Chapter

Lung Health and Hypoandrogenism

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Abstract

Epidemiological reports offer evidence that gender differences mediate respiratory diseases. Male sex is a major risk factor for respiratory distress syndrome and bronchopulmonary dysplasia in neonates. An imbalance between oxidants/antioxidants leads to stress, which has been implicated in airway disease development. It is known that androgens deficiency induces oxidative stress and lipid peroxidation in the lung, synchronically with changes in the expression of cytoprotective markers. Additionally, males are more susceptible to acute and chronic inflammation after toxicant exposure. Besides, nutrition is an important factor, given that lipids are the main blocks for surfactant production and for testosterone synthesis. Also, an adequate amount of Zn in the diet prevents inflammation and is necessary for testosterone and androgen receptor structure and function. This chapter focuses on understanding the effect and clinical implications of testosterone deficiency on lung tissue as well as exploring the role of lipids and zinc in the outcome of several respiratory diseases.

Keywords: androgens, lung, male, inflammation, respiratory diseases

1. Lung structure and sex differences

Biological sex mediates differences in lung disease incidence and pathophysiology, which emerge from sex variations in lung structure and function itself and also in the lung immune cells that are recruited during inflammation [1]. In healthy women, large conducting airways are 30% smaller than in healthy men and sex variations in the airway luminal area persist even after matching for lung size. Larger conducting airways are the main site of airway resistance, linking anatomy to analyzed sex differences in pulmonary physiology [2]. The female lung during intrauterine development has several structural advantages over the male lung. Even if surfactant is produced earlier, the female lung is smaller whereas it has a larger amount of alveoli per unit area. Lung maturation, therefore, is faster in females than in male fetuses. Also, neonatal females have higher expiratory flow rates than males. Regarding respiratory distress syndrome development, bronchopulmonary dysplasia in neonates, and asthma, males present superior risk factors than women during childhood [3].

In this chapter, we also review sex differences in the structure and function of healthy lungs as well as lungs in pathological conditions that depend on the sex

hormones' action. Testosterone deficiency (TD) is very common in older men and is related to different signs and symptoms, such as diminished libido, reduced sexual function, and decreased mobility and energy; which could greatly affect the aging process and quality of life [4, 5]. Androgen receptor (AR) is the intermediary of testosterone effects which is subjected to its sensitivity [6].

Several studies support interdependent sex and endogenous sex hormones effects on lung growth and airways responsiveness that might explain asthma status from puberty to middle age. Puberty is a dynamic process regulated by hormonal signals from the central nervous system that results in sexual maturation. Assessment of the pubertal stage development is different in boys from girls. In boys, androgen production gradually increases both from the testes producing testosterone and from the adrenal glands producing weaker androgens—ultimately leading to puberty. Girls experience increases in estrogen production from the ovaries (driving thelarche and ultimately menarche) and androgens such as androstenedione and DHEA-S from the adrenal glands (driving puberty). In children, pubertal maturation and asthma status may also be affected by corticosteroid treatments [7]. Androgen surge during puberty is capable of conferring protective influences on lung growth in both males and females whereas estrogens could well have deleterious effects in females extending into adult development.

2. Androgen receptor

The androgen receptor (AR) belongs to the steroid and nuclear receptor superfamily. Among this large family of proteins, only five vertebrate steroid receptors are known: androgen, estrogen, progesterone, glucocorticoid, and mineralocorticoid receptors [8–10]. Two subtypes of estrogen receptors have been identified: α and β. Like other steroid receptors, AR is a soluble protein that operates as an intracellular transcriptional factor. AR function is regulated by androgen binding, which initiates sequential conformational receptor changes that affect both receptor-protein and DNA interactions. AR-regulated gene expression is reliable for male sexual differentiation and pubertal changes. The known AR ligands can be classified as steroidal or non-steroidal based on their structure either as agonist or antagonist, based on their ability to activate or inhibit target genes' transcription [8, 9]. AR is mainly expressed in androgen target tissues, such as the prostate, skeletal muscle, liver, lung, and central nervous system (CNS). The highest expression levels are observed in the prostate, adrenal gland, and epididymis as determined by real-time polymerase chain reaction (PCR). AR can be activated by endogenous androgens merging, including testosterone and 5R-dihydrotestosterone (5R-DHT).

Physiologically, functional AR is reliable for male sexual distinction in the uterus and for male pubertal changes. In adult males, androgen is mainly responsible for maintaining libido, spermatogenesis, muscle mass and force, bone mineral density, and also erythropoiesis. Androgens are regularly dispersed all over the entire organism, especially in the lungs.

3. Immune system

Many immune cells in the lungs express ARs and are susceptible to androgens, like ARs on myeloid immune cells (monocytes and macrophages) as they are associated

with healthiness and illness. Particularly, we point out androgen influences on lung diseases, such as asthma, chronic obstructive pulmonary disease (COPD), and lung fibrosis.

Immune response differs between males and females because its type and magnitude are influenced by biological sex and age. Genetic (chromosomal) sex differences and those mediated by the action of sex hormones engendered sex differences in the immune system function. Female hormones, mainly estrogens, have been well studied in their numerous functions, while androgen as modulators of the immune system has not been investigated so extensively [8, 9].

Myeloid cell response in the lung is modulated by androgens, which results in the outcome of different lung diseases. Incidence and pathophysiology of lung diseases are mediated by biological sex. These variations emerge from sex differences in the lung structure and function, and also in the immune cells that populate the lung and are recruited to it during inflammation. Before birth, the female lung has several structural advantages over the male lung, as stated in the first paragraph.

Despite lung contribution to structural dissimilarities between the sexes, those differences in lung function and diseases are also influenced by sex hormones. Testosterone and estrogen affect lung macrophage functions [11]; therefore, this may contribute to particular lung disease development. The amount of AR cellular expression and hormone concentration regulates testosterone's immunoregulatory characteristics.

In fact, when we refer to the physiological function of the lung, alveolar macrophages (AM) are the most abundant cell type of the immune system and one of the first cells in contact with the allergenic stimulus. During the inflammatory process, Th2 immune response polarizes AM to an M2 phenotype [12] and the accumulation of M2-polarized AM in the lung correlates with asthma severity [13]. AM (M2) secretes cytokines that recruit eosinophils during allergic lung inflammation [14].

Keselman et al. [15] analyzed the effect of estrogen on macrophage polarization, suggesting an enhanced M2 polarization, which indicates a long-lasting effect on lung inflammation. On the other side, Becerra Diaz et al. [11] evaluated the role of androgens in lung inflammation, particularly AM polarization in allergic lung inflammation, finding out that AM1 expression was restored to control values with androgen-replacement therapy. Both experiments contribute to explaining the sex differences observed in asthma.

4. Surfactant

Pneumocytes are alveolar cells found on the alveoli surface in the lungs. There are two types of cells that cover the alveoli: type I and type II pneumocytes (PTI and PTII, respectively). They are present in a ratio of 1:2. PTI cells form the majority of the epithelium while PTII cells account for only about 15% of peripheral lung cells [16]. Type I pneumocytes are thin squamous cells that cover almost 95% of the alveolar surface. Pneumocytes are connected to each other by tight junctions. The adjacent PTI cells are connected by tight or occluding junctions that prevent leakage of fluid into the alveolar space. During inspiration and expiration, the flat extensions overlap each other. The type I cells are involved in the gaseous exchange between the alveoli and capillaries.

Type II pneumocytes are cubic in shape and they are characterized by microvilli on their surface. The major functions of the type II cells include the secretion of

surfactant to reduce surface tension. PTII can convert into PTI cells and regenerate the alveolar surface at the time of injury. The coating of these lipids in alveoli is relevant, without which the alveoli may collapse. The surfactant is secreted by secretory granules called lamellar bodies. These tension active are made up of 70–80% of phospholipids and small proteins called surfactant proteins (sp). Surfactant proteins start to be secreted at about 25 weeks of gestation.

Surfactant is produced in fetal life, and, glucocorticoid receptor (GR) is essential in promoting differentiation and maturation of PTII cells during embryonic life [9, 10, 17]. Antenatal glucocorticoid administration accelerates lung maturation in infants at risk of preterm delivery, largely through increased surfactant protein expression.

Ojeda et al. have shown that testosterone absence alters surfactant phospholipid composition, mainly increasing phosphatidylcholine content [18], and leading to damage in the lung parenchyma. Thus, the male sex is a major risk factor for the development of respiratory distress syndrome, bronchopulmonary dysplasia in neonates [9, 10, 17, 18], and asthma in childhood [9, 17]. Androgen receptor (AR) mediates the effects of male sex steroids in a variety of reproductive and non-reproductive tissues both in males and females under physiological and pathophysiological conditions [9, 10, 17, 18].

5. Androgen deficiency and oxidative stress

It is known that redox balance is important in the airways because it is the first contact with environmental contaminants, particles, cigarette smoke (CS), and pathogens.

Chemically, oxidation is a reaction where a substance loses electrons and is oxidized, which can occur by mechanisms that enhance the production of free radicals (unstable substances with unpaired electrons), developing chain reactions. These reactions are uncontrollable as long as they have sufficient substrate to continue developing and can cause damage to the different components of the cells, especially those of a lipid nature. Antioxidants end the reaction by interacting with intermediate compounds and preventing their spread [19].

Therefore, an imbalance between oxidants/antioxidants induces stress, which has been implicated in the development of airway diseases. Several antioxidant enzymes are critical for maintaining cellular homeostasis and preventing cellular damage [20].

Oxidative stress causes an imbalance in the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and their relationship with the antioxidant defense system of lung cells [21]. Some ROS and RNS responsible for oxidative stress such as superoxide, ozone, hydrogen peroxide, hydroxyl radical, nitrate, nitrosyl, and nitrosothiol [22] are produced as by-products of metabolic processes in cells [23] and play a vital role in regulating various biological phenomena, some of which are associated with proinflammatory processes [24].

ROS have a dual involvement in the cell, taking part in different cellular functions, such as defense against infectious agents and signaling systems. On the contrary, its accumulation in biological systems produces oxidative stress, representing an alteration in the pro-oxidant/antioxidant balance, with the ability to oxidize biomolecules (lipids, proteins, DNA), and inhibit their normal structure and function.

One of the indicators of oxidative damage in the lung is lipid peroxidation which causes a considerable amount of DNA-malondialdehyde (MDA) adducts [25]. Lipid

peroxidation affects all cell membranes inducing numerous injuries and loss of functions. On the other hand, ferroptosis is a form of cell death characterized by iron-dependent lipid peroxidation, which induces cell death. During ferroptosis, an accumulation of polyunsaturated fatty acids (PUFAs) occurs. This involves PUFA-driven lipid peroxidation that increases cell membrane permeability making the cell more sensitive to oxidation [26]. Enzymatic antioxidants and non-enzymatic antioxidants act together to detoxify the effects of oxidative stress and lipid peroxidation. This synergistic action can be measured using total antioxidant capacity (TAC) [27].

Additionally, males are susceptible to acute neutrophilic inflammation after a single exposure to toxicants, as well as chronic monocytic inflammation after repeated exposures to them. Exposure to ozone has numerous negative effects on lung health and innate pulmonary host defense. Sex differences in lung histology and BAL measurements of lung injury and inflammation were found. Females showed increased damage compared to males, and the expression of inflammatory mediators also varied with sex under basal conditions and following exposure to ozone. This situation indicated a potential sexual dimorphism in the mechanisms associated with the inflammatory response to this air pollutant. Understanding how differentially expressed genes regulate the response to environmental insults may provide the bases to identify sex-specific targets for therapy against acute lung inflammation and injury [28].

There is abundant evidence revealing the action of heat shock proteins (HSPs), mainly in inflammatory conditions. At 30 days after castration, we have shown [20] an increase in oxidative stress markers such as TBARS and antioxidant enzymes expression such as glutathione peroxidase (GPx). During the period of testosterone supplementation, the expression of cytoprotective markers as HSP70i increased, compared to the control group. Additionally, we have observed a decreased HSP27 expression in the testosterone-deprived group. This situation suggests an absence or decrease in cytoprotective properties, which would correlate with the increased level of TBARS found in the lung.

On the other hand, it has been found that a higher expression of Hsp70 reduces the production of nitric oxide (NO) [29], so the higher immunostaining of HSP70 would explain the absence of variations in the concentration of NO in BAL of castrated rats. Therefore, the expression of these proteins would probably play a protective role against androgen deficiency [20].

Besides, sexual hormones play an important role in airway-related diseases and the immune response, leading to pulmonary injuries [30]. Several studies have shown that sex hormones can affect airway tone and inflammation, and exert effects on different lung cell types, including airway smooth muscle [31] and immune cells. These include lung macrophages, neutrophils, dendritic cells, and eosinophils [32, 33].

Testosterone deficiency is commonly observed in male patients with COPD, which is characterized by chronic inflammation of the airways and pulmonary emphysema [34]. As it was previously mentioned, testosterone affects lung macrophage function and this may contribute to the outcome of particular lung diseases. Low levels of endogenous testosterone have been found in men suffering from pathologies such as asthma, COPD, or tuberculosis.

In experimental situations, when testosterone was administered in castrated rats, oxidative stress parameters were modified. For example, TBARS, catalase (CAT), and GPx activities went back to normal values. The same happened with NADPH oxidase (NOX) and GPx expression which were increased in castrated rats and showed a decrease to control values in rats supplemented with testosterone [20, 35].

Epigenetic events cause hyper-methylation (via the promoter) of GSTP1 and Nrf2, which reduces their expression and severely decreases cellular antioxidant capacity. The excessive production of ROS, due to metabolic alterations, and/or extrinsic environmental factors such as pulmonary inflammation along with androgen receptor activation favor oxidative stress state [36]. It is important to highlight that oxidative stress can modify the activity of nuclear and mitochondrial DNA, generating hypermethylation and mutations [24].

COPD is associated with an abnormal inflammatory response of the airways, alveoli, and microvasculature. Testosterone deficiency also exacerbates COPD symptoms through direct impact on respiratory muscles or decrease exercise capacity. The main cause of the inflammatory process is cigarette smoke [37]. The inflammatory response in COPD progression involves both innate and adaptive immunity [38], which are mediated by multiple immune cell types, including macrophages, T cells, B cells, and neutrophils, as well as epithelial cells [39]. The insufficient control of inflammatory responses to tissue damaging in COPD may be liked to low testosterone.

Overactive tissue and wound healing responses dysregulation in the lung could be used to describe the Th2 response in allergic asthma [3]. Allergic asthma is a chronic disease, which occurs with an altered inflammatory immune response. In the alveolar space of normal lungs, alveolar macrophages are the most abundant immune cells and are the first to come into contact with allergic stimuli. In allergic asthma, Th2 polarizes AM to the M2 phenotype, and the increase of this phenotype is directly related to the severity of pathology. Androgens increase the polarization of AM to M2, although they suppress all other effects of allergic inflammation. These results underscore a little-known role of androgens as modulators of the immune response [3].

Airway epithelial cells are activated to produce inflammatory mediators, including tumor necrosis factor-α (TNF-α), interleukin-1β (IL-1β), granulocyte-macrophage colony-stimulating factor, interleukin-8 (IL-8), and interleukin-6 (IL-6). Nuclear factor kβ (NF-kβ) is crucial for inflammatory pathologies, regulating the transcription of the cytokines TNF-α, IL-1b, and IL-6 [40]. Moreover, androgen deficiency increases inflammation by increasing levels of IL-6, TNF-α, and C-reactive protein [40, 41]. Wang and colleagues [40] found that male castration increased both inflammatory cell recruitment and TNF-α and IL-6 expression. Similar results were found in clinical reports, where higher levels of IL-6, IL-1b, and TNF-α in men with low testosterone levels (hypogonadism) were found [40–42].

In many cases, impaired testicular function and subfertility are associated with obesity, which is a chronic disease associated with metabolic disorders and comorbidity. In this situation, the production of ROS and the release of hormones can affect the hypothalamus-pituitary-testicle axis. Androgen deficiency could further accelerate the increase in adipose tissue and induce a vicious cycle. In individuals where adipose tissue dysfunction and male hypogonadism occur together, a multifactorial pathology of difficult resolution are produced at the pulmonary level [42].

6. Zn deficiency and testosterone

In 1992, Hunt et al. showed that Zn depletion induced a decrease in serum testosterone concentrations in men. Hamdi et al. (1997) also showed a direct action of Zn on testicular steroidogenesis, supporting the idea that Zn deficiency induced hypogonadism mainly from changes in testicular steroidogenesis or indirectly from Leydig cell failure [43, 44].

Omu et al. [45] proved Zn deficiency to be associated with impaired spermatogenesis due to reduced testosterone production, increased oxidative stress, and apoptosis. They showed an obvious reduction of testicular volume, together with increased apoptosis of the testicular cell population. It is known that the zinc transporter (ZnT) family, SLC30a, is involved in the maintenance of Zn homeostasis and in mediating intracellular signaling events.

Zn deficiency has been demonstrated to cause Leydig cells to appear smaller and show endoplasmic reticulum abnormalities when examined under an electron microscope [46, 47]. Chu et al. [48] showed that Zn-deficient (ZnD) Leydig cells were capable of taking up cholesterol and neutral lipids, which are the precursors of sex steroids; however, they could not convert them into sex steroids, thus leading to fertilization impairment due to spermatogenesis arrest.

Two Zn-transporter families regulate Zn homeostasis: Zrt- and Irt-like proteins (ZIPs; SLC39a) and another Zn transporter (ZnT) proteins (SLC30a). ZIPs are responsible for the influx of Zn into the cytoplasm from the cell exterior or from intracellular compartments whereas ZnTs are responsible for Zn efflux to the cells outside or to intracellular organelles [48].

Chu et al. [48] were the first to demonstrate that Znt7 is involved in testosterone synthesis in the mouse testis. The mechanism underlying this process may involve the modulation of the expression levels of testosterone-related factors as well as the expression of the enzymes involved in testosterone synthesis.

On the other hand, according to the crystal structure of the AR DNA binding domain (DBD), each DBD monomer has a core composed of two zinc fingers, each of which consists of four cysteine residues that coordinate a zinc ion. AR, just like other steroid receptors, works as a dimer that binds to the respective response element in the DNA promoter consisting of two equal sites: hexamers sites (5′-AGAACA-3′) separated by a 3 base-pair spacer (IR3). Therefore, this could be another site that could be affected by Zn deficiency, leading to different diseases or deficiencies [49].

Furthermore, in our laboratory we have studied the effect of Zn deficiency in the lung, finding that it induces nitrosative and oxidative stress together with inflammation and alteration in the expression of matrix extracellular proteins [50]. It also increases the expression of apoptosis markers such as Bax and Bad, suggesting that together with the reduced levels of testosterone induced by the same Zn deficiency, the impact on the lung and the risk for chronic and aggressive diseases could be much higher.

7. COVID and testosterone

It has been shown that male individuals are more susceptible to the infection of SARS-CoV-2 than females, and have a higher death rate regardless of age [51].

The explanation for this finding could be: (a) androgens per se are poorly protective over the immune response in males, whereas estrogens (and progesterone) can provide adequate protection to females, stimulating the humoral response to viral infections [52] as a consequence, T levels could not elicit an effective counteracting response to the inflammatory and immunological outcome resulting from a viral infection; (b) a background condition of chronic low T levels—which is estimated to characterize up to 20% of middle-aged/elderly men—may facilitate overall greater incidence and higher severity in men compared to women; and (c) SARS-CoV-2 needs androgen-regulated proteins to invade host cells, including TMPRSS2 for S priming and ACE2 for viral entry, which is expressed in multiple tissues [53].

8. Lung cancer

Lung cancer is the most diagnosed cancer worldwide. Sex hormone concentrations decline as men age, together with increased cancer incidence. For instance, T, DHT, and estrogen (E) were measured in community-dwelling older men and the results revealed that higher levels of androgen were associated with elevated frequency of lung cancer, while they are not associated with the incidence of prostate and colorectal cancer [58]. Therefore, sex hormones may play a role in lung cancer pathophysiology and patient development even if it is not considered as a hormone-sensitive malignancy. An interesting study performed in Canada [59], using a retrospective cohort design, provides further evidence that sex hormones may play a role in lung cancer pathophysiology, and that androgens in particular may have a greater role than previously thought. Male patients, after they were diagnosed with lung cancer, were exposed to androgen pathway manipulation (APM) where most of them received 5-alpha reductase inhibitors and they significantly had better survival when compared to the not exposed ones. Thus, APM utilization in specific lung cancer populations has the potential to be a simple, widely available, and cost-effective treatment for this disease.

It is important to remember that there are two types of lung cancer, non-small cell lung carcinoma (NSCLC) and small cell lung carcinoma, which correspond to 85 and 15% of all lung cancer, respectively. Regarding NSCLC, it is classified into three types: adenocarcinoma, squamous-cell carcinoma, and large-cell carcinoma [54]. The most common is adenocarcinoma that arises from small epithelial type II alveolar cells that produce mucus among other substances [55]. It usually occurs in the lung periphery. When compared to other lung cancers, adenocarcinoma is a slow grower and is usually found before spreading outside the lungs. Squamous-cell carcinoma emerges from early versions of squamous cells from airway epithelial cells in the bronchial tubes in the lungs center.

Large cell carcinoma accounts for 5–10% of lung cancers. This cancer does not show evidence of squamous or glandular maturation therefore it is usually diagnosed by default, excluding other possibilities. It often begins in the central part of the lungs, nearby lymph nodes and into the chest wall [56]. This kind of cancer and tumors are strongly associated with smoking [57].

Female patients generally show better survival rates at any stage of the disease. Histological subtypes of the disease in women include proportionally more adenocarcinoma and less squamous cell carcinoma than in men. Apparently, men have a higher rate of fatal outcomes in lung cancer, but surprisingly, they tend to be less vulnerable to tobacco than women.

9. The analysis of biomarkers

Nowadays, novel therapeutic approaches for the management or monitoring of different lung illnesses are needed. The use of biomarkers and the measurement of their levels as a control for the risk and disease prognosis are considered an encouraging approach. Many types of biomarkers have been identified, which include blood protein biomarkers, cellular biomarkers, and protease enzymes. They have been isolated from different biological sources including sputum, bronchoalveolar fluid, exhaled air, and blood. Sputum samples from patients have been proposed as easily obtained samples that allow complementary diagnostic techniques or alternatives to PCR. By

real-time PCR, reactive oxygen species can be diagnosed from fresh sputum. ROS in sputum could be employed to monitor patients with pathologies such as asthma and COPD. Other modern bioanalytical techniques detect levels of ROS and were used during the COVID-19 pandemic to show oxidative status, at all times [58–61].

Also, higher plasma androgens, particularly DHT, would represent a potential biomarker for lung cancer incidence in older men.

10. Conclusion

We have shown that considerable advances have been made in the understanding of the pathophysiology of lung diseases. It is obvious that the absence of androgens

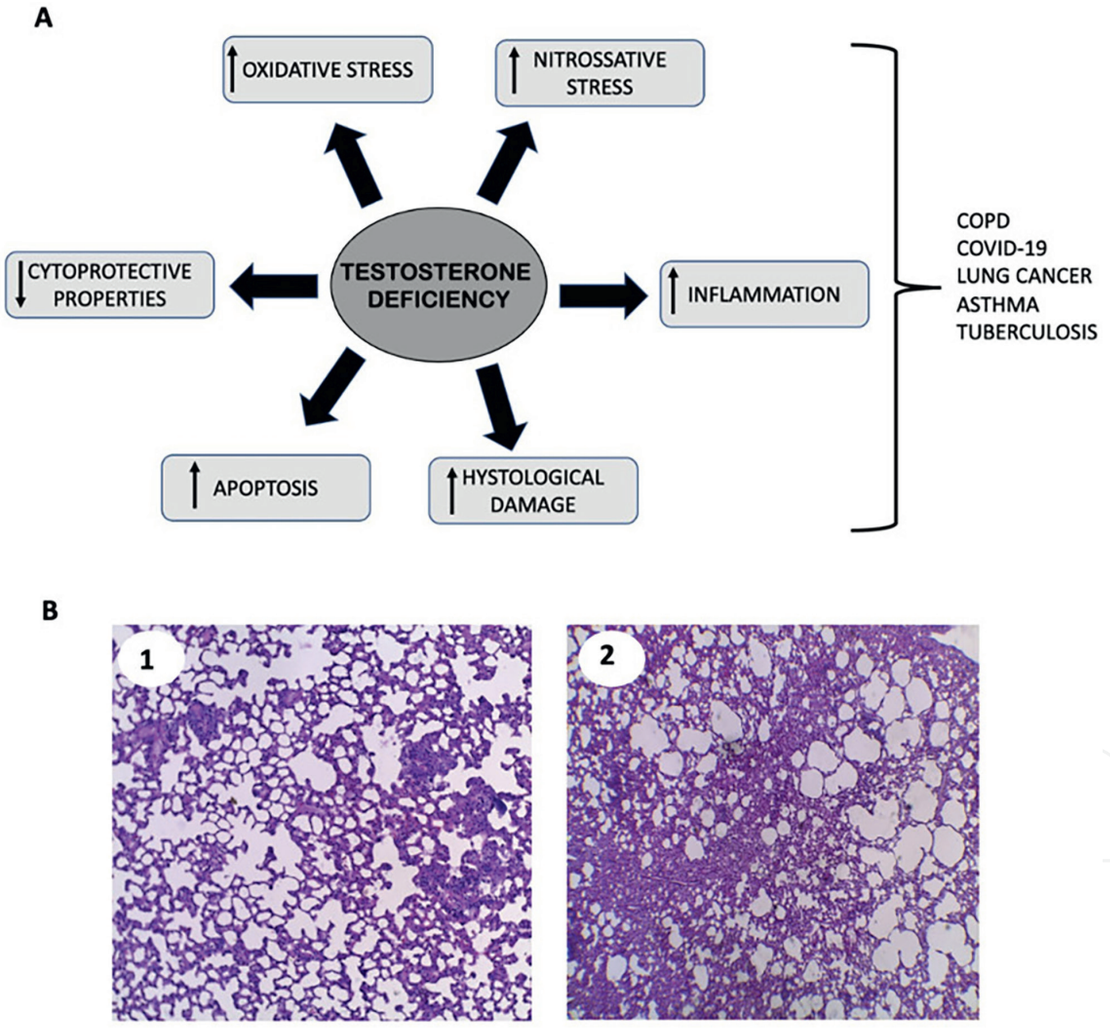

Figure 1.
The different cell functions altered by testosterone deficiency (A). There is an increase in oxidative stress due mainly to a decreased function of antioxidant enzymes. Nitrosative stress is also increased, due to the increased production of NO by iNOS. Inflammation under testosterone deficiency induces a Th1 response. This also induces a decrease in cytoprotective markers, ending in increased apoptosis. Taking together all these effects induces severe histological damage in the lung, making it weaker and more susceptible to diseases, which could end up in COPD, severe prognosis in COVID-19; lung cancer, asthma, and tuberculosis. The histological damage induced by the absence of testosterone after 1 month of treatment (B). (1) Control rat lung. The lung tissue appears normal and the alveoli are homogeneously distributed. The interalveolar septa show typical development of the normal lung. (2) Surgically castrated rat lung. The pulmonary parenchyma presents numerous large spaces caused by the rupture of the interalveolar septa. In other regions, the fibrous connective tissue has increased.

induces oxidative stress and lipid peroxidation in the lung, together with changes in the expression of cytoprotective markers, leading to important alterations in the histoarchitecture of this organ (**Figure 1**). This would lead to a weaker lung, susceptible to undergo several respiratory diseases.

The fact that testosterone levels decrease in elderly men explains the high prevalence of these diseases when compared to women of the same age. All these should be considered to better understand the etiology of respiratory diseases and propose therapies for these patients.

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