IJPSR (2021), Volume 12, Issue 3 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 17 January 2020; received in revised form, 30 August 2020; accepted, 11 September 2020; published 01 March 2021

EFFECTS OF ORAL ZINC SUPPLEMENTATION IN EARLY NEONATAL LIVE ON DEVELOPMENT OF OBESITY AND METABOLIC SYNDROME IN ALBINO RATS

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Keywords:

Zinc, Obesity, Metabolic syndrome and IL-6

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ABSTRACT: Background: Zinc (Zn) is the most common trace element in eukaryote cells and the second most abundant trace element in human tissues and secretions after iron. Zinc is required for normal growth and development from in uteri to puberty. There is a lack of evidence on Zn as a potential therapeutic agent to reduce weight and improve metabolic parameters in obese adults. **Aim:** to evaluate Zn supplementation's effects in early neonatal life on the development of obesity in adult life. **Methods:** Sixty male albino rats were used. The animals were divided into three equal groups 20 rats for each. $ZnSO_4$ supplemented diet was given to rats mothers of group 2 from the first day of delivery, and it was given to rats immediately after weaning until the end of the study. After six weeks, all experimental rats were given a high carbohydrate, high-fat diet. All rats were monitored for body weight, food and water intakes, abdominal circumference; Systolic blood pressure, and Fasting blood sugar was measured in rats after 1, 6 and 12 and 18 wk. After eighth of fasting. At the end of the 18 weeks and After 12 h of night fasting, morning blood samples were collected for chemical analysis. **Results:** The oral zinc leads to a significant decrease in BW, FI, WI, AC, BG, TC, LDL, TG, ALT, AST, urea, and creatinine, while serum insulin, HDL, serum zinc, and IL-6 were significantly higher in oral zinc supplemented groups.

INTRODUCTION: Obesity and overweight remain global medical and public health problems as rates continue to rise [1]. It may affect the normal patterns of children and adolescents growth [2]. Obesity among children and adolescents is continuing to rise and reach up to 18% of children and adolescents aged 5-19 in 2016 according to the World Health Organization (WHO) [3]. The aetiology of obesity is multimodal and multifactorial, which makes it difficult to identify causative and contributing factors [4].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(3).1433-41

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(3).1433-41

Lack of a clear model of etiology makes it a consequence of an interaction between a complex set of factors that are related to the environment, genetics [4]. Also, deficiency in micronutrient is evidently higher in obese individuals [5]; this may be due to intake of high caloric and poor-quality foods, lower intake of fruits and vegetables, and increased adiposity, which may affect the availability and storage of some micronutrients [6]

The deficiency of micronutrients is a silent pandemic that affect all ages and still a major public health problem that affects more than 2 billion people worldwide [7]. Marked trace element deficiency, especially zinc (Zn), in obese patients has been reported [8]. Zinc is an essential micronutrient; it is the most common trace element after iron in eukaryote cells [9]. It has significant structural, catalytic, anti-oxidative, and anti-

inflammatory roles in the human body [10]. Zn is required for the activity of more than 300 enzymes, 1,000 transcription factors and has a role in the control of genetic expression, nucleic acid and protein synthesis, cell replication, tissue growth, and repair [11]. Zinc is necessary for normal growth and development from fetal growth to puberty [12]. Because of the absence of a storage system specific for Zn in the human body, daily intake of Zn is important to maintain its functions [13]. Many foods contain Zn include a variety of foods, such as beans, beef, nuts, poultry, seafood, cheese, cereals, legumes, and grains [14]. During pregnancy, childhood, and adolescence, the daily requirement of Zn is increased [15].

The deficiency of Zn has been linked to many diseases and co-morbidities such as diabetes mellitus type 2, Renal, cardiovascular disease, and metabolic syndrome [9]. Zinc also plays a crucial role in regulating the immune system, and zinc-deficient individuals are susceptible to infection with many pathogenic organisms [7]. Zinc deficiency affects functions of cells of both innate and specific immune systems such as intracellular killing, phagocytosis, and cytokine production [6]. IL-6 is a pleiotropic, multifunctional immunoregulatory cytokine that was first described as a B cell stimulatory factor 2 that enhances antibody production by activated B cells [16]. IL-6 is secreted by macrophages, adipose tissue, contracting skeletal muscles, and many other sources [17]. Several studies suggested an important role for IL-6 in glucose metabolism and fat metabolism by a lipolytic action with an antiobesity effect [18]. The effect of Zn deficiency on obesity development is still unclear with a lack of evidence. Thus, this study aims to evaluate the effects of Zn supplementation in early neonatal life on the development of obesity and metabolic syndrome

MATERIALS AND METHODS:

Experimental Animals: Sixty male albino rats of local strain used in this study were obtained from The Nile Co. For Pharmaceuticals and Chemical Industries (Cairo). The study was started in the animal laboratory of The Nile Co. For Pharmaceuticals and Chemical Industries (Cairo) from the 1st day of the life of rats. After six weeks of age, rats were transported to the animal laboratory of Physiology Department, Al- Azhar Faculty of Medicine (Assuit) and kept in suitable cages (20×32×20 cm for every 3 rats) at room temperature, with the natural light-dark cycle and they were fed on the standard food prepared from commercial rat food formula (El-Nasr-Pharmaceutical Co.) in addition to bread and green vegetables with free water supply.

The Animals were divided into Three Equal Groups 20 Rats for each as follows:

1. **Group (1):** control rats not supplemented with zinc.
2. **Group (2):** ZnSO4 supplemented diet was given to rats mothers from the first day of delivery, and it was given to rats immediately after weaning until the end of the study.
3. **Group (3):** $ZnSO_4$ supplemented diet started at age six weeks of life.

Chemicals:

- Zinc sulfate (ZnSO4): was purchased from Nile Pharmaceuticals Company [19].
- Serum cholesterol kit (Egyptian Company for Biotechnology-Egypt) [20].
- Serum triglycerides kit (Egyptian Company for Biotechnology-Egypt) [21].
- Serum high-density lipoprotein (HDL) kit (Egyptian Company for Biotechnology Egypt) [13].
- Aspartate aminotransferase (AST) and alanine amino transferase (ALT) Kits (Sigma Aldrich Chemie GmbH) [22].
- Serum urea kit (Egyptian Company for Biotechnology [23].
- Serum creatinine kit(Biolabo reagents kits – France) [24]
- Insulin kit [25].
- ACCU-CHEK glucometer (Bayer's Contour, Japan).
- Zinc Assay Kit (Sigma-Aldrich Chemie GmbH- [26].
- IL-6 kits (ELISA –kits).

Study Design: After six weeks, all experimental rats were given a high-carbohydrate, high-fat diet.

The compositions of the diets were (~68% carbohydrates, mainly as fructose and sucrose and ~24% fat from beef tallow) for 12 wk. Zinc sulfate ($ZnSO_4$) was added to the rat chow of group 3 and continue to group 2 by the same rate (180 mg/Kg chow) [27]. All rats were monitored for body weight, food, and water intakes after 1, 6, 12, and 18 wk. Abdominal circumference waist measured after 1, 6, 12, and 18 wk using a standard measuring tape under light sedation with an intraperitoneal injection of Zoletil (toletamine, 15 mg/kg and zolazepam, 15 mg/kg) [28]. Systolic blood pressure was measured in rats after 1, 6 and 12 wk of dietary intervention under light sedation with Zoletil [29].

Fasting blood sugar was measured in rats after 1, 6, and 12 wk. after 8 h of fasting, they used Accu-Chek glucometer. At the end of the 18 weeks and After12 h overnight fasting, morning blood samples were collected from the retro-orbital venous plexus. Blood was collected into a dry clean graduated glass centrifuge tube, and serum was separated by centrifugation at 5000 r.p.m for 10 min. The separated serum was aliquotted and stored frozen in epindorffs, tube at -20 °C until used for the determination of Serum zinc levels, Insulin, Lipid profile: (Triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), and low-density lipoprotein (LDL)), blood urea, creatinine, ALT and AST.

Statistical Methods: Mean and standard deviation were calculated. The obtained data were subjected to analysis of variance one and two-way factorial according to the procedures outlined by Seducer and Cochran [30]. The mean value of treatments was compared according to Duncan's multiple range test (DMRT) [31]. Multiple correlation coefficient analyses were used. The data was analyzed using Co Stat software for windows (version 6.3).

RESULTS: Data in **Table 1**, **Fig. 1,** and **Fig. 2** showed the effect of zinc supplementation on body weight and abdominal circumference. In the first week, there was no significant difference between the three groups in the mean of BW and AC **Table 1**. G1 group gave the highest Bw and Ac followed by G3 then G2 at the same period 6, 12 or 18 **Table 1**, **Fig. 1** and **Fig. 2**. While the two groups G1 and G3, were statistically equal at 6 weeks for BW and AC **Table 1**. G3 group at period 12 week resulted in statistically similar BW and AC to G2 at period 18 week **Table 1**.

TABLE 1: BODY WEIGHT AND ABDOMINAL CIRCUMFERENCE AS AFFECTED BY ZINC SUPPLEMENT AND THE DURATION PER WEEKS

Groups	Duration (Weeks)				P. value
	1	6	12	18	
			BW		
G1	15.75 h ± 5.35	181.0 f ±15.91	340.1 c ± 16.48	508.6 a ± 30.15	
G2	15.65 h ± 5.67	168.6 g ± 10.1	284.8 e ± 19.21	321.45 d ± 67.63	0.00**
G3	15.45 h ± 5.41	178.7 f ± 12.6	316.75 d ± 17.15	404.55 b ± 60.5	
			AC		
G1	5.75 f ±2.14	9.4 d ± 1.88	13.75 b ± 5.35	17.85 a ± 3.39	
G2	5.80 f ± 2.3	6.95 e ± 1.65	9.00 d ± 1.59	12.00 c ± 2.83	0.00**
G3	5.85 f ± 1.98	9.45 d ± 2.00	11.7 c ± 2.26	14.35 b ± 2.85	

Indicate P < 0.01. Means followed by a common letter are not significantly different at the 1% level by DMRT. Where G1: control; G2: breastfed received zinc from 0-6 weeks; G3: weaning received zinc after 6 weeks. Mean ± Standard deviations

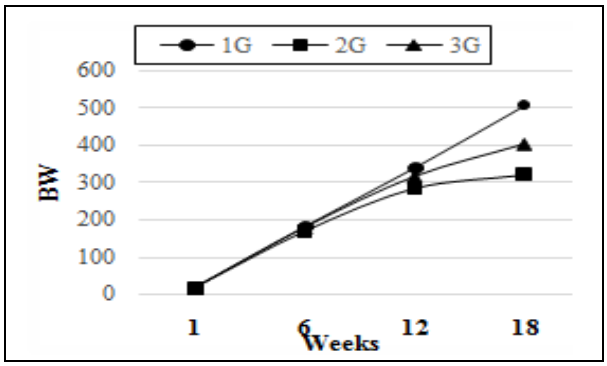

FIG. 1: BW AS AFFECTED BY ZINC SUPPLEMENT AND THE DURATION PER WEEKS

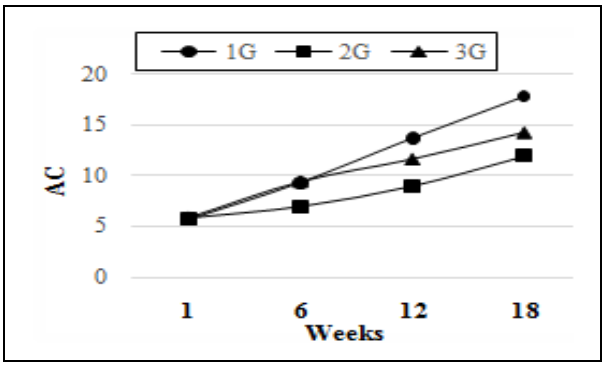

FIG. 2: AC AS AFFECTED BY ZINC SUPPLEMENT AND THE DURATION PER WEEKS

G1: control; G2: breastfed received zinc from 0-6 month; G3: weaning received zinc after 6 months. Data in **Table 2** showed that the group G1 after 12- or 18-week period produced the highest FI than other groups. The group G2 gave an insignificant difference in the mean of FI after 12 or 18 weeks. There was no significant difference between 12 or 18 weeks in FI for G3 group. The increase in FI was ranged from 92 to 94.1% for G1, 52.4 to 59.7 % for G2, and 52.5 to 57.8 % for G3 after 12 and 18 weeks, respectively, compared to 6 weeks period **Fig. 5.**

TABLE 2: FOOD INTAKE AS AFFECTED BY ZINC SUPPLEMENT AND THE DURATION PER WEEKS

Groups	Duration (Weeks)			P.
	6	12	18	
G1	11.31 d ± 1.38	21.71 a ± 4.89	21.95 a ± 4.64	0.00**
G2	9.29 e ± 1.14	14.15 c ± 2.15	14.83 c ± 2.75	
G3	11.25 d ± 1.48	17.15 b ± 1.82	17.75 b ± 5.69	

Indicate P < 0.01. Means followed by a common letter are not significantly different at the 1% level by DMRT. Where G1: control; G2: breastfed received zinc from 0-6 weeks; G3: weaning received zinc after 6 weeks. Mean ± Standard deviations

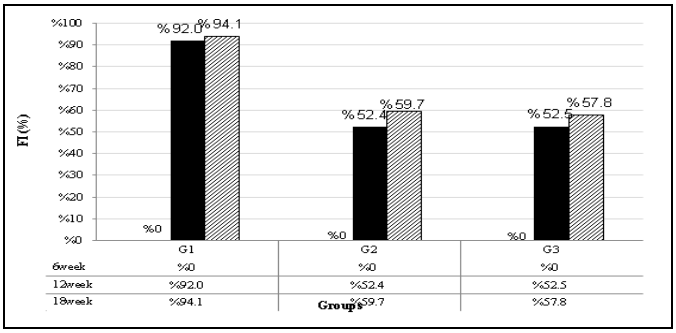

FIG. 3: PERCENTAGE OF FI FOR G_1, G_2 AND G_3 GROUPS AFTER 6 AND 12 WEEKS COMPARE TO FIRST WEEK AS AFFECTED BY ZINC SUPPLEMENT

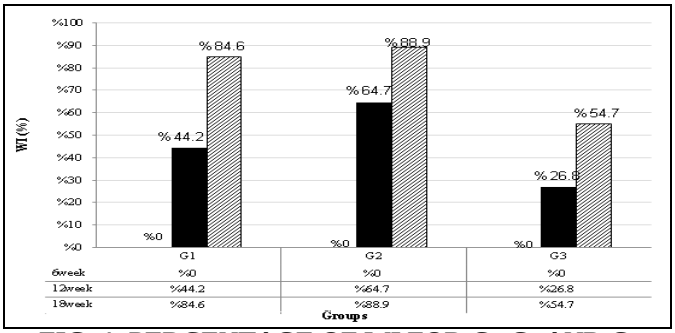

FIG. 4: PERCENTAGE OF WI FOR G_1, G_2 AND G_3 GROUPS AFTER 6 AND 12 WEEKS COMPARE TO FIRST WEEK AS AFFECTED BY ZINC SUPPLEMENT

The group G1 had significantly higher WI as compared to the other two groups G2 and G3, after 12 and 18 weeks **Table 3**. However, no significant difference was observed in WI among G2 after 18 weeks and G3 after 12 weeks.

Fig. 4 showed that the increase in WI was ranged from 44.2 to 84.6 % for G1, 64.7 to 88.9% for G2, 26.8 to 54.7 % for G3 after 12 and 18 weeks as compared to 6 week period in both seasons, respectively.

TABLE 3: WATER INTAKE AS AFFECTED BY ZINC SUPPLEMENT AND THE DURATION PER WEEKS

Groups	Duration (Weeks)			P.
	6	12	18	
G1	27.20 f ± 8.45	39.20 c ± 7.01	50.20 a ± 5.53	
G2	18.40 g ± 4.74	30.30 e ± 5.51	34.75 d ± 6.83	0.00 **
G3	27.15 f ± 7.87	34.40 d ± 3.75	42.00 b ± 4.45	

Indicate P < 0.01. Means followed by a common letter are not significantly different at the 1% level by DMRT. Where G1: control; G2: breastfed received zinc from 0-6 weeks; G3: weaning received zinc after 6 weeks Mean ± Standard deviations

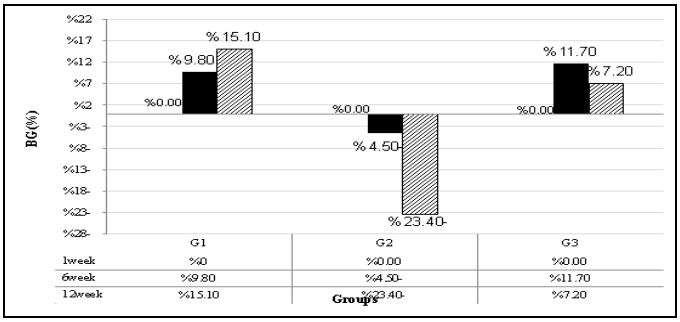

FIG. 5: PERCENTAGE OF BG FOR G_1, G_2 AND G_3 GROUPS AFTER 6 AND 12 WEEKS COMPARE TO FIRST WEEK AS AFFECTED BY ZINC SUPPLEMENT

The obtained data in **Table 4** and **Fig. 5** showed the effect of zinc supplementation on the blood glucose level. In the first week, there were no significant differences between the three groups in the mean of BG. After 12 weeks, the mean BG was significantly greater in G1 group than G2 and G3. BG was not differed significantly between 6 and 12 weeks for G1 or G2. Data in **Fig. 4** showed that the reduction percent of BG for G2 groups ranged from 4.5% to 23.4 % after 6 and 12 weeks, respectively,

compared to the first week. BG was increased relative to the first week by 9.8% and 15.10% after 6 and 12 weeks for G1 **Fig. 5**.

The increase in BG for G3 was 11.70% after 6 weeks, while the percent after 12 weeks was 7.20%.

TABLE 4: BG AS AFFECTED BY ZINC SUPPLEMENT AND THE DURATION PER WEEKS

Groups	Duration (Weeks)			P.
	1	6	12	
G1	104.6 cde ± 33.17	114.85 ab ± 15.64	120.3 a ± 7.79	
G2	102.05 de ± 31.4	97.50 e ± 22.34	78.25 f ± 14.95	0.00**
G3	99.85 de ± 29.05	111.50 bc ± 13.51	106.95 cd ± 8.14	

Indicate P < 0.01. Means followed by a common letter are not significantly different at the 1% level by DMRT. Where G1: control; G2: breastfed received zinc from 0-6 weeks; G3: weaning received zinc after 6 weeks. Mean ± Standard deviations

The effect of zinc supplementation on systolic blood pressure (SBS) was shown in **Table 5** and **Fig. 6**; the highest mean value of SBS was resulted from G1 group after 12 weeks compared to other groups **Table 5**.

At the first week, there was no significant difference between the three groups in the mean of SBS. There is an insignificant difference for G2 group after 1, 6, and 12 weeks in SBS. The increase percent of SBS for G1 groups ranged from 15% to 27 % after 6 and 12 weeks, respectively, compared to the first week **Fig. 6.**

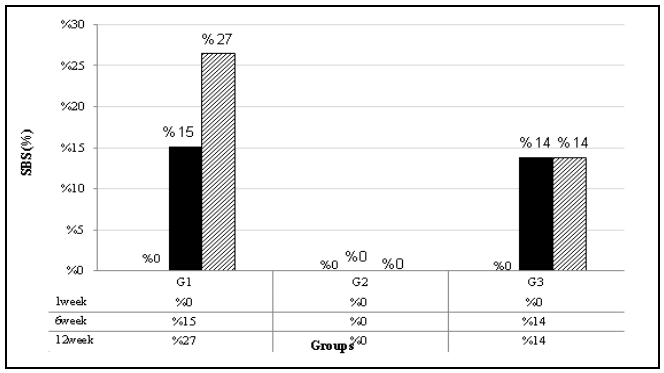

FIG. 6: PERCENTAGE OF SBS FOR G1, G2 AND G3 GROUPS AFTER 6 AND 12 WEEKS COMPARE TO FIRST WEEK AS AFFECTED BY ZINC SUPPLEMENT

TABLE 5: SBS AS AFFECTED BY ZINC SUPPLEMENT AND THE DURATION PER WEEKS

Groups	Duration (Weeks)			P.
	1	6	12	
G1	110.7 c ± 8.56	127.45 b ± 11.38	139.95 a ± 12.59	0.00**
G2	111.95 c ± 8.42	111.95 c ± 8.42	111.95 c ± 8.42	
G3	111.95 c ± 8.42	127.45 b ± 11.38	127.45 b ± 11.38	

Indicate P < 0.01. Means followed by a common letter are not significantly different at the 1% level by DMRT. Where G1: control; G2: breastfed received zinc from 0-6 weeks; G3: weaning received zinc after 6 weeks. Mean ± Standard deviations

Effect of zinc supplementation on lipid profile was shown in **Table 6** and **Fig. 7**, Data in **Table 6** shows that triglycerides (TG).

Total cholesterol (TC) and low-density lipoprotein (LDL) was significantly higher in G1groupwhile G2 gave the highest mean values of high-density lipoprotein (HDL) as compared to other groups.

The lowest values of HDL were recorded by G1 group, while the G2 produced the lowest TG, TC, and LDL. The greatest increase in HDL (131 %) was obtained by G2 as compared with G1 **Fig. 7**.

The reduction ranged from 14:42% for TG, 33.8: 61.7% for TC, and 25. 3:51.6 for LDL of G3 and G2 Groups, respectively **Fig. 7**.

TABLE 6: TRIGLYCERIDES (TG), TOTAL CHOLESTEROL (TC), LOW-DENSITY LIPOPROTEIN (LDL) AND HIGH-DENSITY LIPOPROTEIN (HDL) AS AFFECTED BY ZINC SUPPLEMENT GROUPS

Groups	TG	TC	LDL	HDL
G1	126.9 a ± 8.26	176.05 a ± 25.90	58.6 a ± 8.47	18.05 c ± 2.82
G2	74.25 c ± 20.33	67.55 c ± 12.33	28.4 c ± 6.37	41.75 a ± 3.4
G3	108.7 b ± 6.74	116.55 b ±12.63	43.8 b ± 4.2	30.55 b ± 3.47
P.	0.00**	0.00**	0.00**	0.00**

Indicate P < 0.01. Means followed by a common letter are not significantly different at the 1% level by DMRT. Where G1: No zinc intake (control); G2: Zinc intake from the first date of birth; G3: Weaning at 6 week received Zinc intake from the six week till the end of the experiment. Mean ± Standard deviations

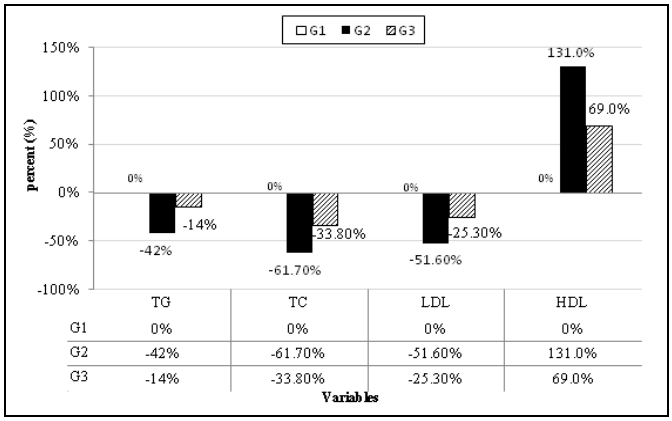

FIG. 7: PERCENTAGE OF TRIGLYCERIDES (TG), TOTAL CHOLESTEROL (TC), LOW DENSITY LIPOPROTEIN (LDL) AND HIGH DENSITY LIPOPROTEIN (HDL) FOR G_2 AND G_3 GROUPS COMPARED TO G_1

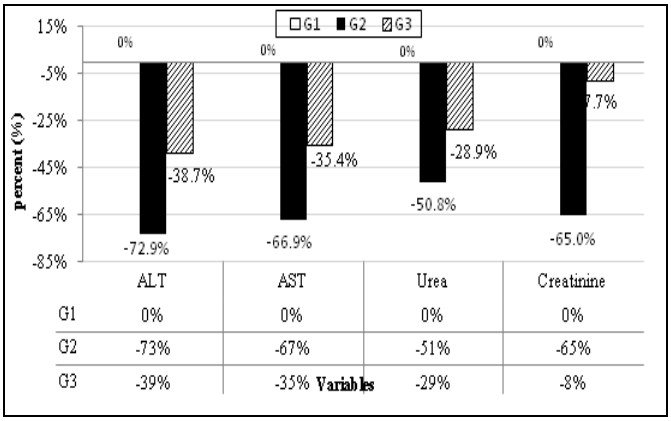

FIG. 8: PERCENTAGE OF ALT, AST, UREA AND CREATININE AS AFFECTED BY ZINC SUPPLEMENT GROUPS

The effect of zinc supplementation on ALT, AST, urea, and creatinine was shown in **Table 7** and **Fig. 8.** ALT and AST were significantly higher mean values in G1 as compared to other groups. The lowest mean values of ALT and AST were recorded by G2. The reduction percent was ranged from 39% and 73% in ALT and 35 % and 67% in AST for G3 and G2, respectively, as compared to G1. Urea and creatinine were significantly higher mean value in G1. The lowest mean values of urea and creatinine were recorded by group G2. The reduction percent was ranged from 28.9 % and 50.8 % for urea and 7.7% and 65% for creatinine of G3 and G2, respectively, as compared to G1.

TABLE 7: ALT, AST UREA AND CREATININE AS AFFECTED BY ZINC SUPPLEMENT GROUPS

Groups	ALT	AST	Urea	Creatinine
G1	49.00 a ± 4.46	32.25 a ± 3.11	18.90 a ± 1.8	1.17 a ± 0.14
G2	13.30 c ± 3.92	10.70 c ± 3.23	9.30 c ± 1.89	0.41 c ± 0.11
G3	30.05 b ± 5.76	20.85 b ± 4.07	13.45 b ± 2.01	1.08 b ± 0.13
P.	0.00**	0.00**	0.00**	0.00**

Indicate P < 0.01. Means followed by a common letter are not significantly different at the 1% level by DMRT. Where G1: No zinc intake (control); G2: Zinc intake from the first date of birth; G3: Weaning at 6 week received Mean ± Standard deviations

TABLE 8: INSULIN, S.ZINC AND IL6 AS AFFECTED BY ZINC SUPPLEMENT GROUPS

Groups	Insulin	S. zinc	IL-6
G1	26.61 c ± 6.6	0.7 c ± 0.04	5.06 c ±1.21
G2	45.65 a ± 2.7	1.06 a ± 0.06	6.85 a ±0.74
G3	31.79 b ± 7.1	0.87 b ± 0.07	6.00 b ± 0.43
P.	0.00**	0.00**	0.00**

Indicate P < 0.01. Means followed by a common letter are not significantly different at the 1% level by DMRT. Where G1: No zinc intake (control); G2: Zinc intake from the first date of birth; G3: Weaning at 6 week received Zinc intake from the six week till the end of the experiment. Mean ± Standard deviations

Effect of Zinc Supplementation on Insulin, S. Zinc and IL6 was shown in Table 8 and Fig. 9: G2 gave the highest mean values of insulin, S. zinc and IL-6 as compared to other groups.

While the G1 produced the lowest mean value of insulin, S.zinc, and IL-6.

The increase in insulin 71.6% for G2and 19.5%, G3and S. zinc was 24 % for G3 and 52 % for G2. The increase in IL-6 was 19 % in G3 and 35 % for G2.

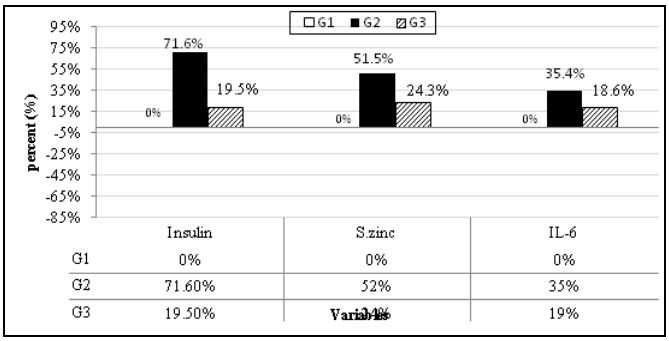

FIG. 9: PERCENTAGE OF INSULIN, S.ZINC, AND IL6 AS AFFECTED BY ZINC SUPPLEMENT GROUPS FOR G2 AND G3 GROUPS COMPARED TO G1

DISCUSSION: The current study showed that early supplementation of Zinc sulfate from the first day of live life by 180 mg/Kg/rat chow lead to a significant decrease in BW, WC , FI , BG, ALT, AST, TG, TC, LDL, SBS Urea and creatinine while HDL, insulin, S. zinc and IL-6 increased remarkably in the intervention group compared to control group. The present study shows a direct association between early zinc supplementation and decreases risk of metabolic syndrome development in high-risk groups.

Serum zinc was also directly associated with lower WC and low SBP and associated with high HDL cholesterol levels. The findings of the present study showed that early supplementation of oral zinc from the first day of live life leads to a significant decrease in the development of obesity in high-risk groups by a significant decrease in BW, WC, and FI in intervention groups. The reduction in BW could be a direct result of decreased food intake that may be due to decreasing effect of zinc on appetite and leptin level.

These results are in agreement with Marreiro *et al,* who reported that a low plasma zinc level is associated with obesity, and with Mantzoros *et al.*, who found that zinc may regulate serum leptin concentration and appetite control. Some studies have reported that Zn has been implicated in adiposity and serum leptin level [28]. Our study results showed that zinc supplementation is expected to be an effective method for preventing metabolic syndrome and diabetes as the blood glucose level was decreased significantly in zinc supplemented groups and insulin was significantly increased.

This decrease in glucose concentrations observed can be explained by the finding of Tobia *et al.*, 2005 who found that animals fed a diet containing 1000 ppm zinc, had higher serum and pancreatic insulin levels and lower serum glucose than those fed low zinc diets [32]. Zinc has also improved β cell function in patients with pre-diabetes as reported by Islam *et al,* 2016 [33]. Interestingly, Burtis *et al.*, 2015 reported changes in insulin resistance following zinc supplementation in diabetic patients. In recent study by Asghar *et al,* 2019, in spite of the insulin level increased significantly, there is no improvement in glycemic control in the diabetic patient, which is explained by the insulin resistance in a patient with type 2 diabetes [34]. The results of the present study showed that there was a significant decrease in TC, LDL, TG, while serum HDL was significantly higher in Zn supplemented groups compared to the normal control group. Some reviews and meta-analyses reported that zinc supplementation has favourable effects on plasma lipid parameters and that it significantly reduces total cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides [35].

A high prevalence of coronary artery disease (hypertension, hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol levels), diabetes, and glucose intolerance was reported in populations consuming lower intakes of dietary zinc [36]. Priyanga, *et al* 2015 demonstrates that Zinc supplementation has favourable effects on plasma lipid parameters [35]. Zinc supplementation significantly reduced total cholesterol, LDL cholesterol, and triglycerides [37]. In addition to that, Zinc supplementation in non-healthy patients demonstrated a significant elevation of HDL cholesterol [35].

The results of the present study showed that there was a significant decrease in liver function tests ALT and AST. This can be explained by a study shows that Zinc is a known fundamental component of the endogenous enzymatic antioxidant system, with antioxidant properties playing an essential role in cell membrane integrity and functions in many aspects of cellular metabolism [38]. These results were compatible with Abuduxikuer and Wang, (2014), who reported that after one month of zinc therapy, the mean serum ALT, AST, and gamma glutamyltranspeptidase (GGT) levels dropped significantly and remained lower thereafter [39].

The results of the present study showed that there was a significant decrease in serum urea and creatinine after zinc supplementation. As zinc has a protective role on renal tissue, as detected by Yoshioka *et al.* 2016. [40]. These results are in agreement with Pelin, *et al* (2009) who found that the application of ethanol increased serum urea and creatinine levels, but treatment with zinc sulfate reduced the serum urea and creatinine levels in the ethanol groups, and this indicates that zinc sulfate

prevents the damage caused by ethanol [41]. It can be concluded from these results that zinc sulfate has a protective role on the kidney. Our study shows a significant increase in serum zinc levels in zinc supplementation groups. Deficiency of Zip13 has been reported to show lipoatrophy, and Zip13-KO deficiency leads to insulin resistance as reported by Fukunaka and Fujitani [42]. The association between Zn deficiency and DM2 may be mediated through the role of Zn in insulin processing and storage as found by Samadi, *et al*. who reported a significant decrease in plasma Zn levels in diabetes [43]. Zn is also involved in insulin synthesis and secretion and blood pressure regulation and has antioxidant and anti-inflammatory properties. Zn has a strong antioxidant effect in DM, as reported by Cruz et al. [44]. Moreover, it has been shown that Zn supplementation prevents cholesterol oxidation and formation of 5, 6-a, and b cholesterol epoxides, 7b hydroxycholesterol, 7-keto-choles-terol in a high-cholesterol model of atherosclerosis in rabbits [43].

Our study shows an increase of IL-6 level after zinc supplementation in adulthood. These results match with that shows Systemic inflammatory biomarkers, such as CRP, IL-6 and TNF-α, were able to predict the gene expressions of zinc transporter and MT in PBMC; in particular, increases in systemic IL-6 concentration were related to increases in the expression of a cluster of zinc transporters, ZnT5, ZnT7, Zip1, Zip7 and Zip10, which are responsible largely for the uptake of extracellular zinc and transport of zinc into intracellular organelles and secretory pathways in Peripheral blood mono-nuclear cells [45]. Also, our results are in agreement with Mariani *et al* who found that zinc supplementation in subjects with low or borderline-normal circulating zinc increased the concentration of this ion and modulated plasmatic IL-6 and MCP-1 as well as NK lytic activity [46]. On the other hand, other studies show that chronic inflammation is characterized by increased levels of inflammatory cytokine production. Some conditions are associated with chronic inflammation, such as obesity, where patients with lower zinc dietary intake present with lower plasma and intracellular zinc concentrations along with up-regulated gene expression of IL-1α, IL-1β, and IL-6 compared to patients with higher zinc intake [47]. As regards the previous results, zinc supplementation can be used as a prophylaxis against different health problems like obesity and metabolic syndrome associated with diabetes. In addition, zinc supplementation in early neonatal life and during pregnancy can keep different orangs like liver, kidney, and heart in a healthy state that can stand against different diseases like atherosclerosis, renal, and liver failure. Also, zinc supplementation increases the level of IL-6 that has an important role in immunity and lipid metabolism, which made zinc supple-mentation more beneficial in metabolic syndrome.

CONCLUSION: Zinc supplementation in early neonatal life possesses a remarkable protective role against obesity and different health problems associated with it and increases the production of IL-6 in adulthood of male albino rats.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: Nil

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How to cite this article:
Nour El-Deen AE, Taha A, Fahmy EM and Mansour AE: Effects of oral zinc supplementation in early neonatal live on development of obesity and metabolic syndrome in albino rats. Int J Pharm Sci & Res 2021; 12(3): 1433-41. doi: 10.13040/IJPSR.0975-8232.12(3).1433-41.