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Gene changes in male infertility and correlation between causes and sperm quality and count

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Abstract
Male infertility is defined as a man's inability to achieve pregnancy with a fertile partner after a year of regular, unprotected sexual activity. It is responsible for nearly 40–50% of infertility cases globally. In India, cultural beliefs often exclude men from being blamed for infertility, although several biological and lifestyle-related factors can impact male fertility. These include hormonal disruptions in the reproductive axis, physical conditions like varicocele and genital infections, genetic issues such as Klinefelter syndrome or Y chromosome deletions, and epigenetic alterations. Additionally, lifestyle habits like excessive alcohol intake, smoking, obesity, physical inactivity, disrupted sleep patterns, and exposure to harmful environmental agents can significantly lower sperm quality.

A six-month observational study conducted on 354 male infertility patients revealed that 80% had abnormalities in at least one sperm parameter, including low sperm count, reduced motility, or irregular morphology. Genetic testing showed a high rate of abnormalities, particularly in individuals with alcohol consumption and radiation exposure. A large portion (89%) of participants led a sedentary lifestyle and were overweight. Irregular sleep cycles and habitual alcohol use (seen in 75% of cases) were common. Although fewer participants (26%) smoked, all exhibited at least one sperm defect. Chronic health conditions such as diabetes, thyroid issues, and hypertension were also frequently observed. Varicocele was present in all individuals studied, indicating a strong link to structural causes of infertility. Many participants worked in software- related jobs, suggesting potential risks associated with prolonged exposure to electronic devices and radiation.

The study concluded that factors such as excess weight, alcohol consumption, lack of physical activity, sleep disturbances, and radiation exposure are major contributors to male infertility. Promoting healthier lifestyles, regular physical activity, weight management, and limiting harmful exposures could improve reproductive health outcomes in men. These insights stress the importance of early screening and lifestyle interventions in addressing male infertility.

Keywords: Infertility, sperm quality, lifestyle, genetic, varicocele

Introduction

Male infertility is the inability of a male to conceive with a fertile female during at least a year of regular unprotected sexual activity. It has been estimated that 48 million couples and 186 million individuals worldwide live with infertility, with the highest prevalence observed in China, followed by India. Many Indians believe that infertility is a curse from God, and men are often not considered responsible for the inability to conceive. However, approximately 20% of infertility cases involve only the male partner, contributing to 40-50% of cases overall.

Male infertility often stems from disarray in control mechanisms of the reproductive system, influenced by factors such as

1. **Hormonal imbalance:** The hypothalamic-pituitary-gonadal axis, regulates hormone levels critical for male sexual development and function. Disruption in this system can cause infertility. Insufficient gonadotropin-releasing hormone (GnRH) from the brain leads to low testosterone and halted sperm production, as seen in conditions like hypogonadotropic hypogonadism including Kallmann syndrome. Insufficient production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH) by the pituitary gland reduces testicular stimulation, leading to decreased testosterone and sperm production. Increased prolactin can reduce sperm production, libido, and cause impotence, potentially leading to infertility in cases of hyperprolactinemia.
2. **Physical Reasons:** Varicocele, an enlargement of the spermatic vessels, affects sperm production and ejaculatory pathways. Testicular torsion, which twists the testicle in the scrotum and reduces blood flow, can damage the testicle. Chronic and acute genital infections commonly cause male infertility. Mumps viral infection can lead to testicular atrophy and infertility. STDs like gonorrhea and chlamydia can cause epididymal obstruction, leading to infertility. Retrograde ejaculation, Retrograde ejaculation, where semen enters the bladder due to anatomical issues with the sphincter, results in infertility.
3. **Genetic Factors:** Genetic factors contribute to 15% of male infertility cases, including chromosomal abnormalities and single-gene mutations. Chromosomal abnormalities denote unusual changes in genetic material at the chromosome level, which can be inherited or acquired. Klinefelter syndrome is the most common genetic cause of azoospermia due to aneuploid sex chromosomes. Chromosomal defects like 47, XYY can cause spermatogenesis malfunction due to increased FSH and Y chromosome. Disomy. Noonan syndrome in men and Turner syndrome in women (XO/XY mosaic) can cause cryptorchidism and spermatogenesis deficiency due to elevated FSH levels. Translocations occur in 3% of severe oligozoospermia

cases, including significant Robertsonian and bilateral types. Inversion is a chromosomal translocation where a chromosome fragment breaks and rearranges within itself. Although these rearrangements are usually balanced, they can sometimes lead to severe oligoasthenoteratozoospermia or azoospermia. Deletions in the Y chromosomes long arm, known as the AZF (azoospermic factor) deletion region, include AZFa, AZFb, and AZFc zones. Micro-deletions result from recombination of similar fragments in palindromic sequences. AZFa deletions cause Sertoli cell-only syndrome, lacking germ cells. AZFb deletions stop spermatogenesis. AZFc deletions result in variable phenotype. Gene mutations with pathological syndromes such as causing congenital bilateral absence of the vas deferens (CBAVD), are linked to infertility due to mutations in the Cystic fibrosis transmembrane regulator (CFTR).

Primary ciliary defects, an autosomal recessive condition affecting eyelash function, occur in half of men with asthenospermia. Non-syndromic infertility is still poorly understood. Many X-linked genes expressed in the testis play critical roles in gametogenesis. Mutations in genes like the AR gene lead to androgen insensitivity syndrome and affect spermatogenesis. Kallmann syndrome, caused by defects in genes that disrupts GnRH neuron migration, causing hypogonadotropic hypogonadism and anosmia.

4. **Epigenetic Factor:** Acetylation and methylation are key epigenetic factors influencing gene expression, crucial in studies on male infertility. Spermatogenesis involves significant epigenetic reprogramming, including histone-to-protamine substitution. Altered sperm epigenetics, such as gene hyper methylation, are observed in men with oligozoospermia and oligoasthenoteratozoospermia, linking to semen parameter deficiencies and infertility.

5. **Sexual Problems:** Intercourse issues like erectile dysfunction (impotence), early ejaculation, and inability to ejaculate can stem from both physical and psychological causes.

6. **Lifestyle and Environmental factors:** Workplace exposure to solvents, insecticides, adhesives, silicones, and radiation can cause male infertility. Radiation exposure can lower sperm production, potentially causing infertility with high doses. Excessive sun exposure can temporarily reduce sperm count. Occupations involving prolonged sitting (such as driving) or exposure to high temperatures (such as in bakeries) can harm fertility. The effects of alcohol and smoking on fertility are uncertain, but cigarette smoking and alcohol consumption may degrade sperm quality. Poor nutrition, including increased saturated fat intake, can reduce sperm concentration. Repeated cocaine and cannabinoid use lower urinary testosterone. Air pollution reduces sperm motility and alters morphology.

Sperm are responsible for fertilizing the female egg and initiating pregnancy. They are formed in the testes through spermatogenesis, and any issues in the process can lead to abnormalities. The WHO defines several terms related to semen analysis as follows:

a. **Sperm count:** *Azoospermia* means no spermatozoa in the ejaculate, *cryptozoospermia* is absence of sperm in fresh samples but presence in centrifuged ones (often <1M/ml), and *oligozoospermia* is low sperm count (<15M/ml).

b. **Sperm Motility:** *Asthenozoospermia* is a condition where sperm have impaired movement, Efficient sperm passage through cervical mucus relies on rapid progressive motility (>25 μm/s). A normal semen analysis requires at least 50% grade A and B motile sperm, as poor motility predicts fertilization failure. *Necrozoospermia* denotes a high proportion of dead or immotile sperm in semen, with variations from complete (all dead) to incomplete (5%-45% viable). It is usually confused with asthenozoospermia.

c. **Sperm Morphology:** *Teratozoospermia* is defined by less than 4% morphologically normal sperm. Sperm structure and shape can be assessed using WHO classification or Kruger's strict criteria. Morphology should be considered alongside other parameters for clinical assessment. Disturbance of all three parameters—sperm count, motility, and morphology— is called *Oligoasthenoteratozoospermia*.

d. **Sperm agglutination:** Spermatozoa adhering to each other, forming clumps that can impair their motility and morphology.

e. **DNA fragmentation:** Normal sperm chromatin is vital for genetic transmission, but defective chromatin (DNA breaks or damage) negatively impacts fertility.

f. **Semen volume and Characteristics:** *Aspermia* is the absence of semen due to retrograde or no ejaculation, while *hypospermia* refers to semen volume being less than 1.5 milliliters. *Leukospermia* involves over 1 million white blood cells per milliliter of ejaculate, and *haemospermia* is the presence of red blood cells.

Diagnosing male infertility involves tests and evaluations to identify the cause, which include

History taking and physical examination are initial steps in evaluating male infertility. Semen analysis assesses sperm count, motility, morphology, and other parameters critical for fertility assessment. Hormone testing involves a blood test to measure testosterone and other hormone levels crucial for sperm production. Genetic testing, such as Y Chromosome Microdeletion Analysis or CFTR Gene Mutation Testing, examines genetic factors impacting fertility. Scrotal and transrectal ultrasound are imaging methods used to detect abnormalities in male reproductive organs. Post-Ejaculatory Urinalysis checks for sperm presence in urine after ejaculation. Testicular Biopsy examines testicular tissue to assess sperm production. Other

specialized tests include Sperm DNA Fragmentation Test, Sperm Chromatin Structure Assay (SCSA), and ROS (Reactive Oxygen Species) Testing.

Treatment of male infertility involves various approaches like, pharmacological treatment

1. **Hormonal Treatment:** The main goal is to maintain the (HPG) axis to increase testosterone. Treatment for secondary hypogonadism depends on its cause. For pituitary insufficiency causing male infertility, standard therapies include Human chorionic gonadotropin (hCG) in combination with Human menopausal gonadotropin (hMG) or purified urinary/recombinant hFSH. Hypothalamic disorders can be addressed with pulsatile GnRH therapy using a portable pump. Pause testosterone during GnRH therapy; resume afterward.

2. **Drugs:** Dopamine agonists like cabergoline treat hyperprolactinemia from prolactinomas by shrinking tumors, lowering prolactin levels, and restoring fertility. Aromatase inhibitors like testolactone and anastrozole increase testosterone, decrease estradiol, and enhance semen parameters. Sympathomimetic agents improve ejaculatory dysfunction by enhancing smooth muscle contraction, especially in diabetic neuropathy cases, However, their effectiveness diminishes over time, becoming less beneficial for most patients. SERMs act on estrogen receptors, increasing GnRH release to boost FSH and LH secretion, thereby enhancing testosterone production and spermatogenesis. Clomiphene citrate is preferred for low testosterone with a normal T/E ratio. Antibiotics improve seminal health by reducing leukocytes, lowering ROS, and enhancing sperm parameters in genitourinary infections. NSAIDs and COX-2 inhibitors reduce leukocytospermia and improve all seminal parameters in a bacterial case. Treatment with NSAIDs followed by carnitine shows greater reduction in ROS and improvement in sperm parameters compared to concurrent treatment.

3. **Supplements (Vitamins and Antioxidants):** Antioxidants combat sperm oxidative damage, aiding male fertility. Carnitine aids sperm energy by transporting fatty acids to mitochondria, boosting cell energetics and membrane phospholipids. Vitamin E disrupts lipid peroxidation, enhances antioxidants, and scavenges free radicals from oxidative reactions. Vitamin C in seminal fluid protects sperm by neutralizing harmful radicals and preventing agglutination. Selenium (Se) protects against sperm DNA damage, and enhances motility and capacity. Carotenoids synergize with Se and vitamin E. Glutathione is a versatile antioxidant that protects lipids, proteins, and nucleic acids from oxidative damage, enhancing sperm motility when combined with vitamin E. N-acetyl cysteine replenishes glutathione, reducing free radicals and ROS. Pentoxifylline, a phosphodiesterase inhibitor, boosts erections by raising intracellular cAMP levels. Zinc and copper regulate antioxidant enzymes like superoxide dismutase, protecting against ROS that can damage sperm and organs.

Non-Pharmacological Treatment

1. **Surgical Treatment:** Correction of anatomical abnormalities or obstructions, include:
   - Transurethral resection of ejaculatory ducts to correct obstruction.
   - Vasoepididymostomy for epididymal obstruction.
   - Vasectomy reversal techniques like vasovasostomy, re-anastomosis, and vasoepididymostomy.
   - Orchiopexy for testicular torsion.
   - Microsurgical and laparoscopic varicocelectomy and open surgical ligation of spermatic vein for varicocele repair.

2. **Lifestyle Modification:** Making a positive lifestyle changes like weight control, reduction of smoking/alcohol, adopting a nutritious diet and use of personal protective Equipment that protect from chemical exposure.

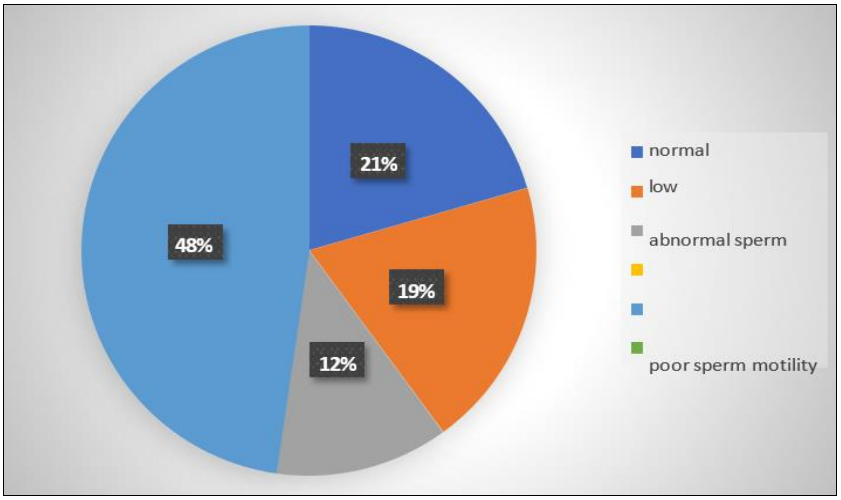
3. **Sperm Retrieval and Assisted Reproductive Technology:** Sperm retrieval is used for men with obstructive azoospermia when anatomic correction isn't possible, and for those with non-obstructive azoospermia, often combined with assisted reproductive technology (ART). It aims to obtain high-quality sperm for immediate use or cryopreservation while minimizing reproductive tract damage. Techniques include retrieval during surgical reconstruction, microsurgical epididymal sperm aspiration, intraoperative testicular sperm retrieval, and percutaneous methods. ART involves procedures manipulating male and female gametes for reproduction, such as *in vitro* fertilization (IVF), intracytoplasmic sperm injection (ICSI), preimplantation genetic diagnosis, embryo cryopreservation, and gestational surrogacy ICSI is the preferred for refractory male infertility, including immunologic infertility, azoospermia, severe oligozoospermia, severe asthenozoospermia, poor sperm morphology, use of surgically retrieved sperm, and previous IVF fertilization failure.

Results

A prospective observational study was conducted in different hospitals on male Infertility to find out the causes of sperm gene abnormality in males. The inclusion criteria of my study in male infertility patients. Exclusion criteria are female patients and normal Fertility patients.

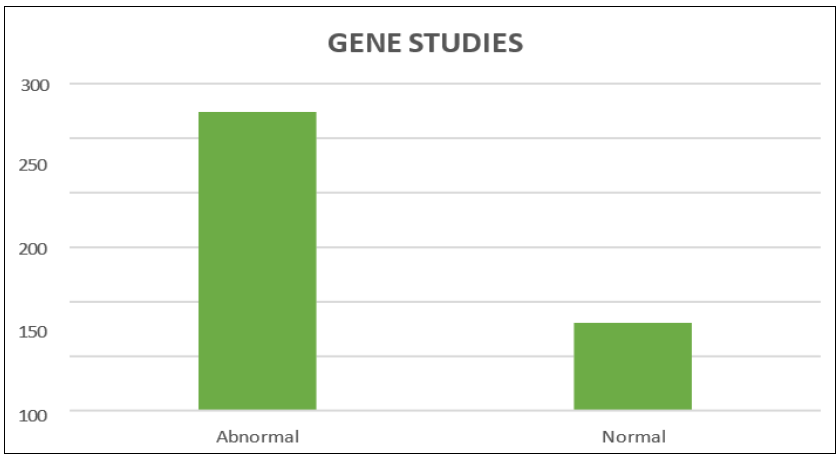
In 6 months of duration, we have collected 354 samples of male infertility patients.

1. Sperm Analysis



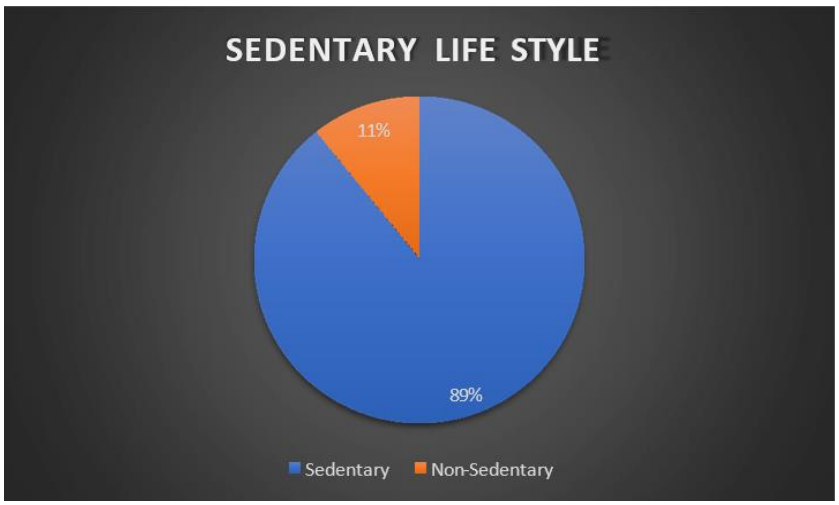
About 80% of the participants' sperm analysis has shown anyone of the sperm abnormality and only 20% of the participants have shown normal sperm analysis.

1. Gene Studies



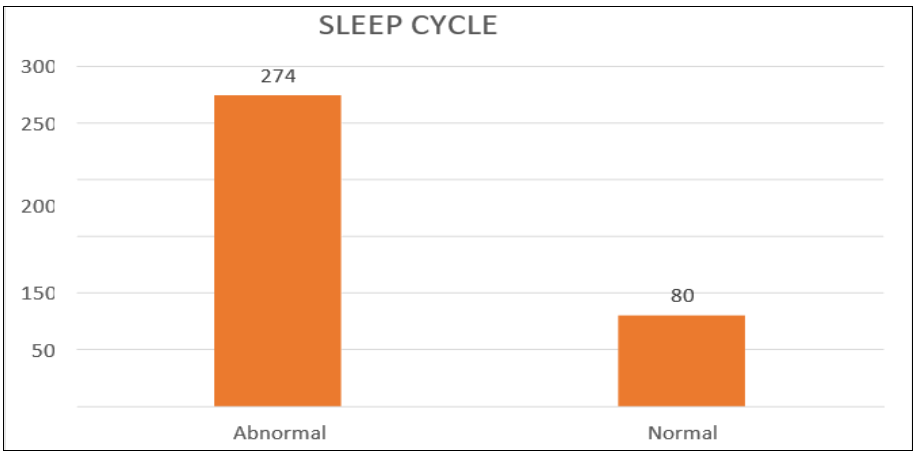
Gene studies revealed that a high number of abnormalities.

2. Sedentary Lifestyle



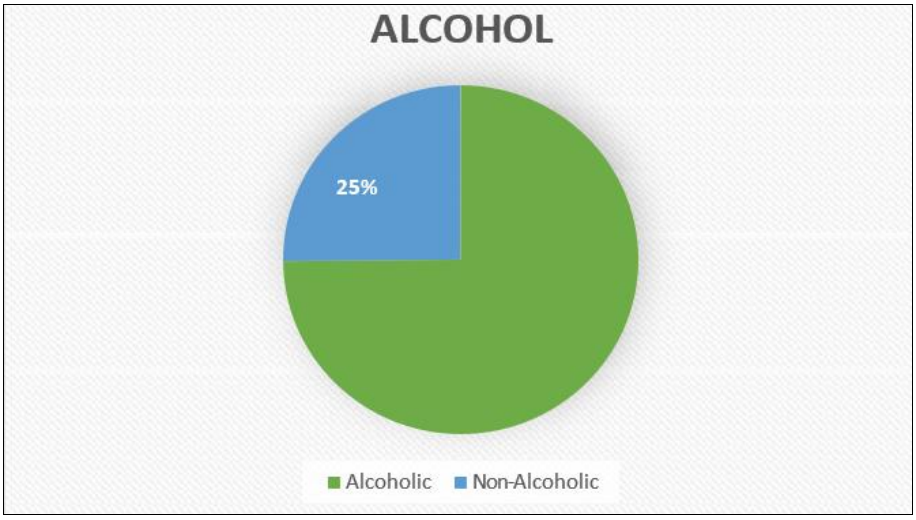
A majority (89%) of the participants follow sedentary lifestyle and only 11% of the participants do follow non-sedentary lifestyle.

3. Sleep Cycle



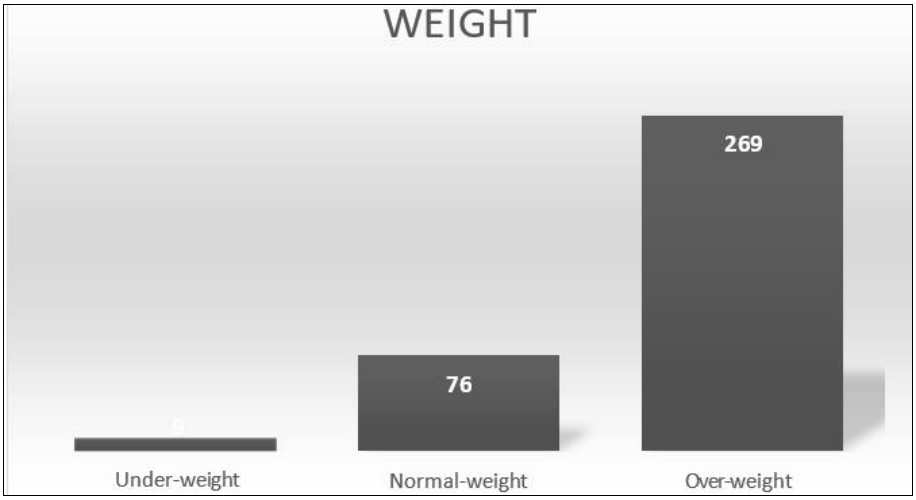
An abnormal sleep cycle is usually observed in most of the participants which depict that sleep cycle affects the fertility in the participants.

4. Alcohol Consumption



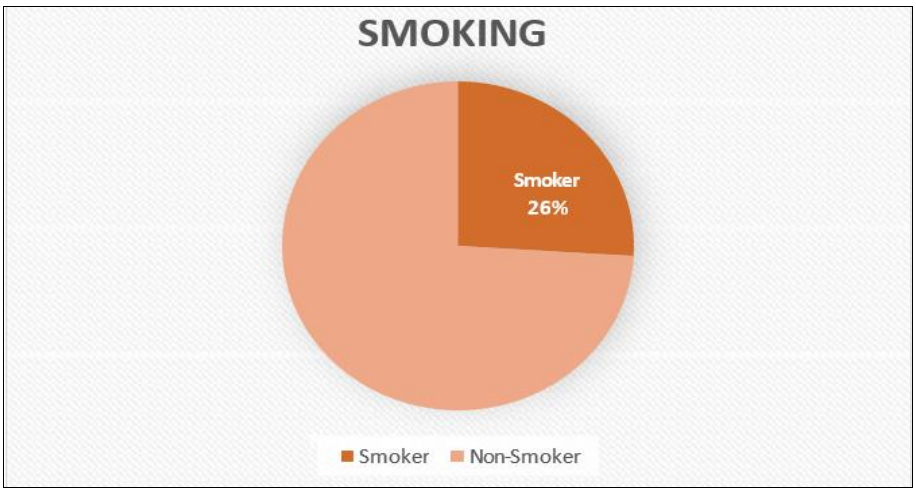
More than half of the participants have shown regular consumption of alcohol which also shows a strong correlation between the consumption of alcohol and male infertility.

5. Weight



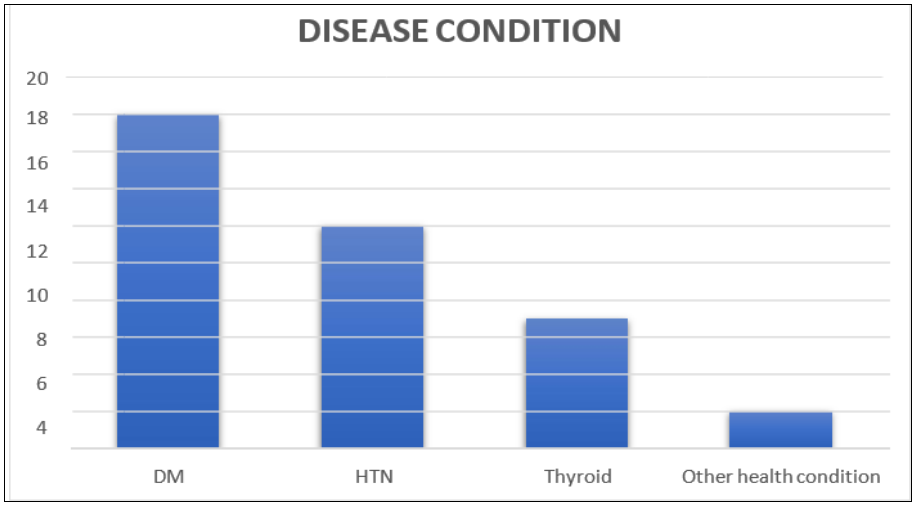
A large number of the participants (269) are overweight, and only small number of the participants are underweight and normal weight.

6. Smoking



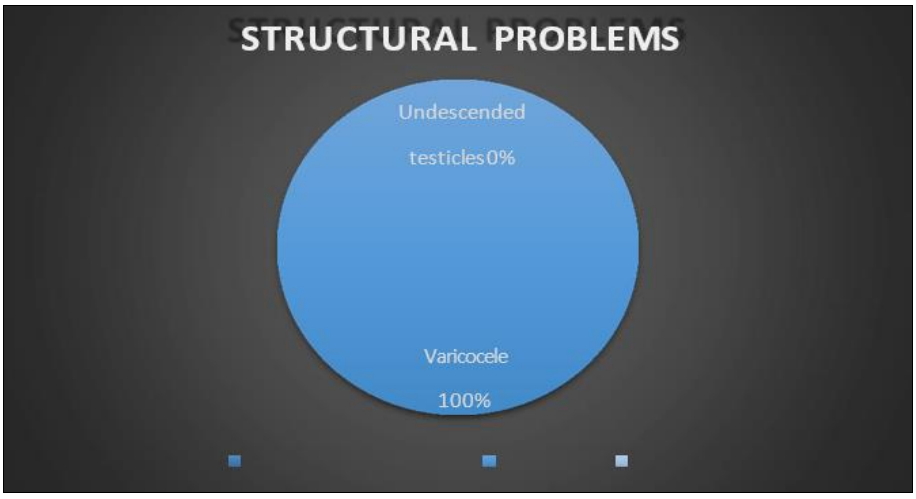
Smoking and infertility are correlated, and in the participants, who smoke (26%) regularly revealed the presence of any one of the sperm abnormalities, which may include poor sperm motility, low sperm count, and/or abnormal sperm morphology.

7. Disease Condition



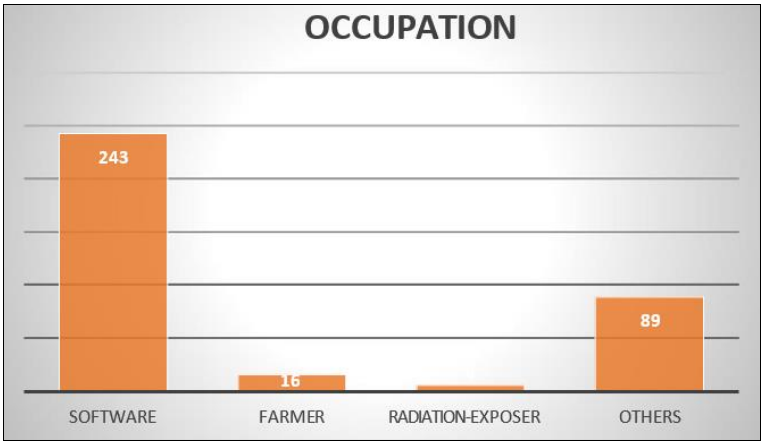
Among the disease conditions – DM, HTN and Thyroid are the most commonly observed comorbidities which may lead in impaired sperm production.

8. Structural Problems



All the study participants have predominantly revealed the presence of Varicocele as the structural problem.

9. Occupation



The occupation-wise distribution of the participants has shown that many of the participants are software employees.

Discussion

This prospective observational study was conducted in different hospital on male infertility to investigate the causes of sperm gene abnormalities in males, in a sample of 354 patients collected over six months.

Our study included only the collection of samples from males who are infertile. Fertile males and females are excluded from our study.

Our primary aim was to identify correlations between lifestyle, genetic, structural, and occupational variables with sperm abnormalities.

The sperm analysis identified 48% - poor sperm motility, 12% - Abnormal sperm morphology, 19% - low sperm count, and only 21% - showed normal parameters. This indicates that a significant majority (79%) of the sampled male patients presented with at least one abnormal sperm parameter. This reflects the growing prevalence of male reproductive issues and highlights the urgency to investigate causative factors.

Gene studies revealed a substantial percentage of abnormalities. Abnormal gene profiles were more prevalent in individuals with exposure to alcohol and radiation. This suggests that environmental and lifestyle induced mutagenic influences can contribute to genetic abnormalities affecting fertility. These mutations can impair the formation of sperms and may result in permanent infertility. The most common chromosomal changes are Y chromosome deletions.

89% of the infertile men - lead a sedentary lifestyle. A sedentary lifestyle may impair testicular function due to increased scrotal temperature and hormonal imbalances.

The strong correlation between inactivity and poor sperm quality (low motility and count) supports this conclusion. Most software people are experiencing infertility problems.

The data of sleep cycle suggests an influence of poor sleep pattern (abnormal sleep cycle) on sperm health. Sleep disruption can affect testosterone levels and increase oxidative stress, both of which impair sperm parameters. About 274 out of 354 participants showed abnormal sleep cycle and hence contributing to poor fertility outcomes.

About 75% of the participants were alcoholics. Chronic alcohol intake is known to lower testosterone levels and increase oxidative damage, which may lead to sperm DNA fragmentation and poor reproductive outcomes.

The majority of the participants were overweight (269 out of 354), who have shown negative fertility outcome or poor reproductive outcomes in compliance with previous studies.

Obesity is associated with hormonal imbalances (e.g.: increased estrogen, decreased testosterone) and increased scrotal temperature, which negatively affect sperm production and function. 26% of the participants were smokers.

Though smoking was less common among the groups compared to other factors, it still plays a detrimental role in sperm DNA integrity, oxidative stress and overall sperm quality.

Several patients had underlying conditions like Diabetes Mellitus (DM) and Hypertension (HTN), and Thyroid disorders.

These chronic illnesses are known to disrupt the hypothalamic - pituitary - gonadal axis, leading to impaired sperm production.

All the participants with fertility or structural issues had varicocele (100%).

Varicocele is a common and co-relatable cause of male infertility, often associated with poor sperm parameters. This presence of structural issues and infertility in these male participants has shown a strong correlation.

A significant number of patients were exposed to radiation, particularly among those in tech or software related jobs.

Exposure to radiation was linked to genetical abnormalities. And prolonged exposure to electromagnetic radiation from devices like laptops, phones, and radiation emitting machinery can disrupt the sperm DNA integrity and result in a lower sperm quality.

Overall, the study clearly identifies obesity, alcohol consumption, sedentary lifestyle and radiation exposure as the key contributors to male infertility.

These factors, often interrelated, seem to drive both functional and genetic damage to sperm. Lifestyle interventions targeting weight loss, physical activity, and reduction in alcohol or radiation exposure may significantly improve reproductive health in patients with fertility issues or poor sperm quality.

Conclusion

According to our study, the most common causes of male infertility are being overweight, alcohol use, sedentary lifestyle, abnormal sleep cycle and radiation exposure. Low count and low mobility were most common in sedentary

lifestyle patients. Gene abnormalities/ chromosomal abnormalities seen in alcoholic, radiation exposure patients. Physical activity and healthy lifestyle will improve the male fertility. The most common chromosomal changes in sperm gene studies are Y chromosome deletions.

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