ISSN 2219-2808 (online)

World Journal of *Clinical Pediatrics*

World J Clin Pediatr 2014 February 8; 3(1): 1-13

Baishideng Publishing Group
www.wjgnet.com

WJCP World Journal of Clinical Pediatrics

A peer-reviewed, online, open-access journal of clinical pediatrics

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World Journal of Clinical Pediatrics

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Quarterly Volume 3 Number 1 February 8, 2014

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World Journal of Clinical Pediatrics
Volume 3 Number 1 February 8, 2014

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NAME OF JOURNAL
World Journal of Clinical Pediatrics

ISSN
ISSN 2219-2808 (online)

LAUNCH DATE
June 8, 2012

FREQUENCY
Quarterly

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Telephone: +852-3177-9906
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PUBLICATION DATE
February 8, 2014

INSTRUCTIONS TO AUTHORS
Full instructions are available online at http://www.wjgnet.com/2219-2808/g_info_20100722180909.htm.

ONLINE SUBMISSION
http://www.wjgnet.com/esps/

World Journal of Clinical Pediatrics

Online Submissions: http://www.wjgnet.com/esps/
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doi:10.5409/wjcp.v3.i1.1

World J Clin Pediatr 2014 February 8; 3(1): 1-5
ISSN 2219-2808 (online)

Recent management of urinary stone disease in a pediatric population

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Received: December 9, 2013 Revised: December 27, 2013
Accepted: January 17, 2014
Published online: February 8, 2014

Abstract

The incidence of stone disease has been increasing and the risk of recurrent stone formation is high in a pediatric population. It is crucial to use the most effective method with the primary goal of complete stone removal to prevent recurrence from residual fragments. While extracorporeal shock wave lithotripsy (ESWL) is still considered first line therapy in many clinics for urinary tract stones in children, endoscopic techniques are widely preferred due to miniaturization of instruments and evolution of surgical techniques. The standard procedures to treat urinary stone disease in children are the same as those used in an adult population. These include ESWL, ureterorenoscopy, percutaneous nephrolithotomy (standard PCNL or mini-perc), laparoscopic and open surgery. ESWL is currently the procedure of choice for treating most upper urinary tract calculi in a pediatric population. In recent years, endourological management of pediatric urinary stone disease is preferred in many centers with increasing experience in endourological techniques and decreasing sizes of surgical equipment. The management of pediatric stone disease has evolved with improvements in the technique and a decrease in the size of surgical instruments. Recently, endoscopic methods have been safely and effectively used in children with minor complications. In this review, we aim to summarize the recent management of urolithiasis in children.

Key words: Stone disease; Pediatric population; Urolithiasis; Surgical management

Core tip: The incidence of stone disease has been increasing and the risk of recurrent stone formation is high in a pediatric population. In recent years, endourological management of pediatric urinary stone disease is preferred in many centers with increasing experience in endourological techniques and decreasing sizes of surgical equipment. The management of pediatric stone disease has evolved with improvements in the technique and a decrease in the size of surgical instruments. Recently, endoscopic methods have been safely and effectively used in children with minor complications. In this review, we aim to summarize the recent management of urolithiasis in children.

Aydogdu O, Karakose A, Celik O, Atesci YZ. Recent management of urinary stone disease in a pediatric population. *World J Clin Pediatr* 2014; 3(1): 1-5 Available from: URL: http://www.wjgnet.com/2219-2808/full/v3/i1/1.htm DOI: http://dx.doi.org/10.5409/wjcp.v3.i1.1

INTRODUCTION

Children with urinary stone disease represent the high risk group for stone recurrence[1]. Since the recurrence rate is higher in children compared to adults, ideally no residual stone fragments should be left behind after any treatment for urinary stones. A previous study showed that 69% of children with residual stone fragments ≤

5 mm following extracorporeal shock wave lithotripsy (ESWL) had an increase in stone size[2].

The standard procedures to treat urinary stone disease in children are the same as those used in an adult population. These include ESWL, ureterorenoscopy (URS), percutaneous nephrolithotomy (standard PCNL or mini-perl), laparoscopic and open surgery. ESWL is currently the procedure of choice for treating most upper urinary tract calculi in a pediatric population[3]. In recent years, endourological management of pediatric urinary stone disease is preferred in many centers with increasing experience in endourological techniques and decreasing sizes of surgical equipment[1,3]. This review aims to summarize the recent management of children with urinary stone disease.

ESWL

The use of ESWL in the treatment of urinary stones in a pediatric population was first reported by Newman *et al*[4] in 1986. ESWL is the preferred treatment in pediatric urinary stone patients with uncomplicated upper urinary tract calculi $\leqslant$ 15 mm[1,3,5,6]. Although stone free rates after ESWL in children range between 68% and 92%, recent stone free rates are difficult to interpret from the current literature due to discrepancies among trials with regard to the lithotripter model used, number of shocks administered and re-treatment rates[1,3,7,8]. Factors which decrease ESWL success rates include increased mean stone burden, increased infundibular length, infundibulopelvic angle greater than 45 degrees, harder stones such as cysteine and whewellite, and lower pole localization[1,9]. In a recent study, the authors aimed to define the preoperative kidney and stone characteristics on noncontrast-enhanced computed tomography that affect the success of ESWL for treatment of renal calculi in pediatric patients. The authors concluded that stone attenuation $\leqslant$ 600 HU and stone length $\leqslant$ 12 mm were significant independent predictors of ESWL success in children[10]. ESWL monotherapy has superior success rates in children compared to adults due to relatively softer stone composition, smaller relative stone volume, smaller body volume to facilitate shock transmission, and easier spontaneous stone passage due to increased ureteral compliance to accommodate stone fragments[1,3,11-13]. In children, ureteral stenting before ESWL is not needed as often as in adults and it is not clear if ureteral stent placement improves stone free outcomes[1,3,11]. ESWL can cause minor complications, including hematuria, perirenal hematoma, bruising and renal colic[1]. Although ESWL has low complication rates, the stone free rate after a single session is approximately 45%[3,14]. The need for multiple ESWL sessions is controversial since anesthesia is required and the effects of shock waves on renal tissue are not clear[1,3,15].

In a previous study, the authors found no negative effect of ESWL on renal function or blood pressure[16]. In another study, the authors found no significant changes in blood pressure or signs of acquired parenchymal renal scarring following ESWL in children[17]. Vlajković *et al*[18] evaluated glomerular filtration rate (GFR) before and after ESWL. The authors showed that GFR normalized or improved at the 3rd month after the ESWL procedure and concluded that ESWL is a safe treatment in children. In a previous epidemiological and questionnaire based retrospective study, the authors found that the patients treated with ESWL had an increased risk of developing hypertension and diabetes mellitus when compared to controls[19]. In contrast, in a different study, the authors prospectively examined 12 patients after ESWL and concluded that it is unlikely that ESWL and diabetes mellitus are related[20].

PCNL

After it was first described in children in 1985, several studies reported the use of PCNL in children with urinary stone disease using adult sized surgical instruments with high success and acceptable complication rates[21-24]. In 1998 Jackman *et al*[25] introduced a novel percutaneous access technique (mini-perc) and reported a 85% total success rate. The authors listed the benefits of this new technique as increased maneuverability, decreased blood loss and shorter hospital stay, with limitations including prolonged operative times and potential impairment of visualization during the procedure, especially for larger stones.

In a previous trial, the authors compared the results of percutaneous nephrolithotomy and shock wave lithotripsy for the treatment of 1 to 2 cm renal stones in children. They concluded that percutaneous nephrolithotomy is better than shock wave lithotripsy for treatment of 1 to 2 cm renal stones in children, yielding higher stone free and lower re-treatment rates[26].

Recently, the success rate of PCNL in a pediatric population was reported to be between 87% and 98.5%[11,23,26,27]. In a previous study, the authors reported the outcomes of 56 children who underwent PCNL[11]. The authors found a stone free rate of 89.8% and that the number and size of the access tracts were significantly associated with a postoperative hemoglobin decrease and transfusion rate. In a different study, the authors reported a 87% stone free rate following a PCNL procedure in 52 children with a mean age of 7.9 years[27]. The authors reported postoperative fever in 30% of the patients included in the study and a blood transfusion rate of 24%.

The European Association of Urology guidelines state that ESWL is the first choice for treating most renal pediatric stones and PCNL can be preferred for larger and complex stones. The guidelines also mention that PCNL can be used as monotherapy in most cases but is also used as an adjunctive procedure to other therapies[28]. Relative indications for PCNL as a primary therapy in a pediatric population include upper pole stones $\geqslant$ 1.5 cm, lower pole stones $\geqslant$ 1 cm, harder stones and potential anatomical abnormalities that can possibly impair urinary

drainage and thus stone clearance, such as ureteropelvic junction obstruction and ureter stricture[1,3]. Potential limitations for the use of a PCNL procedure in children include possible parenchymal damage and associated impairment in renal function, radiation exposure and the risk of major complications, including urinary sepsis and bleeding[3]. Some studies evaluated the potential loss of renal function due to renal scarring after PCNL in children[29,30]. In a previous study, the authors investigated renal scarring on a dimercaptosuccinate (DMSA) renal scan following PCNL and found no renal scarring on DMSA[29]. In the same study, a diethylenetriamine pentaacetic acid renal scan was used to follow-up renal function after PCNL and it was observed that renal function had improved or not changed, except for one patient.

PCNL can be used both as monotherapy and in combination with ESWL in children[3,7]. The use of PCNL in combination with ESWL is preferred to reduce the number of access tracts and associated morbidity rates. In a previous study, the authors reported a 60% stone free rate after PCNL. The stone free rate increased to 100% following an ESWL procedure[30]. In a similar study, the authors reported a 59% monotherapy stone free rate after PCNL in 169 children[24]. Thirty-four point five percent of children with residual stones were treated with ESWL and the overall stone free rate increased to 93.8%. Although PCNL is an invasive treatment, in experienced hands it can be effectively and safely used in children with large stone burdens with the use of smaller sized surgical instruments and more efficient energy sources used for stone fragmentation.

URS

Although previously URS was only used for ureter stones below the iliac crest and for upper urinary tract stones following an unsuccessful ESWL procedure in children, many clinicians prefer to use URS even in young children with the introduction of smaller diameter ureteroscopic instruments and holmium laser[1,3]. URS was first used in 1988 for distal ureteral calculi in children and the authors reported stone free rates between 86%-100% in the early series[1,7,12,13]. In a previous randomized study, the authors compared URS and ESWL in 31 children and found stone free rates of 94% and 43% in the URS and ESWL groups respectively[31]. In a different study, the authors reported their experience using 4.5, 6 and 8 Fr rigid URS for treating proximal ureteral stones in 24 children and reported a stone free rate of 100%[32]. Corcoran *et al*[33] reported the outcomes of 47 children with upper tract stones treated with flexible URS and holmium laser lithotripsy. They reported a stone free rate of 88% and 26% in the children requiring staged procedures.

There was a concern regarding the use of URS in children with urinary tract stones due to potential complications, including ureteral ischemia, ureteral stricture and vesicoureteral reflux (VUR). However, a previous review of 221 URS procedures in a pediatric population showed that only two children had ureteral strictures and eight had low grade VUR[13]. The introduction of flexible ureteroscopes which can bend up to 270° made the removal of renal stones in lower calices possible[1]. In a previous study, the authors reported the success rate of lower pole calculi removal as 76% in 21 children with a mean age of 15 years[34]. In a prospective randomized study comparing ESWL and URS for lower pole calculi up to 1 cm, after three months, 35% and 50% of the patients in the ESWL and URS groups respectively were stone free[35].

Smaller and more durable endoscopes with the introduction of laser technology for the fragmentation of urinary stones allow the use of URS in children to be more prominent. Relative contraindications for URS in children include staghorn stones, anatomical anomalies and previous unsuccessful endoscopic procedures[3].

LAPAROSCOPIC/ROBOTIC/OPEN NEPHROLITHOTOMY

Surgical treatment of children with larger stones is technically challenging. Open surgery is used more in developing countries compared to developed countries, probably due to cost effectiveness[1,3]. Open surgery is preferred in children with concomitant anatomical abnormalities, including ureteropelvic junction obstruction and obstructive megaureter[1,36]. In a previous study, the authors reported a 95.4% stone free rate in children who underwent open nephrolithotomy[37]. In a different study, the authors reported a success rate of 100% with no major complications in 8 children who underwent laparoscopic pyelolithotomy[38]. Lee *et al*[39] reported the outcomes of 5 children who were treated with robotic-assisted laparoscopic pyelolithotomy and mentioned that the technique is feasible and safe as an alternative to open surgery in children.

CONCLUSION

The management of pediatric stone disease has evolved with improvements in the techniques and a decrease in the size of surgical instruments. Recently, endoscopic methods have been safely and effectively used in children with minor complications.

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P- Reviewers: Abdel-Aziz M, El-Assmy A, Liatsikos E, Markic D
S- Editor: Ma YJ **L- Editor**: Roemmele A **E- Editor**: Liu SQ

World Journal of Clinical Pediatrics

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.5409/wjcp.v3.i1.6

World J Clin Pediatr 2014 February 8; 3(1): 6-13
ISSN 2219-2808 (online)

BRIEF ARTICLE

Evaluation of oxidant-antioxidant status in overweight and morbidly obese Saudi children

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Received: June 23, 2013 Revised: January 7, 2014
Accepted: January 17, 2014
Published online: February 8, 2014

Abstract

AIM: To evaluate the antioxidant enzymes and oxidative products in overweight and obese Saudi children before the onset of metabolic complications.

METHODS: The study was carried out on 231 Saudi children. They were classified into three groups: uncomplicated overweight, uncomplicated morbid obesity, and the matched age group as control. All subjects underwent anthropometric measurements and activities of superoxide dismutase, catalase, glutathione peroxidase (GSH-Px), glutathione reductase, the concentrations of reduced GSH, malondialdehyde (MDA) oxidized low-density lipoprotein (ox-LDL) and advanced oxidation protein products (AOPPs) were measured in the blood of these groups.

RESULTS: Overweight and obese children had a significantly higher body mass index, while obese children only had a significantly higher waist-to-hip ratio compared to that of the control group. The enzyme activities under study were significantly elevated in the overweight group, although they were significantly reduced among obese children. The concentration of GSH was reduced in both the overweight and obese groups. The mean values of ox-LDL, MDA and AOPP were non-significantly increased in overweight children, while they were significantly elevated in obese children compared to that of normal weight children. A significant disturbance of oxidant-antioxidant status was observed in severely morbid children.

CONCLUSION: The increase of oxidative stress in obese children is associated with the increase in AOPPs and MDA which reflects an imbalance between reactive oxygen species production and antioxidant defense.

Key words: Saudi children; Body mass index; Malondialdehyde; Superoxide dismutase; Catalase; Glutathione peroxidase; Glutathione reductase; Reduced glutathione

Core tip: Childhood obesity is growing at an alarming rate and is concomitant with an increasing prevalence of oxidative stress. The association between obesity and oxidative stress is illustrated in the present study that showed that obese children with body mass index greater than 35 kg/m^2 had higher oxidative products, *e.g.,* malondialdehyde, advanced oxidation protein products and oxidized low-density lipoprotein concentrations with lower antioxidants, *e.g.,* superoxide dismutase, catalase, glutathione peroxidase (GSH-Px) and glutathione reductase, and GSH. Therefore, the early recognition of these changes in oxidant status in children is important for preventing the long-term complications of obesity and targeting individual subjects who are particularly at risk. In addition, improving the oxidant status in overweight and obese children may reduce obesity-related comorbidities in adulthood.

Albuali WH. Evaluation of oxidant-antioxidant status in overweight and morbidly obese Saudi children. *World J Clin Pediatr* 2014; 3(1): 6-13 Available from: URL: http://www.wjgnet.com/2219-2808/full/v3/i1/6.htm DOI: http://dx.doi.org/10.5409/wjcp.v3.i1.6

INTRODUCTION

Obesity is one of the most common health problems among children and adolescents in developed and high resource countries[1]. In addition, it is a principal causative factor in the development of various diseases, such as dyslipidemia, atherosclerosis, cardiovascular and others, and increases the risk of premature illness and death later in life, raising public health concerns[2-4].

Oxidative stress results from an imbalance between the production of reactive oxygen species (ROS), such as superoxide ($O_2^{\bullet}$) and hydroxyl (·OH) radicals, with antioxidants defenses, which leads to oxidative damage of lipids, proteins and DNA and might be a major mechanism underlying obesity-related complications[5].

The human body has developed several mechanisms to protect biomolecules from the deleterious effects of ROS. These include the antioxidant enzymes, such as superoxide dismutase (SOD), catalase (CAT), glutathione reductase (GSSG-R) and glutathione peroxidase (GSH-Px), as well as water and lipid-soluble antioxidants, such as GSH, ascorbate (vitamin C), α-tocopherol (vitamin E) and β-carotene[6]. They either detoxify ROS, convert superoxide radicals ($O_2^{\bullet}$) into H_2O_2, or metabolize peroxide organic molecules.

Glutathione protects the body organs against oxidative stress of ROS, either directly as an antioxidant or indirectly by maintaining other cellular antioxidants in a functional state[7].

The accumulation of oxidative modified macromolecules has been demonstrated in obese adults. The whole body oxidative stress is best reflected by systemic levels of lipid peroxidation, *e.g.,* malondialdehyde (MDA) and oxidized low-density lipoprotein (ox-LDL), which are considered the most reliable oxidative biomarkers[8]. The levels of MDA were significantly increased in obese children compared with non-obese children. ox-LDL, another marker of oxidative stress, is associated with obesity[9].

Proteins are recognized as oxidants by ROS, which then may undergo structural and functional modifications, leading to endothelial dysfunction. Advanced oxidation protein products (AOPPs) are novel markers of increased oxidative stress, which has some advantages over other markers because of their relatively early formation, greater stability, ease of determination and reliability, and also their longer life span[10], and are considered reliable markers to estimate the degree of oxidant-mediated protein damage.

Although the prevalence of morbid obesity and obesity-related complications in children has greatly increased in the eastern region of Saudi Arabia, the antioxidant enzymes and the more important oxidatively modified macromolecules, *e.g.,* MDA, ox-LDL and AOPP, have not been completely explored in overweight and obese children because only data on antioxidant vitamin levels are available[11-13]. The current study aims to evaluate the activities of SOD, CAT, GSH-Px, GSSG-R, levels of MDA, ox-LDL and AOPP in Saudi overweight, obese and normal weight children to identify obese children who are at risk of complications.

MATERIALS AND METHODS

Children and study protocol

The investigations were carried out in overweight and obese children referred to the Hospital Paediatric Clinic and attendees of the Polyclinic Center at King Faisal University in Al-Ahsa, Saudi Arabia between January 2011 and March 2012. The present study comprised a total of 213 children (6-12 years, mean age 9.5 ± 1.5 years; boys n = 143, 67% and girls n = 70, 33%). The children were free from endocrinological and liver disorders and genetic syndromes associated with obesity. Clinically they were stable without symptoms of any acute infections in order to avoid the possible influence of such conditions on the parameters examined. None of the children were smokers.

Children were classified into three groups: overweight, obese and healthy weight based on body mass index (BMI) (kg/m^2) using the International Obesity Task Force criteria[14]. Group I included 66 uncomplicated overweight children with a BMI = 25-30 kg/m^2 or 85th percentile < BMI < 95th percentile. Group Ⅱ included 83 children with uncomplicated morbid obesity of BMI ⩾ 95th percentile or BMI ⩾ 30 kg/m^2 or more. Group Ⅲ included 64 children of the same age as normal control of BMI = 18.5-25 kg/m^2 or < 85th percentile. BMI was calculated as weight in kilograms divided by height in meters squared[14]. BMI z-scores were calculated based on the United States Center for Disease Control and Prevention reference data[15].

Ethical approval

The study was approved by the Ethical Committee of the King Faisal University.

Data collection

Anthropometry: Anthropometric measures followed the protocols of the International Society for the Advancement of Kinanthropometry[16]. Height was measured with a wall-mounted stadiometer (SECA 770, Hamburg, Germany) in a relaxed position with arms hanging freely and without shoes to the nearest 0.3 cm. Weight was measured using electronic digital scales (TANITA ultimate scale 2000 scales, Tanita Corporation, Tokyo, Japan) to the nearest 0.1 kg, with children wearing only a hospital gown and underwear. Measurements were taken by a single technician to overcome inter-rater error.

Calculation of waist-to-hip ratio: To calculate waist-to-hip ratio (WHR), the waist circumference was measured at its smallest point between the iliac crest and the rib cage and the hip circumference at its largest width over the greater trochanters. Blood pressure was measured using a mercury gravity manometer with proper cuff size in standard conditions and ambulatory blood pressure monitoring was carried out[17].

Demographics/background information: Parents completed a questionnaire to collect information about household income, maternal education, child medications and any medical conditions and oral consent was given by all children.

Blood sampling: Blood samples were freshly withdrawn from the vein of various children groups after an overnight fasting on heparin as inpatients at the Hospital Pediatric Clinic and Polyclinic Center and were immediately transferred to our laboratory at the College of Medicine, King Faisal University in an icebox. Blood samples were immediately centrifuged at 4000 rpm at 4 ℃ and plasma was stored at -20 ℃ until analysis. The 50 μL of RBC were taken and lysed with 1.0 mL ice cold water and the clear lysate obtained after spinning down the cell debris at 8500 g for 10 min at 4 ℃ was used for the assays.

Biochemical analysis

Determination of hemoglobin (%): Determination of hemoglobin (Hb) was estimated spectrophotometrically (Boeco S-20 Spectrophotometer, Hamburg, Germany) by using a kit obtained from Biodiagnostic Cairo, Egypt according to the method of Ranganathanand and Gunasekaran[18]. The values were expressed as g/dL.

Estimation of blood glucose: Blood glucose concentration was estimated spectrophotometrically (Boeco S-20 Spectrophotometer, Hamburg, Germany) through application of the method described by Freund *et al*[19] using an enzymatic test kit (glucose oxidase) supplied by Biodiagnostic, Cairo, Egypt. The results were expressed as mg/dL.

Estimation of total serum protein: The total plasma proteins were estimated by using a spectrophotometric (Boeco S-20 Spectrophotometer, Hamburg, Germany) method of Buiret[20]. The results were expressed as g/dL.

Measurement of concentrations of oxidative products and activities of antioxidant enzymes: (1) Determination of MDA: MDA level, an end product of lipid peroxidation of erythrocytes, was assayed spectrophotometrically (Boeco S-20 Spectrophotometer, Hamburg, Germany) using a diagnostic kit supplied by Biodiagnostic, Cairo, Egypt using the method of Stocks *et al*[21]. The results were expressed as nmol/g Hb; (2) Determination of plasma ox-LDL: ox-LDL level was estimated by using an enzyme-linked immunosorbent assay (Merocdia, Inc., Winston-Salem, NC, United States) kit according to the method described by Hoogerbrugge *et al*[22]. The concentration of ox-LDL was expressed in mg/g protein; and (3) AOPP: determination of AOPP was based on spectrophotometric detection of chloramin T at 340 nm according to the method of Witko-Sarsat *et al*[23]. Concentration of AOPP was expressed in chloramine units (μmol/g protein).

SOD activity (EC 1.15.1.1): The Jaiswal *et al*[24] method was used to estimate the total SOD activity spectrophotometrically (Boeco S-20 Spectrophotometer, Hamburg, Germany) in RBC hemolysate by using a test kit obtained from SpinReact Biodiagnostic, Cairo, Egypt. The results were expressed as U/g Hb.

GSH-Px (EC 1.11.1.9): The activity of GSH-Px in erythrocytes was estimated spectrophotometrically (Boeco S-20 Spectrophotometer, Hamburg, Germany) using the method described by Paglia *et al*[25] using a diagnostic kit provided by Biodiagnostic, Cairo, Egypt. The results were expressed as mU/g Hb.

GSSG-R (1.6.4.2): Erythrocyte GSSG-R activity was determined spectrophotometrically (Boeco S-20 Spectrophotometer, Hamburg, Germany) using a diagnostic kit provided by Biodiagnostic, Cairo, Egypt, as described by Worthington *et al*[26]. The results were expressed as mU/g Hb.

CAT (EC 1.11.1.6): CAT activity was measured spectrophotometrically (Boeco S-20 Spectrophotometer, Hamburg, Germany) using a standard CAT assay kit Biodiagnostic, Cairo, Egypt, through following the decomposition rate of H_2O_2 at 240 nm, according to the method of Al-Essa *et al*[27]. The results were expressed as U/g Hb.

GSH: GSH was assayed using the method of Giustarini *et al*[28]. The results were expressed as mg/g Hb.

Statistical analysis

The data were reported as mean ± SD and analyzed with the SPSS 16.0.7 (SPSS, Chicago, IL, United States) for Microsoft Windows XP (Redmond, WA, United States) statistical software package. Differences between the groups were evaluated using the Student's independent samples *t* test. Group comparison was performed by using a one-way analysis of variance. Differences were considered statistically significant at $P < 0.05$. The graphic was drawn by Graph Pad Prism-5.

RESULTS

Basic characteristics

Clinical characteristics of the normal weight, overweight and obese children groups and their control, glucose and Hb are demonstrated in Table 1. A total of 213 children (normal weight = 66, overweight = 83, obese = 64) were included, with age range from 6-12 years (mean age = 9.7 ± 1.5); boys, *n* = 143; 67.1% and girls, *n* = 70; 32.9%. There were no differences in age, gender distribution and levels of fasting glucose and Hb between the different groups. Most of the overweight and obese children resided in the urban region. Body weight and BMI were significantly of higher levels among overweight and obese children compared to the controls. WHR were significantly higher in obese children than in the normal controls, whereas no difference was observed in the

Table 1 Characteristics, glucose and hemoglobin levels of obese and control children enrolled in the study *n* (%)

Characteristic	Subjects		
	Normal weight (*n* = 66)	Overweight (*n* = 83)	Obese (*n* = 64)
Gender			
Boys	42 (63.6)	60 (72.3)	41 (64.1)
Girls	24 (33.4)	23 (27.7)	23 (35.9)
Age, yr			
Mean ± SE	9.5 ± 1.2	9.7 ± 1.8	9.4 ± 1.5
P value	0.089	0.143[1]	0.163[1]
Residence			
Urban	44 (66.7)	55 (66.3)	40 (62.5)
Rural	22 (33.3)	28 (33.7)	24 (37.5)
Anthropometry			
Height in cm	141.9 ± 2.1	142.3 ± 2.4	141.1 ± 2.9
Mean ± SE			
P value		0.703[1]	0.994[1]
Body weight in kilogram		67.7 ± 5.4	139.7 ± 5.9
Mean ± SE	39.2 ± 3.4	0.0001[2]	0.0001[2]
P value		22.4 ± 2.3	32 ± 3.8
BMI		0.0001[2]	0.0001[2]
Mean ± SE	16.4 ± 1.7		
P value		0.89 ± 1.28	2.16 ± 2.64
BMI z-score		0.0001[2]	0.0001[2]
Mean ± SE			
P value	0.03 ± 0.32		
Waist/hip ratio			
Mean ± SE	0.77 ± 0.15	0.79 ± 0.16	0.88 ± 0.16
P value		0.602[1]	0.0004[2]
Age in years			
Mean ± SE	9.9 ± 1.6	9.9 ± 1.9	9.6 ± 2.1
P value		0.616[1]	0.724[1]
Glucose (mg/dL)			
Mean ± SE	80.1 ± 2.9	81.7 ± 2.3	83.5 ± 2.2
P value		0.719[1]	0.075[1]
Hb (g %)			
Mean ± SE	14.2 ± 1.1	13.9 ± 3.4	13.8 ± 3.9
P value		0.674[1]	0.741[1]
Systolic blood pressure (mmHg)			
Mean ± SE	115.6 ± 6.8	115.5 ± 7.4	116.2 ± 9.1
P value		0.874[1]	0.794[1]
Diastolic blood pressure (mmHg)			
Mean ± SE	68.8 ± 6.4	67.6 ± 5.1	68.8 ± 7.1
P value		0.728[1]	0.835[1]

Values are presented in means ± SE. BMI: Weight in kg/height in m^2. [1]non-significant values of overweight and obese groups *vs* control; [2]significant values of overweight and obese groups *vs* control. Comparison of the means was evaluated by ANOVA. BMI: Body mass index; Hb: Hemoglobin; ANOVA: Analysis of variance.

WHR of overweight children (Table 1).

Oxidant markers

Table 2 depicts the activities of antioxidant enzymes SOD, CAT, GSH-Px and GSSG-R in erythrocytes under study. The erythrocyte activities of SOD, CAT, GSH-Px and GSSG-R were significantly elevated in overweight children compared to the corresponding activities of the control group ($P < 0.001$). The mean activity values of these enzymes were decreased in the obese group compared to the corresponding activities of the normal weight and overweight groups ($P < 0.001$). The glutathione levels were decreased in both overweight and obese children in comparison to the corresponding level in the normal control group.

Table 2 Erythrocyte activities of superoxide dismutase, catalase, glutathione peroxidase, glutathione reductase, and reduced glutathione concentration

Group	SOD (U/g Hb)	CAT (mg/g Hb)	GSH-Px (mg/g Hb)	GSSG-R (mg/g Hb)	GSH (mg/g Hb)
Normal weight					
n	66	66	66	66	66
Mean ± SE	224.6 ± 5.3	85.4 ± 2.7	41.4 ± 2.6	42.4 ± 1.6	69.5 ± 1.9
Over weight					
n	83	83	83	83	83
Mean ± SE	252.7 ± 6.5	99.7 ± 3.7	56.8 ± 3.5	56.3 ± 2.5	66.7 ± 2.8
P value	0.001[1]	0.001[1]	0.001[1]	0.001[1]	0.01[1]
Obese					
n	64	64	64	64	64
Mean ± SE	181.7 ± 7.2	68.3 ± 5.1	37.3 ± 5.9	32.9 ± 4.6	33.3 ± 2.1
P value	0.001[1,2]	0.001[1,2]	0.001[1,2]	0.001[1,2]	0.001[1,2]

Values are presented in means ± SE. [1]Significant values of overweight and obese *vs* control; [2]Significant values of obese *vs* overweight group. Comparison of the means was evaluated by ANOVA. SOD: Superoxide dismutase; CAT: Catalase; GSH-Px: Glutathione peroxidase; GSSG-R: Glutathione reductase; GSH: Reduced glutathione concentration.

The concentrations of MDA, OxLDL and AOPP are shown in Figure 1 respectively. MDA, OxLDL and AOPP were non-significantly increased in the overweight children, although highly increased in obese children compared to the normal weight children ($P < 0.001$).

DISCUSSION

The present study estimated the glucose level to exclude the children with hyperglycemia because this condition may affect the levels of the present parameters. In addition, the present study avoided inherited obesity to exclude its effect on the same parameters and thus investigated the effect of the acquired fatness on the antioxidant status in children. The prevalence of overweight and obese children in the urban region may be attributed to habits of eating fatty foods and lack of physical activity due to the very hot weather.

Growing evidence indicates that the mitochondria of white adipose tissue (WAT), particularly of obese persons, are the main site of ROS generation, *e.g.,* superoxide radicals ($O_2^{\bullet-}$) and H_2O_2, accompanied by augmented expression of NADPH oxidase and decreased expression of antioxidative enzymes[29]. This finding is confirmed by Mahadev *et al*[30] who reported that mRNA expression of NADPH oxidase increased in WAT of obese mice.

The antioxidant defenses against ROS include non-enzymatic, *e.g.,* thiol-containing compounds, and antioxidant enzymes[7]. The major antioxidant enzymes include SOD, GSH-Px, GSSG-R and CAT. In the present study, the overweight children showed an elevation in the activities of SOD, GSH-Px, GSSG-R and CAT, but their activities are depleted in obese children (Table 2). The activation of these antioxidant enzymes in overweight children may be to counteract the effect of oxidative

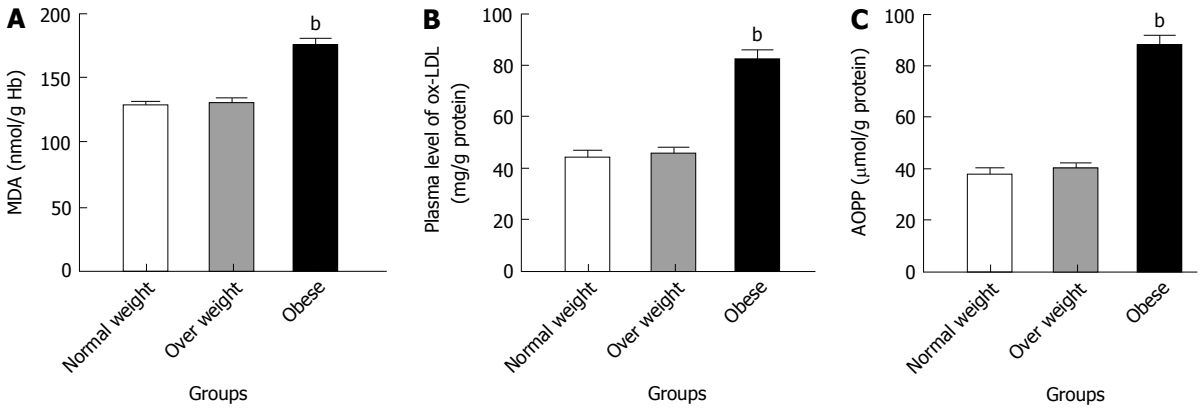

Figure 1 Erythrocyte levels of malondialdehyde (mg/g Hb, A), plasma levels of oxidized low-density lipoproteins (B) and plasma levels of advanced oxidation protein products (C) in normal weight, overweight and obese children. $^{b}P < 0.001$ *vs* control and overweight groups. Results are expressed as mean ± SE. MDA: Malondialdehyde; ox-LDL: Oxidized low-density lipoprotein; AOPP: Advanced oxidation protein products.

stress generated by ROS. The present findings are concordant with prior reports on obese humans and animal models which found that in the early stages of obesity development there may be an initial elevation in antioxidant enzymes to counteract oxidative stress[31]. The depletion of the antioxidant activities in obese children may be attributed to the high production of ROS which may destroy these antioxidant enzymes[32-34]. In addition, the decrease of erythrocyte GSH level (Table 2), which is an essential cofactor for GSH-Px, may lead to reduction of GSH-Px activity in obese children[35,36]. Furthermore, the reduced activities of these antioxidant enzymes in obese children may be attributed to the decreased expression of their mRNA. This finding is confirmed by the studies of Li *et al*[37] and Furukawa *et al*[38] which showed that the mRNA expression levels of antioxidant enzymes, such as SOD, CAT and GSH-Px, decreased in WAT of obese mice. The excess production of MDA (Figure 1A) has additional toxic effects for antioxidant enzymes. MDA may modify the amino acid side chains and oxidation of thiol groups of these enzymes, resulting in a partial or complete loss of their activities and functions[39]. Fang *et al*[40] found that the Ox-LDL correlated negatively with SOD expression and they reported that the decreased activity of SOD may be attributed to excess production of ox-LDL which inhibits the expression of SOD.

GSH plays multiple roles in the cell, including being a free radical scavenger as a primary antioxidant defense[7]. The significant decrease of erythrocyte GSH content in overweight and obese children may be due to its increased turnover into its oxidized form (GSSG) through its detoxification of ROS and other peroxides to challenge the prevailing oxidative stress generated by ROS[41]. This is consistent with GSH function to scavenge oxidants by binding with them covalently[42]. Furthermore, the reduction in erythrocyte GSH content may be attributed to its use in the recycling of vitamin E and semihydroascorbic radicals and reduced oxidized molecules, such as lipid hydroperoxides[43]. In addition, a decrease in the GSH level in the red cells may result from depressed GSSG-R activity (Table 2)[44].

The common approach in the measurement of oxidative stress is the determination of MDA, a product of lipid peroxidation. Thus, the excess production of ROS with insufficient antioxidant enzymes in obese children may have a serious adverse effect on RBC membranes, resulting in lipid peroxidation enhancing production of MDA concentrations similar to our cases (Figure 1A)[38]. This finding is in agreement with the study of Ustundag *et al*[45] which showed the elevation of plasma MDA in smaller groups of obese children when compared with healthy controls.

The current study showed the increase level of ox-LDL (Figure 1B), the second approach in the measurement of oxidative stress in obese children. Increased levels of ox-LDL may be related to excess oxidative stress with lowered antioxidant defense[46]. This finding was demonstrated in 1992 by Parthasarathy *et al*[47] who reported that obese children and adolescents have higher levels of ox-LDL due to generation of ROS compared to a normal weight group.

AOPPs are considered reliable markers to estimate the degree of oxidant-mediated protein damage. The observed increases in AOPP levels in the present study (Figure 1C) suggest that proteins might be an important oxidative target of accumulation of oxidative stress in severe childhood obesity[48]. This argument has been confirmed by the study of Atabek *et al*[49] which found that AOPP levels were increased in obese children and adolescents.

ACKNOWLEDGMENTS

The author thanks the technicians who carried out the blood analysis and Dr. Mosaad Seif, Professor of Biochemistry and Medical Genetics, who aided in the interpretation of the data.

The antioxidant enzymes and the more important oxidatively modified macromolecules, *e.g.,* MDA, ox-LDL and AOPP, have not been completely explored in overweight and obese children because only data on antioxidant vitamin levels are available[11-13]. The current study aimed to evaluate the activities of SOD, CAT, GSH-Px,

GSSG-R, levels of MDA, ox-LDL and AOPP in Saudi overweight, obese and normal weight children to identify obese children who are at risk of complications.

COMMENTS

Background

Alarmingly, obesity and its complications have especially increased in the last three decades among pediatric populations, reaching epidemic proportions in developed and developing countries. Excess body fat expressed as body mass index (BMI) is highly correlated with systemic oxidative stress, which is considered an imbalance between the concentrations of reactive oxygen species (ROS) and the oxidative defense mechanisms. The oxidant-antioxidant status has not been completely studied in overweight and obese children. Therefore, the present study investigates oxidatively modified macromolecules, *e.g.*, malondialdehyde (MDA), oxidized low density lipoproteins (ox-LDL) and advanced oxidation protein products (AOPP), and antioxidants, *e.g.*, superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GSH-Px), glutathione reductase (GSSG-R) and reduced glutathione, in overweight and obese children.

Research frontiers

Studies on obese adults show that oxidative stress is related to BMI. Therefore, the research hotspot is to investigate this relationship in overweight and obese children by estimating oxidative damage products, *e.g.*, MDA, ox-LDL and AOPP, and antioxidant defenses, *e.g.*, SOD, CAT, GSH-Px, GSSG-R and GSH, which are studied as marks of oxidative stresses in obese children.

Innovations and breakthroughs

Due to the lack of availability of information regarding oxidative stress markers in obese children, the novelty of this work is the investigation of oxidative stress within this age group. The children were classified according to their BMI, the precise evaluation of which may be done by a combination of biomarkers that represent a different aspect of oxidative damage products. Examples of such are MDA, AOPP and ox-LDL, and antioxidant defenses, such as SOD, CAT, GSH-Px, GSSG-R and GSH.

Applications

In the future, these findings will be translated into clinical evaluation prior to the overt manifestation of diseases or to assess the benefits of treatment of obese children. In addition, the measurement of oxidant-antioxidant parameters may be useful in understanding the pathophysiology of obesity-related health effects.

Terminology

The authors' findings indicate that severe childhood obesity, represented by BMI, is associated with significantly increased AOPP and ox-LDL concentrations. In addition, the recognition of these changes early in childhood is important for preventing the long-term complications of obesity and targeting individual subjects who are particularly at risk. The authors' results may be helpful in increasing research to expand both prevention and therapeutic strategies for obesity to minimize oxidative stress in children.

Peer review

This is a good descriptive study in which the author did many experiments which illustrated the relationship between BMI and oxidative stress in obese children. The manuscript was interesting to read and the results are interesting. The data and the results in this paper are also very clear and will help the relationship between obese and oxidant-antioxidant status to be understood.

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World J Clin Pediatr 2014 February 8; 3(1): I-V
ISSN 2219-2808 (online)

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Name of journal

World Journal of Clinical Pediatrics

ISSN

ISSN 2219-2808 (online)

Launch date

June 8, 2012

Frequency
Quarterly

Instructions to authors
Full instructions are available online at http://www.wjgnet.com/2219-2808/g_info_20100722180909.htm.

Indexed and Abstracted in
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10 **Sherlock S**, Dooley J. Diseases of the liver and billiary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

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15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: http://www.cdc.gov/ncidod/eid/index.htm

Patent (list all authors)

16 **Pagedas AC**, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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