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Beneficial effect of sugar-sweetened beverages on the risk of urinary tract infections

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ABSTRACT

Urinary tract infections (UTI) are among the most common bacterial infections. Drinking more liquids increases the frequency of urination and it is recommended as part of the prevention and/or management of UTI. The intake of sugar-sweetened beverages (SSB) is associated with obesity, diabetes and metabolic syndrome. However, cola and other SSB increase liquid intake and diuresis and could, thus, affect the risk of UTI and its complications. We hypothesize that intake of cola has a protective effect on UTI and pyelonephritis. Using an animal model of UTI, we have confirmed that dehydration with minimal urine output leads to higher bacterial counts in the kidneys in comparison to control mice ($p = 0.01$). The intake of SSB increased liquid intake and thus also diuresis and decreased renal bacterial counts as a marker of induced pyelonephritis ($p = 0.036$). The preliminary results show that dehydration is a risk factor for UTI and that higher diuresis induced by drinking SSB might be protective against pyelonephritis. The underlying mechanisms could include increased voiding frequency but potentially also active compounds in cola such as caffeine. These findings might have implications for the management of individuals at high risk of UTI. Further studies should verify the hypothesis and evaluate the practical relevance of this concept.

Background

Urinary tract infections (UTI) are among the most common bacterial infections that represent a public health problem associated with high morbidity and high health care costs. UTI are one of the most common reasons for antibiotic use. Thus, the need for non-antibiotic alternative for management of UTI is of critical importance [1].

One of the main clinical risk factors for UTI beyond female gender is poor fluid intake associated with low voiding frequency [2]. A recent *in vitro* study proved that the urodynamic effects and the concentration of bacteria due to lower urine production are the mechanisms underlying the association between low water intake and the risk for UTI [3]. Interestingly, the presumption that higher fluid intake decreases the risk for UTI is supported only by very weak evidence from observational studies and interventional trials [4,5]. A study of 366 women showed a significant reduction in the rate of UTI following significant increases in water intake and urine voiding. This suggests that hydration and subsequent voiding might be beneficial in reducing UTI recurrence [6]. Majority of studies in this area are characterized by substantial limitations (such as lack of urinary osmolality), so it is impossible to draw a relevant conclusion. However, a randomized, open-label, controlled, 12-month trial was recently performed in healthy women with recurrent cystitis. Participants were randomly assigned to drink, in addition to their usual fluid intake, 1.5 L of water daily or no additional fluids for 12 months. Increased water intake was an effective strategy to prevent recurrent cystitis in premenopausal women at high risk for recurrence [7]. Considering these results, the hydration strategy seems to be effective in reducing the rate of UTI in high risk individuals.

Sugar-sweetened beverages (SSB) such as cola have been associated with numerous negative health outcomes, including metabolic syndrome [8]. However, most of the associations have not been supported by direct experimental evidence. Some of the few experiments brought surprising results including improved insulin sensitivity and lower body weight caused by long-term cola intake in rats [9,10]. Although the diuretic effect of SSB has been known before, the effect of cola beverages on UTI has not been described yet.

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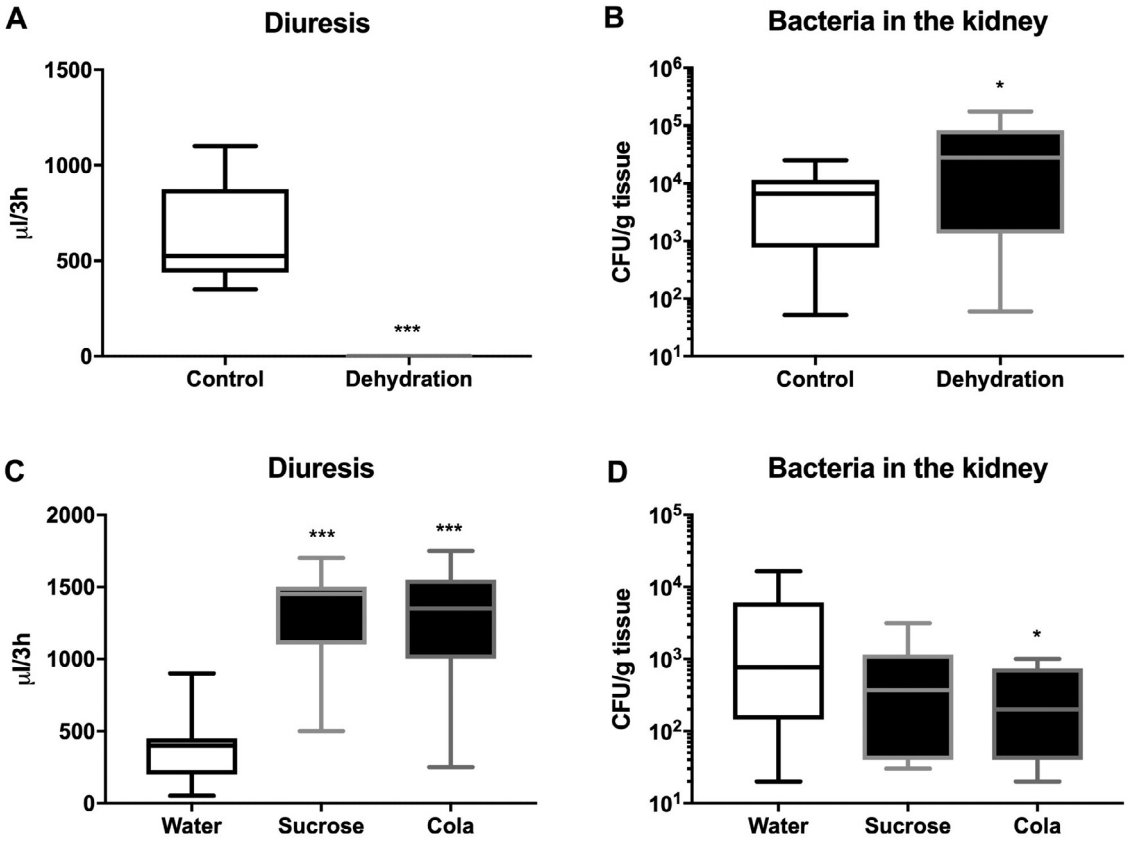

Fig. 1. Diuresis and bacterial count in the Dehydration experiment (A, B) and in the Cola experiment (C, D). Water deprivation leads to minimal urinary output and increased bacterial count in the kidney. Intake of sugar-sweetened beverages increases diuresis and reduces bacterial count in the kidney. * – $p < 0.05$, *** – $p < 0.001$ vs Control or Water, CFU – colony forming units.

The hypothesis

The harmful effects of SSB on numerous health conditions are well known and generally accepted, although experimental evidence is missing. The benefit of cola intake has already been proposed and proved by several research groups. However, none of the studies focused on the effect of cola on the pathogenesis or severity of UTI. We hypothesize that increased intake of SSB might have beneficial effects on urinary tract infections.

The hypothesis is based on the diuretic effect of SSB, which leads to frequent voiding and removal of pathogenic bacteria from the urinary tract. Apparently, increased urination does not necessarily have to be induced by SSB. However, since these beverages are so common and popular worldwide, it justifies our will to investigate the association between their intake and the risk of UTI. We assume that drinking higher volumes of SSB is easier to manage when compared with drinking higher volumes of water. Since the experimental studies describing the mechanisms of the possible negative effects of cola and other SSB on health outcomes are missing, it is legitimate to explore the supposedly unlikely positive effects of SSB on certain conditions.

Evaluation of the hypothesis/idea

Available data on the effectiveness of hydration strategy is all based on studying higher intake of drinking water. The effect of SSB has not been investigated. In addition to increased voiding frequency, SSB could possibly provide another health benefit, such as improved insulin sensitivity or reduced body weight [9,10]. This is especially interesting in specific populations such as obese patients.

The assumed positive effect of SSB on glucose metabolism and weight is unclear, but some data indicate that caffeine might be one of the compounds behind that. There are no direct results from human studies investigating the effect of higher intake of cola on metabolic outcomes. On the other hand, two-weeks of caffeine-free cola consumption led to a higher daylong glycemia and lower insulin secretion in healthy people. However, this study only included caffeine-free cola and thus it is not possible to conclude any effects of regular (caffeine containing) cola beverages [11].

Empirical data

In the first “Dehydration” experiment, adult female CD1 mice (n = 24, Velaz, Praha, Czech Republic) were randomized into two groups. Mice were deprived of drinking water (Dehydration group) or not (Control group). In Dehydration group, water was removed three hours prior to UTI induction and mice were left without water an additional three hours after UTI induction. Subsequently, the mice were put into metabolic cages for three consecutive hours for urine collection. The control group underwent the same procedure; however, water was available all the time. UTI was induced by uropathogenic E. coli (UPEC) strain 536 via transurethral administration under general isoflurane anesthesia. Twenty-four hours after the UTI induction, the mice were sacrificed, and kidneys aseptically removed. Homogenates were prepared using phosphate buffered saline with sterile beads and were used for cultivation and quantification of bacterial counts on agar plates. Experiments were performed in full compliance with the EU Guidelines for Scientific Experimentation on Animals and were approved by the Ethics committee of the Institute of Pathophysiology, Comenius University, Bratislava, Slovakia.

In the second “Cola” experiment with a similar design, adult female CD1 mice (n = 45) had *ad libitum* access to water (Water group), sucrose solution (Sucrose group) or Coca-Cola (Cola group) for 24 h

before and 24 h after the UTI induction. The concentration of sucrose was adjusted to the sugar content of commercially available Coca-Cola (11.2%). Urinary tract infections were induced with the same protocol as in the first experiment. Mice were sacrificed 24 h after UTI induction, however, 3 h prior to sacrifice, mice were placed into metabolic cages for urine collection. Kidneys were processed by the same protocol as in the first experiment. Differences between the groups were evaluated using an unpaired *t*-test or ANOVA with Bonferroni-modified post-hoc *t*-test where appropriate.

In the first experiment, diuresis of control mice in metabolic cages was between 350 and 1100 µl in 3 h. The urine output of mice deprived of water for 6 h was not measurable – a highly significant difference between the groups ($t = 8.2$, $p < 0.001$, Fig. 1A). The average bacterial count was more than 7-times higher in the kidney homogenates from tissues collected 24 h after bladder inoculation of dehydrated mice when compared to controls ($t = 2.8$, $p = 0.01$, Fig. 1B).

In the second experiment, the groups differed in the diuresis ($F = 31.8$, $p < 0.001$, Fig. 1C). In comparison to Water group, the urine output was higher in mice drinking sucrose solution (Sucrose group) or cola (Cola group) (370 vs 1270 vs 1247 µl/3 h, respectively). The intake of sucrose and Cola was significantly higher than the intake of water (0.45 ± 0.24 ml/3 hrs in Water group vs. 2.58 ± 1.40 ml/3 hrs in Sucrose group and 3.57 ± 0.90 ml/3 hrs in Cola group). The number of cultivated bacteria in kidney homogenates tended to be lower (by 81% on average) in the Sucrose group ($t = 2.3$, $p = 0.055$). The cola group mice had significantly lower bacterial counts (more than 10-times) in the kidney when compared to the Water group ($t = 2.5$, $p = 0.036$, Fig. 1D). Based on our results, it can be suggested that drinking sugar-sweetened beverages (at least *ad libitum*) increases diuresis through the higher liquid intake and this might prevent kidney infection in a model of UTI. Moreover, it seems that drinking cola can provide some additional benefit compared to sweetened water. However, the underlying mechanisms and the possible role of caffeine need to be elucidated.

Consequences of the hypothesis and discussion

The experiment was only focused on female mice. Although it is possible to induce the UTI model in male experimental animals, most of the published studies are conducted in females, because of the simplicity of the administration of bacteria via female urethra [12]. Nevertheless, it is likely that the conclusions from our experiment are valid for male mice as well. The effect of increased diuresis on bacteria might be sex-independent. However, sex and strain differences in the diuresis assessed in metabolic cages have been previously described [13]. Thus, our assumption of sex equality in this aspect should be tested in experiments.

The main application of our results is in animal modeling of UTI. Urine production should be carefully monitored in the experiments, because it seems to affect the main outcome parameter – renal bacterial count. Urine production might be affected by the tested treatment, but also by the genetic background of mice that are used – including knockout mice [14]. Drinking sucrose solution or SSB might be potentially useful for tittering the renal infection. The UTI model is known for its high biological and technical variability [15]. Considering our results, monitoring oral rehydration and diuresis in animal models of UTI might help to reduce bias or noise in the experimental data.

It is difficult to claim any direct clinical relevance for the results of our experiments. Especially when a recent interventional study in human volunteers revealed that the diuretic effect of cola and other similar beverages was not different from the diuretic effect of the same volume of water [16].

Additionally, a group from Argentina has shown experimental data supporting the theory of the harmful effects of cola on metabolic status in rats [17]. In their study, 6 months of cola consumption induced hyperglycemia, hypertriglyceridemia, increased body weight and caused negative changes in pancreas morphology. Contrary to these results in our previous experiment, the rats consuming decarbonated cola for three months showed lower blood glucose levels during oral glucose tolerance test, suggesting improved insulin sensitivity [10]. Indeed, several published studies have shown that obesity/metabolic syndrome might increase the risk of urinary tract infections. High BMI was found to be a risk factor for UTI, especially in men, potentially due to low vitamin D [18]. Obese women are at a higher risk for recurrent urinary tract infections, although the mechanism has not been elucidated [19]. In both genders, obesity was found to increase the risk of complications such as pyelonephritis [20]. So, although interventional studies and experiments are needed to prove the causality, it is likely that the metabolic status affects the risk for urinary tract infections and their complications. Several guidelines recommend to treat metabolic syndrome and/or obesity as soon as possible to improve also the UTI outcome. In light of the aforementioned studies, cola or other SSB might possess a hidden metabolic benefit, such as improved insulin sensitivity or reduced weight [9,10]. This effect is unlikely to be observed with water.

Whether drinking SSB could have any protective or therapeutic effect in uncomplicated UTI should be further evaluated before any recommendation for patients is given. The controversy of the metabolic effects of cola beverages needs to be explained by more experimental studies focused on the mechanisms of action. It is likely that the extra energy found in SSB will not itself be beneficial for UTI, especially in diabetic patients. On the other hand, a more rigorous approach including experimental data is required to uncover the real causative relationships between the phenomena such as cola consumption and UTI treatment.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.mehy.2019.04.002.

References

[1] Sihra N, Goodman A, Zakri R, Sahai A, Malde S. Nonantibiotic prevention and management of recurrent urinary tract infection. Nat Rev Urol 2018;15:750–76.
[2] Rudaitis S, Pundziene B, Jievaltas M, Uktveris R, Kevelaitis E. Recurrent urinary tract infection in girls: do urodynamic, behavioral and functional abnormalities play a role? J Nephrol 2009;22:766–73.
[3] Tian Y, Cai X, Wazir R, Wang K, Li H. Water consumption and urinary tract infections: an in vitro study. Int Urol Nephrol 2016;48:949–54.
[4] Lotan Y, Daudon M, Bruyere F, et al. Impact of fluid intake in the prevention of urinary system diseases: a brief review. Curr Opin Nephrol Hypertens 2013;22(Suppl 1):S1–10.
[5] Armstrong LE. Challenges of linking chronic dehydration and fluid consumption to health outcomes. Nutr Rev 2012;70:S121–7.
[6] Su SB, Wang JN, Lu CW, Guo HR. Reducing urinary tract infections among female clean room workers. J Womens Health (Larchmt) 2006;15:870–6.
[7] Hooton TM, Vecchio M, Iroz A, et al. Effect of increased daily water intake in premenopausal women with recurrent urinary tract infections: a randomized clinical trial. JAMA Intern Med 2018;178:1509–15.
[8] Appelhans BM, Baylin A, Huang MH, et al. Beverage intake and metabolic syndrome risk over 14 years: the study of women's health across the nation. J Acad Nutr Diet 2017;117:554–62.
[9] Choi SB, Park CH, Park S. Effect of cola intake on insulin resistance in moderate fat-fed weaning male rats. J Nutr Biochem 2002;13:727–33.
[10] Celec P, Palffy R, Gardlik R, et al. Renal and metabolic effects of three months of

decarbonated cola beverages in rats. Exp Biol Med (Maywood) 2010;235:1321–7.
[11] Busing F, Hagele FA, Nas A, et al. High intake of orange juice and cola differently affects metabolic risk in healthy subjects. Clin Nutr 2018.
[12] Olson PD, Hruska KA, Hunstad DA. Androgens enhance male urinary tract infection severity in a new model. J Am Soc Nephrol 2016;27:1625–34.
[13] Stechman MJ, Ahmad BN, Loh NY, et al. Establishing normal plasma and 24-hour urinary biochemistry ranges in C3H, BALB/c and C57BL/6J mice following acclimatization in metabolic cages. Lab Anim 2010;44:218–25.
[14] Fenton RA, Knepper MA. Mouse models and the urinary concentrating mechanism in the new millennium. Physiol Rev 2007;87:1083–112.
[15] Hung CS, Dodson KW, Hultgren SJ. A murine model of urinary tract infection. Nat Protoc 2009;4:1230–43.
[16] Maughan RJ, Watson P, Cordery PA, et al. A randomized trial to assess the potential of different beverages to affect hydration status: development of a beverage hydration index. Am J Clin Nutr 2016;103:717–23.
[17] Otero-Losada M, Gonzalez J, Muller A, et al. Exercise ameliorates endocrine pancreas damage induced by chronic cola drinking in rats. PLoS ONE 2016;11..
[18] Saliba W, Barnett-Griness O, Rennert G. The association between obesity and urinary tract infection. Eur J Intern Med 2013;24:127–31.
[19] Nseir W, Farah R, Mahamid M, et al. Obesity and recurrent urinary tract infections in premenopausal women: a retrospective study. Int J Infect Dis 2015;41:32–5.
[20] Semins MJ, Shore AD, Makary MA, Weiner J, Matlaga BR. The impact of obesity on urinary tract infection risk. Urology 2012;79:266–9.