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REVIEW ARTICLE

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Are we justified in suggesting change to caffeine, alcohol, and carbonated drink intake in lower urinary tract disease? Report from the ICI-RS 2015

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AIMS: There is increasing evidence that diet may have a significant role in the development of lower urinary tract symptoms. While fluid intake is known to affect lower urinary tract function the effects of alcohol, caffeine, carbonated drinks, and artificial sweeteners are less well understood and evidence from epidemiological studies is mixed and sometimes contradictory. The aim of this paper is to appraise the available evidence on the effect of caffeine, alcohol, and carbonated drinks on lower urinary tract function and dysfunction in addition to suggesting proposals for further research.

METHODS: Literature review based on a systematic search strategy using the terms "fluid intake," "caffeine," "alcohol," "carbonated" and "urinary incontinence," "detrusor overactivity," "Overactive Bladder," "OAB."

RESULTS: In addition to fluid intake, there is some evidence to support a role of caffeine, alcohol, and carbonated beverages in the pathogenesis of OAB and lower urinary tract dysfunction. Although some findings are contradictory, others clearly show an association between the ingestion of caffeine, carbonated drinks, and alcohol with symptom severity.

CONCLUSIONS: Given the available evidence lifestyle interventions and fluid modification may have an important role in the primary prevention of lower urinary tract symptoms. However, more research is needed to determine the precise role of caffeine, carbonated drinks, and alcohol in the pathogenesis and management of these symptoms. The purpose of this paper is to stimulate that research. *Neurourol. Urodynam. 36:874–879, 2017.* © 2016 Wiley Periodicals, Inc.

1 | INTRODUCTION

Urinary incontinence, defined by the International Continence Society as "the complaint of any involuntary leakage of urine,"[1] is known to have a considerable impact on quality of life.[2] A large epidemiological study of urinary incontinence in 27 936 women from Norway (EPINCONT)[3] has shown that overall 25% of women reported urinary incontinence of which 7% considered it to be significant, and the prevalence of incontinence was found to increase with age. When considering the type of incontinence, 50% of women complained of stress, 11% urge, and 36% mixed incontinence.

The majority of patients who complain of urinary incontinence and an overactive bladder will benefit from lifestyle interventions in the first instance as well as fluid management and bladder retraining. The importance of behavioral intervention is supported by current international guidelines. While there are considerable data supporting the use of behavioral modifications, including weight loss and fluid management, there is an emerging body of evidence investigating the effect of diet on urinary incontinence and the symptoms of an overactive bladder. The aim of this paper is to critically appraise the available evidence and to propose ideas

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for future research allowing a more evidence-based approach to management.

2 | METHODS

At the International Consultation on Incontinence-Research Society (ICI-RS) meeting in 2015, a multidisciplinary group of experts participated in a proposal investigating whether health care professionals are justified in suggesting changes to caffeine, alcohol, and carbonated drink intake in urinary incontinence and overactive bladder. The panel appraised the available evidence using the search strategy detailed below prior to discussing the literature and considering how the evidence corresponded with current international recommendations. Proposals for further research were then generated in order to answer those questions that are still not understood.

The search terms "fluid intake," "alcohol," "caffeine," "carbonated," AND "urinary incontinence (UI)," "detrusor overactivity (DO)," "OAB," or "overactive bladder" were used in combination for a literature search of PubMed, Medline, and Embase which served to set the basis for the discussion. However, the work of the group was not intended to be, nor does it represent, a thorough systematic review of the literature and was used as a basis to stimulate research within the area.

The searches were limited to articles published in English but no time limit was used. The reference lists of included studies were also screened seeking for additional relevant articles.

This review was conducted bearing in mind the P.I.C.O. Model for Clinical Questions (Table 1).

2.1 | Inclusion and exclusion criteria

All original studies (ie, randomized controlled trials, prospective observational studies, retrospective series, case reports, editorials, research letters, review articles, and meeting abstracts were included during the review process.

3 | FLUID INTAKE

Fluid consumption is known to have a significant impact on lower urinary tract symptoms[4] although interestingly evidence from bladder diaries would suggest that overall fluid intake is no different in those patients with OAB when compared to asymptomatic controls.[5] However, a 4 week randomized, prospective observational cross over study demonstrated that decreasing fluid consumption significantly decreased voiding frequency, urgency and incontinence episodes in patients with detrusor overactivity, and/or urodynamic stress incontinence. Interestingly, however, in this study caffeine had no impact on urinary symptoms.[6]

Those findings are also supported by a further prospective cross over trial in which 24 patients were asked to either increase or decrease their fluid intake. Overall there was a significant reduction in frequency, urgency, and nocturia in those who reduced their fluid consumption by 25% whereas increasing fluid input by 25% and 50% resulted in worsening of daytime frequency. Consequently, manipulation of fluid consumption may provide an inexpensive and non-invasive conservative measure in the management of women with OAB.[7]

The effect of fluid modification on symptom control has also been examined when used in conjunction with pharmacotherapy. Women with OAB were randomized to tolterodine alone or tolterodine with behavioral intervention and fluid manipulation. While there was a significant reduction in incontinence and urgency episodes in both groups there were no differences between the groups. However, those women who reduced their fluid intake were found to have a significant reduction in daily voided volumes suggesting that advice regarding fluid management may contribute to an improvement in urinary symptoms.[8] Consequently, the evidence would suggest that fluid manipulation may be important in the management of lower urinary tract symptoms although in those studied the type of fluid consumed was not investigated.

TABLE 1 PICO analysis

Population	Men and women with UI/OAB/DO
Intervention	Caffeine/alcohol/carbonated fluids
Comparison	No caffeine/alcohol/carbonated fluids
Outcome	Change in bladder symptoms

4 | CAFFEINE, URINARY INCONTINENCE, AND OVERACTIVE BLADDER

Caffeine, an alkaloid chemically known as 1,3,7-trimethylxanthine, is among the most commonly consumed stimulants worldwide.[9] It is found not only in coffee but also in tea, green tea, carbonated beverages, soft drinks, chocolate, and a wide variety of medications, including appetite suppressants, diuretics, analgesics, and decongestants. It has a bioavailability of 100%[10] and is excreted in the urine[11] making its impact on bladder physiology highly plausible. Low doses of caffeine have been reported to cause transient contraction of detrusor smooth muscle through an increase of cytosolic calcium[12] which might exacerbate the symptoms of OAB. Caffeine is reported to activate non-selective cation channels in rat primary sensory neurons indicated to be TRPV1.[13] This capsaicin-sensitive ion channel expressed both in the urothelium and by bladder sensory afferents, has been linked with normal bladder function in addition to the generation of urgency sensation.[14] Chlorogenic acid (CGA) is a major polyphenolic component particularly abundant in coffee.[15] It survives roasting to varying levels depending on the roast time and is highest in green beans and light

roasted beans. It has been shown to inhibit acetylcholinesterase and butyrylcholine esterase activities thus slowing acetylcholine and butyrylcholine breakdown.[16] Research into the actions of CGA on bladder tissue and whether it affects bladder compliance leading to problems of bladder storage is warranted.

There have been many reported studies investigating the effect of caffeine on lower urinary tract symptoms although overall, the results are conflicting.

The EPINCONT[17] study demonstrated a positive association between coffee consumption and mixed urinary incontinence, although a negative association with stress urinary incontinence. In addition, the Nurse's Heath Study and Nurse's Health Study II, a prospective cohort of 65 176 has demonstrated a weak dose-dependent positive association between caffeine consumption and urgency incontinence although not for mixed and stress incontinence. The attributable risk of urgency incontinence associated with caffeine was reported as 25%. There was no such effect with de-caffeinated coffee.[18]

This "dose response" effect of caffeine intake has also been demonstrated in two studies. The first was an RCT ($n = 95$) that assessed the effects of continence advice including caffeine reduction education on OAB symptoms versus (vs.) continence advice alone without changing caffeine intake. Women in the intervention group reduced their daily caffeine intake to a mean of 96.5 mg, compared to 238.7 mg in the control group and in doing so reduced the number of urgency episodes (61% vs. 12%), and reduced voids per 24 h (35% vs. 23%).[19] The second study was a large North American cross-sectional study of 4309 women, the NHANES study (National Health and Nutrition Examination Survey).[20] Mean caffeine intake was 126.7 mg/day and, after adjustment for multiple factors, caffeine intake ≥204 mg/day was associated with urinary incontinence although not with moderate to severe incontinence.

While there is some evidence to support a dose effect relationship with caffeine intake and urinary incontinence there is conflicting evidence suggesting that higher caffeine intake is associated with a greater risk of symptom progression. A prospective cohort study of 21 564 women with moderate urinary incontinence has shown that disease progression over 2 years was similar across all categories of baseline caffeine intake.[21] Conversely, in the Boston Area Community Health (BACH) cohort ($n = 4144$), women who increased their coffee intake by at least two servings/day during follow up had 64% higher odds of progression of urgency ($P = 0.003$).[22]

However, the epidemiological evidence is mixed and there are contradictory data to suggest that caffeine intake may even have a protective effect. A population based study, based on the Swedish Twin Register enrolled 42 852 twins born between 1959 and 1985, and has demonstrated that those women with a high coffee intake were at lower risk of incontinence (OR 0.78; 95%CI: 0.64-0.98) whereas high tea consumption was associated with an increased risk for OAB (OR 1.34; 95% CI: 1.07-1.67) and nocturia (OR 1.18; 95%CI: 1.01-1.38).[23]

There has been one double blind, randomized, crossover study to assess the effect of caffeinated versus decaffeinated drinks on OAB. It reported that reducing caffeine intake may alleviate the severity of some symptoms and health related quality of life factors. However, this was a pilot study with only 11 participants completing the study.[24]

Consequently, given the evidence available from the published studies, the effects of caffeine consumption on urinary incontinence and overactive bladder remain unclear. This may be related to the different concentrations of caffeine in different types of teas and coffees, and also because significant caffeine levels are found in colas and chocolate.[25] Despite this lack of evidence and conflicting views many clinical guidelines including the International Consultation on Incontinence, National Institute for Care Excellence (NICE), and European Association of Urology (EAU) still generally recommend caffeine reduction in women with urinary symptoms.[26–28]

5 | ALCOHOL

The effects of alcohol consumption have also been investigated in a number of large epidemiological studies. There was no association found in the EPINCONT[17] study and this is also supported by a large Italian study of 5488 subjects which showed no association with alcohol or caffeine consumption.[29]

Conversely, the Boston Area Community Health Survey of 3201 women[30] suggested there may be a link between urinary incontinence and alcohol consumption (OR 3.51; 95%CI: 1.11-11.1). In addition, a smaller study of 298 Japanese women demonstrated a weak association with alcohol intake (OR 1.31; 95%CI: 0.74-2.33) although this was not statistically significant.[31]

Overall the data supporting the association of alcohol and urinary incontinence are weak although there is some more anecdotal evidence suggesting that the type of alcohol consumed may also be relevant. It has been suggested that wines with lower alcohol content and higher sugar content such as a Muscat or late harvest Riesling may cause less discomfort in patients with overactive bladder symptoms and bladder pain syndrome.[32] To date there is little evidence to support this observation and there have not been any reported interventional studies to assess alcohol withdrawal or reduction on LUTS.

While numerous studies report that regular low-to-moderate alcohol (ethanol; EtOH) consumption has significant beneficial effects, particularly on the cardiovascular system,[33] what constitutes "moderate" depends on age, sex, genetic characteristics, co-existing illnesses, and other factors.[34] Moderate alcohol consumption is up to one drink/day for women and two drinks/day for men.[35] A standard drink is approximately 12-14 g of ethanol, which corresponds to 355 mL (12 oz.) of beer, 148 mL (5 oz.) of wine, or 44 mL (1.5 oz.) of 80-proof liquor.[34] Beneficial EtOH effects at low-to-moderate doses are eliminated at only slightly higher intakes (>2-3 standard drinks a day).[35] In humans,

alcohol is converted to acetaldehyde primarily by alcohol dehydrogenase (ADH) and further to acetate by acetaldehyde dehydrogenase (ALDH) and xanthine oxidoreductase[36]; most tissues are capable of alcohol metabolism.[35] Acetaldehyde plays a major causative role in short- and long-term toxicity associated with chronic alcohol use.[33] Pathophysiological mechanisms identified in alcohol-associated tissue and organ injury include oxidative stress, inflammation, and DNA-adduct formation.[35]

Alcohol consumption has been shown in many studies to be associated with LUTS[37]; however, it is not well known how alcohol affects the bladder tissue per se. The epithelial lining of the urinary bladder (urothelium) is especially vulnerable as it is exposed to alcohol and its metabolites on both the serosal (interface with blood) and apical (interface with urine) aspect; in the latter case for long periods of time due to urine storage. Alcohol and its metabolites increase intestinal epithelial permeability[38]; similar impacts on the important urothelial barrier could contribute to LUTS such as OAB. Patients with unhealthy alcohol use often present either asymptomatically, with early stage problems, or with problems that are not recognized as being alcohol-related.[34] Could this also apply to patients presenting with LUTS? Analyses of health risks and benefits of alcohol consumption need improvement to avoid giving patients oversimplified advice about drinking,[39] as the patient may not even think they are over consuming. Thus more research is needed on the direct impact of alcohol on bladder tissue. As alcohol consumption is an integral component of social life in many countries and cultures a good starting point would be to introduce education of its physiological impact into the school curriculum.

6 | CARBONATED DRINKS

In addition to tea, coffee, and alcohol there is increasing evidence to support the effect of carbonated drinks in the development of lower urinary tract symptoms. This may be due to the caffeine content in many soft drinks although it may also be associated with the carbonation process and artificial sweeteners.

Evidence from the Leicester MRC study has demonstrated that the consumption of carbonated soft drinks has been shown to be associated with OAB symptoms (OR 1.62; 95%CI: 1.18-2.22).[10] This is supported by in vitro work demonstrating that low concentrations of artificial sweeteners (acesulfame K, aspartame, sodium saccharin) enhance detrusor muscle contraction by modulation of L-type Ca^{2+} channels.[40]

The BACH study also found that women with recently increased soda intake, particularly caffeinated diet soda, had higher symptoms scores, urgency, and LUTS progression.[15]

Carbonated drinks also contain preservatives and anti-oxidants including ascorbic acid and citric acid, and these have been shown to augment bladder muscle contraction by enhancing Ca^{2+} influx. In addition, ascorbic acid has been shown to increase presynaptic neurotransmitter release.[41] Consequently, the consumption of carbonated drinks may be associated with the development, or aggravation, of OAB symptoms.

This hypothesis has been investigated in 20 asymptomatic volunteers in a four way cross over study comparing carbonated water, Diet Coke, caffeine free Coke, and Classic Coke. There was a significant increase in frequency with Diet Coke and caffeine free Diet Coke compared with carbonated water and Classic Coke. Urinary urgency was also significantly increased with Diet and caffeine free Diet Coke compared to carbonated water and there was a smaller increase with Classic Coke. Overall, those drinks containing artificial sweeteners were associated with an increase in frequency, urgency severity, and urgency episodes.[42] These clinical findings would certainly support the in vitro work performed in the rat model although this was only a small proof of concept study.

Consumption of carbonated soft drinks has been independently associated with the development of overactive bladder.[43] The majority of soft drinks contain artificial sweeteners such as acesulfame potassium, aspartame, and sodium saccharin. Sweet taste receptor T1R2/T1R3 is expressed throughout the bladder urothelium (evidence in human and rat) and may explain how artificial sweeteners augment bladder contraction.[44] It is of interest to consider that detrusor overactivity due to the presence of these sweeteners may be a healthy response of the bladder in order to bring about expulsion of what is sensed as potentially hazardous content. Chemosensory G-protein-coupled receptors (GPCRs) that were originally identified as "taste" receptors have now been found in many tissues outside the tongue, and bitter and sweet taste GPCRs have recently been found to be sentinels of defense against infection in the airway, where they function as a novel arm of innate immunity.[45]

7 | HOW SHOULD WE COUNSEL PATIENTS?

Most National and International clinical guidelines recommend caffeine reduction and dietary changes as the first line management for all patients with LUTS. However, given the lack of evidence for some of these recommendations it raises the question as to how we should best counsel patients about this. Often, patient's reluctance to change long-term habits and belief that it may not make a difference to their symptoms is a major issue for compliance with conservative therapies and it is also important to individualise care as all patients respond differently. Until there is a body of good quality evidence to confirm these recommendations how should we educate the patient to make informed decision about their care? Until this time, it may be necessary to use non-committal phrasing such as "caffeine reduction may improve LUTS."

8 | CONCLUSIONS

Currently, there is some evidence within the literature to support a role of dietary factors in the pathogenesis of OAB and urinary incontinence. While some of the findings tend to be contradictory, others clearly show an association between the ingestion of caffeine, carbonated drinks, and alcohol with symptom severity. Lifestyle interventions and fluid modification may have an important, and cost effective, role in the primary prevention of lower urinary tract symptoms although more research is needed to determine the precise role of caffeine, carbonated drinks, and alcohol in the pathogenesis and management of these symptoms. The purpose of this paper is to stimulate that research.

9 | RESEARCH PRIORITIES

9.1 | Epidemiology

- An appropriately powered randomized prospective study investigating the effect of carbonated drinks on OAB symptoms comparing diet with non diet and caffeinated with non-caffeinated.
- An appropriately powered randomized prospective study comparing caffeinated with decaffeinated coffee/tea.
- Is the type of coffee important? Is an espresso worse than a cappuccino? What is the relationship between caffeine concentration and volume?
- Do some types of alcohol worsen urinary symptoms? How does beer compare with wine and spirits? Is the strength of the alcoholic beverage important?

9.2 | Conservative therapy

- Patient satisfaction with caffeine reduction education for LUTS.
- Compliance in the real world with caffeine reduction, fluid intake management, and bladder drills.
- Qualitative studies on perception of caffeine reduction/ withdrawal programs, motivation, and likelihood of success.

9.3 | Basic science

- Given that caffeine causes the mobilization of calcium ions and muscle contraction; what is the role in OAB?
- Caffeine is also known to be an adenosine agonist; how does this mechanism affect OAB?
- Do carbonated drinks affect urinary pH? Does this have an impact on urinary symptoms?

POTENTIAL CONFLICTS OF INTEREST

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