Review Report

Pathophysiology, diagnosis, and management of testicular degeneration in the bull

Jennifer Koziol,[a] Colin Palmer[b]
[a]Texas Tech School of Veterinary Medicine, Amarillo, USA
[b]Western College of Veterinary Medicine, Saskatoon, SK, Canada

Abstract

Testicular degeneration in the bull is described as diffuse disintegration of seminiferous tubule structure and function causing a profound reduction in sperm concentration, scrotal circumference, and an increase in sperm morphologic abnormalities resulting in subfertility or permanent infertility. Degenerative changes within the seminiferous epithelium occur most commonly after an insult to spermatogenesis or may be idiopathic. Common insults include trauma, stress (environmental, heat, nutritional), or toxins. Idiopathic is most often associated with age-related changes. Clinical signs of testicular degeneration are discussed along with approaches to treatment and potential prognoses as related to treatment and management practices that can be employed by the general practitioner and specialist alike. This review will also encompass a discussion on the pathophysiology of this disease so that the practitioner has a detailed understanding of the disease, which improves their ability to employ evidence-based medicine and sound clinical reasoning.

Keywords: Testicular degeneration, bull, infertility, subfertility, spermatogenesis, spermiogram

Introduction

Testicular degeneration can be described as a diffuse disintegration of seminiferous tubule structure and function causing profound, subfertility of varying duration and in some cases permanent infertility. In bulls, most cases of testicular degeneration involve both testes; unilateral degeneration does occur but is less common. Both literature reports and the authors' clinical impressions suggest that the odds of full recovery are favorable depending on the severity of the degenerative process; however, at diagnosis, the inciting cause is most often speculative warranting at best a guarded prognosis. Softening of the testes, loss of scrotal circumference and sperm quality and quantity are consistently reported clinical signs. Watery, low sperm-concentrated ejaculates may be noticed; particularly in cases of bilateral testicular degeneration with high proportions of morphologically abnormal sperm, often greater than 80%.[1]

Testicular degeneration is an acquired condition usually limited to the seminiferous tubules and rarely extending beyond the tubular basement membrane to affect the interstitial tissue. Testes undergoing degeneration may have predisposing congenital anomalies; however, to enable differentiation from other conditions a diagnosis of testicular degeneration should be reserved for cases where the release of fully formed sperm has been previously evident indicative of postpubertal, seminiferous tubule function. Demonstratable decreases in sperm production, sperm quality, and testicular size are fundamental diagnostic requirements for testicular degeneration. Small testis, oligospermia/azoospermia, and teratozoospermia are also observed in cases of testicular hypoplasia. Usually considered to be a congenital condition, hypoplastic testis(es) do not develop normal functional capacity and never reach mature size; whereas in cases of degeneration the testis has reached mature size and full function prior to reduction in size.[2]

Testicular degeneration most commonly occurs secondary to an insult to the testis. Potential insults include trauma, stress, abnormal testicular thermoregulation, toxins, ischemia, nutritional deficiencies or excess, infection, sperm outflow obstructions, and neoplasia. The extent of testicular degeneration depends on the severity and duration of the testicular insult. Mild and short duration testicular insults may cause a transient increase in sperm morphologic abnormalities evident in the spermiogram with a return to normal sperm production within days to a few weeks.[3,4] In these cases, seminiferous tubule function remains intact and degeneration does not occur. Longer duration disturbances and severe insults that result in substantial tissue disruption may

CONTACT Jennifer Koziol **jkoziol@ttu.edu**

Citation line: Clinical Theriogenology 2023, 15, 9271, http://dx.doi.org/10.58292/CT.v15.9271

progress to degeneration.[5] Testis may be able to partially or fully regenerate after degeneration depending on the extent of the damage and the quality of the repair process. Return to normal seminiferous epithelial function without fibrosis and scarring obviously favors regeneration and return to acceptable sperm quality. Cases of testicular degeneration where no inciting cause can be identified are often classified as idiopathic. Most cases of idiopathic testicular degeneration have been observed in middle to older aged bulls; therefore, it is also referred to as age-related testicular degeneration. As the testes age, production of gametes and the production of hormones are adversely affected. Idiopathic testicular degeneration is usually progressive with a steady decline in fertility that persists indefinitely.

Pathophysiology

Normal testicular function is dependent on appropriate endocrine, autocrine, and paracrine control. In the male, gonadotropin releasing hormone (GnRH) is secreted from the hypothalamus in a pulsatile nature resulting in waves of luteinizing hormone (LH) and follicle stimulating hormone (FSH) release. LH acts on the Leydig cells within the testes that are responsible for synthesizing progesterone – the majority of which is converted to testosterone. This pulsatile nature of LH secretion is necessary for normal testicular function as sustained LH can lead to a refractory response from Leydig cells secondary to a downregulation in the number of receptors. This culminates in reduced secretion of testosterone from Leydig cells. High concentrations of testosterone must be maintained for normal spermatogenesis to occur. The pulsatile release of LH and consequently testosterone prevents negative inhibition of FSH that is needed for the maintenance of Sertoli cells. Sertoli cells convert testosterone to dihydrotestosterone and estradiol along with secreting androgen binding protein (ABP). Approximately 80% of the secreted ABP goes into the lumen of the seminiferous tubule and travels to epididymis whereas the remainder is secreted into the interstitial compartment and is absorbed into the systemic circulation. ABP binds testosterone and is responsible for not only maintaining a high concentration of testosterone within the testes but also transporting testosterone to epididymis. Although a number of causal factors are identified here it is plausible that most have similar effect, or root cause, which is a disturbance in testosterone release. Hence, a decline in testosterone secretion leads to a disturbance in spermatogenesis that may progress to degeneration.

Most common causal factors associated with abnormal spermatogenesis are: abnormal testicular thermoregulation; hormonal imbalances, particularly those associated with stress; and the effect(s) of toxins or expression of deleterious genes.[4] Intratesticular injection with zinc acetate caused varying degrees of testicular degeneration in 10 *Bos indicus* bull calves. The mechanism of action of zinc acetate was unknown but was proposed to be either a direct toxic effect on testicular cells or an autoimmune effect caused by widespread disruption of the blood–testis barrier. Vacuolization of Sertoli cells was also observed in this study, which often precedes a loss of germ cells.[6] At least in this example, the overall significance of disturbed testosterone release likely had a minor role in the pathophysiology of testicular degeneration compared with overwhelming cellular damage leading to what appeared to be permanent degeneration.

Stress typically elevates systemic cortisol concentrations, profoundly decreasing release of LH and ultimately testosterone.[7–9] Stress has many origins, including environment (weather, heat, humidity, nutrition, and social hierarchy) illness, or injury; all causing changes in the spermiogram similar to those induced by disruption of testes thermoregulation. Cells in early meiosis including the primary spermatocyte along with cells in spermiogenesis are extremely sensitive to alterations in the hormonal milieu secondary to stress, illness, or trauma. However, earlier germ cells, including spermatogonial stem cells, along with testicular somatic cells, which include Leydig and Sertoli cells, appear to be more resistant to adverse changes.[10,11]

Alterations in the hormonal milieu within testis affect seminiferous tubules. LH, FSH, and testosterone concentrations are all affected after insults, which in turn, impairs seminiferous tubular function and consequently disrupting spermatogenesis. In some cases, seminiferous tubules may be severely damaged, resulting in sloughing of differentiated cells into the tubular lumen, leaving only Sertoli cells and spermatogonia. When empty tubules in the testes lose turgidity, testes become noticeably softer, and the change is recognized as testicular degeneration.

Testicular degeneration may be permanent but is most often temporary or transitory. After resolution of the insult spermatogonia may repopulate the tubules allowing testes to return to normal size and sperm production. Within a histologic section, there may be some normal tubules and also tubules with cellular damage accounting for varying proportions of normal and abnormal sperm in an ejaculate.

Although there are no large-scale reports to support their belief, the authors of the current article conjecture that testicular degeneration may be a more frequent occurrence in bulls in hotter and more humid climates. Disruption of testes thermoregulation is the most understood cause of testicular degeneration.[12] The most common cause of transitory testicular degeneration is 'summer infertility' associated with seasonally elevated ambient temperatures and humidity.[13] A long duration scrotal insulation study using a 20-day treatment period proved to be very effective in disrupting the testicular thermoregulatory processes sufficiently to cause degeneration in 3 of 5 treated bulls.[14] Somewhat surprisingly testicular degeneration did not occur, or was at least temporary, in 2 bulls suggesting that considerable individual variation did exist. Accumulation of fat in the scrotum also limits testicular thermoregulation. Overconditioning bulls has been recognized as a major factor leading to testicular degeneration in cooler climates.[5] Sustained elevated body temperatures associated with fever can lead to testicular degeneration; however, it appears that the body's stress response may confound the effect of heat. Localized inflammation associated with trauma may result in unilateral testicular degeneration. A number of other localized inflammatory conditions have the potential to disrupt thermoregulatory processes sufficiently to cause testicular degeneration; however, few if any cases clearly indentifying the cause and effect have been documented. Examples include, diffuse scrotal dermatitis, severe diffuse frostbite, and orchitis. Feeding of a high starch diet to growing bulls was associated with inflammation within the testes, disrupted spermatogenesis and evidence of testicular degeneration in some bulls. A suggested cause of the testicular insult was the release of bacterial toxins after ruminal acidosis that could have caused a local inflammatory reaction within the gonadal tissue.[15] Rare, congenital conditions such as congenitally short scrotum and incomplete testes descent into the

Citation line: Clinical Theriogenology 2023, 15, 9271, http://dx.doi.org/10.58292/CT.v15.9271

scrotum, and acquired lesions limiting free movement of these testes may impair thermoregulatory mechanisms enough to cause degeneration.[5] Higher than normal testicular temperatures in one testis may impede thermoregulatory mechanisms in the contralateral testis causing a disruption in spermatogenesis or in severe cases, degeneration of both testes.[13] The examiner may observe that while one testis feels firm, fibrotic, and clearly shrunken the other testis is larger, but soft. These clinical findings coupled with a watery ejaculate and teratozoospermia suggest that both testes are undergoing degeneration but are at different stages of the degenerative process.

A detailed review of the effects of heat stress on bull fertility suggested the need for heightened awareness of the detrimental effects of heat stress on bull fertility in the light of increases in global temperature due to climate change.[16] Age, genetics, and husbandry practices (e.g. access to shade and water) are important considerations for mitigating the effect of heat on testicular function. Older bulls may be more susceptible to heat stress than their younger counterparts and *Bos indicus* bulls are more suited to maintaining fertility in hotter and more humid environments than *Bos taurus* bulls. Without a means of cooling, higher environmental temperatures cause heat stress within the testis. The ensuing hypoxia leads to increased reactive oxygen species production, which when in excess have a negative effect on spermatogenesis.[17] Differences between breeds, individual animals, and the intensity and duration of the heat insult influence the effect on spermatogenesis and whether the disruption in testicular function progresses to testicular degeneration. Scrotal insulation for 8 days was associated with Sertoli and Leydig cell dysfunction.[12] Testosterone concentrations increased initially after scrotal insulation and then declined and remained low for at least 96 days; beyond when normospermia returned. This longer duration scrotal insulation study was the first to demonstrate that scrotal insulation was associated with a decline in testosterone concentrations.

Idiopathic, or age-related testicular degeneration in the bull largely remains an enigma with little evidence that it occurs in bulls in the scientific literature. An age-related decline in daily sperm production caused by a loss of spermatocytes during meiosis has been reported in men. This condition has been associated with a reduction in the number of Leydig cells, interstitial cells, myoid cells, and Sertoli cells.[18] Heightened sensitivity of older bulls to hotter environmental temperatures[16] combined with individual variation in the response to thermoregulatory insult[14] may have a role at least in some cases. Cases of testicular degeneration with no apparent cause, most often observed in mid-aged to older stallions, are often labelled as idiopathic testicular degeneration.[19] Studies of subfertile stallions suggested that a defect in the steroidogenic pathway, likely at the level of the testes, is probably responsible. Xenograft studies using diseased equine testicular tissue cografted with pig testis revealed that the equine tissue continued to degenerate unlike the pig tissue following treatment with exogenous gonadotropins or endogenous hormones.[19]

Clinical assessment

History

Testicular degeneration is most often identified during a breeding soundness examination (BSE) as an incidental, often unexpected, cause of subfertility. Bulls may also be presented for a perceived fertility issue. Astute individuals may notice an obvious decline in scrotal circumference, severe asymmetry of the scrotum, or a failure to establish pregnancy in a cycling female(s). Bulls in use at a stud are likely to exhibit a decline in both quantity and quality of sperm in the ejaculate before other physical signs are evident. A recommended management practice is that all natural service sires should have a BSE within a month or 2 of the impending breeding season. Sires used yearround, as may be the case in bull studs or in dairies employing natural service, should be examined regularly. A properly conducted BSE comprises a physical examination incorporating an examination of the scrotum and its contents including a measurement of the scrotal circumference, and an assessment of semen quality – most importantly sperm morphology.

A complete history is useful in determining a possible inciting reason for testicular degeneration. For example, if the bull experienced a particularly stressful or painful situation (e.g. lameness, severe weight loss, or illness). Bulls that were overconditioned on high-energy diets may experience substantial weight loss when placed in a new environment. All too often, bulls must transition from a high-grain diet to pasture or adapt to a low-energy diet while at the same time facing social dominance or hierarchical challenges. The quality of the feed is of little relevance if the bull cannot eat enough. A decline in scrotal circumference often occurs with a substantial decline in body weight; especially, in bulls that were overconditioned. Generally, this is thought to reflect a loss of fat in the scrotal and testicular interstitial tissue. Feeding high energy rations during the postweaning development period was associated with the deposition of fat in the scrotum causing erroneously larger scrotal circumferences, palpably softer testes, greater difficulty thermoregulating the testes and poor semen quality.[20] Increased fat deposition in the scrotum and testes can effectively insulate the testes severely compromising spermatogenesis and causing testicular degeneration.[20] High ambient temperatures and high humidity for sustained periods have also been linked to the occurrence of testicular degeneration. The clinician should always note the age and breed of the bull. Older bulls may be more susceptible to thermoregulatory challenges or age-related changes.[16] Young bulls with very small testes developed testicular degeneration at 2–3 years of age.[21] Small testes believed to be the result of hypoplasia and poor semen quality is a common finding in bulls of the double-muscled, Belgian Blue breed. A greater amount of interstitial connective tissue postulated to be interfering with internal blood flow within the testes was associated with an increased occurrence of testicular degeneration within the breed.[22] Finally, a review of the bull's previous BSE results can be valuable. Quantifiable changes in scrotal circumference and a reliable assessment of sperm morphology are much better than owner speculation. Recent and timely BSEs can also point to a potential cause of the degeneration.

Testicular degeneration may be confused with testicular hypoplasia. Evidence of declining scrotal circumference coupled with decreasing sperm quality are important initial clues for distinguishing degeneration from hypoplasia.

Physical examination

Testicular degeneration in the bull may present as a unilateral or bilateral condition. Unilateral testicular degeneration is often associated with trauma; local infection; sperm outflow obstruction; or neoplasia. Causal factors for bilateral testicular degeneration are more apt to be: trauma; stress (weather,

nutritional, pain, and social hierarchy); systemic illness associated with fever; insulation of the scrotum (hydrocele, inguinal hernia, fat, etc.); toxins; or age-related changes.

A decrease in testicular volume quantified by a decrease in scrotal circumference coupled with palpable change in the texture of the testes are hallmarks of the disease. A loss of palpable resilience within the testis, commonly referred to as softness, is most evident early in the disease during an increase in testicular temperature.[13] Testicular turgidity or resilience is created by functioning fluid-filled seminiferous tubules, comprising 80% of the volume of a healthy sexually mature testis, surrounded by soft tissue. In long-standing cases the testes may become palpably firm; however, palpable resilience will not be evident. Testicular degeneration and testicular hypoplasia may be difficult to distinguish; especially, in young bulls with an uncertain history as small, undersized testes are common to both conditions.[23,24] Differentiation may be facilitated by comparing the size of the affected testis to corresponding epididymis. Visual assessment and careful palpation of the epididymides are usually sufficient, but the examiner may also want to compare bulls of similar age. If the epididymis is small and proportional in size to the undersized testis, testicular hypoplasia is likely.[25] Conversely, if the epididymis is well developed and near normal size, one can assume that testicular and epididymal development were normal and that testicular degeneration and corresponding testicular atrophy has occurred. It is also important to remember that testicular hypoplasia is a congenital condition.[2]

Severe cases of degeneration can progress to testicular fibrosis. Damage to the seminiferous tubule lining may not be repairable resulting in scarification and calcification of the tissue. Fibrosis appears on ultrasonography as echogenic densities. Reports from western Canada and Argentina indicate that fibrotic lesions in testicular tissue are quite common and not necessarily associated with a tangible decline in fertility.[26] The underlying etiology of testicular changes resulting in testicular fibrosis remains speculative and congenital malformation of the tubule-to-rete connection, infectious disease processes resulting in tubule destruction, and trauma to the testes have all been proposed. Testicular fibrosis may range from a few small areas with no effect on fertility to severe fibrosis throughout the testes. The presence of many fibrotic lesions may not preclude production of an ejaculate with normal morphology, as some bulls with severe fibrosis produced semen with up to 94% morphologically normal sperm in a report. The authors suggested that large amounts of scar tissue would be expected to reduce sperm production, but that changes in semen production by bulls with varying degrees of severity of testicular fibrosis has not been investigated.[26,27]

Ultrasonographic evaluation of the testis will not allow for differentiation between normal testicular tissue and that which has lost germinal epithelium.[28] Ultrasonography after induced testicular degeneration by scrotal insultation failed to demonstrate a correlation between pixel intensity and semen quality during BSE.[29,30] Furthermore, pixel intensity for prediction of future fertility had limited correlation with BSE outcomes.[31–33] Echogenic areas varying in number and size are frequently detected in the testis and associated with fibrosis, but they do not have substantial effect on the percentage of normal sperm within the ejaculate.[26] Summarizing these reports, ultrasonography can be useful for determining that fibrosis is indeed present but is not useful for predicting the quality of sperm produced or the outcome of a BSE.

Semen assessment

Testicular degeneration follows an insult to spermatogenesis. Decreased sperm production and the appearance of teratozoospermia in the ejaculate occur soon after the insult and if monitored regularly over a few weeks, a predictable series of defects will appear sequentially. The seminiferous epithelium is lined with 5-7 layers of germinal cells supported and nourished by Sertoli cells. From A_1 spermatogonia at the basement layer of the tubule epithelium to fully formed sperm ready to be released into the tubule lumen requires ~ 61 days in the bull. An additional 10 days is needed for transport to and through the epididymis during which further maturation of sperm occurs. Cells in meiosis and spermatids undergoing the final metamorphic changes to become fully formed sperm, known as spermiogenesis, are the most sensitive to adversity. Cells lost in meiosis simply degenerate, the process of spermatogenesis ends, and no subsequent generations of cells are produced leading to reduced sperm output. Disruption of critical maturation processes for spermatids, and recently released sperm in the testes and epididymis leads to the appearance of morphologic abnormalities in the spermiogram.[3,11] Mild disturbances may only affect spermatids or epididymal sperm with a short-lived period of increased numbers of morphological abnormalities. A study characterizing the sequential appearance of morphologic abnormalities reported that there were differences between animals in the overall degree of response to the negative stimulus reflected in the proportion of morphologically abnormal sperm and the proportion of certain types of defects.[4] More severe or prolonged disturbances cause destruction of the spermatocytes and spermatogonia. Not all tubules will be affected in the same way; however, it is widespread degeneration in the tubules that causes the noteworthy changes that define the condition. Spermatocytes that are disrupted during meiosis and survive the remainder of the spermatogenic process may have chromatin abnormalities leading to reduced fertility and poor embryo survival.[16] Because testicular degeneration is the outcome of a progressive process, changes in semen characteristics become evident before identifiable changes in scrotal circumference or palpable texture of testis. Oftentimes, an assessment of semen quality does not occur until sometime after the insult when widespread seminiferous tubule disruption has already progressed to degeneration. Physical examination of testes may initiate suspicions of testicular degeneration in these cases and subsequent examination of sperm morphology will help confirm the diagnosis. The appearance of teratozoospermia is commonly observed in cases of testicular degeneration. No single morphological aberration is exclusive to degeneration. Small numbers of spheroids, which are believed to be immature spermatogenic cells may be seen as well as teratoid forms and medusa cells. Distal midpiece reflexes, proximal cytoplasmic droplets, Dag-like and other midpiece disruptions, coiled principal pieces, detached heads, tapered and pyriform heads, knobbed acrosomes, all types of nuclear vacuoles, microcephalic sperm and sperm with abnormal DNA condensation were evident following known insults to spermatogenesis.[3,4] The sperm head or nucleus is largely made up of chromatin. Variations in nuclear shape within a spermiogram may reflect varying levels of chromatin stability. Using conventional microscopic techniques even normal appearing sperm may have poor chromatin and reduced fertility.[34] Bulls recovering from a severe disturbance to spermatogenesis and testicular degeneration often will produce sperm with more variation in nuclear size and shape. In the unstained semen sample immature spermatogenic cells may be confused with white blood cells. Different stages of immature spermatogenic cells typically

appear in an ejaculate that allow for a variation in size of the cells as compared with white blood cells, which are more uniform in size. To differentiate between an immature spermatogenic cell and a white blood cell a semen smear can be air dried and stained in Diff-Quik® (available from numerous suppliers) or very similar Wright-Giemsa stain. Neutrophils and lymphocytes will be stained by Diff-Quik® whereas immatures spermatogenic cells will not be stained sufficiently to allow the practitioner to easily differentiate.[24,35]

The duration of the insult and the time that passed from the initial insult, assuming that it was acute in action, will dictate the sperm morphologic abnormalities that will be observed, and the sequence of the abnormalities noticed.

Oligospermia and asthenozoospermia may also be noticed in ejaculates. The majority of beef bulls in North America are natural service sires and are not trained to an artificial vagina for semen collection. Semen samples collected by other means (e.g. electroejacualtion or transrectal massage) are not representative of a physiologic ejaculation. While sperm concentration can be calculated samples may be more or less concentrated than a natural ejaculation and therefore, not truly representative of what the bull can produce. It is also important to remember that sperm motility can be altered by environmental conditions. Samples obtained by massage are especially prone to chilling. Nevertheless, effectively performed electroejaculation and transrectal massage are both very suitable methods for clinical assessments of quantity and quality of sperm production.[36]

Endocrinologic evaluation

The relationship between plasma hormone concentrations and testicular degeneration in bulls has not been adequately studied. In other species (e.g. the stallion) estimation of circulating hormone concentrations is an unsatisfactory diagnostic tool for testicular degeneration.[24] Due to daily and seasonal fluctuations in hormone, detecting changes between normal and pathological concentrations is difficult for diagnosing testicular degeneration preemptively or during the early stages of disease. By the time that hormone concentrations become consistently inappropriate, the diagnosis is readily apparent by physical examination.[24]

Histopathologic evaluation

Histopathologic evaluation of a testis affected with testicular degeneration will reveal cytoplasmic vacuolization, absence of later stage germ cells and loss of architecture of the seminiferous epithelium.[21] Although histopathologic findings can help to define testicular degeneration and testicular biopsy would provide definitive evidence, it is rarely justified. Once the practitioner has obtained a satisfactory history and performed a proper BSE a diagnosis of testicular degeneration can be made with confidence. It should also be considered that a single biopsy may not be representative of the testes as a whole.[24] Testicular biopsies can be safely performed with no subsequent decrease in sperm quality appreciated after biopsy.[37] This study was performed on normal bulls and no information exists regarding the use of this procedure on the already degenerated or compromised testicle.[37] Although a testicular biopsy may be useful in some cases often the quality of the sperm ejaculated will give a similar insight into the health of the seminiferous epithelium without the potential risks associated with a testicular biopsy. Effects of feeding a high energy feed were studied. A starch rich diet was fed to Angus x Charolais bulls (n = 40) for 94 days with a mean age of 14 ± 1.7 months at the beginning of the trial.[15] After a 10-day period of adaptation, body weight, an assessment of testes size, and ultrasonography of the testes were performed every 28 days from the beginning of the measurement period until day 84. At the end of the experiment each bull underwent electroejaculation and semen analysis. The testes were harvested at slaughter and submitted for an assessment of histological architecture with evidence of degeneration and tissue healing, seminiferous tubule atrophy, and evidence of disruption of spermatogenesis being scored. Mean scrotal circumference and testes volume increased as expected throughout the feeding period yet lesions consistent with degeneration were observed including sperm with vacuoles, tubules with thickened basement membranes, interstitial tissue edema, multinucleated giant cells in the lumen of tubules and tubular atrophy. There was also evidence of permanent tissue damage including fibrosis, microcalcification, and complete loss of seminiferous tubules; although, the frequency of these lesions was low amongst analyzed samples. However, evidence of an insult to spermatogenesis was present on 100% of the histograms.[15] Although examination of testes histopathology is not practical in most settings the occurrence of degenerative changes, including permanent lesions, varied between individuals and areas within the testic.[15]

Treatments, management, and prognosis

Recovery from testicular degeneration is possible in most cases if the initiating cause is removed. Three, 4 or even several months may be required for the seminiferous epithelium to recover to preinsult sperm production. No treatment has been successful in treating testicular degeneration other than removal of the initial trauma or stressor. Partly due to the usual uncertainty in determining the cause of the degeneration compounded by the individual variation that is evident following any insult to spermatogenesis predicting when a satisfactory BSE should be expected is a risky, if not impossible, undertaking. When breeding season is imminent it is usually best to cull and replace all but the most valuable bulls. Valuable bulls may be worth feeding and housing for several months provided a worthwhile return to normal sperm production is plausible.

The use of GnRH treatment in a Belgium Blue bull with testicular degeneration has been described. In that report an osmotic pump was inserted subcutaneously, and the bull received frequent doses (2.5 µl/h) of buserelin for 9 weeks. After treatment an increase in sperm concentration, volume and quality was noticed. The treatment did allow the authors to determine that the bull suffered from hypothalamic dysfunction. One could surmise that once treatment stopped the bull would return to a state of testicular degeneration.[38] No other studies reported on the use of buserelin. In stallions GnRH has not been shown to be effective as a treatment for testicular degeneration in controlled studies.[24,39]

In cases of unilateral testicular degeneration or damage, removal of the compromised testis has been advocated in hopes of salvaging valuable genetics. Especially in those instances where infammation persists; for example, an abscess, sperm granuloma or tumor; heat radiating from the damaged testicle may overwhelm the physiological mechanisms maintaining the contralateral testis 4–5 °C below body temperature leading to secondary testicular degeneration.[40] Aside from weighing the likelihood for recovery, the deciding

factor to perform a hemicastration should be that the inflammation associated with postoperative tissue healing will be short-lived compared with leaving the compromised testis in situ. Another reason to consider hemicastration, is that the blood–testis barrier within the compromised testis may have sustained damage leading to the production of fertility limiting antisperm antibodies.[24,41] Removal of 1 testis often results in hypertrophy of the remaining testicle. The remaining testicle will produce 1.5 X the sperm production of 1 testis leaving a bull at ~ 75% of his original sperm production ability.[42] It should be noted that the hypertrophy only occurs in normal testes and a contralateral testis damaged by excessive heat for prolonged periods or has exposure to antisperm antibodies cannot be expected to achieve such results.

Conclusion

Testicular degeneration in the bull is often discovered on a bull BSE; therefore, determining a cause may be difficult. An insult to the testis(es) resulting in a disturbance of spermatogenesis that progresses to a disruption of the seminiferous epithelium is the most common sequence of events although poorly understood idiopathic or age-related testicular degeneration can be observed in some bulls. Disruption of testes thermoregulatory mechanisms is the most studied model for inducing testicular degeneration and may be the most common cause of spontaneously occurring testicular degeneration with overfeeding, obesity, age, and ambient heat/humidity being substantial risk factors. Although not definite, it appears that both thermoregulatory and stress-induced testicular degeneration involve a disturbance in the hypothalamic–pituitary–gonadal axis resulting in insufficient testosterone concentrations to maintain seminiferous tubule function; however, an endocrine disturbance may not be evident when the animal is presented for a clinical examination. Evaluation of the quality and quantity of sperm combined with examination of testes often supports a definitive diagnosis. Histopathology and ultrasonography may be of benefit in some cases but are often not warranted. Prognosis is dependent on severity and duration of the insult yet often the identity of the cause is speculative warranting a guarded prognosis. Serial semen evaluations over multiple weeks can enhance the ability of the veterinarian to offer a more realistic prognosis for return to appropriate semen quality.

Conflict of interest

Authors have no conflicts of interest to declare.

References

1. Palmer CW: Management and breeding soundness of mature bulls. Vet Clin Food Anim Pract 2016;32:479–495. doi: 10.1016/j.cvfa.2016.01.014
2. Gledhill B: Inherited disorders causing infertility in the bull. Amer Vet Med Assoc J 197;162: 979–982.
3. Barth AD: Bull breeding soundness. 3rd edition. Saskatoon, SK: Western Canadian Association of Bovine Practitioners; 2013.
4. Barth AD, Bowman PA: The sequential appearance of sperm abnormalities after scrotal insulation or dexamethasone treatment in bulls. Can Vet J 1994;35:93–102.
5. Barth AD, Kastelic J: Testicular degeneration. In: Hopper RM: editor. Bovine reproduction. 2nd edition. Hoboken, NJ; John Wiley & Sons Inc: 2021. pp. 144–150.
6. Cavalieri J, Wang M, Johnson L: Chemical sterilisation of *Bos indicus* bull calves following intratesticular injection of zinc acetate: Effects on semen quality and testicular changes. Anim Reprod Sci 2015;156:23–33. doi: 10.1016/j.anireprosci.2015.02.004
7. Welsh T, McCraw R, Johnson B: Influence of corticosteroids on testosterone production in the bull. Biol Reprod 1979;21:755–763. doi: 10.1095/biolreprod21.3.755
8. Welsh T, Randel R, Johnson B: Temporal relationships among peripheral blood concentrations of corticosteroids, luteinizing hormone and testosterone in bulls. Theriogenology 1979;12:169–179. doi: 10.1016/0093-691X(79)90082-7
9. Welsh T, Johnson BH: Stress-induced alterations in secretion of corticosteroids, progesterone, luteinizing hormone, and testosterone in bulls. Endocrinology 1981;109:185–190. doi: 10.1210/endo-109-1-185
10. Knudsen O: Cytomorphological investigations into the spermiocytogenesis of bulls with normal fertility and bulls with acquired disturbances in spermiogenesis. Acta Pathol Microbiol Scand A Suppl 1954;101:1–79.
11. Barth AD, Oko RJ: Abnomal morphology of bovine spermatozoa. 1st edition. Malden, MA; Blackwell Publishing Inc: 1989.
12. Ferrer MS, Palomares RA, Hurley DJ, et al: Changes in serum testosterone and anti-Müllerian hormone concentration in bulls undergoing scrotal insulation. Dom Anim Endocrinol 2022;78:106685. doi: 10.1016/j.domaniend.2021.106685
13. Tate JL, Monke DR: Bull management/artificial insemination centers. In: McSweeney P, McNamara J: editors. Encyclopedia of dairy sciences. Volume 1. 2nd edition. Cambridge: Elsevier; 2022, pp. 178–186.
14. Wolfe DF, Bradley JT, Riddell MG: Characterization of seminal plasma proteins and sperm proteins in ejaculates from normospermic bulls and bulls with thermally-induced testicular degeneration. Theriogenology 1993;40:1083–1091. doi: 10.1016/0093-691X(93)90376-G
15. Cunha MS, Bonato DV, Vrisman, DP, et al: Histopathological and ultrasonographic testicular evaluation of young bulls fed a hyperenergetic diet. Livest Sci 2019;225:85–90. doi: 10.1016/j.livsci.2019.04.006
16. Morrel JM: Heat stress and bull fertility. Theriogenology 2020;153:62–67. doi: 10.1016/j.theriogenology.2020.05.014
17. Garcia-Oliveros LN, Arruda RP, Batissaco L, et al: Chronological characterization of sperm morpho-functional damage and recovery after testicular heat stress in Nellore bulls. J Therm Biol 2022;106:103237. doi: 10.1016/j.jtherbio.2022.103237
18. Barratt CLR: Spermatogenesis. In: Grudzinskas JG, Yovich JL: editors. Gametes – the spermatozoon. 1st edition, Cambridge; Cambridge University Press: 1995. pp. 250–267.
19. Turner RM: Pathogenesis, diagnosis, and management of testicular degeneration in stallions. Clin Tech Equine Pract 2007;6:278–284. doi: 10.1053/j.ctep.2007.09.006
20. Coulter GH, Cook RB, Kastelic JP: Effects of dietary energy on scrotal surface temperature, seminal quality, and sperm production in young beef bulls. J Anim Sci 1997;75:1048–1052. doi: 10.2527/1997.7541048x
21. McEntee K. Reproductive pathology of domestic mammals. San Diego, CA: Academic Press; 1990.

22. Hoflack G, Van den Broeck W, Maes D, et al: Testicular dysfunction is responsible for low sperm quality in Belgian Blue bulls. Theriogenology 2008;69:323–332. doi: 10.1016/j.theriogenology.2007.09.034
23. Watson ED, Clarke C, Else R, et al: Testicular degeneration in 3 stallions. Equine Vet J 1994;26:507–510. doi: 10.1111/j.2042-3306.1994.tb04060.x
24. Turner RM: Declining testicular function in the aging stallion: management options and future therapies. Anim Reprod Sci 2019;207:171–179. doi: 10.1016/j.anireprosci.2019.06.009
25. Koziol JH, Armstrong CL: Society for theriogenology manual for breeding soundness examination of bulls. Montgomery, AL: Society for Theriogenology; 2018.
26. Barth AD, Alisio L, Aviles M, et al: Fibrotic lesions in the testis of bulls and relationship to semen quality. Anim Reprod Sci 2008;106:274–288. doi: 10.1016/j.anireprosci.2007.05.002
27. Curtis SK, Amann RP: Testicular development and establishment of spermatogenesis in Holstein bulls. J Anim Sci 1981;53:1645–1657. doi: 10.2527/jas1982.5361645x
28. Pechman RD, Eilts BE: B-mode ultrasonography of the bull testicle. Theriogenology 1987;27:431–441. doi: 10.1016/0093-691X(87)90231-7
29. Kastelic JP, Cook RB, Pierson RA, et al: Relationships among scrotal and testicular characteristics, sperm production, and seminal quality in 129 beef bulls. Can Vet J 2001;65:111–115.
30. Brito LF, Silva AE, Barbosa RT, et al: Effects of scrotal insulation on sperm production, semen quality, and testicular echotexture in *Bos indicus* and *Bos indicus* × *Bos taurus* bulls. Anim Reprod Sci 2003;79:1–15. doi: 10.1016/S0378-4320(03)00082-4
31. Brito LF, Barth AD, Wilde RE, et al: Testicular ultrasonogram pixel intensity during sexual development and its relationship with semen quality, sperm production, and quantitative testicular histology in beef bulls. Theriogenology 2012;78:69–76. doi: 10.1016/j.theriogenology.2012.01.022
32. Kastelic JP, Brito LF: Ultrasonography for monitoring reproductive function in the bull. Reprod Domest Anim 2012;47 Suppl 3:45–51. doi: 10.1111/j.1439-0531.2012.02042.x
33. Tomlinson M, Jennings A, Macrae A, et al: The value of trans-scrotal ultrasonography at bull breeding soundness evaluation (BBSE): The relationship between testicular parenchymal pixel intensity and semen quality. Theriogenology 2017;89:169–177. doi: 10.1016/j.theriogenology.2016.10.020
34. Ostermeier GC, Sargeant GA, Yandell BS, et al: Relatiosnhip of bull fertility to sperm nuclear shape. J Androl 2001;22:595–603.
35. Koziol JH, Armstrong CL: Sperm morphology of domestic animals. 1st edition. Hoboken, NJ; John Wiley & Sons: 2021.
36. Palmer CW: Welfare aspects of theriogenology: Investigating alternatives to electroejaculation of bulls. Theriogenology 2005;64:469–479. doi: 10.1016/j.theriogenology.2005.05.032
37. Heath AM, Carson RL, Purohit RC, et al: Effects of testicular biopsy in clinically normal bulls. J Am Vet Med Assoc 2002;220:507–512. doi: 10.2460/javma.2002.220.507
38. Contri A, Gloria A, Wegher L, et al: Successful use of a gonadotropin-releasing hormone (GnRH) analog for the treatment of tertiary hypogonadism (GnRH deficiency) in a 5-year-old Belgian Blue bull. Vet Q 2012;32:51–54. doi: 10.1080/01652176.2012.677866
39. Blanchard T, Varner D, Bretzlaff K, et al: Testicular degeneration in large animals: identification and treatment. Vet Med 1991;86:537–542.
40. Brito LF, Silva AE, Barbosa RT, et al: Testicular thermoregulation in *Bos indicus*, crossbred and *Bos taurus* bulls: relationship with scrotal, testicular vascular cone and testicular morphology, and effects on semen quality and sperm production. Theriogenology 2004;61:511–528. doi: 10.1016/S0093-691X(03)00231-0
41. Zhang J, Ricketts S, Tanner S: Antisperm antibodies in the semen of a stallion following testicular trauma. Equine Vet J 1990;22:138–141. doi: 10.1111/j.2042-3306.1990.tb04228.x
42. Wolfe D, Hudson R, Carson, R, et al: Effect of unilateral orichectomy on semen quality in bulls. J Am Vet Med Assoc 1985;186:1291–1293.