped with a paediatric software (version 4.6b). Total body scans were
89 performed with subjects in the supine position. The entire body of each subject was
90 scanned, beginning at the top of the head, with the "medium t" scan mode. The
91 mean measurement time was 15 min; radiation exposure was < 7μSv. Daily quality-
92 assurance tests were performed according to the manufacturer's directions. All scans
93 were performed and analysed by the same operator.

94 **Resting energy expenditure**

95 Resting energy expenditure (REE) was estimated by indirect calorimeter using an
96 open-circuit ventilated-hood system (Sensor Medics 29, Anaheim, CA). All
97 measurements were made in post-absorptive state (12-14 h fast) in a thermoneutral
98 environment (24-26°C) and with no external stimulation. The calorimeter was
99 calibrated at the beginning of each test with two reference gas mixtures (26% O_2
100 and 74 % N_2 the first, 16% O_2, 4.09% CO_2 and 79.91% N_2 the second). The children
101 were rested for a least 20 min before the measurements which were on subjects
102 awake and supine. Approximately 30 min of respiratory gas exchange data were
103 collected. The first 5-10 min of data were discarded, as recommended by Isbell et al
104 [20]. This allowed the children time to acclimatise to the canopy and instrument
105 noise. The average of the last 20 min of measurements was used to determine 24h
106 REE according to standard abbreviated Weir equation [21]:

107 REE (Kcal/day) = [3.941 VO_2 (mL/min) +1.106 VCO_2 (mL/min)] * 1.44.

108 **Dietary intake data**

109 A seven days food diary was used to collect dietary food intake. Parents were
110 trained by dietician in food recording procedures; when the food record was
111 completed, the family came to the Human Nutrition and Eating Disorders Research
112 Centre, and each day of the food record was assessed for completeness by a trained
113 dietician. Incomplete days were excluded from the nutrient analysis. Food records
114 were coded and analysed using the Dieta Ragionata software (Esi Stampa Medica srl,
115 Milano ,Italiy). Total energy intake (EI, kcal), proteins, lipids, carbohydrates, some
116 minerals and vitamins (calcium, phosphate, potassium, iron, zinc, copper, tiamin,
117 riboflavin, niacin, vitamin A vitamin C) were calculated and compared with
118 European Recommended Dietary Allowances for sex and age [22]. The adequacy
119 index was calculated according to the following formula:

120 daily nutrient intake (g)/ recommended allowance (g) for sex and age * 100.

121 **Statistical analysis**

122 Results are expressed as mean ± SD. *t*-tests were used to compare observed with
123 predicted variables in RE children. Adequacy index was calculated to compare the
124 macro and micro nutrient intake with recommended allowance values [22]. Pearson
125 correlation analysis was used to investigate relations between variables; significance
126 is defined as $p < 0.05$. Statistical analysis was done using Statistica for Windows
127 version 4.5 (StatSoft).

128

128 **results and discussion**

129 Children's neurological diseases are show in Figure 1.

130 All children were mildly or severely mentally retarded and had physical
131 developmental delay. Neurological impairment was classified according to difficulty
132 with mobility which was graded as mild (little or no difficulty walking), moderate
133 (difficulty walking but does not need aids or a helper), or severe (needs aids and/or
134 helper or cannot walk). Only 29% of the children had a mild or not difficulty walking
135 whereas 41% had a severe grade. 35% of children presented feeding problems
136 (chewing and swallowing difficulties) and 70% presented an impairment of self-
137 feeding skills.

138 The anthropometric characteristics of the children are shown in table 1. Their mean
139 BW and BH were lower but not significantly different from normal values for sex and
140 age. When we consider individual values, we can observe that seven patients
141 (41,2%) had %BW lower than 80% and can therefore be classified as malnourished.
142 Only one patient had %BW higher than 120%. No patient was stunted. IBW-H for
143 sex and age was found lower but not significantly different in comparison with
144 reference value. Four patients (24,0%) had %IBW-H less than 90 % (wasted) and
145 one patient had a % IBW-H higher than 120%.

146 Mean values of arm circumference (19,52±4,08) and subscapular thickness
147 (6,74±2,76) were found respectively 6% and 4% lower than reference value for sex
148 and age [23] (mean value of arm circumference 20,84±2,67; mean value of
149 subscapular thickness 7,50±2,10).

150 On the contrary mean values of triceps thickness (9,63±6,46) were 20% higher than
151 reference values for sex and age (8,04±1,99) [24]. Three patients had triceps
152 thickness values lower than third percentile.

153 The degree of neurological impairment and the presence of feeding problems was
154 correlated with %BW (r^2= 0,26 and r^2=0,10 respectively). The same results were
155 achieved using, as an index of the nutritional status, the %IBW-H (r^2= 0,32 and
156 r^2=0,17 respectively). This data suggest that the degree of disability itself influences
157 greatly the nutritional status of the children with RE.
158 Mean REE was 5% lower than predicted values with a great variation between
159 subjects (range: from – 49% to + 32%).
160 With regard to body composition, dual-energy X-ray absorptiometry (DXA) was made
161 in a subgroup of children (n=6). Figure 2 shows age-related differences in fat mass,
162 fat free mass and bone mineral content in RE patients in comparison to male and
163 female reference value [25,26]
164 All wasted patients undergoing DXA evaluation showed a severe reduction in fat
165 mass and an increased fat mass (in comparison with sex and age reference values)
166 was found in 3 patients with normal body weight indexes (%BW 97,0%±2,6 and
167 %IBW-H 102,2±11,1)
168 Pearson correlations between %FM from DXA and anthropometric indexes were
169 significant (r^2=0,79 %FM vs %BW; r^2= 0,70 %FM vs %IBW-H).
170 The fat mass distribution appeared modified with a prevailing increase of FM in the
171 limbs (figure 3A).
172 FFM was lower than reference values in all children and there was a strong
173 correlation between FFM from DXA and anthropometric indexes (r^2=0,86 FFM (kg) vs
174 %BW; r^2= 0,95 FFM (kg) vs %IBW-H). Moreover, there appeared a change in FFM
175 distribution with a reduction in the limbs (figure 3B). Children with more severe
176 neurological impairment had the lowest amount of FFM (r^2=0,30).

177 Mean BMD was 0,827 ±0,128 with mean z-score –0,187±1,36. In particular 3
178 children were osteopenic and 1 patient presented osteoporosis at the time of the
179 measurements.
180 Mean daily energy intake (EI) was 1334±295 kcal, different ($p=0.021$) from the
181 recommended energy intake for age and sex (1618±358 kcal) [27] Protein intake for
182 body weight was 2.77±1.03 g/kg.
183 Fat intake average was 39,4±8,3 % and mean intake of saturated acids fatty
184 11.08±3.78 % of energy intake. Cholesterol intake was 153.40±93.58 mg/die.
185 The percentage of total energy intake derived from total carbohydrate was
186 42,7±6,7, greatly lower than recommended values. Complex carbohydrates
187 represented only 19% of total energy intake. Mean daily fibre intake was low
188 (7,3±5,3 g).
189 Because the recommended intakes of micronutrients are different for sex and age we
190 evaluated the adequacy of nutrient intake using the following index: % adequacy =
191 Eurpopean Reccomanded dietary allowances (RDA) for sex and age / estimated
192 intake * 100 . The results are shown in table 3. With the exception of copper, there
193 was a low intake of minerals, in particular calcium, iron and zinc. Also thiamin,
194 riboflavin and niacin were also 25% below the European Recommended Dietary
195 Allowances for sex and age [22].
196 The energy intake normalised for body weight (EI/BW -kcal/kg-) increased in
197 patients with severe neurological impairment (r^2= 0,37) while no correlations were
198 found between EI/BW and feeding problems or impairment of self-feeding skills.
199 The EI/BW was significantly greater in patients with lower values of %BW and
200 %IBW-H (r^2= 0,37 and r^2=0,42 respectively).

201 The measured REE normalised for body weight (REE/BW -kcal/kg-) was higher in
202 children with severe disabilities in comparison to other subjects.

203 Our study aimed to evaluate nutritional status, energy metabolism and food
204 intake in children affected by drug resistant epilepsy. We hypothesised that RE can
205 induce a nutritional status impairment.

206 In our study about 70 percent of patients had a moderate or severe neurological and
207 self-feeding skills impairment.

208 Using some anthropometric indexes (%BW, %BH and %IBW-H) as criterion for the
209 assessment of nutritional status, our results demonstrated the existence of
210 nutritional status impairment. According to these criterions about 40% (applying
211 %BW as index of nutritional status) resulted malnourished and 24% (applying
212 %IBW-H) of children appeared wasted and only one patient resulted over
213 nourished for both indexes. However, all the children had deficits in mean values of
214 both measurements compared with reference values

215 From these data it would seen that the identification of a nutritional impairment
216 depends on which anthropometric criteria is used. In particular by just applying the
217 %IBW-H index, children who are under 80% weight for age value would not be
218 identified. This value is the safety nutritional cut-off that signifies the healthy
219 nutritional status, therefore %BW should be used together with %IWH.

220 Of all of the variables we studied, the degree of neurological impairment was the
221 best predictor of nutritional status, a finding that is consistent with those of a
222 previous study focused on children with cerebral palsy [10].

223 The body composition assessment was used to better define the nutritional status in
224 a subgroup of RE children. FM was reduced in undernourished patients and was
225 well correlated with anthropometric indexes of nutritional status. There was a low

226 fat free mass in all patients although it was more evident in patients with a severe
227 neurological condition. This low FFM in all patients suggesting that even patients
228 with normal anthropometric indexes could be undernourished. More than 50% of
229 the children had a low BMD.
230 Macronutrients intake was unbalanced leading to a hyperproteic, hyperlipidic and
231 hypoglucidic diet with a very low amount of fibre. Moreover the mean daily intake of
232 calcium, iron, copper, tiamin, riboflavin and niacin was greatly reduced compared
233 with European Recommended Dietary Allowances for sex and age [22].
234 On average, daily energy intake was lower than recommended values; however we
235 found an unexpected lack of agreement between EI/BW and nutritional status
236 because the EI/BW was higher in the more malnourished patients. An explanation
237 could be that there was a higher REE/BW in the more malnourished children;
238 REE/BW index was linked to the degree of neurological impairment.
239 Among the children in our study, those with the worst neurological condition were
240 hypercatabolic. Although their EI/BW was higher, they needed more energy than
241 they got from their energy intake, so leading to a malnutrition status.
242 Undernutrition has been recognized in other neurological diseases both in adults and
243 in children [28-30]. The importance of malnutrition in patients with RE is related to
244 the possible influence of nutritional status in the long-term prognosis, as well as to
245 the predisposition to infections [31].
246 In conclusion our study showed that undernutrition is a frequent condition in RE
247 children and it can be easy detected by anthropometric evaluation.
248 Further studies should be made in order to understand which of the anthropometric
249 indexes better defines the nutritional status of these RE children. Furthermore they
250 should undergo a routine evaluation of the body composition, so as to assess their

nutritional status. If the total amount and regional distribution of fat lean body mass and bone mineral content is knows then a personalised diet and physical therapy program could be planned.

The use of standard predictive formulae for the evaluation of resting energy expenditure, has limited applications in this clinical group. However, by combining regular REE measurements with the analysis of the dietary intake, the specific energy requirements could be optimized and the macro, micro nutrient daily intake could be corrected.

Clearly there is much to be learnt to define optimal dietary advice for RE patients, and to define the relation between dietary components and indices of nutritional status.

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List of abbreviations:

%BH= percentage of ideal body height for sex and age at 50th percentile

%BW= percentage of ideal body weight for sex and age at 50th percentile

%IBW-H= percentage of ideal weight for height, sex, and age

BH= Body Height (cm)

BMC= bone mineral content (g)

BMI= Body Mass Index (kg/cm^2)

BW= Body Weight (Kg)

DXA= Dual-energy X-ray absorptiometry

EI/BW= energy intake normalised for body weight (kcal/kg)

EI= Total energy intake (kcal/die)

FFM= fat free mass (Kg)

FM= fat mass (Kg)

RE= Refractory epilepsy

REE/BW=Resting energy expenditure normalised for body weight (kcal/kg)

REE= Resting energy expenditure (kcal/die)

Figure legends

Figure 1: neurological diseases in RE children group (n=17).

Figure 2: body composition age-related difference in fat mass (A), lean body mass (B) and bone mineral content (C) in RE patients (n=6) in comparison to male and female reference values

Figure 3: fat mass (A), fat free mass (B) and bone mineral dendity (C) regional distribution in RE patients (n=6)

Table 1: nutritional status and resting energy expenditure in RE children (n=17).

	Mean (SD)	Range
BMI (kg/m2)	15,7 (3,5)	10,4-24,9
%BW	90,0 (29,0)	45,5-175,7
%BH	96,0 (6,6)	80,4-105,7
%IBW-H	96,0 (19,7)	65.0-147,4
% REE	94,8 (26,3)	51,0-132,0
REE/BW (kcal/kg)	38.5 (8.6)	27.2-49.0
Respiratory Quotient	0.83 (0.09)	0.75-0.91

BMI: body mass index
%BW: percentage of ideal body weight for sex and age
%BH: percentage of ideal body height for sex and age
%IBW-H: percentage of ideal weight for height, sex and age
%REE: percentage of measured REE/ predicted REE

Table 2: daily micronutrients intake and evaluation of adequacy intake in children with RE (n=17)

Micronutrients	Mean (SD)	% adequacy (SD)
Calcium (mg/die)	519,7 (284,9)	51,0 (27,3)
Phosphate (mg/die)	708,2 (186,6)	69,9 (16,7)
Potassium (mg/die)	1594,1 (564,9)	83,6 (35,7)
Iron (mg/die)	6,2 (2,6)	63,7 (1,7)
Zinc (mg/die)	4,1 (1,9)	56,8 (1,5)
Copper (mg/die)	0,8 (0,4)	116,8 (62,2)
Thiamin (mg/die)	0,6 (0,2)	63,6 (22,1)
Riboflavin (mg/die)	0,9 (0,2)	74,1 (38,7)
Niacin (mg/die)	9,4 (6,2)	72,2 (46,4)
Vitamin A (mcg/die)	499,7 (279,7)	97,2 (52,1)
Vitamin C (mg/die)	53,8 (34,9)	116,4 (77,5)

% adequacy = recommend intake for sex and age / estimated intake * 100

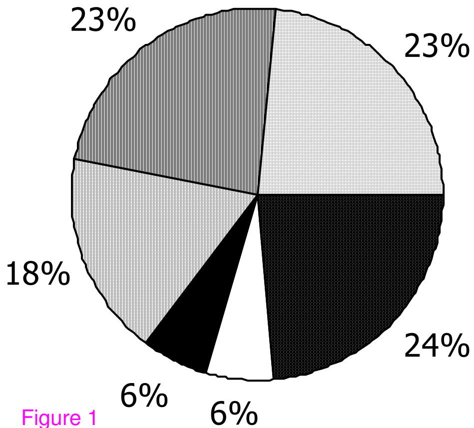
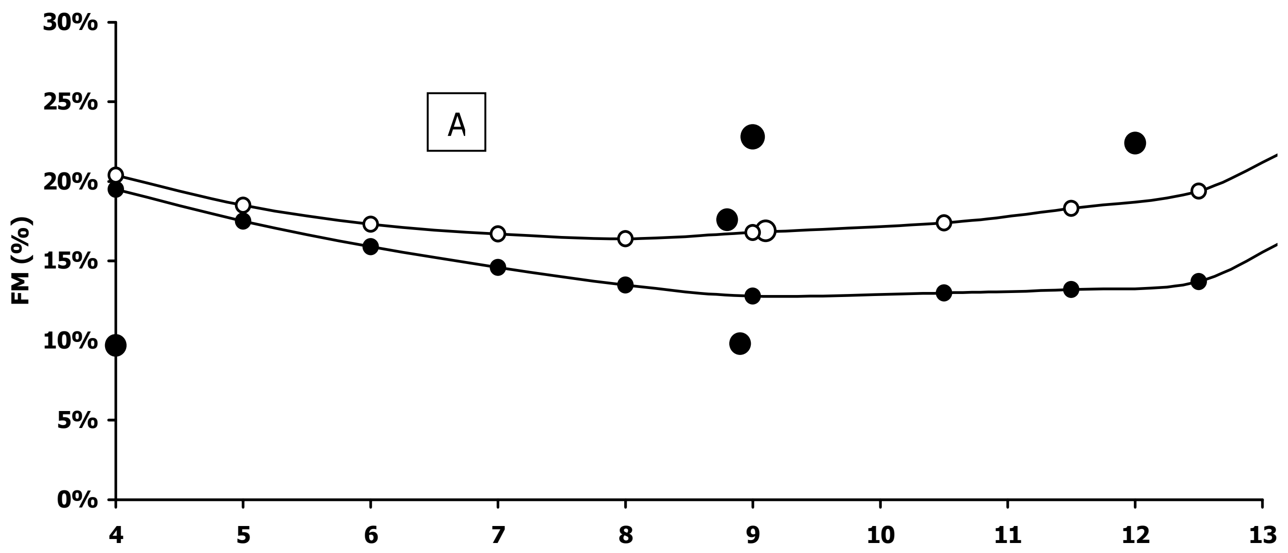
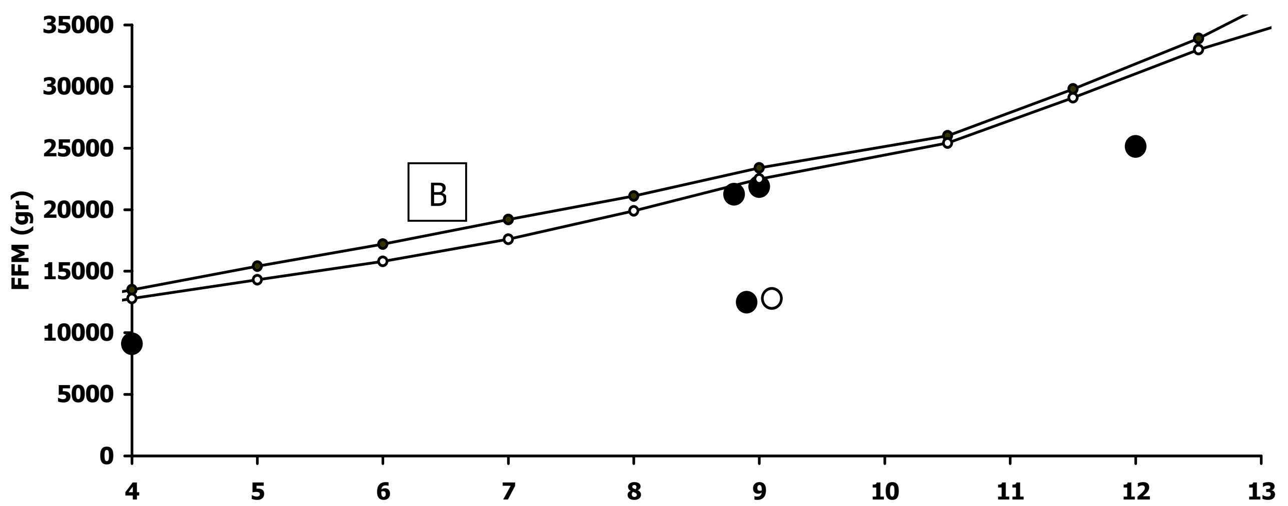


Figure 1





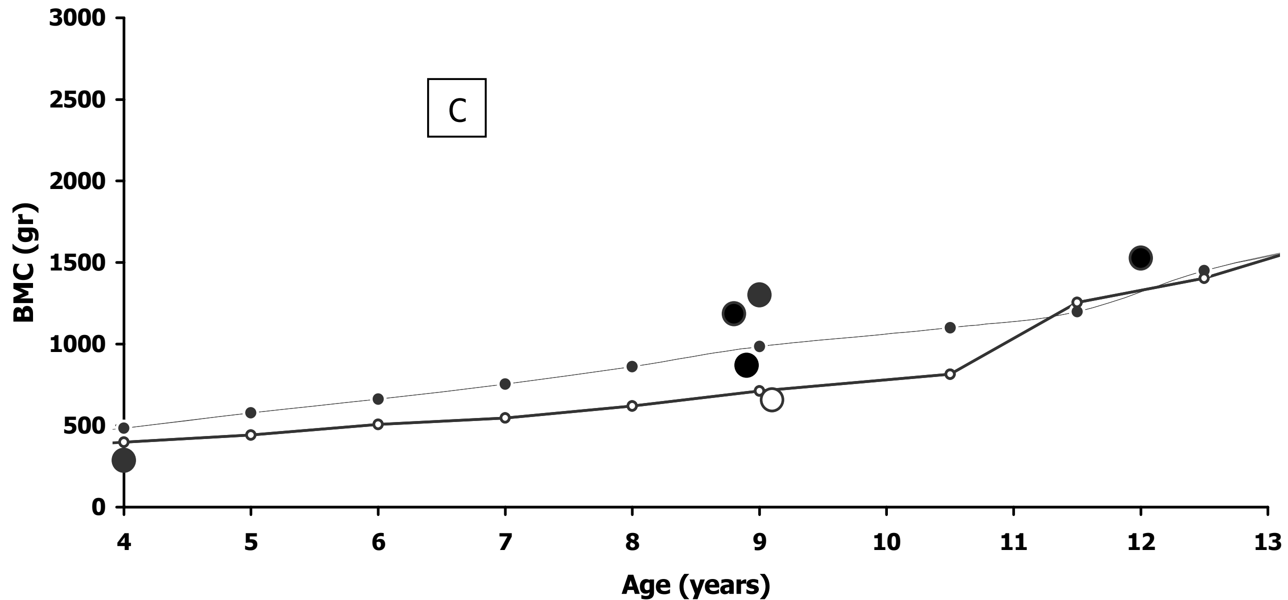
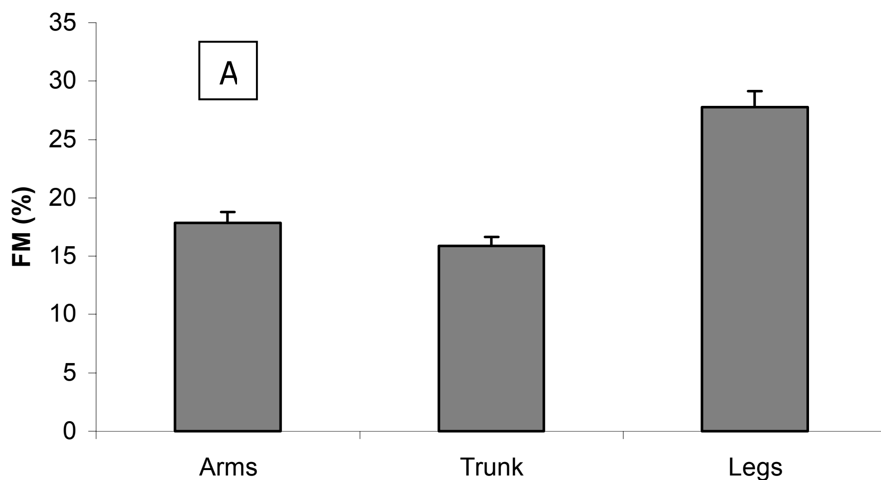
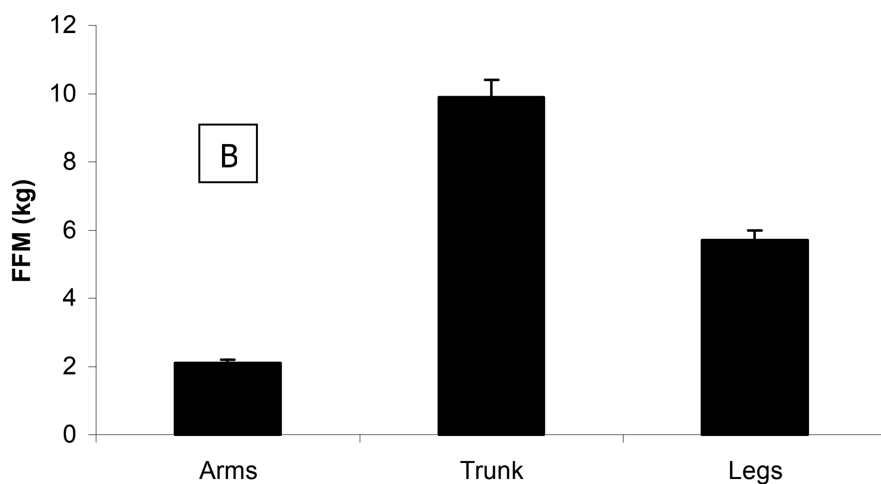


Figure 2





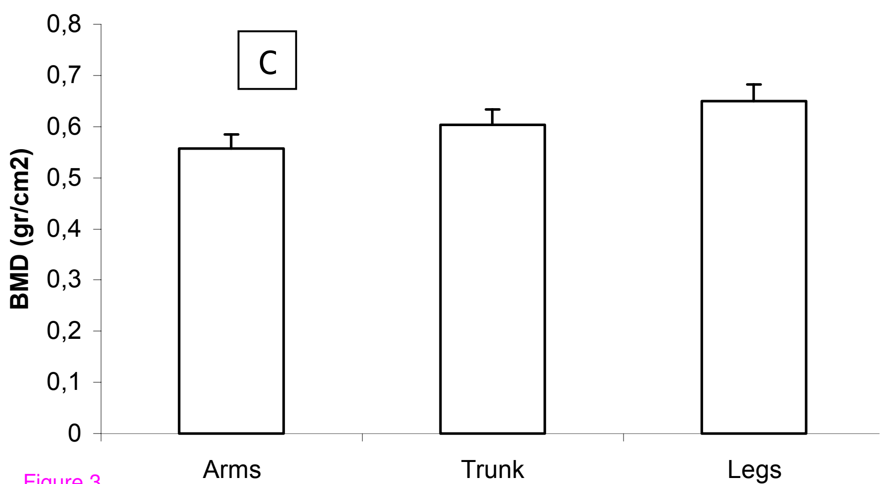


Figure 3