Original Paper

Creatine kinase fluctuations in children with Obstructive sleep apnea syndrome (OSAS)

Is there a relationship?

Afroditi Sakellaropoulou[1], MD, PhD,
Katerina Haidopoulou[2], MD, PhD,
Maria Emboriadou[3], MD, PhD,
Maria Hatzistilianou[3], MD, PhD,
Andreas Giannopoulos[4], MD, PhD

[1]2nd Paediatric Department, Children's General Hospital «Panagioti and Aglaia Kyriakou», Athens, Greece
[2]4th Paediatric Department, Medical School, Aristotle University of Thessaloniki, Greece
[3]Medical School, Aristotle University of Thessaloniki, Greece
[4]2nd Paediatric Department, Medical School, Aristotle University of Thessaloniki, General Hospital "AHEPA", Thessaloniki, Greece

Key words:
- Creatine kinase,
- Obstructive sleep apnea

Correspondence:
Afroditi Sakellaropoulou, Consultant in Paediatrics, 18, Salaminos Street, Brilissia 15235 Athens, Greece;
Tel.: +30 6972881018,
E-mail: afroditisak@gmail.com

ABSTRACT

AIM: Serum Creatine kinase (CK) activity is increased in many diseases or conditions, but in up to 10% of cases, the cause for CK elevation remains unclear. Few reports exist concerning the increase of CK in patients with OSAS. The aim of our study was to evaluate the impact of OSAS on serum CK levels in children. **METHOD:** Forty-two children with symptoms suggestive of OSAS were studied. The presence and severity of OSAS were assessed by full night polysomnography. Clinical, anthropometric and laboratory measurements were also recorded. Statistical analysis was performed with SPSS, version 21.0. **RESULTS:** Based on their age and sex, elevated levels of CK were found in 4 children with OSAS only (10.3%). There was statistical important difference between CK levels and arousal index (p= 0.035, z= -2.109). Fifteen (35.71%) children with OSAS had a Waist to Hip Ratio (WHtR) cut-off point >0.50. Children with increased WHtR presented higher levels of CK compared with those with WHtR< 0.5 (p=0.055, z= 1.921). **CONCLUSIONS:** In conclusion, it appears that a relationship between an elevation in CK concentration and chronic intermittent hypoxia exists, and might be responsible for a substantial number of cases with mild to moderate hyper CK-emia. Moreover, a correlation between CK and abdominal obesity expressed as WHtR was recorded, finding that needs to be further studied in order to be established. Therefore, nocturnal hypoxia appears to be a stimulus for changes in muscle function.

Pneumon 2017, 30(2):85-91.

INTRODUCTION

Obstructive sleep apnea syndrome (OSAS) is characterized by repetitive episodes of pharyngeal collapse and oxygen desaturation during sleep, resulting in sleep fragmentation and day time sleepiness[1]. Sleep stages,

chemoreceptors, and intra-thoracic pressure appear to modulate upper airways' muscle activity. In healthy individuals, protective mechanisms maintain their patency during wakefulness and sleep. In contrast, in patients with OSAS, the patency of upper airways depends mainly on the hyper-activation of pharyngeal dilator muscles during wakefulness[2].

Creatine kinase (CK) is an enzyme expressed by various tissues and cell types. CK concentrations in healthy subjects depend on gender, race, age and physical activity[3,4]. In many diseases or conditions, there is an increase on serum CK activity, but in up to 10% of patients, the cause for CK elevation remains unclear. In these cases, the term idiopathic hyper-CK-emia was applied in 1980 by Rowland et al[5,6]. This syndrome is characterized by the absence of neurological abnormalities and by normal or non-specific findings on laboratory studies[5].

Despite the increase of scientific knowledge, several healthy subjects with hyper-CK-emia still represent a problem for the clinician[6], and few reports exist concerning the elevation of CK in OSAS patients[4].

To account for elevation of serum CK activity, there are two prevalent hypotheses: either CK enters blood from disintegrated muscle cells[7] or CK leaks into blood through muscle membranes, that are physically intact, but functionally leaky[8]. In apnea patients, greater intraluminal negative pressure is generated during inspiration to overcome increased airway resistance. Mechanisms linking OSAS to CK elevation maybe due to repetitive hypoxemic and/or mechanical stress on respiratory and skeletal muscles. Thus, in OSAS subjects, possible pathomechanisms for elevated CK concentrations include: the increased activity of the dilator muscles of the upper airways in order to maintain their patency[4], increased activity of the diaphragm and other inspiratory muscles during apnea (Mueller manoeuvre)[4], the disturbed muscle function and metabolism due to hypoxia[9], and finally, the various inflammatory processes[10].

The aim of our study was to evaluate the impact of OSAS on serum CK levels, including clinical characteristics, anthropometric and sleep parameters.

METHOS

The study was conducted at the Sleep Laboratory of 2nd Paediatric Department, at AHEPA Hospital of Aristotle University of Thessaloniki, Greece during 2009-2011. The initial population of the Sleep Department included 86 children; from those, 42 consecutive patients were randomly selected, and included in this prospective study. Clinical data were obtained at the initial visit. All patients presented with symptoms suggestive of OSAS. The patients' clinical characteristics are presented in Table 1.

Each participating child aged ≥13 years completed a modified version of the "SCOR Sleep and Health Questionnaire". Parents completed the "SCOR Questionnaire" for children aged <13 years[11]. All patients underwent physical examination and their parents were asked about their regular medications and previous medical history. In addition to physical examination, body weigh), heigh), neck circumference (measured at the level of cricothyroid membrane, in cm), and neck length (measured from the edge of the occipital crest to the height of the apophyse of C7 vertebra, in cm) were measured.

In order to compensate for the increase in neck circumference with height in the normal population, patient measurements of neck circumference were expressed as a percentage of the predicted normal circumference. The correction of neck circumference based on the height of neck circumference' (in cm) using the formula: (1000 x neck circumference in cm)/(0.55×310 + height)[12]. The lumbar circumference (in cm) and hip circumference (in cm) were recorded respectively as follows: 1) the perimeter boundaries between the lower side and anterior superior iliac spine, and 2) the average of three consecutive measurements of maximum circumference of the buttocks, with the patient standing upright with clasped feet.

Body mass index was measured as kilogram per square meter (kg/m^2), and also BMI z score with online BMI z score calculator[13]. Waist -to-hip ratio (WHR) is the dimensionless ratio of the circumference of the waist to that of the hips. This is calculated as waist measurement divided by hip measurement. The WHR has been used as an indicator of overall obesity and also a measure of health[14]. Waist height ratio (WHtR) was calculated as the ratio of waist circumference (WC) in cm and height in cm. A WHtR cut-off point of 0.50 was used to define abdominal obesity in males and females[14]. Conicity index was calculated as waist circumference/(0.109 square root of weight/height)[15].

Finally, the Mallampati score or Mallampati classification comprises a visual assessment of the distance from the base of the tongue to the roof of the mouth. In our study, the Modified Mallampati scoring based on Samsoon GL et al[16] was used by two experienced Otorhinolaryngologists in order to classify the visualised oral cavity.

Between 9:00 am and 11:00 am on day one of hospital admission before polysomnography, patients underwent routine blood testing: complete blood count, routine

TABLE 1. Demographic and clinical characteristics of patients with OSAS.

Characteristics	Values
Age (Mean ± SD), years	7.54±3.054
Gender (Males) (n, %)	27 (64.3%)
Parental smoking status (positive) (n, %)	26 (61.9%)
BMI z score (mean ± SD)	0.53±1.27
Neck circumference (mean ± SD)	28.74±5.41
WHR (mean ± SD)	0.97±0.086
WHtR (mean ± SD)	0.49±0.071
Conicity index (mean ± SD)	1.18±1.17
ESS (mean ± SD)	5.28±3.86
AHI (mean ± SD)	10.56±15.68
Arousal Index (mean ± SD)	6.3±9.98
Oral breathing during the night	40/42 (95.23%)
Oral breathing during the day	28/42 (66.7%)
Nasal congestion	25/42 (59.5%)
Nasal speech	25/42 (59.5%)
Difficulty awakening	22/42 (52.4%)
Nausea and vomiting during the morning awakening	4/42 (9.5%)
Headache upon awakening	6/42 (14.3%)
Excessive sweating during the night	17/42 (40.5%)
Snoring	39/42 (92.85%)
Abnormal positions during sleep	12/42 (28.6%)
Referring apneas during sleep	29/42 (69.04%)
Nightmares	9/42 (21.4%)
Somnambulism	3/42 (7.1%)
Confusional arousals	5/42 (11.9%)
Frequent arousals during the night	18/42 (42.85%)
Nocturnal enuresis	10/42 (23.8%)
Restless sleep	6/42 (14.3%)
Easy fatigue in school	8/42 (19%)
Drowsiness	4/42 (9.5%)
Hyperactivity at home	10/42 (23.8%)
Learning difficulties in school	3/42 (7.1%)
Distraction	4/42 (9.5%)
Over-activity	11/42 (26.2%)
Impulsiveness	2/42 (4.8%)
Aggressiveness	1/42 (2.4%)
Hoarseness	10/42 (23.8%)

SD: Standard Deviation, BMI: body mass index, ESS: Epworth Sleepiness Scale

biochemical analysis, including assessment of CK and also thyroid hormone levels. CK levels were categorized into groups based on age and sex[17], and patients were divided into two groups: those with normal values and those with elevated values of CK.

Full night polysomnography assessed the presence and severity of OSAS according to standard criteria of American Academy of Sleep Medicine as 30-s epochs[18]. Polysomnography was performed in each patient with "Sleep Screen" of Jaeger Sleep Diagnostic Company. Polysomnographic measurements included the use of electroencephalography (EEG), electro-oculogram (EOG), electro-myogram (EMG-genioglossus muscle and anterior tibialis muscle), electrocardiograph (ECG), a microphone (for snoring), and a body position electrode. Additionally, nasal and oral flows were recorded with thermistor, and thoracic and abdominal movements were recorded with inductance plethysmography. Arterial oxygen saturation (SaO_2) was monitored by pulse oxymeter, and carbon dioxide with a capnograph. Sleep stages and arousals were scored according to the standard criteria of Rechtschaffen and Kales[19]. In particular, arousals are defined by the criteria of the American Society of sleep disorders[20,21]. According to these criteria, arousal is a sudden change in the electroencephalographic (EEG) frequency, which may comprise «θ», «a» and/or frequencies greater than 16 Hz, but no peaks («spingles»), lasting at least 3 seconds, with at least 10 sec continuous stable sleep before the change. Moreover, the recording and counting of awakenings during sleep requires an accompanying increase in submental Electroencephalographic (EEG) activity for at least 1 second[22].

Patients with a minimal sleep efficacy of 60% were included in the study. Apnea was defined as complete cessation of airflow for at least 10 seconds, while hypopnea was defined as a 50% decrease in airflow accompanied by an arousal or at least 4% drop in oxygen saturation. The overall oxygen desaturations, lowest and average SpO_2 were extracted. In addition to overall oxygen desaturation time, desaturation periods less than 90% and 80% were also recorded. Consideration was also taken for the percentage of sleep duration with oxygen saturation below 90%, and the average of arousals per hour of sleep. The diagnosis of obstructive sleep apnea syndrome was mainly based on apnea-hypopnea index (AHI)[18,19], which was defined as the number of apnoeas and hypopnoeas occurring per hour of sleep.

Abnormal diagnostic criteria for children are considered values of AHI >1/ hour[23]. Since there are no definitive diagnostic criteria for defining the severity of OSAS in children, we select to stage OSAS in children based on their clinical

appearance, the number of obstructive events per hour of sleep, the end-expiratory pressure of carbon dioxide, the incidence and severity of oxygen desaturation and frequency of arousals related to obstructive respiratory events. Mainly, our study was based on the classification of Harvey and al[24], according to which children with OSAS were classified as having mild (1>AHI <5/hour), moderate (5> AHI <9/hour) or severe disease (AHI >10/hour), based on the value of AHI.

The study was approved by the ethics committee of Aristotle University (Protocol number: A24496/10/07/2009), and informed consent was obtained from the parents of each patient.

STATISTICAL ANALYSIS

Data analysis was performed with the use of statistical package SPSS, version 21.0 for Windows (SPSS; Chicago, IL). All variables were tested for normality with Kolmogorov-Smirnov test. One way analysis with Bonferonni correction was used for continuous variables, and χ^2 testing for dichotomous variables in order to access the statistical significance of differences between groups. For all statistical analyses, a value of $p < 0.05$ was considered significant.

RESULTS

In our sleep laboratory, 86 children were examined with symptoms suggestive of OSAS, and forty-two children were randomly included in the study. Demographic and clinical characteristics of patients with OSAS are presented in Table 1. CK levels ranged between 51-215 U/lt (105.82±35.61). In our study, only 4 children (10.3%) had elevated levels of CK, based on their age and sex.

There was only statistical important difference (p=0.037) between CK levels and the presence of mouth breathing during sleep (Figure 1).

No statistical significance was found between CK values and sex (p= 0.491, z= -0.688), and between CK groups

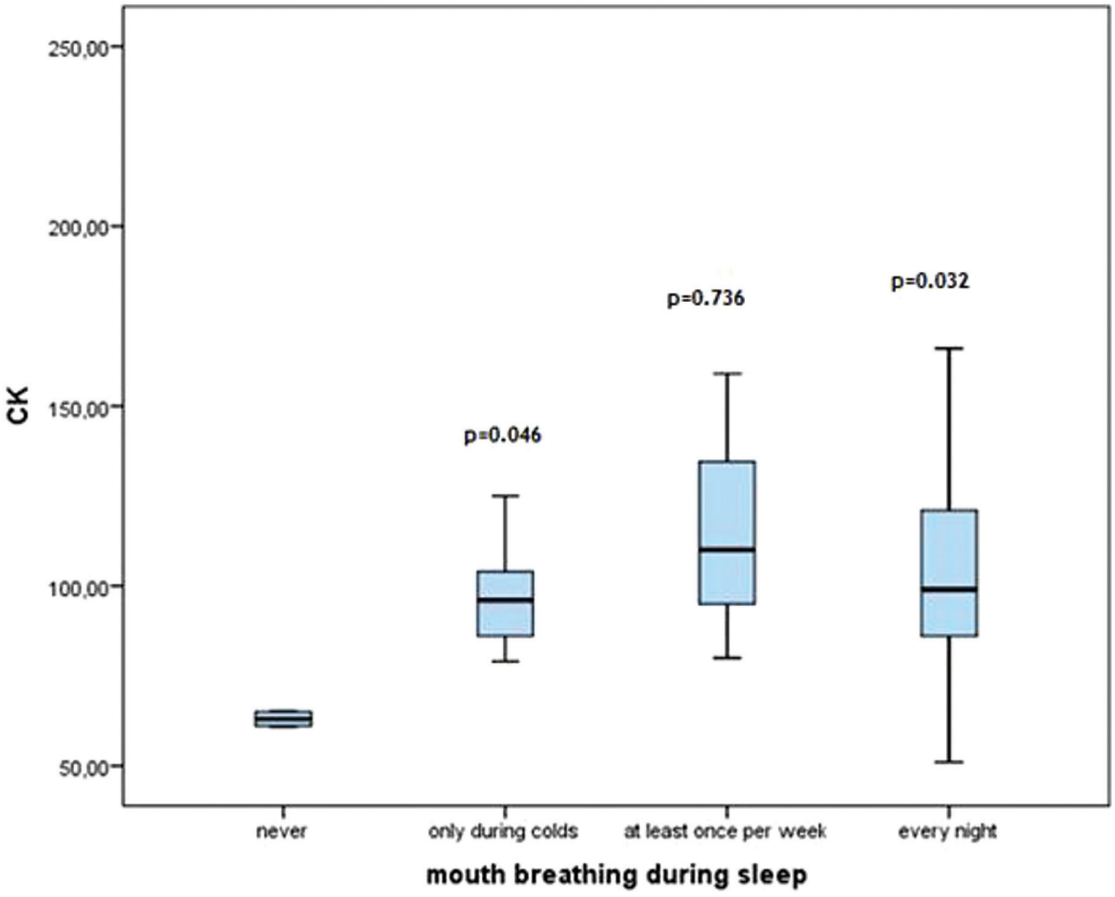

FIGURE 1. CK fluctuations according to the presence of mouth breathing during sleep in children with OSAS.

and the degree of OSAS expressed as AHI (p= 0.459, z= -0.741), or AI (p= 1, z= 0.00), (Table 2).

Hypoxia (average duration of desaturation less than 90%) was negatively correlated with CK levels (p= 0.034, r= -0.341), and patients with more frequent arousals (increased arousal index) presented more elevated levels of CK (p= 0.035, z= -2.109), compared with those who had a more quiet sleep (Table 3).

Fifteen children (35.71%) with OSAS had a WHtR cut-off point >0.50. It seems that abdominal obesity might influence the value of CK, since there was a positive correlation (p= 0.055, z= 1.921) between CK groups and Waist height ratio (WHtR), but this correlation didn't seem to appear in other markers of obesity, such as WHR (p=0.331, z= -0.973), BMI z score (p= 0.247, z= -1.157) and Conicity index (p= 0.287, z= -1.065), (Table 3).

Finally, children with higher levels of CRP appeared to have increased CK levels (p=0.028, z= -2.20), compared with those with normal levels of CRP, while this finding wasn't repeated in cases of other inflammatory markers, such as sedimentation rate (p= 0.228, z= -1.206), or LDH (p= 0.281, z= 0.705), (Table 2).

TABLE 2. Polysomnography results', inflammatory markers and comparisons with normal and increased levels of CK.

Variables	Children with normal CK values (mean ± SD)	Children with increased CK levels (mean ± SD)	P value
Gender (male:female)	22 (56,4%):13 (33.3%)	3 (7.7%):1 (2.6%)	p= 0.632
AHI (events/h)	11.58±16.99	5.55±3.22	p= 0.459, z= -0.741
AI (events/h)	4.42±3.64	3.8±1.22	p= 1, z= 0.00
CRP (mg/dl)	0.48±0.47	0.011±0.016	**p= 0.028, z= -2.20**
Erythrocytes Sedimentation rate of erythrocytes	12.54±9.12	7.33±6.02	p= 0.228, z= -1.206
LDH	417.04±89.52	505±29.05	p= 0.481, z= -0.708
Cholesterol	152.7±34.24	182.66±27.22	p= 0.341, z= -0.951
Triglycerides	59.62±28.23	67.66±36.07	p= 0.601, z= -0.524
HDL (mg/dl)	54.95±17.18	63.33±12.22	p= 0.757, z= -0.309
LDL (mg/dl)	84.95±34.56	105.66±28.03	p= 0.634, z= -0.476

CRP: C-reactive protein, LDH: serum Lactate dehydrogenase, HDL: high density lipoproteins, LDL: low density lipoproteins.

TABLE 3. Correlations between CK values, sleep study characteristics and anthropometric values.

Sleep study characteristics	Mean values of characteristics (mean)	P value
Time spent with desaturations <90%	7.476	p= 0.490, r= -0.14
Average duration of desaturations less than 90%	15.857	**p= 0.034, r= -0.341**
min$SatO_2$	40.214	p= 0.2191, r = 0.214
Number of desaturations	63.761	p= 0.977, r = -0.005
Average low O_2 during desaturations	57.845	p= 0.889, r = -0.023
Sleep efficacy	82.817	p= 0.650, r= -0.076
Sleep onset latency	14.726	p= 0.717, r= -0.060
Total awake time after sleep onset	80.345	p= 0.788, r= -0.044
REM latency	43.881	p= 0.987, r= -0.003
Arousal index	6.300	**p= 0.035, r= -2.109**
BMI z score	0.534	p= 0.627, r= -0.080
WHR	0.972	p= 0.924, r= -0.016
WHtR	0.496	p= 0.469, r= -0.119
Conicity index	1.186	p= 0.112, r= -0.258
Mallampati index	2.117	p= 0.656, r= -0.085

DISCUSSION

Previous studies have shown that chronic hypoxia leads to changes in the structure of skeletal muscles and in several bio-energetic enzymes activities. It is unknown whether these changes also occur in conditions characterised by intermittent hypoxia, such as OSAS. Moreover, changes in structure and in energy profile were recorded in patients with OSAS and intermittent hypoxia, according to Sauleda J et al.[9] Mechanisms linking OSAS to CK elevation may include repetitive hypoxemic and/or mechanical stress on respiratory and skeletal muscles[4]. Silvia Lentini et al,[4] concluded that mean nocturnal SaO_2 was the main predictor of this elevation of CK concentration.

In our study, only 4 children with OSAS had elevated CK levels based on their age and sex. However, in children with OSAS there was significant difference between the average duration of desaturation less than 90% and CK (p= 0.034, r= -0.341), a finding that supports the hypothesis that nocturnal hypoxia is a stimulus for changes in muscle function (Table 3).

In patients with OSAS, reports have been made correlating nocturnal hypoxia, oxidative stress, release of vascular endothelins and endothelial dysfunction[25]. Hypoxic events in association with repeated apnea induce oxidative stress in the vascular endothelium similar to re-perfusion injury. Moreover, inflammation and other metabolic factors may contribute to the development of cardiovascular disease in OSAS patients[26]. It is well known that there is a linear relationship between the severity of OSAS and cardiovascular morbidity and mortality[27].

In our study, there was only statistical important difference between CK groups and CRP levels, while no statistical important differences were recorded between AHI and AI, and other inflammatory markers (such as Sedimentation rate and LDH), as well as between metabolic markers (Table 2).

It is conceivable that Obstructive sleep apnea (OSA) and obesity may interact and potentiate their detrimental consequences. Obesity appears to be a common finding and a major patho-genetic factor in OSA in children[28]. The deposition of fat in the upper airway (UA), and especially at the lateral pharyngeal walls, could result in decrease of the pharyngeal calibre and external compression on the pharynx[29].

In our study 15/42 (35.71%) children had an increased WHtR ratio (>0.5) and there was a statistical important difference between CK levels and WHtR (waist to height ratio). The WHtR is a measure of the distribution of body fat. Higher values of WHtR indicate higher risk of obesity–related cardiovascular diseases, and especially abdominal obesity[30]. Although, no statistical important difference was found between CK and other markers of thoracic, abdominal or neck obesity (such as WHR, Conicity index, BMI z score and Mallampati index), (Table 3). This is probably due to the fact that cases with extreme obesity weren't reported in our study group, probably due to early tracking of children with OSAS.

Collapse of the upper airways (UA) is determined by two processes: a) increased airway resistance with an associated increase in negative intrathoracic pressure, and b) the loss of neuromuscular control of the pharynx. Collapse most often occurs at multiple sites within the pharynx, with the most common site being the nasopharynx, where the soft palate contacts the posterior pharyngeal wall[31].

With UA collapse, the extra work of the diaphragm causes increasingly negative intrathoracic pressure along with concomitant hypoxia and hypercapnia. Apnea-hypopnea episodes increase sympathetic output up to 125% of normal levels, increasing muscle tone, blood pressure, and other processes which cause arousal. The arousals restore the pharyngeal dilator muscle tone, re-oxygenation, and cause an abrupt decrease in sympathetic response[30]. This probably could explain the finding of our study that there was a significant statistical difference between CK levels and arousal index (p=0.035, z= - 2.109), (Table 3). Thus, increased movements might disrupt the path-mechanisms of hypoxia/apnea and restore oxygenation and sleep mechanisms.

Limitations of the study is that the apnea - hypopnea index (AHI) was measured in only one evening, and may vary from one night to another. However, the one night polysomnographic recording is the gold standard, and is the only objective way to have access to breathing disorders during sleep. For this reason, all study participants were studied in the same laboratory, and used the same techniques for recording and scoring of events during sleep.

Patients with a history of neuromuscular disease, malignant hyperthermia, hypothyroidism, recent muscle trauma and excessive muscle activity or drug intake, which could probably lead to elevated CK concentrations, were excluded from the study. Although, neuromuscular disease in the study population was assessed only by taking a medical history and by neurologic examination; the patients didn't underwent any specific electro-diagnostic or histological examinations. Thus, unidentified neuromuscular disease may contribute to our findings.

In conclusion, it appears that a relationship between CK concentration elevation and chronic intermittent hypoxia exists, and a causal association between these two could be responsible for a substantial number of cases of mild-to-moderate hyper-CK-emia. Therefore, if idiopathic hyper-CK-emia is a separate syndrome, the pathophysiological mechanism remains to be elucidated.

ACKNOWLEDGEMENTS

The authors have no relevant affiliations or financial involvement with any organization or entity related to the subject of this review. No writing assistance was utilized in the production of this manuscript.

REFERENCES

1. American Academy of Sleep Medicine Task Force. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 1999;22:667–89.
2. Fogel RB, Malhotra A, Pillar G, et al. Genioglossal activation in patients with obstructive sleep apnea versus control subjects: mechanisms of muscle control. Am J Respir Crit Care Med 2001;164:2025-30.
3. Lang H, Würzburg U. Creatine kinase, an enzyme of many forms. Clin Chem 1982;28:1439-47.
4. Lentini S, Manka R, Scholtyssek S, et al. Creatine phosphokinase elevation in obstructive sleep apnea syndrome: an unknown association? Chest 2006;129:88-94.
5. Rowland LP, Willner J, DiMauro S, et al. Approaches to the membrane theory of Duchenne muscular dystrophy. In: Angelini C, Danieli GA, Fontanari D, eds. Muscular dystrophy—advances and new trends. Amsterdam, The Netherlands: Excerpta Medica; 1980. pp. 3–13.
6. Prelle A, Tancredi L, Sciacco M, et al. Retrospective study of a large population of patients with asymptomatic or minimally symptomatic raised serum creatine kinase levels. J Neurol 2002;249:305-11.
7. Mokri B, Engel AG. Duchenne dystrophy: electron microscopic findings pointing to a basic or early abnormality in the plasma membrane of the muscle fiber. Neurology 1975;25:1111-20.
8. Rowland LP, Layzer RB, Kagen LJ. Lack of some muscle proteins in serum of patients with Duchenne dystrophy. Arch Neurol 1968;18:272-6.
9. Sauleda J, García-Palmer FJ, Tarraga S, et al. Skeletal muscle changes in patients with obstructive sleep apnea syndrome. Respir Med 2003;97:804–10.
10. Shamsuzzaman AS, Winnicki M, Lanfranchi P, et al. Elevated C-reactive protein in patients with obstructive sleep apnea. Circulation 2002;105:2462–4.
11. Gozal D. Sleep-disordered breathing and school performance in children. Pediatrics 1998;102:616-20.
12. Davies RJ, Stradling JR. The relationship between neck circumference, radiographic pharyngeal anatomy, and the obstructive sleep apneoa syndrome. Eur Respir J 1990;3:509-14.
13. Pediatric z score calculator. The Children's Hospital of Philadelphia. http://stokes.chop.edu/web/zscore/
14. McCarthy HD, Ashwell M. A study of central fatness using waist-to-height ratios in UK children and adolescents over two decades supports the simple message-'keep your waist circumference to less than half your height. Int J Obes 2006;30:988–92.
15. Kissebah AH, Krakower GR. Regional adiposity and morbidity. Physiol Rev 1994;74:761–811.
16. Lee A, Fan LT, Gin T, et al. A systematic review (meta-analysis) of the accuracy of the Mallampati tests to predict the difficult airway. Anesthesia and Analgesia 2006;102:1867–78.
17. Neal RC, Ferdinand KC, Ycas J, et al. Relationship of ethnic origin, gender and age to blood creatine kinase levels. Am J Med 2009;122:73-8.
18. Standards and indications for cardiopulmonary sleep studies in children. American Thoracic Society. Am J Respir Crit Care Med 1996;153:866.
19. Rechtschaffen A, Kales AA. A manual of standardized terminology, technique and scoring system for sleep stages of human subjects. Washington, DC: National Institutes of Health 1968; NIH Publication No. 204.
20. American Sleep Disorders Association. EEG Arousals: Scoring rules and examples: a preliminary report from the Sleep Disorders Atlas Task Force of the American Sleep Disorders Association. Sleep 1992;15:173-84.
21. Katz ES, Lutz J, Black C, et al. Pulse transit time as a measure of arousal and respiratory effort in children with sleep-disordered breathing. Pediatr Res 2003;53:580-8.
22. Iber C, Ancoli-Israel S, Chesson A, et al, for the American Academy of Sleep Medicine. The AASM manual for the scoring of sleep and associated events: rules, terminology and technical specifications. Westchester, IL: American Academy of Sleep Medicine, 2007.
23. Sharma SK, Kurian S, Malik V, et al. A stepped approach for prediction of obstructive sleep apnea in overtly asymptomatic obese subjects: a hospital based study. Sleep Med 2004;5:351-7.
24. Harvey JM, O´Callaghan MJ, Wales PD, et al. Aetiological factors and development in subjects with obstructive sleep apnea. J Paediatr Child Health 1999;35:140-4.
25. Narkiewicz K, Somers VK. Sympathetic nerve activity in obstructive sleep apnea. Acta Physiol Scand 2003;177:385–90.
26. Butt M, Dwivedi G, Khair O, et al. Obstructive sleep apnea and cardiovascular disease. Int J Cardiol 2010;139:7-16.
27. McNicholas WT, Bonsigore MR. Management Committee of EU COST ACTION B26. Sleep apnoea as an independent risk factor for cardiovascular disease: current evidence, basic mechanisms and research priorities. Eur Respir J 2007;29:156–78.
28. Schwab RJ, Pasirstein M, Pierson R, et al. Identification of upper airway anatomic risk factors for obstructive sleep apnea with volumetric magnetic resonance imaging. Am J Respir Crit Care Med 2003;168:522-30.
29. Schellenberg JB, Maislin G, Schwab RJ. Physical findings and the risk for obstructive sleep apnea. The importance of oropharyngeal structures. Am J Respir Crit Care Med 2000;162:740-8.
30. Hillman DR, Loadsman JA, Platt PR, et al. Obstructive sleep apnoea and anaesthesia. Sleep Med Rev 2004;8:459-71.
31. Somers VK, Dyken ME, Clary MP, et al. Sympathetic neural mechanisms in obstructive sleep apnea. J Clin Invest 1995; 96:1897-904.