

Features of the morphogenesis of oxalate and urate urinary stones in urolithiasis patients from heavily industrialized region

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ABSTRACT

Aim: Determining the characteristics of urinary stone composition in inhabitants of an industrially advanced region afflicted with oxalate and urate urolithiasis.

Materials and Methods: A comparative analysis of the morphology of 246 kidney stones from residents of one of heavily industrialized region of Ukraine, was conducted. Petrographic examination of the calculi was performed through microscopic analysis. The qualitative composition of the calculi was investigated using X-ray structural analysis of fragments and dust remnants of the stones, which were formed during the preparation of thin sections.

Results: A distinctive characteristic of all mineral components is their varying microblock structure and the presence of organic material inclusions. The inclusion of an organic component reduces the strength of the crystalline layers. Urolith resembles a brittle-hollow environment, which in certain cases allows for the selection of the most effective methods of their destruction (lithotripsy).

Conclusions: A common feature among all mineral components is their diverse microblock structure and the presence of organic inclusions, which diversify the strength characteristics of uroliths. The prior determination of these characteristics allows for the selection of the most effective method for destructive treatment (lithotripsy). The combination of data on the ontogenesis of uroliths, their mineral composition, and the state of the electrolyte balance in the body of a patient with urolithiasis will allow choosing an individually effective method of metaphylaxis of the disease.

KEY WORDS: structure, composition, pollutions, industrial region, Keywords: urolithiasis, urolith ontogenesis

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INTRODUCTION

Minerals of biogenic origin are integral elements of many living organisms. Alongside genetically physiogenic minerals, pathogenic biominerals are also prevalent. Among them are urinary stones, or uroliths, which form as a result of urolithiasis development. Urolithiasis is rightfully referred to as the "disease of civilization" [1-3]. According to the World Health Organization, the incidence of this disease has increased by 1.5 times over the past 12 years. Globally, one person out of a hundred suffers from it. The prevalence of urolithiasis among the adult population in an intensive industrial region exceeds the overall defined indicators by 3.4 times, correlating with indicators of environmental pollution by heavy metals, particularly lead and cadmium, which can accumulate in the renal parenchyma and cause toxic nephropathy, secondary crystalluria, and urolithiasis [2]. Throughout many centuries, information on disease symptoms and treatment methods has been accumulated, but many questions in mineralogy, including uro-

lith ontogeny, remain insufficiently explored. Currently, the ontogeny of minerals is a well-developed branch of genetic mineralogy. It allowed for the initial exploration of the composition and microstructure of kidney calculi in residents of an industrial region in Ukraine [3-6]. Subsequent investigations have demonstrated that the acquired information can assist in reconstructing the conditions of their nucleation and growth by examining the external form and internal structural characteristics of minerals and mineral aggregates. The rich experience in the study of inorganic compounds can and should be effectively applied in biology and medicine to elucidate possible mechanisms of biomineral formation in pathogenic processes based on their geological analogs [7-8].

AIM

Determining the characteristics of urinary stone composition in inhabitants of an industrially advanced region afflicted with oxalate and urate urolithiasis.

MATERIALS AND METHODS

A comparative analysis of the morphology of over 246 renal uroliths from the Dnipropetrovsk region, one of the highly industrialized regions of Ukraine, was performed. Petrographic examination of the uroliths was conducted using a stereoscopic binocular microscope MBS-9 and optical polarization microscope MIN-8. The qualitative composition of urinary calculi was investigated using X-ray structural analysis of fragments and dust remnants of the stones, which were formed during the preparation of thin sections.

RESULTS

During the investigation of kidney stones from residents of the Dnipropetrovsk region using optical petrography methods, we identified the following compounds: oxalates such as weddellite and whewellite; urates including uricite, pseudomalachite, ammonium urate, monohydrate sodium urate; phosphates like struvite, hydroxyapatite, brushite, whitlockite; as well as xanthine, cystine, quartz, gypsum, and goethite. Monomineral formations were exceedingly rare (<1%). Among them, uric acid (urate) stones constituted 14.5%, struvite - 11.3%, calcium phosphates - 11.3%, calcium phosphates + oxalates - 29%, and calcium oxalates - 33.9% (Fig. 1).

Based on morphological characteristics, five types of urinary calculi have been identified. The first type of calculi exhibits a dendritic surface composed of numerous small crystals. In thin sections, there is an evident growth direction of crystals from the center of the calculus to its periphery. The second type of calculi is characterized by a "budding" surface. Individual "nephron" sizes can vary from a few micrometers to several millimeters in diameter. The third type of calculi combines features of the morphology of the first two types, and this surface morphology is referred to as "combined." The surface of the fourth type of calculi is intensely grooved, resembling "bay-like" structures. The fifth type of calculi has irregular shapes. Their forms cannot be categorized into specific types of geometric solids; often, they are cylindrical aggregates with deviations from the long axis, exhibiting numerous branching formations.

In the case of oxalate uroliths, a wide spectrum of colors was observed, spanning from light gray to dark brown. These uroliths exhibited a cluster-like shape with small crystals dispersed irregularly across their surface formations. Notably, the surfaces of these stones displayed a distinct rough and nodular texture, which manifested at varying scales (Fig. 2A). Another configuration of oxalate uroliths showcased a different

color palette, ranging from pure white to dark brown and black. These uroliths assumed an irregular, kidney-shaped form, with occasional nodular structures appearing on the surface, contributing to their unique appearance (Fig. 2B). Furthermore, oxalate uroliths displayed a variation in texture, with a color range from light gray to dark brown and black. Their irregular shape was accentuated by a surface texture characterized by roughness, spikiness, cavernous formations, and nodular protrusions, which could be observed at multiple scales (Fig. 2C).

In contrast, urate uroliths presented a distinct color profile, transitioning from yellowish-white to various shades of orange (Fig. 2D). Their surfaces were primarily uneven, featuring prominent bumps, cavernous features, and occasional fine nodular structures. Notably, a matte shine was observed on the majority of urate uroliths, with occasional instances of a subtle glassy sheen. The macrostructure of these uroliths was primarily fine-grained, with sporadic occurrences of thin-grained patterns.

The microstructure of the majority of uroliths was cryptocrystalline. They consisted of a cryptocrystalline aggregate, primarily composed of individual cryptocrystalline grains of weddellite and whewellite, with minor admixture of uric acid dihydrate (predominantly enriched in the 5th generation, located in the peripheral part of the urolith). The organic material was generally distributed unevenly. The main portion of organic matter accumulated in the 5th generation of stone formation as separate flake-like inclusions and layers. In other generations of stone formation, the organic material was mainly localized as inclusions within the hollow spaces between mineral substance aggregates, high-dispersion film inclusions between individual grains and their microblocks ("organic shell"). Additionally, a slightly smaller amount of organic material was localized within micropores and the "organic core."

Microscopically, the structure of uric acid uroliths was predominantly fine-crystalline and hypidiomorphic. The uric acid stone consisted of an aggregate of small crystals, primarily composed of individual small grains of uric acid monohydrate. On the surface, a thin sprinkling of well-developed crystals of uric acid dihydrate was often observed. In the central part of the uric acid uroliths, calcium oxalate crystals (wedellite) were present, mainly as inclusions ("mineral hostages") within relatively large crystals of uric acid monohydrate, along with occasional accumulations of collophane. The organic material was distributed unevenly. The main portion of organic matter was concentrated as high-dispersion inclusions between individual micro-

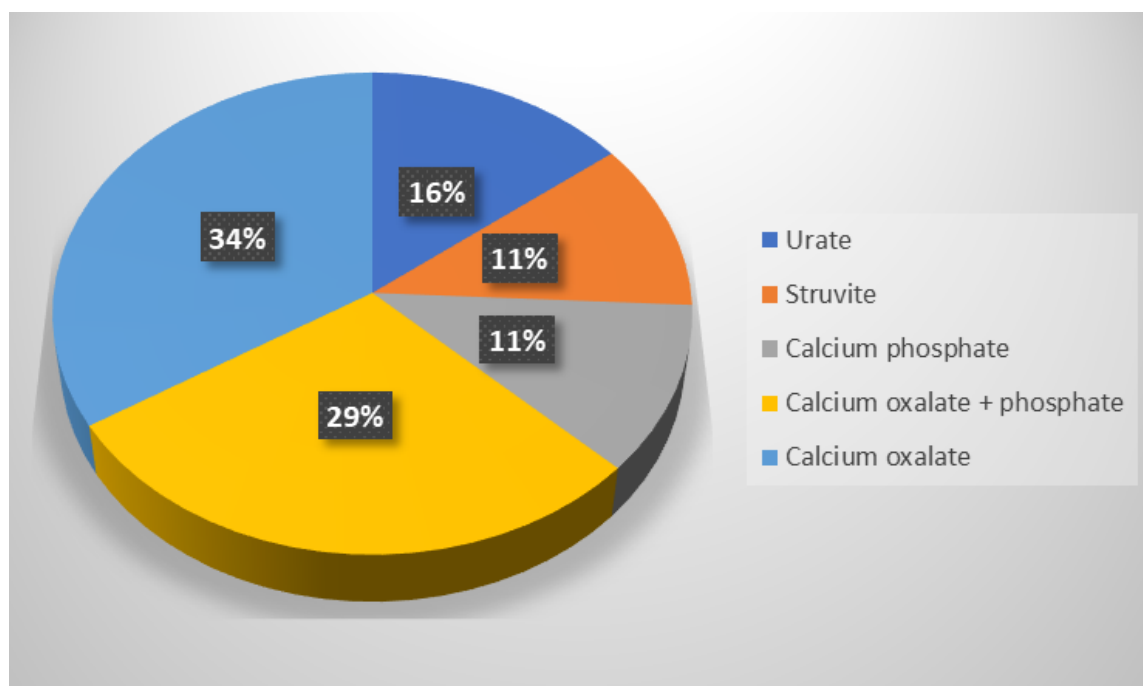


Fig. 1. Results of the study of stones in the kidneys of residents of the Dnipropetrovsk region.

blocks of mineral grains, within fractures and micropores. Simultaneously, some amount of organic material was localized as an irregularly shaped “organic core” resulting from multiple phases of a single generation. The analysis of mineral phase interactions indicated a sequential mineral replacement process: collophane (phosphate) → weddellite (oxalate) → uric acid monohydrate (urate).

Special attention was drawn to various options for the construction of the urate stones themselves. Moreover, the main portion of the examined section was composed of mineral material consisting of polydisperse crystals of uric acid monohydrate (Fig. 3.A). However, inclusions of whewellite (calcium oxalate monohydrate) were observed within the large crystals of uric acid monohydrate. Sometimes, in addition to these inclusions, a second inclusion of phosphate - collophane within the “shell” of vaterite was observed. Furthermore, fragments of the “organic core” with a thin rim of collophane were repeatedly observed. The analysis of these observations also confirms the sequential replacement of mineral phases. The organic matter (matrix) was mainly concentrated in the form of extremely thin films (“organic shell”) along the surfaces of crystals and their microblocks, as well as numerous fine-dispersed inclusions within the microblocks of individual crystals. Occasionally, during the observation, clusters with polygonal microblock crystals of uric acid monohydrate and clusters of collophane accumulation were found.

Characteristics of the structure of the peripheral part of urate (Fig. 3B). The field of view reveals the struc-

ture of a concentric-zonal spherulite predominantly composed of uric acid. At this scale, the presence of 5 zones corresponding to sequential stages of mineral formation is clearly observed. The zones are separated by layered accumulations of organic matter inclusions. A characteristic feature of the structure of the first zone (the central or “core” of the spherulite) is the presence of polygonal crystals of uric acid monohydrate and a relatively large, singular cluster of collophane. The second zone is composed of radially elongated tabular crystals of uric acid monohydrate. The third zone is formed by the largest tabular crystals of uric acid monohydrate, also arranged radially. Analysis of the elongation of crystals in the second and third zones (based on 34 measurements) shows their equality within the margin of error. In contrast to the other zones, the fourth zone is discontinuous and manifested as several thin lenses of collophane grains. The fifth zone is composed of a combination of polygonal and radially elongated tabular grains of uric acid monohydrate. It should be noted that the composition of the third and fifth zones includes individual small crystals of whewellite and uric acid dihydrate.

The peculiarities of the structure of the central part of oxalate uroliths consisted mainly of various fragments tracing the gradual generation of stone formation. This was particularly evident in the conditions of urolith formation with relatively stable saturation of urine with mineral components, without sharp fluctuations in their concentration. The field of view captured distinct areas of stone generation. The first

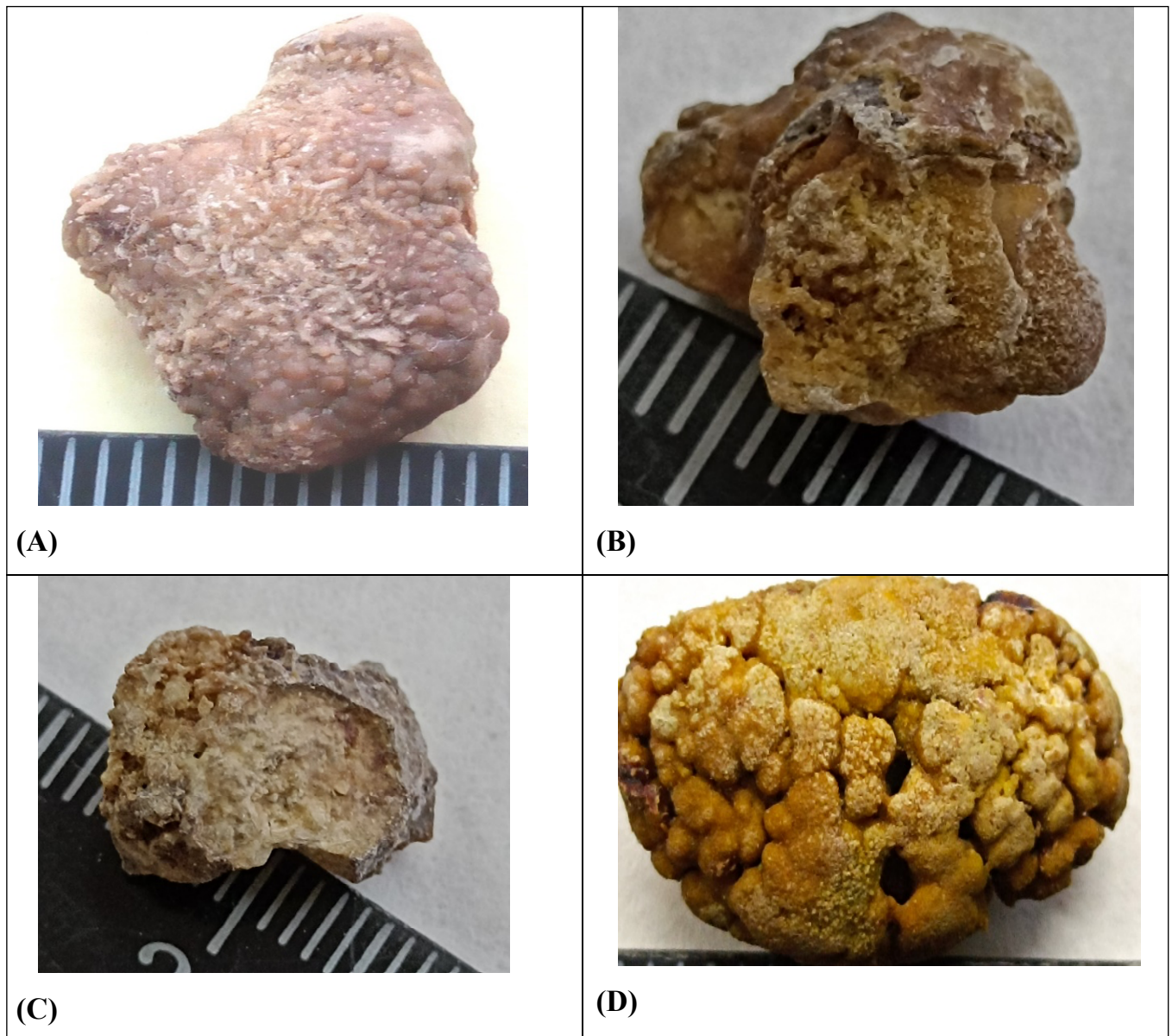


Fig. 2. Macroscopic appearance of uroliths: (A,B,C) Oxalate urolith; (D) Urate urolith.

generation was represented by a concentric-zonal aggregate of whewellite in a bud-like form, formed around the fragment of the “organic core” (Fig. 4A). The mineral substance of the second generation of stone formation, in the form of bud-like aggregates of vaterite with concentric-zonal structure, radially encompassed the aggregate of the first generation. As for the structure of the third generation of stone formation, it often exhibited combinations of spherical aggregates with layered and bud-like alternations, which were immersed in organic matter (Fig. 4C). In terms of mineral composition, there was a slight predominance of vaterite over whewellite.

Features of the construction of the peripheral part of oxalate uroliths consisted of clear variations in the mineral composition, differences in color and forms of

organic matter concentration in the fourth generation (Fig. 4B). The fifth generation of stone formation was characterized by a significant increase in the content of organic matter (up to 62%), the presence of crystals of calcium oxalate dihydrate, a predominance of calcium oxalate dihydrate (weddellite) in the oxalate composition, a finer-grained mineral component, and smaller aggregates.

Additionally, in the microphotographs of the peripheral part of oxalate uroliths, the main component of the mineral composition consisted of various-sized crystals of oxalates (weddellite and whewellite), with a minor presence of urates - dispersed crystals of calcium oxalate dihydrate in the form of small sharp-edged crystals and their aggregates, concentrated around the external surface of the stone and often spatially close to areas

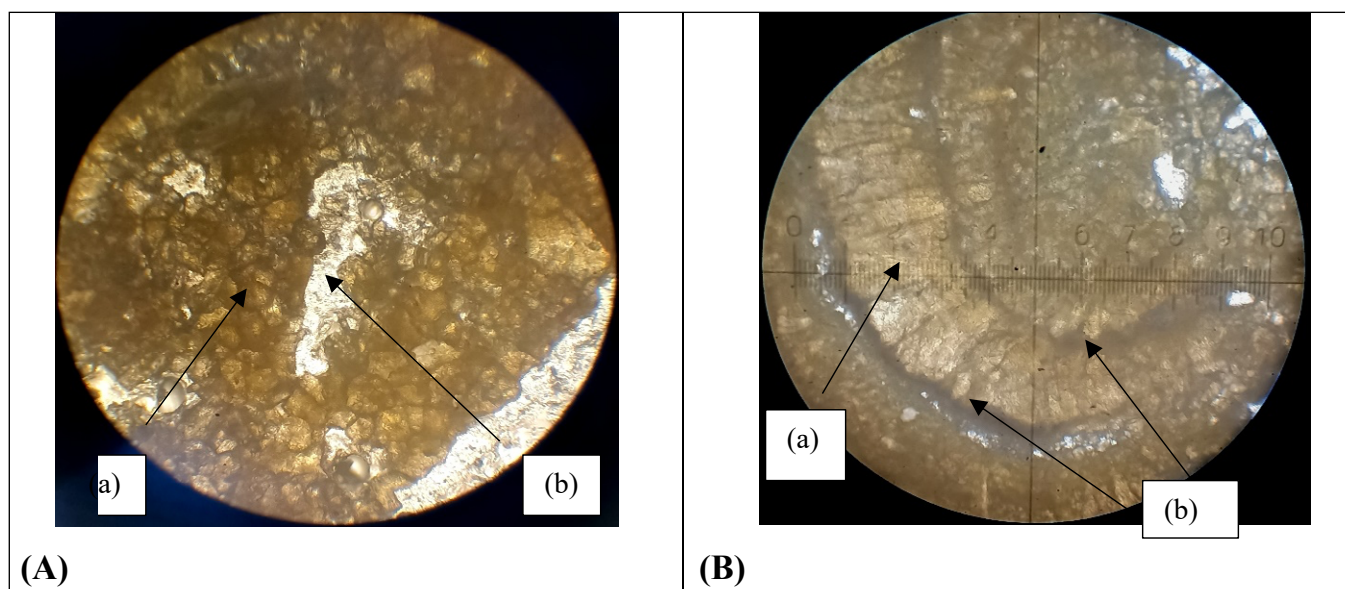


Fig. 3. Microscopic appearance of urates: (A) Central part of the urate structure. Area with polygonal microblock crystals of uric acid monohydrate (a). Formation of colophane (b). Simple transmitted light. Magnification: (x115). (B) Peripheral part of the urate structure. (a)- structure of a concentric-zonal spherulite predominantly composed of urate. (b)- organic matter inclusions. Simple transmitted light. Magnification: (x110).

enriched with organic matter (Fig. 4D). The organic matter was primarily concentrated in separate layers along the perimeter of the stone, less frequently in the form of thin films ("organic shell") on the surface of crystals and their microblocks, as well as in numerous fine-dispersed inclusions within the microblocks of individual crystals.

DISCUSSION

The analysis of stones is an important part of the clinical characterization of urolithiasis. In our study of the qualitative and microstructural composition of kidney stones in residents of heavily industrialized region in Ukraine, we utilized petrographic analysis using a microscopic method and X-ray structural analysis of fragments and dust residues from stones that formed during the manufacturing of thin sections. These methods are widely used worldwide and are continuously being improved and modified.

Indeed, the widespread use of physical methods, such as X-ray diffraction and Fourier-transform infrared spectroscopy (FTIR), has significantly improved the analysis of urinary stones, allowing for precise determination of the chemical nature, crystalline phases, and relative proportions of stone components. However, for common calcium nephrolithiasis, which represents the majority of urinary stones worldwide, simple identification of calcium oxalate (CaOx) and/or calcium phosphate (CaP) as constituents provides incomplete etiological information since stones with the same elemental composition can result from different lithogenic processes [14]. Summarizing the data from microscopic analysis of urolith structure, it can be asserted that their structure

is heterogeneous. This is evident in the fact that urinary stones primarily have a layered structure with varying strength coefficients. The inclusion of an organic component reduces the strength of the crystalline layers. Urolith resembles a brittle-hollow environment, which in certain cases allows for the selection of the most effective methods of their destruction (lithotripsy). However, these data on urolith strength are necessary at the stage of disease diagnosis and determination of strength characteristics before selecting an appropriate method of destruction.

The authors proposed in that Micro-CT has proven to be a powerful modern tool for visualizing urinary stones. The X-ray attenuation values of common stone minerals allow for easy visualization of the stone's structure and identification of minerals, especially when a standard attenuation profile is added to the sample. However, Micro-CT alone cannot identify many rare types of stones, which still require spectroscopic analysis. The 3D visualization capabilities of Micro-CT enable the understanding of the structure of newly formed stones, making this method highly valuable for studying the pathophysiological mechanisms of urolithiasis [8].

The accumulated worldwide experience in studying the treatment and prevention of recurrent urinary stone disease not only highlights its prevalence and continuous increase in many countries but also reveals certain peculiarities in the ontogenesis of stone formation depending on local and general factors in specific regions.

Based on the information from cited literature sources [9-12], a comparative analysis of the composition of

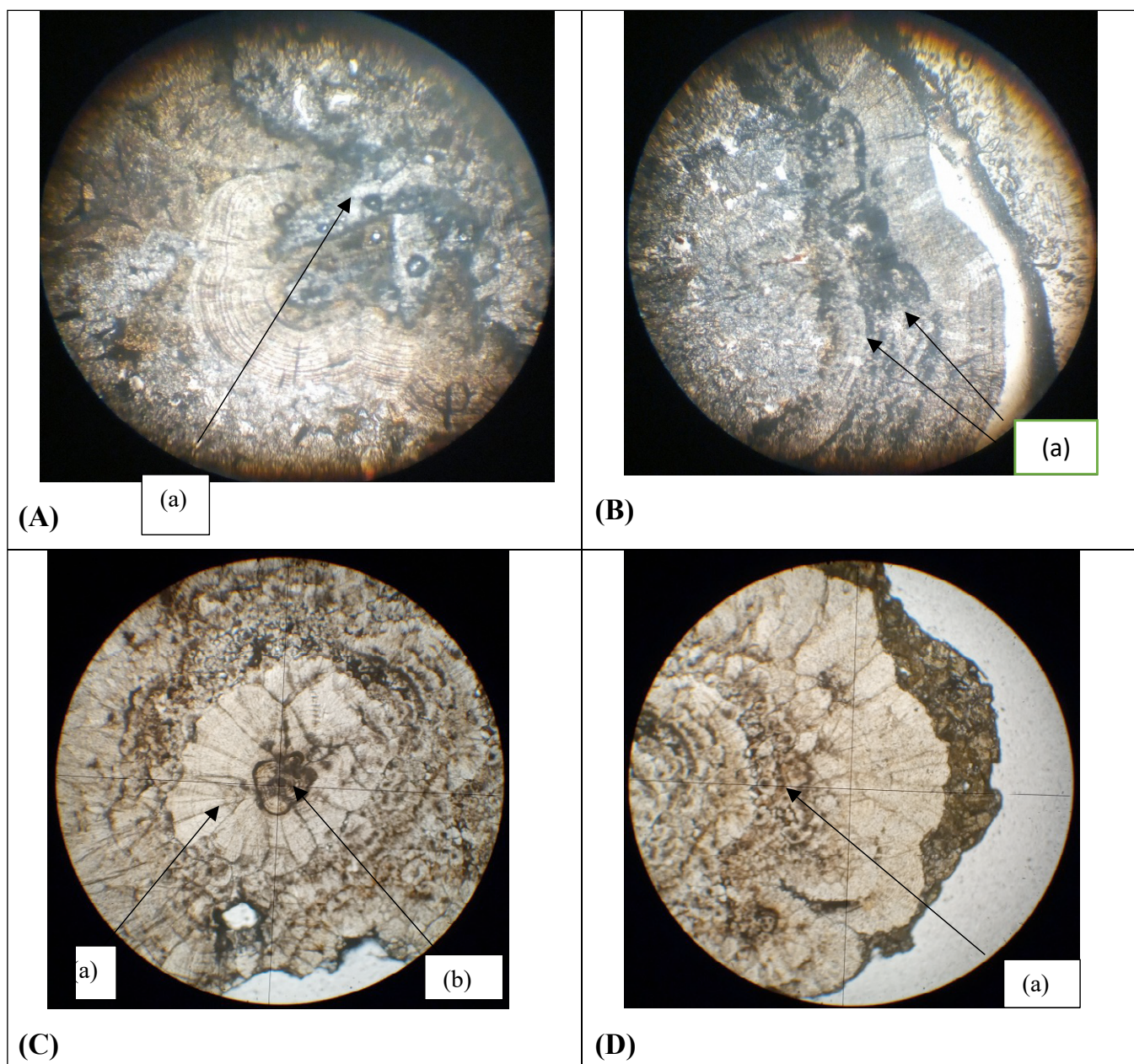


Fig. 4. Microscopic appearance of oxalate: (A) Central part of the oxalate structure. At the crossroads of the threads, there is a vertex of a large weddellite crystal (a). Simple transmitted light. Magnification (x80). (B) Peripheral part of the specimen. Organic matter and the presence of its vein-like form of deposition (a). Simple transmitted light. Magnification (x90). (C) Central part of the oxalate structure. The first generation is represented by a concentric zonal aggregate of bud-like weddellite (a) formed around the "organic core" fragment (b). Simple transmitted light. Magnification (x110). (D) Peripheral part of the oxalate. Boundaries between the 5th, 4th, and 3rd generations of stone formation(a). Simple transmitted light. Magnification (x110).

kidney stones in residents of countries with specific endemic regions afflicted by urinary stone disease has been conducted.

Based on the analysis of the characteristics of urinary stone disease, countries with endemic urinary stone disease have been identified, particularly those located in arid regions with high-temperature climates [13]. In these environments, among various epidemiological factors contributing to stone formation, the factor of high ambient temperature has the most significant impact on the functional status of the kidneys. In the com-

position of kidney stones of residents in these regions, a relatively high level of monocrystalline components is often observed. Moreover, there are significant differences in the frequency of infectious stones depending on the continent and region, ranging from 2.7% in Asia to 13% in South America and 42.9% in sub-Saharan Africa. These differences reflect the infectious risk factors specific to certain population groups, such as dietary habits and the availability of modern medications and antibiotics in each specific locality. Under such conditions, the persistent reduction in renal blood flow leads

to a high concentration of primary urine and constant slowing down of reabsorption processes in the renal tubules. This is evidenced by the relatively high percentage of monomineralic stones and struvite stones.

In industrially developed regions, kidney stones in patients with urinary stone disease predominantly have a mixed composition. However, variations in their composition are minimal and show little difference from one another. In industrially developed countries, there has been a decrease in the number of infectious stones over the course of several decades, but there has also been a continuous increase in the proportion of stones associated with infection [13]. Such significant growth can be attributed to various factors, including the evolution of antibiotic-resistant bacteria and changes in the renal status, the development of secondary nephropathies under the influence of harmful regional factors [2, 3]. Furthermore, the differences in the structure of urinary stones are influenced by various local factors, which may be related to the nature of industrial production, environmental conditions, climatic elements, and more.

The research conducted on kidney stones in residents of our industrial region who suffer from urinary stone disease has shown that they also predominantly have a mixed composition, which depends on various local causative factors. Monocrystalline components of the urinary stones make up less than 1%. However, the presence of a common set of components does not significantly distinguish their composition from the stones in residents of other industrial regions [6].

The multifactorial nature of the influence is reflected in the character of urolithiasis. In the formation of urinary stones, not only thermodynamic but also kinetic factors play an important role [9]. This significantly complicates the physico-chemical analysis of potential crystallization phenomena and necessitates a comprehensive consideration of factors such as the degree of solution saturation, the presence of inhibitors that hinder the formation of microcrystals and their aggregation, the nature of the organic matrix, epitaxial phenomena, as well as the conditions under which nucleation and growth of the urolith occurred [6].

In the studied kidney uroliths, we also examined distinct zones of formation and growth, ranging from 3 to 5 zones, separated by layers of organic matter.

These zones not only differed in their microstructure but also in their chemical composition within the layers. Studying the zonal generation of urinary stones allows us not only to make assumptions that they result from fluctuations in the acid-base balance in the human body but also, through further investigation, to determine the causative factors in urolithic ontogenesis.

Therefore, the obtained information can potentially help in reconstructing the conditions of their nucleation and growth based on their external form and internal structure of minerals and mineral aggregates. Understanding the unique characteristics of the composition of urinary stones in residents of industrially developed regions who suffer from urinary stone disease may contribute to uncovering the underlying causes of their ontogenesis.

CONCLUSIONS

The composition of kidney stones, as determined by optical petrography methods, reveals the presence of 15 mineral species, with oxalate and urate compounds being predominant. A common feature among all mineral components is their diverse microblock structure and the presence of organic inclusions, which diversify the strength characteristics of uroliths. The prior determination of these characteristics allows for the selection of the most effective method for destructive treatment (lithotripsy).

Based on morphological characteristics, five types of uroliths have been identified. The study of the morphological construction of uroliths allows the identification of five zones corresponding to gradually changing stages according to the conditions of mineral formation. These zones are separated by layered accumulation of organic inclusions.

Combining morphological analysis of samples with petrographic research confidently establishes the fundamental patterns of their ontogenesis. This approach also helps determine appropriate and definitive decisions regarding the choice of methods and strategies for preventing this disorder and for the prophylaxis of stone recurrence. The combination of data on the ontogenesis of uroliths, their mineral composition, and the electrolyte balance in the body of a patient suffering from urolithiasis will allow for the selection of an individually effective method of disease prophylaxis.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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