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ORIGINAL ARTICLE

Zinc in nutrition of Rat and its Correlation with Various diet pattern (Fructose, oxonic acid ,fructose and oxonic acid) in induced Hyperuricemic rat

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ABSTRACT
Zinc may not fulfil the correct definition of antioxidant the reason is that it has never been found to interact directly with an oxidant species. In biochemical system the antioxidant mechanism exerted by zinc can be studied by divided into acute and chronic effects
Key words: *Fructose (F), Hyperuricemia, Hyperglycemia*

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INTRODUCTION

Acute effects are generally thought to engage two means including the protection of proteins sulfhydryls and reduction in the form of OH from H2O2 by the antagonism of redox-active metals e.g iron and copper.[1] The chronic effects can be that organism is exposed to zinc on long term basis leading to induction in some other substance that is ultimate antioxidant..In this regard, Metallothioneins are the most studied effectors. Topical application has been shown antioxidant photoprotection for skin. Two antioxidant mechanisms have been anticipated for zinc. First that zinc ions may replace redox active molecules, such as iron and copper, at critical sites in cell membranes and proteins., alternatively, zinc ions may induce the synthesis of metallothionein, sulfhydryl-rich proteins that protect against free radicals[2]

Free radicals from oxygen are formed when oxygen is pre-activated by two methods i.e by being photodynamic and by reduction. By photodynamic oxygen ends as singlet oxygen while when reduced, it can form anion hydrogen peroxide and radical hydroxyl. Reduction is accelerated when transition metals are present including iron ,copper and/or certain enzymes e.g monoxygenase and certain oxydases.[3].

The sources of free radicals can be divided into endogenous and exogenous sources. Endogenous sources include mitochondrial leak, respiratory burst, enzyme reactions, autooxidation reactions etc while environmental sources are cigarette smoke, pollutants, UV light, ionising radiation,Xenobiotics.

The most important free radicals in many disease states are oxygen derivatives, particularly superoxide and the hydroxyl radical. Superoxide is formed from several molecules by oxidation including adrenaline, flavine nucleotides, thiol compounds, and glucose .Superoxide is also produce during important biological reactions including electron transport chain in mitochondria[4], adrenal hormone synthesis, by vascular endothelium to neutralize nitric oxideand by phagocytic cells during respiratory burst[5,6] . The production of hydrogen peroxide is simultanenous observe with superoxide in biological systems as a result of spontaneous dismutation reaction. Although hydrogen peroxide is not a powerful free radical but its most vital property is that it can cross cell membranes which superoxide fails to do so[7,8]. Therefore it is a medium to transmit fee radical injury across cell compartments and between cells.The superoxide and hydrogen peroxide both can be decomposed to hydroxyl radical which and its closely related species are may be the probable final mediator of most free radical induce tissue damage [9,10].

It is because of the fact that its reacts with almost every type of molecules in cells including sugars , aminoacids, lipids and nucleotides[11,12].
They are metal binding lower molecular weight proteins and they are induced by chronic administration of zinc in various organs including liver, kidney and intestine. Metallothionines have antioxidant properties against numerous injuries including radiation, anticancer toxicity, ethanol toxicity etc [13,14,15].
Uric acid levels vary within human on the basis of age and sex This difference in levels in both sexes is due to two reasons, firstly increase production in males because of increase muscle mass and secondly female hormone, estrogen which serves as uricosuric and is instrumental for low blood uric acid as compared to men [16].This also explains the enhanced level of uric acid observed in post menopausal women. Deviation from its normal range is seen in number of pathological conditions. Some of the important factors that can increase the production of urates in human body are diet, Tumour Lysis Syndrome , Enzymatic Defects ,Drugs, Myeloproliferative & Lymphoproliferative disorders ,Hyperthyroidism and Solid Organ Transplant.
Diet is a common but minor cause of hyperuricemia because diet alone generally is not sufficient to cause hyperuricemia.). Fructose can increase the production of uric acid by increasing the formation of ATP which is then converted to uric acid [17].
Fructose a monosaccharide with sources ,is consumed in large scale world wide as being constituent of Table sugar or sucrose (50% fructose and glucose each) and also as High Fructose Corn Syrup(55%fructose and 45% glucose).High Fructose Corn Syrup (HFCS) are major ingredient of soft drinks, desserts and various processed food [18].

MATERIAL AND METHODS

Collection and storage of Animals

Locally bred forty(40) male Albino rats as shown in figure 22-23 with an average weight of 180±20g were purchased. The rats were grouped and housed in environmentally controlled room(ambient temperature 24±2°C and relative humidity of 55±5%) in the animal house and acclimatized for 07 days**.** The animals were fed standard diet and given tap water ad libitum until treatment. The protocols for experimentation was approved and performed in strict accordance with the Guide for the care and use of laboratory animals (Institute of Laboratory Animal Resources on Life Sciences, US National Research Council,1996) and the Institutional Animal Ethical Committee (IAEC) of Baqai Medical University, Karachi. Pakistan All animals housed in standard conditions were initially fed standard diet and allowed adaptation of one (01) week. Albino rats were divided in four(04) groups; A,B,C & D.
Group A:
Ten (10) male albino rats as Control were kept as control and were fed standard diet and water ad libitum for 10 weeks.
Group B:
Ten (10) male albino rats [F]were fed 60% fructose mixed in standard diet and water ad libitum for 10 weeks.
Group C:
Ten (10) male albino rats [FO]were fed 60% fructose mixed in standard diet and water ad libitum for 10 weeks. They were also injected intraperitonealy oxonic acid 250mg/kg every third day for 10 weeks.
Group D:
Ten (10) male albino rats [O]were injected intraperitonealy oxonic acid 250mg/kg every third day for 10 weeks. They were fed standard diet and water ad libitum for 10 weeks.
The amount of diet was measured before giving and then subtracted from the amount of food left over daily.
Collection of Blood : Approximately 10 mls of blood was drawn from heart using disposable syringe .8 mls of blood was transferred in heparanized tube, mixed and centrifuged to separate plasma and divided in two epindorf cups for estimation of uric acid and sugar. 2mls of blood was transferred to glass tube and an equal amount of concentrated HNO_3 was added to heat slowly and intermittently on sand bath avoiding boiling for next couple of days to obtain about 3 mls of clear solution. This solution was diluted with deionized water, filtered and the volume was made up to 10mls with deionized water. Estimation Of Serum Uric Acid was done by Pap method [19.20].

MEASUREMENT OF TRACE ELEMENTS:

Trace element analysis was carried out on a Hitachi Z-8000 atomic absorption spectrometer equipped with Zeeman background correction and a data processor. Flame atomization was used for Copper, Zinc and Magnesium estimation.

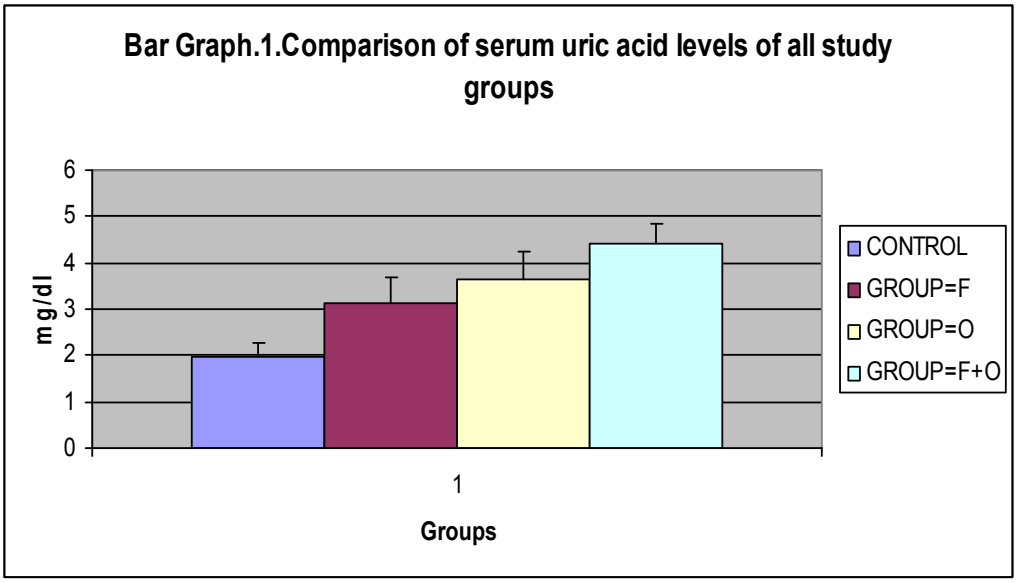
STATISTICAL ANALYSIS
Using SPSS 17 WAS carried out.

RESULTS
Figure 3.1 shows the comparison of mean plasma Uric acid levels of all groups engaged in this study. When plasma uric acid levels of these groups were checked and compared with each other following results were obtained;

3.1.1.COMPARISON OF PLASMA URIC ACID LEVELS OF CONTROL WITH OTHER GROUPS:
Table 3.1.1 shows the comparison of mean plasma uric acid levels of Control with rest of the groups. Mean plasma level of uric acid of Control is found to be 1.97 mg/dl(±0.09) .Group "F"(fructose) showed mean plasma uric acid of 3.15 mg/dl(±0.17) .This reflects that uric acid was raised to 37% in rats which were exposed to diet comprising 60% Fructose than control. On comparing both groups i.e Control with Group "F"(highly significant statistical correlation(P <0.001) was observed.
The mean plasma uric acid levels of Group "O" (oxonic acid) was 3.63 mg/dl(±0.22)which is 45% higher than Control. The probability calculated was highly significant (P<0.001) when both groups were evaluated.
While comparing Group "F+O"(Fructose +Oxonic acid) with Control, highly significant correlation was observed(P<0.001).It was due to high mean plasma serum uric acid level of Group "F+O" which was 4.41mg/dl(±0.14) .The combination of fructose with uricase inhibitor ,Oxonic acid raises uric acid to 55% from control and this level is highest of all these groups.

TABLE 3.1.1:COMPARISON OF URIC ACID LEVELS (mg%) OF GROUP "C" WITH OTHER GROUPS

GROUPS	*MEAN VALUES & SEM(Standard Error of Mean)*	*P-Values*
GROUP CONTROL(C)	1.97 SEM±0.09	
GROUP FRUCTOSE(F)	3.15 SEM±0.17	Gr "C" Vs Gr "F" P<0.001
GROUP OXONIC ACID(O)	3.63 SEM±0.22	Gr "C" Vs Gr "O" P<0.001
GROUP FRUCTOSE+OXONIC ACID(F+O)	4.41 SEM±0.14	Gr "F" Vs Gr "F+O" P<0.001



SERUM URIC ACID

GROUPS	CONTROL	GROUP=F	GROUP=O	GROUP=F+O
M.V	1.97	3.15	3.63	4.43
S.D	0.3	**0.55**	**0.63**	**0.43**

COMPARISON OF PLASMA ZINC LEVELS BETWEEN CONTROL AND STUDY GROUPS :

Figure 3.8 shows the comparison of mean plasma Zinc levels of all groups engaged in this study. When plasma Zinc levels of these groups were checked and compared with each other following results were obtained;

COMPARISON OF PLASMA ZINC LEVELS OF CONTROL WITH OTHER GROUPS:

Table 3.8.1 shows the comparison of mean plasma Zinc levels of Control with rest of the groups. Mean plasma level of Zinc of Control was found to be 17.6 mg/dl(±1.26) .Group "F"(fructose) showed mean plasma Zinc of 15.45 mg/dl(±1.27) .This reflects that Zinc fell down to 14% in rats which were exposed to diet comprising 60% Fructose than control. On comparing both groups i.e Control with Group "F" non-statistical correlation(P >0.01) was observed.The mean plasma Zinc levels of Group "O" (oxonic acid) was 18.6 mg/dl(±1.18)which is only 11% higher than Control. The probability calculated was non-significant (P>0.01) when both groups were evaluated.

Plasma mean Zinc levels While comparing Group "F+O"(Fructose +Oxonic acid) were measured to 13.6mg/dl(±0.93) only 30% decreased than control which gave non-significant correlation(P>0.01) with Control.

COMPARISON OF PLASMA ZINC LEVELS OF GROUP F WITH OTHER GROUPS:

Table 3.8.2 exhibits the correlation between mean plasma Zinc of Group "F"(with rest of the groups.The Group "F" shows non-significant association (P>0.01) with Control as described in section 3.8.1.

The mean plasma Zinc levels in Group O were 18.6mg/dl(±1.18) closely matching with Group "F", therefore the P value calculated were non-significant (P<0.001).

Group F+O mean plasma Zinc was found to be 13.6mg/dl(±0.93) which is only 03%more than Group"F", therefore the non-significant correlation was observed (P>0.01)between these two groups.

TABLE 3.8.1:COMPARISON OF ZINC LEVELS (mg%) OF GROUP "C" WITH OTHER GROUPS

GROUPS	***MEAN VALUES & SEM (Standard Error of Mean)***	***P-Values***
GROUP CONTROL(C)	17.6 SEM±1.26	
GROUP FRUCTOSE(F)	15.45 SEM±1.27	Gr "C" Vs Gr "F" P>0.01
GROUP OXONIC ACID(O)	18.6 SEM±1.18	Gr "C" Vs Gr "O" P>0.01
GROUP FRUCTOSE+OXONIC ACID(F+O)	13.6 SEM±0.93	Gr "F" Vs Gr "F+O" P>0.01

TABLE 3.8.2:COMPARISON OF ZINC LEVELS (mg%) OF GROUP "F" WITH OTHER GROUPS

GROUPS	***MEAN VALUES & SEM (Standard Error of Mean)***	***P-Values***
GROUP FRUCTOSE(F)	15.45 SEM±1.27	
GROUP CONTROL(C)	17.6 SEM±1.26	Gr "F" Vs Gr "C" P>0.01
GROUP OXONIC ACID(O)	18.6 SEM±1.18	Gr "F" Vs Gr "O" P>0.01
GROUP FRUCTOSE+OXONIC ACID(F+O)	13.6 SEM±0.93	Gr "F" Vs Gr "F+O" P>0.01

COMPARISON OF PLASMA ZINC LEVELS OF GROUP "O" WITH OTHER GROUPS:

Table 3.8.3 shows the statistic connection of Group "O"(Oxonic Acid) with the rest of the groups. The comparison of Group "O" with both control and Group F have shown non- significant association(P>0.01) as describe before.

The Group "O" showed significant correlation (P<0.01) with Group F+O as the mean serum Zinc levels of Group "F+O"are 72% lower than Group "O" reflecting that Zinc levels decreased significantly in rats which were treated with oxonic acid along with dietary fructose in comparison to rats which were injected with Oxonic acid alone.

COMPARISON OF PLASMA ZINC LEVELS OF GROUP F+O WITH OTHER GROUPS:

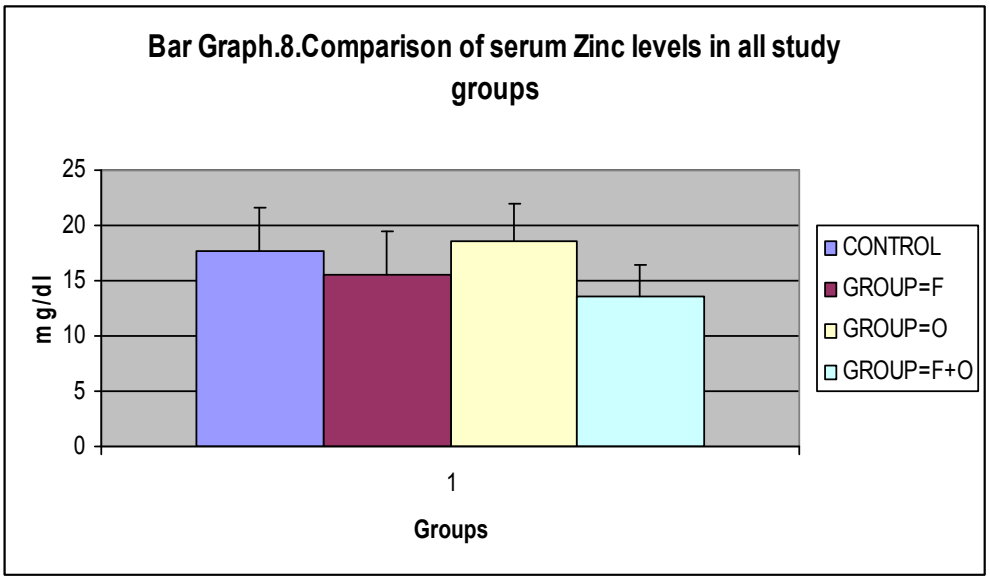
Table 3.8.4 reflects the statistical comparison of Group F+O with the rest of the groups.Mean plasma Zinc of this group(F+O) were 13.6mg/dl(±0.93) which are lowest of all groups. The statistic correlations were found to be non-significant(P>0.01) when Group F+O was evaluated both with Control and Group F while significant when Group F+O was checked against Group O. significant(P<0.01)

TABLE 3.8.3:COMPARISON OF ZINC LEVELS OF GROUP "O" WITH OTHER GROUPS

GROUPS	***MEAN VALUES & SEM(Standard Error of Mean)***	***P-Values***
GROUP OXONIC ACID(O)	18.6 SEM±1.18	
GROUP CONTROL(C)	17.6 SEM±1.26	Gr "O" Vs Gr "C" P>0.01
GROUP FRUCTOSE(F)	15.45 SEM±1.27	Gr "O" Vs Gr "F" P>0.01
GROUP FRUCTOSE+OXONIC ACID (F+O)	13.6 SEM±0.93	Gr "O" Vs Gr "F+O" P<0.01

TABLE 3.8.4:COMPARISON OF ZINC LEVELS OF GROUP "F+O" WITH OTHER GROUPS

GROUPS	***MEAN VALUES & SEM (Standard Error of Mean)***	***P-Values***
GROUP FRUCTOSE+OXONIC ACID(F+O)	13.6 SEM±0.93	
GROUP CONTROL(C)	17.6 SEM±1.26	Gr "F+0" Vs Gr "C" P>0.01
GROUP FRUCTOSE(F)	15.45 SEM±1.27	Gr "F+O" Vs Gr "F" P>0.01
GROUP OXONIC ACID(O)	18.6 SEM±1.18	Gr "F+O" Vs Gr "O" P<0.01



ZINC GROUPS	CONTROL	GROUP=F	GROUP=O	GROUP=F+O
M.V	17.6	15.45	18.6	13.6
S.D	3.97	**4.03**	**3.35**	**2.8**

DISCUSSION

One of the important features of this study is the method by which hyperuricemia have been induced in animal model. First group (G=Fructose) was given fructose , second group(G=Oxonic acid) was treated with "oxonic acid" and third group was offered both fructose and oxonic acid(G=Fructose+Oxonic acid). The principle hyperuricemic factor in this study is fructose as it is extensively used in beverages and

food .It's a rather controversial factor as number of studies both animals and human, are in the favour that fructose can induce hyperuricemia [21]but many studies have opposed this hypothesis [22]and even mixed response has been shown[23] .Present investigation has tried to verify this theory. Very few studies have used this combined model of fructose plus oxonic acid. In order to make conditions similar to human, uricase inhibitor oxonic acid was incorporated to abolish the effect of this enzyme in rats . Also these different regimens were used to establish the extent of hyperuricemia caused by fructose.

In present study uric acid was found to be increased in all three groups,G=Fructose,G=Oxonic acid and G=Fructose+Oxonic acid when the levels were compared with the Control(C),but considerable variations in levels were observed in these groups as shown in Tab3.1.1 and Fig 3.1 in the section of results. The mean serum level of uric acid in G=Fructose+Oxonic was highest of all three study groups being 55% more than control,28% more than Fructose treated only and 18% higher than Oxonic acid treated hyperuricemic rats . These findings are in consistent with several other studies which have shown that fructose can increase uric acid levels [23.24] . The proposed mechanism by which fructose might have increased uric acid production is that fructose is rapidly phosphorylated by fructokinase to fructose-1-phosphate on entering the hepatocytes by passing the regulatory step of glycolysis.[25,26].ADP is generate due to donation of Phosphate by ATP during this reaction.This ADP is then furthur metabolized to uric acid[27].Fructose may also increase latcate production which is a competitive inhibitor for urate excretion [28]. In addition to this Fructose might also have role in hyperinsulinemia which may also have contributed to impairment in urate excretion by promoting renal reabsorption [29] Finaly resultant hyperuricemia due to fructose itself impaired its own excretion as demonstrated in several studies by causing endothelial dysfunction and renal vasoconstriction [30,31]The different magnitude of hyperuricemia observed might be due to the reason that in rats hepatic enzyme uricase (urate oxidase) is present which is responsible for converting uric acid to allontoin .Due to this reason the normal levels are kept in range of 0.5 to1.5mg/dl[32].This was well demonstrated in present study in the G= Oxonic acid and G= Fructose+ Oxonic acid in which uric acid considerably increased when uricase inhibitor “Oxonic acid” was added.

CONCLUSION

Fructose a hexose sugar is responsible for hyperuricemia in albino rat. Zinc level were statistically significant and correlated between control and other group. It was noted down that serum levels of Zinc in all four groups, were found to be in normal ranges with lowest of all that is 13.6 mg/dl were observed in the group which was treated with 60% fructose and 2% oxonic acid(G-Fructose+Oxonic acid) as shown in Graph and Table 3.8.There is in significant relationship between hyperuricemia and zinc are available.

RECOMMENDATION

Antioxidants such as copper and zinc and some vitamins like C ,E and A are important to include in diet. It is recommended to include Zinc containing vegetables and fruit daily to reduce their deficiency.

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