Serum leptin levels in children with cerebral palsy: Relationship with growth and nutritional status

Ayten Yakut, Ener Cagri Dinleyici, Sadi Idem, Coskun Yarar, Nesrin Dogruel & Omer Colak

Department of Pediatric Neurology, Eskisehir Osmangazi University, Faculty of Medicine, Eskisehir, Turkey.

Correspondence to: Ener Cagri Dinleyici, M.D.
Department of Pediatrics
Eskisehir Osmangazi University, Faculty of Medicine
TR-26480 Eskisehir, TURKEY
PHONE/FAX: +90 222 2290064
EMAIL: timboothtr@yahoo.com

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Abstract

AIM: Children with Cerebral Palsy (CP) are generally undernourished and growth retarded than normal children. The reasons of malnutrition are not only due to poor nutritional status but also nonnutritional factors including negative neurotrophic effects and indirect factor such as immobility, endocrinological abnormalities or spasticity that energy requirements might be contributing factors. Several studies indicated that leptin which is produced by adipocytes, might regulate energy intake and expenditure. The aim of this study is to determine serum leptin levels in children with CP and to investigate the relationship between nutritional status and anthropometric measurements.

METHODS: Forty children with CP and 18 healthy controls were included in this study. The weight, height, body mass index (BMI), upper arm length (UAL) and triceps skinfold thickness (TST) was measured in all children. Serum leptin, growth hormone, C-peptide and cortisol levels were studied. Based on TST measurement CP patients were divided as DSF group (decreased subcutaneous fat) and non-DSF group (nondecreased subcutaneous fat).

RESULTS: UAL were shorter and TST measurements were thinner than control group ($p<0.05$, $p<0.01$). Group DSF had lower leptin concentrations compared to Group non-DSF and controls ($p<0.001$, $p<0.001$). On the other hand non DSF group had higher leptin levels than controls ($p<0.05$). There was a positive and significant correlation between leptin and anthropometric measurements, especially TST in children with CP. Serum leptin levels were also lower in non-ambulatory children than ambulatory children with CP ($p<0.05$).

CONCLUSION: This study has shown that triceps skinfold thickness is better index for the evaluation of nutritional status in children with CP. Serum leptin levels were lower in CP, especially in DSF group. The possible explanation of this finding may not only related with malnutrition, but also immobility related other factors such as bone metabolism and spasticity. We concluded that leptin which regulates energy intake might have a role of nutritional disorders in cerebral palsy. To better understand this relationship further studies are needed.

ORIGINAL ARTICLE

Introduction

Cerebral palsy (CP) is an umbrella term covering a group of non progressive but often changing, motor impairment syndromes secondary to lesions or anomalies of the brain arising in the early stags of its development [1]. In addition to motor dysfunction, children with CP have medical and neurologic complications and also they have more growth failure and malnutrition than normal children [1–3]. Both nutritional and non-nutritional factors such as oral motor dysfunction, feeding problems, teeth decays, malocclusion, sucking and chewing difficulties, inadequate nutrient intake and have been proposed to explain the malnutrition in these children [2-4]. On the other hand, seizures, neuroendocrine abnormalities, spasticity and abnormal physical activity that energy requirements and the lack of potentially growth promoting activity such as weight bearing and ambulation, might be contributing factors for malnutrition in CP [5–10]. Also children with CP are at high risk for growth failure even without malnutrition [11].

The assessment of linear growth and nutritional status is difficult in children with CP because of spasticity and joint contractures [2, 3, 8, 12]. Triceps skinfold thickness (TST) and upper arm length (UAL) measurements are generally used for evaluation of the nutritional status and growth in these children. Triceps skinfold thickness may reflect the malnourished state more rapidly. It has been demonstrated that subcutaneous adiposity was decreased according to the measurement of TST in children with CP [2–3, 7–8].

Several studies have indicated that leptin might play a role in the regulation of energy expenditure in humans. Leptin is a protein product of the obesity gene whose expression is mainly localized in adipose tissue, regulates body weight and adipose tissue mass through a feedback metabolism. Leptin is thought to reduce food intake, stimulate energy expenditure, inhibit insulin secretion from the pancreas, increase insulin utilization, induce lypolysis, and affect triglyceride synthesis [13–16]. It has been reported that serum leptin concentrations are decreased in children with malnutrition and increased in most obese patients [17–21]. To our best knowledge serum leptin levels have not been reported in cerebral palsied children.

The aim of this study is to determine serum leptin levels of children with CP and to investigate the possible relationship between nutritional status, linear growth parameters and serum cortisol, growth hormone (GH), and C-peptide level.

Materials And Methods

In this study 40 children (17 girls and 23 boys) aged between 3 to 17 years with CP who were diagnosed at Pediatric Neurology Unit of Osmangazi University Faculty of Medicine, were studied. The control group consisted of 18 (6 girls and 12 boys) age-matched healthy children. Clinical classification of CP included 36 with spastic type and 4 with mixed type. According to motor dysfunction spastic CP was divided as quadriparesis (n=28), hemiparesis (n=5), and dyplegia (n=3). A 50% (n=20) of children with CP had epilepsia and 77.5% of them were mentally retarded. A 72.5% (n=34) of the children with CP were non-ambulatory. Hypothyroidism was excluded by measuring thyroid function tests. Children with CP were excluded from the study if they had any other chronic illness or used any medications known to affect growth and body composition. Electroencephalography was done in patients who have a history of epilepsy. Brain magnetic resonance imagings were also performed.

All the children with CP were evaluated by anthropometric measurements including weight, height, upper arm length (UAL), triceps skinfold thickness (TST), and body mass index (BMI). Weight and height measurements were carried out with the children wearing light clothes. Height was measured with a Harpenden portable stadiometer to the nearest 0.1 cm and weight with a Seca scale to the nearest 0.1 kg. The UAL was measured as then distance from the acromion to the head of the radius, with the child sitting or standing [8]. Body mass index was calculated with this formula: weight (kg) / height^2 (m^2) [22]. Skinfold thickness was measured to 0.1 mm on the non-dominant side of the body at the triceps sites, using Holtain skinfold calipers. Each skinfold measurement was taken in triplicate. The mean of the three skinfold measurement was calculated and used in the analysis. The patients were classified to be malnourished if their TST were below the 15th centile for age [8]. According to TST measurements cerebral palsied children divided two groups as follows: the group that decreased subcutaneous fat (DSF) and non-decreased subcutaneous fat (nDSF).

Serum electrolytes, glucose, blood urea nitrogene, creatinine, alkaline phosphatase, total cholesterol, triglyceride, HDL-C, urinary and blood amino acids, TSH, T3, T4, C-peptide, growth hormone, cortisol levels were studied for all children. Blood samples for leptin assay were obtained from all subject and kept at –70^{o}C until the time of hormone assay. Serum total cholesterol, triglyceride, calcium, phosphorus, alkaline phosphatase levels were determined by enzymatic assay (Roche Diagnositc Kits) with BM HITACHI 717/7150 modular autoanalyser. Serum HDL-C was determined after precipitating serum with phosphotungstic acid and magnesium reagents. Serum C-peptide and GH levels were evaluated with chemiluminoassay technique by Immulite one hormone autoanalyser and using commercial kits. Serum T3, T4, TSH and cortisol levels were evaluated with chemiluminoassay technique by Immulite 2000 hormone autoanalyser and using commercial kits. Leptin concentrations were determined by ELISA using commercially available kit (ELISA DSL Human Leptin Kit).

All analyzes were performed with the SPSS 11.0 software package (Chicago, IL, USA). All anthropomet-

Table-I: Comparisons of anthropometric measurements of the study groups

	Cerebral Palsy			Control (n=18)
	DSF n=20	Non-DSF n=20	**Total n=40**	
Age (months)	68.8 ± 10.9	91.6 ± 13.1	94.0 ± 9.3	87.0 ± 10.3
Gender(Female/Male)	9/11	8/12	17/23	6/12
Weight (kg)	14.8 ± 1.3[a]	26.1 ± 2.1	20.5 ± 1.5	25.3 ± 3.1
Height (cm)	101.5±4.6 [a,b]	124.6 ± 4.9	113.0 ± 3.8	120.2 ± 5.5
VKI (kg/m^2)	14.2 ± 0.5[c]	16.4 ± 0.6	15.3 ± 0.4	16.5 ± 0.4
UAL (cm)	17.8 ± 0.9 [a]	23.5 ± 0.9	20.7 ± 0.8[d]	23.5 ± 1.0
TST (mm)	5.25 ± 0.33	9.70 ± 0.39	7.47 ± 0.43[e]	9.28 ± 0.43

* data shown as mean ± SEM.**DSF: decreased subcutaneous fat
a- p<0.001, DSF group vs control and DSF group vs non-DSF group
b- p<0.05, DSF group vs control.
c- p<0.01, DSF group vs. control and DSF group vs non-DSF group
d- p<0.05, total CP group vs. control
e- p<0.01, total CP group vs. control

Table-II: Serum leptin levels according to TST measurements in cerebral palsy and control group*

	Cerebral Palsy Group			Control (n=18)
	DSF (n=20)	Non-DSF (n=20)	Total (n=40	
Leptin (ng/dl)	1.45a,b (1.14-2.56)	4.35c (4.07-8.15)	3.77 (2.57-4.95)	2.52 (1.81-3.23)

* data are present as median (95% CI)
a- p<0.001, DSF group versus nDSF
b- p<0.05, DSF group versus control group
c- p<0.01, nDSF group versus control group

ric values were expressed as mean ± SEM. Statistical analysis comparing the two groups was made using the non-parametric Mann-Whitney U test. Correlation analysis was performed using Pearson's correlation test. In all analysis p value <0.05 was accepted as statistically significant.

Results

Anthropometric measurements of the study group are presented in Table I. There were no significant differences in body weight or body height or BMI between the cerebral palsied children and healthy controls. The children with CP were significantly shorter UAL measurements than normal children (20.6 ± 0.8 vs. 23.5 ±1.0 cm, p<0.05). Triceps skinfold thickness were significantly lower in CP than normal children (7.47 ± 0.43 vs. 9.28 ± 0.43; p<0.01). Fifty percent of children with CP have decreased subcutaneous fat according to TST. Weight, height and BMI were lower in DSF group than non-DSF group (p<0.001, p<0.001, p<0.01 respectively). The DSF group showed shorter UAL than non-DSF group (17.8 ± 0.9 vs. 23.5 ± 0.9; p<0.001) and control group (p<0.001). Weight, height, UAL and BMI measurements were similar between DSF and control groups.

Overall serum leptin levels were not statistically significant when compared to control group (p>0.05) (Table II, Figure 1). But in DSF group serum leptin levels were significantly lower than non-DSF and also control group (p<0.001, p<0.05). On the other hand in non-DSF group serum leptin levels were significantly higher than control group (p<0.01) (Table II, Figure 2).

There was no statistically significant difference in serum C-peptide, cortisol and basal GH levels between CP and control groups and also no differences between DSF, non-DSF and control groups (p>0.05 for all).

According to ambulatory status weight, height, BMI, UAL, and TST values are lower in non-ambulatory children with CP than ambulatory children with CP (p<0.05, p<0.05, p<0.01, p<0.01, p<0.05). Serum leptin levels were lower in non-ambulatory (1.72; 3.05–13.6 ng/dl) groups than ambulatory groups (5.67 ng/dl; 0.636–12.8 ng/dl) (p<0.05).

In CP group; serum leptin levels were positively correlated with age (r=0.324, p<0.05), height (r= 0.411, p<0.01), weight (r=0.623, p<0.001), BMI (r=0.576, p<0.001), UAL (r=0.500, p<0.01), TST (r=0.702,

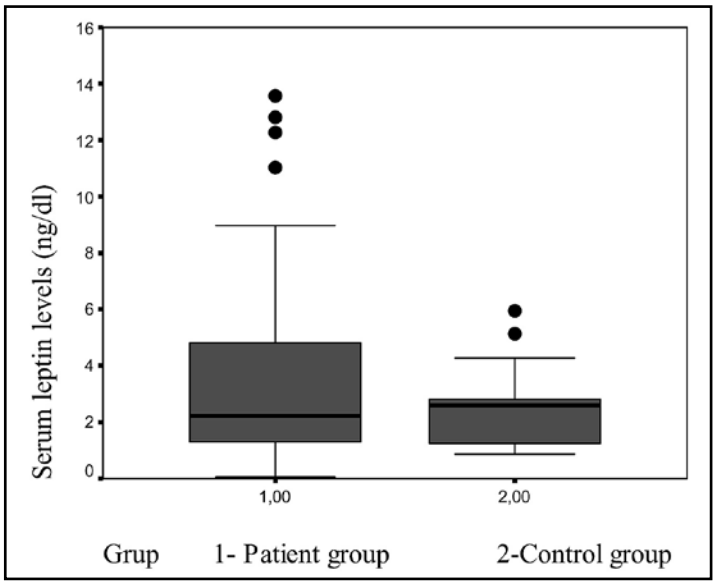

Figure 1. Comparisons of the serum leptin levels between patient and control group.

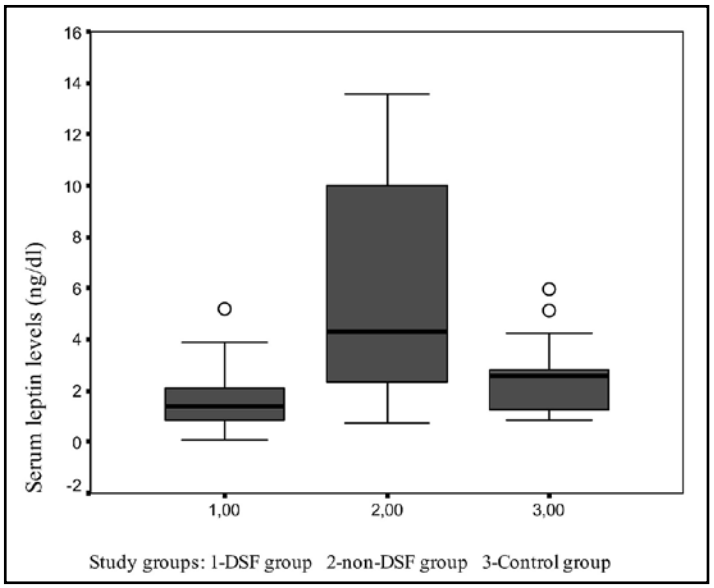

Figure 2. Comparisons of the serum leptin levels accoridng to TSFT levels.

p<0.001) and negatively correlated with basal GH levels (r=–360, p<0.05). Stepwise multiple regression analysis model including all correlated parameters and ambulatory conditions (R^2=0.739), TST predicted serum leptin levels positively (p<0.001) (Figure 3).

Discussion

Malnutrition and growth retardation are frequently seen but underestimated in children with CP because of joint contractures, immobility, and unclear interpretation of weight for height [2–3, 7–8]. Weight for height centile may not be valid nutritional indicator in children with disabilities [23]. Undernourished children with CP have changes in body composition and proportion compared with normally developing children [2–3, 6, 8]. Alterations include increased total body water, severely depleted peripheral fat stores, short stature and decreased bone density. Percentage of body fat measurements offer additional information in nutritional status as an indicator of total body energy reserves [11, 24]. Thus alternative anthropometric measures such as skinfold thickness, upper arm length, BMI, have more ability to identified linear growth in these children [3]. In our study TST measurements were significantly decreased and UAL were shorter in spastic cerebral palsied children than normal children despite of weight and height measurements were not different in both groups. Fifty percent of spastic cerebral palsied children have decreased TST which reflects the fat stores and indirect criteria of nutrition. In addition shorter UAL indicated that inadequate nutritional status. BMI was not different in cerebral palsied children than control group.

Although nutritional and non-nutritional factors may play a role developing malnutrition, the mechanism of growth deficiency in children with CP is unclear [5–6, 9]. The causes of malnutrition and growth retardation are not only related to inadequate energy intake but also abnormal patterns of energy expenditure in

these patients [25]. Cerebral palsy itself effects growth patterns negatively even with absence of malnutrition [6, 25]. Also spastic quadriparesis had negative effect on nutritional status in CP $_6$. The ratio of total energy expenditure to resting energy expenditure, which is indicating energy for nonbasal needs such as physiological activity and spasticity, was significantly lower in the spastic quadriplegic cerebral palsied children [26].

Recently it was reported that leptin is though to reduce food intake, induce lipolysis and therefore regulates of energy expenditure [27]. Because leptin is a protein derived from adipose tissue and is correlated with the thickness of subcutaneous fat, we measured the thickness of subcutaneous fat of all children. In our study 50% of CP patients have malnutrition according to TST. According to our results low leptin levels were correlated with the decreased subcutaneous fat and might be explained with malnutrition. Overall serum leptin levels were normal in CP group but it was low in DSF group than non-DSF group and control group. Recent reports demonstrated that serum leptin levels were decreased in malnourished children like our study and steadily increased with weigh gain [18–19]. Hytinantti et al. [15] hypothesized that factors other than adiposity, such as hormonal milieu, may interfere with the association with between leptin and adiposity. Serum leptin concentrations in humans are shown to be positively correlated with body fat ratio, BMI and serum insulin and cortisol levels [17, 21]. In our study serum leptin levels were positively correlated with mainly TST and negatively correlated with basal GH levels. To our study, serum leptin levels were lower in non-ambulatory children with CP We suggested that not only immobility but also immobility related other factors such as spasticity and bone disease might be contributing factors of malnutrition in these children.

Interestingly serum leptin levels in non-DSF group were higher than DSF and control groups. There were no obese patients in non-DSF group. In our study low serum leptin levels of cerebral palsied children with malnutrition might be expecting findings. However some studies in literature reported high serum leptin levels in some neurological disorders. Freeman et al. [28] reported that similar results that support the findings of our study. They reported that 15 children with neurologic impairment out of 41 children with mixed disabilities had significantly high serum levels than non-disabled children. Several hormones and cytokines were shown to alter serum leptin levels and also central nervous system alterations may be affected serum leptin levels. Huang et al. [29] reported elevated leptin concentrations in adult people after spinal cord injury and they explained this finding with sympathetic denervation, peripheral nerve palsy, recurrent infections and central neurotransmitter alterations. In our study, none of the patients were obese, but serum leptin concentrations were positively correlated with BMI, like other anthropometric features. Recently, Hjeltnes et al. [30] reported hyperleptinemia in adult patients with tetraplegia. They explained this finding with possibly impairment regulation of leptin metabolism and this might be distort thermogenesis and energy expenditure, thus explaining the enhanced risk of the metabolic syndrome and of osteoporosis among tetraplegic subjects.

In conclusion triceps skinfold thickness is better index than anthropometric measurements for the evaluation of nutritional status in cerebral palsied children. On the other hand, there was significant positive correlation in between serum leptin levels and TST. We concluded that growth retardation and malnutrition as reflected by triceps skinfold thickness, was not only associated with poor nutritional status but also nonnutritional factors and leptin which regulates energy intake might have a role in malnutrition with cerebral palsied children. However we could not conclude whether serum leptin level is the cause or the consequence of malnutrition. Although we could not measured total and resting energy expenditure in our patients, low leptin levels of DSF group can not be explained only by malnutrition but also immobility or muscle energy expenditure probably due to spasticity. Therefore further investigations should be done for the explanation of this mechanism.

REFERENCES

1 Mutch L, Alberman E, Hagberg B, Kodama K, Perat MV. Cerebral palsy epidemiology: where are we now and where are we going? Dev Med Child Neurol 1992; **34**: 547–51.
2 Stallings VA, Charney EB, Davies JC, Cronk CE. Nutrition-related growth failure of children with quadriplegic cerebral palsy. Dev Med Child Neurol 1993; **35**: 126–138.
3 Stallings VA, Charney EB, Davies JC, Cronk CE. Nutrition-related growth failure of children with diplegic or hemiplegic cerebral palsy. Dev Med Child Neurol 1993; **35**: 997–1006.
4 Gisel EG, Patrick J. Identification of children with cerebral palsy unable to maintain a normal nutritional state. Lancet 1988; **6**: 283–286.
5 Shapiro BK, Green P, Krick J, Allen D, Capute AJ. Growth of severely impaired children: neurological versus nutritional factors. Dev Med Child Neurol 1986; **28**: 729–733.
6 Stevenson RD, Roberts CD, Vogtle L. The effects of non-nutritional factors on growth in cerebral palsy. Dev Med Child Neurol 1995; **37**: 124–130.
7 Stevenson RD, Hayes RP, Cater LV, Blackman JA. Clinical correlates of linear growth in children with cerebral palsy. Dev Med Child Neurol 1994; **36**: 135–142.
8 Stevenson RD. Measurement of growth in children with developmental disabilities. Dev Med Child Neurol 1996; **38**: 855–860.
9 Coniglio SJ, Stevenson RD, Rogol AD. Apparent growth hormone deficiency with cerebral palsy. Dev Med Child Neurol 1996; **38**: 797–804.
10 Kong CK, Tse PW, Lee WJ. Bone age and linear skeletal growth of children with cerebral palsy. Dev Med Child Neurol 1999; **41**; 758–765.
11 Chad KE, McKay HA, Zello GA, Bailey DA, Faulkner RA, Snyder RE. Body composition in nutritionally adequate ambulatory and non-ambulatory children with cerebral palsy and a healthy reference group. Dev Med Child Neurol 2000; **42**: 334–339.
12 Troughton KEV, Hill AE. Relation between objectively measured feeding competence and nutrition in children with cerebral palsy. Dev Med Child Neurol 2001; **43**: 187–190.

13 Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse gene and its human homologue. Nature 1994; **372**: 425–432.
14 Yu WH, Kimura M, Walczewska A, Karanth S, McCann SM. Role of leptin in hypothalamic-pituitary function. Proc Natl Acad Sci USA 1997; **94**: 1023–8.
15 Hytinantti T, Koistinen HA, Koivisto VA, Karonen SL, Andersson S. Changes in leptin concentration during the early postnatal period: adjustment to extrauterine life?. Pediatr Res 1999; **45**: 197–201.
16 Fruhbeck G, Jebb SA, Prentice AM. Leptin: physiolgy and pathophysiology. Clin Physiol 1998; **18**: 399–419.
17 Falorni A, Bini V, Molinari D, Papi F, Celi F, DiStefano G, et al. Leptin serum levels in normal weight and obese children and adolescents: relationship with age, sex, pubertal development, body mass index and insulin. Int J Obes Relat Metab Disord 1997; **21**: 881–890.
18 Kılıc M, Taskın E, Ustundag B, Aygun AD. The evaluation of serum leptin level and other hormonal parameters in children with severe malnutrition. Clin Biochem 2004; **37**: 382–387.
19 Soliman AT, ElZalabany MM, Salama M, Ansari BM. Serum leptin concentrations during severe protein-energy malnutrition: correlation with growth parameters and endocrine function. Metabolism 2000; **49**:819–825.
20 Kirel B, Dogruel N, Akgun N, Kilic FS, Tekin N, Ucar B. Serum leptin levels during childhhod and adolescence: relationship with age, sex, adiposity and puberty. Turk J Pediatr 1999; **41**: 447–455.
21 Hassink SG, Sheslow DV, de Lancey E, Opentanova I, Considine RV, Caro JF. Serum leptin in children with obesity: relationship to gender and development. Pediatrics 1996; **98**: 201–203.
22 Cole TJ, Bellizzi, MC, Flegal KM, Dietz WH. Establishing a standard definition for child overweight and obesity worldwide: international survey. BMJ 2000; **320**: 1–6.
23 Samson-Fang LJ, Stevenson RD. Identification of malnutrition in children with cerebral palsy: poor performance of weight-for-height centiles. Dev Med Child Neurol 2000; **42**: 162–8.
24 Spender QW, Cronk CE, Stallings VA, Hediger ML. Fat distribution in children with cerebral palsy. Ann Hum Biol 1988; **15**: 191–196.
25 Hemingway C, McGrogan J, Freeman JM. Energy requirements of spasticity. Dev Med Child Neurol 2001; **43**: 277–278.
26 Stallings VA, Zemel BS, Davies JC, Cronk CE, Charney EB. Energy expenditure of children and adolescents with severe disabilities: a cerebral palsy model. Am J Clin Nutr 1996; **64**: 627–634.
27 Van Gaal LF, Wauters MA, Mertens IL, Considine RV, De Leeuw IH. Clinical endocrinology of human leptin. Int J Obesity Relat Metab Disord 1999; **23** (Suppl 1): 29–36
28 Freeman AC, Yousafzai AK, Filteau SM, Pai M. Serum leptin in disabled and non-disabled children in an Indian slum population. Eur J Clin Nutr 2002; **56**: 967–72.
29 Huang TS, Wang YH, Chen SY. The relation of serum leptin to body mass index and to serum cortisol in men with spinal cord injury. Arch Phys Med Rehabil 2000; **81**: 1582–1586.
30 Hjeltnes N, De Groot P, Birkeland KI, Falch JA, Iversen PO. Tetraplegic subjects have hyperleptinaemia with marked circadian variation. Clin Endocrinol (Oxf) 2005; **62**: 223–227.