Inflammatory damage during both shock wave and intracorporeal laser lithotripsy.

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Abstract

Nephrolithiasis is a condition that in most cases requires the use of either shock wave lithotripsy or intracorporeal laser lithotripsy. Although both treatments are considered to be non-invasive, or minimally invasive, respectively, some reports have shown that they produce mechanical and/or thermal damage to the renal tissues, and at least the shock wave lithotripsy is also involved in the induction of ischemia-reperfusion at the kidneys. As such, a predominantly innate immune response arises where monocytes/macrophages, natural killer cells and neutrophils are involved in the amplification of kidney damage, whereas M2 macrophages and T-regulatory cells are involved in the mitigation of such inflammation-dependent damage. In this way, the modulation of inflammation during the therapeutic process may be an adequate target to limit lithotripsy-induced kidney injury. However, much specific research is needed in order to propose a pharmacological strategy for this.

Highlights

The safety of a widely-used therapy is discussed.

Shock wave lithotripsy produces mechanical damage.

Intracorporeal laser lithotripsy produces thermal damage.

Keywords

Lithotripsy

Shock wave

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1. Introduction

Acute kidney injury (AKI) is a syndrome characterized by a rapid (hours to days) decrease in renal excretory function, which causes the accumulation of many nitrogen metabolism-derived products, among of which creatinine and urea stand out because they are clinically measured. Other traits that strongly associate with AKI are a decreased urine output, accumulation of metabolic acids, and increased potassium and phosphate concentrations ¹; nonetheless, the extent of such variations has a wide margin. Such principles have led the Acute Dialysis Quality Initiative to propose a definition/classification for AKI that is called RIFLE, an acronym for risk, injury, failure, loss of function and end-stage criteria ², where the elevation of serum creatinine concentration and the decrease in glomerular filtration rate (GFR) are measured to determine if a patient is at risk of AKI, has an episode of AKI, and the extent of damage induced by it. AKI is typically thought to be produced as a consequence to nephrotoxicity, ischemia, mechanical stress that leads to tissue injury, sepsis and acute decompensation of heart failure ^{1,3-5}. And interestingly, all of these conditions involve some degree of local kidney inflammation, as thoroughly discussed in ^{4,6}.

Furthermore, chronic kidney disease (CKD) is defined as a massive loss of GFR and/or the presence of kidney damage, measured as pathological changes documented on imaging or biopsy and proteinuria ⁷. By itself, CKD represents a serious condition that may impact negatively on the function of many organs, but it may also progress to end-stage renal disease (ESRD). CKD is thought to be a consequence of prolonged and severe AKI, especially when it goes without treatment ⁸, which is frequent as there is a vast unawareness among patients with CKD markers about their kidneys' health ^{9,10}. Moreover, health practitioners may also be unaware of some of the etiological entities that may induce a certain degree of AKI that could progress to CKD, as both conditions are vastly understudied and thus, not entirely understood. This phenomenon, in part, is due to the lack of animal models that are truly representative of the human pathology, but also because its study in humans depends upon biopsies taken from cadavers, that already have suffered a death-derived ischemia ^{4,6}.

On the other hand, nephrolithiasis (kidney stones) is one of the most common nephrological pathologies ¹¹, and it has a high worldwide prevalence, with rates ranging from 7 to 13% in North America, 5–9% in Europe, and 1–5% in Asia ¹². It is a complex disease where many epigenetic/environmental triggers such as climate, diet, fluid intake and occupation have been described, but also genetics, gender, and age appear to play a role in the disease ¹³. Kidney stones are already perceived as a highly unpleasant nuisance by patients and doctors alike, but the general concern regarding its long term consequences has recently increased ¹⁴⁻¹⁶, as it has been pinpointed as a cause of AKI, CKD and ESRD ¹⁷⁻¹⁹, both of which could be prevented by means of appropriate treatment and follow up ²⁰.

One of the most common treatments for such a condition is lithotripsy, where there are two main approaches: the shock wave lithotripsy (SWL), which comminutes stones by acoustic waves, and the intracorporeal laser lithotripsy (ILL), that destroys stones by light waves. Strikingly, SWL has been shown, both in animal models ²¹⁻²³ and human studies ²⁴⁻²⁷ to produce renal inflammation and thus AKI. Additionally, recent research in animal models have shown that AKI occurs also by laser lithotripsy ^{28,29}. Nonetheless, the modifications to the conventional SWL protocol that have to be made in order to control inflammation do not allow for a full spectrum of stone comminution, so that standard SWL has been slowly but steadily been replaced by ILL, which has the potential to induce thermal damage to the kidneys, and thus induce a different kind of inflammation ²⁸, although research regarding this topic has been neglected.

In such an understanding, we think that it may be important to review the current knowledge in the field of lithotripsy with aims to understand the inflammatory process behind such a therapeutic approach, as it may serve the purpose of enhancing awareness about its potential to produce AKI and CKD, but it may also be of use to pinpoint the need to investigate new combinatorial therapeutic approaches that may limit inflammatory damage by this necessary, and currently irreplaceable, therapy.

2. Urolithiasis: types and clinical management

Urinary tract stones exhibit great variations in their physical, chemical, anatomical and pathogenical conditions, thus requiring different therapeutic approaches ^{30,31}. Urinary stones can be classified according to the following aspects: chemical composition, size, and location; although the etiology of stone formation must also be taken into account ³².

2.1 STONE LOCATION

Urinary stones are primarily classified by their localization within the urinary tract. When they are located in the kidney, the pathology is called nephrolithiasis, in the ureter is called ureterolithiasis or in the bladder, cystolithiasis. Within the kidneys the stones can be located in the renal papillae, upper calyx, middle calyx or lower calyx, as well as in the renal pelvis ³³. They form over long periods of time, by a slow process of mineral aggregation, and can stay adhered in such locations, or suddenly detach to travel through the ureters and out of the body with the urine. But any kidney stone is also prone to get stuck in the urinary tract and block urine deposition. It is thought that a patient might remain unaware of kidney stones until stone detachment and further movement within the urinary tract, which causes tissue damage and pain.

2.2 STONE SIZE

Kidney stones can be as small as a grain of sand or as large as a pearl, ranging from 1 mm to ≥ 20 mm ³³. Stone size is usually given in one or two dimensions, and stratified into those measuring up to 5, 5-10, 10-20, and > 20 mm in their largest diameter ³⁴. Small stones are treated with a conservative management (hydration, analgesics, prophylactic antibiotics, and α -blockers to favor stone expulsion), but stones above 5 mm in size are less likely to pass spontaneously and patients should be remitted to other treatment options, such as percutaneous nephrolithotomy, or most commonly, some kind of lithotripsy ^{35,36}.

2.3 STONES CLASSIFIED BY ETIOLOGY

The stones are classified by etiology in non-infection related, infection related and genetic related causes.

2.3.1 NON-INFECTION RELATED STONES

This group has an intimate relationship with the gradual accumulation and concretion of the minerals in the urine until a stone is formed, within the main types of such calculi are those made of calcium oxalate, calcium phosphate and uric acid. This group has no direct relationship with infections. If these type of stones are not completely removed, they will keep growing by the addition of new crystals ^{37,38}.

2.3.2 INFECTION-RELATED STONES

This type of stones are formed when a persistent pyelonephritis exists, in which urease-producing bacteria like *Proteus mirabilis*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Enterobacter spp.* that enzymatically transform urea to ammonia, which has a tendency to aggregate within the kidneys to form stones ³⁹.

2.3.3 GENETIC-RELATED STONES

Cystine stones are very rare, as they are the product of a defective transport of such amino acid dimer in the renal tubules that occur due to mutations in the SLC3A1 and SLC7A9 genes, which code for the subunits of the rBAT/b amino acid transporter. As such, cystinuria causes cystine to accumulate in the kidneys and form a stone ⁴⁰.

2.4 STONE COMPOSITION

One of the most important classification of stones is made according to their chemical composition, so that they are named after its predominant mineral contents. The most common stones, in order, are calcium-based stones, struvite, uric acid and cysteine ⁴¹. Chemical composition is strongly linked with size, shape and density, so that it is a primal determining factor on the clinical management of the case.

2.4.1 CALCIUM STONES

With a prevalence of 75–80% these are the most common type of kidney stones³¹. Calcium calculi are usually conjugated with oxalate (a natural chemical found in most foods), phosphate or both (4–5). Calcium oxalate (CaOx) stones account for 50% of calcium stones, but calcium can also be conjugated with phosphate (CaP, termed as apatite) (5%), or a mixture of both (45%)⁴². CaOx is called brushite when it is hydrated, or less frequently hydroxyapatite, when it is hydroxylated⁴³. Many factors contribute to CaOx stone formation such as hypercalciuria, hypercystinuria, hyperuricosuria, hypomagnesuria, hypocitraturia, and hyperoxaluria⁴⁴. Also a urine pH of 5.0 to 6.5 promotes CaOx stone formation, but CaP stones occur when pH is greater than 7.5³¹.

2.4.2 STRUVITE STONES

The struvite stones, also called triple phosphate stones, are composed by magnesium, ammonium and phosphate, and they have a prevalence of 15%⁴⁵. These stone's etiology is associated with different types of urinary tract infections, in which bacteria make ammonia through urea cleavage. The pathogens that most commonly associate with this type of lithiasis include *Proteus mirabilis*, *Klebsiella pneumonia*, *Pseudomonas aeruginosa*, and *Enterobacter spp*³⁰. Struvite stone formation is dependent upon bacterial urease activity, which is necessary to cleave urea to ammonia and CO₂, making urine more alkaline, so phosphate precipitates onto the insoluble ammonium products, aggregating to form large stag-horn-like stones⁴⁵, which is mostly impossible to extract without a previous lithotripsy treatment.

2.4.3 URIC ACID STONES

These type of stones have a prevalence of 6–10%³¹, and they are often formed when the urine is too acidic. Uric acid can form stones by itself or in combination with calcium. These are characteristically seen in patients with hyperuricemia induced by diets that are high in purines, or in animal proteins, such as meat and fish, which results in hyperuricosuria and low urinary pH (pH < 5.05), both characteristics that exacerbate uric acid crystal aggregation, and thus stone formation⁴⁶.

2.4.4 CYSTINE STONES

These are made of cystine, a chemical that the body makes naturally, and are very rare as they have a 1% prevalence. Cystine stones tend to happen in patients who have a defective cystine transporter in the proximal tubule, leading to a decreased reabsorption of such aminoacid dimer^{31,47}.

As made obvious in this section, nephrolithiasis is not a single disease, but a group of diseases. This compels nephrologists and urologists to adapt their therapeutic strategies in order to provide the best solution for each case.

After emergency situations have been ruled out and adequate analgesia has been achieved, the next step is to formulate a strategy for managing the stone. There

are three major prognostic factors that aid in such decisions: stone size, density and location.

2.4.5 THERAPEUTIC APPROACH

Stones with less than 5 mm have >90% of opportunities to be eliminated through urination. In fact, for stones less than 4 mm in size generally pass within one to two weeks ⁴⁸, while 80 % percent of this patients require no intervention beyond analgesia ⁴⁹, or even β -blockers to help in smooth muscle relaxation and stone expulsion. On the other hand, uric acid calculi can sometimes be dissolved by prolonged (4 to 6 months) alkalization of the urine by potassium citrate oral intake ⁵⁰, however this treatment is not effective for other types of stones. Moreover, for stones with a diameter ≥ 2 cm, an irregular shape ⁵¹, or that could not be comminuted by SWL ⁵², the preferred choice is the percutaneous nephrolithotomy which consists on opening a small incision on the infracostal fraction of the back to insert a nephroscope, which is a small catheter with a camera and tools to remove the stones ⁵³.

If a stone is more than 5mm in its biggest diameter, but does not reach 2 cm in size, and it has a chemical composition different from uric acid, then the preferred therapy is lithotripsy, which will be discussed in the section below.

Either way, pain management is usually achieved by the use of opioids such as morphine and fentanyl or non steroideal antinflammatory drugs like Ketorolac. Also, persistent vomiting due to nausea and excruciating pain, if it happens, can be treated with an antiemetic ^{54,55}. However, no other drugs have been tried during the process, and to no other purpose than pain and vomiting control medication has been employed.

As such, it is evident that the divergences between the different types of stones compel the clinical practitioners to treat each type of nephrolithiasis differently, but it is also evident that in most cases some type of lithotripsy can be considered the treatment of choice (3). Accordingly, it is important to discuss the pathophysiological changes that arise as a consequence of such treatment, to include the vastly neglected inflammatory damage that derives from such procedure.

3. Lithotripsy: different types of therapy and different types of damage

As a consequence to the aforementioned diversity in renal calculi, lithotripsy (which is considered as the main therapeutic strategy to break them) has been diversified into, mainly, two types: the extracorporeal SWL (ESWL), which uses particular kinds of high energy acoustic waves to break the stones, and the flexible ureteroscopy and laser lithotripsy (FURSL) or ILL, which uses infrared-spectrum light to comminute the calculi.

3.1 SHOCK WAVE LITHOTRIPSY: USES AND RISKS

Shock waves (SW) are defined as a sequence of single sonic pulses with a high peak pressure (in the range of 10 to almost 100 MPa) and a fast rise pressure (≈ 10 ns), with a duration of around 1 second. An advantage of SW is that they can be focused at specific regions from the outside of the body, so that they can be used extracorporeally ⁵⁶. In this way, ESWL is a non-invasive method that is able to comminute calculi through sonic vibrations ⁵⁷.

Although ESWL has been the standard treatment for most nephrolithiasis cases since its introduction in the 80's, there has been much debate regarding the types of physical properties the SW must have to properly comminute stones, and avoid complications at the same time. Moreover, although ESWL is considered as a non-invasive method, it has been associated with side effects and complications, where the main mechanisms for damage induction are mechanical injury to parenchymal cell membranes ⁵⁸ and renal vascular damage, which relates to the induction of ischemia, which produces further necrosis of the kidney's parenchyma ⁵⁹. A clinical sign of kidney trauma is haematuria, and the collection of perirenal, subcapsular, or intrarenal fluid ⁶⁰, and enhanced levels of serum creatinine ⁶¹. Such vascular injury is associated with a transient decrease in renal blood flow and glomerular filtration rate in the treated kidney, as well as some acute changes including enlargement of the treated kidney, loss of corticomedullary demarcation, and low-intensity perinephric fat changes in 63% to 85% of the patients ⁶². Some other side effects that ESWL had are pain in the costovertebral angle, petechiae at the entry and exit point of the shock waves, microscopic or gross hematuria, fever, nausea with vomiting and acute urinary retention ⁶³.

In such debate, many types of SW have been explored, in order to find the best results at stone destruction, while producing the least amount of AKI. For instance, it has been described that high SW energy levels are able to destroy almost every other type of calculi, but studies show that better results arise when a low energy (13–14 kV) is used at first but it gradually increases in intensity ⁶⁴. In contrast, some researchers have shown that lower frequencies (60 Hz) perform better than higher (120 Hz) ⁶⁵ at stone comminution. Such data is supported by a clinical study performed by Chacko *et al.* ⁶⁶ which included 349 patients with renal and proximal ureteric stones of 1–2 cm and showed that 70–80 shocks/minute had better results in comparison with 120 shocks/minute.

On the other hand, many studies about kidney injury have shown that the extent of damage is related to the number of shocks, level of energy delivered and the focal size of the shock wave, as thoroughly reviewed in ⁶⁷. As such, treatments using 2000–3000 SW and 16–24 kV have been described to produce the most damage to both the renal parenchyma and the renal blood vessels, whereas treatments with 100–500 SW and a maximum of 12 kV have been described to produce the least amount of it ^{21,23,68}. In contrast, Mustafa and colleagues showed that the treatment with an electrohydraulic lithotripter that started with an energy level of 12 kV and gradually increased to 19 kV produced less damage than an electromagnetic lithotripter that used an energy level in the range of 1 to 7 kV, while both lithotripters used a rate of SW delivery of 60 SW/min. AKI was demonstrated by three urine cytological examinations, one made pre-SWL treatment, another im-

mediately post-SWL and the last one 10 days after SWL, where they found a significant increase in the number of red blood cells and epithelial cells of the post-SWL cytological examination from the electromagnetic lithotripsy-treated group⁵⁸.

Taken together these data show that despite its no-invasiveness, SWL is able to induce AKI. Although some research has been done with aims to optimize stone comminution and reduce SWL-induced damage, there is not an entirely clear panorama about the best way to perform such therapy. One option has been to adapt the kind of lithotripsy to the stone's characteristics, for example, as higher density calculi require a greater level of SW-energy, which induces an enhanced damage, this type of stones is preferably treated with ILL⁶⁹.

3.2 INTRACORPOREAL LASER LITHOTRIPSY: USES AND RISKS

Despite the success that ESWL has had in the management of urolithiasis, ILL has been proposed as a more modern and safer alternative. In this way, it is also important to review the current data about its safety, especially as some recent data indicates that ILL is not entirely harmless.

In ILL, laser activation causes the release of energy from the fiber-tip, which creates a vapor channel, allowing direct absorbance of radiation by the stone, which leads to a photothermal reaction that causes chemical decomposition of the calculus. All this effects depend on the total power (Watts) delivered to the stone, and this power is the product of the pulse energy and frequency⁷⁰. Next-generation holmium lasers can be adjusted in pulse energy (Joules), frequency (Hertz) and pulse duration (microseconds), because in that way stone fragmentation can be enhanced, while calculi retropulsion can be avoided, and laser fiber-tip degradation can be delayed⁷¹. The retropulsion is a shortcoming of ILL that occurs while the procedure is being carried out, in which the fluid surrounding the calculi evaporates and expands, creating a vapor bubble, and its collapse leads the stone to move away from the laser tip⁷², which decreases fragmentation efficiency may produce mechanical damage as the moving stone scratches the internals of the kidney.

Although the optical energy emitted from the laser fiber-tip or pulse energy (PE) can vary from 0.2 to 6.0 J, the users commonly occupy the range between 0.2-2 J. The final choice of PE-intensity is dependent upon the hardness and density of the calculi, i.e. higher PE such as 1.0 J is ideal for comminuting harder and denser stones (such as those made of calcium), but this method has to be followed by active basket retrieval, because it produces bigger stone fragments, in a process called "pop-dusting", and such fragments may not be eliminated spontaneously, allowing for calculi re-concretion. On the other hand, when a calculi is softer and less dense, a "dusting" technique to create very small sub-millimetric fragments that are candidate to spontaneous passage is used by turning the lithotripter to a lower PE, such as 0.2 J^{72,73}.

Moreover, frequency is the number of optical pulses emitted in one second, a range of 15 to 80 Hz is commonly the first choice. On the other hand, the duration

of time in which a single optical pulse is emitted is called pulse duration, and it is divided into two types: short pulses that varies from 150 to 350 μ s, and long pulses which can last up to 1,200 μ s. The main advantage of using long pulse is that this decreases retropulsion distances. In this way, shorter pulses are preferred in order to avoid stone-retropulsion mediated mechanical damage, while a more intense PE is the optimal choice when the stones are harder. Because of its higher effectivity at comminuting harder stones, the offered possibility of adapting its parameters to act better against certain types of stones and the idea that it is safer than SWL, ILL has become the treatment of choice in the recent years⁷⁴. However, recent data indicates that no differences between SWL and ILL exist regarding damage production²⁸. In such an understanding, we think that it may be important to analyze this topic.

Laser lithotripsy induces stone fragmentation through the direct absorption of energy by the calculus. In this way, laser energy is transmitted to the stone surface by means of radiating energy transfer, and an accompanying vapor bubble that is created at the fiber tip during activation of the laser. Additionally, the collapse of the vapor bubble may also produce a weak acoustic effect⁷⁵. Lower pulse energy settings result in smaller stone fragments and less retropulsion. As the pulse energy is increased, fragment size increases, as does the degree of retropulsion⁷⁶. But, additionally, recent *in vitro* studies where heat generation was measured in relation to differences in laser pulse length and pulse type showed that long pulses, and greater power produced significantly higher maximum temperatures^{77,78}. Furthermore, a recent study by Aldoukhi, *et al.*²⁹ showed that in a high power setting, the increase in the temperature of the calyx fluid is enough to induce a considerable heat-derived damage to the kidneys, while hematomas were also produced. The effects of increased irrigation on temperature were also investigated, finding that an *in situ* irrigation rate of 40 ml/min was enough to mitigate such thermal damage. Despite this, the kidneys face a great internal pressure under the aforementioned irrigation conditions, which may still cause enough vascular damage to develop renal hematomas⁷⁹⁻⁸¹.

These data taken together make apparent that both types of lithotripsy are linked to some degree of AKI. Although these arguments do not pretend to discard such a good and non-invasive therapeutic option, we think that more research is needed in order to develop strategies that limit the lithotripsy-associated damage. As such, the first step that becomes necessary is to understand the inflammatory responses that are triggered by lithotripsy, in order to pinpoint the pathophysiological mechanisms that may be blocked to limit damage.

4. Immunopathology in lithotripsy

AKI, has been described as a rapid decrease in kidney function as measured by increases in serum creatinine, a process that can manifest from a few hours to less than 3 months after damage induction⁸². AKI involves hemodynamic alterations, and endothelial/epithelial cell injury, which causes inflammation to further

potentiate damage. What strikes as interesting is the fact that during lithotripsy, tissue damage occurs mainly in two ways: i) due to direct mechanical injury to the renal parenchyma, and ii) due to ischemia ⁸³. In SWL mechanical injury is mainly caused by the increased movement and vibration of the stones, whereas in ILL it appears to be caused by a thermal increase. Either way, the innate and adaptive immune responses induced during lithotripsy have been linked to enhanced AKI, which could derive in CKD. Nonetheless, we lack data regarding the long term effects of both types of lithotripsy.

4.1 SHOCK WAVE LITHOTRIPSY AND MECHANICAL-DAMAGE INDUCED INFLAMMATION

As SWL is an acoustic technique that comminutes stones by causing vibrations, it has been described that these move within the kidney, retrotracting away from the focal point. In this way, it has been recommended to point at the renal calyx, or to use additional devices to contain stone movement ^{84,85}. Nonetheless, such migration may produce mechanical damage to the internal zone of the kidneys. To our knowledge, there are no data regarding the possibility of shock waves directly damaging the renal tissue, but such pathophysiological mechanism should not be ruled out as tissue damage by lithotripsy has been detected not only in the surroundings of the calculi, but also deep into the renal medulla and cortex. Either way, acute tissue damage has been detected to induce a local innate immune response, which elevates the expression of tissue damage, oxidative stress and inflammation markers.

For instance, recent research by Chung *et al* ²¹ shows that rat kidney tissue had enhanced levels of inflammatory markers like intracellular adhesion molecule-1 (ICAM-1), heat shock protein-70 (HSP-70), macrophage chemotactic protein (MCP-1) and tumor necrosis factor- α (TNF- α), when treated with SWL. The levels of such markers increased when the rats were treated for more than one time, suggesting that repeated therapies may enhance the inflammatory response to SWL. Moreover, it has been described that SWL-treated pigs have an enhanced TNF- α and IL-6 excretion in urine ²² as well as increased expression of oxidative stress-derived markers ⁸⁶. Importantly, although the treatment with low power SWs was shown to completely dampen TNF- α urination, tissue levels of IL-6 and hemoxygenase-1 (HO-1) (a marker of oxidative stress) were not entirely abrogated ⁶⁸. Interestingly, nitric oxide (NO) production has been linked as the main immunopathogenic mechanism of damage induction by SWL, as the inhibition of NF- κ B (and therefore NO) by the pretreatment with curcumin has shown a significant reduction in glomerular and tubular damage ⁸⁷ (Fig. 1).

Such observations on animal models are paralleled by clinical studies (reviewed in ²⁴) where a correlation between SWL and the elevation of inflammatory cytokines like IL-6 ^{88,89} and IL-1 α ⁸⁸ has been detected. We lack data to confirm the participation of such inflammatory markers in the induction of further inflammation-derived damage in human patients, but using the data available from animal models it can be inferred that the innate immune response and the production of high levels of NO may be among the most important factors associated to the process (Fig. 1).

4.2 SHOCK WAVE LITHOTRIPSY AND ISCHEMIA-REPERFUSION MEDIATED INFLAMMATION

Both the endothelium and small arterioles have been documented to suffer damage by SWL application. As a consequence of the local vascular compromise increased levels of the vasoconstrictors endothelin-1, angiotensin II, thromboxane A2, leukotrienes C4 and D4 are produced ⁹⁰, as well as many necrotic debris. This impacts producing a considerable reduction in blood flow to the outer medulla, thus affecting kidney perfusion ⁹¹. Such process is thought to enhance cell necrosis by hypoxia induction, thus amplifying tissue damage, and potentiating inflammation. As a consequence, an increased expression of cell adhesion molecules such as ICAM-1 ⁹² and of proinflammatory cytokines TNF- α , IL-1 β , IL-6, IL-12, IL-15, IL-18, IL-32 have been detected ⁹³. Such cytokines have diverse effects on the activation of both the innate and adaptive immune responses, which include a rise in the expression of Toll-like receptors (TLR) 2 and 4 ⁸³, as well as MHCII ⁹⁴, and the costimulatory molecules CD28, B7-1 and B7-2 ⁹⁵ on the surface of the remaining tubule cells in order to enhance a Th1 adaptive immune response ⁹⁶ (Fig. 1).

Necrosis-derived damage associated molecular patterns (DAMPs) like extracellular ATP and chromatin, along with ICAM-1 expression, platelet activation and IL-1 β production seem to be able to recruit and activate neutrophils, which potentiate tubule necrosis by reactive oxygen species (ROS) and myeloperoxidase deposition, as well as neutrophil extracellular traps (NETs) formation ⁹⁷. Neutrophils have been clearly linked with renal ischemia reperfusion-derived damage, as reduced serum creatinine, urea nitrogen and renal tissue damage have been detected in animal models where neutrophil recruitment is abrogated through the use of antiinflammatory agents, such as celecoxib ⁹⁸ and rutaecarpine ⁹⁹. Additionally, a pharmacologically-induced increase in kidney blood flow with both pentoxifylline ⁹⁸ or clopidogrel ¹⁰⁰ was demonstrated to block neutrophil recruitment, and thus damage. Moreover, when the recruitment of both neutrophils and NK-cells was blocked by osteopontin neutralizing antibodies, reduced levels of blood urea nitrogen and creatinine were detected, suggesting that also NK cells have an important role in the inflammatory pathophysiology of such treatment ¹⁰¹ (Fig.1).

Moreover, macrophage numbers increase in the mouse kidney 1 hour after ischemia-reperfusion, peaking at 24 hours and persisting for 7 days¹⁰² to potentiate damage and inflammation, as they produce ROS, IL-1 β and TNF- α ⁸³. The inhibition of its migration using periodate-oxidized ATP, an antagonist of the P2X7 receptor is able to considerably dampen macrophage-mediated damage¹⁰³. Moreover, Masola and colleagues recently showed¹⁰⁴ a crosstalk between hypoxic tubular cells and macrophages, where the former are able to induce the latter's recruitment and activation into the proinflammatory M1 phenotype, leading them to produce high nitric oxide synthase (iNOS) levels, IL-1 β and TNF- α through the production of heparanase, a hypoxic-related stress protein. When the expression of heparanase was inhibited by a small hairpin RNA, ischemic damage was very limited, suggesting a potentially important role for M1 macrophages and their NO production in the induction of renal damage after reperfusion. Interestingly, a rat model of renal ischemia reperfusion injury showed that the treatment with atorvastatin was able to induce the transition from an inflammatory M1 to an anti-inflammatory M2-type of macrophages, reducing the levels of several AKI markers, TNF- α and IFN- γ ¹⁰⁵.

In this way, both macrophage and neutrophil-derived damage appear to be dependent upon NO production, in such a way that the general inhibition of oxidative stress has been shown to be protective in the setting of renal ischemia-reperfusion¹⁰⁶. Nonetheless, the role of effector T-cell responses is rather unclear. First, both memory and effector T-cytotoxic and T-helper cells, as well as B-cells have been described to rapidly recruit after ischemia reperfusion, remaining in the reperfused kidney for at least 6–8 weeks. Moreover, the depletion of the whole CD4⁺ and CD8⁺ T cell fraction before, but not after, ischemia-reperfusion significantly reduced damage to the renal medulla and production of IFN- γ ¹⁰⁷, whereas Th17-differentiation of CD4⁺ T-cells through STAT3 signaling¹⁰⁸ and IL-17 production have been linked to the worsening of renal pathology¹⁰⁹. In this way, the role of adaptive immunity in the potentiation of renal damage seems somewhat clear. Nonetheless, excellent recent investigations about the role of CD4⁺ T-cells in such pathology pose an interesting contradiction to the role for adaptive immunity in the whole phenomenon (Fig. 1).

For instance, Xue *et al.*¹¹⁰ showed that IkB α Δ N-Tg mice, which have a T-cell specific genetic ablation of NF- κ B, have reduced serum creatinine, BUN, and pathologic damage, with a significant downmodulation of both T-cell and neutrophil recruitment after kidney ischemia reperfusion. But, on stark contrast, Guo and colleagues¹¹¹ showed that the T-cell specific knockout of the NF- κ B activating kinases IKK2 or NEMO were related to increased AKI, correlating with enhanced levels of Th17 cells, which presumably activate neutrophils. On the other hand, Yano *et al.*¹¹² showed that IL-18 α -deficient mice had increased levels of BUN, tubular damage, and bigger CD4⁺ T cell, neutrophil, and macrophage infiltration levels, while having an increased mRNA expression of proinflammatory cytokines like IL-1 β , IL-12p40, and IL-18, as well as chemokines like MCP1. These effects were linked to the downmodulation of the apoptosis-promoting FasL protein, suggesting that the Th1 response occurs as a strategy to limit necrosis by promoting apoptosis. Moreover, IL-17-treated mesenchymal stem cells are able to

reduce tubular necrosis, serum creatinine and BUN, also recruiting an enhanced population of Treg cells ¹¹³ (Fig. 1).

As such, we think that the role for both the Th1, and the Th17 cells in renal ischemia reperfusion is not clear, and the only consensus regarding T-cell activity during such pathology is that Treg cells are able to modulate the intensity of the whole pathology, as the depletion of CD4⁺ CD25^{high} CD127^{low} T-regulatory cells by means of α CD25 antibody have demonstrated that such a cellular fraction is involved in damage regulation and improved renal function preservation ^{114,115} (Fig. 1).

Figure 1. Shock wave lithotripsy (SWL) produces inflammation. SWL mechanically damages the renal parenchyma, causing the production of DAMPs and cytokines, while necrotic cells enhance the expression of vasoconstrictor agents and proinflammatory costimulators, thus causing necrosis. DAMPs and cytokines are able to induce macrophage, neutrophil and NK-cells' activation and recruitment, and these enhance SWL-induced damage. CD8⁺ cells appear to potentiate ischemia-reperfusion, while the role of Th1 and Th17 cells is unclear. Both Tregs and M2 macrophages appear to play an important role in the mitigation of the inflammatory response.

5. A putative model for heat-derived inflammation on intracorporeal laser lithotripsy

To our knowledge, there is no data regarding the topic of inflammation produced by heat-derived damage in the kidneys, so that, as for ILL-induced thermal injuries, we can only surmise a general pathophysiological mechanism based on information on other models of heat damage-derived inflammation.

Burnt tissues are not only obviously damaged, but are also prone to be infected, so that the recognition of pathogen-associated molecular patterns (PAMPs) and DAMPs is readily active, thus activating dendritic cells (DCs), monocytes and neutrophils to produce a vast array of both proinflammatory and antiinflammatory cytokines as well as chemokines ¹¹⁶ that orchestrate the recruitment and activation of many leukocytes. Pro-inflammatory cytokines produced by such cells include TNF α , IL-6, IL-12 and IL-1 β , while they also produce the anti-inflammatory cytokines IL-10 and TGF- β ¹¹⁷. Activated DCs, monocytes and macrophages locally process phagocytosed antigens for their display in major histocompatibility (MHC) class II molecules, to activate both an exacerbated Th17 and a late regulatory Th2-immune response ¹¹⁸.

Through the release of IL-17, Th-17 cells induce the recruitment and activation of neutrophils, with aims to control the propagation of microbes and clean necrotic debris as early as 3 hours post-burn ¹¹⁹. In the first week, pro-inflammatory cytokines such as TNF α , IL-6, IL-8, IL-1 β along with anti-inflammatory cytokines such as IL-10 are increased ¹²⁰, nonetheless, a predominant Th2-type arises later, as to orchestrate tissue scarring and healing ¹¹⁸. While this is a good way to restrain damage progression in many tissues, enhanced fibrosis in the kidneys may lead to CKD.

6. Conclusions

Nephrolithiasis is an increasingly common disease that is very diverse in its clinical presentations, which compels the use of different clinical approaches. However, most kidney stones are treated with either SWL or ILL, both being effective and non-invasive therapies. Although these therapeutic approaches are considered to be relatively safe, they are prone to produce mechanical and thermal damage to the renal tissues, as well as ischemia, which further enhances damage through the induction of an interesting inflammatory response.

Much research about the roles of inflammatory mediators in such therapy is needed in order to understand its pathophysiological mechanisms. In that way, a pharmacological approach may be taken to limit the extent of damage induced by lithotripsy, and thus enhance the ability of this therapy to heal nephrolithiasis and avoid AKI. Also, the potential role of lithotripsy in the induction of CKD has

been neglected, in such a way that there are no studies regarding the long-term effects of such therapy, much less, studies that analyze the role of inflammation in the production of such pathology. It is a rather unlikely scenario, but it should not be ruled out, especially considering that very few studies show its implications in CKD production.

As to the question if lithotripsy is a friend or a foe, it is clearly a friend, as it has a proven efficacy in the management of nephrolithiasis. Nonetheless, the oxidative stress that arises as a consequence of such therapy has to be managed, and perhaps an effective way to do it is to control inflammation during the process. In regards to such an inflammatory response, it seems clear the intimate involvement of innate immunity, as neutrophils and macrophages appear to play an important role in damage induction. At the same time, Tregs also seem to play an important role in such cells-derived damage mitigation. These data render macrophages and neutrophils as plausible targets to dampen inflammation, whereas Treg-induction may be a central piece to such strategy.

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8. Conflicts of interest

None of the authors have any conflict of interest to declare.

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