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Research Article

HAEMATOLOGICAL ALTERATIONS IN WISTAR RATS AFTER DIETARY ZINC DEFICIENCY AND SUPPLEMENTATION

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ABSTRACT

Aim: Study was conducted to determine the effect of dietary zinc deficiency and supplementation on the hematological parameters of male Wistar rats. **Methods:** Pre-pubertal rats (40-50 g) were divided into two groups with 6 sub-groups each viz. zinc control (ZC)[100µg/ gm zincdiet], pair fed (PF) [100µg/ gm zincdiet], zinc deficient (ZD) [<1µg/ gm zinc diet], zinc supplementation control (ZCS) [100µg/ gm zinc control diet], zinc supplementation pair-fed (PFS)and zinc supplementation deficient (ZDS) [100µg/ gm zinc control diet].Experiments were set for 2- and 4-weeks followed by 4 weeks of zinc supplementation. **Results:** Duration dependent significant (P<0.05) decrease in red blood corpuscle count, haemoglobin content, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), erythrocyte sedimentation rate (ESR) and platelet count in both ZD and PF groups was observed with respect to control groups (2- & 4-weeks). The total leucocyte count (TLC) and clotting time showed a significant (P<0.05) increase in ZD groups as compared to control and pair-fed groups (2- and 4-weeks). After 4-weeks of zinc supplementation Hb, MCV, MCH and MCHC, RBC as well as platelet count demonstrated a non-significant decline while decrease observed in ESR and PCV values were found to be significant (2ZDS group).Although 4ZDS groups showed significant decline (P<0.05) in Hb, PCV, MCH, MCV, MCHC, RBC and platelet count, the decline was less as compared to 4ZD group. TLC and clotting time after zinc supplementation revealed non-significant (2ZDS) and significant (4ZDS) increase in ZD groups when comparisons were carried out between the groups. **Conclusion:** The findings revealed that zinc deficiency leads to marked deterioration of haematological parameters. Zinc supplementation appears to have beneficial effects by restoring the altered hematological indices.

INTRODUCTION

Zinc is a micronutrient of exceptional biologic and public health importance.[1-3] It is ubiquitous in sub-cellular metabolism and an essential component of catalytic site in hundreds of enzymes and in thousands of protein domains.[4,5] This metal has a function in every conceivable type of biochemical pathway and has diverse physiological functions including DNA and protein synthesis, cell proliferation, genomic stability, transcriptional regulation, cytoskeletal and membrane integrity, antioxidant functions, intracellular signaling, apoptosis etc.[6-8]Zinc deficiency is a serious health problem worldwide.[2,9] An estimated 17.3% of the world's population is at risk of inadequate zinc intake. [10] The vicious cycle of sub-optimal nutrition and repeated infection results in high burden of zinc deficiency in both the developed as well as developing countries.[2, 11]Periods of growth and development such as pregnancy, lactation, early infancy, puberty and tissue repair appear to be most susceptible to perturbations in zinc nutriture indicating infants, children, adolescents, pregnant and lactating women at increased risk of zinc depletion.[12] Blood is one of the major homeostatic systems of body in humans and animals, supporting normal viability, integrity and adaptive responses. The complete blood count with key indices such as haemoglobin, RBC indices and white blood cell counts provides information to aid diagnosis of a range of conditions, including anaemia, infection, leukaemia, myeloma and lymphoma.[13] Thus, the present study investigates the effect of dietary zinc deficiency and supplementation on the hematological parameters of prepubertal Wistar rats.

MATERIALS AND METHODS

Preparation of Basal Diet

The basal diet was prepared by ICN Research Diet Protocol, [1999]. The composition [per kg diet] was as follows: Egg

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albumin, 180 gm; Corn oil, 100 gm; Corn starch, 443 gm: Sucrose, 200 gm; Cellulose, 30 gm; Choline chloride, 2 gm; DL-methionine, 7 gm; D-biotin, 20 mg; American Institute of Nutrition [AIN]-76 salt mixture, 35 gm; AIN-76C vitamin-antibiotic mixture, 10 gm. Zinc contents of basal diets from each lot was estimated at 213.9 nm in air-acetylene flame on GBC 902 atomic absorption spectrophotometer [AAS] [GBC Scientific Equipment, Dandenong, Victoria, Australia] and concentration was adjusted to 1.00µg/ gm and 100µg/ gm by addition of appropriate amounts of zinc sulphate.

Animals: Albino rats of the Wistarstrain *Rattusnorvegicus* were used. The animals were housed in polypropylene cages in the departmental animal house under hygienic conditions. The animals were maintained on the standard laboratory feed and water*ad libitum* before the period of experimentation.The experiment was conducted within the framework of Institutional Animal Ethical Clearance guidelines.

Experimental Design: Pre-pubertal Wistar rats [30-40 days; 40-50gm] were divided into two groups with 6 sub-groups each:

I Group

1. 2ZC [Zinc control]: n=12; Animals were fed ICN zinc control diet, 100µg/ gm
2. 2PF [Pair-fed]: n=12; Animals were fed ICN zinc control diet but the amount of feed was equal to the [average] amount consumed by zinc deficient group the previous day. This group was run so as to study starvation effects due to reduced intake of diet and stress effects of the synthetic diet.
3. 2ZD [Zinc deficient]: n=12; Animals were fed < 1.00µg/ gm zinc diet.

With the exception of PF group, animals were allowed access to food and water *ad libitum.* Six animals from each of the above group were sacrificed after 2 weeks and remaining six animals were carried forward for 4 week of zinc supplementation.

4. 2ZCS [Zinc Supplementation control]: n=6; ICN zinc control diet *ad libitum.*
5. 2PFS [Zinc Supplementation Pair-fed]: n=6; ICN zinc control diet *ad libitum.*
6. 2ZDS [Zinc Supplementation deficient]: n=6; ICN zinc control diet*ad libitum.*

II Group

1. 4ZC [Zinc control]: n=12; Animals were fed ICN zinc control diet, 100µg/ gm
2. 4PF [Pair-fed]: n=12; Animals were fed ICN zinc control diet but the amount of feed was equal to the [average] amount consumed by zinc deficient group the previous day. This group was run so as to study starvation effects due to reduced intake of diet and stress effects of the synthetic diet.
3. 4ZD [Zinc deficient]: n=12; Animals were fed< 1.00µg/ gm zinc diet.

With the exception of PF group, animals were allowed access to food and water *ad libitum.* 6 animals from each of the above group were sacrificed after 4 weeks and remaining 6 animals were carried forward for 4 week of zinc supplementation

4. 4ZCS [Zinc control]: n=6; ICN zinc control diet *ad libitum.*
5. 4PFS [Pair-fed]: n=6; ICN zinc control diet *ad libitum.*
6. 4ZDS [Zinc deficient]: n=6; ICN zinc control diet*ad libitum.*

Collection of Blood Samples: Animals were anaesthetized under light ether anesthesia and blood was drawn from the heart by cardiac puncture using a sterile syringe and needle. Samples were collected in the heparin containing evacuated tubes. Haemoglobin (Hb), haematocrit/packed cell volume (PCV), red blood cells (RBCs) and white blood cell (WBCs) count, mean corpuscular haemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular haemoglobin concentration (MCHC), Erythrocyte Sedimentation Rate (ESR) and platelet counts were estimated.

Statistical Analysis: Data were expressed as mean ± SEM. Further, analysis of 2- and 4-weeks treatment groups was carried out separately using One way Analysis of Variance [ANOVA] and if the difference was found to be significant then post-hoc test [Duncan's Multiple Comparison Test] was applied. $P<0.05$ was considered to be significant. Statistical analysis was performed by Sigma Stat 3.5 software [Cranes Software International, Banglore, India].

RESULTS

Significant ($P<0.05$) decrease was observed in red blood corpuscle count, haemoglobin content, packed cell volume (PCV), mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), erythrocyte sedimentation rate (ESR) and platelet count in both ZD and PF groups with respect to control groups (2- & 4-weeks experiment). The total leucocyte count (TLC) and clotting time showed a significant ($P<0.05$) increase in ZD groups as compared to control and pair-fed groups (2- and 4-weeks). (Tables 1 & 2)

Table 1 Haematological parameters of Wistar rats after 2 weeks of zinc deficiency. Mean ± SEM

S.No.	Parameters	2ZC	2PF	2ZD
1.	RBC count (million/cu mm)	3.55 ± 0.0563	3.183± 0.0307 ^{a*}	3.017± 0.0307 $^{b* c*}$
2.	WBC count (Th/mm^3)	3.85 ± 0.0619	4.40 ± 0.0365 ^{a*}	4.70 ± 0.0365 $^{b* c*}$
3.	Platelet count (Lakh/ mm^3)	1.917 ± 0.04	1.657± 0.016 ^{a*}	1.417± 0.030 $^{b* c*}$
4.	ESR (mm/hr)	8.52± 0.0516	7.56 ± 0.061 ^{a*}	5.53 ± 0.0416 $^{b* c*}$
5.	Clotting Time (mins.)	3.333 ± 0.221	3.5 ± 0.224	4.50 ± 0.224 $^{b* c*}$
6.	Haemoglobin (%)	10.117±0.047	9.883±0.0833 ^{a*}	9.617±0.0543 $^{b* c*}$
7.	Haematocrit (%)	32.617±0.194	30.117±0.194 ^{a*}	27.284±0.214 $^{b* c*}$
8.	MCV (fl)	95.017±0.017	94.667±0.126	89.80±0.208 $^{b* c*}$
9.	MCH (pg)	29.867±0.178	30.827±0.198 ^{a*}	31.38±0.286 ^{b*}
10.	MCHC (g/lt)	31.05±0.22	32.11±0.178 ^{a*}	35.017±0.247 $^{b* c*}$

ZC Vs PF = a * P < 0.05 Significance level
ZC Vs ZD = b PF Vs ZD = c

Table 2 Haematological parameters of Wistar rats after 4 weeks of zinc deficiency. Mean ± SEM

S.No.	Parameters/ Groups	4ZC	4PF	4ZD
1.	RBC count (million/ cu mm)	3.95 ± 0.042	3.40 ± 0.036 ^{a*}	2.70 ± 0.036 $^{b* c*}$
2.	WBC count (Th/mm^3)	4.22 ± 0.049	4.63 ± 0.055 ^{a*}	5.37 ± 0.055 $^{b* c*}$
3.	Platelet count (Lakh/ mm^3)	2.383 ± 0.03	1.937 ± 0.009 ^{a*}	1.60 ± 0.124 $^{b* c*}$
4.	ESR (mm/hr)	8.50± 0.0297	5.90 ± 0.0306 ^{a*}	5.20 ± 0.0486 ^{b*}
5.	Clotting Time (mins.)	3.66 ± 0.0.21	5.00 ± 0.36 ^{a*}	5.50 ± 0.22 ^{b*}
6.	Haemoglobin (%)	11.984 ±0.094	9.60±0.036 ^{a*}	7.417±0.030 $^{b* c*}$
7.	Haematocrit (%)	35.584± 0.214	30.95± 0.262 ^{a*}	24.80 ±0.963 $^{b* c*}$
8.	MCV (fl)	92.184 ± 0.26	90.117±0.18 ^{a*}	87.817± 0.25 $^{b* c*}$
9.	MCH (pg)	30.081± 0.35	29.864±0.25	28.707± 0.42 $^{b* c*}$
10.	MCHC (g/lt)	32.267± 0.076	31.61± 0.236 ^{a*}	29.28± 0.236 $^{b* c*}$

ZC Vs PF = a * P < 0.05 Significance level
ZC Vs ZD = b PF Vs ZD = c

After 4-weeks of zinc supplementation Hb, MCV, MCH and MCHC, RBC as well as platelet count demonstrated a non-significant decline while decrease observed in ESR and PCV values were found to be significant (2ZDS group). 4ZDS groups showed significant decline (P<0.05) in Hb, PCV, MCH, MCV, MCHC, RBC and platelet count.TLC and clotting time after zinc supplementation revealed non-significant (2ZDS) and significant (4ZDS) increase in ZD groups when comparisons were carried out between the groups. (Tables 3 & 4)

Table 3 Haematological parameters of Wistar rats after 2 weeks of zinc deficiency followed by 4 weeks of zinc supplementation. Mean ± SEM

S.No.	Parameters	2ZCS	2PFS	2ZDS
1.	RBC count (million/cu mm)	4.03 ± 0.061	3.80 ± 0.068	3.78 ± 0.087
2.	WBC count (Th/mm^3)	4.18 ± 0.079	4.23 ± 0.71	4.31 ± 0.079
3.	Platelet count (Lakh/ mm^3)	2.218 ± 0.017	2.120 ± 0.051	2.122 ± 0.061
4.	ESR (mm/hr)	8.583± 0.219	8.02 ± 0.048	7.605±0.030 $^{b* c*}$
5.	Clotting Time (mins.)	4.06 ± 1.02	4.25 ± 0.088	4.31 ±0.125
6.	Haemoglobin (%)	12.23± 0.269	11.78±0.23	11.51±0.202
7.	Haematocrit (%)	35.18± 0.105	30.33±0.046 ^{a*}	29.50±0.279^{b*}
8.	MCV (fl)	87.48± 0.145	86.72± 0.102	85.20±0.47
9.	MCH (pg)	33.17± 0.258	32.65±0.24	32.29±0.385
10.	MCHC (g/lt)	38.35± 0.457	37.28 ±0.307	36.82±0.349

ZC Vs PF = a * P < 0.05 Significance level
ZC Vs ZD = b PF Vs ZD = c

Table 4 Haematological parameters of Wistar rats after 4 weeks of zinc deficiency followed by 4weeks of zinc supplementation. Mean ± SEM

S.No.	Parameters/ Groups	4ZCS	4PFS	4ZDS
1.	RBC count (million/ cu mm)	4.51± 0.070	4.00 ± 0.113 ^{a*}	3.85 ± 0.243 ^{b*}
2.	WBC count (Th/mm^3)	4.13 ± 0.088	4.65 ± 0.042 ^{a*}	4.86 ± 0.095 ^{b*}
3.	Platelet count (Lakh/ mm^3)	2.473±0.032	1.90 ± 0.073 ^{a*}	1.76 ± 0.076 ^{b*}
4.	ESR(mm/hr)	8.568±0.020	7.216±0.067 ^{a*}	6.655±0.051 $^{b* c*}$
5.	Clotting Time (mins.)	4.50±0.081	4.81±0.105 ^{a*}	5.00 ± 0.106 ^{b*}
6.	Haemoglobin (%)	15.48 ± 0.280	13.21±0.13 ^{a*}	12.016 ± 0.18 $^{b* c*}$
7.	Haematocrit (%)	38.28 ± 0.31	33.86 ± 0.04 ^{a*}	31.60 ± 0.218 $^{b* c*}$
8.	MCV (fl)	85.08± 0.26	82.80 ± 0.42 ^{a*}	78.352 ± 0.98 $^{b* c*}$
9.	MCH (pg)	33.65 ± 0.47	32.26 ± 0.19 ^{a*}	31.89 ± 0.42^{b*}
10.	MCHC (g/lt)	39.89 ± 0.14	38.56 ± 0.25 ^{a*}	38.18± 0.25 ^{b*}

ZC Vs PF = a * P < 0.05 Significance level
ZC Vs ZD = b PF Vs ZD = c

DISCUSSION

Red blood cells or erythrocytesare highly specializedand the most abundant cells in the bloodstream and contains hemoglobin, the compound that carries oxygen through the body. Present study revealed significant decrease in RBC count, haemoglobin content, PCV, MCV, MCH, MCHC, ESR and clotting time in a duration dependent manner (both 2- and 4 -weeks) in zinc deficient groups. El-Hendy *et al*[14] reported decrease in hematological parameters (Hb, total erythrocyte count and PCV) in male and female rats after 10-week zinc deprivation period. Reduction in Hb may be due to increased disruption or reduction in the rate of formation of erythrocytes. [15] These results were similar to those reported in hypozincemicsheep.[16]Zinc is the co-factor of several enzymes and plays a role in iron metabolism and zinc deficiency aggravates iron deficiency anemia (IDA).[17]Prasad[2] reported that nutritional deficiency of iron and zinc always coexist in the developing world as majority of rural people subsist on high cereal protein diet which is rich in phytate, which renders unavailability of Fe and Zn for absorption. Zinc binds to haemoglobin and increases oxygen affinity and reduces red cell membrane deformability. [18] Zinc appears to be an important micronutrient for haemoglobin synthesisas it plays an important role in the activation of aminolevulinic acid dehydratase (δ-ALAD, also called porphobilinogen synthase), which is required for normal heme synthesis.[19] Zinc supplementation to lithium-treated rats effectively raised the activities of the enzymes δ-ALAD and Na(+) K(+) adenosine triphosphatase in rat blood. [20]Akhtar*et al*[21] reported a significant correlation between plasma zinc levels on one hand and Hb levels as well as RBC counts on the other hand. Baltaci *et al*[22] suggested that zinc deficiency negatively affects the hematological parameters whereas zinc supplementation has a positive influence. Decrease in PCV was due to decreased erythrocyte count as PCV gives the percentage of RBCs in a given volume of blood. [14]Sharma *et al*[23] demonstrated that zinc deficiency adversely affected RBC morphology and enhanced osmotic fragility which would influence circulation, although these alterations were reversed after zinc supplementation to some extent being dose and days dependent. Zn status can account for hematological abnormalities while its supplementation improves Hb concentration, number of RBCs and reticulocytes and total iron binding capacity (TIBC) in middle-aged women.[24]

Alterations in RBC indices viz. MCV, MCH and MCHC indicates anemia. Defective hemoglobin synthesis results in small cells (low MCV) as observed in the present study. Zinc deficiency stimulates the hypothalamus-pituitary adrenal stress axis, leading to increased serum corticosterone levels, thymic atrophy, adrenal hypertrophy and white blood cells (granulocytes and monocytes) distribution. [25] Present study revealed significant increase in the number of total WBC's in ZD groups which may indicate an activation of animal's defense mechanism and immune system. Increased WBC in male albino rats after 6 weeks of dietary zinc deprivation was also observed.[26] The continuous migration of immune cells promotes cellular interactions that enable the immune system to execute response against the antigens.[27]Thymulin, a thymic hormone involved in T-lymphocyte maturation, is known to be zinc dependent and is adversely affected by Zn deficiency. [28]Several authors reported beneficial effect of zinc supplementation on immunity. [29,30]Zinc deficiency compromises proper immune function in elderly population causing dysregulation in adaptive immunity resulting in increased production of pro-inflammatory cytokines contributing to immunosenescence.[31] Studies with oral zinc supplementation show the potential to improve the immune response of elderly people by restoration of the zinc levels. Zinc plays a central role in the immune response and its homeostasis is critical for sustaining proper immune function.[32] Reduced ESR indicates marked changes in blood viscosity as observed in the present study. ZD causes deterioration of blood viscosity as zinc is physiologically involved in the regulation of erythrocyte deformability.[33] Sobhanirad and Naserian[34] also demonstrated beneficial effect of zinc supplementation on hematological and biochemical parameters of dairy cows. Zinc being second most abundant trace element in blood also plays an important role in haemostasis and thrombosis.[35] Hyperzincemia predisposes to increased coagulability and hypozincemia to impaired platelet aggregation and increased bleeding time.[36] Appropriate zinc intakes can regress the blood clotting disturbances and clots formed in presence of zinc were

more stable and resisted rupture and attenuates fibrinolysis. [37]Zinc has protective effect on some of the haematological parameters (RBC, PCV and Hb) against the thioacetamide induced liver cirrohosis in albino rats. [38]Al-Habib*et al*[39] showed that zinc deficient and zinc overdose diet induced a negative effect on RBC count, HCT%, Hb, MCV, MCH, and MCHC in weaned female Albino rats. Silva *et al*[40] reported beneficial effect of zinc supplementation on haematological parameters (Hb, PCV) and serum Fe and Zn concentration in children of 12-59 months of age. The present study revealed the alterations in packed cell volume, erythrocyte indices (MCV, MCH and MCHC) and concentrations of hemoglobin, red blood cells, platelets and total leukocyte count. Zinc deficiency leads to marked deterioration of haematological parameters. Zinc supplementation appears to have beneficial effects by restoring the altered hematological indices.

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