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A Systematic Review on Infertility in Men Due to Sperm DNA Damage: Causes Investigations, & Management

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ABSTRACT

The prevalence of sperm DNA damage is common in infertile men, caused by several factors. This systematic review aims to conclude causative agents, advanced and effective diagnostic aids, and treatment plans. After a critical review of 1123 articles and research papers collected from Google Scholar, Pub-Med, the Database of Abstracts of Reviews of Effects, Embase, PsycINFO, Ovid Medline, and Cochrane Central Register of Controlled Trials, 14 reviews have been included in this systemic review according to PRISMA guidelines. Included studies describe sufficiently regarding cause, investigations and management of infertility in men caused by sperm DNA damage. According to the results, 14 reviews have been eligible for this systemic review. The subject of these reviews is associated with sperm DNA damage in men, causing infertility. These reviews summarised Oxidative stress as one of the major causative factors. Different diagnostic tools have advantages, making them suitable for the scenario. It summarises that the factors affecting male infertility are general worldwide. This review could provide fundamental strategic plans dealing with specific risk factors and managing accordingly.

INTRODUCTION

Infertility has been present in around 20 – 30 % of males worldwide. It is observed that almost one-third time, the cause of infertility in couples is men (Babakhanzadeh *et al.*, 2020). Infertility relates to the failure to conceive a pregnancy after a suitable time of sexual intercourse. Although, it could be due to the inability of the pregnancy via natural means, or it could be a successful pregnancy that does not lead to a newborn baby (Brugo-Olmedo *et al.*, 2001). The inability to cause infertility has many causative agents, including a person's lifestyle. Increased use of mobile phones, decreased physical activity, increased alcohol intake, and smoking. The destruction of the human male genital system causes disruptions in spermatogenesis, which could lead to infertility (Muratori & De Geyter, 2019). Infertility in men could be due to the impacts of the environment, nutritional deficiency, and genetics, and it may be idiopathic (Bisht *et al.*, 2017).

The disruption of the chromosomes could also affect the characteristics and functioning of the sperm (Sharma, 2017). Environmental factors are also responsible for deviating from the physiologic nature of human systems. These factors are mostly related to the inclusion of xenobiotics in the diet. It includes chemical substances which could disturb the endocrine system and estrogen metabolism. Metals with high atomic mass, including Cadmium (Cd), lead (Pb), and mercury (Hg), damage the human reproductive system by destroying the hypothalamic-pituitary communication axis and disrupting spermatogenesis. This would produce semen with abnormal properties (Sharma, 2017).

Oxidative stress plays the most important role in the development of genetic disorders. Its presence is caused due to excessive production of Reactive Oxygen Species (ROS). The ROS could modify the DNA into single and double strands, break DNA fragmentation, alter nitrogen bases and deoxyribose properties, and change crosslinking. These modifications of DNA could interpret the genetic stability and causes replication errors. DNA fragmentation is the last step of the ROS action, resulting in single or double-stranded fragments (Bui *et al.*, 2018).

Diabetes Mellitus, Obesity, Hyperthermia, and Genital tract infections could also be the causative agents of infertility. Varicocele is a condition in which the veins of the scrotum have enlarged and dilated due to defective valves. It causes impairment of sperm production, decreased blood circulation, and reduced functions of Leydig cells. Varicocele positively affected ROS and sperm DNA fragmentation (Panner Selvam *et al.*, 2021).

There is a need for an effective diagnostic strategy. Different and effective investigations, including assays, would be used to diagnose infertility in men caused by sperm DNA damage. However, infertility is a major health concern and exacerbates negative effects on a couple's life and pregnancy. Explanation of causative agents, diagnosis, and proper management are extremely important. This systematic review presents leading factors, investigating aids, and worldwide treatment planning.

LITERATURE REVIEW

Infertility is a complex condition that impacts approximately 15% of couples, characterised by the inability to naturally conceive after engaging in regular unprotected sexual intercourse for 12 months or more. Notably, male factors are accountable for nearly 50% of all infertility cases, making an equal contribution to

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female factors (Omolaoye *et al.*, 2022). Numerous factors and risk elements have been established as contributors to male infertility. Among these are smoking, alcohol consumption, substance abuse, obesity, historical or ongoing testicular infections, contact with environmental pollutants, prolonged exposure of the testes to elevated temperatures, hormonal imbalances, past testicular injuries, and difficulties related to ejaculation or achieving an erection, among various others (Okonofua *et al.*, 2022). In diagnosing male infertility, conventional assessment methods often rely on analysing standard semen parameters, as outlined by the World Health Organisation (WHO) guidelines. Nevertheless, many males experiencing infertility do not receive a definitive diagnosis, leaving their condition as idiopathic or unexplained (Mannucci *et al.*, 2022).

The assessment of semen parameters following the WHO guidelines is currently considered the gold standard for diagnosing male infertility. Nevertheless, numerous studies have indicated that sperm quality can be adversely affected by oxidative stress-induced sperm oxidation, leading to a decline in sperm's ability to fertilise (Mannucci *et al.*, 2022). Given this compelling evidence, there is a growing need for novel tests to assess male fertility by monitoring oxidative stress levels. These new assays for detecting oxidative stress have the potential to revolutionise male infertility diagnosis and management by offering simpler, faster, and more cost-effective techniques (Agarwal, Parekh, *et al.*, 2019). Oxidative stress can be assessed through biochemical tests, including plasma, serum, urine, and bodily fluids such as follicular, peritoneal, and seminal fluid. These assessments provide a precise overview of the body's redox status, enabling the potential implementation of therapeutic antioxidant supplementation when necessary (Agarwal, Parekh, *et al.*, 2019). Various assays for evaluating oxidative stress are available, focusing on measuring ROS production, lipid peroxidation products, and total antioxidant capacity. When it comes to measuring ROS levels in semen, there are several methods to choose from, including chemiluminescence, the Nitro Blue Tetrazolium (NBT) test, cytochrome c reduction test, and electron spin resonance (Dutta *et al.*, 2019b; Mannucci *et al.*, 2022).

The absence of well-defined guidelines for treating male infertility associated with oxidative stress is partly due to an incomplete understanding of its underlying causes (Agarwal *et al.*, 2018). However, over recent years, numerous clinical trials have sought to explore the impact of antioxidant supplementation, such as l-carnitine, selenium, Coenzyme Q10, ubiquinol, vitamin C, and E on oxidative stress levels in seminal fluid and various semen parameters (Alahmar *et al.*, 2021). Many of these trials have reported encouraging findings regarding the positive effects of antioxidants on critical aspects like sperm concentration, motility, morphology, and DNA fragmentation. Specifically, the analysis included twenty clinical trials that focused on the effects of anti-oxidant therapy on seminal oxidative stress. Notably, nineteen of these trials demonstrated improvements in sperm redox status and semen parameters, often correlating with improved pregnancy outcomes (Alahmar *et al.*, 2021).

The use of antioxidant treatment to treat male infertility is critical to emphasise. Infertile men who received antioxidant treatment for three months did not experience any discernible improvements in DNA fragmentation or semen characteristics, according to one randomized clinical trial (Alahmar *et al.*, 2021). Additionally, this study found no appreciable improvements in pregnancy or live birth rates. These observations highlight the ongoing uncertainty surrounding using antioxidants in addressing male infertility. Nonetheless, the combined evaluation of traditional semen analysis and oxidative stress assessment holds substantial promise for accurately assessing infertile patients (Gambera *et al.*, 2019).

MATERIALS AND METHODS

The systemic review has been completed according to the guidelines regulated by Preferred Reporting Items for Systemic Research and Meta-Analysis (PRISMA) (Page *et al.*, 2021).

Search Strategy

Search strategy based on the use of MeSH terminologies which were related to the topic, mentioned in Table 1. The terms have been utilised appropriately using Boolean operators: AND, OR, and NOT. A typical summary of the study search has been described through the PICO model in Table 2.

Table 1: Search Strategy

Sr. no	Search Strategy
1	Sperm DNA Damage [Abstract & Keywords] OR Male Infertility [Abstracts & Keywords] OR Infertility [Abstract & Keywords] OR Causes of DNA Damage [Abstract & Keywords] OR Reproductive System [Abstract & Keywords] OR Oxidative Stress [Abstract & Keywords] OR DNA Fragmentation [Abstract & Keywords]
2	Defective Sperm Production [tw] OR Immobile Sperm [tw] OR Unsuccessful Pregnancy [tw] OR Infertility of Male [tw] OR Internal and External Factors [tw] OR Factor causing Sperm Immobility [tw] OR Factors causing Sperm DNA Damage [tw] OR Detection [tw] OR Treatment [tw] OR Management [tw]
3	Treatment Options [Abstract & Keywords] OR Defective Spermatogenesis [Abstract & Keywords] OR Sperm DNA Fragmentation [Abstract & Keywords] OR Assisted Reproductive Technologies [Abstract & Keywords] OR Reactive Oxygen Species [Abstract & Keywords] OR Fertilisation Failure [Abstract & Keywords] OR Infertility [tw] OR DNA Integrity Tests [tw]

Table 2: PICO Model

Population	Male, Adult, Mature, Infertile.
Intervention	Analysis of the studies regarding causes of sperm DNA damage, types of investigation to detect DNA damage, and management plan to treat infertility caused due to sperm dysfunction.
Comparison	Reviews had been included having views favouring the management of infertility and against this approach.
Outcome	This systemic review contained a novel idea of new and distinctive management methods which would benefit patients facing Infertility.

Study Selection & Eligibility

The databases used to complete the search strategy and collect the required articles include Google Scholar, Pub-Med, the Database of Abstracts of Reviews of Effects, Embase, PsycINFO, Ovid Medline, and Cochrane Central Register of Controlled Trials. Selective Keywords were used according to the required topics. Original Articles, Case reports, and Systematic Reviews published from January 2018 to March 2023 have been selected and analysed according to their principal objective and presented topic. The studies focused primarily on managing infertility in men and secondarily on causes of and diagnostic options for sperm DNA damage.

Inclusion Criteria

Reviews published between January 2018 to March 2023 have been included. Reviews could be performed in any part of the world. Men with infertility caused due to sperm DNA damage were the sample size. Sperm DNA damage is caused due to several internal and external causes, mainly increased oxidative stress and Apoptosis. DNA damage has been confirmed using different laboratory methods, including sperm DNA integrity tests and sperm DNA fragmentation testing. Included studies had delivered proven and justifiable data and results. They had published in the English language. Systemic reviews have been chosen related to the pathophysiology, aetiology, and management of infertility in men due to sperm DNA damage. These reviews have a high impact factor.

Exclusion Criteria

Reviews conducted before January 2018 were excluded. Excluded studies had inaccurate and inappropriate data published in languages other than English. Studies had been excluded due to difficulty accessing their full text; also, Dissertations and Thesis had been rejected due to the inclusion of only articles that used different epidemiological methods.

Data Extraction and Risk of Bias

The two authors reviewed and decided to include all reviews independently based on the PICO model (Table 2). Using Microsoft Excel and a standardised data extraction form, the researchers extracted and sorted the sample size, study type, duplicates, full-text articles, and empirical studies, making the systematic review approach practicable. Information of variables includes the author, year of publication, and number of studies. The two reviewers assessed the methodological qualities by using the 7-item scale of risk of bias developed by the Cochrane Bias Methods Group. This review used the PRISMA guideline and flow diagram to lower the risk of bias. The sources of bias assessed included outcomes, population, study selection process, incompleteness of data, and time frame and setting.

Quality of Systematic Reviews

The expert team members assessed the quality of the systematic reviews, including questions regarding the degree to which the systematic reviewers had evaluated the risk of bias in individual studies. Systematic reviews with major limitations were excluded. The Authors have assessed the methodological quality of studies in sperm DNA fragmentation based on the review authors' assessments of risk of bias in the primary studies they had included.

Summary Measures and Synthesis of Results

The authors analysed the data collected by the members of the expert team. Due to the expected heterogeneity of studies regarding participants, interventions, outcomes and study designs, a quantitative summary measure of the results was not planned. We did a qualitative and narrative summary of the results of the systematic reviews. The literature review results were presented and discussed in two workshops intending to validate results.

RESULTS AND DISCUSSIONS

A total of 1123 studies have been reached through search engines, including Google Scholar, Pub-Med, the Database of Abstracts of Reviews of Effects, Embase, PsycINFO, Ovid Medline, and Cochrane Central Register of Controlled Trials. These studies have been sorted according to their keywords and text words. After screening for duplicate and ineligible studies, 561 studies were excluded, according to PRISMA guidelines, as mentioned in Figure 1. Out of 562 studies, 341 have been rejected due to not meeting inclusion criteria. The reports of 179 studies could not be retrieved. 28 studies have been excluded due to some other reasons. After completing the literature search, 14 studies were retrieved, included in this systemic review and noted in Table 3.

The central idea of included studies revolves around the causes, diagnostic aids, and management strategies of infertility in men. The studies included being from January 2018 to March 2023. The included reviews specifically highlighted the causes and significance of existing methods used for this purpose. They have discussed and

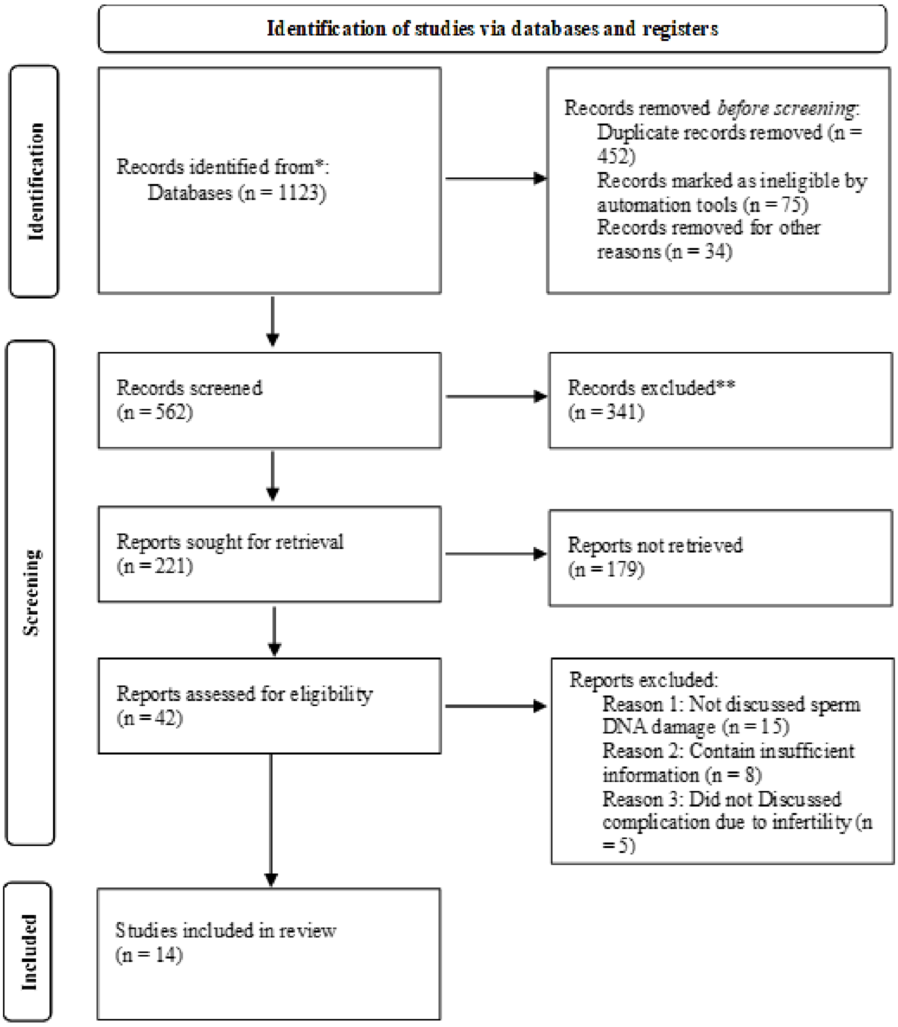

Figure 1: PRISMA flow diagram of article selection criteria

Table 3: Studies included in the Systemic review

Sr. no	Title	Reference	Sample size	Description	Year
1	Role of sperm DNA fragmentation in male factor infertility: A systematic review	29	150	This systemic review highlighted the importance of DNA integrity assays in infertility diagnosis. It provides a new pathway for clinicians to detect infertility in men by applying SDF testing.	2018
2	A systematic review on sperm DNA fragmentation in male factor infertility: Laboratory assessment	38	87 studies & 8 book chapters	This systemic review discusses and compares different techniques used in diagnosing impotence. Its main emphasis was on the TUNEL method.	2018
3	The effects of varicocelectomy on the DNA fragmentation index and other sperm parameters: a meta-analysis	47	289 patients from 7 prospective studies	This meta-analysis discusses the significance of varicocelectomy in an infertile male. Results show a positive impact on sperm mobility, concentration, and morphology.	2020
4	Obesity and metabolic syndrome associated with systemic inflammation and the impact on the male reproductive system	11	N/A	This review article deeply elaborates on the effects of obesity and metabolic syndromes on the prevalence of infertility. These may negatively affect semen quality and spermatogenesis.	2019

5	Sperm DNA Damage and Its Relevance in Fertility Treatment: A Review of Recent Literature and Current Practice Guidelines	12	N/A	It discusses the treatment methods for male infertility, including surgical and non-surgical procedures. These techniques include the use of testicular sperms, varicocelectomy, and use of microfluidic sperm sorting.	2023
6	Etiologies of sperm DNA damage and its impact on male infertility	7	N/A	This review elaborates on the mechanisms of DNA damage and its impact in different scenarios of male infertility associated with spontaneous and assisted reproduction. It also reviews the clinical applicability of sperm DNA fragmentation testing in the management of male infertility	2021
7	What should be done for men with sperm DNA fragmentation?	34	N/A	This review explains that sperm DNA damage testing methods do not have standardised cut-off levels. Each method has advantages and disadvantages, making it difficult to proclaim one as a universally preferable method.	2018
8	Oxidative stress and sperm function: A systematic review on evaluation and management	25	N/A	According to this review article, Oxidative stress is an important cause of male factor infertility. Its assessment provides essential information to guide treatment strategies to improve the male's reproductive potential.	2019
9	The effects of oral antioxidants on the semen of men with idiopathic oligoasthenoteratozoospermia	54	N/A	Most of the studies in this review were randomised controlled studies that explored the effects of oral antioxidants in men with idiopathic OAT. They reported improvements in at least one semen parameter (motility, concentration, normal morphology, and antioxidant capacity). Still, the most remarkable effect was that multiple antioxidants for 3–6 months increased sperm motility and concentration.	2018
10	Sperm DNA damage and its impact on male reproductive health: a critical review for clinicians, reproductive professionals and researchers	33	N/A	This review discusses the origin and factors contributing to sperm DNA damage, the molecular changes, especially proteomic alterations caused due to SDF, risk factors associated with SDF, methods used to analyse SDF, clinical implications of SDF, and CPG recommendations for SDF testing	2019
11	Oxidative stress and reproductive function: sperm telomerase, oxidative stress, and infertility	22	N/A	This review article emphasises the proper diagnosis and measurement of oxidative stress before any telomere evaluation in the ART setting. This review is focused on the telomere; the implications of the proposed mechanism extend far beyond that to any GQ sequence and offer novel, added insight into oxidative stress-induced epigenetic regulation/ dysfunction of the paternal genome.	2022

12	Effect of varicocele repair on sperm DNA fragmentation: a review	45	N/A	It explains the role of varicocele repair in alleviating SDF and improving fertility and critically appraises the evidence-based algorithm recently issued by the Society for Translational Medicine to guide urologists on using SDF testing in men with varicocele-seeking fertility.	2018
13	Single and Double Strand Sperm DNA Damage: Different Reproductive Effects on Male Fertility	41	N/A	This review explains the etiology of sperm DNA damage highlighting the single and double-strand DNA damage. It also covers the management strategies to treat or reduce the effects of sterility in men due to DNA fragmentation.	2019
14	Sperm DNA fragmentation: causes and identification	43	N/A	This review describes the main causes of sperm DNA fragmentation and the tests commonly used to evaluate sperm DNA fragmentation.	2020

compared treatment options based on their requirements and effectiveness.

This systemic review consists of a total of 20 studies which includes review articles, original studies, randomised control trials, and systemic considerations. These studies provided valid and accurate information regarding the pathophysiology, mechanism of action, causes and aetiology, investigations and treatment plans. The main focus is on the advanced and new ways of management of infertility in men. The germ cells in men are equally responsible for pregnancy. Damage to their genetic material affects their morphology and physiology and produces its outcome in future offspring. Most of the studies elaborate on different causes of sperm DNA damage, which triggers the process of DNA fragmentation. These causes include abortive Apoptosis, increased oxidative stress, and endocrinal issues (Homa *et al.*, 2019; Kuchakulla *et al.*, 2021).

Risk Factors for Infertility

According to Leisegang *et al.* (2019), obesity and metabolic syndromes have affected the population worldwide with the complex underlying pathophysiological phenomenon. Metabolic syndromes result from an increased ratio between energy intake and energy consumption. Excessive energy deposits in the body affect body functions due to reduced physical activities. Environmental toxins, diet quality, inactive and sedentary lifestyles, hormonal changes, and pharmaceutical agents also cause metabolic imbalance and obesity (Leisegang *et al.*, 2019). Avoidance of Selective Serotonin Reuptake Inhibitors (SSRI), cigarette smoking, air pollution, and cancer treatments could be useful in decreasing the prevalence of sterility. These are risk factors for sperm DNA fragmentation (Esteves *et al.*, 2021; Marinaro & Schlegel, 2023; Schulte *et al.*, 2010; Sharma *et al.*, 2016; Ståhl *et al.*, 2006; Tanrikut *et al.*, 2010).

Sperm DNA fragmentation caused due to several extrinsic and intrinsic factors. Intrinsic factors include immature germ cells, abortive Apoptosis, and increased oxidative stress, while extrinsic factors include negative impacts of medicines, environmental factors, and lifestyles (Barazani *et al.*, 2014; Muratori *et al.*, 2019; Sakkas *et al.*, 1999). Reactive Oxygen Species (ROS) are a major cause of sperm DNA fragmentation. These species produce in the mitochondrial DNA of sperm and induce cascades and pathways leading to germ-cell Apoptosis (Agarwal *et al.*, 2020; Moazamian *et al.*, 2022). The process of spermatogenesis and sperms are more prone to damage from radiation than other body cells. Side effects of radiotherapy include male infertility and testicular cancer. However, non-ionising radiation produced by mobile phones, Wi-Fi, microwave, and laptops could also damage the genetic material of sperm (Kesari *et al.*, 2018; McGill & Agarwal, 2014).

Dysfunctional spermatozoa cause an increased ROS body production, which develops through two pathways. The most abundant species is superoxide (O2-), which undergoes chemical reactions to yield Hydrogen peroxide (H_2O_2). Any inflammatory or infectious response could ignite the production of macrophages and lymphocytes, producing many ROS species (Agarwal *et al.*, 2003; Dutta *et al.*, 2019a). The dilation of veins entering the testicles, known as varicocele, is one of the major reasons for male sterility. It increased the internal temperature of the testes and decreased oxygen level causing hypoxia. A higher incidence of ROS bodies is proportional to the presence of varicocele, reducing semen and sperm quality (Agarwal *et al.*, 2006; Dutta *et al.*, 2019a).

Effects of sperm DNA fragmentation on the human body, including pregnancy loss, Intrauterine Insemination (IUI), and In-Vitro Fertilization (IVF). Due to the increased ratio of SDF, the chances of conceiving became negligible. A systematic review including around 3000 couple sample size indicates a high value of pregnancy loss of about 2.16 times when using semen specimens with high SDF (Robinson *et al.*, 2012). There is a strong relationship between increased SDF and bad IUI outcomes. A raised

SDF index of >27% has a negative impact on pregnancy assisted by the IUI procedure (Bungum *et al*., 2007; Cho & Agarwal, 2018). Controversial results explain the correlation between SDF and successful pregnancy after IVF and Intracytoplasmic Sperm Injection (ICSI). The reason behind this could be the difference in their methods. There is a chance of sperm exposure to oxidative stress during laboratory steps of culture in IVF, whereas in ICSI, the spermatozoon is directly injected into an oocyte. This may cause a decrease in SDF due to less exposure to oxidative stress (Cho & Agarwal, 2018; Dumoulin *et al*., 2010; Lewis, 2013).

Diagnostic Aids

There are many techniques for investigating DNA damage, divided into two kinds, including direct DNA integrity assessment and indirect DNA integrity assessment. One of the well-known methods is the terminal deoxynucleotidyl transferase-mediated deoxyuridine triphosphate nick end labeling (TUNEL) method. This method directly measures the sperm DNA damage using deoxyuridine triphosphate (dUTP), which binds to single and double-stranded DNA. It could detect a small sample of sperm and should be applied on fresh or frozen samples. TUNEL is a time-consuming process that requires a standardised criterion among the laboratories. It also cannot evaluate immature sperms compared to other tests (Agarwal, Panner Selvam, *et al*., 2019; Evgeni *et al*., 2014; Gorczyca *et al*., 1993; Kim, 2018). Sperm Chromatin Structure Assay (SCSA) was initiated in the 1970s and became popular after some remodeling. It investigates the sensitivity of sperm DNA to denaturation and deformation. This test is simple to perform with a commercially available kit. It could be used on several spermatozoa for detection, and its results could also be compared with the results of other tests (Evenson *et al*., 1980; Kim, 2018). It requires expensive equipment, trained personnel to perform tests, and many spermatozoa (Agarwal, Panner Selvam, *et al*., 2019; Selvam & Agarwal, 2018). The comet assay or SCGE test is the qualitative testing of DNA damage by detecting deformation in single and double DNA strands using electrophoresis (Kim, 2018; McKelvey-Martin *et al*., 1997). It is a simple and affordable process whose results are based on the tail length of sperm. The tail end of the sperm carries fragments of DNA which indicates DNA damage. Due to this reason, this test is not recommended by investigators (Agarwal, Panner Selvam, *et al*., 2019; Cho & Agarwal, 2018; Singh *et al*., 1989).

Sperm Chromatin Dispersion (SCD) or Halo test is a highly standardised process based on extracting proteins after acid denaturation producing halo characteristics. It detects single and double-stranded breaks in sperm DNA (Fernández *et al*., 2005; Ribas-Maynou & Benet, 2019). It is used extensively due to its low cost and quick results with quality. Sometimes it is difficult to differentiate the proximal borders of the halo having low chromatin density from the background (Evgeni *et al*., 2014; Kim, 2018). Chromomycin A3 (CMA3) staining detects the deficiency of chromatin in sperm DNA by competing with protamine for the same binding site. Protamine deficiency indicates male infertility. This test strongly correlates with other SDF assays (Agarwal & Allamaneni, 2005; Cho & Agarwal, 2018; dos Santos Hamilton & Assumpção, 2020; Selvam & Agarwal, 2018).

Management

There are several ways of managing infertility in men based on the cause. There are intrinsic as well as extrinsic factors causing sterility in men. Varicocele is a significant reason for male infertility, causing 15% of the male population of mature age. Dubin's grading system is used to diagnose it and indicates its severity. There is a rise in ROS and apoptosis markers in the cytoplasm in patients diagnosed with varicocele (Miyaoka & Esteves, 2011; Roque & Esteves, 2018). It causes testicular hyperthermia, affects endocrine functions, elevates hypoxia, causes defective spermatogenesis, and damages nuclear and mitochondrial DNA. Its treatment includes surgical intervention, that is, varicocelectomy, assisting in lowering the factors and reducing infertility. According to studies, after performing varicocelectomy using any technique retroperitoneal, inguinal, or subinguinal, there is a significant difference in the values of preoperative and postoperative SDF levels in semen (Birowo *et al*., 2020; Schauer *et al*., 2012).

Another study shows a mark reduction in the value of SDF after Varicocelectomy along with the mast cell stabilisers. It positively affects sperm mobility, concentration and increased sperm count. The degranulation of mast cells is correlated with increased ROS production; a combination of varicocelectomy and induction mast cell stabiliser has a more pronounced effect (Zaazaa *et al*., 2018). Varicocelectomy has increased venous blood drainage, decreasing ROS production and enhancing spermatogenesis and semen quality. The researchers do not recommend varicocelectomy in patients with normal semen quality and asymptomatic varicocele. Varicocelectomy indicates defective sperm motility and morphology (Birowo *et al*., 2020; EAU annual congress, 2020; Zavattaro *et al*., 2018).

Oral antioxidant therapy has a depressing effect on the production of ROS. Both intrinsic and extrinsic antioxidant can play their part in eliminating the ROS and shifting the curve toward the normal range. They could assist in destroying ROS bodies in semen and restore the redox balance (Agarwal, Panner Selvam, *et al*., 2019; Showell *et al*., 2014; Smith *et al*., 2006). Several antioxidants include vitamin A, vitamin C, and vitamin E. Several successful studies suggest antioxidants as one of the best therapies for infertility with promising results (Adewoyin *et al*., 2017; Alahmar, 2018; Cho & Agarwal, 2018; Tremellen, 2008). Lifestyles have also exerted a significant impact on infertility. Obesity and metabolic disorders cause incompetency and are severe systemic disorders, mostly caused due to sedentary lifestyle. A healthy lifestyle and a balanced and hygienic diet are strongly associated with reduced male infertility (Omer & Atassi, 2017). A diet rich in carbohydrates, antioxidants containing vegetables, fibre, biogenic seeds, and seafood reduces inflammatory markers. These nutrients are related to an improved immune and neurological system, reduced fat accumulation and increased DNA integrity (Leisegang *et al.*, 2019).

LIMITATIONS

Even though our search was broad and included many medical libraries, conference abstracts, and other unpublished pieces of literature may get overlooked, causing limiting our conclusions. However, there is no literature on the routine investigations of defective DNA in infertile men. Also, the mechanism of antioxidants against the ROS bodies at the molecular level is not present, explaining its effects on semen quality, duration of treatment and the choice of therapeutics. In the future, this evidence could be taken into consideration.

Strengths

The review uses a comprehensive search strategy across multiple databases to gather relevant studies on male infertility caused by sperm DNA damage. It includes various study types, including review articles, original studies, randomised controlled trials, and systematic reviews. Moreover, the review's clear presentation makes it easy to follow. The findings can inform clinical practice and guide healthcare professionals in improving patient care. Furthermore, the review also discussed emerging management methods, highlighting its forward-looking approach and potential future developments in the field.

CONCLUSION

This systemic review summarised the most common causes of infertility in men, damaging sperm DNA. This would include a sedentary lifestyle and intrinsic and extrinsic risk factors, which increase the level of ROS in the testicular spermatozoa. The risk of DNA damage is more evident during ejaculation. Oxidative stress could be controlled by prescribing antioxidants and planning a healthy and hygienic diet. Surgical intervention includes varicocelectomy, which also reduces the level of ROS in the mitochondrial and nuclear DNA of the sperms. Genital tract infections also cause infertility which should be diagnosed earlier and treated with broad-spectrum antibiotics. This review will provide substantial knowledge regarding the major causes of infertility and how to improve it. Implications of new management methods have been discussed, which could benefit the patients.

Novelty of Research

This review provides a comprehensive and up-to-date information regarding male infertility due to sperm DNA damage. It focuses on recent research, a comprehensive approach, and emerging management methods. The review considers factors such as lifestyle, environmental exposures, and genetic influences. It also discusses established and emerging management strategies for male infertility. The research offers practical insights for healthcare professionals and patients, guiding decision making and patient care. The inclusion of various study types adds depth and diversity to the analysis. Overall, this review offers a unique perspective on male infertility.

Research Gap

This review on male infertility caused by sperm DNA damage identified several research gaps. These include the lack of long-term follow-up studies, the impact of lifestyle interventions, standardisation of diagnostic tests, environmental factors, psychological impact, cost-effectiveness analysis, and exploring novel treatment approaches. The review also highlighted the need for more research on male infertility's psychological and emotional implications, cost-effectiveness analysis, and more diverse study populations. Additionally, the review suggested the development of biomarkers for predicting treatment success and a stronger emphasis on patient-centered outcomes. These gaps could contribute to a more comprehensive understanding of male infertility and the development of more effective diagnostic methods and treatments.

Contribution to Knowledge

The systematic review on male infertility caused by sperm DNA damage provides a comprehensive overview of the current state of knowledge. It identifies causal factors, diagnostic methods, treatment strategies, and impacts on reproductive outcomes. The insights have practical implications for healthcare providers, researchers, and policymakers, enabling them to develop evidence-based treatment plans. The review also contributes to patient education by raising awareness of factors contributing to male infertility and available diagnostic and treatment options.

Abbreviations

ROS: Reactive Oxygen Species; DNA: Deoxyribose Nucleic Acid; SDF: Sperm DNA Fragmentation; ICSI: Intra Cytoplasmic Sperm Injection; IVF: In Vitro Fertilization; CMA3: Chromomycin A3; SCD: Sperm Chromatin Dispersion; SCSA: Sperm Chromatin Structure Assay; TUNEL: Terminal Deoxynucleotidyl Transferase dUTP Nick End Labeling; DFI: DNA Fragmentation Index; IUI: Intra Uterine Insemination; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; OS: Oxidative Stress; ART: Assisted Reproductive Technology.

Statement and Declarations

Data Availability Statement

The data utilised in writing this systemic review is obtained from previously presented original articles and reports. No new data or evidence has been created during this period.

Authors Contribution
Conceptualisation, Data curation, supervision, validation, Writing-review and editing has been done by Author (MR). Methodology, software analysis, and writing of the original draft have been done by Author (MK).

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