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Comprehensive morpho-constitutional analysis of urinary stones improves etiological diagnosis and therapeutic strategy of nephrolithiasis

Michel Daudon [a, b, *], Arnaud Dessombz [c, d], Vincent Frochot [a, b], Emmanuel Letavernier [a, b], Jean-Philippe Haymann [a, b], Paul Jungers [e], Dominique Bazin [c, f]

[a] AP-HP, Hôpital Tenon, Service des Explorations Fonctionnelles, 4, rue de la Chine, 75970 Paris cedex 20, France
[b] Unité INSERM UMR S 1155, UPMC, Hôpital Tenon, 4, rue de la Chine, 75970 Paris cedex 20, France
[c] Laboratoire de Physique des Solides, Université Paris-11, 91405 Orsay, France
[d] INSERM, UMR 1138, Centre de Recherche des Cordeliers, Laboratoire de Physiopathologie Orale Moléculaire, Équipe Berdal, Université Paris-7, Unité INSERM, Paris, France
[e] AP-HP, Hôpital Necker, Département de Néphrologie, 149, rue de Sèvres, 75743 Paris cedex 15, France
[f] CNRS, LCMCP-UPMC, Collège de France, 11, place Marcelin-Berthelot, 75231 Paris cedex 05, France

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ABSTRACT

The generalized use of physical methods, X-ray diffraction and Fourier transform infrared spectroscopy (FTIR) decisively improved urinary stone analysis by allowing to accurately identify the chemical nature, crystalline phases and relative proportions of stone constituents. Such compositional analysis is sufficient to identify stone diseases involving a single specific component such as cystine, 2,8-dihydroxyadenine (DHA), struvite, uric acid, ammonium hydrogen urate or a drug. However, for common calcium nephrolithiasis, which represents by far the largest part of urinary stones throughout the world, the simple identification of calcium oxalate (CaOx) and/or calcium phosphate (CaP) as constituents provides incomplete etiologic information because a same elemental stone composition may result from different lithogenic processes.

A more comprehensive method combining careful morphologic examination of the surface and the section of stones with detailed FTIR analysis of the nature, location, crystalline phases and a respective proportion of stone constituents, therefore termed 'morpho-constitutional' analysis, as used in our laboratory for four decades provides more complete etiologic information. In common idiopathic CaOx nephrolithiasis, the predominance of the monohydrate form (COM) was shown to be associated with elevated urine Ox concentration, whereas the dihydrate form (COD) was associated with hypercalciuria, thus orienting dietary and/or pharmacological intervention. A major contribution of the method is to immediately orient the diagnosis of rare, but severe, diseases leading to a loss of renal function, when stone analysis reveals a peculiar morphology of common constituents. The most salient examples are the type Ic morphology of COM stones, pathognomonic of primary hyperoxaluria, type Ie morphology, which is highly suggestive of absorptive hyperoxaluria as seen in inflammatory bowel diseases and pathologies inducing steatorrhea, type IIId morphology of ammonium urate stones, which orientates towards chronic diarrhea with dietary imbalance and loss of electrolytes, and type IVa2 morphology of carbapatite, specific of distal renal tubular acidosis of congenital or acquired origin, and

* Corresponding author. AP-HP, Hôpital Tenon, Service des Explorations Fonctionnelles, 4 Rue de la Chine, 75970 Paris Cedex 20, France.
E-mail address: michel.daudon@tnn.aphp.fr (M. Daudon).

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distinctive aspect of 2,8-DHA stones. In conclusion, the proposed morpho-constitutional method should be recommended for routine stone analysis, inasmuch as it is simple, rapid, reliable, clinically relevant and cost-effective.

1. Introduction

The analysis of urinary stones is currently performed by physical methods, namely X-ray diffraction (XRD) or Fourier transform infrared spectroscopy (FTIR). These methods allow to identify the chemical nature of stone constituents and to provide semi-quantitative evaluation of their respective proportions within a calculus. This global analysis classifies calculi as mainly composed of calcium oxalate (CaOx), calcium phosphate (CaP), uric acid, struvite and cystine, which together represent approximately 98% of all urinary stones, with calcium stones accounting for more than 80% of the total [1]. Although they also allow to identify the crystalline phases of CaOx, namely CaOx monohydrate (COM) or whewellite and CaOx dihydrate (COD) or weddellite, this distinction is not provided in most laboratory records, which generically report 'calcium oxalate' without more precision, thus lacking a clinically relevant indication.

Physical methods reliably identify specific forms of nephrolithiasis involving a single component such as struvite, ammonium acid urate, cystine, 2,8-dihydroxyadenine (DHA), xanthine or drugs, because in this case, the chemical nature of the stones by itself defines the type of renal stone disease. However, these cases are infrequent, as they account for only 1–2% of the total in Western countries, whereas in the case of common calcium stones and, sometimes, of uric acid stones, simple identification of the chemical nature of stone constituents does not provide full etiopathogenic information.

Because XRD or FTIR analysis is usually performed on a powdered sample of the whole stone, no indication is provided as to the respective location (in the core or peripheral layers) of the diverse stone constituents in common calcium oxalate or phosphate calculi, which most often are of mixed composition, whereas the nature of the core, the initial site of stone formation, may differ from that of surrounding layers. In addition, the respective abundance and location of components are to be considered in CaOx or CaP mixed stones made of several crystalline phases such as COM, COD, carbapatite or brushite.

Moreover, a same elemental composition such as CaOx in the form of COM or COD as the main component may correspond to very different etiopathogenic conditions, each of which is reflected by a distinct morphology of both the surface and section of calculi, thus emphasizing the importance of morphological examination of stones in complement to analysis of their composition.

Accordingly, we developed, since the early 1980s, a comprehensive method of stone analysis termed morpho-constitutional because it combines the morphological examination of the surface and inner structure of the calculus with constitutional analysis by FTIR, the term constitutional encompassing the chemical nature, crystalline phases, relative proportions and location of the stones' chemical components.

2. The morpho-constitutional method of urinary stone analysis

The method we adopted for the morpho-constitutional stone analysis over the past four decades has been described in detail elsewhere [2]. In short, the standardized protocol comprises two steps:

- First, a morphologic examination by means of a stereomicroscope (magnification ×10–40) of the surface and section of the calculus, with the identification of the nucleus (or core) and description of the inner organization, is carried out. The main points to be recorded in each stone are size, form, color, aspect (smooth, rough or spiky) of the surface, presence of a papillary imprint (umbilication), presence of Randall's plaque, aspect of the section (well organized with concentric layers and/or radiating organization, or poorly organized and loose structure) and location and aspect of the nucleus.
- Thereafter, an analysis is performed by FTIR of a sample of each part of the calculus (nucleus, mid-section and surface), whenever allowed by the size of the stone, and in all cases, the determination of the global proportion of components in a powdered sample of the whole stone.

Using this method, urinary stones could be classified into 6 main morpho-constitutional types, themselves subdivided into a variable number of morphological subtypes, each corresponding to a peculiar etiological or pathophysiological condition. Indeed, the morphology of stones is determined by a number of factors, such as the size and shape of the constitutive crystals, the kinetics of stone growth and the location of the first steps of stone formation within the urinary tract [3]. For example, uric acid and struvite, which form large crystals and aggregates in urine, lead to rapidly growing and poorly organized stones. Conversely, COM stones, made of very small crystals, show a dense and organized structure.

The kinetics of stone growth also influence the inner structure of stones. Common COM calculi exhibit a well-organized inner structure with concentric layers and radiating crystallization, dark brown in color, which suggests a slow stone growth due to intermittent peaks