

Indicative and Prognostic Ramifications in the Assessment of DNA Sperm Damage: The Essential Standards, the Blueprint Procedures, Clinical Procedures, Clinical Importance and Implications of These Tests: A Systematic Review

Ria Margiana¹, Silvia W. Lestari²

¹Department of Anatomy, Faculty of Medicine, University of Indonesia, Republic of Indonesia, ²Department of Medical Biology, Faculty of Medicine, University of Indonesia, Republic of Indonesia

Abstract

Sperm is not the primary transporter of fatherly hereditary data, but rather its part broadens apparently past treatment. The integrity of sperm DNA is a fundamental pre-essential for the birth of solid posterity and the assessment of sperm ought to involve DNA integrity examination. Sperm integrity investigation is a superior indicative and prognostic marker of sperm conception potency. Conventional semen analysis accentuates on sperm focus, practicality, motility, and morphology, and it has been turned out to be a poor pointer of conception potency and pregnancy result. The aim of the study was to conquer the downsides related to conventional semen investigation, more expensive tests and atomic biomarkers have been investigated. Distinctive tests have been developed for surveying the potential of sperm regenerative, and tests for sperm DNA quality are also encouraging. Sperm DNA damage has been nearly connected with various pointers of regenerative wellbeing including preparation, incipient organism quality, implantation, unconstrained premature birth, innate contortions, and adolescence infections. It, in this manner, has extraordinary potential as a prognostic test for both *in vitro* and *in vivo* originations. This audit exhibits a refreshed record of tests that have better indicative and prognostic ramifications in the assessment of sperm DNA damage. In this paper, a novel review was conducted to address the issue of infertility in males due to sperm DNA damage. The articles selected for the review consist of state of the art techniques developed to address the issue of infertility in men due to sperm DNA damage and the novel treatments used to help such individuals.

Key words: Chromatin, DNA, male infertility, quality, sperm

INTRODUCTION

One of the most concerning issues confronted by the couples attempting to have an infant is infertility. As for a gauge, right around 15–20% of the couples face this issue.^[1-5] Male infertility adds to half of these cases. The standard semen examination is the initial move toward the treatment, and it is a standout among the most important research test center. The parameters canvassed in this test are the fixation, mortality, morphology, and their essentials. The standard consequences of the test, be that as it may, cannot discount the men from the issue of infertility.

From the extensive research, obviously, the quality and honesty of the semen are of extreme significance for the conceptive capability of men. Sperm DNA is known to add half of the genomic material of the developing organism. Sperm chromatin is the essential element identified with the strength of sperm from testis to its last goal in fallopian.^[6-10] Reliable

Address for correspondence:

Ria Margiana, Department of Anatomy, Faculty of Medicine, Universitas Indonesia, Republic of Indonesia. Tel.: 62-21-727-0020. E-mail: riamargiana@yahoo.com

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sperm genomic is important for conventional treatment. The abnormal sperm genomic state can bring about the subfertility or even infertility in a portion of the cases. From the above talk, it is plainly to address the issue of infertility on more learning of the sperm's chromatic profiles which include etiology, component, location strategies, and treatment may give the answers for this problem. In this audit, we are talking about relevant parameters identified with sperm parameters *in vivo* and *in vitro* treatment capacity of people.^[11-15]

STRUCTURE OF THE PAPER [FIGURE 1]

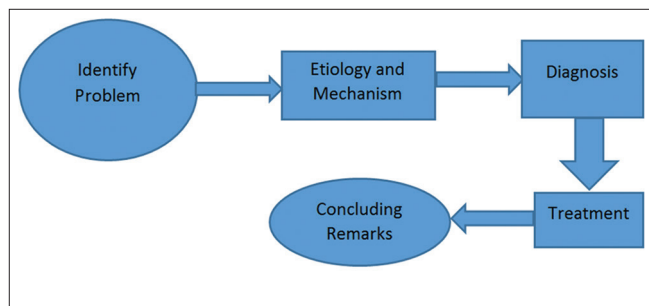


Figure 1: Outline of the paper

ETIOLOGY OF SPERM DAMAGE

Numerous components add to the harm of sperm DNA which may bring about male infertility for the men. One of the real parts is known as leukocytospermia which is the presentation of leukocytes in the sperm DNA. This may occur because of some contamination or aggravation. It can expand the harm by presenting the reactive oxygen specifics (ROS).^[1-10] Smoking can likewise bring about the presentation of ROS and leukocytes in the sperm. The leukocytes make a large grouping of ROS in the sperm bringing about the increase of oxidation ability of the sperm.

Moreover, a part of the sperm arranging and cryopreservation traditions could reduce sperm chromatin uprightness.^[16,17] It has been exhibited that quick and ultra-snappy hardening streak setting in liquid nitrogen starts insignificant harm to sperm in the midst of cryopreservation.^[18] Malignancies -for instance, leukemia, Hodgkin's infection, and testicular reproach - could impact sperm chromatin uprightness without any other individuals or bring after their treatment with cytotoxic meds and also radiation treatment.^[19-22]

Numerous drugs may moreover influence the semen quality and augment sperm DNA damage.^[23-25] In fact, even a couple sorts of natural cures may activate sperm DNA damage. Finally, a creating array of affirmations shows that average and words related to the exposures of the substance experts, warmth, and social toxic substances could expect a section in sperm DNA harm.^[10] In a present survey, it has been exhibited that extended scrotal warmth lessens the way of

semen parameters, and it also deals with sperm chromatin uprightness.^[26,27] While the correct explanations behind sperm DNA harm have not yet been altogether outlined, a couple of interrelated parts have been proposed^[28-30] [Table 1]. These frameworks are delegated to strange chromatin packaging, apoptosis, and oxidative nervousness.^[19-22]

IRREGULAR CHROMATIN PACKAGING

The sperm chromatin is limited to a high degree, and it has a stable structure which must be created, especially to fulfill this first thick state.^[31] This DNA association gives more shielded and more secure trade of paternally inherited information to the egg and the individuals to come. Sperm chromatin is dealt with in a way thoroughly not the same as that of generous cells.^[32,33]

In the midst of changes in sperm chromatin compaction, histones are supplanted by moving proteins. These proteins are then replaced by more basic proteins named protamine [P1, P2], which are accountable for the last buildup and modification of sperm DNA.^[34] Sperm DNA interfaces with protamines, so it changes over the twisting of sperm DNA into toroidal subunits indicated as "Doughnut circles."^[35] Although deformations can rise at any period of this strategy, the most surely understood issues are a result of unordinary DNA loop range plan and they hit on protamine substitution.^[34]

TREATMENT

Sperm preparing techniques emphatically impacted the determination of the sound populace of spermatozoa. The chromatin honesty of prepared sperm is usually more than that of un-prepared semen.^[35,36] Straightforward planning strategies, for example, and thickness inclination centrifugation can advance typical sperm morphology and ordinary atomic honesty.^[37,38] This enhancing impact of depth slope centrifugation can be the clarification for the little prognostic estimation of sperm parameters before arrangement on treatment and pregnancy utilizing antiretroviral therapy (ARTs).^[37,38] This significant impact relates with - to some degree - the high post-IVF preparation rate using a straightforward swim-up strategy^[37,38] [Table 2].

In vitro culture of testicular tissue has likewise been appeared to expand the motility and recuperation rate of testicular spermatozoa.^[39] The ROS creation increments when spermatozoa are refined in medium contain leukocytes, abnormal spermatozoa, and moving metals. Hence, utilizing the handling technique itself might be the reason for sperm DNA. In many cases, supporting information demonstrate that culture of testicular tissue does not expand the obligation of its sperm to chromatin damage. In sperm retrieval, it forms obstructive azoospermia, the extent of spermatozoa with single-stranded DNA breaks diminished impressively

taking after 3 days of *in vitro* culture ($P = 0.005$).^[40] In like manner, juvenile germ cell is refined *in vitro* for 48 h, making it conceivable to choose TUNEL-negative spermatids.

While ROS generation is the fundamental driver of sperm chromatin damage, cancer prevention agent treatment might be the real way to deal with to secure sperm chromatin trustworthiness. At the point when ascorbic acid (600 mmol/l), alpha-tocopherol (30 and 60 mmol/l) and urate (400 mmol/l) are added to culture media, it gives critical security ($P < 0.001$) from DNA harm taking after introduction to X-ray.^[40] In this manner, supplementation of culture media with cancer prevention agents exclusively can give advantageous impact to the sperm chromatin trustworthiness [Table 3].

Plant-determined mixture of genistein and equol isoflavones has cancer prevention agent movement. Thus, capacity is recommended for them in the treatment of male infertility. In correlation with ascorbic corrosive and alpha-tocopherol, genistein is the most powerful cancer prevention agent, trailed by equol, ascorbic destructive, and alpha-tocopherol in the way of life medium. Genistein and equol in the blend

Table 1: Problem identification

Lessons learned

DNA's sperm health is an important parameter for addressing infertility problem

There are many elements contributing to damaging DNA's sperm profile

ROS should be kept under check to improve the DNA's health

Some medicines also contribute to DNA damage

ROS: Reactive oxygen species

Table 2: Treatment summary

DNA treatment

Alpha-tocopherol reduces the sperm oxidative stress

The state of testis tissue gives an indication of the damage done to the DNA, such as infection and varicocele

Avoiding the exposure of hazardous materials, such as toxin and hazardous materials

Table 3: Correlation of factors and result of semen investigation

Factors	Result
Infection inflammation	Causes infertility and need to be addressed before having treatment
Oxidative stress	ROS Profile increases due to DNA damage resulting in oxidative anxiety. Cautions are advised to address this issue
Recommended medicine	Genistein and equol mixture, folic acid, zinc sulfate, carnitine

ROS: Reactive oxygen species

are more defensive to kill the oxidative anxiety. As per above outcomes, these mixtures likewise may take part in cancer prevention agent security sperm chromatin honesty and keep from DNA harm.^[36]

What is more, a few reviews demonstrated that the organizations of cancer prevention agent supplements, for example, ascorbic acid, alpha-tocopherol, beta-carotene, retinol, coenzyme Q (Q10), and so on in blend with medications, such as folic acid, zinc sulfate, carnitine, and so on. They can enhance the standard parameters of semen, sperm chromatin respectability, and support the results of ARTs.

CONCLUSION

It has as of late been acknowledged that sperm chromatin trustworthiness is a free file of sperm quality and has better indicative and prognostic limits in the relationship with standard semen investigation comes about for both *in vivo* and *in vitro* richness. Despite the fact that there are various strategies to assess sperm chromatin respectability, every methodology should be institutionalized for increasingly routine use in indicative andrology lab. Nonetheless, these techniques crush sperm amid the assessment procedures. Presenting strategies with some impacts on entire sperm respectability will enhance results of ARTs utilizing spermatozoa with affirmed chromatin trustworthiness. The outcomes may help the doctors to direct infertile couples alluded for ART in a superior way.

Limitations

No experimental tests were conducted to validate the results of the literature reviewed for this paper. The authors of the selected papers might have some sorts of bias due to their hypothesis. Moreover, support of pharmaceutical companies might also result in devising the appropriate treatment for the identified problem

REFERENCES

- Kidd SA, Eskenazi B, Wyrobek AJ. Effects of male age on semen quality and fertility: A review of the literature. *Fertil Steril* 2001;75:237-48.
- Schoor RA. Prostatitis and male infertility: Evidence and links. *Curr Urol Rep* 2002;3:324-9.
- Lewis SE, Agbaje I, Alvarez J. Sperm DNA tests as useful adjuncts to semen analysis. *Syst Biol Reprod Med* 2008;54:111-25.
- Love CC, Kenney RM. Scrotal heat stress induces altered sperm chromatin structure associated with a decrease in protamine disulfide bonding in the stallion. *Biol Reprod* 1999;60:615-20.

5. Aitken RJ, Sawyer D. The human spermatozoon not waving but drowning. *Adv Exp Med Biol* 2003;518:85-98.
6. Alvarez JG. DNA fragmentation in human spermatozoa: Significance in the diagnosis and treatment of infertility. *Minerva Ginecol* 2003;55:233-9.
7. Tomlinson MJ, White A, Barratt CL, Bolton AE, Cooke ID. The removal of morphologically abnormal sperm forms by phagocytes: A positive role for seminal leukocytes? *Hum Reprod* 1992;7:517-22.
8. Sigman M, Lopes L. The correlation between round cells and white blood cells in the semen. *J Urol* 1993;149:1338-40.
9. Cohen PE, Pollard JW. Cytokines and growth factors in reproduction. In: Bronson R, editors. *Re-productive Immunology*. Cambridge, MA: Black-well Science; 1996. p. 52-102.
10. Reichart M, Kahane I, Bartoov B. *In vivo* and *in vitro* impairment of human and ram sperm nuclear chromatin integrity by sexually transmitted Urea-plasma urealyticum infection. *Biol Reprod* 2000;63:1041-8.
11. Kunzle R, Mueller MD, Hanggi W, Birkahuser MH, Drescher H, Bersinger NA. Semen quality of male smokers and nonsmokers in infertile couples. *Fertil Steril* 2003;79:287-91.
12. Potts RJ, Newbury CJ, Smith G, Notarianni LJ, Jefferies TM. Sperm chromatin damage associated with male smoking. *Mutat Res* 1999;423:103-11.
13. Comhaire FH, Mahmoud AM, Depuydt CE, Zalata AA, Christofe AB. Mechanism and effects of male genital tract infection on sperm quality and fertilizing potential: The andrologist's view point. *Hum Reprod Update* 1999;5:393-8.
14. Aitken RJ, Buckingham DW, Brindle J, Gomez E, Baker HW, Irvine DS, *et al.* Analysis of sperm movement in relation to the oxidative stress created by leukocytes in washed sperm preparations and seminal plasma. *Hum Reprod* 1995;10:2061-71.
15. Fraga CG, Motchnik PA, Wyrobek AJ, Rempel DM, Ames BN. Smoking and low antioxidant levels increase oxidative damage to sperm DNA. *Mutat Res* 1996;351:199-203.
16. Donnelly ET, Steele EK, McClure N, Lewis SE. Assessment of DNA integrity and morphology of ejaculated spermatozoa from fertile and infertile men before and after cryopreservation. *Hum Reprod* 2001;16:1191-9.
17. Donnelly ET, McClure N, Lewis SE. Cryopreservation of human semen and prepared sperm: Effects on motility parameters and DNA integrity. *Fertil Steril* 2001;76:892-900.
18. Duty SM, Singh NP, Ryan L, Chen Z, Lewis C, Huang T, *et al.* Reliability of the comet assay in cryopreserved human sperm. *Hum Reprod* 2002;17:1274-80.
19. Giwercman A, Petersen PM. Cancer and male infertility. *Baillieres Best Pract Res Clin Endocrinol Metab* 2000;14:453-71.
20. Richter MA, Haning RV Jr., Shapiro SS. Artificial donor insemination: Fresh versus frozen semen; the patient as her own control. *Fertil Steril* 1984;41:277-80.
21. Revel A, Haimov-Kochman R, Porat A, Lewin A, Simon A, Laufer N, *et al.* *In vitro* fertilization-intracytoplasmic sperm injection success rates with cryopreserved sperm from patients with malignant disease. *Fertil Steril* 2005;84:118-22.
22. Kobayashi H, Larson K, Sharma RK, Nelson DR, Evenson DP, Toma H, *et al.* DNA damage in patients with untreated cancer as measured by the sperm chromatin structure assay. *Fertil Steril* 2001;75:469-75.
23. Chatterjee R, Haines GA, Perera DM, Goldstone A, Morris ID. Testicular and sperm DNA damage after treatment with fludarabine for chronic lymphocytic leukaemia. *Hum Reprod* 2000;15:762-6.
24. Cai L, Hales BF, Robaire B. Induction of apoptosis on the germ cells of adult male rats after exposure to cyclophosphamide. *Biol Reprod* 1997;56:1490-7.
25. Li H, Jian Y, Rajpurkar R, Dunbar JC, Dhabu-wala CB. Cocaine induced apoptosis in rat testes. *J Urol* 1999;162:213-6.
26. Ondrizek RR, Chan PJ, Patton WC, King A. An alternative medicine study of herbal effects on the penetration of zona-free hamster oocytes and the integrity of sperm deoxyribonucleic acid. *Fertil Steril* 1999;71:517-22.
27. Perez-Crespo M, Pintado B, Gutierrez-Adan A. Scrotal heat stress effects on sperm viability, *Avicenna* journal of medical biotechnology, vo sperm chromatin integrity sperm DNA integrity, and the offspring sex ratio in mice. *Mol Reprod Dev* 2008;75:40-7.
28. Aitken RJ, De Iuliis GN. Origins and consequences of DNA damage in male germ cells. *Reprod Biomed Online* 2007;14:727-33.
29. Tesarik J, Mendoza-Tesarik R, Mendoza C. Sperm nuclear DNA damage: Update on the mechanism, diagnosis and treatment. *Reprod Biomed Online* 2006;12:715-21.
30. Ozmen B, Koutlaki N, Youssry M, Diedrich K, Al Hasani S. DNA damage of human spermatozoa in assisted reproduction: Origins, diagnosis, impacts, and safety. *Reprod Biomed Online* 2007;14:384-95.
31. Carrell DT, Emery BR, Hammoud S. The etiology of sperm protamine abnormalities and their potential impact on the sperm epigenome. *Int J Androl* 2008;31:537-45.
32. Evenson DP, Larson KL, Jost LK. Sperm chromatin structure assay: Its clinical use for detecting sperm DNA fragmentation in male infertility and comparisons. *J Androl* 2002;23:25-43.
33. Ward WS. Deoxyribonucleic acid loop domain tertiary structure in mammalian spermatozoa. *Biol Reprod* 1993;48:1193-201.
34. D'occhio MJ, Hengstberger KJ, Johnston SD. Biology of sperm chromatin structure and relationship to male fertility and embryonic survival. *Anim Reprod Sci* 2007;101:1-7.
35. Balhorn R, Cosman M, Thornton K, Krishnan VV, Corzett M, Bench E, *et al.* Protamine mediated condensation

- of DNA in mammalian sperm. In: Gagnon C, editor. *The Male Gamete: From Basic Knowledge to Clinical Applications*. Illinois: Cache River Press; 1999. p. 55-70.
36. Sakkas D, Mariethoz E, Manicardi G, Bizzaro D, Bianchi PG, Bianchi U, *et al*. Origin of DNA damage in ejaculated human spermatozoa. *Rev Reprod* 1999;4:31-7.
 37. Henkel R, Hajimohammad M, Stalf T, Hoogendijk C, Mehnert C, Menkveld R, *et al*. Influence of deoxyribonucleic acid damage on fertilization and pregnancy. *Fertil Steril* 2004;81:965-72.
 38. Lewis SE, Aitken RJ. DNA damage to spermatozoa has impacts on fertilization and pregnancy. *Cell Tissue Res* 2005;322:33-41.
 39. Vogt PH. Molecular genetics of human male infertility: From genes to new therapeutic perspectives. *Curr Pharm Des* 2004;10:471-500.
 40. Carrell DT, Emery BR, Hammoud S. Altered protamine expression and diminished spermatogenesis: What is the link? *Hum Reprod Update* 2007;13:313-27.

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