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ORIGINAL ARTICLE

Basic Study

Urinary supersaturation as a diagnostic measure in urolithiasis

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Abstract

AIM

To demonstrate that urinary supersaturation *per se* is not a reliable diagnostic measure of the risk for stone formation.

METHODS

Available physical and chemical data for calcium oxalate monohydrate (COM) and calcium hydrogen phosphate dihydrate (brushite, BRU), and urinary supersaturations with respect to COM and BRU in healthy individuals and stone formers, were obtained from the literature. Classical theory of nucleation was used for calculations.

RESULTS

It was found that the rate of homogeneous nucleation (unaided by substrates) of COM and BRU is nil at all conceivable supersaturations of urine. Consequently spontaneous formation of crystals in urine requires the presence of nucleation substrates for (heteronuclei).

CONCLUSION

Urinary supersaturation with respect to lithiatic compounds is a necessary, but not a sufficient condition for nephrolithiasis. The absence of crystallization inhibitors and the presence of efficient nucleation promoters (heteronuclei) in urine are further necessary conditions of urolithiasis occurrence. Urinary supersaturation per se is not a reliable diagnostic measure of the risk of kidney stone formation.

Key words: Urinary supersaturation; Heterogeneous

nucleation; Urolithiasis

Core tip: The supersaturation of urinary compounds has been considered during long time as a key risk factor for renal lithiasis. Nevertheless, theoretical studies demonstrate that the rate of spontaneous (homogeneous) nucleation of calcium oxalate monohydrate and brushite only occurs at urinary supersaturations much higher than conceivable in any individual. This demonstrates the necessity of presence of efficient substances or foreign solid particles for induced nucleation (heterogeneous) of lithiatic compounds. Consequently, urinary supersaturation per se is necessary but not sufficient condition for stone development. Fundamental condition of renal stone formation and development is presence of heteronuclei and significantly reduced content of crystal growth inhibitors. Identification of nucleation promoters and absence of crystal growth inhibitors is very important as a diagnostic aspect to avoid urolithiasis.

Söhnel O, Grases F. Urinary supersaturation as a diagnostic measure in urolithiasis. *World J Clin Urol* 2017; 6(2): 40-43 Available from: URL: http://www.wjgnet.com/2219-2816/full/6/i2/40.htm DOI: http://dx.doi.org/10.5410/wjcu.v6.i2.40

INTRODUCTION

The supersaturation of urine with respect to lithogenic compounds as a key risk factor for urolithiasis has been introduced by Robertson *et al*[1]. Rodgers recently showed that urinary supersaturation of calcium oxalate monohydrate (COM) and calcium hydrogen phosphate dihydrate (BRU) varied widely among healthy individuals and stone formers and that it was impossible to discriminate between these two groups based on urinary supersaturation levels. Rodgers therefore concluded that urinary supersaturation *per se* is not useful as a diagnostic measure of the risk of stone formation[2].

The aim of this contribution is to demonstrate that the conclusion of Rodgers is fully substantiated based on the theory of precipitation.

MATERIALS AND METHODS

The driving force for the transfer of one "molecule" of a solute (electrolyte) composed of v ions from solution into the solid phase, ϕ, is the difference of the chemical potentials of the solute in solution and in a macroscopic crystal, $\Delta\mu$, expressed as a positive quantity[3].

$$\phi = -\Delta\mu = k\,T\,\ln(a_{soln}/a_{cryst}) \quad (1).$$

where k is the Boltzmann constant (1.38×10^{-23} J/K), T is the absolute temperature (K), a_{soln} is the activity of a solute in solution and a_{cryst} is the activity of a solute in a macroscopic solid. The activity of a ionic solute $A^{vA}B^{vB}$ (electrolyte) is[2]: $a_{soln,cryst} = a_{\pm}{}^{v} = a_A{}^{vA}a_B{}^{vB}$ (2).

where a_A and a_B are the activities of ions A and B, v_A and v_B are the stoichiometric coefficients and $v = (v_A + v_B)$ is the number of ions that form "molecule" of solute. The driving force for mass transfer can be expressed as: $\phi = v\,k\,T\,\ln S$ (3).

The supersaturation S is a measure of the thermodynamic driving force for crystallization at a constant temperature (our case) defined as: $S = a_{\pm,soln}/a_{\pm,cryst}$ (4).

where $a_{\pm}$ is the mean activity of an electrolyte. The activity of a solute in a macroscopic crystal is equal to the activity of solute in a saturated solution. No mass transfer of solute to solid phase, *i.e.*, crystallization, can proceed if S = 1.

The supersaturation of COM) and BRU is defined as: $S = [(a_A a_B)/K_{a,sp}]^{1/2}$ (5).

where $K_{a,sp}$ is the respective thermodynamic solubility product. The supersaturation SS used by Rodgers[2] and the supersaturation S defined by eq. (5) are related by $S = (SS)^{1/2}$.

The classical model of nucleation assumes the formation of a solid phase nucleus in a supersaturated solution by gradual attachment of building units (ions) to the already formed crystalline "cluster" of these units. The rate of homogeneous nucleation, *i.e.*, spontaneous formation of crystalline nuclei in the bulk solution by accretion of ions that is not facilitated by a solid substrate, in 1 m^3 per second can b expressed as[3]: $J_{hom} = (2\,D/d^5)\exp(-\Delta G^*/kT)$ (6).

where D is the diffusion coefficient of the solute (10^{-9} m^2/s), d is the molecular diameter, ΔG^* is the change of Gibbs energy accompanying formation of the critical nucleus and k and T are as defined above.

The rate of heterogeneous nucleation, *i.e.*, spontaneous formation of crystalline nuclei facilitated by a solid substrate, in 1 m^3 per second is[4]: $J_{het} = (2D/d^5)\exp[-\Delta G^* f(\Theta)/Kt]$ (7).

The correction factor $f(\Theta)$ is smaller than 1 and can be best considered as a measure of the nucleation enhancement by the foreign substrate without ascribing to it any precise physical interpretation. Heterogeneous nucleation occurs at a lower supersaturation then homogeneous nucleation.

The energetic barrier for formation of a nucleus is[3]: $\Delta G^*/kT = (\beta\,v^2\,\sigma^3)/[(kT)^3(v\ln S)^2]$ (8).

where β is the geometrical factor (32 for a cube), v is the molecular volume, σ is the interfacial tension.

Nuclei smaller than the critical size are unstable and disintegrate, whereas nuclei of the critical size or larger further grow to macroscopic sizes. The number of molecules, N^*, forming the critical nucleus is[3]: $N^* = 2\beta\,v^2\,\sigma^3/\phi^3$ (9).

RESULTS

COM has a molecular weight of 0.1461 kg/mol, density of 2120 kg/m^3, surface tension of 0.123 J/m^2[5], $K_{a,sp}$ =

2.24×10^{-9} $mol^2 L^{-2}$ at 37 ℃[6], molecular volume of 1.14×10^{-28} m^3, molecular diameter of 4.85×10^{-10} m. BRU has a molecular weight of 0.1721 kg/mol, density of 2310 kg/m^3, surface tension of 0.068 J/m^2[7], $K_{a,sp} = 2.74 \times 10^{-7}$ mol^2L^{-2} at 37.5 ℃[8], molecular volume of 1.24×10^{-28} m^3 and molecular diameter of 5.0×10^{-10} m.

The rate of homogeneous nucleation of COM for $S = \sqrt{12} = 3.5$ (maximum S reported in[2]) at 37 ℃ according to eq. (6) is: $J_{hom} = 3.7 \times 10^{37} \exp(-4722) \sim 0$.

The rate of homogeneous nucleation of BRU for $S = \sqrt{2.5} = 1.6$ (maximum S reported in[2]) at 37 ℃ is: $J_{hom} = 3.2 \times 10^{37} \exp(-2178) \sim 0$.

A nucleation rate of 1 nucleus in 1 cm^3 per second, *i.e.*, $J = 10^6$ $m^{-3}s^{-1}$, can be considered as the threshold for the onset of homogeneous nucleation. This rate is achieved when the supersaturation S with respect to COM and BRU is 35.9 and 13.6, respectively.

The critical nucleus of COM at S = 3.5 according to eq. (9) consists of 1257 "molecules" (ion pairs) and has a diameter of 6×10^{-9} m. The critical nucleus of BRU at S = 1.6 consists of 4757 "molecules" (ion pairs) and has a diameter of 11×10^{-9} m.

DISCUSSION

The urine of most people is supersaturated with respect to COM and BRU, the predominant constituents of kidney stones. However, only small fraction of people suffer from urolithiasis.

The first step in stone formation is the establishment of a tiny stable nucleus of a solid compound either in the liquid volume inside the kidney or on an inner wall of the kidney. A nucleus formed in the liquid volume must be retained within the kidney and grow to a macroscopic size.

Spontaneous unaided formation of a stable nucleus of COM or BRU in a liquid volume, this is by the mechanism of the homogeneous nucleation, only occurs at urinary supersaturations much higher than conceivable in any individual. Therefore the present analysis based on the theory of precipitation indicates that kidney stones cannot originate by homogeneous nucleation.

A necessary condition for the formation of solid phase nuclei in bulk urine is the presence of efficient substrates for nucleation. Spontaneous formation of crystals in urine can occur when value of the factor $f(\Theta)$ in eq. (7) is equal or lower than 0.015 for COM and 0.033 for BRU. Such low values of the factor $f(\Theta)$ indicate that substrates which are highly efficient in promoting nucleation must be present for the solid crystalline phase to appear. The phenomenon of crystalluria demonstrates that under special conditions macroscopic crystals with size up to 35×10^{-8} m and concentration of about 2×10^5 m^{-3} can originate in bulk urine[9]. This concentration of crystals is typical for heterogeneous nucleation.

The critical nucleus is very small and can be retained in the kidney after formation directly on the kidney wall or after attachment to the wall following formation in the liquid phase. However, some renal stones do not attach to the kidney wall. The nuclei of these stones must have originated in a cavity with poor urodynamics, and as they grew they formed an agglomerate that was large enough not to be washed from the kidney.

Nuclei formed in urine and retained in the kidney reach a macroscopic size by the accretion of additional building units (ions or ion pairs) and by subsequent agglomeration. The development of nuclei is strongly influenced by crystal growth modifiers naturally present in the urine that impede or completely stop solute attachment to the nucleus. Inhibitors, such as citrate, chondroitin sulphate, serum albumin, transferrin, osteopontin and Tamm-Horsfall protein[10,11], interact with COM crystal surfaces and impede growth. Protein lysozyme and lactoferrin, which occur in the organic matrix of renal stones, promote the growth of COM crystals[12]. Citrate, phytate, pyrophosphate and polyphosphates are effective inhibitors of BRU crystallization[13,14].

Nuclei that are formed and retained in the kidney can reach macroscopic size only in the absence of growth inhibitors and/or the presence of growth promoters.

Renal stones composed of COM and/or BRU are formed only in the case that: (1) urine is supersaturated with respect to these compounds; (2) efficient substrates for solid phase nucleation (heteronuclei) are present; and (3) inhibitors of crystallization are absent and/or promoters of crystallization are present. In the presence of suitable nucleation substrates and a deficiency of inhibitors, higher urinary supersaturation enhances formation and the development of stones. Urinary supersaturation *per se* is a necessary but not a sufficient condition for urolithiasis and is therefore not a reliable diagnostic measure of the risk of stone formation. If conditions of stone formation (2) and (3) are fulfilled the magnitude of supersaturation indicates the probability of nephrolithiasis.

COMMENTS

Background

The supersaturation of urinary compounds has been considered during long time as a key risk factor for renal lithiasis. Recently it has been demonstrated that urinary supersaturation of calcium oxalate monohydrate (COM) and calcium hydrogen phosphate dihydrate varied widely among healthy individuals and stone formers.

Research frontiers

The previously presented studies have been developed exclusively using information related to urinary biochemical parameters of patients and healthy individuals and checking that the values of supersaturation do not allow a good discrimination between both groups.

Innovations and breakthroughs

This study analyzes, using the classical theory of crystalline nucleation, the possibility of formation of crystals of COM or brushite (BRU) in human urine, as

a function of supersaturation.

Applications

This study demonstrates that the formation of COM and/or BRU renal calculi in urine supersaturated with these substances can only take place in the presence of efficient substrates for the nucleation of the corresponding solid phases (heteronuclei) and in the absence or deficit of crystallization inhibitors. Therefore, supersaturation is a necessary but not sufficient condition for the development of these stones. Supersaturation is therefore not a reliable diagnostic measure of the risk of stone formation. Nevertheless, in the presence of heteronuclei and crystallization inhibitory deficit, the magnitude of supersaturation may indicate the probability of nephrolithiasis. Identification of nucleation promoters and deficit of crystallization inhibitors is therefore very important as a diagnostic aspect to avoid urolithiasis.

Peer-review

The paper deals with theory of renal stones development; the paper is well written, clear and concise.

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