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Foundational Science and Mechanistic Insights for a Shared Disease Model: An Expert Consensus

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Pelvic floor disorders (PFDs) are complex conditions that impact millions of women worldwide. It is estimated that PFDs will affect approximately 30%–50% of women older than 50 years and incur a 20% lifetime risk of undergoing at least 1 surgical procedure to repair either pelvic organ prolapse (POP) or stress urinary incontinence (SUI) by age 80 years.[1] The surgical costs alone are estimated to exceed $10 billion annually,[1–6] and this does not account for the cost of nonsurgical and conservative treatments. Although a large body of epidemiological literature provides important information regarding the risk factors for PFDs, the pathogenesis of POP and SUI continues to be poorly understood. Consequently, POP and SUI are associated with significant health care expenditure primarily due to lack of preventive measures, high failure rate of available interventions, and the need for retreatments. Furthermore, the long-standing gaps in mechanistic insights into the pathophysiology of POP and SUI represent one of the major barriers to the development of scientifically rational preventive and therapeutic strategies. Women's health across the life span depends on a better understanding of the anatomy and physiology of the female pelvic floor (PF) and the causal links between the multifactorial epidemiological risk factors and POP/SUI.

PURPOSE

In this first edition of the e-book, we present a comprehensive review of the mechanistic insights centered around the priorities identified during a “think tank” brainstorming session (see below). The overarching goal of the e-book is to synthesize and interpret the available mechanistic data and to build a shared disease model of 2 PFDs—POP and SUI—that will serve to (1) further our understanding of the pathogenesis of these PFDs, (2) recognize important knowledge gaps and pinpoint research priorities, (3) identify novel targets for interventions, and (4) facilitate economically viable cross-disciplinary research initiatives.

Various scientific advances in molecular biology, -omics (eg, genomics, proteomics, metabolomics), and bioengineering enabled significant advances in the study of cancer, cardiovascular disease, neurological disorders, and men’s health. However, as the full-text report (or e-book) will highlight, women’s health advances in pelvic medicine lag behind even much less prevalent disorders (click here to access the e-book: https://www.augs.org/assets/1/6/AUGS_IUGA_eBook.pdf). Understanding how the various risk factors for PFDs (eg, POP and SUI) interact is particularly important to inform a shared disease model that can be leveraged to design scientifically robust preventive strategies and effective treatments for POP and SUI. This book is intended to be a “living e-book”; as scientific advances continue to broaden our understanding of these disorders and other PFDs (eg, accidental bowel leakage, sexual dysfunction, etc), this book can be updated to further develop a “shared disease model.”

METHODS

At the 2019 American Urogynecologic Society (AUGS)/International Urogynecological Association (IUGA) Joint Annual Scientific Meeting in Nashville, Tenn, we engaged clinicians and researchers from around the world to identify what was known and unknown about the pathophysiology of POP and SUI. Attendees at the AUGS/IUGA PFD Week Basic Science Symposium 2019 were invited to participate in an open think tank to discuss the various knowledge gaps in what is known about the fundamental mechanisms of these morbid and costly conditions. Sixty-five participants attended this think-tank session at the main meeting. Senior researchers were chosen among the group by the AUGS Basic Science Subcommittee and IUGA Special Interest Group, respectively, to lead this effort as section editors. Twentythree individuals from various disciplines were then invited to contribute as part of the primary writing group of this “living” e-book by the e-book editors-in-chief and section editors. The expertise of the think-tank attendees and the writing group members spanned female pelvic medicine and reconstructive surgery (FPMRS), urology, biomechanics, muscle physiology, bioengineering, immunology, cellular and molecular biology, steroid hormones, and aging science.

Attendees at the main meeting were subdivided into 4 breakout groups to foster multidimensional deliberations and interdisciplinary approaches to building a shared disease model of POP and SUI. Each group, led by a moderator with extensive expertise in the subject matter, discussed what was known and what were the remaining major gaps in knowledge. Specifically, participants focused on the questions that needed to be answered in

order to optimize treatments and identify preventive strategies for POP and SUI. Extensive notes were taken and then independently transcribed by the editors of this e-book. Members of the subsequent writing group expanded upon the ideas generated from the inperson think-tank session and performed a review of the literature to identify what we understand about the pathogenesis of POP and SUI. The authors threaded together a cogent description of a shared disease model and, in the process, identified important research areas that should be addressed in order to make a significant leap forward in the field of FPMRS.

The areas of focus aligned with the 4 think-tank groups: (1) PF structural anatomy and the mechanism of disease, (2) biomechanics of the female PF, (3) the impact of hormonal milieu on the female PF structure and function, and (4) the role of aging and immunity in the pathogenesis of POP and SUI. The e-book highlights anatomical, biomechanical, hormonal, aging and inflammation-related pathways and underscores the interdependence of these factors with respect to their impact on the PF and lower urinary tract (LUT). The chapters emphasize the importance of the deeper dive into various phenotypes and genotypes that is necessary to foster personalized medicine in the field. This approach is also essential to drive discovery science to address long-standing but still unanswered questions related to POP and SUI pathogenesis, recurrence after surgical interventions, and the mechanisms behind the epidemiological risk factors. The authors specifically attempt to describe the interactions between inciting and promoting events along a woman's life span. The latter has been difficult in the field of urogynecology as much of the research published to date has been compartmentalized without making meaningful interdisciplinary connections. Therefore, this e-book also serves as a call for scientific action, as it outlines the major areas of insufficient evidence and proposes a path forward. It is clear that for meaningful discoveries and improved clinical outcomes, we must embrace a team science approach to capitalize on the bench-to-bedside-and-back research paradigm. Future efforts should also concentrate on the impact of racial and ethnic diversity as well as social determinants of health on the mechanisms that govern POP and SUI pathogenesis and response to treatments.

Pelvic Floor Structural Anatomy and the Mechanism of Disease: State of the Science and Future Directions

Mechanistic and translational research into structural anatomy, as it relates to the etiology of PFDs, is critical to improving our understanding of these conditions, innovating treatments, and developing novel preventive strategies. The purpose of this chapter is to review recent advances in pelvic structural anatomy and illuminate the questions that remain unanswered regarding the structural causes of POP and SUI.

This chapter describes structural anatomy, including the bony pelvis, skeletal muscles, smooth muscle, connective tissues, and the nerves and vasculature. The authors go on to identify how the risk factors (such as race, genetics, repetitive loading, and childbirth) affect the structural components of the pelvis. Many knowledge gaps are identified by the authors who call for urgent investigations focused on genetic influences on disease phenotype, reliable biomarkers, and noninvasive imaging techniques to identify those factors most strongly associated with POP and SUI. Once we have a more comprehensive understanding of the intrinsic and extrinsic factors leading to structural impairments in prolapse and

incontinence, preventive approaches can then be designed to target high-risk women, and novel therapeutic regimens can be identified.

Biomechanics of the Female Pelvic Floor

Biomechanics, which is the study of the action of external and internal forces on the living body, is intimately related to structural anatomy. Pelvic floor disorders occur when the PF structures are no longer able to sustain mechanical forces needed to support the pelvic organs. However, the field of FPMRS lags behind other fields, such as orthopedics, in considering forces on structures as an important component of the therapeutic paradigm. Recent evidence, outlined in this chapter, provides insight into the importance of these considerations for moving the field forward.

The chapter starts with the review of the fundamental concepts of tissue mechanics and describes some of the work that provides understanding of the tissue-level changes that are associated with POP and SUI. The next section covers how computational modeling uses image analyses and experimental data to develop hypotheses and predictive simulations that, if validated, have the potential to enable patient-specific phenotypes for improved clinical diagnoses and individualized surgical planning. Finally, the chapter concludes with a summary of the significant amount of work that remains to be done to understand the biomechanics of PF function and dysfunction.

The authors describe the clinical challenges that arise when the in vivo load-bearing capacity of the PF and supportive structures is poorly understood. Further, it is important to understand how PF tissue remodels in response to changes in mechanical stimuli (eg, pregnancy and vaginal delivery) and how this process can be leveraged to identify new implant materials to augment surgical repairs. This is a growing area of research, and the potential for major improvements in the quality of life for women is extremely high. It is hoped that the reader will come away with an appreciation of the interconnectedness of biomechanical research with other areas covered in the e-book, including structural anatomy, molecular biology, hormonal actions, aging, and immunity.

The Impact of Hormonal Milieu on the Female Pelvic Floor Structure and Function

The mechanisms by which menopause contributes to POP and SUI are unclear. A widely held belief is that estrogen depletion promotes the progression of POP; however, results from the Women's Health Initiative demonstrated that the stage of POP did not improve with oral menopausal hormone therapy (MHT) and that urinary incontinence worsened in women given MHT.[7–9] Conversely, basic science tissue-level studies have consistently shown that estrogen loss promotes "weaker" pelvic tissues and that estrogen replacement decreases extracellular matrix degradation and strengthens PF tissues.[10–12] Vaginal local estrogen therapy is often used for the treatment of genitourinary syndrome of menopause and may also be useful for wound healing in women undergoing surgery for POP and SUI.[13–15] Although there are many positive outcomes with the use of local estrogen therapy, MHT has been shown to negatively impact vaginal mechanical properties, which may have an adverse effect on tissues following POP repair.[16]

The complex pathophysiology of obesity and the associated conditions, such as metabolic syndrome, diabetes, and alterations in the inflammasome and immunity, may also play a role. Obesity is metabolically a proinflammatory and nitro-oxidative stress state, characterized by increased plasma free fatty acids, known to exert negative vascular effects and oxidative stress.[17,18] The chapter describes a number of mechanistic pathways that underscore the relevance of the systemic metabolic milieu to the pathophysiology of POP and SUI. In addition, the chapter highlights the putative relationships between imbalances in other hormones—including androgens, thyroid hormones, and vitamin D—and PFDs. These hormones are understudied but, given their effects in other tissues, likely play a role in PFDs. The improved understanding of the independent and combinatorial impact of hormonal factors and their deprivation is essential for informing the multimodal shared model of POP and SUI.

The Role of Aging and Immunity in the Pathogenesis of POP and SUI

This chapter describes the mechanistic influences of aging and immunity on the PF and LUT cells and tissues, the relationship between age-related changes and the pathogenesis of POP and SUI, and the impact of aging and immune response upon the success of surgical interventions. Among the many risk factors associated with PFDs, aging is certainly among the most impactful. Women older than 50 years represent the majority of patients presenting for management of clinically significant POP.[4] Aging is not a modifiable risk factor for POP and SUI; nevertheless, understanding discrete mechanisms may elucidate novel targets for treatment and preventive strategies.[19,20] It is imperative to expand our comprehension of the critical molecular pathways associated with aging as the number of older women suffering from POP and SUI is expected to continue to increase significantly.[4,21]

The mechanistic underpinnings of aging of cells and tissues and how these changes contribute to the pathogenesis of POP and SUI are detailed in the context of the hallmarks of aging.22 The large body of knowledge on how genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intracellular communication affect nonpelvic tissues and organ systems should be exploited to study the effects of aging on the female PF and LUT.

To date, clear associations have been established between cellular dysfunction and tissue degradation and POP and SUI. However, the detailed mechanistic insights and the causal links between the effects of aging on the PFand LUT resident epithelial, fibromuscular, neuronal, and immune cells and the pathogenesis of PFDs are lacking. In addition, research focused on the effects of aging on the immune cells of both the innate and adaptive immune systems, termed *inflammaging* or *immunosenescence*, is widely emerging in other fields. Inflammaging is likely to have a significant impact on both the pathogenesis of POP/SUI and the individual's response to treatments.

Understanding aging mechanisms relevant to the PF and LUT will also assist with a "personalized medicine" approach to care. For example, identification of a particular hallmark of aging biomarkers in individual patients could enable targeted individualized therapeutic approaches for women with POP/SUI. Such approaches have a high potential

to inform the choice of specific implant material for reconstructive pelvic surgery in the individual older women based on changes in immunity and inflammaging that affect wound healing and tissue regeneration. In addition, knowledge regarding whether and how PF physical therapy and physical activity mitigate the untoward effects of aging and inflammation on the female PF and LUT is lacking, precluding development of maximally effective preventive algorithms.

Validated models to study the role of aging and POP/SUI pathogenesis are needed. The hallmarks of aging provide an excellent framework for identifying experimental in vitro and in vivo models to study senescence of the female PF and LUT at the cell, tissue, and organ system levels. Addressing these gaps could contribute to healthy aging for millions of women worldwide.

Conclusions

The main goals of this volume of our shared e-book are (1) to review the existing fundamental knowledge and mechanistic insights relevant to POP and SUI and (2) to highlight the need to engage in more robust interdisciplinary research to fully elucidate the disease model for these disorders. Overall, there is a clear need to dive deeper into the mechanisms responsible for pathogenesis of POP and SUI along women's life span. Each chapter underscores the importance of applying the existing contemporary research tools, as well as developing and validating novel instruments, to generate physiologically relevant multidimensional data that will allow clinicians to personalize preventive and therapeutic interventions to counteract POP/SUI.

Interdisciplinary research, which integrates information, data, techniques, and tools of 2 or more disciplines to advance understanding beyond the scope of any single discipline or practice, will greatly facilitate bridging the gaps underscored in each chapter.[23] The value of this approach is having multiple experts from different fields collaborate to answer critical questions that will have the greatest impact on the field. While a multidisciplinary approach requires that fields remain separate—arguably what has already occurred in the studies of POP and SUI—interdisciplinary research allows each group to expand beyond a single point of view to explain more complex phenomena and generate innovative therapeutic options. Rigorous interdisciplinary studies will lead to transdisciplinary research, which is defined as creating a new discipline from 2 or more.[24] Transdisciplinary research enables innovations not possible within a single discipline and may ultimately lead to a unique discipline. The field of urogynecology is an example of a transdisciplinary field as it is defined by the core principles of gynecology, urology, gastroenterology, colorectal surgery, biomechanics, and physical rehabilitation. As our field moves to further advance our mechanistic understandings of PFDs and to identify novel therapeutic paradigms, embracing transdisciplinary team science would allow multiple stakeholders to capitalize on their combined expertise and innovations from various areas of science and medicine to make substantial leaps forward in FPMRS, while potentially affecting policy changes relevant to women's health.

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REFERENCES

1. Hunskaar S, Burgio K, Diokno A, et al. Epidemiology and natural history of urinary incontinence in women. Urology 2003;62(4 Suppl 1):16–23. doi:10.1016/s0090-4295(03)00755-6. [PubMed: 14550833]
2. Boyles SH, Weber AM, Meyn L. Procedures for pelvic organ prolapse in the United States, 1979–1997. Am J Obstet Gynecol 2003;188(1):108–115. doi:10.1067/mob.2003.101. [PubMed: 12548203]
3. Chong EC, Khan AA, Anger JT. The financial burden of stress urinary incontinence among women in the United States. Curr Urol Rep 2011; 12(5):358–362. doi:10.1007/s11934-011-0209-x. [PubMed: 21847532]
4. Wu JM, Kawasaki A, Hundley AF, et al. Predicting the number of women who will undergo incontinence and prolapse surgery, 2010 to 2050. Am J Obstet Gynecol 2011;205(3):230.e1–230.e5. doi:10.1016/j.ajog.2011.03.046. [PubMed: 21600549]
5. Subak LL, Waetjen LE, van den Eeden S, et al. Cost of pelvic organ prolapse surgery in the United States. Obstet Gynecol 2001;98(4):646–651. [PubMed: 11576582]
6. Wilson L, Brown JS, Shin GP, et al. Annual direct cost of urinary incontinence. Obstet Gynecol 2001;98(3):398–406. [PubMed: 11530119]
7. Handa VL, Garrett E, Hendrix S, et al. Progression and remission of pelvic organ prolapse: a longitudinal study of menopausal women. Am J Obstet Gynecol 2004;190(1):27–32. doi:10.1016/j.ajog.2003.07.017. [PubMed: 14749630]
8. Hendrix SL, Cochrane BB, Nygaard IE, et al. Effects of estrogen with and without progestin on urinary incontinence. JAMA 2005;293(8):935–948. doi:10.1001/jama.293.8.935. [PubMed: 15728164]
9. Nygaard I, Bradley C, Brandt D. Pelvic organ prolapse in older women: prevalence and risk factors. Obstet Gynecol 2004;104(3):489–497. doi:10.1097/01.AOG.0000136100.10818.d8. [PubMed: 15339758]
10. Clark AL, Slayden OD, Hettrich K, et al. Estrogen increases collagen I and III mRNA expression in the pelvic support tissues of the rhesus macaque. Am J Obstet Gynecol 2005;192(5):1523–1529. doi:10.1016/j.ajog.2004.11.042. [PubMed: 15902152]
11. Moalli PA, Klingensmith WL, Meyn LA, et al. Regulation of matrix metalloproteinase expression by estrogen in fibroblasts that are derived from the pelvic floor. Am J Obstet Gynecol 2002;187(1):72–79. doi:10.1067/mob.2002.124845. [PubMed: 12114891]
12. Moalli PA, Talarico LC, Sung VW, et al. Impact of menopause on collagen subtypes in the arcus tendineous fasciae pelvis. Am J Obstet Gynecol 2004; 190(3):620–627. doi:10.1016/j.ajog.2003.08.040. [PubMed: 15041990]
13. North American Menopause Society. The role of local vaginal estrogen for treatment of vaginal atrophy in postmenopausal women: 2007 position statement of the North American Menopause Society. Menopause 2007;14 (3 Pt 1):355–369; quiz 370–371. doi:10.1097/gme.0b013e31805170eb. [PubMed: 17438512]
14. Alperin M, Burnett L, Lukacz E, et al. The mysteries of menopause and urogynecologic health: clinical and scientific gaps. Menopause 2019;26(1): 103–111. doi:10.1097/gme.0000000000001209. [PubMed: 30300297]
15. Karp DR, Jean-Michel M, Johnston Y, et al. A randomized clinical trial of the impact of local estrogen on postoperative tissue quality after vaginal reconstructive surgery. Female Pelvic Med Reconstr Surg 2012;18(4): 211–215. doi:10.1097/SPV.0b013e31825e6401. [PubMed: 22777369]

16. Feola A, Duerr R, Moalli P, et al. Changes in the rheological behavior of the vagina in women with pelvic organ prolapse. Int Urogynecol J 2013;24(7): 1221–1227. doi:10.1007/s00192-012-2002-x. [PubMed: 23208004]
17. Boden G. Obesity and free fatty acids. Endocrinol Metab Clin North Am 2008;37(3):635–646, viii-ix. doi:10.1016/j.ecl.2008.06.007. [PubMed: 18775356]
18. Cătoi AF, Pârvu AE, Andreicuţ AD, et al. Metabolically healthy versus unhealthy morbidly obese: chronic inflammation, nitro-oxidative stress, and insulin resistance. Nutrients 2018;10(9):1199. doi:10.3390/nu10091199.
19. Rieger M, Duran P, Cook M, et al. Quantifying the effects of aging on morphological and cellular properties of human female pelvic floor muscles. Ann Biomed Eng 2021;49(8):1836–1847. doi:10.1007/s10439-021-02748-5. [PubMed: 33683527]
20. Burnett LA, Cook M, Shah S, et al. Age-associated changes in the mechanical properties of human cadaveric pelvic floor muscles. J Biomech 2020;98:109436. doi:10.1016/j.jbiomech.2019.109436. [PubMed: 31708240]
21. Wu JM, Matthews CA, Conover MM, et al. Lifetime risk of stress urinary incontinence or pelvic organ prolapse surgery. Obstet Gynecol 2014; 123(6):1201–1206. doi:10.1097/aog.0000000000000286. [PubMed: 24807341]
22. López-Otín C, Blasco MA, Partridge L, et al. The hallmarks of aging. Cell 2013;153(6):1194–1217. doi:10.1016/j.cell.2013.05.039. [PubMed: 23746838]
23. Committee on Facilitating Interdisciplinary Research, National Academy of Sciences, National Academy of Engineering, Institute of Medicine. Facilitating Interdisciplinary Research. Washington, DC: National Academies Press; 2004.
24. Rosenfield PL. The potential of transdisciplinary research for sustaining and extending linkages between the health and social sciences. Soc Sci Med 1992;35(11):1343–1357. doi:10.1016/0277-9536(92)90038-r. [PubMed: 1462174]