Potential Risk Of MSG-Induced Infertility in Males: A Review of Reproductive Toxicity

Deepak Chand[1], Dr. Aruna Singh[2]
[1]*Assistant Professor, Smt. Vidyawati College of Education Jhansi*
[2]*Assistant Professor, Department of Science, Bhagwan Adinath College of Education Lalitpur*

***Abstract*—A common taste enhancer in processed foods, monosodium glutamate (MSG) has caused serious health concerns because of possible harm to the male reproductive system. This review examines how MSG affects male fertility, including data from a number of experimental investigations using animal models. Results show that exposure to MSG is linked to significant histological and morphological changes in reproductive organs, including the prostate gland, testes, epididymis, and seminal vesicles. Seminiferous tubule shrinkage, germinal epithelium degradation, decreased sperm motility and count, and an increase in sperm abnormalities are some of these alterations. Hormonal disturbances were also regularly noted, including reduced levels of gonadotropin-releasing hormone (GnRH), follicle-stimulating hormone (FSH), luteinizing hormone (LH), and testosterone. Additionally, MSG-induced oxidative stress and inflammatory responses are demonstrated by immunohistochemical experiments, which show decreased PCNA reactivity and increased NF-κB expression. All of these results point to the possibility that MSG use may harm male reproductive health by interfering with spermatogenesis, hormone balance, and cellular integrity. To evaluate the relevance of these findings in human populations, more clinical research is required**

***Index Terms*—Monosodium Glutamate, Testis, Epididymis, Prostrate Gland, Hormone**

I. INTRODUCTION

Monosodium glutamate (MSG), also known as Ajinomoto, sodium glutamate, or E621. Sodium glutamate, is a sodium salt of glutamic acid. MSG is found naturally in some foods including tomatoes and cheese in this glutamic acid form. MSG is used in cooking as a flavor enhancer with a savory taste that intensifies the umami flavor of food, as naturally occurring glutamate does in foods such as stews and meat soups. It considered the fifth basic taste, and is produced by fermenting substances like sugarcane or molasses using microbes. The substance is widely used in processed foods. Monosodium glutamate (MSG) is a commonly used food additive that enhances the flavor of many ingredients and processed foods found in supermarkets. It produces a unique savory taste known as umami, a flavor often described as meaty or broth-like (Xiong et al., 2009; Schiffman, 2000). The term umami is originally Japanese and refers to the deep, savory taste found in foods like certain fish and soups. With lifestyle changes and a growing reliance on processed foods, MSG consumption has increased globally.

According to the European Food Safety Authority (EFSA), the Acceptable Daily Intake (ADI) for MSG is set at 30 mg per kilogram of body weight per day. In Europe and the U.S., typical daily intake ranges from 0.3 to 1.0 grams, whereas in many Asian countries, it is significantly higher at 1.2 to 1.7 grams per day. Some estimates suggest that individuals in Asia may consume 10 to 20 times more MSG than those in Europe and the U.S., averaging between 1,200 to 3,000 mg daily (Brosnan et al., 2014). For context, the average daily intake from processed foods is about 1 gram in Europe, 4 grams in Asia, and 10 grams in Germany (Park et al., 2014). Most toxicity studies on MSG have focused on very high doses given to animals — typically 2,000 to 8,000 mg/kg of body weight — far exceeding the levels humans would realistically consume (Shin et al., 2010). In restaurants and street food stalls, the exact amount of MSG used is often unregulated and not measured precisely.

The potential health risks of food additives, including MSG, have been under evaluation since the mid-20th century by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) (Heinemeyer, 2019).

Despite its popularity and effectiveness in improving food flavor, MSG's impact on human health has been studied for decades, with mixed findings. Animal research, particularly involving neonatal mice, has shown that MSG can be neurotoxic at high doses. It may disrupt the hypothalamic-pituitary-adrenal (HPA) axis and damage neurons in the hypothalamic region (Pizzi et al., 1977; Garattini, 2000). Early experiments in rats found that administering MSG during the first 6–10 days of life affected the brain's regulation of reproductive hormones like FSH and LH (Lamperti & Blaha, 1976). Further studies in adult Wistar rats have demonstrated that long-term MSG exposure can lead to low sperm count (oligozoospermia) and a rise in abnormal sperm shapes (Onakewhor et al., 1998). Other research has confirmed dose-dependent effects on testicular weight, sperm motility, sperm count, and sperm head structure (Ekaluo et al., 2013). Experiments on male mice revealed that MSG can damage GnRH neurons, which are crucial for reproductive function, and that such damage does not naturally heal over time (Wang et al., 2021). The reproductive system is particularly vulnerable to glutamate toxicity because glutamate receptors are found in both reproductive organs and sperm. This can cause excitatory damage, leading to hormonal imbalances in the hypothalamic-pituitary-gonadal (HPG) axis (Igwebuike et al., 2010). Ultimately, MSG exposure has been shown to impair testicular structure and function — reducing testicular size, the thickness of the germinal layer, sperm count, and increasing abnormalities in sperm development.

II. HISTORY AND DISCOVERY

The discovery of monosodium glutamate (MSG) is a story that spans multiple decades, cultures, and scientific advances. Here is a detailed breakdown of how MSG came to be understood, identified, and produced. The foundation for the discovery of MSG began with the isolation of glutamic acid by Karl Heinrich Ritthausen, a German chemist, in 1866. While studying wheat gluten, Ritthausen extracted this amino acid through hydrolysis. He was unaware of its flavor properties at the time, but his work laid the chemical groundwork for later discoveries.In the early 20th century, Kikunae Ikeda, a Japanese chemist and professor at Tokyo Imperial University, became intrigued by the unique savory taste found in traditional Japanese dishes—especially in dashi, a broth made from kombu (a type of seaweed, Laminaria japonica).He noticed that the taste of dashi was distinct from the four basic tastes known at the time: sweet, sour, salty, and bitter. He called this new taste "umami", a Japanese word meaning "deliciousness" or "pleasant savory taste. "In 1908, Ikeda began experimenting with kombu to determine the source of this umami taste. Through a process of aqueous extraction and crystallization, he successfully isolated glutamic acid as the key compound responsible for the taste. He found that glutamic acid produced a rich, meaty, savory flavor, especially when dissolved in water—this was the umami taste he had identified. Ikeda realized that pure glutamic acid was not very stable or soluble in water. So, he tested various salts of glutamic acid—such as those of potassium, calcium, and magnesium—to find a more usable form. In 1909, shortly after his discovery, Ikeda partnered with the Suzuki brothers, who began the first commercial production of MSG under the brand name "Aji-no-moto", which translates to "essence of taste" in Japanese. This marked the beginning of MSG as a commercial food additive. It quickly gained popularity in Japan and later around the world, especially in processed foods, snacks, soups, and seasonings. Though umami was described in 1908, it was not widely accepted as a fifth basic taste until many decades later. Modern research has since confirmed that the human tongue has specific receptors for glutamate, proving that umami is indeed a distinct taste, alongside sweet, salty, sour, and bitter.

III. PROPERTIES AND USES

Monosodium glutamate (MSG) is a white crystalline powder used as a flavor enhancer to add a savory, umami taste to foods. Its properties include a strong flavor-enhancing effect, the ability to improve food texture, and a long shelf life.

Uses range from enhancing soups, snacks, and processed meats to being a component in some medical treatments.

- Appearance: White or off-white crystalline powder.
- Flavor: Imparts a savory, meat-like umami taste that intensifies other flavors.
- Solubility: Highly soluble in water (740g/L).

- Thermal Stability: Stable at high temperatures, making it suitable for industrial food preparation.
- Natural Occurrence: Found naturally in foods like tomatoes, cheese, and mushrooms.
- Chemical Structure: A sodium salt of the amino acid glutamic acid.

Uses

- Flavor Enhancer: Used in a wide variety of foods, including soups, stews, sauces, gravies, snacks, and processed meats, to intensify savory flavors.
- Salt Reduction: Can be used to reduce the amount of sodium in a product while still maintaining flavor.
- Texture Improvement: Can help improve the texture of certain foods, such as making meat more tender.
- Preservative: Inhibits the growth of microorganisms, extending the shelf life of some products.
- Other: Used in spice blends, canned foods, and to enhance the taste of tobacco. It is also used in some medical treatments and diagnostic aids.

IV. EFFECT OF MSG

A.MORPHOLOGICAL AND ANATOMICAL STUDY OF MALE REPRODUCTIVE ORGAN

Numerous studies have explored the morphological and anatomical impacts of monosodium glutamate (MSG) on the reproductive organs. For example, an experimental study on male hamsters found that administering 4 or 8 mg of MSG per gram of body weight from Days 1 to 5 significantly reduced the weights of the testes, adrenal glands, and pituitary glands, though seminal vesicle weights remained unchanged compared to the control group. When the same doses were given from Days 6 to 10 or throughout Days 1 to 10, all organ weights were considerably lower, and at 8 mg/gm, the testes appeared atrophic (Lamperti and Blaha, 1976) In another study, Kadir et al. (2011) observed that animals exposed to the highest MSG dose showed increased aggression. While they consumed more food and water, their body weight did not increase, and they experienced slower growth rates, with the highest dose group showing the most reduced growth. Nossier et al. (2012) reported that all MSG-treated animals had smaller testes compared to age-matched controls. Similarly, Ekaluo et al. (2013) found that MSG exposure led to testicular and epididymal toxicity, reflected in decreased organ weights. Further, Sakr and Badawy (2013) observed that MSG-treated rats had smaller seminiferous tubule diameters and reduced germ cell height, while Alalwani (2013) documented symptoms such as severe diarrhea, frequent and foul-smelling urination, testicular hemorrhage, increased appetite, and weak limb movement. In male rats, MSG treatment also led to a reduction in the size of the epididymis, vas deferens, and seminal vesicles (Iamsaard et al., 2014; Mohamed et al., 2017) A study on mice revealed that by 60 days of age, those exposed to MSG showed several physical abnormalities, including dull fur, short and stocky bodies, thick subcutaneous fat, short penis length, underdeveloped testes, and failure of the testes to descend. These abnormalities were still present at 90 days of age (Wang et al., 2021). Collectively, these studies demonstrate that MSG exposure can cause serious morphological and anatomical alterations, particularly in the male reproductive system, potentially leading to a range of biological dysfunctions.

B.HISTOMORPHOLOGICAL ALTERNATION

1. TESTES

Monosodium glutamate (MSG) administration has been linked to various histomorphological alterations in male reproductive organs, particularly the testes. In a study by Lamperti and Blaha (1976) on hamsters, treatment with 8 mg MSG/g body weight from days 6 to 10 after birth led to shrinkage of testicular tubules and suppressed spermatogenesis, with no spermatids or spermatozoa observed in the affected tubules. Das and Ghosh (2010) also reported that MSG caused histological changes in the germinal epithelium and Leydig cells, including a reduction in spermatogenic cells in many seminiferous tubules and an increase in the pachytene stage of primary spermatocytes. Additionally, Leydig cells showed signs of hypertrophy. In contrast, Igwebuike et al. (2011) found no significant pathological lesions in the seminiferous tubules of male rats treated with 4 mg MSG/g body weight, indicating that lower doses might not produce visible damage. However, more extensive histological investigations by Kadir et al. (2011) revealed that MSG exposure resulted in a decrease in sperm cell count and structural disorganization in the seminiferous tubules, which also became less

convoluted. Nosseir (2012) observed further deterioration in testicular structure in MSG-treated rats, including atrophy of the seminiferous tubules, disruption of the germinal epithelium, and loss of spermatogenic cells such as spermatocytes and spermatids. The tubule lumina showed epithelial depletion, often retaining only Sertoli cells and spermatogonia. Signs of degeneration and necrosis were evident in the spermatogenic cells, including vacuolated cytoplasm and chromatin abnormalities, with variously sized vacuoles present in the lumina. Leydig cell numbers were significantly reduced. A comparative study by Iamsaard et al. (2014) indicated that at a lower dose of 0.25 g/kg body weight, MSG did not cause major histological changes. However, higher doses led to mild sloughing of spermatogenic cells, vacuolization, and shrinkage of interstitial tissue. In a separate study, Alalwani (2013) found that MSG injections in rats resulted in damage to spermatogenic cells, irregular basement membranes, necrosis of Leydig cells, and loss of interstitial connective tissue. Similarly, Hamza and Harbi (2014) reported spermatogenic arrest, where sperm formation was halted, and only primary spermatogonia were present. Further histological changes reported by researchers include: Heavily pigmented nuclei in Sertoli cells, abnormal germ cells with pyknotic nuclei, and vacuoles between germ cells (Mohamed et al., 2017), Decreased sperm concentration in the epididymal and prostate lumens, and folding of the basal membrane (Abu Hanipah et al., 2018), Congestion of interstitial blood vessels and degeneration of spermatogonial cells (El-Masry). In summary, these studies collectively demonstrate that MSG exposure—particularly at higher doses—can lead to severe histological damage in male reproductive tissues, affecting both the structure and function of the seminiferous tubules, Leydig cells, and spermatogenic process.

2. PROSTRATE GLAND:

A study conducted by Jubaidi et al. (2019) found that MSG exposure in rats led to atrophy of the prostate gland lumen, and the prostate epithelium became thinner and showed reduced folding.

3. SEMIVAL VESICLE:

The seminal vesicles of rats treated with monosodium glutamate (MSG) showed a reduction in mucosal folding, and the epithelial lining exhibited irregular and disorganized cellular structures, unlike the more uniform structure observed in control groups (Jubaidi et al., 2019). Additionally, El-Masry and El-Sayed (2019) reported blood vessel congestion, tissue hyperplasia, and vacuolation within the serosal layer of the seminal vesicles. These results suggest that MSG supplementation can cause significant histomorphological alterations in the male reproductive system. Given the negative impact on tissue structure and the importance of these findings, further clinical studies are essential to validate and expand upon these observations.

4. EPIDIDYMIS:

Only a limited number of studies have examined the histological effects of MSG on the ductus epididymis in rats. Sakr and Badawy (2013) observed the presence of vacuolated cells in this region following MSG treatment. In a study by Hanipah et al. (2018), it was reported that the epididymis showed a marked reduction in the concentration of spermatozoa within the lumen, along with the presence of irregularly shaped nuclei. The overall sperm mass was significantly diminished. Another investigation found that male rats exposed to MSG experienced congestion and degeneration of the columnar epithelial cells and their stereocilia in the epididymal tissue. Additionally, the epididymal lumen lacked sperm entirely (Al Husseini et al., 2022).

C. HORMONAL STUDY

Numerous studies have documented that monosodium glutamate (MSG) administration leads to alterations in hormone levels, particularly those related to male reproductive function. For example, Igwebuike et al. (2011) found that both young and adult rats exposed to low, medium, and high doses of MSG showed reduced average serum testosterone levels. Similarly, Fernandes et al. (2012) reported a decrease in plasma testosterone, along with reductions in follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels. Sakr and Badawy (2013) also observed lowered testosterone and LH levels following MSG exposure. Expanding on this research, Iamsaard et al. (2014) noted that rats treated with higher MSG doses (3 g/kg and 6 g/kg) had significantly reduced plasma testosterone, whereas rats given a lower dose (0.25 g/kg) showed no significant hormonal changes.

Ichimoku et al. (2014) reported declines in GnRH, LH, testosterone, and thyroid hormone levels, while Ochiogu et al. (2015) similarly found a drop in GnRH, LH, and testosterone. In male rabbits, Okoye et al. (2016) identified significant reductions in serum LH, testosterone, and cholesterol, as well as lower levels of ALT activity. Other studies confirmed these trends: Khaled et al. (2016): Reduced blood testosterone levels, Mohamed et al. (2017): Decreased testosterone and LH, Jubaidi et al. (2019): Lower LH levels at 120 mg/kg MSG dose, though FSH and testosterone remained unchanged, El-Masry and El-Sayed (2019): Significant reduction in LH and testosterone after six weeks of oral MSG exposure, Kianifard et al. (2020): Lower testosterone level, Mohamed El Kotb et al. (2020): Decreases in both testosterone and L H, Wang et al. (2021): Reduced FSH, LH, and thyroid hormone levels, Abdul Hamid et al. (2021): Reported lower serum testosterone levels in rats. These findings consistently suggest that MSG can negatively affect male fertility by disrupting key reproductive hormones such as testosterone, LH, FSH, and GnRH. However, to fully understand the risks posed to human health, it's essential to consider how long MSG was administered, the dosages used, and the routes of administration in these animal studies.

D. SPERM ANALYSIS AND COUNT

MSG exposure has been widely linked to various sperm abnormalities and reduced sperm quality, as demonstrated by multiple studies. Kumar et al. (2008) reported a significant increase in abnormal sperm tails, a notable reduction in the number of normal sperm, and a rise in overall sperm deformities following MSG treatment. In a related study, Igwebuike et al. (2011) found that epididymal sperm reserves in adult male rats were significantly lower across all MSG-treated groups. Furthermore, sperm from these groups showed reduced forward progressive movement, with the highest MSG doses resulting in the greatest percentage of abnormal sperm morphology, including misshapen heads (curved or rounded) and irregular tail lengths (either too short, long, or duplicated). Kadir et al. (2011) also observed a statistically significant increase in sperm with abnormal shapes, along with altered sperm motility and head structure. Ekaluo et al. (2013) confirmed these findings, reporting clear differences in sperm count, motility, and head abnormalities in MSG-treated animals. Iamsaard et al. (2014) found that epididymal sperm concentration was considerably lower in rats given 6 g/kg of MSG on days 14, 28, and 42. The mean cauda epididymal sperm reserves (CESR) were significantly reduced across all treated groups. Similarly, Ochiogu et al. (2015) observed the lowest CESR values in rats that received 1.0 g/kg of MSG, both subcutaneously and orally, particularly on days 14 and 28. In male rabbits, Khaled et al. (2016) reported significantly reduced sperm motility, fewer motile and functional sperm, and lower initial fructose levels, accompanied by a marked increase in dead and abnormal sperm. Radhiah Najm Abd (2017) found that oral administration of MSG to male mice over 7, 14, and 21 days led to a significant decline in normal sperm count, compared to control groups. The sperm abnormalities included headless, tailless, hookless sperm, and other abnormal head shapes. Similarly, El-Sawy et al. (2018) reported that MSG caused a significant reduction in sperm motility and percentage of normal sperm, while increasing sperm deformities. Jubaidi et al. (2018) also noted that treatment with 120 mg/kg body weight of MSG led to a significant decrease in sperm count, motility, and viability, along with a higher proportion of sperm with abnormal morphology. According to El-Masry and El-Sayed (2019), sperm deformities in MSG-treated rats could be categorized into head, neck, middle piece, and tail defects, all contributing to abnormal sperm. However, Kianifard et al. (2020) observed a non-significant decrease in various sperm analysis parameters in rats exposed to MSG.

Collectively, these studies suggest that MSG negatively impacts sperm quality, causing abnormal morphology, reduced motility, lower sperm count, and impaired viability, all of which may contribute to male reproductive dysfunction.

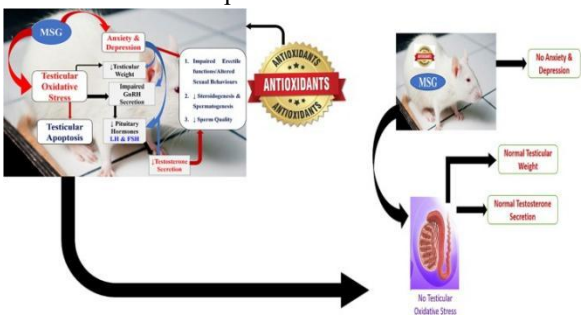
E.IMMUNO HISTO CHEMICAL ALTERATION

In the study conducted by Mohamed El Kotb et al. (2020), it was found that the control group displayed strong proliferating cell nuclear antigen (PCNA) immunoreactivity in the nuclei of all germ cells, indicated by a deep brown nuclear staining. In contrast, the MSG-treated group showed PCNA staining only in a small number of germ cells, mainly spermatogonia, and a notable reduction in PCNA reactivity was observed in some karyolytic cells. Additionally, an immunohistochemical analysis by Al Husseini et al. (2022) examined the expression of

nuclear factor kappa B (NF-κB) in the testes and epididymis of male rats after 28 days of MSG intake. In the control group, no NF-κB immunoreactivity was detected in these tissues. However, in Group A (rats given a lower MSG dose), mild NF-κB expression was observed in Leydig cells, with stronger immunoreactivity in the germinal epithelium of the seminiferous tubules. In Group B (rats treated with a higher dose of 120 mg/kg), NF-κB expression was evident in the interstitial tissue, germinal layer of the seminiferous tubules (including Leydig cells), and mildly in the epididymis. These immune histochemical findings suggest that MSG consumption can trigger an inflammatory response in the male reproductive system, as demonstrated by the increased expression of NF-κB, a key inflammatory regulator. Such inflammation could potentially impair male fertility, highlighting the reproductive risks associated with MSG as a food additive.

V. MECHANISHM OF MSG IN ANIMAL

The effects of MSG on the structure and function of male reproductive organs may result from its diverse impact on cellular processes. These effects can disrupt sperm production, cause oxidative stress, trigger tissue-level (histological) alterations, and create hormonal imbalances. Together, these changes may contribute to male reproductive disorders.



VI. CONCLUSION

Overconsumption of monosodium glutamate (MSG) can harm male reproductive organs, resulting in damaged testicular tissue, decreased testosterone levels, and decreased sperm quality and count. Histomorphological alterations in the testes and other reproductive organs are caused by mechanisms such as oxidative stress and hormonal imbalance, which are linked to the effects. Even though studies on animals demonstrate these impacts, more investigation is required to fully comprehend the long-term consequences on human health.

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