



Vision and Strategies for Men's Health Research in an Aging Society

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In an aging society, the nation's total medical expenditures increase. Furthermore, the rising demand for social security benefits places an astronomical financial burden on the nation. The aging of a society involves not only individuals' health problems, but also major social costs, such as increases in the tax rate derived from increases in medical expenditures. In this sense, through focusing on the prevention and treatment of aging-associated diseases in men, men's health research may suggest better solutions for aging-associated diseases at the individual level. It is also expected that applying the findings of men's health research in clinical practice can contribute to alleviating the suffering caused by those diseases, along with reducing medical costs and expenditures at the level of society.

Men's health research covers the following topics: 1) testosterone and late-onset hypogonadism; 2) prostate and prostate-related diseases (benign prostatic hyperplasia [BPH], prostate cancer, and prostatitis); 3) men's reproductive organs and related disorders (erectile dysfunction [ED], premature ejaculation [PE], and Peyronie disease); 4) semen, sperm, and infertility; and 5) chronic diseases affecting testosterone, the prostate, and sexual function (e.g., diabetes mellitus, obesity, and hypertension). With age, the prevalence of male climacteric-related disorders such as BPH, prostate cancer, ED, and

sexual dysfunction sharply increases, in contrast to analogous aging-related disorders in women. Therefore, men's health research is broadening its scope and gaining more attention.

The number of published clinical and basic science research papers related to testosterone was 658 in 2010, 691 in 2011, 751 in 2012, 761 in 2013, 834 in 2014, 839 in 2015, 846 in 2016, and 806 in 2017. According to the number of published papers, the amount of testosterone-related research continuously increased from 2010 to 2014, peaked between 2015 and 2016, and then showed a sharp decrease in 2017. This trend reflects the fact that a wide variety of studies related to testosterone were conducted in basic science fields, elucidating the role of testosterone and its mechanism of action, as well as in clinical practice fields, due to the release of many new drugs for testosterone replacement therapy (TRT), including oral drugs, patches, gels, and injections such as Nebido[®]. However, in the most recent years, no remarkable new drugs have been developed and no strikingly new topics related to testosterone have emerged in the field of basic science, which may explain the recent decrease in the number of published papers in this area. Of note, some researchers have recently argued that TRT can have negative effects on the cardiovascular system, which is raising concerns

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about practicing TRT in the clinical setting. Several meta-analyses have been conducted to clarify this issue, but none have provided decisive results. Therefore, further research in both basic science and clinical practice is needed in order to investigate the effects of TRT on the cardiovascular system. Many patients who need TRT are likely to have some pre-existing cardiovascular issues, since they are mostly elderly. In the absence of clear evidence regarding the effects of TRT on the cardiovascular system, it is questionable whether TRT is safe, which leads to variation in the treatment of late-onset hypogonadism patients.

Prostate research is one of the most important fields in men's health, which is reflected in the number of published papers (7,237 in 2017) in the field, 10 times higher than the number of published papers related to testosterone. Due to the increased prevalence of prostate cancer, oncologists also focus on the prostate, contributing a large amount of research. The number of published papers related to the prostate continuously increased from 2010 to 2017, and this trend is expected to continue. For the early detection of prostate cancer, new biomarkers have been studied by investigating blood, urine, prostatic or seminal fluid, and prostate tissue. Two of those markers (pro-prostate-specific antigen [pro-PSA] and PSA 3, prostate cancer antigen 3) were recently approved by US Food and Drug Administration (FDA) for clinical use. Other markers are not FDA-approved yet, but are available from Clinical Laboratory Improvement Amendment-certified clinical laboratories [1]. A handful of the numerous markers tested have entered clinical (human) use, but none have been shown to perform better than PSA as a screening test. Therefore, future studies may focus on finding new biomarkers that can replace PSA.

The pathophysiology of BPH is complex and not fully understood. Drug development for BPH is stagnant, and it is difficult to use anti-androgens to treat BPH due to their adverse effects, such as sexual dysfunction. For these reasons, many studies of BPH have focused on developing new surgical treatments, rather than drug treatments. New surgical treatments using lasers and applying Urolift® in clinical practice are 2 new modalities under study that are gaining attention [2]. These new treatments show superior efficacy to drug treatment, and lead to far fewer adverse effects and complications compared to the previous surgical treatments.

Drugs for the treatment of ED, such as Viagra, Cialis, and Levitra, have been developed and used in clinical practice, although some of them, such as Uprima® (apomorphine), were withdrawn from the market because of insufficient efficacy and adverse effects. Many pharmaceutical companies are continuing to develop various type of drugs for ED, including oral drugs, film-based drugs, orally disintegrating tablets, and creams. Some of them, such as nasal-spray apomorphine, an alprostadil cream, and gene therapy, are in clinical trials. For example, hMaxi-K Gene is in a phase 2A study targeting humans. However, developing a new drug that outperforms existing drugs is challenging, since the existing drugs, such as Viagra, have already shown outstanding effects. One new approach for ED is to use stem cells. Stem cell therapy has been attempted not only in cases of diabetic ED, but also in cases of hormonal, vascular, and neurogenic ED [3]. Stem cells can be classified depending on where they are collected, and the following types of stem cells have been used: adipose-derived stem cells, bone marrow-derived stem cells, placental-derived stem cells, and urine-derived stem cells. So far, 4 clinical trials have examined stem cell therapy for ED and shown improvements in erectile function. No critical adverse reactions have been reported [4]. However, those clinical trials only recruited a limited number of subjects and were conducted using non-standardized methods, raising concerns about actual use in patients. Thus, large-scale clinical trials using standardized methods should be conducted. Furthermore, in addition to surveys such as the International Index of Erectile Function, a new, objective method for determining therapeutic effects is needed. Although gene therapy was in the limelight in the past, it has been studied less, and fewer papers related to gene therapy have been published after the emergence of stem cell therapy. Furthermore, gene therapy has not been meaningfully applied in clinical practice, and good results from animal experiments are less likely to be extended to human beings. Among the genes used for gene therapy, the endothelial nitric oxide synthase gene has consistently shown good results in a variety of studies. Future studies should investigate how to apply the remarkable results observed for the endothelial nitric oxide synthase gene in human treatments.

Conducting research into the pathophysiology of PE is extremely challenging due to the difficulty of creat-

ing a suitable animal model, which hinders the development of treatments for PE because of the limited knowledge of the disease's mechanism of action. Biologic mechanisms associated with neurotransmitters such as norepinephrine, serotonin, oxytocin, gamma-aminobutyric acid, and nitric oxide, as well as the hormone estrogen, play central roles in ejaculation, and subsequently may mediate PE [5]. Various treatment options have been used in clinical practice, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, tramadol, phosphodiesterase 5 inhibitors, alpha 1-adrenoceptor antagonists, and topical anesthetics. Although Dapoxetine[®], a short-acting SSRI, is used for PE, patients' satisfaction has been reported to be less than expected, and several issues such as price and adverse reactions have been pointed out. Therefore, the frequency of long-term prescriptions of Dapoxetine[®] is gradually decreasing. For this reason, creating an animal model for PE should precede research into treatment of this disease, and by doing so, innovative treatments can be developed.

Fifty-eight clinical and basic science research papers regarding Peyronie disease were published in 2017, which is similar to the number of papers published on PE. Presumably, this is because these 2 diseases are not as common as prostate disease or ED. Carrying out Peyronie disease research is relatively easy because creating an animal model is comparatively straightforward. A recent animal model is created by administering repeated micro-trauma to a rat's penile tunica albuginea to induce Peyronie disease [6]. Regardless of its simple pathophysiology, it has been challenging to develop a treatment for Peyronie disease, resulting in

stagnation in related studies. Most studies regarding Peyronie disease have investigated surgical treatments, rather than non-surgical approaches, such as drug therapy. Practically, inhibiting the progressive fibrosis of penile tissue is considered to be the fundamental way to treat Peyronie disease. Extracorporeal shock wave therapy has also been studied as a candidate treatment for this disease, but there is no standardized research method, and large-scale clinical trials are needed.

Disclosure

The author has no potential conflicts of interest to disclose.

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