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Overweight and obesity among children with congenital adrenal hyperplasia (CAH)- An experience at tripoli university hospital, Tripoli, Libya

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Abstract
Obesity is one of the global epidemics in children and adult. Children with Congenital Adrenal Hyperplasia (CAH) have a higher risk of obesity. CAH is a group of genetic condition that affects adrenal gland steroidogenesis. Classic congenital adrenal hyperplasia (CAH) is a rare, life threatening, endocrine disorder that affects boys and girls equally. There are few studies reporting on higher rates of overweight and obesity among children with CAH. Lack of such study in Libya warrants the researcher to undergo this study.
Data were collected from the total 56 patients (36 with CAH include Classic salt wasting and Simple Virilizing types and 20 normal/control group) with 6-15 years young children who attended at Tripoli University Hospital, Tripoli, Libya for one year from September 2018 to August 2019.
The effect of CAH is severe in young age, more prevalence in girls than boys and more cases diagnosed at the 0-1 year young with simple virilizing type. BMI and Lipid profile have no much role in the increase of severity in number of cases. Family history like Obesity and CAH play a major role among the children. CAH affected children have high BP. Ideal dose of Hydrocortisone (HC) for the early treatment of CAH is about 10-15mg/m^2/day. Careful dosing during early childhood is needed to prevent increased weight gain and an early adiposity rebound. Larger and longer-term studies are needed to confirm our results.

Keywords: congenital adrenal hyperplasia, classic salt wasting, simple virilizing and tripoli university hospital

Introduction
Overweight and obesity are an abnormal or excessive fat accumulation, which impairs health. Congenital adrenal hyperplasia (CAH) is the most common inherited adrenal disorder in childhood. It is a group of autosomal recessive disorders that occur as a result of a mutation in the genes (Volkl *et al*., 2006) [13]. This interferes with the cortisol synthesis pathway and leads to decreased cortisol synthesis with or without aldosterone deficiency and increased production of adrenocorticotropic hormone through negative feedback (Charmandari *et al*., 2002) [3]. More than 95% of all CAH cases have 21-hydroxylase deficiency, characterized by decreased cortisol and aldosterone levels and simultaneously increased production of adrenal androgens and steroid precursors (Falhammer and Thoren, 2012).
The presence of three or more of these conditions leads to the metabolic syndrome, increasing the risk of cardiovascular morbidity and mortality. At the same time, chronic androgen excess may contribute to the metabolic disorder by its association with increased visceral adiposity and insulin resistance and their metabolic consequences (Eugster, 2001) [5].
In growing children, it is well known that an elevated cumulative daily dose of glucocorticoids adversely affects linear growth. Glucocorticoids interfere with the normal interactions in the growth hormone (GH)/IGF-1 signaling cascade at the level of the hypothalamus, pituitary, and target organ as well as adversely affect hormone release, signal and gene transduction and mRNA processing (Hochberg, 2002) [8]. It is essential to carefully adjust HC dosing in CAH children, especially during early childhood, to prevent increased weight gain and an early adiposity rebound. The adiposity rebound is defined as the second increase in BMI that happens in preschoolers until the age of 7. An early age at adiposity rebound is a risk factor for adult obesity (Sarafoglou, 2017) [12].
Aim of this present research is to study the Overweight and Obesity level among CAH affected Libyan children (6-15 years young) in Western part of Libya and the way to reduce those effects by treatment without surgery.

Materials and methos
This study was conducted at Tripoli University Hospital (TUH), Tripoli, Libya for one year from September 2018 to August 2019 from the children with overweight, obesity and CAH who attended TUH Pediatric Endocrinology department. Total 56 patients (36 with CAH include Classic salt wasting and Simple Virilizing types and 20 normal/control group) with 6-15 years young children were included in this study. An ethical consent was taken from the parents of the cases and The Director of the hospital, TUH, Tripoli, Libya. The data like age, sex, BMI, age at diagnosis, treatment used and family history of obesity were collected through questionnaire.
Lipid profile (Blood total cholesterol (TC), Serum Triglycerides (TG), High density lipoprotein (HDL) and Low density lipoprotein (LDL) of was analyzed using Screen Master 2000, Eudutiun, Italy). Blood sugar (Beckman Glucose analyzer 2, USA) and Thyroid hormones (T3 and T4) was analyzed using Automatic instrument (Viteos, EOQ, Johnson & Johnson, USA).

Results and discussion

Congenital adrenal hyperplasia associated with deficiency of steroid 21-hydroxylase is the most common inborn error in adrenal function and the most common cause of adrenal insufficiency in the pediatric age group. The Children with CAH in the study area were more (25 persons) in the group of 6– 9 years young. The normal /control group of same family children without any CAH symptoms are more in the age group of 9.1- 12 years young. The affected children numbers reduced with an increase of age in female (Table 1). Gender is not having much role in the rise of CAH cases in studied area.

Table 1: Distribution of Age in Normal and Experimental group of CAH and Obesity study.

S. No.	Age (years)	Normal				Experimental			
		Male		Female		Male		Female	
		Nos.	%	No	%	Nos.	%	No	%
1	6.0-9.0	03	05.36	04	07.14	08	14.28	10	17.85
2	9.1-12.0	04	07.14	05	08.93	06	07.14	07	12.50
3	12.1-15.0	02	03.57	02	03.57	02	03.57	03	05.36
4	Total	09	16.07	11	19.64	16	28.57	20	35.71

(% calculated from the total 56 cases)

In both control and experimental (CAH) group, female participation is more. Present result is in contradicting to Volkl *et al* (2006) [13] study. Their finding showed there is no significant relation of Age and gender with the CAH cases. Usually the CAH prevalence is more with the children have XX chromosomes than the XY chromosomes (Dessens *et al*., 2005) [4].

Table 2: CAH diagnosed at the age of children.

S. No.	Age (years)	Normal		Experimental	
		Nos.	%	Nos.	%
1	0-1	00	00	25	44.65
2	1.1-2.0	00	00	08	14.29
3	2.1-3.0	00	00	01	01.78
4	>3.0	00	00	02	3.57
5	Total	00	00	36	64.29

(% calculated from the total 56 cases)

Symptoms of CAH can be diagnosed even at the birth stage or few days after the birth of the children. In this study also large number of cases (25 persons/44.65%) was diagnosed at 0- 1 year young (Table 2). Simple virilizing type of CAH cases more (22 persons/39.29%) in Tripoli area than the Salt wasting (Salt losing) (14 cases/25.00%) (Table 3). The symptoms of classical CAH are severe and noted early childhood than the Non-classical type of CAH which is noted in the early adult. A study found that approximately one child in every 18,000 born in Great Britain has CAH. Similar numbers of boys and girls present clinically in the first year of life but boys present with more severe manifestations, such as salt-wasting crises (Khalid *et al*., 2012). Salt-losing CAH accounts for about three quarters of cases reported and non-salt-losing CAH for one quarter.

Table 3: Type of CAH among the Children involved in this study.

S. No.	Type of CAH	Normal		Experimental	
		Nos.	%	Nos.	%
1	Salt Wasting	00	00	14	25.00
2	Simple Virilizing	00	00	22	39.29
3	Total	00	00	36	64.29

(% calculated from the total 56 cases)

Table 4: Relationship of BMI with CAH in this study.

S. No.	BMI	Normal		Experimental	
		Nos.	%	Nos.	%
1	<85	12	21.42	13	23.21
2	86-95	05	08.93	15	26.77
3	>95	03	05.36	08	14.28
4	Total	20	35.71	36	64.29

(% calculated from the total 56 cases)

BMI play a major role in the childhood and adulthood with CAH. Relationship of BMI with CAH of children in this study showed a different result from other study. Here more children with CAH (15 cases/26.77%) were observed with BMI of 85 -95 and followed by <85. Control group children BMI is lesser than 85 (Table 4). This shows that there is a relation between BMI of the body and CAH cases. Sarafoglou *et al*., (2017) [12] report also similar to the present research saying that Children with CAH are at higher risk for early onset obesity and overweight with or without using BMI_{HA} but rates of persistent obesity were lower than previously reported. Careful HC dosing during early childhood is needed to prevent increased weight gain and an early adiposity rebound.

Table 5: Family History (F/H) of CAH and Obesity in the Children involved in the study.

S. No.	F/H of CAH	Normal		Experimental	
		Nos.	%	Nos.	%
1	Yes	20	35.71	32	57.15
2	No	00	00.00	04	07.14
3	Total	20	35.71	36	64.29
	Obesity	Normal		Experimental	
		Nos.	%	Nos.	%
1	Yes	01	01.78	31	55.37
2	No	19	33.93	05	08.93
3	Total	20	35.71	36	64.29

(% calculated from the total 56 cases)

Family history with inherited or carrier parents with CAH and obesity have higher risk for the development of CAH in children. Present study also revealed the data with 32 cases (57.15%) cases have CAH complications and 31 cases (55.37%) cases with obesity of previous family history (Table 5). Other symptoms like the development of Diabetes and Hypothyroidism were also observed (Table 6). 33 cases (58.94%) in this study had the complications of Diabetes (Juvenile). Insulin sensitivity has been found to be lower in patients with both classic and non-classic CAH compared with BMI-matched controls (Charmandari *et al*., 2002) [3]. Thyroid hormones like T3 and T4 low level in the cases with CAH in children affect their growth and overall livelihood of them.

Table 6: Presence of other symptoms in the Children involved in this study.

S. No.	Diabetes Mellitus	Normal		Experimental	
		Nos.	%	Nos.	%
1	Yes	02	03.57	33	58.94
2	No	18	32.15	03	05.36
3	Total	20	35.71	36	64.29
	Hypo T3 & T4	Normal		Experimental	
		Nos.	%	Nos.	%
1	Yes	00		35	62.51
2	No	20		01	01.78
3	Total	20	35.71	36	64.29

(% calculated from the total 56 cases)

In adults, a tendency toward higher body mass index (BMI) and elevated blood pressure (BP) has been found. Reports on BP in children and adolescents are heterogeneous and based on rather small cohorts (Bonfig *et al*., 2016) [1]. High BP was observed in more cases with CAH in the present study (Table 7). This result is similar to the results of Bonfig *et al*., (2016) [1]. They found a higher prevalence of arterial hypertension in younger patients with CAH compared to older patients.

Table 7: BP Level in both Normal and Experimental group in this study.

S. No.	BP (mm Hg)	Normal		Experimental	
		Nos.	%	Nos.	%
1	Low (<90/60)	02	03.57	12	21.43
2	Normal (120/80)	14	25.00	11	19.65
3	High (>130/89)	04	07.14	13	23.22
4	Total	20	35.71	36	64.29

(% calculated from the total 56 cases)

Table 8: Lipid profiles of the CAH and Normal children involved in this study.

S. No.	Lipid Profiles	Normal		Experimental	
		Nos.	%	Nos.	%
	Total Cholesterol (mg/dl)				
1	Low (<100)	01	01.78	06	10.72
2	Normal (100-200)	16	28.58	23	41.08
3	High (>200)	03	05.36	07	12.50
4	Total	20	35.71	36	64.29
	Tri Glycerides (TG) (mg/dl)				
1	Low (<60)	00	00.00	01	01.78
2	Normal (61-150)	11	19.65	20	35.72
3	High (>151)	09	16.07	15	26.79
4	Total	20	35.71	36	64.29
	High-Density Lipoprotein (HDL) (mg/dl)				
1	Low (<40)	03	05.36	08	14.29
2	Normal (41-60)	16	28.58	24	42.86
3	High (>60)	01	01.78	04	07.14
4	Total	20	35.71	36	64.29
	Low-Density Lipoprotein (LDL) (mg/dl)				
1	Low (<60)	00	00.00	02	03.57
2	Normal (60-130)	05	08.93	19	33.93
3	High (>130)	15	26.79	15	26.79
4	Total	20	35.71	36	64.29

(% calculated from the total 56 cases)

Glucocorticoids have been implicated in the development of several abnormalities of lipoprotein metabolism. The long term administrations of Glucocorticoids lead to an elevation of total cholesterol (TC) and Triglyceride (TG) in the human blood. In the present study, the total cholesterol in normal level is with 23 cases (41.08%) with CAH (Table 8). Only 7 cases (12.50%) had high level of Total Cholesterol in their blood. Similarly most of the cases blood had high level of Triglycerides (TG) in 20 cases (35.72%), HDL in 24 cases (42.86%) and LDL in 19 cases (33.93%). These results indicate that the affected children got proper hormonal therapy to reduce the effects of CAH in the studied children. Present findings are not related to the results of Botero *et al*., (2000) [2]. Moreira *et al*., (2014) [11] have observed that there was an adverse result in Lipid profile in the cases with CAH after gene polymorphism.

All the cases were treated with Hydrocortisone replacement therapy. But the dose varied from the cases.10-15 mg/m^2/day Hydrocortisone was used in the treatment of large number of cases (23 cases/41.06%) (Table 9). The same dose level is also suggested by Witchel (2017) [14]. Glucocorticoid dosage, chronologic age and parental obesity contributed to elevated BMI, whereas used glucocorticoid, dosage were not associated with obesity. Therefore, children with CAH who become obese should be tightly monitored and should participate concurrently in weight management programs that include obese family members. Careful HC dosing may reduce the complications arise by CAH.

Table 9: Treated the affected Children with Hydrocortisone (HC) with different doses.

S. No.	HC Doses (mg/m2/day)	Normal		Experimental	
		Nos.	%	Nos.	%
1	<5	---	---	03	05.36
2	5.1-10	---	---	10	17.87
3	10.1-15	---	---	23	41.06
4	Total	---	---	36	64.29

(% calculated from the total 56 cases)

In addition to the normal HC treatment, mineralocorticoid also used in some cases (7 cases/12.50%) (Table 10). Glucocorticoid and mineralocorticoid replacement therapies are the mainstays of treatment of CAH (Kamoun *et al*., 2013) [9]. Mineralocorticoid therapy extended only to the necessary cases. Optimal replacement therapy, close clinical and laboratory monitoring, early life-style interventions, early and regular fertility assessment and continuous psychological management are needed to improve outcome.

Table 10: Treated the affected children with Mineralocorticoid.

S. No.	Mineralo Corticoid treatment	Normal		Experimental	
		Nos.	%	Nos.	%
1	Yes	00	00.00	07	12.50
2	No	20	35.72	29	51.79
3	Total	20	35.71	36	64.29

(% calculated from the total 56 cases)

The treatment with glucocorticoids and mineralocorticoids may predispose for arterial hypertension. Children with CAH are steroid dependent for life and the goal of daily maintenance treatment is to replace deficient levels of cortisol and/or aldosterone while minimizing androgen excess, preventing virilization, optimizing growth and protecting fertility (Flemming *et al*., 2017).

Conclusion and recommendations

Children with CAH are at higher risk for early onset obesity. Researcher concludes that the effect is severe in young age, CAH prevalence more in girls than the boys and more cases diagnosed at the 0-1 year young with simple virilizing type. BMI and Lipid profile have no much role in the increase of severity in number of cases. Family history like Obesity and CAH play a major role among the children. DM and the Hypothyroidism are the complications or co-morbidity of CAH.

CAH affected children have high BP. Ideal dose for the early treatment of CAH is about 10-15mg/m^2/day. Careful HC dosing during early childhood is needed to prevent increased weight gain and an early adiposity rebound. However, it is difficult to achieve definite conclusions regarding long-term co-morbidities, as previous studies included patients with classical and non-classical forms in children require different approaches to hormonal control

during CAH management.

Parents of the affected children should be instructed properly about the management of their children in emergency times. Future studies with an emphasis on family experience and management would enhance the current state of the science and provide a much-needed window into interventions aimed at improving the lives of families and children with CAH. Larger, longer-term studies are needed to confirm our results.

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