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INVITED REVIEW

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Ageing and inflammation in the male reproductive tract

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Summary

Ageing is usually characterised by a mild chronic proinflammatory state. Despite the tight association between both processes, the phenomenon has recently been termed *inflammageing*. Inflammation in the male reproductive tract is frequently linked with bacterial or virus infections but also with a broad range of noninfectious processes. Prostatitis, epididymitis and orchitis, among others, can lead to infertility. However, in spite of the inflammation theory of disease, chronic inflammation in male urogenital system does not always cause symptoms. With advancing age, inflammatory processes are commonly observed in the male reproductive tract. Nevertheless, the incidence of inflammation in reproductive organs and ducts varies greatly among elderly men. Inflammageing is considered a predictor of pathogenesis and the development of age-related diseases. This article briefly summarises the current state of knowledge on inflammageing in the male reproductive tract. Yet, the precise aetiology of inflammageing in the male urogenital system, and its potential contribution not only to infertility but most importantly to adverse health outcomes remains almost unknown. Thus, further investigations are required to elucidate the precise cross-links between inflammation and male reproductive senescence, and to establish the impact of anti-inflammatory drug treatments on elder men's general health status.

KEYWORDS

accessory sex organs and ducts, immune cells, inflammageing, prostaglandins, testis

1 | INTRODUCTION

Ageing constitutes a universal, multi-factorial, progressive and irreversible process. Ageing and inflammation are two closely linked processes. Many theories attempting to establish whether inflammation is a cause or effect in ageing have been developed. However, no single theory explains all aspects of ageing, leading to the assumption that multiple processes (i.e. oxidative stress, mitochondrial damage, immunosenescence, endocrinosenescence, epigenetic modifications and age-related diseases) contribute and that all are interconnected with inflammatory responses (Jenny, 2012).

The term *inflammageing* is currently used to describe the up-regulation of the inflammatory response that occurs with advancing age (Baylis, Bartlett, Harnish, Patel, & Roberts, 2013). Inflammageing is a challenging and promising new branch of ageing-related research fields as it affects almost all tissues and cell types (Xia et al., 2016).

This review summarises the state of the art and the recent developments with regard to the impact of inflammation and ageing on the male reproductive tract. In particular, data highlight the relevance of inflammageing not only to male infertility but, more importantly, to a healthy senescence.

2 | AGEING AND INFLAMMATION IN EXTRATESTICULAR DUCTS AND MALE ACCESSORY SEX ORGANS

Epididymitis, prostatitis, seminal vesiculitis, urethritis, Cowperitis and vasitis, refer to the inflammation of the epididymis,

prostate, vesicular glands, urethra, Cowper or bulbourethral glands and vas deferens, respectively. Infections of the extratesticular ducts and male accessory sex organs commonly result from canalicular spreading of an infectious agent, either a bacterium or a virus. Haematogenous infections of the male urogenital system are unusual. The most common infectious agents are *Neisseria gonorrhoeae* and *Chlamydia trachomatis*, which are sexually transmitted (Krause, 2008). Noninfectious causes of inflammation in the extratesticular ducts and male accessory sex organs include, among others, trauma, medication, dietary factors, hormonal changes and urine reflux (De Marzo et al., 2007; Eddy, Piercy, & Eddy, 2011; McConaghy & Panchal, 2016; Trojian, Lishnak, & Heiman, 2009). However, there are still inflammatory processes of the male urogenital system, in which microbiological pathogens are not found and the causes remain unidentifiable (Brannigan, 2011; Jonsson & Hedelin, 2008; Vriend, Donker, van Bergen, van der Sande, & van den Broek, 2009). Untreated inflammation of the extratesticular ducts and male accessory sex organs can develop into persistent detrimental effects leading, eventually, to infertility (Krause, 2008; Rusz et al., 2012). Interestingly, inflammation of the urogenital system of known and unknown aetiology is often regarded as part of ageing.

In older men, epididymitis is frequently caused by enlargement of the prostate gland, which increases the risk of bladder infections. Older patients with inflammation of the epididymis show pyuria and fever more often than younger patients (Yamamichi, Shigemura, Arakawa, & Fujisawa, 2017). Mueller, Hermo, and Robaire (1998) reported that the principal cells of the epididymis in young Brown Norway rats express glutathione S-transferases (GSTs). However, in aged animals, some principal cells of the proximal cauda region do not express specific subunits of GSTs. Having in mind that GST enzymes protect cellular components from electrophilic and oxidative attacks, the lack of GST expression in certain principal cells might render the aged epididymis unable to combat oxidative stress. Reactive oxygen species (ROS) activate a variety of transcription factors leading to the expression of over 500 different genes including growth factors and inflammatory cytokines (Reuter, Gupta, Chaturvedi, & Aggarwal, 2010). Consequently, oxidative stress might lead to chronic inflammation, cellular degeneration and vacuolization, common findings in the epididymis of aged rats (De Grava Kempinas & Klinefelter, 2015). However, certain ROS and particularly H_2O_2 may also act as second messengers regulating signal transduction pathways involved, among other, in epididymal transport and spermatozoa maturation (Leisegang, Henkel, & Agarwal, 2017). Because some ROS not only act as prooxidant substances but also as signalling molecules, a fine balance between free radical scavengers and factors promoting oxidative stress is critical for the maintenance of an adequate function of the male reproductive tract and fertility (Leisegang et al., 2017; Rossi et al., 2016).

Benign prostatic hyperplasia (BPH) is a chronic prostate inflammation, which represents the most common urologic disease among elderly men (Chughtai, Lee, Te, & Kaplan, 2011). In this regard, upregulation of some inflammatory mediators including chemokines (CXCL1, CXCL2, CXCL5, CXCL6, CXCL12) and interleukins (IL-11, IL-33) has been described in ageing prostate stroma (Robert et al., 2009). These inflammatory mediators promote proliferation of both epithelial and fibroblastic/myofibroblastic cell types, a process that characterises the ageing-associated development of BPH (Robert et al., 2009). The aetiology of BPH inflammation is linked to infectious as well as to noninfectious processes, the latter possibly as a consequence of autoimmune responses against self-antigens such as the prostate-specific antigen (PSA). In this context, PSA antigenicity has been associated with the impairment of cellular tolerance processes and/or hormonal changes in ageing men (Chughtai et al., 2011). Chronic inflammation and advanced age are pointed out as risk factors for the development of prostate cancer. Cyclooxygenase 2 (COX2), inducible isoform of the key enzyme in the biosynthesis of prostaglandins, is overexpressed in prostate cancer (Gupta, Srivastava, Ahmad, Bostwick, & Mukhtar, 2000; Kirschenbaum et al., 2000). Hobisch et al. (2000) proposed a role of IL-6 in prostate cancer initiation and/or progression. Moreover, upregulation of the macrophage inhibitory cytokine 1 (MIC-1) has previously been described in prostate cancer (Cheung et al., 2004; Nakamura et al., 2003). Recently, soy and green tea showing anti-inflammatory properties have been associated with decreased prostate cancer risk (Hsu, Bray, & Ho, 2010). Furthermore, a meta-analysis reported a reduced risk of prostate cancer with the use of nonsteroidal anti-inflammatory drugs (NSAID) such as aspirin, although the effect seems to be small (Jafari, Etminan, & Afshar, 2009).

Seminal vesiculitis is the most common inflammatory condition affecting the reproductive tract of the bull. As seminal vesiculitis negatively affects semen quality, it represents a serious source of economic loss (Cavalieri & Van Camp, 1997). Interestingly, seminal vesicle inflammation more commonly affects aged bulls than young animals. Furthermore, while young bulls with vesiculitis recovered with or without treatment after several months, older bulls rarely recovered (Hull & Vogel, 2008). In mice, seminal vesiculitis significantly correlates with longevity (Sell, Kleinman, & Monnier, 2000), and it was found to be attenuated by calorie restriction in C57BL/6NNia mice. In this context, it is well known that ageing can be delayed by dietary restriction (Anderson & Weindruch, 2010; Bartke, 2015; Masoro, 2005).

The highest incidence of urethritis caused by gonorrhoea and/or Chlamydia is generally found in young men of urban areas. In contrast, nonspecific urethritis is more often diagnosed in older men (Vriend et al., 2009).

In elderly patients, bulbourethral glands can show calcification leading to ductal obstruction with less or no fluid secretion during the excitement period (Chughtai et al., 2005), and apoptotic events have been described mainly in the glandular duct epithelium (Boronikhina & Iatskovskiĭ, 2006). The glycoprotein profile detected in the glandular secretion is also affected by age, showing a decrease in the ratio of acid/neutral glycoprotein in senescent men (Boronikhina & Iatskovskiĭ, 2007).

Vasitis is a rare condition. The more commonly described inflammation of the vas deferens is called vasitis nodosa, a benign

condition usually associated with a history of vasectomy, which has been described as independent of the patients' age (Hirschowitz, Rode, Guillebaud, Bounds, & Moss, 1988). Tuberculous vasitis was also found in young adults as well as in aged patients (Yang et al., 2014).

Infections can promote inflammation of the ejaculatory duct and the formation of scars leading to a blockage and azoospermia. In this context, uni- or bilateral ejaculatory duct obstruction is a rare cause of infertility. Obstruction of ejaculatory ducts can also be a congenital condition (Modgil, Rai, Ralph, & Muneer, 2016). It has been proposed that in older men, ejaculatory ducts are mainly blocked by both chronic prostatitis and BPH (Jequier, 2000).

Taken together, literature clearly points out that, in extratesticular ducts and accessory sex organs, ageing and inflammation are part of a closely interconnected network affecting male reproductive function and, ultimately, health and fertility.

3 | AGEING AND INFLAMMATION IN THE TESTIS

Orchitis is an inflammatory reaction of the testis, which usually occurs secondary to an infection. Most cases of orchitis are associated with a viral mumps infection. However, other bacteria and viruses can also cause orchitis. In addition, noninfectious aetiologies of orchitis have been described. When epididymitis and orchitis coexist, orchitis results from the spread of epididymis inflammation to the adjacent testis (Trojian et al., 2009).

In prepubertal males, the majority of orchitis cases result from a viral mumps infection, whereas most cases of bacterial orchitis occur in sexually active men or alternatively, in aged men showing urinary infection or BPH. Focal mononuclear orchitis is listed among the most common age-related changes occurring in the human testis (Johnson, 1989).

Autoimmune orchitis is a chronic testicular inflammation characterised by degeneration and apoptosis of germ cells, increased number of macrophages, dendritic cells and T cell subsets including Th1, Th17 and T(regs) cells, as well as by the presence of specific antisperm antibodies and chemokines, which alter the normal immunosuppressor microenvironment of the testis, principally through the secretion of proinflammatory cytokines such as interferon γ, IL-6 and TNFα (Guazzone, Jacobo, Theas, & Lustig, 2009; Jacobo, Guazzone, Theas, & Lustig, 2011; Tung, 1995). Several histological changes described in the autoimmune orchitis are similar to those observed in aged testes. For example, a higher incidence of apoptotic events has been described in Leydig cells and the tubular compartment during ageing (Barbutska & Koeva, 2015; Barnes, Covington, & Lee, 1999; Kimura et al., 2003; Matzkin et al., 2016). In addition, testicular macrophages increase in number and change ultrastructurally (Giannessi, Giambelluca, Scavuzzo, & Ruffoli, 2005). Human testicular macrophages express and secrete IL-1β and TNFα (Frungieri, Calandra, et al., 2002). Increased levels of the circulating proinflammatory cytokines IL-1β, IL-6 and TNFα have been reported in elderly men (Krabbe, Pedersen, & Bruunsgaard, 2004; Maggio et al., 2005). Interstitial macrophages are physically associated with Leydig cells (Frungieri, Calandra, et al., 2002) suggesting that these two cell types are functionally linked. However, in aged testes, macrophages and Leydig cells retain their close morphological association, but the cytoplasmic interdigitations are lost (Giannessi et al., 2005). Changes in aged Leydig cells lead to a reduced capacity of androgen production (Chen, Midzak, Luo, & Zirkin, 2007; Paniagua, Nistal, Sáez, & Fraile, 1991; Zirkin & Chen, 2000). The progressive reduction in total and free serum concentrations of androgens (testosterone, dihydrotestosterone, 3α-androstanediol, 3α-androstanediol glucuronide) in men with advancing age, is accompanied by an increase in the gonadotropins circulating levels and in the peripheral aromatisation of androgen to oestrogen, as well as by a decrease in testicular size, the number of Sertoli and Leydig cells, the volume occupied by the seminiferous tubules and the sperm quality (Baker et al., 1976; Chen et al., 2007; Feldman et al., 2002; Harman, Metter, Tobin, Pearson, & Blackman, 2001; Paniagua et al., 1991). Sertoli and Leydig cells usually present multinucleation, vacuolation and dedifferentiation. A mosaic of different lesions which vary from tubules with complete spermatogenesis to tubules with complete sclerosis is observed. Although accelerated apoptosis of primary spermatocytes has been described in ageing men (Kimura et al., 2003), alterations of spermatogenesis do not seem to significantly compromise fertility in the elderly (Sibert, Lacarrière, Safsaf, & Rives, 2014).

There is an increasing amount of evidence indicating that the imbalance between the levels of pro and anti-inflammatory molecules represents one of the fundamental mechanisms of ageing. Thus, it is reasonable to assume that inflammation is usually implicated in the testicular ageing process. In fact, the age-dependent decrease in the testicular steroidogenic and spermatogenic capacities has been associated with an increase in the inflammatory status of the tissue (Gravance, Breier, Vickers, & Casey, 1997; Jiang et al., 2014; Sibert et al., 2014; Zirkin & Chen, 2000). Low levels of serum androgens in elderly men correlated with increased levels of the circulating proinflammatory cytokines (Krabbe et al., 2004; Maggio et al., 2005). Macrophages are hyperactivated with ageing resulting in upregulation of COX2 expression and an increased production of prostaglandins (well known mediators of inflammation) (Lloberas & Celada, 2002; Plowden, Renshaw-Hoelscher, Engleman, Katz, & Sambhara, 2004). It has been established that IL-1β and its receptors are expressed in macrophages and Leydig cells of the human testis, and that this cytokine induces COX2 expression and prostaglandins production in both cell types (Matzkin et al., 2010). COX2 mRNA levels increase with age in Norway rat Leydig cells (Syntin, Chen, Zirkin, & Robaire, 2001). Incubation of aged Leydig cells in the presence of the COX2 inhibitor NS398 led to a significant increase in testosterone production (Wang et al., 2005). Furthermore, in aged rats fed with the COX2 inhibitor DFU [5,5-dimethyl-3-(3-fluorophenyl)-4-(4-methylsulphonyl)phenyl-2(5*H*)-furanone], blood testosterone concentrations and testicular steroidogenic acute regulatory protein (StAR) expression levels increased over those found in rats receiving no DFU (Wang et al., 2005).

Altogether, these results support a key role for testicular macrophages and certain mediators of inflammation such as IL-1β, TNFα and prostaglandins in the age-related decline of testosterone biosynthesis. In fact, incubation of Leydig cells with PGF2α significantly decreases hCG-stimulated testosterone production (Frungieri et al., 2006), and both proinflammatory cytokines, IL-1β and TNFα, negatively regulate Leydig cell steroidogenesis (Hales, 2002). Furthermore, testicular macrophages show an increment of lipid vacuoles with age that could be associated with alterations in cholesterol metabolism (Hales, 2007). Because 25-hydroxycholesterol produced by testicular macrophages is transferred to Leydig cells and used in the androgen biosynthetic pathways, the loss of macrophage-Leydig cell interdigitations during ageing might contribute to the decreased age-related Leydig cell steroidogenesis (Hales, 2007). Aged testicular macrophages also accumulate lipofuscin granules, which might be related to the increased cytokine production and further contribute to the decline of steroidogenesis during senescence (Giannessi et al., 2005; Hales, 2007).

On the other hand, macrophages are the major source of ROS (Nagata, 2005). The mitochondrial electron transport chain is the most important cellular site of free radical production. In Leydig cells, ROS are additionally produced by the P450 enzymes, which use molecular oxygen for steroid biosynthesis (Chen, Ge, & Zirkin, 2009). Because ROS production and lipid peroxidation in Leydig cells increase with age (Cao, Leers-Sucheta, & Azhar, 2004; Chen et al., 2001), it has been postulated that free radical damage might be responsible for age-dependent reduction in Leydig cell function. In this regard, hydrogen peroxide inhibits Leydig cell steroid production (Stocco, Wells, & Clark, 1993), and long-term supplementation with the antioxidant vitamin E delays the effect of ageing on Leydig cell steroidogenesis (Chen et al., 2005). Furthermore, chronic suppression of steroidogenesis in Brown Norway rats prevented or at least delayed the age-related functional deficits in Leydig cells (Chen & Zirkin, 1999).

De la Fuente and Miquel (2009) have proposed the oxidation-inflammation theory as the main cause of ageing. In the human testis, a recent study reported that the proinflammatory prostaglandin 15d-PGJ2 induces the generation of ROS (Schell et al., 2010). Bearing this in mind, we have recently used adult mice with delayed or accelerated ageing to examine whether variations in longevity affect the development of testicular inflammatory-oxidative processes (Matzkin et al., 2016). It is well established that the growth hormone (GH) signalling pathway participates in the regulation of ageing and lifespan (Bartke, List, & Kopchick, 2016). Overexpression of GH reduces life expectancy in mice, increasing the levels of proinflammatory cytokines, enhancing the expression of inflammatory markers and decreasing antioxidant activity in several nonreproductive tissues (Bogazzi et al., 2011; Brown-Borg, Bode, & Bartke, 1999; Coschigano et al., 2003, 2010; Danilovich, Bartke, & Winters, 2000; Masternak & Bartke, 2012). On the contrary, GH deficiency or resistance extends longevity, increases resistance to oxidative stress and reduces inflammatory activity and apoptotic events in several organs, which are not directly related to reproduction (Brown-Borg & Rakoczy, 2003; Bruunsgaard, Pedersen, & Pedersen, 2001; Chandrashekar, Bartke, Coschigano, & Kopchick, 1999; Csiszar et al., 2008; Gesing et al., 2011).

Regarding testicular ageing, our results clearly demonstrated that reduced longevity in GH transgenic mice is directly associated with several gonadal changes including, among others, an increment in COX2 expression, prostaglandin production, the overall macrophage population, lipid peroxidation, the expression of antioxidant enzymes and the occurrence of apoptotic events (Matzkin et al., 2016). In contrast, extended longevity in growth hormone–releasing hormone (GHRH) knockout mice and Ames dwarf mice did not affect the testicular expression of antioxidant enzymes but markedly decreased the remainder of the parameters assessed (Matzkin et al., 2016). Thus, an increased longevity seems to confer

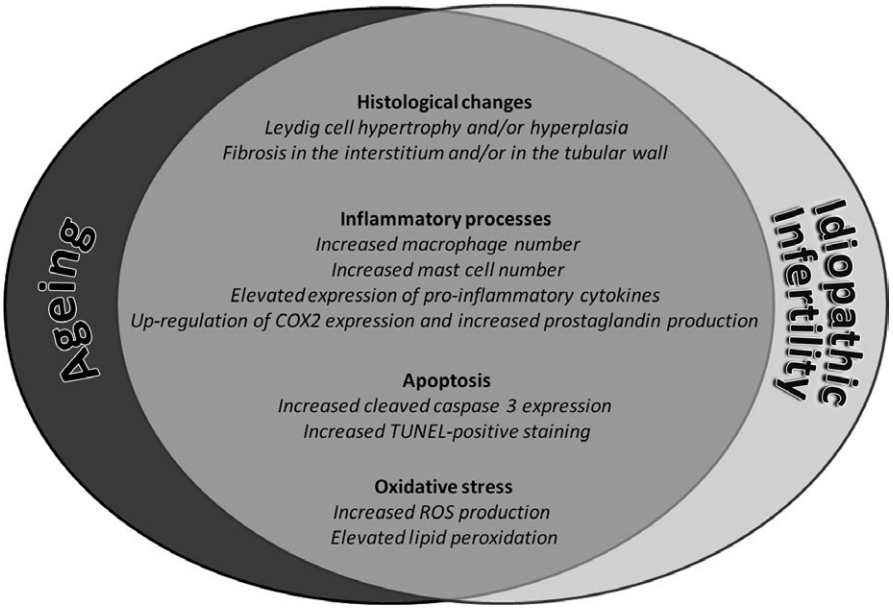

FIGURE 1 Summary view of the changes occurring in the gonads of adult men with inflammatory-associated idiopathic infertility as well as in the aged testis

anti-inflammatory, antioxidant and antiapoptotic capacities to the adult testis, whereas mice with accelerated ageing exhibit testicular inflammatory, oxidative and apoptotic processes.

Interestingly, Zhao et al. (2013) proposed beneficial effects of moderate lifelong exercise counteracting testicular oxidative stress and inflammation and consequently, preserving testes function in aged-mice through regulation of the nuclear factors Nrf2 and NF-κB.

On the other hand, aged transgenic mice overexpressing P450 aromatase (AROM+) show Leydig cell hypertrophy and hyperplasia, a marked increase in the number of mast cells and activated macrophages expressing high levels of CD68 and TNFα, as well as fibrosis in the testicular interstitium (Li et al., 2006).

Our group previously reported that testicular biopsies from adult patients with Sertoli cell only (SCO) and germ cell arrest syndromes show Leydig cell hyperplasia (Gonzalez et al., 2010), thickening of the tubular wall (Frungieri, Weidinger, Meineke, Kohn, & Mayerhofer, 2002; Meineke, Frungieri, Jessberger, Vogt, & Mayerhofer, 2000) and increased numbers of tryptase-immunoreactive mast cells and CD68-positive macrophages expressing the proinflammatory cytokines IL-1β and TNFα (Frungieri, Calandra, et al., 2002; Meineke et al., 2000). In this regard, it has been reported that higher than normal levels of the proinflammatory cytokines TNFα, IL-1α and IL-1β are very harmful to sperm production (Azenabor, Oloruntoba Ekun, & Akinloye, 2015). Immunohistochemical studies revealed that COX2 is only detected in testes showing abnormal spermatogenesis but not in normal testes (Frungieri, Weidinger, et al., 2002). Because tryptase is a serine protease known to cause fibroblast proliferation, we hypothesise that tryptase released from testicular mast cells might target not only peritubular cells causing fibrosis, but also PAR2-immunoreactive interstitial cells leading to COX2 induction and upregulation of prostaglandin synthesis (Frungieri, Albrecht, Raemsch, & Mayerhofer, 2005; Frungieri, Weidinger, et al., 2002). In addition, elevated ROS have been described in infertile men with impaired spermatogenesis, at least in the tubular wall (Kampfer et al., 2012).

Thus, similar findings to those observed in the testis of aged rodents have been described in testes of adult men with inflammation-associated idiopathic infertility. In view of these observations, it is possible to conclude that there is a clear parallelism between the changes taking place in the aged testis and the alterations that occur in gonads of young adult infertile men (Figure 1).

4 | CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

The study of inflammation and ageing in the male reproductive tract appears to be a promising field of research with a potential impact not only on fertility but also on general health status of older men. Thus, future investigations concerning the impact of drugs targeting inflammation at the level of the testis and/or the male accessory sex organs and ducts could lead to new therapeutic approaches to male reproductive senescence.

Corticosteroids are the most effective anti-inflammatory therapy for many chronic inflammatory diseases. A continuous low-dose corticosteroid therapy is useful in the treatment of testicular tumour of adrenogenital syndrome and in the therapy of testicular inflammation due to the presence of specific antisperm antibodies (Naouar, Braiek, & El Kamel, 2017; Omu, al-Qattan, & Hamada, 1996).

The impact of nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) including COX inhibitors such as indomethacin, paracetamol and aspirin is currently being assayed in the human testis (Albert et al., 2013; Kristensen et al., 2016, 2018; Rey-Ares et al., 2018).

On the other hand, mast cell blockers (i.e. ketotifen and tranilast) have already been tested in an attempt to treat male infertility (Azadi et al., 2011; Hibi et al., 2001; Schill, Schneider, & Ring, 1986; Yamamoto, Hibi, & Miyake, 1995).

Cocuzza et al. (2008) described an ageing-related increase of ROS in semen of healthy fertile men. Bearing in mind the oxidation-inflammation theory of ageing and the role of oxidative stress in the reproductive decline during senescence, it is important to mention that the use of antioxidants such as resveratrol and melatonin, improved reproductive parameters (Mendes et al., 2016; Rossi et al., 2014). Nevertheless, among all ROS, H_2O_2 is also a critical player in reproductive processes such as spermatogenesis, sperm motility, capacitation and the acrosome reaction. Thus, although antioxidants show beneficial effects on male infertility and reproductive ageing, particular attention should be payed in the abuse of these compounds that could lead to inhibition of essential molecular pathways of the male reproductive tract (*Leisegang* et al., 2017).

In summary, anti-inflammatory drugs and antioxidants are currently being developed or are already in clinical use for a variety of conditions. However, the impact of these drugs on male reproductive ageing and, consequently, their future as potential therapeutic targets to improve the health and quality of life of the elderly men remain to be thoroughly investigated.

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