Original Article

Exstrophy bladder: Effect of sigmoid colocystoplasty on physical growth and bone mineral density

M. Ragavan, N. Tandon[1], V. Bhatnagar
Departments of Pediatric Surgery and [1]Endocrinology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence: Prof. V. Bhatnagar, Department of Pediatric Surgery, All India Institute of Medical Sciences, New Delhi - 110 029, India. E-mail: veereshwarb@hotmail.com

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ABSTRACT

Background and Aims: Introduction of intestinal tissue in the urinary tract results in numerous metabolic changes. This study investigates the effects of augmentation sigmoid colocystoplasty on the physical growth and bone mineralization in bladder exstrophy patients. **Materials and Methods**: Physical growth, serum biochemistry and bone mineral density were assessed pre and post augmentation in 34 of 54 patients who were treated by staged sigmoid colocystoplasty for classical bladder exstrophy during the period 1985–2007. Physical growth was determined by comparing the height and weight for age with standard growth charts. Serum biochemistry included calcium, phosphate and alkaline phosphatase levels. Bone mineral density (BMD) was determined at the femoral head using the dual energy X-ray absorptiometry (DEXA) scan at 15 ± 4.5 months after the augmentation. The DEXA scan findings were compared with 22 normal Indian children who served as controls and 18 unaugmented patients with bladder exstrophy. In 13 augmented patients, the DEXA scan could be repeated after an interval of six months. **Results**: The mean percentile height and weight were comparable in the pre and post-augmentation period with no statistically significant difference (P=0.135 for height and P=0.232 for weight). Biochemical parameters of bone metabolism also did not show any statistically significant changes after colocystoplasty. The BMD was 0.665 ± 0.062 g/cm^2 in the controls and 0.612 ± 0.10 g/cm^2 in the unaugmented bladder exstrophy patients. In the augmented patients, the BMD was 0.645 ± 0.175 g/cm^2 and six months later it was 0.657 ± 0.158 g/cm^2. These differences were not statistically significant. **Conclusions:** In our study, no significant effects on the physical growth and bone mineral metabolism were observed in exstrophy bladder patients following sigmoid colocystoplasty.

KEY WORDS: Bone mineral density, colocystoplasty, Exstrophy bladder, physical growth

INTRODUCTION

The effect of intestinal cystoplasty on the physical growth and bone mineralization is a controversial issue.[1] The bone changes that occur after augmentation enterocystoplasty have been attributed to metabolic changes, among which metabolic acidosis is the prime factor. However, there is evidence to suggest that reduction in bone mineral density may occur even in children with normal acid base status.[2] The aim of our study is to assess the effect of sigmoid colocystoplasty on physical growth and bone mineral density in bladder exstrophy patients.

MATERIALS AND METHODS

This study is a long-term evaluation of physical growth and bone mineral metabolism of classical bladder exstrophy patients who had undergone augmentation colocystoplasty using detubularized sigmoid colon. Patients who underwent bladder exstrophy reconstruction during 1985 to 2007 were included in the study. During this period, a total of 54 patients had undergone colocystoplasty. Seven patients

had failed to follow up; of the 47 cases studied, 40 were males and 7 were females. The augmentation colocystoplasty was done as a staged procedure following primary bladder closure and bladder neck repair in 30 patients, along with bladder neck repair in 13 cases and as a primary procedure in 4 children as their bladder plate was too small to be closed primarily. The mean age at colocystoplasty was 4.3 years and the duration of follow up ranged from 3 months to 19 years with a mean of 4.7 years. The mean age at analysis of data was 9.4 years.

Prior to bladder augmentation with colon, the height and weight were recorded and serum calcium, phosphate and alkaline phosphatase levels were measured. The height and weight were compared with Indian standard anthropometric (CDC 2000) reference charts to obtain the respective percentiles. Abnormalities of renal function were ruled out by biochemical tests (blood urea and serum creatinine) and radionuclide scintigraphy (renal dynamic scans and creatinine clearance).

During follow up, the anthropometry and biochemical parameters were repeated at varied intervals and the mean was used for analysis. The patients were also submitted for bone densitometry scan of upper end of femur for detecting the bone mineral density using QDR 4500A model dual energy X-ray absorptiometry (DEXA), Hologic, USA during the period 2005-2007. Bone densitometry scan was done in the Department of Endocrinology and Metabolism. The DEXA scan machine calculates the surface area of the bone in centimeter square and bone mineral content (BMC) in grams. The bone mineral density (BMD) is calculated by dividing the bone mineral content with surface area of the bone. The pre-operative BMD values (g/cm^2) were available in 34 bladder exstrophy patients who had undergone augmentation cystoplasty using detubularized sigmoid colon and these were compared with the values of age and sex matched 22 normal Indian children (control group) and 18 exstrophy bladder patients who were not augmented. The control group comprised of otherwise healthy children who visited the Pediatric Surgery outpatient clinic for the treatment of inguinal hernia. In the augmented group, bone densitometry scan was also repeated six months after the first study in 13 patients, to look for any change. Another observation in DEXA scan, the 'T' score, can be generated for people who have achieved the age of peak bone mineral mass, by comparing the BMD of the study group with normal age and sex matched general population. It was not used in our study because our study group comprised of children between 3 and 15 years, who would not have achieved the peak bone mineral mass.

Statistical analysis

The corresponding pre-operative and post-operative mean and standard deviation values of the variables were compared by applying, student's paired *t* test. '*P*' value less than 0.05 was considered as statistically significant.

RESULTS

The percentile height and weight have been presented in Tables 1 and 2 respectively. The percentile values calculated from the CDC 2000 reference chart were categorized into three subgroups as: <50, 50-75 and >75th percentiles. The number of cases in each group before augmentation and after augmentation has been tabulated.

The median percentile of height and weight was 50. The mean percentile of height and weight were nearly the same in pre and post-augmentation period with no statistically significant difference.

Biochemical parameters of bone metabolism included serum calcium, phosphate and alkaline phosphatase levels and these showed no statistically significant changes after colocystoplasty as shown in Table 3. The normal reference ranges, as used in our laboratory, were 9–11 mg/dl for serum calcium and 2.5–5 mg/dl for serum phosphate. The changes between the pre-augmentation and post-augmentation levels were not statistically

Table 1: Pre and post augmentation height

Percentile height	Number of cases (percentage)	
	Pre augmentation*	Post augmentation*
< 50	7 (14.89%)	8 (17.02%)
50–75	32 (68.08%)	30 (63.83%)
> 75	8 (17.02%)	9 (19.15%)

*P = 0.135

Table 2: Pre and post augmentation weight

Weight percentile	Number of cases (percentage)	
	Pre augmentation*	Post augmentation*
< 50	6 (12.77%)	3 (6.38%)
50–75	34 (72.34%)	39 (82.98%)
> 75	7 (14.89%)	5 (10.64%)

*P = 0.232

Table 3: Mean pre and post augmentation biochemical parameters

Variable	Pre-augmentation (Mean ± SD)	Post augmentation (Mean ± SD)	'*P*' value
Serum calcium (mg/dl)	9.88 ± 0.67	9.80 ± 0.55	0.448
Serum phosphate (mg/dl)	5.11 ± 0.75	5.44 ± 0.87	0.053
Alkaline phosphatase (IU)	217 ± 175	458 ± 310	*

*'*P*' value not calculated; likely to change with age and significance may be false

significant. Although the alkaline phosphatase appears to be elevated in the post-augmentation patients, it was within the normal pediatric range (80-800 IU).

The post-augmentation DEXA was performed at a mean of 15 ± 4.5 months after augmentation colocystoplasty. The mean BMD in the control group was 0.665 ± 0.06 g/cm^2. The BMD of unaugmented exstrophy bladder patients was 0.612 ± 0.10 g/cm^2 and post augmentation study group was 0.645 ± 0.17 g/cm^2. There was no statistically significant difference while comparing with normal children (P=0.291 for exstrophy group and 0.713 for augmentation group). The repeat BMD in 13 augmented patients done six months after the first scan showed a mean of 0.657 ± 0.158 [Table 4].

DISCUSSION

Augmentation of urinary bladder, by interposition of bowel, has allowed the preservation of renal function and provision of urinary continence. However, it is not without complications; the association between enterocystoplasty and retardation in the growth and development has been reported.[3,4]

The hypothesis for retardation of growth after colocystoplasty has been attributed to metabolic acidosis, urinary tract infection and anemia.[5,6] Bone has crucial buffering action in controlling the systemic pH changes due to the presence of buffers such as phosphate, carbonate, and calcium in it. Chronic acidosis is buffered by carbonate extraction from the bone accompanied by the release of calcium into blood from the bone reserve. The calcium is lost in urine leading to hypocalcemia and bone weakness.[7] The bone changes occur after a period of six months at least.[4] Acidosis also causes reduced conversion of 25 hydroxyl vitamin D3 to 1,25 dihydroxyl vitamin D3 and increased levels of parathormone and calcitonin, eventually resulting in demineralization of the cortical bones, leading to pain and fracture.[5,6]

Mundy *et al.*[1] described a 20% reduction in growth in three of six children who had undergone colocystoplasty. However, this was a retrospective study and the definition of growth rate was not clearly defined; hence the results remained provocative yet unsubstantiated.[3] Wagstaff *et al.*[8] measured height in 60 of 183 patients and found reduced growth in 12 patients only. The study was also confounded by nine patients having increased growth.[4,8] Although Wagstaff initially reported growth failure in 12 patients, subsequent follow up 10 years later had refuted the initial finding.[9] We could find no decrease in the percentile heights or percentile weights of children after augmentation colocystoplasty, when compared with their pre augmentation values. There was also no decrease in the linear growth rate. Our findings are further supported by five of the seven most recent studies, which show no change in linear growth. In a study of 15 children, 5 with bladder exstrophy and 10 with neurogenic bladder, there was no growth impairment reported.[10] Similarly, in another study of 28 children who underwent enterocystoplasty, no change in growth was reported in children augmented with colon.[11] In children augmented with sigmoid, the average linear growth had decreased during the first year postoperatively, but had recovered to preoperative percentiles two years after surgery.[11] Mingin *et al.*[4] had reported no change in linear growth among 22 augmented meningomyelocele patients and 11 augmented exstrophy children when compared to their controls. Further, a study by the Toronto group, on looking at 25 patients with bladder exstrophy, determined that none of them in the augmented group had an alteration in supine height measurement.[12] Finally, in a study excluding meningomyelocele patients, Gerharz *et al.*[9] reported that after enterocystoplasty 85% of their 123 patients remained the same or even reached a higher percentile. Although two studies, one conducted by Gros *et al.*[2] and another by Feng *et al.*,[13] reported delayed linear growth, there were two potential problems in their study; combining both the studies, only 35 patients were evaluated compared to a total of 227 patients in the five studies showing no change in growth. In addition, looking at the number of height measurements done in the two studies, it was either none[13] or only a maximum of 2–3 measurements done in the other.[2] But, Mingin *et al.*[4] and Gerharz *et al.*[9] have made a minimum of eight and ten height measurements, respectively. Although not completely conclusive, the literature would suggest that, to date, growth may not be affected to the extent reported by Feng *et al.*[13] and Gros *et al.*[2] Hence, this goes in favor of the results of our study which shows no reduction in the linear growth and weight gain of augmented children. This hypothesis is supported by a number of investigations e.g. unilateral ureterosigmoidostomy with no acidosis also develops bone demineralization; patients with colocystoplasty may have elevated serum phosphate, alkaline phosphatase, parathormone and calcitonin while the calcium level can be normal or low; normal serum calcium and 24 h urinary calcium excretion.[14]

Table 4: Bone mineral density (g/cm^2)

Category (number of cases)	Bone mineral density (Mean ± SD)
Controls (*n*=22)	0.665 (±0.062)
Unaugmented exstrophy children (*n*=18)	0.612 (±0.10)
Post augmentation (*n*=34)	0.645 (±0.175)
Repeat BMD in augmented children (*n*=13)	0.657 (±0.158)

In our study, to obtain an objective measurement of bone mineral content, bone scans were performed (femoral neck) in 34 augmented children at a mean duration of 15 months after augmentation. Bone densities were not significantly different after augmentation and they showed an uptrend. Our results are supported by several studies and animal experiments. Both Mingin *et al*.[4] and Clementson Kockum *et al*.[10] reported no significant change in BMD in augmented exstrophy patients. The average length of follow-up in both studies was 3.7 years. Ugur *et al*.[15] have evaluated BMD after enterocystoplasty in children with and without myelomeningocele and concluded that after augmentation the BMD in early post-operative period of patients with myelomeningocele was lower than that of the patients with non-neurogenic bladder. They have also postulated that the lower BMD of myelomeningocele group depended more on the underlying neurologic pathology and its locomotor consequences rather than the enterocystoplasty itself.[15] On experimenting with uremic rats, Brkovic[16] had found that in contrast to the ileal augmented rats, which showed a significant decrease in BMD at lumbar spine on comparison with normal controls, rats with colocystoplasty and gastrocystoplasty showed no significant decrease. Of all the intestinal segments suitable for urinary tract reconstruction, colon appears to be safe and ileum appears to harbor the greatest risk of bone mineral loss, especially in the state of mild uremia.[16] It has also been concluded based on numerous other experiments on rats that, colonic augmentation had no significant effect on bone strength or bone mass.[17,18] Looking into the study on other urinary diversion procedures, Stein *et al*.[19] had evaluated the skeletal bone density and whole body potassium up to 30 years after different types of urinary diversion procedures and found that the bone densitometries were normal in all patients. The finding of our study is concordant with all these afore mentioned studies and experiments.

In contrast, Hafez *et al*.[12] studied 25 patients and reported a mild reduction in bone density between 1 and 2 standard deviations in 12% of their exstrophy patients, severe reduction of more than 2 standard deviations in 20% of patients. The average length of follow up of this study was 8.9 years. Similarly, Abes *et al*.[6] have also reported decreased BMD in four out of six patients who had undergone augmentation colocystoplasty. This interpretation must be viewed with caution as these studies were based on relatively small number of patients.[3]

Our study may be criticized for rather short follow up, and it can be argued that bone demineralization may take years to develop. However, Rosenstein *et al*.[20] have studied that DEXA scan is a key tool for studying bone growth soon after bladder augmentation, where changes in bone mineral content can be detected within six months of surgery. Further, 32 of our 34 patients were followed up for more than six months after colocystoplasty.

Hence, it can be concluded that the assumption that colocystoplasty or colonic reservoirs have a higher risk of developing metabolic bone disease could not be confirmed by numerous clinical data, even those reported over a follow up of upto 30 years.[17,19] There is no significant difference in percentile heights or weights in children augmented with colon. In pediatric population, long-term life expectancy warrants meticulous observation of changes after augmentation enterocystoplasty, BMD by DEXA scan can be used for monitoring of patients with metabolic acidosis and bony demineralization.

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