ABSTRACT
Background: Longitudinal growth assessment is essential in children at an early period. Short stature can be promptly recognized only with accurate measurements of growth, critical analysis of growth data as well as thorough history and physical examination. The objective of this study was to determine the pattern of short stature among patients referred to Makassed General Hospital, to ascertain the etiological profile of short stature and to compare them with the worldwide studies. Methods: This is a retrospective review of patients referred to Makassed General Hospital with a complaint of short stature during the period from January 2009 to December 2014 after a proper detailed medical history, growth analysis and physical examination, followed by a radiological and laboratory screening. Results: During the period under review, 643 patients were evaluated for short stature. 538 children were found to fit the definition of short stature and 105 were non short and were excluded from the study. Their age ranged from 6 months to 15 years. The most common etiology was normal variant short stature followed by growth hormone deficiency. Conclusions: Normal variant short stature is the leading cause of short stature. Adequate monitoring of growth as well as early identification of abnormal growth patterns in both girls and boys equally is essential.

KEYWORDS: Short stature; Growth hormone deficiency; Normal variant.

INTRODUCTION
Short stature is a common problem in children globally encountered by practicing pediatrician especially in developing countries.[1] Growth is a continuous biologic process subject to genetic, environmental, nutritional and hormonal influences as well as effects of chronic diseases and physical activity.[1] A disturbance at any point of these levels may adversely affect growth resulting in short stature and emotional stress.[2] Short stature is defined as height or length below third percentile for age and gender or less than two standard deviations (SD) for that specific age and sex.[3,4]

There are diverse causes of short stature that ranges from normal variants like familial short stature and constitutional growth delay that are beyond the first two years of life and need no medical treatment to a more pathologic condition like endocrine and systemic diseases.[5,6]

In familial short stature, the final adult height is short but within the target range of height for the family. Constitutional delay of growth and maturation is a defect in growth hormone insulin like growth factors (GH- IGF) axis and obligates higher rates of overall energy expenditure. This increased metabolism may result in impaired tempo of growth.[7,8]

Endocrine causes are associated with being overweight for height as congenital hypothyroidism and growth hormone deficiency.[9] Severe malnutrition is one of the common causes of short stature mainly in the third world countries. Vitamin D deficiency is another important cause of short stature.[10] Short stature may be also seen with severe intrauterine growth retardation (IUGR) or infant born small for gestational age and in numbers of dysmorphic syndromes.[1,3,11] Idiopathic short stature is considered when no causative disorder can be identified.[12]

Early diagnosis of children with short stature is very important because of the emotional stress associated with it which could be alleviated either by education to the parents or by treating the cause.[13]

Data addressing the frequencies of different causes of short stature in Lebanon is not generous. So, the aims of this study were to:
- Detect the etiological profile of short stature in children presenting to Makassed General Hospital.
- Compare the findings of our study with the worldwide studies.

**MATERIALS AND METHODS**

This is an observational retrospective study, conducted at the Pediatric Department at Makassed General Hospital after obtaining approval from the Institutional Review Board. It was carried out over a period from January 2009 to December 2014. The medical records of children from both genders, 6 months to 15 years of age with an admitting diagnosis of short stature were reviewed.

Patients with contractures and kyphoscoliosis in whom height could not be measured as well as patients who did not fit the proper definition of short stature were excluded from the study.

Thorough history and physical examination were recorded. History of low birth according to gestational age was recorded. Nutritional status was assessed, and stages of puberty were determined according to the classification of Tanner stage.

Detailed birth and family history were noted including birth length, weight and parental height which were calculated to identify the genetic growth potential using following formula:

\[
\frac{(\text{father’s height (cm)} + (\text{mother’s height (cm)} + 13))}{2} \text{ for boys and } \frac{(\text{father’s height (cm)} – 13) + \text{mother’s height (cm))}{2} \text{ for girls.}
\]

Standing height without head or foot gear (measured with a stadiometer), upper to lower segment ratio, weight and head circumference were measured. Recorded growth parameters were first plotted on 2000 CDC growth charts and all those children with height below third percentile were included in the study as the fitting category.

Laboratory investigations included (complete blood count, ESR, urinalysis, hepatic and renal parameters, bone profile, Anti tissue transglutaminase (Anti-tTG IgA & IgG), serum free T4 and TSH levels and vitamin D level). The patients who had raised levels of Anti-tTGs were confirmed with endoscopic duodenal biopsy. Radiograph of left hand and wrist (bone age) were done in some patients.

Short stunted patients with chronic diseases were diagnosed on the basis of history, physical examination and relevant investigations. Karyotyping was done for syndromic patients.

Growth hormone was assessed by provocation test with insulin and glucagon tolerance test in patients who had strong clinical suspicion of growth hormone (GH) deficiency having baseline investigations within normal limits.

The final cause of short stature was decided in consultation with the Pediatric endocrinologist. All the details of the study and all the related terminologies were clearly defined as follows:

**Short Stature:** Height below 2SD or 3rd percentile for age and sex.

**NVSS (Normal variant short stature):** They include Constitutional delayed growth and maturation (CDGM) and Familial short stature (FSS).

**Constitutional Delayed Growth and Maturation:** Bone age equal to height age, both are less than chronological age.

**Familial Short Stature:** Bone age equal to chronological age and both are more than height age.

**Growth Hormone Deficiency (GHD):** Levels less than 10ng/ml on insulin stress test.

**Primary Malnutrition (3rd Degree):** Weight less than 60% of the expected weight for age and sex according to NCHS (National Child Health Services) standard and nutritional history of decreased caloric intake.

**Celiac disease:** Duodenal mucosal changes consistent with Celiac Disease on small intestinal biopsy and raised tissue transglutaminase antibodies i.e. IgA above 7U/ml and IgG above 17U/ml.

**Hypothyroidism:** Free T4 less than 0.93ng/dL and TSH more than 6.4 uIU/ml.

**Genetic Syndromes:** Like (Down syndrome, Turner’s syndrome, Noonan’s syndrome, Russel Silver syndrome).

**Chronic Diseases** like (chronic kidney disease, insulin dependent diabetes mellitus, and bronchial asthma) were diagnosed from clinical profile and relevant investigations.

**Statistical analysis**

Data were analyzed using SPSS version 19. Descriptive statistics were applied. Mean and standard deviation for age were computed. Chi square test was done to determine the frequency of various causes of short stature (CDGM, FSS, GHD, IDDM, primary malnutrition, celiac disease, hypothyroidism, genetic syndromes, and chronic diseases) was calculated. P-value<0.05 was considered significant.

**RESULTS**

A total of 643 children were identified as having short stature as the admitting diagnosis between January 2009 and December 2014.

105 children who did not fit the proper definition of short stature were excluded from the study.
A total of 538 cases (253 male (47%), female 283(53%)) were identified with mean chronological age of 7(±3.6) year, mean height of 114 (± 19.7) cm and mean mid parental height was 116.9 cm (± 4.6 cm).

All children who fell below third percentile for their height on 2000 CDC growth charts are included and the frequencies of various causes of short stature in this study are shown in Table 1.

Normal variant short stature was the most common cause of short stature identified in 158 children (29.4%); 77 children (14.3%) have familial short stature and 81 children (15.1%) have constitutional growth delay whereas growth hormone deficiency was diagnosed in 145 children (27%).

Chronic diseases such as anemia, congenital heart disease, asthma and renal diseases represent 84 children (15.6%) of the total number.

64 patients (12.1%) had idiopathic short stature followed by hypothyroidism27 patients (5%), malnutrition 19 patients (3.5%), coeliac diseases 19 patients (3.5%), small for gestational age 13 patients (2.4%) and syndromic causes 8 patients (1.5%) such as achondroplasia. Down syndrome and Turner syndrome.

With respect to the age categories; in our study we found that 160 (29.8%) children were evaluated within the age of less than or equal 5 years, compared to 277 (51.5%) children within a period between 6 and 11 years and 101 (18.8%) children were more than 11 years of age (Table 2).

**Table 1: Causes of short stature.**

<table>
<thead>
<tr>
<th>Causes of short stature</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Variant short stature</td>
<td>158 (29.4%)</td>
</tr>
<tr>
<td>Constitutional</td>
<td>81 (15.1%)</td>
</tr>
<tr>
<td>Familial</td>
<td>77 (14.3%)</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>145 (27.0%)</td>
</tr>
<tr>
<td>Chronic disease</td>
<td>84 (15.6%)</td>
</tr>
<tr>
<td>Idiopathic short stature</td>
<td>65 (12.1%)</td>
</tr>
<tr>
<td>Hypothyroidity</td>
<td>27 (5.0%)</td>
</tr>
<tr>
<td>Celiac disease</td>
<td>19 (3.5%)</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>19 (3.5%)</td>
</tr>
<tr>
<td>Low birth weight</td>
<td>13 (2.4%)</td>
</tr>
<tr>
<td>Genetic Syndromes</td>
<td>8 (1.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>538 (100%)</td>
</tr>
</tbody>
</table>

**Table 2: Age characteristics of short patients.**

<table>
<thead>
<tr>
<th>Age category</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤5 years</td>
<td>160 (29.8%)</td>
</tr>
<tr>
<td>6-11 years</td>
<td>277 (51.5%)</td>
</tr>
<tr>
<td>&gt;11 years</td>
<td>101 (18.8%)</td>
</tr>
</tbody>
</table>

**Table 3: Comparison of etiology of short stature with other studies.**

<table>
<thead>
<tr>
<th></th>
<th>Cola co P et al. (%)</th>
<th>Lindsey R et al. (%)</th>
<th>Moayeri H et al. (%)</th>
<th>Own study (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Variant short stature</td>
<td>20.5%</td>
<td>80%</td>
<td>47%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>19.5%</td>
<td>2.5%</td>
<td>23.4%</td>
<td>27%</td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>8.5%</td>
<td>10%</td>
<td>4%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14.2%</td>
<td>1%</td>
<td>8%</td>
<td>5%</td>
</tr>
<tr>
<td>Genetic syndrome</td>
<td>7.4%</td>
<td>1.5%</td>
<td>4.5%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

**Table 3: Comparison of etiology of short stature with other studies.**

<table>
<thead>
<tr>
<th></th>
<th>Bhadda Sk et al. (%)</th>
<th>Song Kc et al. (%)</th>
<th>Malhoob sultan et al. (%)</th>
<th>Own study (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Variant short stature</td>
<td>15.9%</td>
<td>44.7%</td>
<td>32.3%</td>
<td>29.4%</td>
</tr>
<tr>
<td>Growth hormone deficiency</td>
<td>7.4%</td>
<td>38.9%</td>
<td>6.1%</td>
<td>27%</td>
</tr>
<tr>
<td>Systemic diseases</td>
<td>12.4%</td>
<td>13.7%</td>
<td>17%</td>
<td>15.6%</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>14.2%</td>
<td>0.5%</td>
<td>5.6%</td>
<td>5%</td>
</tr>
<tr>
<td>Genetic syndrome</td>
<td>7.4%</td>
<td>11.4%</td>
<td>5.6%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

Chronic diseases such as anemia, congenital heart disease, asthma and renal diseases represent 84 children (15.6%) of the total number.
DISCUSSION
Growth is an important parameter for child’s health. Longitudinal growth measurement is essential in child care to assess for short stature knowing that short stature is not a disease per se; it may be a manifestation of several diseases. It is recognized only with accurate measurements of growth and critical analysis of growth chart.[12]

Causes of short stature have been studied extensively worldwide, but similar studies are quite few in Lebanon. For this reason, any child with an abnormally slow growth rate, height below 3rd percentile or height considerably below the genetic potential deserves further evaluation.[13]

In this study, if we categorize the causes of short stature in three main etiological categories, the most frequent were NVSS, followed by endocrinological causes and then the non endocrinological causes.

Similar observation was made by Shu et al. in their study and found that NVSS were the most common cause and comprise as much as 65% of the short children. On the other Hand, Cola Coetal found that endocrinological causes were almost as common as normal variant short stature among Indian children.[14,15]

In this study, the most common single etiology of short stature found was NVSS, constitutional growth delay 81 (15.1%) patients and familial short stature 77 (14.3%) patients making it the leading cause of short stature.

This was followed by growth hormone deficiency which was seen in 145 (27%) cases and which is found to be 23.4%, 22.8% and 13.9% in studies done by Moayeri et al, Zarger et al and Aland Awan TM et al respectively.[16,17,18]

When comparing our study to the worldwide studies we found the same results that normal variant short stature were the most common causes of short stature.

Lindsey et al in their study on 555 American children, found that 80% of the study population were a normal variant of growth, this also was supported by a study done by moayeri et al in Iran where 47% of the study population (426 children) were found to have normal variant short stature as a most common cause of growth delay.

Bhadda SK et Al. studied the frequency of various causes of short stature and their etiological contribution among Indian population, 352 patients were enrolled and the result showed that in males constitutional growth delay was the most common cause while in females familial short stature is the leading cause making normal variant short stature the most common cause with 15.9%.

A case series done by Mahboob sultan et al among Multan children in Europe, two hundred and fourteen children (140 boys and 74 girls), ranging from 02 to 15 years presenting with short stature were studied, and they concluded that Constitutional growth delay and Familial short stature were the most Common causes of short stature in boys and girls respectively representing 32.3% of the study population.

Moreover, Song KC et al studied the etiological profile of short stature among 3371 Korean children and found the same result that normal variant short stature was the most Common cause by 44.7% of the study population.

Thus, it is very important to remember that many cases of short stature in general population may be normal, as determined by meticulous measurements, and determination of bone age using standard charts and expert’s radiological opinion.

Timely identification of such cases not only helps to avoid extensive and unnecessary investigations but also alleviates parental anxiety and psychological burden on the child itself.

In this study, 38.6% of short stature children had non endocrinological causes, out of them the most common non endocrinological causes were chronic diseases (15.6%) such as asthma, anemia, thalassemia, congenital heart diseases, renal diseases and coeliac diseases (3.5%) with malnutrition (3.5%). These results are consistent with many worldwide studies. Utah growth study concluded that malnutrition and malabsorptive syndromes were responsible of 10% of short stature[19] as well as Mahboob Sultan et al they found in their study that malnutrition is responsible of 9.8% of short statured children. (Table 3).

Few rare cases of multiple growth abnormality syndromes (1.5%) were also diagnosed with presentation mainly of short stature and abnormal features and were proven by Karyotyping and other genetic testing such as Turner syndrome, Down syndrome and achoondroplasia.

Other causes of short stature identified are low birth weight (2.4%) and hypothyroidism (5%) in which appropriate follow up is a gold standard for treatment and achievement of final appropriate height.

Many causes of short stature have been discovered over the past few years, but there are other factors that are not yet understood. Idiopathic short stature refers to short stature that does not have a diagnostic explanation and falls into this latter category, it is defined as children having a height significantly shorter than the normal population (i.e., shorter than 1.2% of the population of the same age and gender. They represent 12.1% of total cases of short stature in our study.[19]
Although the reasons for Idiopathic Short Stature are not yet totally understood, it is known that the administration of growth-promoting treatments may help affected children.

Among 538 patients, 277 children presented for evaluation of their short stature with an age 6-11 years compared to 160 children ≤ 5 years and 101 children > 11 years. Because short stature in infants, children and adolescents may be due to variation in normal growth or to pathological states, early and accurate assessment and monitoring of growth is of critical importance for early identification of defects associated with treatable conditions versus growth variations associated with normal conditions.

This supports our findings that early identification of abnormal growth patterns and prompt referral to specialist care offer children with growth failure and/or short stature the greatest chance for appropriate diagnosis, treatment, and improved clinical outcomes.²²⁰

Although when comparing male to female pattern of distribution of short stature, we found that 283 (53%) females presented for evaluation of short stature compared to 253 (47%) males patients.

In the literature, we found that referral patterns reveal substantial sex differences in the evaluation and treatment of short stature. Boys are referred for evaluation more often, at younger ages and for less severe height deficits as compared with girls. As an example, in one retrospective review of 288 children referred to a single center for assessment of short stature, the male: female ratio was 1.9:1. At the time of referral, the height deficit was significantly greater for girls than boys (median height Z-score, -2.4 versus -1.9), and organic disease was more common among girls (40 versus 15 percent). Similarly, studies of growth hormone registries have shown preferential treatment of boys compared with girls with an approximate ratio of 2:1.

This apparent gender bias may be due to under-appreciation of growth problems in girls, leading to fewer evaluations of girls for short stature. Alternatively, it may be due to increased societal pressure for tall stature in boys, leading to increased referral and growth hormone treatment of boys without organic causes of short stature. These findings emphasize the need for accurate growth monitoring during the health care maintenance of all children to ensure appropriate referral and treatment.

Despite that boys who are short are more likely to come to medical attention than girls who are short, our findings in this study support the contrary were we found an almost equal referral for evaluation with respect to gender.

Boys do appear more likely to have idiopathic GHD or constitutional delay of growth and development.²²¹

The evaluation of short stature should be addressed for both genders equally and recognition of the cause at an early age is an important value to predict treatable conditions and its associated academic, behavioral or psychological effects that a short child might have in life whether it was a girl or a boy.²¹

Regardless of the genetic background, short stature may be a sign of a wide variety of pathologic conditions or inherited disorders. Thus, accurate longitudinal growth assessment is a fundamental aspect of health maintenance in children as well as the recognition of symptoms and laboratory findings associated with short stature should be done only if indicated.

During the evaluation of our patient we found a strong association between Vitamin D deficiency, H. pylori gastritis and short stature.

Reduced intake of calcium and vitamin D during periods of growth can have a negative influence on bone development, causing not only rickets, but also interfering with attainment of genetically programmed height.²²² This was also found in our study in which 87.2% of children presented for evaluation for their short stature and were below third percentile had low vitamin D level.

During puberty and adolescence, calcium requirements are greater than at any other stage of life, due to the accelerated muscular, skeletal and endocrine development.²²³ Bone mineral deposition during pubertal growth appears to depend on dietary absorption of calcium, and on reducing its excretion, and this is dependent on adequate vitamin D status. Despite this, understanding the relationship between calcium absorption and vitamin D and growth is limited.²²⁴

Abrams et al. compared the heights of 315 girls between 5 and 15 years old with their dietary calcium absorption and found a positive relationship, demonstrating that an increase in absorption efficiency is, in part, regulated in order to meet the requirements of the final skeletal size. However, this relationship remains uncertain and may be due to genetic components.²²⁴

Prentice et al. evaluated the effect on bone acquisition and bone growth of supplementation with calcium versus placebo. The intervention resulted in improved bone mineral content and an increase in height equivalent to 7 mm.²²⁵

Moreover, results published by Black et al. confirmed the hypothesis that children with long histories of low milk intake have low dietary calcium intake and poor bone health compared with children who drink milk.²²⁶
In our study, we found 35 patients have positive H. pylori gastritis confirmed by gastroscopy. It can be suggested that H. pylori may be associated with short stature through mechanisms that are independent of poor living conditions, although low.

Socioeconomic status could determine acquisition of infection. The mechanisms by which H. pylori infection might influence growth needs further investigation.

Ertem et al. reported the findings regarding H. pylori and its possible effect on growth in 327 healthy school children aging between 3 and 12 years. The H. pylori status was determined by 13C-urea breath test in the study group. Almost one half of the study population (49.5%) was infected with H. pylori, and the prevalence increased with increase in age (18.2% in children younger than 4 years and 63% in children older than 10 years.¹¹²¹

Takahashi M et al. evaluated short patients aged from 1 to 16 years. These patients were divided into a growth hormone deficient short stature group (n = 27) and an idiopathic short stature group (n = 14). A control group included children with normal growth and no abdominal pain (n = 47). Anti-H.Pylori antibodies were measured in each group (total of 88), the antibody positivity rates for each group were as follows: growth hormone deficient short stature group, 7.4%; idiopathic short stature group, 28.6%; and control group, 6.4%. The H. pylori antibody positivity rate in the idiopathic short stature group was significantly higher than in the control group. These findings suggest an association between H. pylori infection and idiopathic short stature.²²

**Limitations**
The shortcomings of this study include failure to calculate and plot growth velocity which requires a regular follow-up at six months to twelve months interval, which was not possible in this retrospective study.

Secondly, it was a single center study. The difference in frequency of various causes of short stature reported from different centers can be due to many factors like genetic, socioeconomic, nutritional and other related factors.

Relation between short stature and vitamin D deficiency as well as H. pylori gastritis needs further studies and larger sample size.

**CONCLUSION**
Normal variant short stature (familial short stature and constitutional growth delay) are the leading causes of short stature in children whereas growth hormone deficiency is relatively less common. Thus, the growth hormone axis should only be investigated in selective cases.

Adequate monitoring of growth, early identification of abnormal growth patterns in both girls and boys equally and prompt referral to specialist care offer children with short stature the greatest chance for appropriate diagnosis, treatment, and improved clinical and psychological outcome.

Early detection of treatable causes would be helpful in a better long – term prognosis.

Vitamin D deficiency and H. pylori gastritis have a strong association with short stature and appropriate management could prevent further unnecessary investigations. Larger scale and community based studies are required.

**REFERENCES**