Oxidative stress is an imbalance between the level of ROS and antioxidants. Sperm membranes are rich in polyunsaturated fatty acids and are very sensitive to increased free radicals. Increasing the level of ROS can lead to an increase in lipid peroxidation in sperm membrane, decrease in their flexibility, and ultimately a decrease in sperm motility. Also, oxidative stress may impair sperm axonemal and mitochondrial function, as well as DNA integrity, RNA and protein synthesis. Several studies have shown that antioxidants are beneficial to human health and are used to prevent cancer and coronary artery disease. Based on the present review, there are more documents in protective effects of antioxidants on sperm cells. Studies showed adding in vitro antioxidants to sperm samples can increase sperm parameters such as sperm motility, morphology and decrease sperm membrane lipid peroxidation and sperm DNA damage. Also in vivo or oral antioxidants supplementation has protective effects on sperm from ROS negative effects. Since the causes of infertility are various, the lack of antioxidants action in reducing the sperm DNA damage, the level of antioxidant activity depends on the type, dose and duration of intake, so more studies are needed to determine the appropriate antioxidant type, the dosage and timing of administration in vivo and in vitro.
damage (6, 7).
Exposure to pesticides and metals such as lead, cadmium and phthalates is associated with increased levels of oxidative stress and sperm DNA degradation (8-10). There are also studies showing an association between varicocele and high levels of oxidative stress and sperm DNA damage (11, 12).

Literature Review
Article collection for the present narrative review searched by male reproductive oxidative stress, antioxidant, sperm, and sperm DNA damage key words in the PubMed database. We only focused on the clinical trials related to the male reproductive oxidative stress and the effects of antioxidants on the male reproductive system. All studies including in vitro and in vivo included in this present study.

ROS is a term defined as all oxygen contains with high reactive molecules. In the biology this species named free radicals. Hydroxyl radical, anion superoxide radical, hydrogen peroxide, oxygen radical, nitric oxide (NO), hypochlorite and various lipid peroxides are the main types of ROS. Free radicals and ROS in normal levels have progressive special effects in human biological activities. On the other hand they were not harmful in normal level and when the level of ROS increase and system balance disrupted, they are harmful. ROS are the main intracellular messenger and the regulation of gene expression. Consequently, ROS in normal level is an important factor for progress cell function (13).

Interestingly ROS in high level are dangerous for human body, because they can generate harmful effects on all parts including cell membrane, cytoplasmic organelles, enzymes and proteins, genetic substance and nucleic acids (11, 14).

Pathological role of oxidative stress on sperm
Oxidative stress is an imbalance between the level of ROS and antioxidants. Sperm membranes are rich in polyunsaturated fatty acids and are very sensitive to increased free radicals. Increasing the level of ROS can lead to an increase in lipid peroxidation in sperm membrane, decrease in their flexibility, and ultimately a decrease in sperm motility. Also, oxidative stress may impair sperm axonemal and mitochondrial function, as well as DNA integrity, RNA and protein synthesis (9, 15).

It can evoke single stranded (ss), double stranded (ds) DNA breaks and small chromosomal deletions (15). Recent studies have reported high levels of free radicals in 30 to 80 percent of infertile men (16).
Sperm motility is an important factor to move through the female reproductive tract and successful fertilization. A negative correlation was shown between increase the level of ROS and reduce of sperm concentration, morphology and motility (17, 18). The residual cytoplasm in immature spermatozoa contains high level of glucose-6-phosphate dehydrogenase (G-6-PDH), which catalyzes NADPH generation and NADPH is involved in the production of ROS (19).

Antioxidants
Oxidation is a phenomenon that plays a role in the production of free radicals, and antioxidants are compounds that inhibit the process of oxidation. Antioxidants can be endogenous or exogenous. Endogenous antioxidants play an important role in maintaining proper cellular function, but when oxidative stress occurs, they are usually insufficient and require exogenous antioxidants. Antioxidants are exogenous or endogenous. They can also be enzymatic or non-enzymatic. Glutathione peroxidase, catalase and superoxide dismutate are the most important enzymatic antioxidants. Vitamin E, C, melatonin, carotenoids and natural flavonoids are also non-enzymatic antioxidants (20). Several studies have shown that antioxidants are beneficial to human health and are used to prevent cancer and coronary artery disease (21-23). In addition, antioxidants are used in food preservatives, cosmetics and anti-corrosion materials for metals (24).

Seminal fluid antioxidants
One of the main sources of antioxidant in male reproductive system is seminal fluid. The seminal fluid is containing many different enzymatic and non-enzymatic antioxidants. Some antioxidants in the seminal fluid are vitamins E and C, superoxide dismutate, glutathione, lycopene and thioredoxin (25). These antioxidants can protect sperm cells from ROS activities (26, 27). There were some documents that showed each disruption in seminal fluid antioxidant level can create dysfunction in sperm cells, sperm DNA damages, decrease quality of sperm and finally male infertility happened (28, 29). The high level of oxidative stress in seminal fluid is harmful because can create peroxidation in the sperm plasma membrane and disturb DNA integrity (30). There is usually a balance between the amount of ROS and the oxidative stress elimination system. One of the natural ways to neutralize the effect of oxidative stress is to increase the stress-removal system in the seminal plasma (31). Researchers have tested different antioxidants in different compositions with different dosage in several time periods and consequently by this enormous study, with various design and control of individuals, there was not a definite conclusion in this regard. Because
Antioxidants and sperm parameters
Antioxidants can play an important role to protect sperm cells from ROS negative effects. The studies showed vitamin E can increase sperm morphology and motility (33, 34). Another antioxidants such as vitamin C and Q-10 coenzyme are high protective factor and prevent spermatozoon motility from oxidative stress (35). Studies reported in patients with defects in sperm parameters, in vitro incubation of sperm in rich antioxidant medium for a day can increase sperm motility in comparison with control group (36, 37).

More studies reported 90 days oral antioxidant supplementation were effective for improvement of sperm parameters including sperm motility and morphology (38, 39). The results of a study of stress-induced albino rats showed that oral administration of moderate (20 mg/kg/day) to high doses (30 mg/kg/day) of vitamin C significantly increased sperm count and motility (40). (Table 1)

Antioxidants and sperm membrane lipid peroxidation
Sperm membrane is containing fatty acids and oxidative stress has negative effects on sperm membrane. Many factors such as high temperature, medications, disease and ageing can elevate sperm membrane lipid peroxidation. (41, 42). In last decay more studies plan to assess several methods to prevent sperm membrane from ROS effects. The results of studies showed in vitro incubation of sperm cells in superoxide dismutase (SOD) or vitamin E is effective for decrease sperm lipid peroxidation (43, 44). (Table 1)

Antioxidants and sperm DNA
Many studies have reported the role of antioxidants in reducing the fragmentation of DNA from oxidative stress. (45, 46). In a double blind randomized controlled clinical trial, 115 infertile men with varicocele participated, and after surgery, they were given 250 mg of vitamin C for three months. The vitamin C treatment group provided better sperm motility and morphology and DNA integrity statistically than their placebo group (47).

Supplementation of selenium – vitamin E on 690 infertile men showed on improve in semen quality and pregnancy rate (48).

In a study, 20 infertile men diagnosed with terato-asthenozoospermia received a pill containing of creatine, vitamin E, C, B9, B12, quinidine Q10 and selenium for three months daily. Their results showed improve in sperm parameters and DNA integrity. Also DNA fragmentation was decreased in study group. So they suggested prescribing these antioxidants before assisted reproductive techniques (ART) (49).

Greco et al. found that daily administration of vitamin E and C for two months in infertile men with high levels of DNA Fragmentation (≥ 15%) reduced the rate of DNA Fragmentation in 76% of patients. They also showed that these antioxidants improved intra-cytoplasmic sperm injection (ICSI) outcome in these patients (50). Another study revealed that oral administration of zinc sulfate to infertile men, significantly improves sperm DNA integrity in this patients (51).

Infertile men with high levels of oxidative stress, ROS, and sperm DNA damage received capsules containing of vitamin E, C, zinc, selenium and folate daily for three months. The researchers found that sperm DNA damage, protein deficiency, ROS and sperm apoptosis were reduced. But they did not see any clear statistical changes in the improvement of sperm parameters (52).

Gual - Frau et al. administered a combination of several supplements including selenium, coenzyme Q10, L-carnitine, vitamins C, E, B9, Zinc B12, to twenty patients with grade 1 varicocele for three months orally. These patients usually show a high level of sperm DNA damage. After three months, they showed a 22.1 percent reduction in sperm DNA damage (53).

In an in vitro study, sperm samples taken from twelve infertile men were subjected to oxidative stress with hydrogen peroxide. In the experimental group, 2 hours before induction of stress, the samples were incubated with 5 micromoles of lycopene. The results showed that the in the experimental group, lycopene was able to protect the patient’s sperm from DNA damage, but did not improve sperm motility (54).

Antioxidants are able to protect sperm DNA from free radicals endogenous (55-57) and exogenous (58, 59).

Sperm washing raises the level of ROS, which in turn can have a negative effect on sperm DNA (60). Also, sperm freezing and thawing may result in over generation of ROS which lead to DNA fragmentation. E. Tvrda et al. found that lycopene can decrease the oxidative sperm DNA damage in treated group compared to control group (61). In another study, supplementation with methionine, inositol and carnitine before the cryopreservation protected the sperm DNA integrity against the cryodamage (62). (Table 1)

Trolox is a derivative of vitamin E with potent of antioxidant property. Supplementation of Trolox for two weeks significantly improved the sperm motility in post – thawed human spermatozoa (63).
Table 1. Summary of studies about antioxidants and sperm cell

<table>
<thead>
<tr>
<th>Reference</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dryuha (2016) (25)</td>
<td>Seminal fluid is containing many different enzymatic and non-enzymatic antioxidants.</td>
</tr>
<tr>
<td>Atig (2017) (26)</td>
<td>Antioxidants can protect sperm cells from ROS activities.</td>
</tr>
<tr>
<td>Esmizade (2017) (31)</td>
<td>Seminal plasma can remove effect of oxidative stress by the stress-removal system.</td>
</tr>
<tr>
<td>Gvozdjakova (2015) (35)</td>
<td>Vitamin C and Q-10 coenzyme can prevent sperm motility from oxidative stress.</td>
</tr>
<tr>
<td>Biagi (2019) (37)</td>
<td>In vitro incubation of sperm in rich antioxidant medium can increase sperm motility.</td>
</tr>
<tr>
<td>Sabeti (2017) (38)</td>
<td>Oral antioxidant supplementation were effective for improvement of sperm parameters.</td>
</tr>
<tr>
<td>Vijayprasad (2014) (40)</td>
<td>Vitamin C significantly increased sperm count and motility.</td>
</tr>
<tr>
<td>Kobayashi (1991) (43)</td>
<td>Incubation of sperm cells in superoxide dismutase (SOD) can decrease sperm lipid peroxidation.</td>
</tr>
<tr>
<td>Rolf (1999) (44)</td>
<td>In vitro incubation of sperm cells in vitamin E is effective for decrease sperm lipid peroxidation.</td>
</tr>
<tr>
<td>Cyrus (2015) (47)</td>
<td>Vitamin C treatment has positive effect on sperm DNA integrity.</td>
</tr>
<tr>
<td>Abad (2013) (49)</td>
<td>Creatinine, vitamin E, C, B9, B12, quindidine Q10 and selenium for three months can improve in sperm parameters and DNA integrity.</td>
</tr>
<tr>
<td>Raigani (2014) (51)</td>
<td>Oral administration of zinc sulfate to infertile men, significantly improves sperm DNA integrity.</td>
</tr>
<tr>
<td>Tunc (2009) (52)</td>
<td>Vitamin E, C, zinc, selenium and folicate can decrease sperm DNA fragmentation.</td>
</tr>
<tr>
<td>Gual-Frau (2015) (53)</td>
<td>Selenium, coenzyme Q10, L-carnitine, vitamins C, E, B9, zinc and B12 can decrease high level of DNA damage.</td>
</tr>
</tbody>
</table>

Overall, the evidence suggests that the use of antioxidants in cryoprotectants may protect the spermatozoa from cryodamage but it is important to know that the method of freezing and the type of cryoprotectants are important (64).

In addition, oxidative stress is one of the causes of male infertility, and these compounds may only be useful in cases where the cause of DNA damage is oxidative stress (65, 66).

Conclusion

Based on the present review, there are more documents in protective effects of antioxidants on sperm cells. Studies showed adding in vitro antioxidants to sperm samples can increase sperm parameters such as sperm motility, morphology and decrease sperm membrane lipid peroxidation and sperm DNA damage. Also in vivo or oral antioxidants supplementation has protective effects on sperm from ROS negative effects. Since the causes of infertility are various, the lack of antioxidants action in reducing the sperm DNA damage, the level of antioxidant activity depends on the type, dose and duration of intake, so more studies are needed to determine the appropriate antioxidant type, the dosage and timing of administration in vivo and in vitro.

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Conflict of Interest

The authors declare no conflict of interest.

References

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