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INVESTIGATION OF IGF-1 SERUM LEVELS IN HEALTHY CHILDREN DURING SYRIAN CONFLICTS

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ABSTRACT: Purpose: Insulin-like growth factor-1(IGF-1) is an important growth hormone that promotes the anabolic effect and linear growth in adults and children. This study aimed to assess serum levels of IGF-1 in healthy Syrian children during Syrian conflicts. **Materials and Methods:** This study was approved by Al Wataniya Private University ethical committee. In total, 83 children, 49 males and 34 females (3-16 years) were enrolled. Demographic data were registered after obtaining written informed consent from children's families. Venous blood samples were drawn from children to measure serum IGF-1 levels. GraphPad Prism5.0 was applied to analyze data. Pearson and Mann-Whitney tests were used. **Results:** The averages of age, weight, height, and body mass index were 6.86±2.69 years, 20.36±7.8 kg, 112.56±16.4 cm, and 15.5±1.7 kg/m^2, respectively. The average level of IGF-1was 85.44±60 ng/ml. A third of participants had IGF-1 levels below the normal index for their ages, and there was a significant difference in IGF-1 levels and height between these children and the others. 22.8% of participants had short to limit short statures (≤3rd percentiles), eleven of which had low IGF-1 levels. **Conclusion:** This study provides a relative estimation of the IGF-1 levels in Syrian children during Syrian conflicts and highlights its importance as a marker for children's growth.

INTRODUCTION: Insulin-like growth factor 1 (IGF-1) is a key peptide hormone necessary for normal development and growth in children and has an anabolic effect in adults [1-3]. It was first isolated along with IGF-2 from human serum by Rinderknecht and Humbel, who named them IGF-1 and IGF-2 due to their structural similarity with pro-insulin [4].

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This similarity justifies the affinity of IGF-1 to the insulin receptor. IGF-1 peptideis encoded by *IGF1* gene localized on the long arm of chromosome 12q23 [5] and consists of two promoters and six exons [6]. This hormone is a single small peptide chainof 7,649 Daltons as molecular weight and consists of 70 amino acids with three intramolecular disulfide bridges [7].

Several tissues produce IGF-1 and the secretory site determines its function. It is mainly synthesized as an endocrine hormone in the liver [8] and acts locally as a paracrine hormone in other tissues such as cartilaginous tissues [9]. IGF-1 may also play a role as an oncogene in an autocrinemode [10]. Synthesis and secretion of IGF-1 is stimulated by nutritional intake and growth hormone (GH) [11]. In case of long-term malnutrition, growth hormone production is affected by the levels of leptin and neuropeptide Y (NPY). Normal serum level of leptin synthesized in adipose cells [12] is indispensable for GH release. Studies in animals demonstrated that decreasing leptin levels by administration of leptin anti-serum could reduce the secretion of GH [13]. This may occur through direct blocking of hypothalamic leptin receptors or by the indirect effect of NPY. Leptin inhibits the release of NPY in the hypothalamus, which prevents GH secretion [14-15].

In starvation status, the low level of leptin is accompanied by a high concentration of serum NPY, which can lessen GH release. IGF-1 enhances the growth of different cells in the body [16-17]. At human birth, plasma levels of IGF-1 are hardly detectable. The production continues during life, where the peak is shown at pubertal growth to 40 years of age then it decreases gradually [18]. During pregnancy, maternal plasma levels of IGF-1 is high [19]. Production of IGF-1 may slow down by bad nutrition [11], lack of sensitivity of GH and loss of GH receptors [20]. The greatest part of serum IGFs binds to a cluster of binding proteins (BP) that regulate the presence of free IGF-1 in the tissues [21].

Although six binding proteins are present in the body 22, most IGF-1 binds specifically to and forms a ternary complex with one molecule of the acid-labile subunit of 88 KDa and one IGFBP-3 [21]. IGFBP-3 is primarily regulated by GH and to some extent by IGF-1 [23]. As the Syrian conflict enters its tenth year, the Syrian Arab Republic has been experiencing one of the most relevant humanitarian crises. Children, in their turn, continue to pay the heaviest price. According to UNICEF, more than 2.8 million children are out of school in Syria, and many more go without vital immunizations or other medical treatment [24].

In addition, over 3 million infants under 5 years of age and 1.6 million pregnant and lactating women are in high need of suitable nutrition [24]. This is the first study during the conflicts aimed to investigate serum levels of IGF-1 in healthy Syrian children from the city of Homs and its countryside. Since 2011, Homs has suffered terribly from the civil war in Syria. The massive destruction of civilian infrastructure (schools, homes, water sanitation, and hospitals) led citizens to flee their homes and translocate to other safer parts of the city. Most of these new residents could not afford the new situation and experienced a miserable life.

MATERIALS AND METHODS: The present study was approved by the Ethics Committee of Al Wataniya Private University in Syria. The study included 83 healthy children (age 3-16 years, 49 boys and 34 girls) from different regions of Homs city in Syria. Samples were collected between November 2018 and April 2019. Children who had shown signs or symptoms of infection in the preceding week were excluded.

The height and weight of the children were examined and registered by a pediatrician in a private clinic. Weight was measured by SECA digital scale, suitable for participant's age and height by a soft tape measure, and growth failure was determined as z score of height and weight are below 2 standard deviations. The author used the charts of the WHO to measure growth and BMI indices [25]. 2-3 ml of venous blood samples were drawn from all children by Vacumed® blood collection system – FL MEDICAL, Italy. Samples were then centrifuged for 10 min at 1,700 ×g and stored at -20°C till analysis. Serum IGF-1 levels were analyzed by a chemiluminescent assay system (IMMULITE® 1000 immunoassay systems, Siemens, Germany). IGF-1 values were expressed as ng/ml. Written informed consent was taken from parents or guardians for their children's participation in the study. The informed consent includes personal information (age, length, weight) and past or current diseases of each child.

Statistical Analysis: GraphPad Prism 5.0 was used for the statistical tests. The data were presented as standard deviation SD, minimum, maximum, and mean values. Pearson test was used to determine the correlation between IGF-1 with different variables, whereas the Mann-Whitney test measured the differences between groups. A p-value of less than 0.05 was considered to be statistically significant.

RESULTS: Overall, 83 children, 49 (≈59%) males and 34 (≈41%) females, were enrolled in the study, **Table 1**. No significant difference was found between male and female participants in scores of height or weights (p=0.5). The Z score of weight was 0.0047±1 for males and -0.07±0.99 for females. The Z score for height was 0.1±1 for males and 0.2±0.99 for females. No difference was seen regarding the mean age p=0.1) or serum level of IGF-1 (p=0.46) between both sexes (6.9±3 years, 81.48±57.88 ng/ml for males and 6.9±2.1 years, 91.14±63.5 ng/ml for females). The average age of all children was 6.86±2.69 years. The averages of weight, height, and body mass index were20.36±7.8 kg, 112.56±16.4 cm, and 15.5±1.7 kg per m^2, respectively.

TABLE 1: DEMOGRAPHIC, EXPERIMENTAL AND CLINICAL FINDINGS OF PARTICIPANTS

Variable	Mean ± SD*	Min.	Max.
Age, yr	6.86±2.69	3	16
height, cm	112.56±16.4	56	163
weight, kg	20.36±7.8	10	50
IGF-1 level ng/ml	85.44±60	15.5	315

Note: *SD=standard of deviation.

Average Serum Level of IGF-1: The average level of IGF-1 in children of all ages was (85.44±60). Twenty-seven children (32.5%) had serum levels of IGF-1 less than the normal index for their age (49.2±39.3 ng/ml, 6.5±3.4 years), **Table 2.**

TABLE 2: EXPERIMENTAL AND CLINICAL DATA OF CHILDREN WITH LOW IGF-1 LEVEL

Number of children	Age/ year	Experimental IGF-1 ng/ml	Reference ranges of IGF-1 ng/ml	Height/ cm	Z-score of IGF-1
1	3	25	49-289	88	-0.59389
2	3	25	49-289	80	-0.59389
3	3	38.6	49-289	89	-0.19556
4	3	34.5	49-289	85	-0.31565
5	4	29	49-283	93	-0.47673
6	4	25.1	49-283	85	-0.59096
7	4.5	33.4	49-283	101	-0.34786
8	4	32.4	49-283	94	-0.37715
9	5	36.2	50-286	99	-0.26585
10	5	25.5	50-286	96	-0.57925
11	5	25	50-286	100	-0.59389
12	5	39.4	50-286	101	-0.17213
13	5	29.4	50-286	101	-0.46502
14	5	22	50-286	98	-0.68176
15	6	45.1	52-297	104	-0.00518
16	6	15.4	52-297	101	-0.87506
17	6	40.8	52-297	103	-0.13112
18	6	37.4	52-297	107	-0.23071
19	7	49.8	57-316	110	0.132476
20	7	54.8	57-316	120	0.278921
21	8	61.7	64-345	114	0.481015
22	8	38.5	64-345	115	-0.19849
23	9	42	74-388	126	-0.09598
24	12	85.2	143-693	132	1.169307
25	13	102	183-850	140	1.661362
26	14	184	220-972	158	4.063059
27	16	153	226-903	163	3.1551

There was a significant difference in IGF-1 levels and height between these children and the others (p<0.0001, p=0.007 respectively), but not in age (p>0.05). The WHO charts of growth indices measured height-for-age percentiles of children. 19 (22.8%) out of 83 children (7.6±2.5 years) had short or limited short statures (≤3^{rd} percentiles). Ten of which also had low IGF-1 levels, **Table 3.** Thirteen children (15.6%) in this study were underweight as their BMI-for-age percentiles were ≤5^{th}, accompanied by a limit to low levels of IGF-1, **Table 4.**

TABLE 3: IGF-1LEVELS AND HEIGHT-FOR-AGE PERCENTILES IN SHORT STATURE CHILDREN

Number of children	Age/year	Experimental IGF-1 ng/ml	Reference ranges of IGF-1 ng/ml	Height-for-age percentile	Z-Scores of height
1	3	25	49-289	<3rd	-2.19074
2	6	45.1	52-297	<3rd	-0.53
3	6	15.4	52-297	<3rd	-0.73
4	6	62.5	52-297	<3rd	-0.80
5	6	69.9	52-297	<3rd	-0.46
6	6	40.8	52-297	<3rd	-0.60
7	6	37.4	52-297	3rd	-0.32
8	6	54.4	52-297	3rd	-0.46
9	7	132	57-316	<3rd	-0.53
10	7	49.8	57-316	3rd	-0.11
11	7	90.6	57-316	3rd	-0.11
12	7	79.6	57-316	3rd	0.02
13	8	38.5	64-345	<3rd	0.22
14	8	61.7	64-345	<3rd	0.15
15	8	129	64-345	3rd	0.23
16	11	117	111-551	<3rd	1.33
17	12	167	143-693	<3rd	1.67
18	12	85.2	143-693	<3rd	1.40
19	13	102	183-850	<3rd	1.95

TABLE 4: IGF-1 LEVELS, BMI-FOR-AGE PERCENTILES IN UNDERWEIGHT CHILDREN

Number of children	Age/ year	Experimental IGF-1 ng/ml	BMI kg/m^2	BMI-for-age percentiles	Z-Score of BMI
1	3	38.6	13.89	<5th	0.70
2	4	25.1	13.84	5th	0.60
3	5	53.1	12.50	<5th	-2.27
4	5	62	13.54	<5th	-0.05
5	5	25	13.00	<5th	-1.19
6	5	39.4	13.72	<5th	0.35
7	5	29.4	13.72	<5th	0.35
8	5	22	13.54	<5th	-0.05
9	6	69.9	13.61	<5th	0.10
10	6	40.8	13.20	<5th	-0.78
11	6	37.4	13.98	5th	0.88
12	11	117	13.40	<5th	-0.34
13	12	85.2	14.35	<5th	1.68

Note: BMI= body mass index, values in bold indicate to a low level of IGF-1.

Average Serum Level of IGF-1 Based on Age Groups: Participants were divided into two groups less or equal (29 children) and more (54 children) than five years of age.

Mean serum level of IGF-1 in the first group was (48.7±21.7 ng/ml) while it was in the other group (105.16±64.7 ng/ml). Results have shown a significant difference of IGF-1 levels between the two groups (p<0.0001).

Correlation of IGF-1 Levels with Other Variables: By using the Pearson correlation test, significant correlations p<0.0001 were found between age, height and weight with IGF-1 levels (r=0.66, r=0.7, r=0.76, respectively) for all children. A moderate relation was detected between IGF-1 and BMI values (r=0.48, p<0.0001). There was a good correlation between the height and IGF-1 levels in the 19 short stature participants (r=0.59, p=0.007), but there were no differences between normal and short stature groups in terms of IGF-1 levels or height values (p>0.05).

After that, the linear regression test was performed as the next step after the person correlation. This test is used to predict the relationship between height and BMI (dependent variables) with IGF-1 levels (independent variables) for all children. Our results confirmed the significant relationship between height and IGF-1levels and that the height values are dependent on IGF-1 levels (r^2=0.7, p<000.1. In other words, IGF-1 is responsible for the linear growth of children, **Fig. 1.** The outcomes demonstrated a weak but significant linear regression between BMI and IGF-1 levels (r=0.4, p<0.0001, **Fig. 2.**

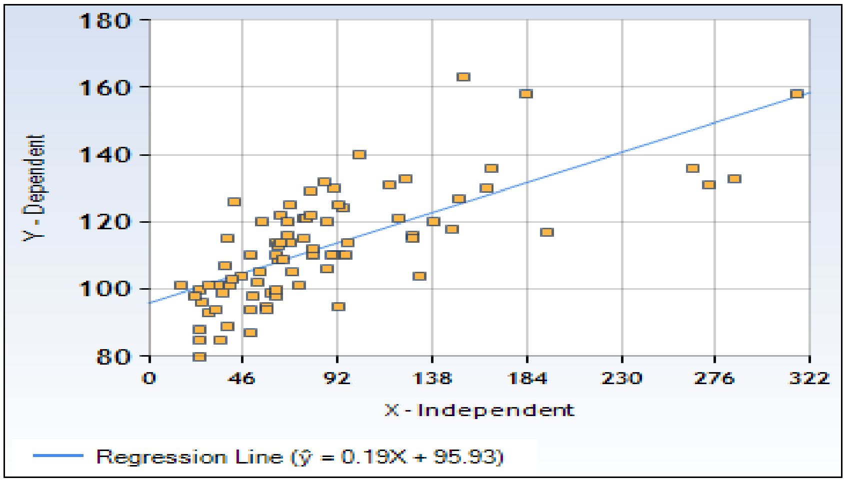

FIG. 1: THE RELATION BETWEEN HEIGHT AND IGF-1 LEVELS IN ALL PARTICIPANTS

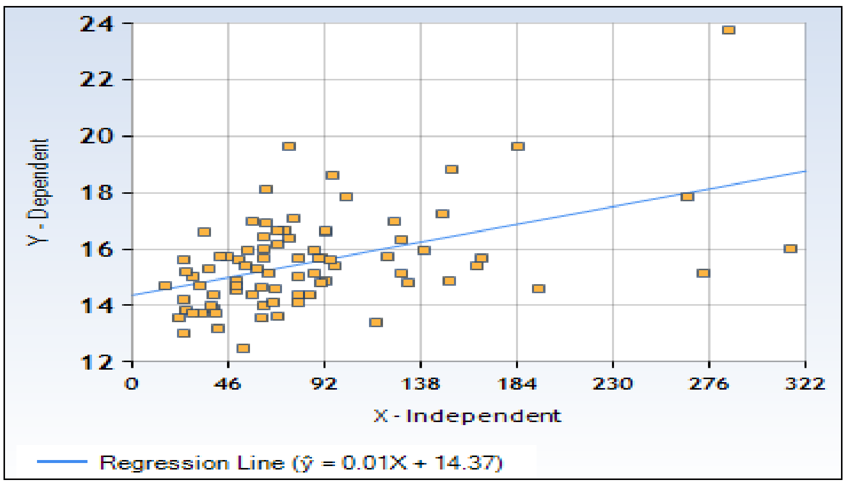

FIG. 2: THE RELATION BETWEEN BMI AND IGF-1 LEVELS IN ALL PARTICIPANT

All the above results confirm the importance of this key hormone in the normal growth of healthy children.

DISCUSSION: More than nine years since the Syrian conflict began in the Syrian Arab Republic, where the situation is still one of the most terrible humanitarian crises. There are serious and complex humanitarian needs, especially for children, attributed to the persistent threat in multiple districts, new and prolonged relocation and the disintegration of community strength. According to the United Nations, 11 million Syrian citizens need humanitarian support, 4.7 million of which are children. Overall, in the years of civil war, people cannot get primary social services. 2.1 million children between 5-17 years are not attending school. As estimated by the WHO and UNICEF, more than half a million newborns need routine vaccination, and about 300,000 children between 13-59 months did not receive all required vaccines 24. This study aimed to determine IGF-1 serum levels of healthy Syrian children during the Syrian conflicts.

Samples were collected from Homs city in the middle of Syria, one of the places most affected badly by the civil war. 32.5% 27 of children had serum levels of IGF-1 less than the normal index for their age (49.2±39.3 ng/ml, 6.5±3.4 years). In addition, 10 participants had the minimum normal value of the range given by the manufacturer for IGF-1. Indeed, the author thinks this percentage (32.5%) is less than the expected value and does not reflect the real situation among Syrian children. This may be partially explained by the fact that the cost of IGF-1 hormone analysis is expensive comparing to the average income of Syrian population. Many people especially displaced ones, could not afford the height cost of medical analysis and prefer consulting doctors at national hospitals to get only the free medical analysis; IGF-1 test is not offered freely. So, most of them cannot perform the test for their children even when it is really needed. All samples utilized in this study were collected and analyzed by a private medical laboratory. Nineteen (22.8%) children (7.6±2.5 years) had short to limit short statures (≤3rd percentiles).

Among them, ten (12%) with low IGF-1 levels. There was a good correlation between the short stature and the low levels IGF-1 in these children ($r=0.59$, $p=0.007$). This consolidates the role of IGF-1 in induction the of linear growth in children (16-17). It has been shown that IGF-1 level is stimulated by nutrition and is considered as a marker for the nutritional state (11-16-17). Acute or chronic variation of plasma IGF-1 concentration is highly affected by the dietary situation, so an explanation of IGF-1 findings necessitates knowledge of the nutritional status of children. According to UNICEF, over 3 million infants under 5 years need suitable nutrition aid24. Thirteen (13) children (15.6%) in this study were underweight as their BMI-for-age percentiles were ≤5th, and a limit accompanied that to low levels of IGF-1.

IGF-1 secretion is stimulated by growth hormone (GH); thus, detecting IGF-1 serum levels is widely used to investigate the GH/IGF-1 axis (26-27). Both GH signaling and nutritional status impact on concentration of IGF-1, so understanding their influences on IGF-1 synthesis and secretion is crucial for the suitable interpretation of child's IGF-1 serum concentration. This outcome raises alert to the importance of giving these children special attention and providing them with sufficient dietary supplementation as to stay healthy with normal levels of IGF-1. Educating people is necessary to increase community awareness against children's malnutrition. However, results have shown two overweight children (girl, 7 years, IGF-1 64.4 ng/ml, BMI 18.14, height 122 cm and boy, 6 years, IGF-1 148 ng/ml, BMI 17.2, height 118 cm) and one obese (boy 5 years, IGF-1 95.7 ng/ml, BMI 18.6, height 110 cm). Finally, results have revealed a significant difference in IGF-1 levels in children under five years of age compared to those older than five ($P<0.0001$). IGF-1 production increases gradually by age, reaching the top-level at puberty (18).

CONCLUSION: IGF-1 is an essential hormone for growth and development. At least a third of children from Homs city in Syria had low serum levels of IGF-1, which was correlated with limited short to short stature in many cases. This outcome triggers an alert to the necessity of improving the health state of Syrian children and ensuring their normal development.

This could be achieved by raising the awareness of the population, child protection associations, and UNICEF about the importance of providing infants and young children with a suitable diet or treatment with recombinant IGF-1 when it is needed. It also sheds light on the serum IGF-1 test as an indicator of the healthy growth of children.

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