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Zinc supplement alleviates redox alterations mediated by doxorubicin-induced testicular oxidative stress

Abstract

Background: This study investigated the activities of zinc (Zn) supplement on redox status of animal model of doxorubicin-induced testicular oxidative stress; in order to ascertain whether Zn supplement could be beneficial on altered testicular redox status mediated by doxorubicin (a known anticancer drug).

Methods: Single dose of doxorubicin (10mg/kg b.wt. i.p.) was used to induce testicular oxidative stress on DOX group as well as DOX+Zn group; DOX group was left untreated, while DOX+Zn was treated with Zn (10mg/kg b.wt. p.o.) daily for 14days after induction of testicular oxidative stress. Results were compared with control and Zn-only group as well as between DOX group and DOX+Zn group. Statistical significance was considered at $P<0.05$.

Results: Doxorubicin (DOX) induced testicular oxidative stress by increasing lipid peroxidation (malondialdehyde; MDA) and decreasing glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD) and total antioxidant capacity (TAC) when compared to control, $P<0.05$. Zn treatment decreased testicular MDA and improved testicular GPx, CAT, SOD and TAC; when Zn-only group is compared to control as well as comparison between DOX group and DOX+Zn group at $P<0.05$.

Conclusion: Zinc supplement alleviates redox alterations mediated by doxorubicin-induced testicular oxidative stress by improving testicular GPx, CAT, SOD, TAC and decreasing testicular MDA; forming basis for inclusion of Zn supplement as a combatant of doxorubicin-induced testicular oxidative stress.

Keywords: doxorubicin, zinc supplement, redox status, oxidative stress, testis, reproductive system

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Abbreviations: Zn, zinc; DOX, doxorubicin; MDA, malondialdehyde; GPx, glutathione peroxidase; CAT, catalase; SOD, superoxide dismutase; TAC, total antioxidant capacity; ROS, reactive oxygen species

Introduction

Redox status refers to the balance or equilibrium between antioxidants and oxidants in tissues, organs or system.[1,2] Impaired homeostasis of the redox status of a tissue, organ and/or system causes oxidative stress as well as inducing toxcity.[3,4] Toxicants (lead, acrylamide, calcium carbide, etc.) and over dose of drugs like acetaminophen was shown to induce physiological alterations in stomach, blood, kidneys, testis.[5–8]

Reproductive system which is vital for procreation and avoidance of extinction of a particular system has been affected adversely by several factors ranging from technology to herbs and toxicants.[9–11] Doxorubicin, a known anticancer drug has been reported to induce reproductive toxicity; its oxidative stress impact on testis was also demonstrated in animal models.[12,13] This study was designed to evaluate the impact of Zinc supplement on redox status of animal model of doxorubicin-induced testicular oxidative stress following the beneficial report of Zn supplementation on reproductive functionality and pathophysiological conditions.[14–16]

Materials and methods

This study was performed strictly in accordance to the principle of use and cares for laboratory animals (NIH, Publication, No 85-23); Wistar rats gotten from the animal farm of Gregory University, Uturu was housed in standard, clean, comfortable and aerated cages under a dark/light cycle. The rats were allowed access to standard growers chow and water *ad libitum*. The animals were allowed a period of 14 days to acclimatize. Thereafter, Single dose of doxorubicin (10m/kg b.wt. i.p.) was used to induce testicular oxidative stress on DOX group as well as DOX+Zn group. DOX group was left untreated, while DOX+Zn were treated with Zn (10mg/kg b.wt. p.o.) daily for 14days after induction of testicular oxidative stress. Doxorubicin-induced testicular oxidative stress model was adopted from Saalu et al.,[17] while Zn dosage was adopted from Maremanda et al.[18]

Redox status was evaluated by measuring testicular GPx, CAT, SOD, MDA as described by Nwosu et al.,[11] and TAC as described by Gökçe et al.[19] Data obtained was statistically analyzed using GraphPad Prsim (8); Results were compared with control and Zn-only group as well as between DOX group and DOX+Zn group. Statistical significance was considered at $P<0.05$.

Results

Zinc supplement activities on MDA levels of animal model of doxorubicin-induced testicular oxidative stress

Zn supplement significantly decreased MDA levels of doxorubicin-induced testicular oxidative stress on comparison between DOX and DOX+Zn ($P<0.05$) (Figure 1); which suggests an improvement of redox status as MDA a known oxidant was reduced.[1]

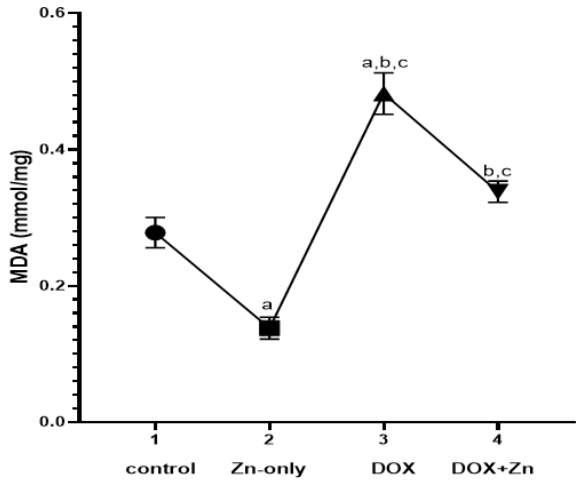

Figure 1 MDA (mmol/mg) levels in all experimental groups (n=5); a = significance when compared to group 1 (control), b = significance when compared to group 2 (Zn-only), c = significance on comparison between group 3 (DOX) and group 4 (DOX+Zn).

Zinc supplement activities on GPx, CAT, SOD and TAC of animal model of doxorubicin-induced testicular oxidative stress

Zn supplement significantly enhanced GPx, CAT, SOD and TAC of doxorubicin-induced testicular oxidative stress on comparison between DOX and DOX+Zn ($P<0.05$) (Table 1) suggesting an improvement in the redox status via increased antioxidants.

Table 1 GPx, CAT, SOD and TAC in all experimental groups (n=5)

Groups	GPx (µ/mg)	CAT (µ/mg)	SOD (µ/mg)	TAC (mmol/g protein)
1. Control	22.08±1.16	21.11±1.40	30.11±1.58	3.03±0.14
2. Zn-only	47.51±3.23 a,	46.04±2.60 a,	67.11±9.54 a	4.61±0.18 a,
3. DOX	13.45±1.33 b, c	13.33±1.18 b, c	18.50±2.62 b, c	0.53±0.12 a, b, c
4. DOX+Zn	29.64±3.32 b, c	29.29±3.13 b, c	43.42±4.06 b, c	1.72±0.14 a, b, c

Values are expressed as Mean ± Standard Error of Mean (SEM); a = significance when compared to group 1 (control), b = significance when compared to group 2 (Zn-only), c = significance on comparison between group 3 (DOX) and group 4 (DOX+Zn).

Discussion

Reproductive toxicity is mediated by oxidative stress via alteration of redox status.[2,20] In this study it was observed that doxorubicin (drug used for chemotherapy) induced oxidative stress on testicular tissue by increasing lipid peroxidation (MDA) and inhibiting glutathione peroxidase (GPx), catalase (CAT), superoxide dismutase (SOD) and total antioxidant capacity (TAC) suggesting an induction of reproductive toxicity. Zinc supplements reported to have beneficial input on the reproductive system[14–16] was able to reverse the testicular oxidative stress mediated by doxorubicin by decreasing MDA and increasing GPx, CAT, SOD and TAC of the testicular tissue suggesting that Zinc supplement was able to improve redox status of the testicular tissue; this is because MDA is a known byproduct formed when polyunsaturated fatty acids undergo peroxidation in cells. Elevated levels of free radicals lead to an excess of MDA production. Consequently, MDA serves as a well-known indicator of oxidative stress in the body.[5] Hence, reduced MDA mediated by Zinc supplement suggests beneficial inputs on testicular oxidative damage. Antioxidants are substances that protect materials within living cells from oxidation, including proteins, lipids, carbohydrates, and DNA. They form the antioxidant defense system, preventing or delaying the damage caused by free oxygen radicals on specific tissues.[3] GPx is an essential antioxidant enzyme found inside cells. It works by enzymatically converting hydrogen peroxide into water, thereby preventing its damaging effects on the cells[3,11] and this study suggests that zinc supplement was able to increase GPx when compared to the decreased impact caused by doxorubicin. CAT is an enzyme present in living organisms that catalyzes the breakdown of harmful hydrogen peroxide into water and oxygen. By performing this detoxification process, catalase helps safeguard cells from oxidative damage caused by hydrogen peroxide, a reactive oxygen species (ROS) generated during biochemical reactions.[1] Zinc supplement improved CAT level which made it beneficial for doxorubicin-induced testicular oxidative stress. SOD is an enzyme found in living organisms which convert superoxide radicals into less harmful substances like hydrogen peroxide and molecular oxygen through an enzymatic reaction. By doing so, SOD plays a critical role in the antioxidant defense system, safeguarding cells from oxidative damage caused by superoxide radicals, which are highly reactive oxygen species generated during cellular metabolism and exposure to environmental stressors. This helps maintain cellular health and protects against oxidative stress.[1,5] This study result showed improved SOD level mediated by zinc supplement in the experimental doxorubicin-induced testicular oxidative stress which accounts for the observed ameliorative impact. TAC is a measure of the collective ability of a biological sample or system to counteract the harmful impact of reactive oxygen species (ROS) and free radicals. It reflects the overall antioxidant activity present in the sample, indicating its capacity to protect against oxidative damage. This study showed that Zn supplement was able to enhance the activity of TAC in doxorubicin-induced testicular oxidative damage.[1] The results of the measured parameters (MDA, GPX, CAT, SOD and TAC) was in correspondence with study that suggests that antioxidants increases in protecting tissue while MDA decreases which reflected in the activities of the Zn supplement suggesting a prospective therapeutics for doxorubicin-induced testicular oxidative stress.

Conclusion

Zinc supplement may be beneficial for side effects of doxorubicin which predisposes to testicular oxidative damage as this study demonstrated that Zn supplement was able to reverse alteration of redox status posed by doxorubicin.

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Conflicts of interests

The authors declare that there are no conflicts of interest.

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