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ORIGINAL ARTICLE

Role of reactive oxygen species in male infertility: An updated review of literature

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KEYWORDS

Reactive oxygen species;
Male infertility;
Free radicals;
Antioxidants

ABBREVIATIONS

4-HNE, 4 hydroxynonenal;
ATP, adenosine triphosphate;

Abstract ***Objectives:*** To review the literature and provide an updated summary on the role of reactive oxygen species (ROS) in male infertility.

Methods: A review of PubMed, Cochrane review, and Web of Science databases for full-text English-language articles published between 1943 and 2017 was performed, focusing on the aetiology of ROS, physiological role of ROS on spermatic function, pathological role of ROS in infertility, evaluation of ROS, and role of antioxidants in oxidative stress.

Results: ROS play a role in spermatic function and fertilisation. The literature describes both a physiological and a pathological role of ROS in fertility. A delicate balance between ROS necessary for physiological activity and antioxidants to protect from cellular oxidative injury is essential for fertility.

Conclusion: Although elevated levels of ROS are implicated as a cause of infertility, there is no consensus on selecting patients to test for ROS, which test to perform,

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CAT, catalase;
ESR, electron spin resonance;
G-6-PDH, glucose-6-phosphate dehydrogenase;
GPX, glutathione peroxidase;
MAGI, male accessory gland infections;
MDA, malondialdehyde;
NADH, nicotinamide adenine dinucleotide;
NO, nitric oxide;
SOD, superoxide dismutase;
ROS, reactive oxygen species

or if treatment for ROS can have a positive impact on infertility rates and pregnancy.

Introduction

Infertility affects up to 15% of the population globally [1]. Male infertility is the cause in about 20% of cases but may contribute to 40% of infertile couples [2]. Reactive oxygen species (ROS), as a potential contributor to male infertility, have been reported in the literature since the 1940s [3]. Oxidative stress leading to defective sperm function was demonstrated in early studies illustrating the toxic effect of endogenously generated hydrogen peroxide (H_2O_2) on sperm metabolism and motility [4]. There has been a vast improvement in understanding the effects of ROS on infertility and spermatic function since these early studies. The current literature reports that ROS may be a contributing factor in 30–80% of infertile men [5]. The present article reviews the literature for updates on the aetiology of ROS, the role of ROS on sperm development and function, ROS as part of infertility evaluation, available ROS testing, and the physiological role of antioxidants.

Methods

A search of PubMed, Cochrane review, and Web of Science databases for full-text English-language articles published between 1943 and 2017 was performed. Various combinations of the following search terms were used: ‘spermatozoa’, ‘male infertility’, ‘reactive oxygen species’, ‘oxidative stress’, ‘antioxidants’, ‘antioxidant paradox’, ‘seminal oxidative stress’, ‘peroxidative damage’, ‘apoptosis in sperm’, ‘sperm deoxyribonucleic acid (DNA) fragmentation’, ‘oxidative DNA damage’, and ‘infertility testing’. For the present review, we included original research studies and selected reviews. Emphasis was placed on studies addressing the following topics: aetiology of ROS, physiological role of ROS on spermatic function, pathological role of ROS in infertility, evaluation of ROS, and physiological role of antioxidants in oxidative stress. We excluded commentaries and case reports. In all, 3780 articles were identified. Eighty-three articles were excluded as they were written in a language other than English and 400 were found to be duplicates. A total of 3297 articles were reviewed and 2950 of these were excluded after review of the title or the abstract. Thus, 347 articles were screened, of these 293 were excluded as not applicable (Fig. 1). The reference lists of the 54 selected articles were also reviewed for relevant publications.

Biochemical review

A free radical is a molecule or element with an unpaired electron that is extremely reactive in an attempt to reach an electronically stable state. ROS are free radical derivatives of oxygen (O_2) containing molecules. However, not all ROS are true free radicals. For example, H_2O_2 does not have an unpaired electron but is highly reactive. Some of the clinically important ROS identified in infertility include: peroxyl ($^{\cdot}ROO^{-}$) and hydroxyl ($^{\cdot}OH$) radicals, superoxide ($^{\cdot}O_2^{-}$) anion, and H_2O_2 [6]. Although not technically a ROS, nitrogen compounds such as nitric oxide (NO) and peroxynitrite anion ($ONOO^{-}$) also appear to play a role in oxidation and reduction reactions in infertility.

Oxidative stress describes when a system has an imbalance between oxidation and reduction reactions, leading to generation of excess oxidants or molecules that accept an electron from another reactant [6]. Common molecules that receive the unpaired electron are lipids in membranes and carbohydrates in nucleic acids [7]. This leads to potential cellular and DNA damage when ROS are greater than the antioxidant carrying capacity.

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