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ORIGINAL PAPER

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Citric acid or citrates in urine: which should we focus on in the prevention of calcium oxalate crystals and stones?

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Abstract In order to distinguish between normocitraturia and hypocitraturia, the 24 h urine excretion value of citric acid is evaluated in relation to the established limit value of 2.5 mmol/day. We propose changing this widely-used excretion value to a "minimum contribution" of citric acid to the total urine's ionic strength, since the inhibitory effect of citric acid on crystallization depends on citrate anions being available to complex calcium ions or to associate with the crystal surface. A total of 714 24 h-urine samples, taken from 74 healthy persons and 58 calcium stone formers, were investigated for pH, citric acid concentration ([CA]), and related relative calcium oxalate supersaturation (RS). Based on the Henderson-Hasselbalch-equation, the individual concentrations of the differently charged citrate anion species in each of the urines were calculated from the urinary pH and [CA]. From the anion concentrations determined, the contribution of the urine's citric acid to the total urine's ionic strength, ISCA, was calculated. Referring to the limit value of 2.5 mmol/day and assuming an average urine volume of 1.5 l/day, a hypothetical concentration limit of 1.67 mmol/l can be obtained. Grouping the samples into "stone-formers" and "non-stone-formers" as well as into three different ranges of RS revealed: (1) that the groups' median [CA]-values were below 1.67 mmol/l, and (2) that [CA] was not inversely associated with the risk of stone formation. Within the pH-range of 5 and 7, the ISCA-values which are related to, for example, [CA] = 1.67 mmol/l, vary considerably by a factor of nearly three between 2.48 mmol/l and 6.64 mmol/l. The use of a fixed citric acid excretion level for the distinction of normocitraturia from hypocitraturia does not take into account the different citrate species which actually modify the urine's crystallization behaviour. The proposed ISCA approach takes this fact into consideration. From this parameter, a desirable "minimum impact of citric acid" can be derived. In a first approach, a potential ISCA-limit value, which currently distinguishes between urines indicated by a "normo-protective" impact and those indicated by a "hypo-protective" impact with respect to calcium oxalate precipitation, may be set at 2.48 mmol/l.

Keywords Urolithiasis · Prophylaxis · Citrate therapy · Limit value

Introduction

Citric acid (CA), is undoubtedly one of the most prominent physiological modifiers protecting urine from (1) precipitation of calcium salts, and (2) the formation of pathologically large crystals or aggregates. A number of studies have demonstrated that citric acid modifies the calcium oxalate stone formation processes by, for example, affecting crystal nucleation, crystal growth and crystal aggregation in aqueous solutions and urines [4, 9, 15, 23, 27, 33, 34]. The divalent citrate anion acts not only as a "true" chelator of calcium ions by forming a calcium-citrate-complex, but also as a so-called "crystal poison" since it may bind on crystal surfaces ("true inhibition" [20, 36]). In particular, the citrate^{3-} ion binds tightly to the surface of calcium oxalate crystals (CaOx) by the formation of a $(CaOxcit)^{3-}$ complex. In doing so, crystal growth and aggregation are effectively reduced [1] and crystaluria remains without consequences as particles can pass through the urinary tract.

CA also interacts synergistically with Tamm-Horsfall-protein (THP) [10, 13, 17], the most common macromolecular constituent of human urine. THP and citric acid concentration, [CA], are linearly related to calcium oxalate monohydrate agglomeration inhibition [10]. It is assumed that citric acid reduces the self-aggregation tendency of THP which is favoured at low pH, high ionic strength, and at high concentrations of calcium and THP [36].

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The role of a continuous hypocitraturia, i.e. a CA-excretion below 2.5 mmol/day [7], in urolithiasis, however, has been discussed controversially as the observed incidences of this phenomenon in CaOx stone-formers vary considerably between 15% [22] and 50% [25].

Even terms with quite different meanings, such as "citric acid" and "citrate", are often used interchangeably. This may be due to the fact that, under physiological urinary pH-conditions, most of the urinary CA is dissociated, i.e. the sum of the three citrate species concentrations nearly equals [CA]. However, the concentration ratios between these citrate species depend on the solution's pH-value. This enables CA to act with a differently weighted effect on citrate complex formation in urine either as a more Ca^{2+}-chelating agent by forming a Ca-citrate complex, thus lowering the urinary $[Ca^{2+}]$, or by forming a $(CaOxcit)^{3-}$-complex which results in the enhanced inhibition of aggregation of already formed CaOx-crystals.

The ionic strength (IS) is a measure of ion concentrations in electrolyte solutions which takes into account all ionic species in a solution with regard to their individual charge. The IS of a solution strongly influences the ion activities, the sizes of the ion's hydration shells, and the zeta potential (electrokinetic potential) of any suspended particle in the solution. The ion activities generally decrease as IS increases (Debye-Hückel-equation); the decrease in the activity coefficient that occurs with an increase in IS is more pronounced the higher the charge number of the ion. Thus, activity coefficients are generally much lower for tri- and divalent than for monovalent ions. However, for most biological fluids (e.g. urine), it is difficult to calculate the ion activities accurately because of the high uncertainty of the contribution of protein ions to IS.

The effect of citric acid on the risk of CaOx-formation cannot be determined by its total urinary concentration or daily urinary excretion. Rather, it must be determined, for example, from its contribution to the overall urinary ionic strength. This fraction is dependent on the individual concentrations of the three citrate anions. In the following, the fraction of the total ionic strength which is exclusively induced by CA is termed ISCA.

As small changes of the $citrate^{3-}$ concentration are related to a considerable change in the ISCA value (eqn. 3), the urinary $citrate^{3-}$ concentration may play a significant role in the prevention or modification of precipitation processes within the urinary tract. The potential importance of the $citrate^{3-}$-anion was already described by Ashby et al. and Györy et al. [2, 3, 14] who introduced a novel urinary risk index. This index is calculated, with the assumption that urine is a saturated solution, from the sum of moles per litre of calcium solids (CaOx + brushite) divided by the activity of the $citrate^{3-}$-anion.

Assuming IS to be a real measure of the impact of a substance on the processes of salt precipitation, it would be important to investigate the consequences for urolithiasis treatment and its prevention. In most persons, a rise in urinary pH as well as CA-excretion (and [CA]) can be induced by the oral intake of alkali-citrate preparations [16, 35] (Na-K-citrate [12], K-Mg-citrate [30], Na-citrate [32], K-citrate [5, 21, 24, 28, 29, 31]. Only in a few cases has no correlation between citric acid excretion (concentration) and urinary pH been observed. This may be due to a genetic defect [26].

The "ionic strength model" supports the assumption of Ashby et al. and Györy et al. [2, 3, 14] who emphasize the role of the $citrate^{3-}$ in stone prevention. It may explain why a low urinary citric acid concentration alone is not a sufficient risk factor for stone formation.

Materials and methods

In urolithiasis research, excretion values instead of concentration values are used as limit values to distinguish between a normal metabolic situation and disturbed situations. However, the parameter "excretion" is less suitable for the evaluation of a person's crystallization risk. Unfortunately, no limit values in terms of concentrations are given.

In order to distinguish between of normocitraturia and hypocitraturia the excretion limit value of 2.5 mmol/day has been established [7]. We assume a reasonable (pre-treatment) average urine volume of 1,500 ml/day in order to transfer the excretion value to the hypothetical concentration limit of 1.67 mmol/l. This concentration may be interpreted as a desirable minimum urinary citric acid concentration.

Data sets

In this study, analyses of 714 24 h-urine samples taken from 94 healthy persons (54 men, 40 women) and 86 calcium stone formers (58 men, 28 women) were investigated with respect to pH, [CA], ISCA, and relative CaOx-supersaturation (RS) [11, 37]. The data set was compiled from different studies; all analyses were performed in our laboratory under the same analytical conditions.

Due to the metabolic coupling of urinary pH and CA excretion, a person's [CA] vs ISCA course will follow lines with a positive gradient. In order to obtain an estimate of such a course during alkali-citrate medication, we compared the results of two studies which investigated the effect of the two potassium-sodium-citrate preparations Lithurex (PHÖNIX-Laboratorium, Bondorf, Germany) and Oxalyt-C (Madaus, Köln, Germany) on urinary composition. Both studies were carried out in our department under the same standardized dietary conditions. The Oxalyt-C-study was performed with 24 healthy men (mean age 29.2 years) [19, unpublished data]; the Lithurex-study investigated 23 recurrent stone-formers (10 men, 13 women, mean age 43.2 years) [18, unpublished data]. The alkali-citrate dosages in both studies amounted to 5.1 g/day. After 3 days without treatment ("run-in"), the test persons took the alkali-citrate preparations for 2 days ("loading days"). After the fifth day, a 24 h urine was collected and analyzed.

Calculations

Based on the Henderson-Hasselbalch-equation:

$$pH = pK + \log\frac{[A^-]}{[HA]} \tag{1}$$

the concentration of the i-th charged citrate anion species in the solution can be computed according to:

$$[A^i] = \frac{[A^{(i-1)}] \times 10^{(pH-pK_i)}}{1 + 10^{(pH-pK_i)}} \tag{2}$$

with pH as the solution's pH-value and pK_i as the dissociation constant of the i-th dissociation step. $[A^i]$ and $[A^{(i-1)}]$ indicate the i-th charged anion-concentration and the concentration of the corresponding acid (i.e. the anion concentration of the preceding dissociation step), respectively. The pK-values of citric acid are: $pK_1 = 3.13$, $pK_2 = 4.77$, and $pK_3 = 6.40$ [6].

The ionic strength induced by citric acid, ISCA, can be obtained by calculating:

$$ISCA = 0.5 \times \sum_{i-1}^{3} \left([A^i] \times i^2\right), \qquad (3)$$

whereby the sum of all species A^i (i = 0, 1, 2, 3) equals [CA], which is measured by routine analysis.

In the appendix, a calculation scheme is given for illustration.

Results

The computed mean urinary pH-value amounts to 6.33 ± 0.37, the normalised mean concentration ratios $[CA^{i-}]/[CA]$ are 0.10:1.17:1, for i = 1, 2, 3, respectively. These ratios can differ considerably for a particular urine sample. No relevant linear correlation between urinary [CA] and pH exists (r = 0.19).

Figure 1 indicates the expected range of ISCA-values depending on [CA], calculated for pH-values between 5 and 7 (i.e. the physiological range). Assuming ISCA to be a parameter for the determination of the modifying impact of CA on CaOx stone formation, all urines whose combinations of urinary pH and [CA] result in the same value of ISCA are indicated by the same protective effect of citric acid. Consequently, the [CA]-limit value of 1.67 mmol/l can be lowered to 0.63 mmol/l by taking into account the urinary pH, which has to be increased from 5 to 7. Both combinations of [CA] and pH show the same ISCA of 2.48 mmol/l (Fig. 1).

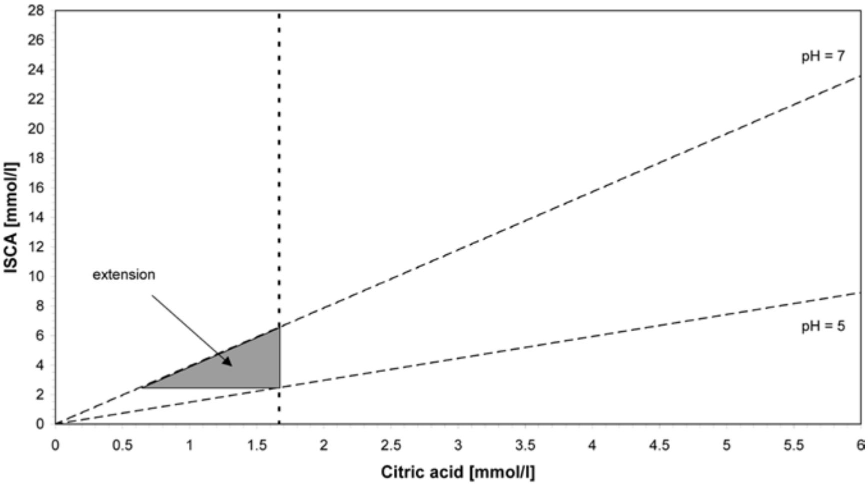

Fig. 1. The pH-dependence of ISCA at a given citric acid concentration is shown for the pH range between 5 and 7. Based on the established excretion limit of 2.5 mmol/day [7], which discriminates normocitraturic from hypocitraturic urine, and an assumed urine volume of 1,500 ml/day, a "limit concentration" of 1.67 mmol/l was calculated. Assuming the ISCA-parameter to be a measure for the effect of citric acid on native urine, an area can be drawn in which the citric acid concentration is below the limit concentration, while its ISCA-value is equal to or higher than the ISCA-value derived from the limit concentration at pH 5

In the following, the range between 0.63 mmol/l ≤ [CA] ≤ 1.67 mmol/l at pH-values between 5 and 7 is termed the "extended range" (ER).

The dependence of the urinary [CA] and related ISCA-value of the intake of alkali-citrate is shown in Fig. 2. The different gradients of the regression lines indicate that the effects of the alkali-citrate preparations on the urinary citric acid concentration and related ISCA are quite different. The Lithurex treatment on stone-formers considerably increases [CA] but enhances the urinary pH only slightly. The administration of Oxalyt-C in healthy subjects, on the other hand, results in a more pronounced increase in urinary pH but in a less effective [CA]-enhancement. Whether these differences reflect the different groups of investigated persons or a different metabolic effectiveness of Lithurex or Oxalyt-C remains unanswered.

Figure 3 shows that most urine samples have pH-values between 5 and 7 (mean 6.33 ± 0.37). The [CA]-values vary between 0.037 mmol/l and 5.7 mmol/l. Approximately 53.6% of all samples plot into the supposed ER (Fig. 1). From all samples, 31.1% exceed a citric acid concentration of 1.67 mmol/l, and 15.3% plot below the ER. For all samples, a negligibly small, quite weak, and inverse statistical dependence of RS on [CA] (r = 0.15) and ISCA (r = 0.14) was found. This result changed when samples were divided into three groups according to RS: (1) RS ≤ 2.5, (2) 2.5 < RS ≤ 5, and (3) RS > 5. The median values of [CA] and ISCA of the samples of the three groups clearly plot into the supposed ER. Linear regression lines through the origin for each data group show slightly different gradients and similar regression coefficients: RS ≤ 2.5:3.21 (r = 0.96), < RS ≤ 5: 3.01 (r = 0.93), and RS > 5: 2.63 (r = 0.91).

Grouping the data in "stone-formers" and "healthy subjects", the medians of [CA] and ISCA of both groups also plot into ER (Figure 4). Computation of the linear regression lines through the origin revealed gradients of 3.08 (r = 0.94) and 2.97 (r = 0.93), respectively.

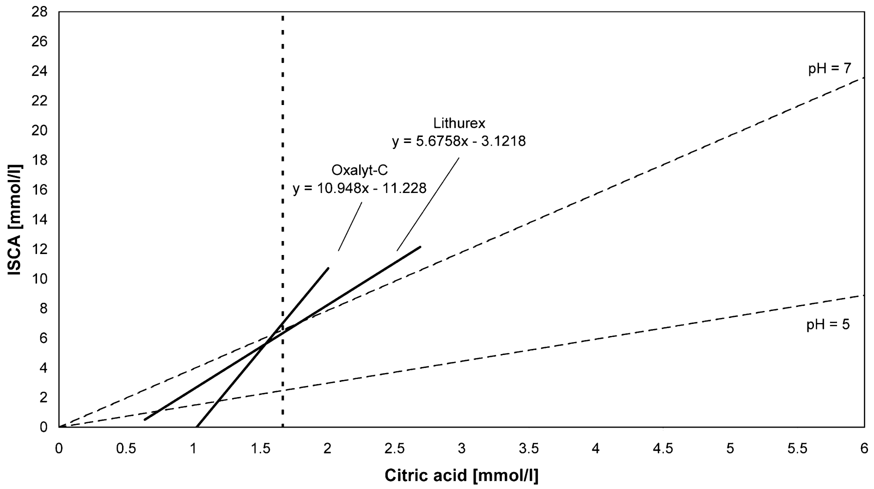

Fig. 2. Generalized courses of the urinary citric acid concentration and related ISCA-value after treatment with two different alkali-citrate preparations. The Lithurex-study was performed with 23 healthy men; the Oxalyt-C-study investigated 24 recurrent stone-formers. The alkali-citrate dosages in both studies amounted to 5.1 g/day

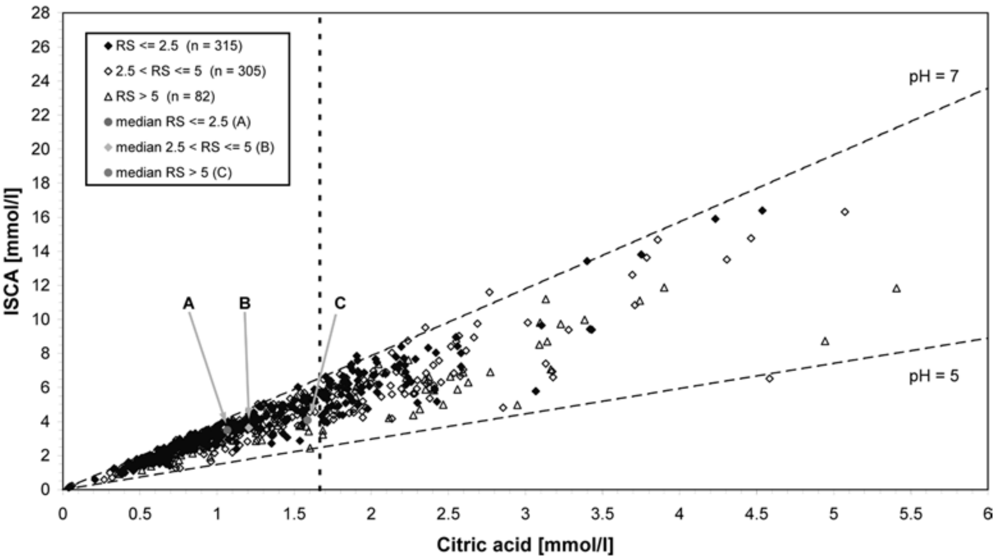

Fig. 3. Plot of urinary citric acid concentrations, [CA], vs calculated ISCA, (eq. 3) of 702 24 h-urine samples. The samples were grouped into three data sets according to their calculated relative supersaturation, RS. The supposed "extension" range, ER, (Fig. 1) covers approximately 53.6% of all samples. A total of 31.1% of all samples show [CA]-values exceeding the limit concentration of 1.67 mmol/l

Discussion

Although the supposed ER only covers a small area, 53.6% of all samples plot within this field. Surprisingly, not only the medians of the stone-formers and high RS samples plot into ER but also the medians of the non-stone-formers and low RS samples. This outcome is a clear indication that low [CA]-values (< 1.67 mmol/l) alone are not decisive for a person's health status with respect to calcium oxalate stone formation.

The result of an inverse relationship between [CA] and RS, as observed in Fig. 3, is in accordance with the observation of Curhan et al. [8] on 807 stone-formers and 239 persons without a history of stone formation, which showed that urinary CA is not inversely associated with the risk of stone formation.

The ISCA approach allows the extension of the present "rigid limit value strategy" by way of introduction of an "equal impact approach". In doing so, different urinary [CA]-values may, under favourable pH-conditions, show an equally modifying impact on stone-formation.

Figure 5 demonstrates that within the pH-range of 5 and 7, the ISCA-values which are related to the hypothetical, but reasonable, limit concentration of 1.67 mmol/l vary considerably between 2.48 mmol/l and 6.64 mmol/l. This clearly indicates that the rigid citric acid excretion limit of 2.5 mmol/day is not a very meaningful parameter to estimate a person's calcium oxalate stone formation risk. Only in extreme cases of disturbed citric acid metabolism does the excretion value allow for a clear decision as to whether or not a person forms stones due to hypocitraturia.

Instead of a constant limit of citric acid excretion as the discriminating parameter, the distinction between normocitraturic and hypocitraturic urines should be defined in the sense of a desirable "minimum impact of citric acid". The contribution of citric acid to the overall urinary ionic strength, i.e. the ISCA-value may be such a measure. A potential limit value, which distinguishes between urines indicated by a "normo-protective" impact from those indicated by a "hypo-protective" impact with respect to calcium oxalate precipitation, may be set at ISCA = 2.48 mmol/l.

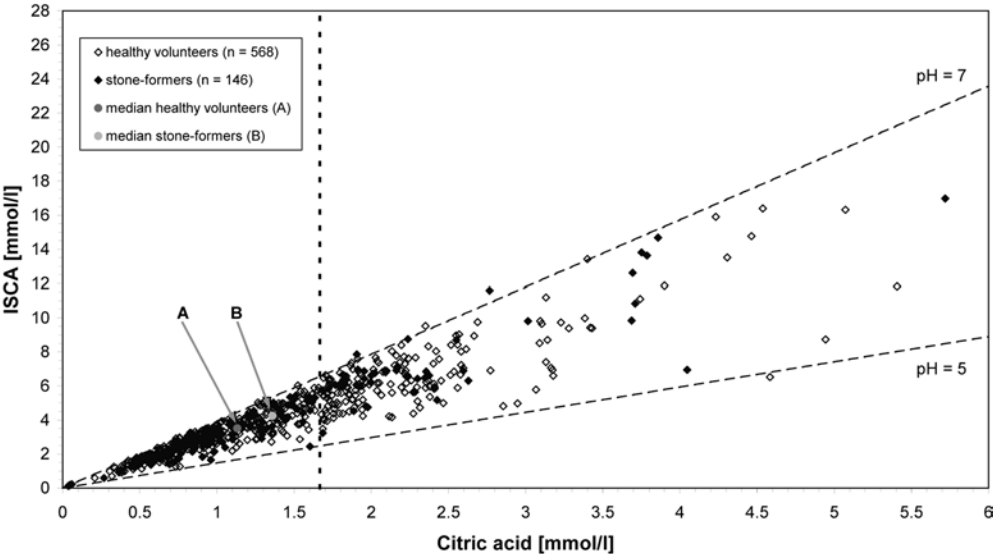

Fig. 4. Plot of same data as shown in Fig. 3, now grouped into stone-formers and healthy subjects. Both groups show median values of the same order of magnitude

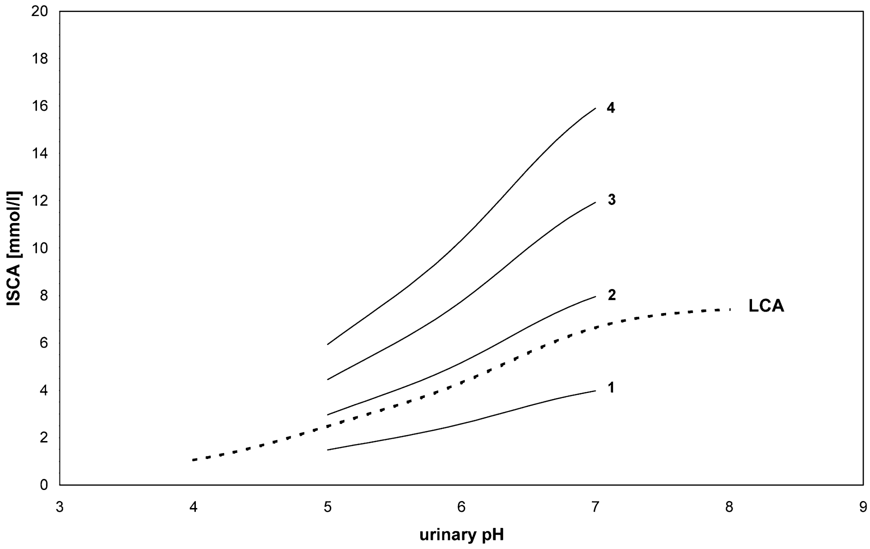

Fig. 5. Plot of urinary pH vs ISCA for citric acid concentrations, [CA], of 1, 2, 3, and 4 mmol/l. LCA: "low-[CA]urine" according to the CA-excretion limit value for hypocitraturia of 2.5 mmol/day [7] and an urine volume of 1,500 ml/day; this corresponds to [CA] = 1.67 mmol/l. The higher the initial value of the urinary [CA], the more pronounced the effect of an increased pH on ISCA

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Appendix

Example for the iterative calculation of the concentrations of the three anion species of citric acid (eq. 2) and related ISCA-value (eq. 3). A urinary citric acid concentration of 1 mmol/l at pH = 7 is given. The pK-values are $pK_1 = 3.13$, $pK_2 = 4.77$, $pK_3 = 6.40$ [6]:

$$[CA]^{*1-} = \frac{1\ \text{mmol/l} \times 10^{(7-3.13)}}{1+10^{(7-3.13)}} = 0.99987\ \text{mmol/l}$$

$$[CA]^{*2-} = \frac{0.99987\ \text{mmol/l} \times 10^{(7-4.77)}}{1+10^{(7-4.77)}} = 0.98091\ \text{mmol/l}$$

$$[CA]^{*3-} = \frac{0.98091\ \text{mmol/l} \times 10^{(7-6.40)}}{1+10^{(7-6.40)}} = 0.78398\ \text{mmol/l}$$

$$\begin{aligned}
[CA]^{1-} &= [CA]^{*1-} - [CA]^{*2-} &&= 0.01895\ \text{mmol/l}\\
[CA]^{2-} &= [CA]^{*2-} - [CA]^{*3-} &&= 0.19693\ \text{mmol/l}\\
[CA]^{3-} &= [CA]^{*3-} &&= \underline{0.78398\ \text{mmol/l}}\\
&\quad\ \text{SUM} &&= 0.99986\ \text{mmol/l}
\end{aligned}$$

The remaining deviations from 1 mmol/l denote the concentration of undissociated citric acid at the given pH conditions. The corresponding ISCA-value amounts to approximately 3.931 mmol/l.

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