A Review on the Impact of Bisphenol A on the Male Genitourinary System

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ABSTRACT

Bisphenol A (BPA) is a widespread environmental pollutant caused mainly by the production, use, or disposal of plastics and the degradation of industrial plastic-related wastes. Growing data from studies on humans, lab animals, and wildlife supports the idea that BPA has a detrimental effect on male renal and reproductive function by disrupting the endocrine system. We reviewed the literature for a better understanding of the negative effects of BPA exposure, focusing on the impacts of BPA on kidney, prostate, and testicular health. Current data suggest an impaired renal function in individuals with chronic BPA exposure and raise an important issue regarding the presence of this plastic chemical in the dialysis product. The method by that BPA affects prostate tissue is intricated. The frequency of precancerous or cancerous lesions, such as a PIN or even prostate cancer, is rising among elderly males who have had their stem cells reprogrammed by estrogen-like action. Various studies revealed that early exposure to BPA could cause the prostate to develop several different epigenetic modifications, leading to neoplastic alterations of prostate cells. The idea that BPA has an endocrine-disrupting effect and adversely affects male reproductive function is supported by mounting data from studies on laboratory animals, wildlife, and people. By altering the production, expression, and activity of specific receptors for hormones (such as LH and FSH, androgen, and estrogen), BPA has an impact on the hypothalamic-pituitary-testicular axis (ER, AR). Sperm parameters are changed by these effects. By blocking antioxidant enzymes and promoting lipid peroxidation, BPA also causes oxidative stress in the testis and epididymis.

Key-words: Bisphenol A, kidney, prostate cancer, testicular function

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INTRODUCTION

In the last 70 years, there has been a sharp rise in the number of environmental contaminants generated by humans. Both animal and human health are negatively impacted by environmental contaminants. The majority of these substances are categorized as endocrine disruptors (EDCs), which can alter the production, secretion, metabolism, transport, and elimination of several endogenous steroid hormones and, as a result, have a negative impact on the health of the organism or its offspring [1]. EDCs (endocrine disrupting chemicals) are a widespread issue. Due to a lack of research and testing, this is a widespread problem and health risk that is not adequately addressed. Few EDCs are known, while the others are either suspected or have not yet been investigated. EDCs are a broad category of manufactured or natural compounds that are widely circulating in the environment. This can be absorbed, inhaled, ingested, and may be present in trace or significant concentrations in serum, placenta, fat, umbilical cord blood, and other tissues. EDC exposure can start as early as during pregnancy or youth and have an impact on later stages of life. EDCs have the potential to change our body's natural physiological processes, which can cause a variety of endocrinological issues in both children and adults [2].

In today's society, bisphenol A (BPA) is a chemical that is practically everywhere. It is frequently employed in the production of epoxy resins, which are utilized as protective coatings on steel pipes, steel drums, and food containers made of plastic. Since BPA is a substance that comes into touch with food, it is almost unavoidable in everyday utensils and canned goods. Epoxy resins made from BPA are also frequently employed for their adhesive qualities [3]. BPA plays a significant role in the manufacturing of polycarbonate plastics, which are used to make eyewear, optical equipment, and medical supplies. BPA is also used as an addition in the production of polyvinyl chloride plastics, which have several uses in construction materials, pipelines, wire insulation, and healthcare consumables [4]. This substance can be found as colorless crystals or as a powder, and plastic objects can release it into foods and beverages when heated or exposed to acidic or basic conditions. In fact, the rate of BPA transfer to the human body is accelerated when polycarbonate plastics are exposed to high temperatures, such as when heating food held in packages or infant bottles. Additionally, polymeric materials release more BPA when they come into touch with acids or bases, high quantities of sodium chloride, or vegetable oils [5]. It can be absorbed by touch or breath. For instance, the receipts' thermal paper may emit this substance when it comes into contact with the epidermis. The cashiers have also been discovered to have extremely high amounts of BPA in their plasma and urine, despite the fact that they come into greater contact with thermal paper. The discharges from municipal wastewater treatment facilities, the burning of household garbage, and the breakdown of plastic products are additional exposure pathways [6,7]. Recent research on metabolism and toxicokinetics has revealed that BPA is rapidly absorbed orally. Once ingested, this substance is coupled with glucuronic acid in the liver. BPA glucuronate is a reliable exposure biomarker and is adequately stable [8]. Numerous studies indicate its negative consequences. Due to its lipophilic nature, BPA can build up in various human and animal tissues, impairing their physiological processes and having a negative impact on health [9,10].

BPA functions as an agonist on estrogen receptors and an antagonist on androgen receptors due to its anti-androgenic effect. It has recently been demonstrated that BPA affects spermatogenesis and male reproductive health. BPA also has a deleterious impact on sperm motility in humans, mice, fish, bovines, and chicken [11]. It's interesting to note that BPA influences glucose metabolism, the initiation and development of various cancers, and immunological function by interacting with various receptors, controlling transcription factors, and causing epigenetic modifications. The majority of these findings have been achieved in cellular cultures, rats, and humans. Many plastic goods were banned as a result of public concern over the potential health effects of BPA, especially those used for babies and young children [12].

The globe produces at least 2.2 million tons of BPA annually, with the USA contributing a sixth of the total. BPA was discovered in 1891 and has been produced in large quantities at least since the interwar period. As a result, BPA has contaminated

our ecosystem and is now practically ubiquitous in human exposure [13]. This review aims to highlight the impact of this EDCs compound on the male genitourinary system.

The impact of BPA on kidney disruptions

Based on recent research on how BPA can impact the kidneys, the European Food Safety Authority (EFSA) has established a tolerated daily intake (TDI) of up to 4 g/kg body weight/day. Comparatively to other organs and systems like the reproductive or endocrine systems, the BPA-kidney paradigm is only briefly discussed in papers [14-16]. Several epidemiological investigations on human subjects have discovered intriguing connections between blood or urine BPA concentrations and the likelihood of developing kidney disease. Depending on the parameter associated with kidney injury, various analyses were done. Two studies looked into the idea of low-grade albuminuria, which is defined as an increase in urine albumin excretion that is consistently less than the threshold deemed abnormal (30 mg/g creatinine). Accordingly, Trasande et al. [17] and Li et al. [18] hypothesized that persons who presented higher levels of urine BPA were more likely to present with a higher concentration of albuminuria while analyzing the "healthy" population. When looking at a cohort of 441 Korean adult women, Kang et al. [19] found that there was a statistically significant inverse connection between creatinine-corrected BPA and ACR (albumin to creatinine ratio) in several regression models (adjusted for age, region, education, and diabetic, obesity and cardiovascular factors). In the general Korean population, Lee et al. [20] discovered a statistically significant inverse connection between BPA and eGFR. Children with kidney illness showed a negative correlation between BPA and eGFR, according to Jacobson et al. [21].

A rapid decline in renal function is known as acute kidney injury (AKI), and it is linked to significant morbidity and death. Numerous factors, such as ischemia-reperfusion, sepsis, and nephrotoxic chemicals, can lead to AKI [22]. In a recently published study, Wachirasek Peerapanyasut et al. demonstrated the strong impact of BPA in determining AKI and worsening renal ischemia [23].

Furthermore, patients with end-stage renal illness receiving hemodialysis are frequently exposed to BPA from the dialyzer's parts, notably the polycarbonate housing and polysulfone dialysis membranes [24,25]. It is demonstrated that BPA blood levels in hemodialysis patients are significantly greater than in controls, leading to multiple additional problems arising from the accumulation of this toxic plastic, especially in a crippled patient as is the one found in the end-stage of renal disease and requiring hemodialysis [26].

The role of BPA in prostate cancer

Prostate cancer is the fourth most common cancer among males in the world and the most frequently diagnosed male malignancy [27]. In 2020, this amounted to about 1.5 million newly diagnosed cases and 375,000 fatalities worldwide due to this illness [28]. Fortunately, the majority of prostate tumors grow slowly, are low-grade, have a modest risk, and are not particularly aggressive [29]. Age, ethnicity, obesity, and family history are the main risk variables that are now understood. Male gender, advanced age, a favorable family history, increased height, obesity, hypertension, lack of exercise, consistently high testosterone levels, exposure to Agent Orange, and ethnicity are all risk factors for prostate cancer [30]. Other risk factors have been sought after in recent years, with an emphasis on endocrine-disrupting chemicals, including BPA, its most prevalent and widely used representative. Controlling normal growth and functional activities is a good representation of androgens' primary effects on prostate tissue. ADT (androgen deprivation therapy) works by ablating the activity of the androgen receptor (AR), via which they primarily exert their biological effects. The principal function of the androgen receptor, which is a member of the nuclear receptor superfamily, is that of a ligand-dependent transcription factor. The AR is present in the cell prior to ligand activation but is maintained inactive by the inhibitory heat stock proteins [31].
It is important to emphasize the molecular action of BPA, given the significant role that BPA mutagens play in the advancement of prostate cancer and activation of the androgen receptor. When compared to DHT, the prostatic response to BPA is thought to be different due to differences in ligand

binding, the degree of the proliferative response, or the diverse ligand-induced kinetics of androgen receptor recruitment to various regulatory gene regions [32]. Additionally, it is well known that various ligands regulate the specificity of the target gene at nuclear receptor sites. Although numerous in vitro studies showed that BPA directly binds to and activates the mutant androgen receptor, it is also known that BPA can activate the ER and ERß receptors, which are found in a variety of prostate cancer cell lines (e.g. adenocarcinoma cell line). Even though the androgen receptor must be activated for cellular proliferation caused by BPA to occur, its activity can be blocked with an androgen receptor antagonist, such as Casodex, undo BPA's effects on tumor cell proliferation [33]. In animal models, prenatal BPA exposure can cause a multifocal inflammation at the ventral or posterolateral prostate. It can identify abnormal cells linked to the prostate's papillary intraepithelial neoplasia (PIN), a precursor lesion for prostate cancer. As a result of the inflammatory infiltration, several writers also noted the existence of folded acinar epithelium, fewer reticular fibers, rearranged periacinar stroma, and collagen buildup. When compared to control rats, the same BPA-exposed animals had higher amounts of both estrogen and androgen receptors [34]. It was claimed that BPA could cause DNA adduct formation; however, these harmful effects might necessitate extremely high exposure levels. BPA caused the production of DNA adducts in rat embryonic cells in a dose-dependent manner. According to studies, physiological exposure to BPA can predict K-Ras mutation and significant alterations in DNA synthesis, serving as an accurate predictor of the association between BPA and genetic modification and the development of cancer. Numerous BPA derivatives share this chemical compound's carcinogenic characteristics. BPA changes into quinone derivates by oxidation, generating DNA adducts both in vitro and on an animal model. According to data, EDC modifications could affect how bioavailable they are. Additionally, nitrosylation of BPA might result in DNA adduct mutations [35,36].

Numerous studies showed that early-life exposure to BPA could result in a variety of epigenetic changes in the prostate. The methylation of the same gene is caused by even modest concentrations of BPA or estrogen during the developing phase, showing similar involvement pathways in prostate carcinogenesis. These epigenetic changes explain the rising prevalence of prostate cancer lesions in senior men, which raises the possibility that fetal BPA exposure contributed to the formation of neoplastic modification. DNA methylation processes may also be the epigenetic factors linked to greater cancer susceptibility in adult prostate due to early exposure. Estradiol and BPA both have the ability to prevent the histone expression-modifying enzymes SIRT1 and SET8, which are essential for converting prostate cancer cells through gene expression [37,38].

The correlation between Bisphenol A and impaired testicular function

Concern has been raised recently about the downward trend in male reproductive health, which is most pronounced in industrialized nations. According to a recent study, the fertility rate has significantly decreased in the United States, Europe, Japan, Singapore and South Korea [39,40]. Environmental toxicant exposures are one of the causes of male infertility. One of the most common and dangerous environmental pollutants is bisphenol A. BPA's first synthesis is credited to two researchers: Zincke, who supposedly created the chemical in 1905, and Dianin, who is claimed to have designed it first in 1891. Since that time, BPA has been created in large quantities and is frequently utilized as a component in the production of plastics. Plastics play a significant role in practically all product categories and are widely incorporated into modern society. The widespread and intensive usage of plastics has helped distribute BPA throughout the environment [41-43]. After in utero exposure, the detrimental effects of BPA on male reproductive function have been extensively researched in experimental animals like mice. One study of male mice exposed to prenatal BPA demonstrated larger preputial glands, smaller epididymis, and decreased sperm production efficiency (daily sperm production). In adult male offspring exposed to BPA, a decline in fertility, daily sperm production, sperm count, and motility was also noted [44,45].

The BPA's suppressive action on the steroidogenic proteins in testicular Leydig cells is likely what causes the testosterone inhibition. Following BPA exposure, protein expression of the LHR is also

impaired, which could result in testicular Leydig cells secreting less androgen [46]. The testosterone levels increased in 9-week-old male pups exposed to BPA both in utero and during breastfeeding, and this could be related to the mitogenic effect that BPA has on Leydig cells, which produce testosterone. In addition to altering Leydig cells, prenatal exposure to BPA in 6-week-old male mice caused down-regulation of numerous genes linked to Sertoli cell activity, rupturing the blood-testis barrier (BTB) and affecting spermatogenesis [47].

The hypothalamic-pituitary-testicular axis and the thyroid gland regulate the process of spermatogenesis in mammals. Spermatogenesis may be stopped or altered as a result of axis dysfunction brought on by endocrine disruptors like BPA. Testicular atrophy is one side effect attributed to BPA, as was observed in a Swiss study on male adult mice treated with BPA [48]. Male chicks treated with BPA from 2 to 25 weeks of age in a different study from 2006 demonstrated smaller testes as well as growth suppression of androgen-dependent organs like the comb and wattle. The development of the seminiferous tubuli and spermatogenesis in the chicks given a greater BPA dose were inhibited, conditions that were probably caused by decreased testosterone production [49].

The altered sperm parameters that were found serve as an example of how the antiandrogenic and estrogenic effects of BPA were linked to the impairment of male goldfish's spermatogenesis (viz., reduction in total sperm number, density, volume, velocity and motility) [50]. Brown trout exposed to BPA during the late prespawning and spawning periods also showed worse semen quality [51]. Another study that exposed adult male guppies to BPA for 21 days found decreases in total sperm counts. These harmful effects of BPA on fish spermatogenesis have been shown in rodents after postnatal, pubertal, and adult life [52]. The disruption of the pro-oxidant-antioxidant balance of the testis, which results in testicular function impairment, is another significant mechanism through which environmental toxicants exercise their detrimental effects on male reproductive function. The testicular function is involved with the formation of reactive oxygen species (ROS) that are regulated by an antioxidant system under normal physiologic conditions. Testicular oxidative stress results from increased ROS production brought on by environmental toxins like BPA. In one study, male rats were given BPA orally for 14 days. Testicular antioxidant enzymes such as glutathione reductase, glutathione peroxidase, superoxide dismutase, and catalase were found to be decreased. In the testes and spermatozoa of BPA-treated mice, the concentrations of hydrogen peroxide (H2O2) and lipid peroxidation were likewise elevated [53].

CONCLUSIONS

BPA is primarily utilized in the production of epoxy resins and plastics. Studies conducted in vivo and in vitro have revealed that BPA may have cancer-causing properties. BPA exposure may have a considerable effect on a range of cell types, including cancer cells, in terms of growth, survival, proliferation, invasion, migration, and apoptosis, according to studies employing various model systems. Various studies on human and animal models demonstrated a strong connection between BPA and Kidney impairment, promoting the proliferation of preneoplastic and cancerous mutations of the prostate and interfering with normal testicular function leading to alteration of testicular cells and sperm production.

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