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REVIEW

Antioxidants in experimental ischemia-reperfusion injury of the testis: Where are we heading towards?

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Abstract

Testicular torsion (TT) is a medical emergency that primary affects newborns and young adolescents. It causes testicular injury due to the torsion of the spermatic cord and its components, initially in the venous blood flow and finally in the arterial blood flow. Prompt diagnosis and early surgical management are necessary in managing this urgent situation. The process of the pathophysiological events in ischemia-reperfusion is multifactorial and deals with the perception of the oxidative stress responsible for the consequences of ischemia/reperfusion (I/R) stress following TT. Duration and severity of torsion also play a significant role in the oxidative stress. A detrimental result of the defense system of the testes takes place resulting finally in testicular atrophy and impaired function. Antioxidant factors have been experimentally studied in an effort to front this state. They have been classified as endogenous or exogenous antioxidants. Endogenous antioxidants comprise a structure of enzymic enzymatic and non-enzymic enzymatic particles presented within cytoplasm and numerous other subunits in the cells. Exogenous antioxidants include a variety of natural and pharmaceutical agents that may prevent or ameliorate the harmful effects of I/R injury. In this study we review those factors and their ability to enhance the oxidative status of the testis. A feature insight into where we are heading is attempted.

Key words: Testis; Torsion; Experimental; Ischemia-reperfusion injury; Antioxidants

Core tip: Testicular torsion is an emergency condition, most commonly seen in newborns and adolescents, which can be considered as an ischemia-reperfusion injury. We provide an overview of the molecular pathogenesis of the disease, and the current evidence of antioxidants use in the experimental torsion-detorsion situation. Possible adaptation of the experimental factors in the clinical practice is discussed.

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INTRODUCTION

Testicular torsion (TT) is one of the most serious surgical emergencies, deriving from the twisting of the spermatic cord and its contents, and causing decreased blood flow to the affected testis and finally testicular atrophy[1,2]. The testis is exclusively prone to ischemic insults due to anatomical reasons (terminal arteries without anastomoses) and the inflexible properties of the tunica albuginea which restricts satisfactory expansion of the testis[3]. Although, TT can be detected at any age, it is usually seen during perinatal period and puberty[4-6]. Two main types of TT exist: Extravaginal and intravaginal[3]. Extravaginal TT is usually seen during perinatal period, and is ought to the absence of normal fixation between testicular coverings and tunica vaginalis resulting in abnormal motility of the testis within scrotum. Intravaginal TT is most commonly seen in adolescent boys and results from a long mesorchium which allows a greater mobility of the testis within the tunica albuginea[4].

TT has an annual incidence of about 3.8 per 100000 males less than 18 years[7], and in cases of bilateral torsion, there is evidence that may be inherited[8]. If left untreated within 4 to 6 h, loss of spermatogenic cells will occur[9] leading to harmful results such as infertility and subfertility[10]. The degree of twisting of the spermatic cord may also play an important role. In animal studies, 720° torsion caused significant reduction blood flow when compared with a twisted spermatic cord of 360° or less[11].

There are two kinds of injuries responsible for testicular necrosis after TT: The first is related to ischemia (I) injury during torsion, and the second to reperfusion (R) injury during detorsion[12]. I/R injury can cause cell damage from generation of reactive oxygen species (ROS), proinflammatory cytokines and adhesion molecules, lipid peroxidation, apoptosis, anoxia and alteration in microvascular blood flow, which finally lead to testicular atrophy[13]. Although the testicular environment is characterized by low oxygen tensions, testes are susceptible to oxidative stress due to the plethora of highly unsaturated fatty acids and the presence of ROS[14].

Antioxidants represent the first line defense of the organism in order to prevent the harmful consequences of I/R injury occurring in the environment of the testicular cell[15]. Antioxidants may be classified as endogenous and exogenous[15]. Endogenous antioxidants include a variety of enzymatic molecules that are presented within the cytoplasm. Common existing endogenous antioxidant enzymes include superoxide dismutase (SOD), catalase, and peroxidases[15,16]. Exogenous antioxidants include natural derived components such herb productions[17-25], vitamins[26-31], selenium[32], hormones[33-36], hormones receptors[37,38], vascular agents[39-41], phosphodiesterase inhibitors[42,43], anesthetic and non-steroid anti-inflammatory drugs[44-47], mucolytic agents[48], and hyperbaric oxygen[49]. All have been used in an effort to prevent the consequences of the oxidative stress in I/R injury.

The aim of this review is to present the pathophysiological changes that take place during I/R injury and to summarize the current literature regarding the role of antioxidants in the prevention of experimental I/R injury. Possible translation from the experimental laboratory studies to clinical practice is discussed.

SEARCH

Literature search

We conducted a search focusing on TT and experimental I/R injury in PubMed publishing over the last five years, between 2012 and 2016. The following search terms were used: "testicular torsion", "experimental ischemia-reperfusion injury", "protective agents". A total number of 22 full papers were extracted.

Pathophysiologic alterations during I/R injury

The pathophysiological alterations during I/R injury are multifactorial and difficult to understand. A cascade of events take place during the course of ischemia and further perturbations of biomolecules in cells are seeing during the blood re-establishment after reperfusion. The basic mechanisms of I/R are described below.

Ischemia injury: The role of Ca^{2+}: During ischemia a decrease of cell pH is observed due to accumulation of lactic acid, protons and NAD^+. To balance these alterations, the cell forces out H^+ *via* the Na^+/H^+ exchanger system[50]. Thereafter, Na^+ ions are swapped for Ca^{2+} by the plasmalemmal Na^+/Ca^{2+} exchanger, which results in increase of Ca^{2+}, exacerbated furthermore during reperfusion. These huge alterations in Ca^{2+} stimulate an array of systems, which finally contribute to cell death[50-52]. For instance, Ca^{2+} entry into the mitochondria *via* a mitochondrial protein further increases the lethal concentration of Ca^{2+}[53-55]. In addition, the Ca^{2+} cytosolic elevation during I/R can trigger the Ca^{2+}/calmodulin-dependent protein kinases, which further added to cell death and tissue dysfunction[53]. Additionally, the activation of calpains, a family of cysteine proteases by Ca^{2+} elevation, further degrades a group of intracellular proteins, including cytoskeletal, endoplasmic reticulum, and mitochondrial proteins[56]. Furthermore, Ca^{2+} forces the creation of calcium pyrophosphate structures and uric acid, a pair that binds to a protein complex called inflammasomes which in turn increase the production

of cytokines IL-1β, and TNF, which lead to a cytokine cyclone that irritate further the I/R injury[53].

Reperfusion injury: Studies have shown that during reperfusion, the returned oxygenated blood restores the ATP production but also results in production of ROS, which in turn may modify every biomolecule found in cells, producing further cell dysfunction (oxygen paradox)[57,58]. Redox molecules derived from nitric oxide (NO), the so called reactive nitrogen species (RNS) interact with ROS and lead to the production of reactive nitric oxide species (RNOS), such as peroxynitrite, responsible for harmful damage of macromolecules, initiation of death of endothelial and parenchymal cells, stimulation and release of pro-inflammatory mediators by various cell groups, and induction of adhesion molecules supporting leukocyte/lymphocyte-endothelial cells interactions, and reduction of protective NO[57-59].

Oxidative stress: The classic theory of oxidative stress was that it arises from an imbalance between pro-oxidants *vs* antioxidants intracellular compounds[39]. Currently, it is believed that oxidative stress is involved in three mechanisms in I/R injury: (1) indirect, through non-radical oxidants such as hydrogen peroxide (H_2O_2); (2) modulator, *via* molecular bond, oxidative or nitrosative modification of principle regulatory proteins; and (3) direct damage by oxidant radicals of DNA, proteins, lipids and carbohydrates[53,60].

Superoxide anion radical (O_2^-) is the first product of ROS during I/R injury, and subsequently all the other reactive species are derived from interactions or dismutation with other reactive species[39]. This is supported by experimental studies showing that I/R were considerably attenuated by treatment with SOD or SOD analogues[53,61,62]. O_2^- oxidizes various biomolecules and inactivates enzymes such as NADH, creatine kinase, and calcineurin[58]. Sources of O_2^- are xanthine oxidoreductase, NADPH oxidase, cytochrome P450, and uncoupled nitric oxide species (NOS)[53].

Nitric oxide stress: Nitric oxide (NO^-) is elicited during oxidation of arginine to citrulline, through nitrite or nitrate through the action of xanthine oxidoreductase, or by mitochondrial cytochrome c[63,64]. NO^- plays a protective role in the vascular system by producing dilation of blood vessels, modulating platelets aggregation and adhesions, and inhibiting leukocyte-endothelial adhesive interactions and angiogenesis[53]. Interactions of NO with O_2 or O_2^- forming N_2O_3 or peroxynitrite, are associated with overproduction of NO and O_2^- resulting in pathophysiological nitrosative and oxidative stress[53].

In summary, the oxidative/nitric oxide stress may have negative impact on the cell function in I/R stress through three ways: (1) destruction of cellular macromolecules such as membrane lipids, proteins, and DNA; (2) production of possibly toxic peroxynitrite and other RNOS; and (3) side effects on distinct cellular systems and functions[53].

Current antioxidant treatment of I/R injury in experimental TT

Comparable to other tissue-cells which live under aerobic conditions, spermatozoa produce ROS which is a physiological process activity[65]. Moreover, spermatozoa contain an array of ROS scavengers such as SOD, catalase, and substances such as ascorbic acid, taurine, hypotaurine, albumin, and carnitine to balance any ROS high concentration. However, any increased concentration of toxic metabolic products over the ROS scavenging ability, may cause loss of sperm motility and viability[66-68].

A substantial number of experimental studies by using different agents have studied experimental TT focusing on the effect of I/R injury on ipsilateral and contralateral testis, on treatment and prevention of this injury[53]. However, conflicting results are raised due to different animal species, such as rats or pigs, model of I/R injury, age, and technique that has been performed to evaluate the I/R damage[69]. Furthermore, several experimental studies proposed that the contralateral testis is not affected by unilateral torsion[70-72]. Nevertheless, there is evidence that both testes are affected, and contralateral testis is not disturbed by initial removal of the torsed testis and pretreatment with antioxidants[73-75].

There are two therapeutic opportunities to counteract oxidative stress. In the first, the superoxide radical and hydrogen peroxide are eliminated by using specific enzymes such as SOD, catalase, and glutathione peroxidase (GPX) either by administration of these enzymes or by increasing them *in vivo* actions. In the second, radical production is prevented by antioxidant scavenging systems[66].

Some authors showed that apigenin may prevent lipid peroxidation and protect the antioxidant system[76,77]. We also found a decrease in immunoreactivity of TNF and IL-10, suggesting a synergistic action of apigenin with endogenous IL-10. This antioxidant effect may be due to the H^+ donation of the OH^- aromatic group[6]. Among others, we demonstrated[42] that intraperitoneal injection of erythropoietin and sildenafil protects against I/R injury.

Amlodipine is a calcium channel blocker with antioxidants properties, effectively decreasing experimental vascular ischemia-induced damage in the liver and other tissues[78]. Dogan *et al*[79] examined the effect of amlodipine in a rat model of TT injury. They found a significant decrease of TNF and transforming growth factor-beta in the treatment group, decreases in free radicals and increases in antioxidants such as SOD and GSH.

Goji berry (GB) is a traditional Chinese plant product, from the Solanaceae family with antioxidant effects. In experimental studies, GB has been shown to reduce blood sugar and lipid levels, and exhibits male fertility-enhancing effects, immunomodulating,

antitumor, and anti-fatigue properties. GB is composed from six monosaccharides and influences its effects *via* ion exchange chromatography. In a rat experimental study of TT, administration of GB reduced I/R injury by the antioxidant effects of GB[9].

Mannitol is usually administered before partial nephrectomy to reduce renal damage due to intravascular volume expansion and its free-radical scavenging[80]. Kurt *et al*[81] in a rat model of TT, demonstrated that the treatment with mannitol group had less seminiferous tubules disruptions when compared to the TT group without mannitol treatment.

Hesperidin, is another antioxidant compound belonging to flavones with significant antioxidant effects in many tissues[82,83]. Hesperidin was given intraperitoneally by Celik *et al*[12] in an experimental group of rats underwent TT and the sample was compared to control group. They found a reduced effect on histological examinations of the hesperidin group when compared to control, while MDA levels were increased, and SOD, catalase and GSH levels were decreased as compared to the control group, concluding that hesperidin has positive results in cases of TT.

Polyphenolic catechins are components of green tea and comprise (-)- epicatechin, (-)- epigallocatechin, (-)- epicatechin gallate, and (-)- epigallocatechin gallate (EGCG)[84]. Sugiyama *et al*[85] studied an experimental rat model by producing 4 hours' ischemia and giving orally a single dose of (-)- EGCG 1 h before reperfusion. Histologic examination 4 wk after reperfusion found that EGCG protected against testicular damage from I/R injury and inhibited a further decrease in the activity of SOD.

Dexketoprofen, is a racemic mixture from the arylpropionic acid family of NSAIDS. Yildirim *et al*[86] studied the intraperitoneal effect of dexketoprofen in a rat model of I/R injury. Malondialdehyde (MDA) levels were investigated in tissue and serum of torsioned testicles in the dexketoprofen group and control group. They found a statistically lower serum MDA levels in the dexketoprofen group compared to control group, and decreased, but not statistically significant, pathological changes in the spermatogenic cells of the control group.

Tyrphostin AG 556 is a tyrosine kinase inhibitor and belongs to the tyrphostin group which has been assessed in animal models of spinal cord and coronary I/R injury[87,88]. Karaguzel *et al*[89] investigated the effect of Tyrphostin AG 556 by giving it intraperitoneally and measured the following biochemical parameters: MDA, ischemia modified albumin, signal peptide-CUB (complement C1r/C1s, Uegf, and Bmp1), epidermal growth factor like domain-containing protein1, oxidative stress index, total oxidant status, and total antioxidant status. They concluded that tyrphostin AG 556 has a protective effect on I/R injury

The protective effect of udenafil citrate, piracetam and dexmedetomidine in different doses was evaluated by Tuglu *et al*[90] and found that all these agents have antioxidant effects on I/R injury.

Grape seed proanthocyanidin extract has been reported to display better antioxidant activity than other antioxidants such as vitamin C, vitamin E, and gallic acid[91]. Bayatli *et al*[92] examined the protective effect of grape seed proanthocyanidin after TT performed for 2 h and administered it daily for a week prior to torsion/detorsion. They reported that grape seed proanthocyanidine prohibited the rise of MDA, apoptosis and endothelial nitric oxide synthase expression and enhanced testicular morphology.

Carnosine, is a dipeptide found in high amounts in mammalian tissues[93]. Abbasoğlu *et al*[94] demonstrated that carnosine treatment has a protective effect on prooxidant and antioxidant status in rat testes with I/R injury.

Ozone has been studied as a potential therapeutic agent for the treatment of various physio-pathologic conditions expressing high levels of ROS[95,96]. Ekici *et al*[97] assessed the potential effects of ozone in testicular function and morphology in a rat experimental study, in a mixture of ozone/oxygen and compared the results with those of melatonin. They found similar results in the amelioration of I/R injury between melatonin and ozone, but in different pathways.

Ethyl pyruvate, a ROS scavenger, has been found to ameliorate in different conditions such as sepsis, acute pancreatitis, burn, radiation injury and hemorrhagic shock[98,99]. Turkmen *et al*[100] reported that ethyl pyruvate has a positive effect on torsion-detorsion associated I/R injury in an experimental rat model.

Carvedilol is a third generation vasodilator agent which has been used in the treatment of hypertension, congestive heart failure and ischemic heart disease[101,102]. Parlaktas *et al*[103] investigated the antioxidant effects of carvedilol against I/R injury, and found a decrease in MDA and protein carbonyl and an increase in the level of antioxidant enzymes SOD, and GPX, but not histopathological changes against the control group. They concluded, that carvedilol may have a potential therapeutic value and improve fertility in the clinical practice in patients with TT.

Jiang *et al*[104] investigated the effect of intraperitoneally injected hydrogen rich saline solution on the protection against testicular damage induced by I/R injury in rats. They found a significant decrease of MDA and a significant improvement of SOD activity in the group of rats which received hydrogen rich saline solution. Therefore, hydrogen rich saline solution may have a protective and therapeutic action against testicular damage.

Inhaled hydrogen gas has been shown to produce a therapeutic activity in a middle cerebral artery occlusion in a rat model and reduce infarct volumes of brain, liver, and myocardium[105,106]. Lee *et al*[107] studied the possible therapeutic properties of inhaled 2% hydrogen in pubertal rat model underwent testicular I/R injury. The results of histopathological and biochemical studies suggested that inhalation of hydrogen gas has anti-apoptotic and anti-oxidant properties in cases of TT.

Alpha-lipoic acid is an eight-carbon endogenous cofactor which works against oxygen radicals[108]. It is established that α-lipoic acid catches hydroxyl and nitric oxide radicals, peroxynitrite anions and hydrogen peroxide. Moreover, α-lipoic acid may act indirectly by enhancing the level of other natural antioxidants such as glutathione, ascorbic acid and tocopherol[31,109-111]. Ozbal *et al*[108] investigated the role of α-lipoic acid in testicular I/R injury in rats and concluded that it is a potential beneficial agent in preserving testicular function.

Genistein is an isoflavone extracted by soy[112] which displays anti-oxidant and anti-inflammatory properties[113]. Furthermore, genistein promotes steroidogenesis by restriction progesterone synthesis and decreases secretion of cortisol and corticosterone in mature female pigs[114] In addition, it has a protective role against gamma irradiation-induced testicular dysfunction[115]. Recently, Al-Maghrebi *et al*[116] reported that genistein protects the extracellular matrix of the testis which is responsible for the structural integrity of the testicular components, and prevents spermatogenesis's suppression, mitigating oxidative stress and apoptosis in experimental testicular I/R injury.

Nuclear factor kappa B plays a crucial role in immune response, cellular proliferation, inflammatory, and apoptosis[117]. Pyrrolidine dithiocarbamate (PDTC) is a stable low-molecular thiol compound which acts by neutralizing ROS[118]. Kemahli *et al*[118] studied the antioxidant effect of PDTC in a TT model and found that administration of PDTC exaggerates the antioxidant system by lowering MDA levels, increasing SOD activity and improving Johnson scores of biopsy specimen.

Urocortin, is a 40-amino acid peptide found in different organs, such as digestive tract, cardiovascular and reproductive system[119]. For instance, urocortin has been shown that protect cardiovascular system against I/R injury[120]. Sumii *et al*[121] investigated the role of urocortin in testicular apoptosis in an experimetnal I/R rat model and found a cytoprotective role in germ cells through the activation of anti-apoptotic proteins.

Melatonin is an endogenous compound secreted by the pineal gland and influences reproduction *via* its activity on the hypothalamus[122]. Kurcer *et al*[123] reported that melatonin protects testicular tissue against oxidation and alleviates histopathologic changes after experimental testicular I/R injury. Metformin belongs to the biguanide family and has the capacity to reduce ROS[124]. Asghari *et al*[125] investigated a combined use of melatonin and metformin in a rat model and found that may protect the testes from I/R injury by restoring SOD activity, and MDA and myeloperoxidase levels.

Very recently Erol *et al*[126] investigated the effect of a antioxidant factors combination, constituting either by l-carnitine, fructose, citric acid, ascorbic acid, cyanocobalamin, selenium, coenzyme Q10, zinc and folic acid or fructose, cellulose microcrystalline, pygeum shell, L-arginine, L-carnitine, zinc, vitamin E, folic acid, vitamin B6, sodium selenite, and hydroxypropyl methyl cellulose. They found that combined antioxidants were more effective than one protective antioxidant by reducing apoptosis and preventing I/R injury.

Antioxidants and I/R injury in clinical practice

The large body of experimental studies demonstrated undoubtedly that oxidative stress is a dominant factor in the creation of testis impairment after I/R injury. Furthermore, all these antioxidative compounds have been sought to be clearly capable to protect testicular function from oxidative stress. However the relationship between experimental results and clinical practice has not come together until now. A feature mandatory pursuit is to advance understanding of the basic mechanism of oxidative stress in the male reproductive tract and to develop optimizing antioxidant factors in order to treat the pathological consequences from imbalance in the oxidation state of testicular tissue. These mandatory demands are beyond laboratory ways that outline the present approach to counterbalance the deleterious effects of TT.

CONCLUSION

Currently, a large number of studies investigate the role of I/R injury in experimental animal models and many antioxidants and free radical scavengers have been studied to indicate their possible application in human beings. However, the molecular mechanism by which these agents may control the harmful effect of TT has to be clarified. Moreover, experimentally checked drugs or compounds still anticipate clinical utilization. Additional experimental and future clinical studies have to be performed to further assess the effects on antioxidant therapy.

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