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ROLE OF OXIDATIVE STRESS, INFLAMMATION AND INFERTILITY WITH SPECIAL EMPHASIS ON NF kB GENEMUTATION

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ABSTRACT
This in-depth review investigates the intricate interplay between oxidative stress, inflammation and infertility, placing specific emphasis on the crucial involvement of NF-kB gene mutation. The delicate equilibrium within these biological processes significantly influences reproductive health. The investigation covers the impact of oxidative stress on fertility, the inflammatory mechanisms contributing to reproductive dysfunction and the growing importance of NF-kB gene mutation in the realm of infertility. Comprehending the molecular connections between these elements is vital for unraveling the complexities of reproductive disorders. The review explores noteworthy discoveries, potential targets for therapeutic intervention and future directions for research, shedding light on the interwoven role of oxidative stress, inflammation and NF-kB gene mutation in the intricate landscape of infertility.

KEY WORDS: oxidative stress, antioxidants, reactive oxygen species, inflammation, infertility, NF kB gene mutation

INTRODUCTION

The failure to become conceived over one year of regular, unsecured sexual activity is commonly referred to as infertility [1]. Walker and Tobler revealed that this condition can affect both the female and male reproductive systems, which can cause significant stress for both persons in terms of their emotional, physical and mental well-being [2, 3]. According to statistics on the prevalence of infertility worldwide, 48 million couples and 186 million people are impacted by the challenging issue [1].

The body reacts to detrimental stimuli such as toxic substances, pathogens, irritation, or damaged cells through a process known as inflammation [4]. In the findings of Vaisi-Raygani and Asgari, they affirmed that inflammation is a sophisticated defensive response that occurs in reaction to detrimental stimuli. This process has the potential to induce structural irregularities in the body, possibly resulting in conditions such as infertility and pelvic adhesions [5]. Azenabor et al., claimed that certain reproductive tract problems are linked to inflammation and they can impact male as well as female fertility [6].

Banerjee and Bhattacharya's theory posits that oxidative stress ensues when there exists a dysregulation in the equilibrium of pro-oxidants, which includes reactive oxygen species (ROS) and reactive nitrogen species (RNS), in comparison to antioxidants. [7]. Aitken's findings illustrate that this imbalance in males could result in damage to spermatozoa, sperm DNA fragmentation anomalies in sperm and potential occurrences of testicular torsion and varicocele. Conversely, in females, it has the potential to exacerbate conditions such as premature ovarian failure, endometriosis and polycystic ovarian syndrome (PCOS) [7,8].

The initiation of inflammation can be facilitated by oxidative stress through the activation of various signaling pathways. Conversely, the inflammatory process can also serve as the origin of oxidative stress [9]. Research by Anderson et al., and Flohe et al., indicated that hydrogen peroxide and reactive oxygen species (ROS) have the potential to trigger inflammation by activating the transcription factor NF-kB [9, 10].

Initially, NF-κB is identified as a protein binding to a sequence in the enhancer of the immunoglobulin κ light chain in B cells upon exposure to lipopolysaccharide [11]. Jimi et al., evaluated that c-Rel, RelA (p65), RelB p100/p52 (NF-κB2) and p50/p105 (NF-κB1) constitute the five commonly expressed proteins forming the NF-κB family of transcription factors [12]. This thorough analysis presents a concentrated review of the function of NF-kB

gene mutations by synthesizing the body of knowledge regarding the complex relationships among inflammation, oxidative stress and infertility.

METHODS

The principal goal of this study is to examine the intricate relationships among oxidative stress, inflammation and infertility with a specific focus on understanding the implications of NF-kB gene mutations. To facilitate a thorough analysis that is both comprehensive and practically manageable, we randomly selected 100 articles from the subset that aligns with the predefined inclusion criteria. The research will particularly emphasize articles obtained from Google Scholar and PubMed; two well-regarded biomedical databases known for their credibility.

INFERTILITY

Infertility stands out as a highly stressful circumstance for married couples, representing a significant challenge [13]. Uadia and Emokpae characterized it as a profound life-altering issue, causing considerable psychological distress despite its non-fatal nature [14]. Cadieux and Eskandari reported Twenty to thirty percent of instances are caused by a combined male and female component [15]. Sekhon and colleagues said an idiopathic or unexplained infertility diagnosis is made if the outcomes of a conventional infertility evaluation are normal [16]. It is generally acknowledged that oxidative stress plays an integral part in the pathophysiology of infertility, affecting approximately 15% of couples, independent of the cause of the infertility [15, 16].

Oxidative stress

Sekhon et al., argued that a disparity between protective antioxidants and reactive oxygen species (ROS) occurs in the reproductive aging process of both genders, giving rise to oxidative stress [16, 17]. Reactive oxygen species (ROS) are molecules that communicate during physiological processes; Agarwal and Allamaneni proposed that ROS may be involved in specific physiological processes [18,19, 20]. Antioxidants typically function to prevent the synthesis of reactive oxygen species (ROS), remove already-existing free radicals and help repair the structural damage that ROS caused to cells [20].

Oxidative stress and infertility

The state of gametes and their interactions are significantly impacted by oxidative stress. The creation of pro-oxidant molecules during aerobic metabolism and the availability of protective antioxidants are out of balance, as researchers like Sekhon and colleagues have highlighted, and this imbalance results oxidative stress [16]. Jana et al., examined that reactive oxygen species (ROS) have an impact on the microenvironments of spermatozoa, embryos and oocytes. The sperm-mediated oocyte activation, interactions between sperm and oocytes, quality of oocytes, implantation and early embryonic development are directly affected by the microenvironments of peritoneal fluid, follicular fluid and hydrosalpingeal fluid [20, 21]. The studies conducted by Agarwal and Prabakaran emphasized the significant influence of oxidative stress (OS) on pregnancy rates, implantation and impacting early embryo development. In infertility research, a noteworthy focus is on investigating OS as a potential causative factor [13].

Infertility is estimated to impact approximately one in six couples, with male factor infertility constituting 30% of diagnoses in infertile couples, as reported by Makker et al., in 2009 [22]. In Nigeria, 40–50% of infertility cases are attributed to male factor infertility, and its occurrence exhibits regional variations. As per Hull et al., the most commonly recognized cause of male factor infertility is considered to be sperm dysfunction [23]. In roughly 25-40% of semen samples acquired from men grappling with infertility, increased ROS level biomarkers indicate a possible link or involvement of ROS in the documented infertility in these individuals [22]. Reactive oxygen species (ROS) have a physiological charecter in ensuring the proper functioning of sperm, being involved in essential processes such as hyperactivation, acrosome reaction, capacitation and motility. Sekhon et al., have highlighted that the presence of leukocytes and immotile or morphologically defective spermatozoa can result in elevated levels of ROS [16].

Alvarez and Storey explained that sperm exposed to ROS displayed increased levels of polyunsaturated fatty acids in plasma membrane and cytoplasm [24]. According to de Lamirande and Gagnon, this susceptibility is reflected in a reduction in sperm motility, associated with a rapid depletion of intracellular ATP leading to axonemal damage [25]. The vulnerability has a detrimental effect on sperm viability, mid-piece morphological flaws, acrosome response and sperm capacitation. Sperm membrane lipid peroxidation is the main

mechanism responsible for ROS-induced damage to sperm, which results in infertility [26, 27, 28].

As per Sharma and Agarwal, infertility may be influenced by aberrant spermatozoa and leukocytes generating an excessive quanty of ROS in semen [29]. ROS in human spermatozoa is mostly produced by hydrogen peroxide, according to research by Kemal Duru et al. Slightly increased hydrogen peroxide concentrations affect sperm immobility by reducing intracellular ATP levels, which in turn lowers phosphorylation of axonemal proteins, even though they have minimal influence on sperm survival [30, 31]. According to Agarwal and Prabakaran, elevated levels of hydrogen peroxide led to lipid peroxidation, culminating in cellular demise [13].

In a study by Pasqualotto et al., males who were infertile showed far lower antioxidant levels in their seminal plasma compared to those who were fertile [32]. In the initial semen sample [32], a correlation was observed wherein there was an adverse relationship between sperm quality and the quantity of reactive oxygen species (ROS) generated by spermatozoa. Zini et al., discovered that increased reactive oxygen species (ROS) in the seminal plasma of infertile men are probably due to increased ROS formation rather than decreased antioxidant capability [33]. Nearly all human ejaculates include reactive oxygen species (ROS), which can originate from two different sources: aberrant spermatozoa and leukocytes [34]. These ROS can cause oxidative damage and consequent functional decline in some spermatozoa. Consequently, the degree of illness rather than just its existence or absence determines the effect of ROS on male infertility.

Regarding female infertility, as indicated by Mascarenhas et al., approximately 48 million women are expected to be affected, with the highest frequency of the condition observed in Central Europe, North Africa/Middle East, Central Asia, Sub-Saharan Africa and South Asia [35]. The impact of infertility on women worldwide and the differences in societal and cultural stigma around it were studied by Yu and Yap. As per Yu and Yap's study, the frequency of female infertility varies based on the age of women, ranging from 7% to 28% [36]. While the incidence and cause of infertility vary, Duckitt concluded that between 40 and 50 percent of the causes of infertility are related to female factors [37].

Ray et al., outlined those diverse mechanisms, such as lipid damage, protein synthesis inhibition and ATP depletion, contribute to the emergence of pathological effects [38]. The etiopathogenesis of various disorders, including tubal factor infertility, polycystic ovarian

disease, endometriosis, hydatidiform mole and unexplained infertility, is linked to oxidative stress [39]. A growing body of research led by Loeken has explored the role of oxidative stress in pathophysiological field of birth difficulties caused by pre-eclampsia, free radicals [40, 41] and other conditions including abortions [42].

According to Agarwal et al., there are several ways in which oxidative stress causes infertility in women [43]. The antioxidant defense of the follicular fluid may be overwhelmed by excess ROS, directly harming the oocytes. Defective fertilizations can result from damage to the DNA of spermatozoa and oocytes [44]. Even in cases where fertilization is successful, apoptosis caused by oxidative stress can lead to embryo poor placentation, fragmentation, miscarriage, poor implantation and birth defects [43]. According to research by Iborra et al., the endometrium, which typically supports the growth of the embryo, may be hampered by an excess of reactive oxygen species [45]. Oxidative stress, as identified by Agarwal and Allamaneni, is correlated with luteal regression and inadequate hormonal support during the maintenance of a pregnancy [20].

Table 1: Oxidative stress and its impact on infertility

Oxidative stress	**Impact on infertility**	**References**
Effects on sperm	DNA damage, reduced sperm motility, impared sperm function	[46, 47]
Effects on oocyte	Impared oocyte quality,disrupted embryo development	[48,49, 50]
Antioxidant defence mechanism	Essential for counteracting oxidative stress, protecting reproductive cells	[51,52]
Impact on male reproductive system	Reduced semen quality, increased risk of infertility	[53,54,55]
Impact on female reproductive system	Impared ovarian function, decreased egg quality	[56,57,58]

NF kB GENE MUTATION

Oeckinghaus and Ghosh stated that the nuclear factor-κB (NF-κB), oversees a broad spectrum of genes engaged in diverse immune and inflammatory response pathways [59]. Haga et al., concluded that these proteins have the ability to form various homodimers and

heterodimers [60]. When ligands such as lipopolysaccharide (LPS), interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α), receptor activator of NF-κB ligand (RANKL) and lipopolysaccharide (LPS) connect to transmembrane receptors, the NF-κB signaling pathway is activated [61]. These receptors trigger downstream signaling, which includes NF-κB essential modulator and inhibitor of κB (IκB) kinases (IKKs) a, b. [12, 60]. Sun provided documentation stating that a group of inhibitory proteins, which encompasses members of the IκB family and related proteins distinguished by the presence of ankyrin repeats, confines the NF-κB proteins to the cytoplasm [62]. The two main signaling routes that are evaluated by Vallabhapurapu and Karin involved in NF-κB activation are the conventional and noncanonical (alternative) pathways [63]. Though their signaling pathways differ, both are essential for controlling inflammatory and immunological responses [63]. Numerous stimuli, including members of the TNF receptor (TNFR) superfamily, pattern-recognition receptors (PRRs), ligands from different cytokine receptors and receptors like the T-cell receptor (TCR) and B-cell receptor (BCR), have been proposed by Zhang and Sun as activators of the canonical NF-κB pathway [64]. Karin and Delhase clarified that the inducible degradation of IκBα is the basic mechanism behind conventional NF-κB activation. The complex multi-subunit IκB kinase (IKK) facilitates the phosphorylation of particular sites, which initiates this degradation [65]. Sun and Ley elaborated on the composition of IKK, highlighting that it comprises the regulatory component IKKγ, also recognized as NF-κB necessory modulator (NEMO), with the presence of catalytic subunits IKKα and IKKβ [66]. Israel explained that the activation of IKK by various substances, including cytokines, growth factors, mitogens, microbiological elements and stressors [67]. Oeckinghaus and Ghosh suggested that IKK phosphorylates IκBα upon activation, which causes ubiquitin-dependent proteasome destruction [59]. Hayden and Ghosh evaluated that conventional NF-κB members especially the p50/RelA and p50/c-Rel dimers translocate quickly into the nucleus [68].

Relation between oxidative stress and NF kB gene mutation

Oxidative stress has the potential to impact numerous biological processes, including apoptosis, viral proliferation and inflammatory reactions [69]. Dharshini et al., revealed that during these processes, gene transcription factors like nuclear factor-κB (NF-κB) and activator protein-1 (AP-1) function as sensors for oxidative stress, undergoing their distinct cycles of oxidation and reduction [70]. Proteins undergo chemical modifications through oxidation and reduction processes, a phenomenon known as redox regulation. Rothwarf and Karin suggested that the transcription factor NF-κB translocates from the cytoplasm to the

nucleus in reaction to an extracellular signal [71]. Serasanambati and Chilakapati observed that NF-κB is implicated in the onset and worsening of various diseases [72]. Gloire et al., have recently acquired a multitude of novel insights into the involvement of oxidative stress in activating NF-κB [73]. Addabbo et al., evaluated that the mitochondrial respiratory chain is commonly recognized as the principal source of active oxygen species [74].

Inflammation

Upon encountering infections and tissue damage, the host triggers a protective mechanism referred to as inflammation. As outlined by Castellheim et al., this reaction entails procedures like vasodilation and the enlistment of plasma proteins and immune cells to the infection or tissue injury sites [64,75]. According to Tabas and Glass, inflammation can be properly cured and is beneficial for the host under normal circumstances. Acute or chronic inflammatory illnesses might arise due to long-lasting tissue damage brought on by protracted or severe inflammatory reactions [76]. Xiao and Ghosh have brought attention to the crucial role that NF-κB plays in both innate and adaptive immune cells as a mediator in the initiation of pro-inflammatory genes. [77, 78].

Inflammation and infertility

Inflammation plays a major part in the pathophysiology of endometriosis, affecting the development of both localized and systemic symptoms and indicators [79]. In light of this, inflammatory mediators may be used as therapy targets or biomarkers for diagnostics [69]. As well as inflammatory mediators (prostaglandin, chemokines, and cytokines), the endometrial tissue also creates a localized inflammatory response [80]. T cells, neutrophils, macrophages, eosinophils and monocytes will all be drawn to the chemokines [81]. Macrophages exhibit reduced phagocytic activity, concomitant with an upsurge in inflammatory mediators. Increased levels of tumor necrosis factor-alpha (TNF-α), interleukin one beta (IL-1β) and interleukin six (IL-6) are noted, along with heightened angiogenic factors (VEGF), growth factors, and adhesion molecules [82,83]. These components collectively contribute positively to the initiation, perpetuation and progression of endometriosis [84]. Significantly, there is a rise in the count of white blood cells observed in the peritoneal fluid of women with endometriosis. This finding substantiates the inflammatory hypothesis in endometriosis [85, 86].

Table 2: Relation between inflammation and infertility

Factors	Description	Impact on infertility	Reference
Chronic inflammation	Associated with obesity and autoimmune disorder	Desrupt hormonal balance which lead to structural damage to reproductive organ	[87, 88, 89]
Immune dysfunction	Abnormal immune response affecting reproductive process	Rejection of embryos or compromise the implantation process	[90, 91, 93]
Oxidative stress	Increased production of reactive oxygen species	Damage cells, protein, DNA in the reproductive organ	[94,95,96]
Hormonal dysfunction	Interference with normal endocrine function	Disrupt deliocate hormonal balance crucial for reproductive health	[97,98,99]
Altered reproductive micro environment	Inflammatory mediators such as cytokines and chemokines create an unfavourable environment within the reproductive tract	Interfere with sperm function, egg maturation and embryo development may lead to implantation failure or miscarriage	[100, 101, 102]

Association between NF kB gene mutation and inflammation

NF-kB has been found in a number of dimeric configurations, the most common of which is a heterodimer made up of the p50 and p65/RelA subunits, as described by Quaedackers et al. The genes RelA and NFKB1 encode these subunits, respectively [103]. The gene has a substantial insertion/deletion polymorphism (−94 insertion/deletion ATTG, rs28362491) between two putative important promoter regulatory regions, as reported by Barbosa et al. This polymorphism, located on 4q24 (GeneBank ID 4790, MIM 164011), suggests that NFKB1 may have a functional genetic variation. A 4-base-pair (bp) deletion reduces promoter activity by interfering with binding with nuclear proteins. [104]. Barbosa et al., noted an association of this genetic variation between inflammatory and immune disorders, which consists oral squamous cell carcinoma, nasopharyngeal carcinoma, dilated cardiomyopathy and psoriasis [105], [106].

Relation between NF kB gene mutation and infertility

Based on the findings by Bianco et al., a potential link is suggested between the -94 insertion/deletion ATTG polymorphism in the NFKB1 gene and the presence of endometriosis and/or infertility in the Brazilian population [107]. This study marks the first investigation in the literature exploring the possible association between this polymorphism and infertility associated with endometriosis. The results disclosed a noteworthy correlation, emphasizing the connection between endometriosis and infertility in the context of the −94 insertion/deletion ATTG polymorphism [107].

The association between endometriosis susceptibility and the functional −94 insertion/deletion ATTG polymorphism found in the NFKB1 gene promoter region was investigated by Zhou et al. [108]. They genotyped 206 endometriosis-affected women and 365 healthy, similarly ethnically matched controls using polymerase chain reaction–polyacrylamide gel electrophoresis. DNA sequencing confirmed the genotyping method and the polymorphism remained in Hardy–Weinberg equilibrium in both the case and control groups. Among individuals with endometriosis, the frequency of the ATTG2/ATTG2 genotype and ATTG2 allele was significantly higher than in controls (59.7% vs. 37%, odds ratio = 3.069, $p < 0.001$ for ATTG2/ATTG2 genotype; 75.2% vs. 59.7%, odds ratio = 2.049, $p < 0.001$ for ATTG2 allele), suggesting a connection with the −94 insertion/deletion ATTG polymorphism in the NFKB1 promoter and endometriosis. The study implies that this functional polymorphism is linked to an increased risk of endometriosis [108].

CONCLUSION

The exploration of oxidative stress, inflammation and infertility, with a specific emphasis on NF-kB gene mutation, emphasizes the intricate and interconnected nature of these processes within the realm of reproductive health. The delicate equilibrium within these biological mechanisms significantly impacts fertility outcomes and the emergence of NF-kB gene mutation introduces an additional layer of complexity to our comprehension.

Oxidative stress, serving as a disruptive force, exerts profound implications on fertility by influencing cellular function and contributing to reproductive dysfunction. The inflammatory environment, characterized by elevated cytokines and angiogenic factors, further complicates reproductive challenges. The distinct emphasis on NF-kB gene mutation underscores its growing significance as a molecular contributor to infertility, influencing the initiation, perpetuation and potentially, the progression of reproductive disorders.

A profound understanding of the molecular connections between oxidative stress, inflammation and NF-kB gene mutation is crucial for unraveling the intricacies of infertility. The review consolidates pivotal findings, unveiling potential therapeutic targets that have the capacity to reshape intervention strategies. While navigating the complexities of reproductive disorders, the integrated role of these elements in the intricate landscape of infertility becomes clearer, opening avenues for future research directions and innovative approaches aimed at enhancing reproductive outcomes. Ultimately, this exploration emphasizes the necessity for a holistic comprehension of these interconnected pathways to effectively address the multifaceted challenges presented by infertility.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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