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Integrative Medicine and Urology: Lifestyle Changes, Supplements and Acupuncture—Noncancerous Conditions

Learning Objective: At the conclusion of this continuing medical education activity, the participant will be able to propose evidence-based lifestyle, supplement and other integrative medicine recommendations for primarily noncancerous urological conditions, and assess the utilization of perceived integrative medicine interventions with minimal or negative clinical research.

This AUA Update aligns with the American Board of Urology Module on Core/General Urology. Additional information on this topic can be found in the AUA Core Curriculum sections on Urolithiasis and Infertility.

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INTRODUCTION

Lifestyle changes, dietary supplements and acupuncture-based integrative medicine (IM) for noncancerous urological conditions represent a diverse range of topics in excess of what can be reviewed in a single manuscript. Beneficial interventions, adverse potential outcomes and those agents with no impact should receive attention, especially those more relevant and minimally reviewed topics in the urological literature. Acupuncture is included in this Update because of newer disease-specific data and awareness of issues in a variety of urological conditions, as well as the fact that many acupuncturists recommend supplements or herbal products as a part of their clinical practice, which potentially impacts patients and other practitioners within urology.[1] Other relevant IM topics, such as overall quality control issues with dietary supplements, have been reviewed in a recent Update.[2]

CHRONIC UROLOGICAL PAIN SYNDROMES

Any IM treatment that results in safe nonaddictive pain relief should be of interest. Acupuncture appears to be more accepted, evidence-based and reimbursed in a variety of medical disciplines.[3] For example, patients on Medicare are currently eligible to receive up to 12 acupuncture treatments during a 90-day period if they have nonspecific lower back pain of at least 12 weeks' duration.[4] Other pain syndromes could benefit from acupuncture treatments. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) could be significantly improved (eg National Institutes of Health–Chronic Prostatitis Symptom Index total score, pain domain etc), via a minimum of 6 and up to 18 acupuncture treatments, beyond what is observed with sham treatments.[5] Multiple potential mechanisms from increased concentrations of diverse endorphins, serotonin and immunomodulation have been proposed mechanisms of action. Preliminary findings also suggest minimal adverse events from past clinical studies.

Approximately 20 years ago, a North American pilot study of acupuncture for standard therapy-refractory patients with a mean followup of 33 weeks appeared to significantly improve total National Institutes of Health–Chronic Prostatitis Symptom Index and all symptom index domains.[6] Patients received twice-weekly treatments for at least 6 weeks, and the safety, efficacy and durability of these results were notable. Positive additional data since this time have not resulted in a large-scale, methodologically rigorous completed clinical trial of acupuncture for CP/CPPS despite the disappointment during this time with diverse monotherapy medications. Interstitial cystitis/bladder pain syndrome (IC/BPS) is another chronic pain condition where positive preliminary benefits have been observed with acupuncture.[7]

Lifestyle and dietary supplement interventions should also be noted. Some of the largest prospective studies, derived from observing health care professionals, have suggested minimal impact of basic modifiable behaviors or parameters for CP/CPPS.[8] These data sources are limited, at times, by some baseline characteristics, for example a mean body mass index (BMI) of 25, with 8% of the participants being obese vs 40% in the U.S. population.[9] Still, within this same cohort, a reduction in CP/CPPS with moderate to vigorous physical activity (including brisk walking) was observed,[10] and preliminary randomized studies of CP/CPPS patients unresponsive to conventional therapies have also found significant potential benefits of exercise, including pain reduction.[11] An underappreciated advantage of instructional or group vs solo exercise appears to be the socialization effect for enhancing outcomes, although dropout rates are a limitation of exercise research in general, mirroring what is observed in some drug clinical trials.

CP/CPPS heterogeneity in terms of identifying UPOINTS ("urinary, psychosocial, organ specific, infection, neurological and muscle tenderness") clinical phenotypes has resulted in improved individualized treatment success.[12] Quercetin (500 mg bid) or standardized pollen extract (cernilton, 2 capsules every 8 hours) supplements are potential options for the "organ specific" domain based on preliminary efficacy data along with favorable side effect profiles, and exercise has been suggested for the "tenderness" phenotype as a part of multimodal treatment. However, exercise could also assist in improving cases within some or most phenotypes. Ample ancillary data, outside of urology, exist on treatment of patients with IM that fit within these different categories. For example, depression or catastrophizing is found within the "psychosocial" phenotype, which can be severe in some patients with CP/CPPS,[13] and the preliminary positive data with exercise are profound compared to numerous other researched interventions.[14,15] Perhaps part of the issue has been the past emphasis on the design and implementation of primarily monotherapy approach clinical trials, which enroll participants with essentially any type of CP/CPPS (not phenotypes) for the purpose of drug approval or disapproval.[16] Embracing and testing multiple or concomitant treatments in future clinical trials could achieve greater efficacy within such a heterogeneous common condition.

A majority of patients (up to 90%) with IC/BPS have flares or increased symptomatic severity after consuming specific foods or beverages, such as coffee, other caffeinated and acidic beverages, spicy foods or alcohol, but again these and other provoking products need to be individually recognized.[17] Food diary utilization, working with an experienced dietitian, should be recommended to assist not only in the diagnostic evaluation, but also in treatment regimens. Most clinical IC/BPS guidelines recommend and emphasize some form of dietary advice as a part of treatment, but perhaps they need to place even more emphasis on the increased utilization of specific food diaries for diagnostic evaluation and treatment assistance. An individual-

ABBREVIATIONS: AUA=American Urological Association, BMI=body mass index, BPH=benign prostatic hyperplasia, CAMUS=Complementary and Alternative Medicine for Urological Symptoms, CP/CPPS=chronic prostatitis/chronic pelvic pain syndrome, FAZST=Folic Acid and Zinc Supplementation Trial, FDA=U.S. Food and Drug Administration, IC/BPS=interstitial cystitis/bladder pain syndrome, IM=integrative medicine, LDL=low-density lipoprotein, LUTS=lower urinary tract symptoms, MOXI=Males, Antioxidants, and Infertility Trial, OAB=overactive bladder, PTNS=percutaneous tibial nerve stimulation, STEP=Saw Palmetto for the Treatment of Enlarged Prostate

ized approach to dietary changes should be as noteworthy as the recommended approach to individualizing conventional treatment. Regardless, most guidelines do recommend patient education with lifestyle or behavioral modification options such as timed voiding, modifying fluid intake and bladder training.

Symptom phenotypes for IC/BPS have also been proposed from specific clinical guidelines,[18] which again suggest a notable impact for IM. Some suggest acupuncture, and although preliminarily promising, again more clinical research is needed. Intravesical agents being considered include compounds such as hyaluronic acid and chondroitin sulfate, which are arguably better known by consumers as oral dietary supplements utilized for other chronic pain conditions such as osteoarthritis. Preliminary research suggests these oral supplementation options have some efficacy within IC/BPS.[19] Calcium glycerophosphate supplementation also has preliminary positive data in many patients attempting to reduce acidic symptomatic triggers and should still be considered. Other notable antacid products should be researched and compared to this product. Additionally, the role, if any, of cannabidiol for CP/CPPS and IC/BPS should be of future research interest based on recent widespread availability, other nonurological chronic pain issues being currently investigated and the lack of any concerning psychoactive effects compared to THC (tetrahydrocannabinol) in marijuana. However, the potential quality control issues and drug interactions with cannabidiol abound and also need to be resolved.[2]

IM for IC/BPS should also recognize the dearth of any form of exercise (aerobic, resistance, flexibility etc) research in preventing and treating this condition. Older positive case reports and the heterogeneity of this condition suggest exercise remains an untapped potentially synergistic intervention (somewhat similar to CP/CPPS).[20] If behavioral changes and stress management alone improve up to half of the patients with this condition, then the already well-documented ability of mind-body (Tai chi, yoga etc) or other forms of exercise to serve as potent stress ameliorative interventions[21] should receive more urological emphasis.

BLADDER

Perhaps one of the most emblematic representations of how IM can positively impact a conventional medical specialty is the utilization and supportive data for a type of electro-acupuncture known as percutaneous tibial nerve stimulation (PTNS). Randomized trials and guidelines have supported the utilization of PTNS for adults, and in some cases children, with overactive bladder (OAB) issues and those refractory to or intolerant of medications.[22,23] Concern over the numerous potential clinical visits or the quantity of time required for an effective course of PTNS is valid. However, the consistent safety record should also be emphasized compared to current and emerging concerns with short-term and especially long-term use of some of the prescription medications within select pediatric and elderly patients.[24]

Multiple concerns should also be noted with the potential use of any form of traditional acupuncture, including cost, insurance exclusion, minor or rare side effects (bleeding at the insertion site, temporary hypotension, infection etc), lack of proper training in urological care, minimum to maximum number and frequency of treatments, best forms (auricular, traditional whole body, electro-acupuncture etc) of disease-specific treatment, impact of the practitioner on outcomes, need for more comparisons to sham acupuncture and, again, ancillary herbal product recommendation and utilization.[2] This is not to imply herbal products do not have a role in some urological care scenarios, but rather the probability that being under the care of some acupuncturists could result in the recommendation and utilization of some ancillary herbal medications. **Most supplements touted for OAB, which potentially mimic drug mechanisms of action, should currently be discouraged without at least the same amount of safety and efficacy data as pharmacological options.**

Other areas of ongoing interest for acupuncture within urology are limited by minimal clinical observational data and the urgent need for more rigorous clinical research. The only notable exceptions exist within urologic oncology, where acupuncture continues to garner evidence for ameliorating specific notable adverse effects of conventional treatment (hot flashes, neuropathy etc).[25,26] Still, it is imperative for urological practitioners to locate regional and nonregional acupuncturists with experience for potential vetting and referral. Otherwise, ancillary acupuncture training is also plausible with conventional practitioners who seek to eventually offer this option within their own practice. Table 1 summarizes the potential impact of acupuncture within urology.

Lifestyle advice within urology is evidence-based, even in regard to water intake and OAB. For example, some external "expert" nonevidence-based sources recommend 8 glasses of water per day to improve overall health, but this advice was found to be without scientific merit.[27] Level 1 urological evidence suggests unjustified general increases in fluid intake could exacerbate OAB urinary frequency. Preliminary prospective and randomized research suggests a reduction in fluid intake (25% or more) could reduce 1 or multiple OAB symptoms (frequency, urgency, nocturia) and improve quality of life. However, level 1 evidence in other urological situations suggests increases in fluid consumption are correlated with a decrease in kidney stone risk and recurrence, which could also be the case for recurrent urinary tract infection prevention.[28]

BENIGN PROSTATIC HYPERPLASIA (BPH)/ LOWER URINARY TRACT SYMPTOMS (LUTS)/ NOCTURIA

BPH may not increase the risk of prostate cancer, but potential lifestyle risk factors shared between these 2 conditions are noteworthy.[1,29,30] Some lifestyle changes could even impact the progression of one or both conditions. For example, the impact of exercise on nocturia continues to garner evidence.[31,32] Exercise also has the ability to promote improved quantity and quality of sleep, or better sleep efficiency, which becomes more compromised with aging.

Obstructive sleep apnea is associated with worsening LUTS, but lifestyle changes and conventional treatments such as CPAP (continuous positive airway pressure) can potentially improve a diverse range of subjective and objective parameters.[33] Other forms of treatment for insomnia, such as melatonin-based prescription products (with supplements needing more research), could also be of ancillary benefit. Disruption of circadian rhythm could be associated with BPH or more aggressive prostate cancer.[34] Sleep inefficiency could alter immune func-

tion, suppress peak production of some anti-cancer hormonal compounds, and disrupt circadian-impacted genes associated with cell proliferation and apoptosis or cell-cycle control. Alcohol also impairs sleep efficiency, and excessive intake is associated with worsening LUTS and an increased risk of aggressive prostate cancer, which also appears to be the case for current smokers.[35]

Unhealthy potentially modifiable parameters could compromise the effectiveness of conventional BPH treatments.[36,37] Obesity reduces drug efficacy, and is a higher probability predictor of treatment failure. Excessive or heavy alcohol intake also negates some of the potential benefits of pharmacological BPH interventions.[38] It is also interesting that nonmodifiable risk factors, such as race, family history and genetics, are associated with more aggressive BPH or prostate cancer, and increasing age elevates the incidence of both conditions. Regardless, despite the inherent desire to uncouple the risk or etiology of one condition compared to the other, both share an increasing plethora of similar associations, which could provide a comprehensive educational platform to improve general prostate health, associated (eg sexual function) or other urological conditions (male infertility etc), and even serve to reduce overall morbidity and mortality. Table 2 contains an updated summary of some shared potentially modifiable risk factors that can be used in consultation with select patients.

Several reasons exist for at least initially discouraging treatment of BPH/LUTS with an over-the-counter product, or in some cases, a pharmacological agent, apart from potential improvements observed with lifestyle changes.[37,39] Approximately 20%–30% of men with untreated BPH/LUTS experience minimal risk of progression or potential long-term stabilization. The term "active surveillance" has become prevalent within the prostate cancer vernacular, but no similarly used recognizable term within BPH is appreciated at this time in the public discourse. Overuse of dietary supplements for milder symptoms that do not require intervention should also be addressed, as should long-term poor compliance rates for any pill for any degree of BPH severity. It is not surprising that BPH supplements are popular. What is surprising is the lack of more recent data in general to support the utilization of many of these options. Methodologically rigorous clinical trials over the last 20–25 years are in short supply, with the exception of saw palmetto studies.

Beta-sitosterol. Why is beta-sitosterol, or other added plant sterols, arguably among the most popular ingredients found in past and current over-the-counter BPH supplemental products? More than 20 years ago, beta-sitosterol enjoyed a heightened level of positive research reviews and meta-analyses from reputable journal sources, and past clinical studies using concentrated dosages of 60–195 mg per day found no apparent overt or acute safety concerns.[40] Furthermore, during this same period a qualified health claim by the U.S. Food and Drug Administration (FDA) was permitted, which suggested higher concentrations or dosages of plant sterols added to some processed foods such as margarine and other products could potentially decrease heart disease via modest low-density lipoprotein (LDL) control or reductions.[41] Perhaps, this is one mechanism whereby beta-sitosterol could have been found to be beneficial over placebo in older studies, since no primary or consistent mechanism of action within past BPH studies was identified. Studies using proven pharmacological LDL-reducing agents have found the potential for decreasing, or at least controlling, prostate volume and inhibiting BPH progression.[42-44]

However, the current controversy surrounding beta-sitosterol and plant sterols added to processed products should be discussed with patients. Beta-sitosterol has not received more rigorous recent research within BPH, and recent controversies over the past qualified heart health claims should also be addressed for perspective.[45] Whether this compound currently is more effective than a high-quality placebo or could enhance or compete with any approved pharmacological BPH agents in a rigorous urological study has not been answered. Also, arguably the older reputable meta-analysis for BPH and the heart healthy claim for plant sterols were misconstrued. Methodological issues were a noted concern to the authors, with the quality of treatment allocation deemed "unclear" in most BPH trials, as well as the need for studies of longer duration and more validated urological end points.[40]

Furthermore, the heart healthy claim from the FDA did not imply a clear cause and effect benefit, and a simultaneous emphasis on improving overall dietary quality within this same document appeared to garner minimal attention.[41] Additionally, despite plant sterols exhibiting an ability to reduce LDL via inhibiting the absorption of dietary cholesterol, there have been no rigorous studies to date demonstrating a reduction in hard clinical cardiovascular end points with these products.[45] Finally, the demonstration of genetic or individual variability to plant sterol cholesterol responses, as well as the rare medical condition known as "sitosterolemia," has received minimal to no attention in the urological literature. The true prevalence of this autosomal recessive inherited medical condition is not known. What is appreciated in cardiovascular medicine is that greater exposure to larger and more concentrated plant sterols could paradoxically lead to an increase in cardiovascular issues in these select patients. Again, this author appreciates the rare nature of this genetic condition, but until more studies of the true penetrance of these mutations are conducted, there should be some awareness of these "rare" issues.

This author's primary current generalized concerns for clinicians treating BPH patients are the cost and subsequent exposure to higher caloric manufactured plant sterol products during this time of an unprecedented obesity epidemic. The limitations of many of these products now appear to exceed the potential benefits. In the meantime, clinicians and patients should ideally place more emphasis on healthy, whole, unprocessed, nutrient dense dietary sources of plant sterols (nuts, seeds including flaxseed and pumpkin, legumes, fruits, vegetables etc), rather than concentrated or isolated manufactured sources of these ingredients, until some or all of these controversies are resolved.

Pygeum africanum bark (extract of African prune tree). An approximately 20-year-old meta-analysis of 18 randomized trials (1,562 men) with a mean study duration of 64 days was arguably the last notable updated publication on *P. africanum*,[46] and recent rigorous trials are lacking. The majority of studies utilized dosages of 75–200 mg. Beta-sitosterol is one of many ingredients in *P. africanum* believed to be impactful, which again is also the case for numerous other herbal BPH supplements.[47]

What needs more awareness within the urological literature is the past and ongoing concern regarding the potential overuse of the bark of the African prune tree (a major source of

P. africanum), including the current placement of this species on some country-based conservation or vulnerability lists.[48] **This topic needs further attention to determine the true relevance of these concerns, solutions and whether certain companies or manufacturers are sensitive to or attempting to solve this issue, for example, using more farmed alternative planet-friendly viable sources vs the natural/wild procurement of more endangered sources. Perhaps this issue should receive more attention in general with many herbal sources within and outside of urology.**

Saw palmetto. Few herbal supplements have received more initial positive attention for the treatment of a medical condition compared to saw palmetto and BPH/LUTS symptoms. It is also one of the few popular herbal products to have been arguably subject to 2 sequential rigorous phase III trials, known as STEP (Saw Palmetto for the Treatment of Enlarged Prostate) and CAMUS (Complementary and Alternative Medicine for Urological Symptoms).[49,50] STEP used a well-known standard dosage of saw palmetto (320 mg/day) over 12 months,[49] and CAMUS used increasing dosages (320, 640 and 960 mg/day) over 18 months.[50] Both trials found saw palmetto safety and efficacy similar to a higher quality or virtually indistinguishable placebo product. **Interestingly, a modest but significant improvement in American Urological Association (AUA) Symptom Index was observed during the single-blind placebo run-in period in both arms of STEP. This is fascinating and could suggest the initial enthusiasm of participating in a dietary supplement trial does increase the probability of a statistically significant short-term placebo effect, which dampens over time. Still, it should be reiterated from evidence-based AUA guidelines that saw palmetto is not recommended for the treatment of LUTS due to BPH.**

The controversy over saw palmetto since the STEP and CAMUS publications has not subsided, but rather continues to be debated and dissected. It appears that the carbon dioxide–extracted saw palmetto product used in STEP[48] and the ethanolic extraction product used in CAMUS[49] as well as rigorous primary and secondary end points, independent funding sources and, again, the general inability to identify the intervention over the placebo were not sufficient to quell some critics. One notable observation that does deserve credibility, regardless of the reason(s), is that the popular standardized n-hexane lipidosterolic extract of saw palmetto, ie Serenoa repens, known as Permixon® (Pierre Fabre Medicament, Castres, France), which is commonly used in Europe, was not included in STEP or CAMUS. Permixon does have consistent positive clinical research data in patients with BPH, even when preliminarily tested against some conventional oral prescription drugs.[51] Could it be that the different extraction or isolation procedures are indeed so critical to eventual efficacy? This is endlessly debatable without a head-to-head comparison trial. Could it be the various reports of a higher total and individual free fatty acid (eg lauric or oleic acid) content with Permixon, or even a potentially higher plant sterol content such as beta-sitosterol? The total free fatty acid content of the saw palmetto product utilized in STEP and CAMUS was arguably similar, but the individual fatty acids were never proven to be identical to Permixon. Perhaps it is the rigorous quality control used with Permixon, since it is essentially manufactured and handled in a similar fashion to a prescription oral intervention. Could it be a less rigorous, or a distinguishable, placebo being used against Permixon in past studies? This is also debatable, but just being compared to a placebo, or a higher quality placebo today, is difficult enough to achieve in some pharmaceutical clinical trials. For example, some more recently approved combination drug therapies were not tested against a placebo for approval.

The future ideal urological integrative clinical trial would be another independent, multicenter trial comparing Permixon, an alpha blocker, a 5alpha-reductase inhibitor and an updated indistinguishable placebo. Another suggestion would be to request the immediate availability of Permixon in other countries, such as the U.S., as an over-the-counter or prescription medication to determine individual efficacy and observational data collection. Additionally, some BPH drugs, at least in lower dosages, could also achieve immediate over-the-counter status, which also improves access and better objective overall assessment of all options.[52] This has been successfully accomplished in countless other specialties, including dermatology, gastroenterology, rheumatology and others.

Finally, the lack of reporting baseline BMI status in both initial publications of STEP and CAMUS should also be of interest, which today would be unusual in general and within urology. What was the average BMI in these trials? Did it, or could it, have had any impact on outcomes? Regardless, since BMI increases over the last 25 years have been dramatic, its reporting could have placed a greater conclusion in proper perspective.

MALE INFERTILITY

Elevated cardiovascular risk factors are associated with unhealthy effects on fertility.[53,54] Obesity negatively impacts semen parameters, and recent observational data of over 76,000 men initially diagnosed with male factor infertility suggest higher subsequent risks of dyslipidemia, hypertension, heart disease and diabetes compared to controls. This association remained regardless of ethnicity/race, education, income and geographic region. Sleep inefficiency and psychological stress also appear to compromise male fertility.[33,53] The impact of tobacco is well recognized, and marijuana is preliminarily associated with increases in the risk of male infertility and testicular cancer.[55,56] Increasing paternal age raises the risk of a variety of heart unhealthy issues and is also independently associated with male infertility.

Past and recent high-profile meta-analyses have suggested, despite low quality evidence, a potential for adequate safety and benefits in a variety of semen characteristics along with improved pregnancy and live birth rates when utilizing a diverse range of individual and combination ingredient supplements.[57] **However, 2 more recently published, higher quality, multicenter, randomized, placebo controlled trials demonstrated disappointing results and some potential preliminary concerns.[58,59] The Folic Acid and Zinc Supplementation Trial (FAZST) used 5 mg/day folic acid and 30 mg/day elemental zinc vs placebo in 2,370 men (couples) undergoing infertility treatment in the U.S., and no significant impacts on semen parameters over 6 months or live birth rates over 9 months were observed.[58] A statistically significant increase in DNA fragmentation was observed with this intervention as well as higher rates of gastrointestinal symptoms and erythema.** Fetal and maternal complications were identical between groups, but a significantly higher risk difference (1.9%) in preterm birth was found in the supplement group, which could have been due

to chance since this study was not powered to effectively evaluate this end point.

The second separate multisite study was the Males, Antioxidants, and Infertility Trial (MOXI), which used a diverse daily combination of antioxidants (500 mg vitamin C, 400 mg vitamin E, 0.20 mg selenium, 1,000 mg L-carnitine, 20 mg zinc, 1 mg folic acid, 10 mg lycopene and 2,000 IU vitamin D) in 174 men with male factor infertility.[59] No difference was found compared to placebo in semen parameters or DNA integrity at 3 months, or pregnancy and live birth rates at 6 months, which was the maximum time participants could use the intervention. If couples could not conceive naturally over the first 3 months, then clomiphene citrate with intrauterine insemination was used in the female partner during months 4 to 6. Overall, no differences in semen characteristics, DNA integrity, pregnancy or live birth rates occurred among the groups. There was a statistically significant difference in sperm concentration (p=0.03), total sperm count (p=0.02) and total motile sperm count (p=0.04) in favor of placebo when analyzed at the 3-month intervention period. There was no difference in overall and serious adverse events between the antioxidant and placebo groups. The only p value that approached significance (p=0.063) for male adverse events was a higher number of reported headaches (17.6% vs 8.1%) in the supplement group.

Perhaps greater awareness of lifestyle changes could be derived from FAZST and MOXI. For example, in the FAZST study, mean male age was 33 years and mean BMI was 30. In MOXI, the mean age was 34 years and mean BMI was approximately 28. **This is of interest because men in both major clinical trials on average were obese or approaching obesity, and were younger adults.** Mean blood pressure was elevated (above 120 mm Hg) in FAZST, and female partner mean BMI was 28–29 vs 24 in MOXI, while mean age was 31 years in both trials. Recent alcohol consumption was documented in approximately 90% of the trial participants in MOXI. The implication is not intended to initially suggest that changes to the baseline metabolic or lifestyle issues definitely would have altered male infertility, but rather there would be minimal harm in the attempt, and the potential for overall health benefits could be substantial in the short and long term for these patients. These trials provide so-called "larger picture" lessons for future patients, including individuals consumed by an extrinsic debatable solution to the issue itself. Interestingly, another recent small rigorous randomized trial demonstrated no significant impact on semen parameters with a lower overall dosage multi-ingredient supplement vs placebo over 6 months in slightly older subfertile men (77 patients, mean age 38 years) with a higher DNA fragmentation index (≥25%) and a normal mean BMI, testosterone and other reproductive hormone levels.[60] In fact, DNA fragmentation index nonsignificantly increased in the antioxidant group, and sperm concentration increased in both groups after 6 months. These recent studies raise greater questions as to the ideal subgroup for future clinical trials utilizing supplements.

Otherwise, the enthusiasm for universal or generalizable specific products throughout medicine, arguably over lifestyle changes, appears fueled by association and not causation or recent diverse results from major randomized trials.[2,61] The recent association of suboptimal vitamin D levels with increased male infertility could be another pertinent example since men with 1 or more heart unhealthy behaviors or parameters, such as obesity, have a higher risk of vitamin D and testosterone insufficiency or deficiency.[62] **The 25-OH vitamin D blood level is a negative acute phase reactant in some patients rather than a reason for supplementation.[2] Obesity (especially), diabetes, dyslipidemia, hypertension, tobacco exposure, stress, depression, low testosterone … the list of heart unhealthy conditions associated with low vitamin D continues to accrue. Another related issue is the lack of validation for what precisely constitutes a "normal" vitamin D blood level.**

Supplementation costs may also be a consequence for many couples, and there is extensive latitude in the combinations of fertility ingredients, dosages and quality control. Some of the individual ingredients used in these commercial products and past studies were used in other notable urological phase 3 cancer prevention trials, such as SELECT, at similar dosages (for example vitamin E) and were found to have the potential for significant harm.[63] Still, it is appropriate to assume younger men or couples share a similar goal with older men or couples, which is receiving up-to-date prostate or other cancer prevention information before choosing a product for a different and unproven clinical situation.

Additionally, provoking word(s) such as "oxidative stress," "free radicals" and "inflammation" conjure thoughts and advertisements of ameliorating these issues with pills, but in specific dosing situations, some of these so-called "antioxidants" act as "pro-oxidants."[64] Unhealthy lifestyle factors should be considered a more definitive source of chronic oxidative stress, free radical damage and inflammation, and lifestyle changes counter these effects. There should also be a candid discussion of parenthood and the importance of being in appropriate overall health not only to raise children, but to be fortunate enough to be present and participate as a grandparent. Improving heart and fertility health simultaneously increases the probability that they will live out a lifespan that allows for such remarkable events.

UROLITHIASIS

Manuscript word quantity limits do not allow for more extensive urological coverage of other IM options or supplements. **However, an updated comprehensive list of supplement categories or ingredients that have potential or documented increased kidney stone risk or recurrence has been absent within the general urological literature. Table 3 contains a summary of the most recent list.[65–74]**

Lifestyle data continue to demonstrate consistent short-term and long-term benefits and should continue to be emphasized. For example, documented heart healthy diets such as Dietary Approaches to Stop Hypertension (DASH), healthy BMI status, increased fluid intake, normal intakes of dietary (not supplemental) calcium and decreased sugar-sweetened beverage intake could synergistically reduce the risk of kidney stones by over 50%.[75] What pill is associated with equivalent data?

CONCLUSION

IM utilization continues to be prevalent throughout medicine and within most urological subgroups. One potential immediate benefit of IM is its inherent primary emphasis on multiple healthy lifestyle changes to potentially improve conventional health outcomes. Yet arguably the more controversial issue for clinicians is in maintaining an appropriate knowledge base or pace for the more extrinsic IM options, for example dietary

supplements. The antiquated concept of numerous IM options being benign and that they probably "can't hurt" should now be dismissed, especially in urology, where serious potential negative impacts have already been demonstrated in past notable clinical trials and continue to be concerning with some noncancerous conditions. However, other extrinsic options continue to accrue preliminary positive evidence that should be a reminder that this broad discipline cannot be generalized and should continue to be primarily judged on condition-specific merits.

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DID YOU KNOW?

- Acupuncture, or a form of acupuncture, should be further evaluated and considered within the multimodal treatment guidelines for the common urological pain syndromes CP/CPPS and IC/BPS, and has a current role in OAB treatment as well as other clinical situations with few definitive and safe treatment options (eg hot flashes and chemotherapy-induced peripheral neuropathy).
- The past and recent common associations between modifiable risk factors for moderate to severe BPH and aggressive prostate cancer should encourage heart healthy lifestyle behaviors to potentially reduce the risk of these and other common urological conditions, which could ultimately result in greater patient compliance toward lifestyle changes and reduce all-cause morbidity and mortality.
- BPH supplements in general harbor some extrinsic and intrinsic controversies associated with their use, which have received minimal to no attention in the urological literature. These interventions have not been subject to large, rigorous, independently funded clinical trials over the last 20–25 years, with the possible exception of saw palmetto (STEP, CAMUS), which in general has an efficacy similar to placebo and thus is not recommended based on AUA guidelines. However, Permixon, the European product with arguably the most consistent safety and efficacy research over this same period, should be tested against a drug and a high-quality placebo option in a phase 3 trial.
- Male infertility supplements have failed to demonstrate benefits in the most recent methodologically rigorous clinical trials (FAZST, MOXI) and have also increased the concern for potential harm as well as the need to further address ever-increasing obesity rates observed from couples in these same clinical studies, or heart unhealthy factors that, if reversed, could potentially improve fertility and reduce all-cause morbidity and mortality.
- The list of ingredients in supplements believed or known to potentially elevate kidney stone risk continues to increase (cranberry, inosine, melamine, vitamin C concentrated products etc), and clinicians and patients need to become more aware of this ever-expanding updated list, which has not been published until now.

Table 1. Potential use of acupuncture within diverse areas of urological care

Acupuncture Potential Benefit for Specific Urological Conditions	Commentary
Androgen deprivation therapy side effects—hot flashes/flushes/ night sweats (vasomotor symptoms)	One of the only interventions where safety concerns are minimal and preliminary overall impact is consistently positive, but more sham acupuncture comparison groups and larger studies are needed
Cancer pain (general) and cancer medication-induced discomfort	Acupuncture and acupressure have preliminary data in this area, including discomfort (arthralgia and myalgia) caused by some medications
Chemotherapy side effects (chemotherapy-induced peripheral neuropathy)	Few safe or even proven effective options exist for chemotherapy-induced peripheral neuropathy, but preliminary data suggest a reduction in neuropathic pain even beyond what is observed with sham acupuncture
CP/CPPS and other potential urological-associated pain syndromes (IC/BPS)	Urological pain syndrome improvements are one of the more promising integrative options in urology
OAB	A form of electro-acupuncture is already a standard of care (PTNS). Other forms of acupuncture also hold promise. Pediatric nocturnal enuresis and OAB also appear to benefit
Miscellaneous	BPH, female sexual dysfunction, erectile dysfunction and premature ejaculation lack reliable consistent data and need more research. Other acute or chronic pain urological clinical situations would be interesting to research, such as specific postoperative or other acute and chronic post-treatment pain outcomes, to reduce the need for and addictive potential of some medications

Urologic oncologic conditions are also provided for more comprehensive educational perspective when consulting with patients.

Table 2. Commonly shared risk factors for prevention of moderate to severe BPH/LUTS/nocturia and aggressive prostate cancer, which could also include other common urological conditions and are potentially modifiable and treatable

Alcohol in excess
Comorbidity score/index (includes number and severity)
Diabetes, prediabetes, insulin resistance
Dietary quality and/or quantity (caloric excess)
Dyslipidemia
Hypertension (increased sympathetic activity)
Inflammation (chronic)
Metabolic syndrome
Obesity
Physical inactivity/poor cardiorespiratory fitness
Resting heart rate and heart rate abnormalities
Sarcopenia (quality, quantity and function of lean muscle)
Sleep inefficiency issues (eg quantity, quality, circadian rhythm issues, obstructive sleep apnea)
Stress, anxiety or depression (chronic)
Supplements in excess (eg DHEA [dehydroepiandrosterone], vitamin E)
Tobacco/smoking

Modifiable and/or treatable risk factors include prostate cancer and other common urological conditions (erectile dysfunction, female sexual dysfunction, infertility, stones, low testosterone etc). Many of the risk factors listed in the table can also reduce conventional treatment efficacy.

Table 3. Current updated list of supplement categories, or ingredients within supplements, that could potentially increase risk of nephrolithiasis

Dietary Supplements with Potential or Proven Increased Risk of Kidney Stones	Commentary
Calcium carbonate	Increased risk of kidney stones from phase 3 trials such as the Women's Health Initiative, especially when combined with vitamin D; increased fortification of calcium in the food supply only further increases the risk from supplementation.
Cranberry	Some products increase oxalate and uric acid and may also contain vitamin C, which further increase the potential risk. Supplements should ideally report the presence (or not) of oxalate, and the average amount if present.
Dietary derived high in oxalate products (miscellaneous)	Potential average oxalate content of different supplements derived from food sources known to harbor higher concentrations of oxalate (eg beetroot powder, tea product supplements) has not been adequately tested in large-scale studies.
Ginger	Potentially high in soluble oxalates, but average concentration in supplements has not been determined.
Inosine	A known precursor to uric acid. It has been preliminarily tested against Parkinson's disease and multiple sclerosis and was found to increase the risk of uric acid kidney stones. This supplement is also utilized in other areas today, such as athletic enhancement.
Melamine	Contamination with this additive/adulterant (a source of nonprotein nitrogen, which falsely increases the claimed protein content amounts) in some diverse supplements and products could increase the risk of stone/kidney disease in children and adults, and testing should be part of quality control standards.
Protein concentrated products (animal-based, eg whey, albumin)	Large intakes of animal protein from dietary sources could increase the risk of hypercalciuria, hyperuricosuria, hypocitraturia, hyperoxaluria and stones, but more concentrated protein dietary supplement sources have not been tested. Individual increases in urinary calcium, sodium and urinary pH reductions could occur in individuals with suggested intakes. Plant protein supplements should also be tested.
Silicon dioxide	Common ingredient in all types of dietary supplements, and the quantity is individualized in each product to avoid clumping of pills or to keep ingredients from sticking together. Higher exposure in vulnerable individuals has been shown to increase the risk of silicate-based calculi.
Turmeric	High in soluble oxalates, and the average amount in supplements or derivatives of this product, such as curcumin, has not been studied.
Vitamin C	Increases oxalate and kidney stone risk in higher dosages.
Vitamin C "superfood" novel products	Plant sources naturally high in vitamin C concentrations are now being sold as powders/other options, for example where just 1 teaspoon utilized in beverages could contain 250–1,000 mg vitamin C. Some examples include Kakadu plum, camu-camu and acerola. Please refer to each individual "nutrition facts" label for evaluation.
Vitamin D	Hypercalcemia and hypercalciuria risk increases, especially based on recent clinical trials, and there is a potential for increased risk of stones not only when added to calcium supplements, but also when individual supplementation is added to the already increasing fortification amounts in the food supply.

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Study Questions Volume 40 Lesson 33

1. The most consistently recognized and utilized IM treatment for patients with medication-refractory OAB is
   a. electro-acupuncture
   b. chiropractic care
   c. herbal supplements
   d. meditation

2. The percentage of IC/BPS patients with flares or increased symptomatic activity after consuming specific trigger foods or ingredients is
   a. <39%
   b. 40%–59%
   c. 60%–79%
   d. 80%–100%

3. Many popular BPH supplements contain a low dose of the cholesterol-lowering approved food ingredient
   a. pumpkin seed oil
   b. beta-sitosterol
   c. pygeum
   d. zinc

4. The BPH herbal supplement product that is a vulnerable species and is on conservation watch lists is
   a. saw palmetto
   b. St. John's wort
   c. beta-sitosterol
   d. *Pygeum africanum*

5. Uric acid kidney stone incidence or recurrence may be increased by supplemental doses of
   a. vitamin B6
   b. vitamin B12
   c. fish oil
   d. inosine