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REVIEW

Low-Intensity Extracorporeal Shockwave Therapy (LI-ESWT) in Renal Diseases: A Review of Animal and Human Studies

Sune Moeller Skov-Jeppesen[1,2], Nicky Anúel Petersen[1], Knud Bonnet Yderstraede[2,3], Boye L Jensen[4], Claus Bistrup[2,5], Lars Lund[1,2]

[1]Department of Urology, Odense University Hospital, Odense, Denmark; [2]Clinical Institute, University of Southern Denmark, Odense, Denmark; [3]Department of Endocrinology, Odense University Hospital, Odense, Denmark; [4]Department of Cardiovascular and Renal Research, Institute of Molecular Medicine, University of Southern Denmark, Odense, Denmark; [5]Department of Nephrology, Odense University Hospital, Odense, Denmark

Correspondence: Sune Moeller Skov-Jeppesen, Department of Urology, Odense University Hospital, Sdr. Boulevard 29, Odense, 5000, Denmark, Tel +45 51210911, Fax +45 65411726, Email sun_mjep@hotmail.com

Background: Low-intensity extracorporeal shockwave therapy (LI-ESWT) has been suggested as a treatment for vascular diseases such as ischemic heart disease, diabetic foot ulcers, and erectile dysfunction. Primarily, LI-ESWT is known for its ability to stimulate angiogenesis and activation of stem cells in target tissues. Application of LI-ESWT in chronic progressive renal diseases is a novel area. The aim of the present review was to summarize available data on the effects of LI-ESWT used in the setting of renal diseases.

Methods: We systematically searched PubMed, Medline, and Embase databases for relevant studies. Our review included the results from preclinical animal experiments and clinical research.

Results: Eleven animal studies and one clinical study were included in the review. In the animal studies, LI-ESWT was used for the treatment of hypertensive nephropathy (n=1), diabetic nephropathy (n=1), or various types of ischemic renal injury (ie, artery occlusion, reperfusion injury) (n=9). The clinical study was conducted in a single-arm cohort as a Phase 1 study with patients having diabetic nephropathy. In animal studies, the application of LI-ESWT was associated with several effects: LI-ESWT led to increased VEGF and endothelial cell proliferation and improved vascularity and perfusion of the kidney tissue. LI-ESWT reduced renal inflammation and fibrosis. LI-ESWT caused only mild side effects in the clinical study, and, similarly, there were no signs of kidney injury after LI-ESWT in the animal studies.

Conclusion: LI-ESWT, as a non-invasive treatment, reduces the pathological manifestations (inflammation, capillary rarefaction, fibrosis, decreased perfusion) associated with certain types of renal disease. The efficacy of renal LI-ESWT needs to be confirmed in randomized clinical trials.

Keywords: review, kidney disease, extracorporeal shockwave therapy, ESWT

Background

Low-intensity extracorporeal shockwave therapy (LI-ESWT) is a novel treatment method suggested to stimulate angiogenesis and tissue regeneration in target organs. LI-ESWT is defined as shockwave therapy applied with energy flux density up to 0.35 mJ/mm^2, which is significantly lower than shockwave lithotripsy (ESWL, typically at energy >0.75 mJ/mm^2). In coronary heart disease and peripheral artery disease, LI-ESWT has been applied to increase perfusion and reduce ischemic symptoms.[1,2] Additionally, LI-ESWT promotes healing of chronic diabetic foot ulcers[3] and may be an effective treatment for patients with vasculogenic type of erectile dysfunction.[4]

Shockwaves constitute a type of acoustic waves characterized by a high, short-lasting peak pressure followed by a mild, tensile phase. In biological tissues, the shockwaves induce shear stress upon cell membranes, cytoskeleton, and extracellular matrix. The effect is mediated through the process of mechanotransduction meaning that the physical pressure stimulus is converted into a biological response via sensory molecules on the cell surface.[5] In the molecular

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scale, vascular endothelial growth factor (VEGF) and nitric oxide (NO) are released from endothelial cells in response to LI-ESWT which in turn increases endothelial cell growth, vascular relaxation, and angiogenesis.[6–8]

Chronic kidney disease (CKD) is characterized by irreversible pathological lesions of the kidney tissue including vascular rarefaction, interstitial fibrosis, and tubular atrophy. In particular, diabetic nephropathy and hypertensive nephropathy are major culprits leading to end-stage kidney disease that is associated with microvascular degeneration and glomerulosclerosis. Other causes that might promote CKD include acute transient renal ischemia, toxic insults/effects, and autoimmune disorders. LI-ESWT could prove as a feasible method to ameliorate the chronic manifestations of renal diseases and preserve kidney function.

The aim of the present systematic review was to assemble current data on LI-ESWT as a potential treatment option for renal diseases. Accordingly, our objective was to systematically collect and summarize existing literature on LI-ESWT treatment for renal diseases. We included both animal and human research data. We excluded studies where shockwave therapy was used in the setting of urological stone disease and cell culture/ex vivo studies.

Methods

We performed a systematic database search for studies on LI-ESWT in combination with renal disease. Both human and animal studies were included. We searched PubMed, Medline, and Embase databases. The following search string was used in PubMed: (shockwave or shockwaves or shock waves or shock wave or ESWT or SWT) and (kidney or kidneys or renal). We used the same terms for search build in the other databases. The databases were searched on August 29, 2022. No restrictions on publication year or language were applied. The search yielded a total of 14,894 articles which was reduced to 7043 different articles after removal of duplicates. Duplicates were identified in EndNote based on similarity between author, title, and year of publication. Finally, the 7043 articles were screened for eligibility by two researchers (S.M.S.J and N.A.P) based on title, abstract, and full-text reading (Flowchart, Figure 1). The two researchers worked

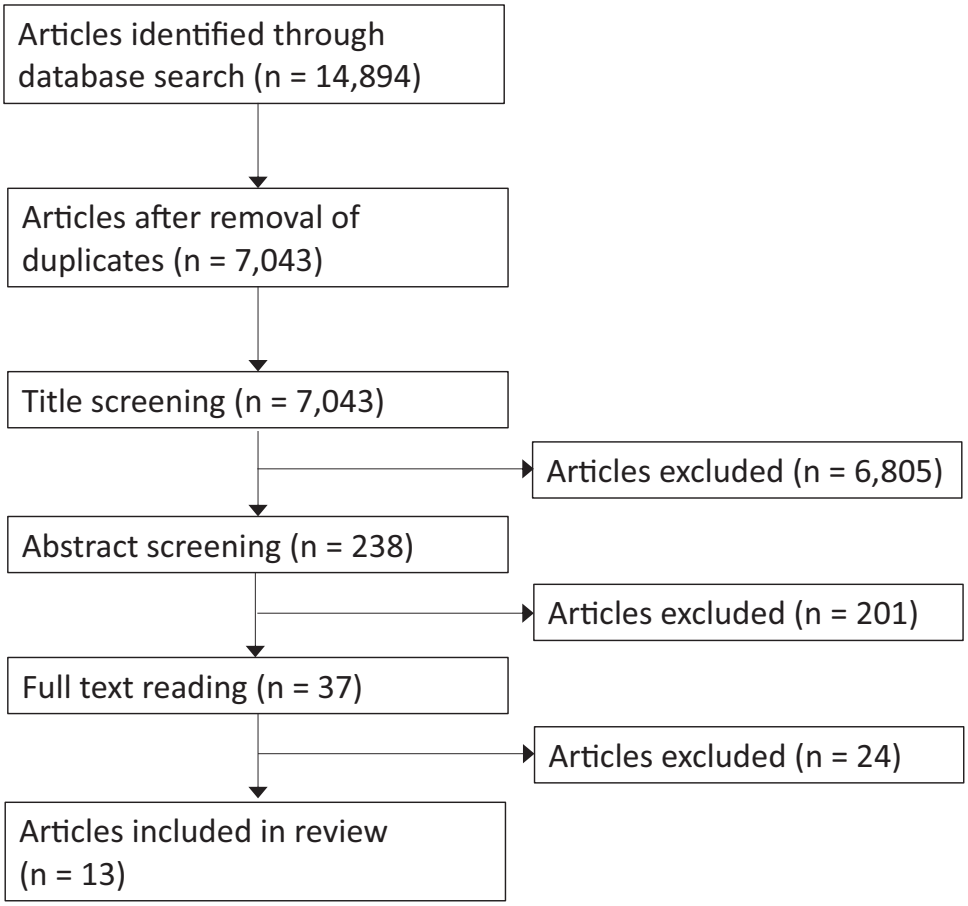

Figure 1 Flowchart.

Box 1 Eligibility Criteria

Inclusion Criteria

- LI-ESWT used as intervention for renal disease
- Human and animal experimental studies

Exclusion criteria

- Lithotripsy/stone disease
- Malignant renal disease
- Shockwave therapy used for ramping or preconditioning in conjunction with lithotripsy
- Study on adverse effects in relation to shock wave lithotripsy
- Non-experimental study (eg, review, editorial, comment, letter).

independently screening the articles before meeting to decide which studies to include in the review. A third researcher (L.L) would take the decision on study eligibility in case of disagreement between the first two researchers. Furthermore, the literature lists of the eligible studies were screened for additional studies. Inclusion and exclusion criteria for the studies selected for this review are listed in Box 1. LI-ESWT was defined as shockwave therapy carried out with focal zone energy flux below 0.35 mJ/mm^2 (low to medium energy level) in accordance with the guidelines provided by the International Society for Medical Shockwave Treatment (ISMST).[9] Risk of bias was not assessed for the included studies since no randomized clinical studies were identified.

We screened the WHO International Clinical Trials Registry Platform, ClinicalTrials.gov, the EU Clinical Trials Register, and the Australian New Zealand Clinical Trials Registry for further studies. The registries were searched using the same terms as in our database search.

Results

We identified a total of 12 eligible studies. Of these, 11 were animal studies[10–20] and one was a clinical study.[21,22]

We found two preclinical animal studies[23,24] and two clinical studies[25,26] that were non-eligible since they were only published in abstract format. Three unpublished clinical studies were located at ClinicalTrials.gov (Identifier: NCT03914157) and WHO International Clinical Trials Registry Platform (Main ID: JPRN-UMIN000030768 and JPRN-UMIN000030448). One unpublished clinical study was located at ClinicalTrials.gov (Identifier: NCT03445247), but the study had been suspended due to a lack of participants. The methods and results of the studies published in abstract format are not further described in the present review, but an overview is included in an Additional File (see Additional Tables 1 and 2).

Animal Studies

Six of the animal studies used rats[10,12,15–17,20] and five studies used pigs.[11,13,14,18,19] In the animal studies, different types of renal disease were induced by either N$^{\omega}$-nitro-L-arginine methyl ester (L-NAME) ingestion (hypertension, n=1),[10] streptozotocin injection (type 1 diabetes mellitus, n=1),[15] or renal artery occlusion/stenosis (hypoxic ischemia, n=9).[11–14,16–20] The number of LI-ESWT treatment sessions varied from one single treatment[12,20] up to a maximum of 12 treatments.[10] The most common protocol for LI-ESWT treatment was two sessions per week for 3 weeks (n=5).[11,13,14,18,19] LI-ESWT was applied either unilaterally (n=9)[10–14,16,18–20] or bilaterally (n=2).[15,17] In the studies with rats, the dosage of LI-ESWT per session varied from 180 shocks/kidney[16] up to 400 shocks/kidney.[10] In the five porcine studies, the dosage of LI-ESWT was the same: the stenotic kidney was divided into 24–26 small zones and each zone was treated with 200 shocks, ie, 4800–5200 shocks/session.[11,13,14,18,19] The lowest energy level was 0.09 mJ/mm^2[10,11,13,14,18,19] and the highest energy level that was used was 0.13 mJ/mm^2.[15] Control groups were used in all of the studies, but only five studies[10–12,18,20] applied a healthy (negative) control group to be treated with LI-ESWT to study potential side effects to LI-ESWT. Treatment with LI-ESWT was carried out using Storz Duolith SD1 (n=2),[16,17] Medispec Omnispec Vetspec (n=5),[11,13,14,18,19] Wikkon.HK. ESWL-Vm (n=1),[12] special Medispec device (n=1),[10] High Medical Technologies EvoTron R05,[15] or EMS DolorClast.[20]

Clinical Studies

Skov-Jeppesen et al[21,22] published a safety report from a clinical study that included measurement of renal functional outcomes after LI-ESWT in patients with diabetic nephropathy. Other studies have reported data only in abstract format. The study by Skov-Jeppesen et al[21,22] was a single-arm cohort study with relatively small study population including 28 patients. In this study, LI-ESWT was applied with a Storz Modulith SLX-2 device and both kidneys were treated on upper, middle, and lower zone with 1000 shocks/zone and energy 0.265 mJ/mm^2.[21]

The design and methods of the animal and clinical studies are summarized in Table 1.

Molecular Effects

The protein expression of VEGF was higher in the kidney tissue after LI-ESWT in the studies by Zhang et al,[11] Sung et al,[16] Hsiao et al,[15] and Zhao et al[18] However, there was no change in VEGF mRNA expression after LI-ESWT in the study by Caron et al[10] Chen et al[14] found that the protein expression of VEGF was unaffected by LI-ESWT. In the study by Yoshida et al,[17] the expression of VEGF mRNA was upregulated in the contralateral, non-treatment kidney. In relation to nitric oxide synthase (NOS) expression, the studies by Zhang et al 2016,[11] Sung et al,[16] and Zhao et al[18] found higher endothelial NOS (eNOS) expression after LI-ESWT. On the other hand, in the studies by Caron et al[10] and Yoshida et al,[17] there was no significant effect on eNOS expression. Xue et al[12] found lower levels of inducible NOS (iNOS) after LI-ESWT. Chen et al[19] found that there was no effect of LI-ESWT monotherapy on the expression of eNOS but combination therapy with mesenchymal stem cells caused an upregulation of eNOS. Skov-Jeppesen et al[22] reported that nitric oxide metabolites in urine tended to be higher in patients with diabetic nephropathy after treatment with LI-ESWT, but the results were not statistically significant. Furthermore, there seemed to be a transient decrease in VEGF 1 month after LI-ESWT in the clinical study by Skov-Jeppesen et al but the evidence was not strong ($p=0.056$).[22] Other findings included lower levels of inflammatory and apoptotic markers after LI-ESWT[15,16,19] as well as less oxidative stress.[12,15,16,19] A few studies also investigated the mechanotransduction signal of LI-ESWT suggesting that the shock wave pressure stimulus was mediated through membrane proteins such as focal adhesion kinase (FAK) and beta 1-integrin.[11,14] Furthermore, LI-ESWT seemed to downregulate TGF-beta expression in the studies by Zhang et al 2016,[11] Sung et al,[16] and Hsiao et al[15] This could indicate that LI-ESWT counteracts the initiation of fibrosis. Stromal cell-derived factor-1 (SDF-1), a chemoattractant for endothelial progenitor cells, was higher after LI-ESWT in the setting of renal ischemia,[11,18,20] diabetic nephropathy,[15] and proteinuric CKD[16] but not in hypertensive renal disease.[10] In summary, available data do not show consistent changes in VEGF and NO-synthase in kidney tissue subjected to LI-ESWT.

Cellular and Histological Effects

A common finding was lower interstitial fibrosis after LI-ESWT as demonstrated by trichrome staining at 4 weeks,[11,13,18,19] 7 weeks,[14] and 60 days.[16] Nonetheless, two studies found no effect of LI-ESWT on the degree of renal fibrosis at 4 days[17] and 4 weeks[10] after the treatment. LI-ESWT promoted endothelial cell proliferation[16,20] and increased renal vascularity.[11,14] On microCT scan, Zhang et al[11] and Chen et al[19] demonstrated that the density of small renal vessels recovered after LI-ESWT. Three studies[14,18,19] found higher number of peritubular capillaries after LI-ESWT. Other studies reported ameliorated vascular and glomerular lesions after LI-ESWT[15] as well as lymphangiogenesis.[17] In diabetic rats, LI-ESWT promoted regeneration of glomerular podocyte cells.[15] Intriguingly, the homing of circulating endothelial progenitor cells to kidney tissue was enhanced by LI-ESWT.[16,18,20] Also, LI-ESWT improved inflammation as indicated by lower infiltration of macrophages.[14,15] However, LI-ESWT did not affect the number of macrophages after ischemia-reperfusion injury in the study by Yoshida et al[17] In summary, available data show stimulatory effects of LI-ESWT on kidney microvessel density and growth.

Renal Functional Effects

The effect of LI-ESWT on GFR was assessed directly in four of the animal studies[11,14,18,19] and in the human study.[21] Four studies[11,14,18,19] demonstrated that single kidney GFR was significantly higher in pigs 4 weeks after LI-ESWT administration as evidenced by multidetector computed tomography (MDCT). In the clinical study,[21] GFR was measured in patients by means of chrome-EDTA clearance. After six sessions of LI-ESWT, GFR was stable in patients with diabetic nephropathy up to 6 months.[21,22] In five of the animal studies, LI-ESWT lowered the plasma concentration of creatinine, BUN, or cystatin

Table 1 Design and Methods

Study	Design	Condition	Intervention	Experimental Groups	LI-ESWT Treatment
Caron et al[10]	Animal study (rats)	Hypertensive, proteinuric renal disease induced by L-NAME ingestion	Left kidney treated 3 times per week for 4 weeks using special Medispec device	1) Non-hypertensive 2) Hypertensive 3) Non-hypertensive +LI-ESWT 4) Hypertensive + LI-ESWT	400 shocks per session at energy 0.09 mJ/mm^2
Zhang et al[11]	Animal study (pigs)	Ischemic renal disease induced by unilateral renal artery stenosis (RAS)	Stenotic kidney treated 2 times per week for 3 weeks using Medispec Omnispec Vetspec device	1) Normal 2) RAS 3) Normal +LI-ESWT 4) RAS + LI-ESWT	Kidney divided in 24–26 small zones. Each zone treated with 200 shocks per session at energy 0.09 mJ/mm^2 and 2 Hz
Xue et al[12]	Animal study (rats)	Renal ischemic reperfusion injury after unilateral renal artery occlusion for 45 minutes	Kidney was treated 1 time before renal artery occlusion using Wikkon HK.ESWL-Vm device	1) Normal 2) Reperfusion injury 3) Normal +LI-ESWT 4) Reperfusion injury + LI-ESWT	200 shocks at energy 12 kv and 1 Hz
Zhang et al[13]	Animal study (pigs)	Ischemic renal disease induced by unilateral renal artery stenosis (RAS)	Stenotic kidney treated 2 times per week for 3 weeks using Medispec Omnispec Vetspec device	1) Normal 2) RAS 3) RAS + LI-ESWT	Kidney divided in 24–26 small zones. Each zone treated with 200 shocks per session at energy 0.09 mJ/mm^2 and 2 Hz
Chen et al[14]	Animal study (pigs)	Renal reperfusion injury induced by unilateral renal artery stenosis (RAS) followed by PTRA	After stenosis, before reperfusion, stenotic kidney was treated 2 times per week for 3 weeks using Medispec Omnispec Vetspec device	1) Normal 2) RAS 3) RAS +PTRA 4) RAS + PTRA + LI-ESWT	Kidney divided in 24–26 small zones. Each zone treated with 200 shocks per session at energy 0.09 mJ/mm^2 and 2 Hz
Hsiao et al[15]	Animal study (rats)	Diabetic renal disease induced by Streptozotocin injection	Both kidneys treated 1 time per week for 6 weeks using High Medical Technologies EvoTron R05 device	1) Normal 2) Diabetic 3) Diabetic + LI-ESWT	200 shocks at each kidney per session at energy 0.13 mJ/mm^2 and frequency 200 shocks/minute.
Sung et al[16]	Animal Study (rats)	Proteinuric chronic renal disease induced by unilateral nephrectomy and contralateral ligation of 2/3 renal blood supply	Endothelial progenitor cells (EPC) were administered intravascularly and supported by DPP4-inhibition and LI-ESWT 1 time per week for 3 weeks on remaining kidney using Storz Duolith SD1 device	1) Normal 2) Renal disease 3) Renal disease + EPC 4) Renal disease + LI-SWT 5) Renal disease + EPC + LI-ESWT	180 shocks per session at energy 0.12 mJ/mm^2
Yoshida et al[17]	Animal study (rats)	Renal ischemic reperfusion injury after unilateral renal artery occlusion for 45 minutes	After reperfusion, both kidneys were treated 3 times over 3 days (early phase study) or 9 times over 16 days (late phase study) using Duolith SD1 device	1) Normal 2) Reperfusion injury 3) Reperfusion injury + LI-ESWT	200 shocks at each kidney per session at energy 0.10 mJ/mm^2 distributed over two sites per kidney
Zhao et al[18]	Animal study (pigs)	Ischemic renal disease induced by unilateral renal artery stenosis (RAS)	Stenotic kidney treated 2 times per week for 3 weeks using Medispec Omnispec Vetspec device	1) Normal 2) RAS 3) Normal +LI-ESWT 4) RAS + LI-ESWT	The entire kidney was divided in 1 cm^2 zones. Each zone was treated with 200 shocks per session at energy 0.09 mJ/mm^2 and 2 hz
Chen et al[19]	Animal study (pigs)	Ischemic renal disease induced by unilateral renal artery stenosis (RAS)	Stenotic kidney treated 2 times per week for 3 weeks using Medispec Omnispec Vetspec device followed by administration of mesenchymal stem cells (MSC) delivered through the renal artery	1) Normal 2) RAS 3) RAS + LI-ESWT 4) RAS + LI-ESWT + MSC	Kidney divided in 24–26 small zones. Each zone treated with 200 shocks per session at energy 0.09 mJ/mm^2 and 2 Hz
Liu et al[20]	Animal study (rats)	Renal ischemic reperfusion injury after unilateral renal artery occlusion for 45 minutes	Pre-treatment with one session LI-ESWT using DolorClast device. Endothelial progenitor cells (EPC) were administered intravascularly to a subset of animals in each group before intervention.	1) Normal 2) Reperfusion injury 3) LI-ESWT 4) Reperfusion injury + LI-ESWT 5) Normal + EPC 6) Reperfusion injury +EPC 7) LI-ESWT +EPC 8) Reperfusion injury + LI-ESWT + EPC	200 shocks applied to the kidney immediately before ischemic reperfusion injury at energy 0.1 mJ/mm^2 and 1 Hz.
Skov-Jeppesen et al[21,22]	Clinical single-arm cohort study with 28 patients	Patients with diabetic renal disease and eGFR 30–60 mL/min/1.73m^2	Both kidneys treated 2 times per week for 3 weeks using Storz Modulith SLX-2 device	1) Diabetes + LI-ESWT	Kidneys divided in upper, middle, and lower part. Each part treated with 1000 shocks per session at energy 0.265 mJ/mm^2 and 4 Hz

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C[11,12,16,17,20] but there was no significant effect on these parameters in the studies by Caron et al[10] and Chen et al[14] In the animal studies, LI-ESWT improved tissue oxygenation as demonstrated by blood oxygen-level dependent magnetic resonance imaging (BOLD MRI)[11,14,19] as well as renal arterial flow.[16,18,19] Two studies, however, did not demonstrate a significant effect of LI-ESWT on renal arterial blood flow.[11,14] Importantly, LI-ESWT ameliorated albuminuria and proteinuria in preclinical settings. In rats, proteinuria was lower 60 days after LI-ESWT in proteinuric CKD,[16] and albuminuria was lower than 6 weeks after LI-ESWT in diabetic nephropathy.[15] In pigs with renal ischemia, Zhao et al[18] demonstrated that the urinary protein excretion was lowered at 4 weeks after LI-ESWT. However, the studies by Caron et al[10] and Zhang et al[11] did not corroborate this. In human diabetic nephropathy, there were no significant changes in median albuminuria 6 months after LI-ESWT.[21,22] Other functional changes after LI-ESWT included improved arterial blood pressure[11,13,15,18] which was, however, not confirmed in an animal model of hypertensive nephropathy[10] and a model of renal ischemia.[19] In the human study, ambulatory blood pressure was unchanged after LI-ESWT.[21,22] In pigs treated with LI-ESWT, Zhao et al[18] demonstrated that the renal blood flow was significantly higher in response to a systemic dose of acetylcholine which could indicate an improvement of the renal microvascular endothelial function. Nonetheless, LI-ESWT monotherapy did not enhance the vascular response to acetylcholine in pigs in the study by Chen et al[18] In summary, LI-ESWT is neutral or slightly beneficial on GFR and albuminuria, but material is scarce and follow-up time is limited.

Safety

LI-ESWT was applied to a healthy control group in four of the animal studies allowing the study of side effects to the treatment. In rat studies, no histological changes were seen after application of LI-ESWT to healthy animals.[10,12,20] LI-ESWT did not adversely affect urinary protein excretion, arterial blood pressure, or renal function.[10,20] Furthermore, plasma levels of NGAL and KIM-1 remained unchanged at 24 hours and 1 week after LI-ESWT.[12] In pigs, a single session of LI-ESWT caused no micro- or macroscopic haematuria and no signs of haemorrhage or tubular injury.[11] Furthermore, urinary NGAL and protein levels and renal function were stable.[11] There were no differences found between healthy pigs treated with six sessions of LI-ESWT and healthy pigs that received no intervention.[11,18] In the remaining animal studies,[13,14,16,17,19] LI-ESWT did not negatively affect any of the measured or observed variables. Xue et al[12] found lower iNOS after LI-ESWT which can be interpreted as reduced oxidative stress/macrophage activation and therefore not a negative finding. In the published study with data from patients with diabetes, there was transient macroscopic haematuria in six out of 28 patients after LI-ESWT.[22] Treatment with LI-ESWT caused short-lasting flank tenderness in the majority of the patients, and ultrasound scanning revealed no signs of renal hematoma.[21,22] There were no correlations between the presence of haematuria and negative functional outcomes in the patients.[21,22] During the intervention, the patients experienced LI-ESWT as a stinging sensation, but pain was only reported in 1/14 patients.[21] Importantly, in patients with diabetic nephropathy, LI-ESWT had no negative impact on urinary kidney injury markers (KIM-1, calbindin, clusterin, osteoactivin, trefoil factor-3).[22]

The results of each study are listed in Table 2. Furthermore, Table 3 shows selected molecular, cellular and functional effects of renal LI-ESWT treatment.

Table 2 Results

Study	Main Findings
Caron et al[10]	• No effect of LI-ESWT on urine protein excretion, systolic blood pressure, plasma creatinine and BUN, or renal histological lesions • No increases in the mRNA expression of VEGF, VEGF-R2, eNOS, or HIF-1alpha after LI-ESWT • No side effects to LI-ESWT
Zhang et al[11]	• LI-ESWT restored microvascular density (microCT), renal oxygenation (BOLD-MRI), and stenotic kidney GFR • Expression of angiogenic markers VEGF, eNOS, and angiopoietin-1 increased, and fibrosis decreased after LI-ESWT • Beta1-integrin and FAK were upregulated after LI-ESWT indicating a potential role in mechanotransduction • No side effects to LI-ESWT (no haematuria, microscopic haemorrhage, or elevated proteinuria and NGAL levels)
Xue et al[12]	• LI-ESWT improved NGAL, KIM-1, creatinine, and cystatin C serum levels as well as renal histology injury scores • Markers of oxidative stress (iNOS and malondialdehyde) were decreased by LI-ESWT • The effects of LI-ESWT seemed to weaken after one week • LI-ESWT did not cause any side effects in regard to any of the measured parameters

(*Continued*)

Table 2 (Continued).

Study	Main Findings
Zhang et al[13]	• LI-ESWT reduced mean arterial blood pressure • Renal medullary and cortical fibrosis were reduced after LI-ESWT as demonstrated by trichrome staining
Chen et al[14]	• Renal cortical oxygenation was restored by LI-ESWT as demonstrated by BOLD-MRI • Stenotic kidney GFR, serum creatinine, renal vein renin activity, and VEGF expression were not significantly different between PTRA compared to PTRA+LI-ESWT • Fewer inflammatory macrophages and increased number of reparative macrophages in kidney after LI-ESWT • LI-ESWT increased the density of peritubular capillaries as well as attenuated medullary fibrosis and tubular injury
Hsiao et al[15]	• LI-ESWT reduced albuminuria and restored renal VEGF expression to normal levels. • Renal inflammation was reduced as shown by reduced IL-6 and IL-1beta and increased anti-inflammatory M2 macrophages and IL-10. • LI-ESWT reduced oxidative stress (↓8-OHdG, ↑HO-1), renal fibrosis (↓TGF-beta1, ↓collagen-1, ↓fibronectin), and glomerular hypertrophy. • Podocyte regeneration and cellular proliferation were improved by LI-ESWT.
Sung et al[16]	• LI-ESWT reduced renal fibrosis and injury as well as markers of oxidative stress (NOX1, NOX2, oxidized protein), apoptosis (mitochondrial Bax, c-caspase3, c-PARP), and inflammation (TNF-alfa, NF-kappaB, MMP-2) • LI-ESWT increased endothelial cells and expression of angiogenic factors (eNOS, CD31, and VEGF) • Renal blood flow, serum BUN and creatinine levels, and urine protein excretion were improved by LI-ESWT • The positive effects of LI-ESWT were enhanced in combination with EPCs + DPP4-inhibitor
Yoshida et al[17]	• Plasma creatinine was reduced in early phase after LI-ESWT • LI-ESWT upregulated cortical VEGF mRNA in the non-occluded kidney in early phase and promoted lymphangiogenesis in the occluded kidney in late phase • No significant effect of LI-ESWT on renal interstitial fibrosis, macrophage infiltration, or eNOS mRNA expression
Zhao et al[18]	• LI-ESWT restored GFR, perfusion, urinary protein excretion, arterial blood pressure, and endothelial function (vascular flow response to acetylcholine) • The number of circulating EPCs was increased by LI-ESWT. There was a negative gradient of EPCs from renal arterial blood to renal vein blood suggesting a retention of EPCs in the kidney after LI-ESWT • Circulating levels of SDF-1 and angiopoietin-1 were increased in pigs treated with LI-ESWT • LI-ESWT improved the number of peritubular capillaries, increased the expression of VEGF and eNOS, and alleviated renal fibrosis (trichrome staining)
Chen et al[19]	• LI-ESWT monotherapy improved microvascular density (microCT), renal oxygenation (BOLD-MRI), and stenotic kidney GFR • LI-ESWT monotherapy reduced renal fibrosis (trichrome staining) and inflammation (↓TNF-alfa, ↓MCP-1, ↑IL-10) • LI-ESWT in combination with MSC therapy improved the expression of eNOS and endothelial function (vascular flow response to acetylcholine) • MSC therapy enhanced the positive effects of LI-ESWT on oxidative stress and peritubular capillary density • Arterial blood pressure was not improved by LI-ESWT with or without MSC therapy. However, renal vein renin activity was significantly decreased by LI-ESWT
Liu et al[20]	• LI-ESWT monotherapy attenuated changes in BUN, serum creatinine, and cystatin C after ischemic reperfusion injury • LI-ESWT reduced renal tubular injury and apoptosis • LI-ESWT increased cell proliferation, microvessel density, and amount of EPCs • LI-ESWT increased the recruitment of circulating EPCs via upregulation of SDF-1 and CXCR7 receptor in the kidney
Skov-Jeppesen et al[21,22]	• LI-ESWT caused short-lasting macroscopic haematuria in 6 out of 28 patients • Most patients experienced flank tenderness up to 2 days after LI-ESWT • GFR and 24-hour urinary excretion of albuminuria were stable up to 6 months after LI-ESWT • No haematoma detected on ultrasound and ambulatory blood pressure remained stable • No negative impact of LI-ESWT on kidney injury markers (KIM-1, calbindin, clusterin, osteoactivin, TFF3) • Nitric oxide metabolites tended to increase in urine after LI-ESWT. VEGF decreased transiently one month after LI-ESWT (not strong evidence, p=0.056).

Abbreviations: VEGFR2, vascular endothelial growth factor receptor 2; HIF-1alfa, hypoxia-inducible factor 1-alpha; BOLD-MRI, blood-oxygen-level-dependent magnetic resonance imaging; FAK, focal adhesion kinase; NGAL, neutrophil gelatinase-associated lipocalin; KIM-1, kidney injury molecule-1; iNOS, inducible nitric oxide synthase; PTRA, percutaneous transluminal renal angioplasty; 8-OHdG, 8-hydroxy-2'-deoxyguanosine; HO-1, heme oxygenase-1; TGF-beta1, transforming growth factor-beta1; NOX, NADPH oxidase; c-PARP, cleaved poly ADP ribose polymerase; TNF-alpha, tumor necrosis factor-alpha; NF-kappaB, nuclear factor kappa-light-chain-enhancer of activated B cells; MMP-2, matrix metalloproteinase-2; EPC, endothelial progenitor cells; DPP4, dipeptidyl-peptidase 4; SDF-1, stromal cell-derived factor-1; MCP-1, monocyte chemoattractant protein-1; MSC, mesenchymal stem cells.

Discussion

Shockwave therapy was invented originally for renal lithotripsy almost 40 years ago.[27] The application of LI-ESWT as a treatment for kidney parenchymal diseases is a novel therapeutic approach, and data in this field are limited. The earliest study we identified was published in 2016, and, since then, nine additional preclinical animal studies and one human study have been published with renal outcome as primary effect parameter.

Taken together, data from animal studies vary from neutral to positive findings that range from improved GFR, attenuated proteinuria and inflammation, improved renal blood flow, and lower blood pressure. Variation between the

Table 3 Selected Effects of LI-ESWT

Study	Molecular Effects			Cellular and Histological Effects			Renal Functional Effects		
	VEGF	NO/eNOS	TGF-Beta	Vascularization	Fibrosis	Inflammation	GFR	Perfusion	Blood Pressure
Caron et al[10]	No effect	No effect	NA	NA	No effect	NA	NA	NA	No effect
Zhang et al[11]	Positive	Positive	Positive	Positive	Positive	NA	Positive	Positive	Positive
Xue et al[12]	NA	Negative[a]	NA	NA	NA	NA	Positive[b]	NA	NA
Zhang et al[13]	NA	NA	NA	NA	Positive	NA	NA	NA	Positive
Chen et al[14]	No effect	NA	NA	Positive	Positive	Positive	Positive	Positive	NA
Hsiao et al[15]	Positive	NA	Positive	NA	NA	Positive	NA	NA	NA
Sung et al[16]	Positive	Positive	Positive	Positive	Positive	NA	Positive[b]	Positive	NA
Yoshida et al[17]	Positive	No effect	NA	Positive	No effect	No effect	Positive[b]	NA	NA
Zhao et al[18]	Positive	Positive	NA	Positive	Positive	NA	Positive	Positive	Positive
Chen et al[19]	NA	Positive[c]	NA	Positive	Positive	Positive	Positive	Positive	No effect
Liu et al[20]	NA	NA	NA	Positive	NA	NA	Positive[b]	NA	NA
Skov-Jeppesen et al[21,22]	No effect[d]	No effect[d]	NA	NA	NA	NA	No effect[d]	NA	No effect[d]

Notes: [a]Lower iNOS after LI-ESWT. [b]GFR not measured directly. Improved GFR was indicated by lower cystatin C, BUN, or creatinine after LI-ESWT. [c]LI-ESWT in combination with MSC therapy caused an upregulation of renal eNOS. [d]The clinical study by Skov-Jeppesen et al was conducted as a single arm-interventional study with no comparative control group. Accordingly, the statement of "No effect" should be interpreted as no significant changes from baseline to follow-up.

results can be ascribed to different models of renal disease, different species, and different therapeutic protocols. In light of the non-invasive intervention, there is a need for functional and tissue data from human intervention trials.

Previous studies, focusing on other organs than kidneys, showed that the effect of LI-ESWT was mediated through different receptors and proteins associated with cell surfaces, including specific mechanosensory complexes, toll-like receptors, and ATP receptors that were activated by ATP released from cytoplasm in response to LI-ESWT.[28–30] This way, LI-ESWT acts as a physical stimulus that potentially influences several types of cell surface receptors. The beneficial downstream signalling effects of LI-ESWT involve local angiogenesis as well as anti-inflammatory processes summarizing into reduced fibrosis. At the level of signalling pathways, LI-ESWT upregulates VEGF and NO which act as trophic factors for endothelium and stimulation of angiogenesis. VEGF and VEGF receptor activation were previously shown to be higher after LI-ESWT in heart, skeletal muscle, skin, and penile tissue.[31–35] The activation of angiogenesis by LI-ESWT leads to improved tissue perfusion and oxygenation as shown clinically in ischemic myocardium and diabetic foot ulcers.[36–38] Also, treatment with ESWL has previously been associated with increased levels of plasma nitrite and cyclic 3', 5'-guanosine monophosphate (cGMP) suggesting that shockwaves stimulate the NO-cGMP signaling pathway.[39–41]

Histologically, LI-ESWT may promote tissue remodelling through activation of M2 reparative macrophages and inhibition of M1 inflammatory macrophages.[42] In severe burn wounds and myocardial infarction, treatment with LI-ESWT suppressed pro-inflammatory cytokines and neutrophil and macrophage infiltration.[43,44] LI-ESWT ameliorated TGF-beta expression and tissue collagen and fibrocyte content as demonstrated in ischemic heart diseases.[44–46] Interestingly, a few studies indicated a synergistic effect between administration of endothelial progenitor cells and LI-ESWT to induce angiogenesis and improved tissue viability.[47,48] It is likely that LI-ESWT upregulates the local production of SDF-1 which may attract circulating endothelial progenitor cells.[47,49] This way, LI-ESWT treatment could provide a method to enhance cell-based therapies.

Only a few studies have tested the dose–response relationship of LI-ESWT. The treatment can be administered with lower or higher energy within the spectrum from 0.01 to 0.35 mJ/mm^2. In the hind limb of rats, tissue oxygen tension was significantly higher after application with energy at 0.30 mJ/mm^2 compared to energy at 0.10 mJ/mm^2.[50] On the

other hand, an inappropriate high number of shockwaves might induce tissue necrosis.[51] Furthermore, repetitive sessions of LI-ESWT have been found to negatively affect wound healing.[52] With regard to the optimal timing of treatment, application of LI-ESWT to acutely injured skin showed there was no difference whether treatment was applied before or after ischemic injury.[53] Hypothetically, another useful application of LI-ESWT could be a preconditioning treatment in relation to surgical procedures that induce renal ischemia, ie, partial nephrectomy or renal transplantation. Furthermore, LI-ESWT can be applied as either focused or radial therapy. Radial shockwaves differ from focused shockwaves in that they propagate in the body as spherical waves and do not focus the energy in a small, targeted area.[5] In renal diseases, LI-ESWT was carried out as focused therapy in all of the studies and the potential of radial LI-ESWT is unknown.

In the present review of data from studies with primary renal outcome, LI-ESWT elicited beneficial effects as found in other organs, but some of the findings were not consistent between the studies with different renal disease models. In particular, Caron et al[10] demonstrated no positive effects of LI-ESWT treatment. Of note, their study was based on rats with hypertensive renal disease induced by administration of L-NAME. The majority of the animal studies were based on renal artery stenosis/clamping and thus studied ischemia recovery and reperfusion injury. However, Hsiao et al[15] based their renal disease model on streptozotocin injection to induce type 1 diabetic nephropathy and found positive effects of renal LI-ESWT. In relation to the method of LI-ESWT administration, we identified no simple differences that could explain the discrepancy between the outcomes. LI-ESWT was administered in the same way through all of the porcine studies, and the reported outcomes in these studies were overall positive and constitute the only data in large animals. However, only one type of renal disease model (ischemic renal disease) was used in the porcine studies. It remains unclear whether the protocol for LI-ESWT implemented in the porcine studies is also efficient in other types of renal diseases. In general, LI-ESWT was applied with energy densities in the lower end of the spectrum in the animal studies (0.09–0.13 mJ/mm^2). Conversely, patients included in the clinical study were treated with relatively high energy levels at 0.265 mJ/mm$^{2.}$ There were no clear associations between the frequency or number of sessions of LI-ESWT and the outcomes. The most frequently used protocol for LI-ESWT was twice per week for 3 weeks for a total of six sessions but ranged from one session up to 12 sessions in total. A consistent finding across the preclinical studies was that there was no evidence of injury or damage to the kidneys.

The single human study was conducted as phase 1 study in order to first establish the clinical safety of LI-ESWT in renal parenchymal disease.[21,22] In this study, transient macroscopic haematuria was observed in a minor part of the patients. Flank tenderness was more commonly reported after bilateral LI-ESWT. These side effects are well-known also from ESWL. The side effects did not require any intervention or treatment and were short-lasting after LI-ESWT. There were no reported signs of renal hematoma or negative functional outcomes (drop in GFR, hypertension, or albuminuria) related to LI-ESWT, and further clinical research is encouraged. In particular, future clinical studies should test the dose–response relationship of LI-ESWT considering the positive results demonstrated in animal studies at relatively low energy settings. Moreover, the optimal frequency of LI-ESWT and whether intervention can be repeated should be clarified.

Conclusions

LI-ESWT has shown several beneficial outcomes in ischemic cardiac disease, erectile dysfunction, and skin injury. Data on the effect in renal parenchymal diseases are scarce. In preclinical animal studies, LI-ESWT showed no adverse effects. In some cases, significant improvement was found in VEGF synthesis and renal vascularity with reduced renal fibrosis and improved renal function. There was a large heterogeneity between the studies with regard to the administration of Li-ESWT (intensity, frequency) and the type of renal disease. In a clinical setting, LI-ESWT has proven as a safe treatment in a small study population of patients with diabetic nephropathy. Future randomized controlled clinical trials are needed to determine the efficacy of LI-ESWT in renal diseases.

Abbreviations

LI-ESWT, low-intensity extracorporeal shockwave therapy; VEGF, vascular endothelial growth factor; NO, nitric oxide; eNOS, endothelial nitric oxide synthase; GFR, glomerular filtration rate; SDF-1, stromal cell-derived factor-1; BOLD MRI, blood oxygen-level-dependent magnetic resonance imaging.

Data Sharing Statement

All articles included in this systematic review are referenced in the manuscript.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas. All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors declare that they have no competing interests.

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