Immunologic Research (2023) 71:287–313
https://doi.org/10.1007/s12026-022-09352-2

REVIEW

Lipocalin 2—not only a biomarker: a study of current literature and systematic findings of ongoing clinical trials

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Received: 24 November 2022 / Accepted: 14 December 2022 / Published online: 19 December 2022

Abstract

Lipocalin 2 (Lcn2), also known as neutrophil gelatinase–associated lipocalin, is an innate immune protein encoded by the LCN2 gene. In this study, we investigated various roles and functions of Lcn2 characterized in a systems-based format and evaluated its therapeutic potentials and clinical relevance for diagnosis and prognosis. An additional systematic presentation was presented for 70 ongoing clinical trials utilizing Lcn2 in the diagnostic and prognostic setting as a key outcome measure. With trials being conducted through December 2030, Lcn2 will become all the more relevant given its associations with diseases as a prognostic biomarker. Data also suggests that it plays a role in pathological conditions. The gaps in our understanding of Lcn2, once filled, may improve the immune mediation of acute and chronic disease.

Keywords Lipocalin 2 · Innate immunity · Pathophysiology · Biomarker · Clinical trials

Introduction

Lipocalin 2 (Lcn2), an innate immune protein also known as neutrophil gelatinase–associated lipocalin (NGAL), is encoded by the LCN2 gene. Lcn2 was initially identified in 1989 by identification of its messenger RNA named 24p3 in simian virus 40 (SV-40)–infected kidney cells of mouse models [1]. It was originally named neutrophil-gelatinase-associated lipocalin (NGAL) as it was first isolated in neutrophil granules of humans [2]. It is a member of the lipocalin protein family that is a group of diverse proteins with a complex β-barrel 3D structure forming an enclosing calyx [3]. The flexible structure also contains a hydrophobic pocket allowing the Lcn2 protein to carry out key functions in cell regulation, proliferation, and differentiation [4]. It is a 25-kDa glycoprotein with key expression in bodily fluids and tissues and is protease-resistant due to its complex formation with matrix metalloprotease-9 (MMP-9) in human neutrophils [5, 6]. The release of Lcn2 is strongly upregulated during inflammation by epithelial cells, and it is also released by epithelial cells, macrophages, hepatocytes, and adipocytes. It transports small hydrophobic molecules such as lipids, steroid hormones, and retinoids [7].

As an organic chelator of iron, Lcn2 limits bacterial growth by sequestering iron-containing siderophores [8, 9]. This promotes the bacteriostatic action potential of Lcn2 by depriving the bacteria of their nutrition and inhibiting their growth [8]. Due to its high affinity to iron, it acts as a regulator of iron-responsive genes [6]. The strong affinity of Lcn2 for iron is also evident in its effects on human proteins including norepinephrine [6]. Previous studies conducted on mice have reported increased susceptibility to bacterial infections following a lack of the LCN2 gene. Other functions of the Lcn2 protein include the moderation of the immune and inflammatory response, induction of apoptosis, and maintenance of skin homeostasis and insulin sensitivity [10–13]. The Lcn2 protein, measured in blood, urine, and feces, also serves as a significant biomarker during inflammation, ischemia, infection, and acute kidney injury [14, 15]. In this study, we investigated various roles and functions

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of Lcn2 and evaluated its therapeutic potential and clinical relevance as a diagnostic and prognostic marker.

Methodology

A literature review was conducted to report existing evidence of lipocalin. This was divided into different systems including (i) inflammatory mediation and iron homeostasis, (ii) malignancy, (iii) kidneys, (iv) gastrointestinal tract, (v) biomarker potential, (vi) other potential functions, and (vii) therapeutic potential. To identify and include the studies in the literature review portion, a search was conducted in the PubMed database and the Google Scholar search engine. The keywords used in this study are found in Table 1. The findings were discussed based on the aforementioned systems in a literature-based scoping format.

In the inclusion of ongoing clinical trials of lipocalin 2, a systematic strategy was adopted as recommended by PRISMA Statement 2020 guidelines. A search was conducted on ClinicalTrials.Gov where public and privately funded clinical trials are stored. A search of the World Health Organization's International Clinical Trials Registry Platform was also conducted until November 20, 2022. A total of 232 records were located, of which 94 were reviewed in full. Of these, 70 records were added to this review, post-reviewed by two mid-career researchers (Z.S. and A.S.). No limitations were made for the gender or age groups of the included participants in the clinical trials. Disagreements of the tabulations during the systematic review inclusion phase were resolved through active consensus. The extraction was led by all researchers. The findings of all records were tabulated under the following headings: NCT number, Title, Current status, Target conditions, Interventions, Outcome measures, Enrollment, Funded by, Study type, Study designs, Completion date, and Locations. During the inclusion phase, the inter-reviewer kappa score was 0.915 suggesting excellent agreement between the reviewers.

Lcn2 as a modulator of inflammation and iron homeostasis

Lcn2 is a critical regulator of iron homeostasis during physiological and inflammatory processes. The role of Lcn2 as an inhibitor of bacterial growth has been well established, and it is able to prevent the bacteria from acquiring iron. Many acute-phase reactants have been identified including C-reactive protein, serum amyloid A, ferritin, and hepcidin, and they have effects on the ongoing inflammatory process. Recently, Lcn2 was identified and is observed to regulate host responses to inflammation by maintaining iron homeostasis. Lcn2 does not bind to iron directly and instead forms a ternary complex with it along with a siderophore serving as a cofactor. Siderophores have a high affinity for insoluble ferric irons and are classified into chemical groups namely catecholates, carboxylates, and hydroxamates. Lcn2 is not able to sequester hydroxamates, but it is able to bind to the other two chemical groups of siderophores [13]. All microbes except *Lactobacillus* and *Borrelia* spp. [16] require iron for maintaining growth in their hosts. The role of Lcn2 as a binder of catecholate- and carboxylate-type siderophores promotes nutritional immunity against iron-dependent microbes in humans.

Inflammatory bowel disease

The role of Lcn2 has been observed in the innate immune response, but its mechanisms of action in intestinal inflammation are less known. The underlying pathophysiology of inflammatory bowel disease has been correlated with increased expression of Lcn2, but its role has not been explored until recently [5]. Janas et al. identified

Table 1 Keywords used for the literature review

Lipocalin 2	lipocalin 2: "lipocalin-2"[MeSH Terms] OR "lipocalin-2"[All Fields] OR "lipocalin 2"[All Fields]
Inflammatory	"inflammatories"[All Fields] OR "inflammatory"[All Fields]
Iron, homeostasis	"iron"[MeSH Terms] OR "iron"[All Fields] "homoeostasis"[All Fields] OR "homeostasis"[MeSH Terms] OR "homeostasis"[All Fields]
Malignancy	"malign"[All Fields] OR "malignance"[All Fields] OR "malignances"[All Fields] OR "malignant"[All Fields] OR "malignants"[All Fields] OR "malignities"[All Fields] OR "malignity"[All Fields] OR "malignization"[All Fields] OR "malignized"[All Fields] OR "maligns"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "malignancies"[All Fields] OR "malignancy"[All Fields]
Kidney	"kidney"[MeSH Terms] OR "kidney"[All Fields] OR "kidneys"[All Fields] OR "kidney's"[All Fields]
Gastrointestinal	"digestive system"[MeSH Terms] OR ("digestive"[All Fields] AND "system"[All Fields]) OR "digestive system"[All Fields] OR "gastrointestinal"[All Fields] OR "gastrointestinally"[All Fields] OR "gastrointestine"[All Fields]
Biomarker	"biomarker's"[All Fields] OR "biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biomarker"[All Fields]
Therapeutic	"therapeutical"[All Fields] OR "therapeutically"[All Fields] OR "therapeuticals"[All Fields] OR "therapeutics"[MeSH Terms] OR "therapeutics"[All Fields] OR "therapeutic"[All Fields]

the elevation of serum NGAL in children presenting with inflammatory bowel disease (IBD) [5]. Mouse models of inflammatory bowel disease (IBD) have ascertained the role of Lcn2 during intestinal inflammation and gut bacterial dysbiosis. Mouse models were observed for Lcn2 expression in murine colitis models and during microbiota ablation/restoration. Lcn2 was induced during inflammation, and it was due to the presence of gut microbiota and MyD88 signaling [17]. The activation of toll-like receptors (TLRs) is carried out by bacterial products, and it results in the subsequent encoding of genetic products specifically aimed to promote host defenses. The intestine consists of a wide range of commensal bacteria, and the role of TLRs may not be limited to that of an on/off switch. Flagellin receptor TLR5 plays a critical role in protecting the enteric microbiota. Vijay-Kumar et al. (2007) conducted a study where mice lacking TLR5 developed spontaneous colitis, but the subsequent deletion of TLR4 served as a protective mechanism. In instances where both TLR4 and TLR5 were deleted, bacterial loads were high in the colon but there were no elevated laboratory markers or clinical evidence of colitis [18]. The findings suggest the correlation of innate immune deficiency with higher incidences of inflammatory bowel disease [18]. Higher serum Lcn2 levels were also observed in mice with elevated serum amyloid A (SAA), an acute-phase marker representing the degree of intestinal inflammation in both mice and humans [18–20].

Malignancy

In the past few decades, Lcn2 has gained prominence for its role as a potential biomarker and modulator of malignancy. Its ability to serve as an intracellular iron carrier and protector of MMP-9 from proteolytic degradation allows it to serve contradictory functions in malignant cells. Elevated Lcn2 levels have been observed in multiple epithelial tumors including ovarian tumors [21]. Lcn2 is also over-expressed in other tumors and functions by inhibiting apoptosis in thyroid cancer–infected cells, modulating invasiveness and angiogenesis in pancreatic cancer cells, and increasing invasiveness in breast and colorectal cancer [22]. Chronic inflammation has been identified as a risk factor for the development of epithelial-derived malignancies (Bower et al., 2005). Clinical oncology is paying close attention to the potential roles of Lcn2 as a diagnostic and prognostic biomarker for early diagnosis and response to treatments [23].

Breast cancer

Lcn2 levels in plasma and urine are consistently elevated in invasive breast cancer. The functions of Lcn2 in breast cancer progression are observed by its actions on mesenchymal markers. The protein elevates vimentin and fibronectin while downregulating the epithelial marker E-cadherin. As a result, the cell motility and invasiveness are increased leading to an epithelial-to-mesenchymal transition (EMT). Contrarily, the silencing of Lcn2 in invasive breast cancer results in reduced invasiveness. Lcn2 also reduces the expression of estrogen receptor (ER) α and increases the expression of Slug, the primary transcription factor responsible for EMT [22]. Inhibition of Lcn2 prevents breast tumorigenesis and invasion as observed in mouse models. Without Lcn2, mice had delayed the formation of mammary tumors and invasion as well as a reduced migration ability of Her2 + cells [24].

Thyroid cancer

NF-κB is activated in tumors of thyroid origin, especially those of anaplastic origin, and blockade of its activity leads to an increased susceptibility of thyroid cancer cells to undergo chemotherapy-induced apoptosis in mice models. Proteomic analysis allowed Lcn2 identification, and it is secreted by the anaplastic thyroid cancer cell line, FRO cells. Owing to Lcn2's ability to bind to and transport intra-cellular iron, NF-κB works in conjugation with Lcn2 and worsens the prognosis of thyroid cancers of anaplastic origin [25].

Gastric cancer

High levels of MMP-2, MMP-9, and Lcn2 have been identified in human gastric cancers. Sampieri et al. identified elevated levels of MMP-9 mRNA levels as well as Lcn2-MMP-9 complexes in gastric cancer cells. This has clinical importance since Lcn2 prevents the degradation of MMP-9 when combined. However, further studies are required to ascertain the role of Lcn2 in gastric cancers [26].

Pancreatic cancer

Lcn2 is being reviewed for its potential as a biomarker in pancreatic cancer, suggesting its role in early diagnosis. Moniaux et al. reported a 27-fold increase of Lcn2 in pancreatic cancer cells [27]. While Lcn2 levels were markedly elevated in pancreatic cancer, they were also higher than normal in pancreatitis. Lcn2 levels may be used to detect the early stages of pancreatic cancer, and it may be possible to use Lcn2 as a biomarker in pancreatitis [27]. Recently, Tong et al. observed the function of Lcn2 in mouse models of pancreatic cancer since it is poorly understood [28]. Lcn2 plays a significant role by partly reducing adhesion and invasion via suppression of FAK activation. It also inhibits angiogenesis by reducing levels of VEGF in pancreatic cancer cells [28].

Colorectal cancer

Neoplastic disorders of colorectal origin also affect the barrier function of the mucosa which disrupts intestinal bacterial homeostasis. Lcn2's ability to bind to bacterial formyl peptides allows it to scavenge bacterial products. Its mechanisms of action were replicated using mRNA in situ hybridization and immunohistochemistry in both inflammatory and neoplastic diseases and healthy colon by Nielson et al. in 1996 [29]. The study reported high levels of epithelial-derived Lcn2 in the inflammatory regions of the colonic epithelium in benign, pre-malignant, and malignant conditions. Lcn2 was especially abundant in the transitional mucosa and in the superficial ulcerated regions. However, Lcn2 was not present in the adjacent lymph nodes and the normal colon only had traces of the anti-inflammatory protein.

Ovarian epithelial cancer

Ovarian cancer is the fifth leading cause of death in women and is the most common gynecological cancer. If diagnosed early, ovarian cancer has a 90% 5-year survival rate, and over 90% of ovarian malignancies are of epithelial origin [30][30]. While the focus of serum marker use has been on CA-125, Lcn2 was detected in human ovarian surface epithelial (HOSE) cells indicating its potential application as a serological marker [32]. Neutrophil counts are significantly higher in tumors of ovarian origin [33]. It is reasonable to correlate Lcn2 expression upregulation in pre-malignant stages owing to the underlying inflammatory process. Cho et al. noted that while healthy ovarian cells were negative for Lcn2 expression, immunoreactivity was observed in tumor cells with evidence of elevated Lcn2 mRNA expression in the cancer cell lines [21, 32]. Lcn2 expression reflects the extent of epithelial differentiation and is lost once tumor differentiation is poor in later stages [21].

Kidneys

Acute kidney injury

Acute kidney injury (AKI) leads to a sudden decline in kidney function owing to injury and is followed by functional and structural alterations. Lcn2 has recently been discovered as a novel acute-phase biomarker released in acute kidney injury [23, 34]. To determine the risk of developing AKI in kidney transplant recipients, the cut-off for urinary NGAL that was observed at 2 h was 204 ng/mL [35].

Chronic kidney disease

The underlying pathophysiology of chronic kidney disease (CKD) has not been entirely established. Recent studies have explored the predictability of the Lcn2 protein during the progression of CKD. As the number of functional nephrons decreases, there is a compensatory growth of the functional nephrons owing to ensuing molecular and cellular events [36]. However, the compensatory growth may result in the development of pathological renal lesions and progression to end-stage renal failure. Many complications occur including fibrosis of the tubulo-interstitium as a consequence of tubular atrophy, and it compromises the renal erythropoietin capacity leading to anemia [37]. Experimental models of CKD incorporate the evolutionary mechanisms of the disease by mimicking renal deterioration. The pathways discovered by the experimental models led to the therapeutic discovery of widely used renal-angiotensin inhibitors [38]. These experimental models are now being used to ascertain the role of the Lcn2 gene in CKD and other renal pathologies.

Induction of Lcn2 by mRNA

The remnant kidney model (RKM) was used in rats and mice to establish evidence of genetic factors in the progression of CKD [39]. Maximal transcriptional induction was conducted using downregulated mRNAs (38%) in mouse strains to record the profiling of gene expression using the RKM. The study conducted by Viau et al. was able to correlate Lcn2 with lesion progression in CKD in both mice and humans [40]. Using real-time PCR, Lcn2 mRNA and protein were observed to rise by tenfold in 2 months following the reduction of nephrons in mice. The surplus of burden represented by Lcn2 was in the proximal convoluted tubules, and some of the proteins and mRNA were isolated in the renal ascending loop of Henle and collecting ducts. On microscopic examination, Lcn2 was isolated in cytoplasmic granules in the subapical zone indicative of its glomerular infiltrate origin. The proximal epithelial cells dilated owing to the ongoing disease process, and the cystic transformation contained in situ Lcn2 and antibodies against Lcn2, providing evidence for endocytosis of Lcn2 and subsequent local synthesis and secretion in the kidneys. The levels of Lcn2 mRNA identified in the kidneys were in direct proportion to the intensity of ongoing tubular damage [40].

Disease severity and progression

Bolignano et al. established the independent and inverse association of urinary and serum Lcn2 with the progression of CKD thereby identifying its contribution as a risk marker for progression [23]. Lcn2 has been observed to provide

real-time detection of kidney damage in mouse models, and the urinary protein biomarker is able to reveal the onset and resolution of kidney injury [41]. It also serves as an excellent diagnostic marker for IgA nephropathy, the most common presentation of glomerulonephritis [42]. Lcn2 is one of the most promising biomarkers for acute kidney injury (AKI), and it may be isolated in both urine and plasma. AKI may occur in the intensive care unit, as well as during kidney damage. Lcn2 is also able to identify sub-clinical AKI in the absence of elevated serum creatinine [43]. Lcn2 upregulation observed late after AKI has been linked with progression to CKD [44].

Gastro-intestinal tract

Gut-origin sepsis

Lcn2 serves as an anti-inflammatory in the intestinal tract and regulates the composition of the gut microbiota. It plays a key role in the pathogenesis of sepsis by providing protection to the gut barrier against injury. It maintains homeostasis of the microbiota and exerts antioxidant stress. It also promotes the deactivation of macrophages and induces immune cell apoptosis to terminate systemic hyper-inflammation. Sepsis has been a key concern in the field of critical care, and the World Health Organization recognized the condition as a global health priority in 2017 [45]. Sepsis was re-defined as a life-threatening condition accompanied by organ dysfunction and caused by a dysfunctional response to infection by the host [46]. The gut comprises the epithelium, immune system, and microbiome—all of which are impacted in critically ill patients and are likely to propagate an ongoing pathology in these patients [47]. Gut-origin sepsis is understood by the analogy of the gut acting as the "motor" component in patients with systemic inflammatory response syndrome (SIRS) and/or multiple organ dysfunction syndromes (MODS) [47, 48].

Gut-specific functions of Lcn2

Major protective mechanisms are present in the gut during gut-origin sepsis including (1) restoration of the microbiota homeostasis by promoting decontamination of selective regions in the gut as well as the use of probiotics and (2) protection of the intestinal barrier by providing antioxidants, enteral nutrition, and immune nutrition [49]. Overgrowth of the pathological gut microbiome is termed "dysbiosis." Lcn2-negative mice demonstrated higher levels of gut bacterial dysbiosis with the major burden of the dysbiosis carried out by gram-negative bacteria. Conversely, germ-free mice had low levels of serum and fecal Lcn2. The levels were increased when contents from the cecum were injected via oral gavage from wild mice. Singh et al. suggest the importance of Lcn2 as a microbiota inducer, and it may serve as a pre-requisite for intestinal homeostasis [17]. Lcn2 is bacteriostatic against *Escherichia coli* owing to its affinity for catecholate-type siderophores as observed in mouse models [50]. Lcn2 is released by neutrophils and epithelial cells, and it facilitates bacteriostasis by recruiting neutrophils in a paracrine as well as autocrine manner [51]. Resistance has been observed by bacteria against Lcn2 owing to resistance siderophores [52]. The anti-oxidant effects of Lcn2 have been observed in vitro against H_2O_2 toxicity [53]. This allows Lcn2 to protect the intestinal barrier against oxidative stress and reduce the impact of intestinal barrier injury during sepsis. Lcn2 acts as an inflammatory modulator to prevent the further release of pro-inflammatory cytokines by enhancing phagocytic bacterial clearance in macrophages [54].

Biomarker potential

Lcn2 is being investigated as a diagnostic and prognostic marker in a wide range of diseases including inflammatory and neoplastic conditions [6]. In children, early detection of acute kidney injury (AKI) is established by measuring urinary NGAL in the first 6 h following admission and a cut-off of 50 mg/dL serves as optimal [55]. The definitions of AKI depend on the elevation of serum creatinine, but serum and urinary NGAL are reported to have higher sensitivity. In healthy children, differences in urinary NGAL were observed to be determined by sex or ethnicity. Females were reported to have consistently higher levels of NGAL than males [56].

Low-grade inflammation due to a wide range of disorders including cancer may be ascertained by measuring fecal Lcn2 using ELISA, as observed in the mouse model [14]. Its use allows for non-invasive, sensitive, and cost-effective means to measure intestinal inflammation as described by Chassaing et al. [14]. In mouse models mimicking the progression of chronic kidney disease (CKD), the intensity of tubular damage was directly proportional to the levels of expressed Lcn2 protein and mRNA. Levels of Lcn2 protein may be measured in the urine using ELISA owing to the kidney being a major source of Lcn2 expression and release [40]. While Lcn2 is not ready for use in clinical practice, it is worthwhile to explore its potential in predicting CKD progression, AKI diagnosis, and risk of cardiovascular disease in CKD [57]. In critically ill patients at high risk of developing cardiovascular complications, measurement of urinary NGAL was able to provide earlier detection of AKI as compared to creatinine. Serum and urinary NGAL are elevated 24 h before creatinine rises to lead to timely

Table 2 Characteristics of the included current clinical trials

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT04573998	Study on the Mechanism of lcn2 in Obesity	Recruiting	Obesity; endocrine	Procedure: LSG	LCN2 level; meet the criteria of metabolism in the 2017 Chinese guideline; FBG; PBG
NCT05450523	Neutrophil Gelatinase-Associated Lipocalin (NGAL) Rapid Test (Colloidal Gold) Clinical Trial Protocol	Recruiting	Peritoneal dialysis–associated peritonitis		Assessment reagent test results and clinical reference standard statistics; statistical analysis of non-professional self-testing test
NCT05439538	Serum NGAL IN Patients with Multiple Myeloma	Not yet recruiting	Multiple myeloma (MM)	Diagnostic test: serum NGAL	Serum neutrophil gelatinase–associated lipocalin in patients with multiple myeloma
NCT04354467	Assessment of Urinary Neutrophil Gelatinase-Associated Lipocalin to Predict AKI in the NICU	Active, not recruiting	Acute kidney injury; nephrotoxicity; neonatal	Drug: acute kidney injury due to nephrotoxic medications in the NICU	Percentage of patients with elevated urine NGAL
NCT04191785	Evaluation of the Plasmatic NGAL as a Predictive Marker of Renal Injury in Children With Urinary Infection	Recruiting	Urinary tract infections	Diagnostic test: plasmatic NGAl and MRI	Compare plasmatic neutrophil gelatinase–associated lipocalin (NGAL) with gold standard Reno vesical magnetic resonance imaging (MRI); define performance of plasmatic NGAL for the diagnostic of renal abnormality due to a pyelonephritis; performance and area under the curve (AUC) of C-reactive protein (CRP) for the diagnostic of pyelonephritis; performance and area under the curve (AUC) of procalcitonin (PCT) for the diagnostic of pyelonephritis; compare the AUC of plasmatic NGAL and CRP; compare the AUC of plasmatic NGAL and PCT.; performance of urinary NGAL; performance of Doppler echography
NCT05349292	Acute Normovolemic Hemodilution on Urine Neutrophil Gelatinase-associated Lipocalin Levels	Not yet recruiting	Acute kidney injury	Other: ANH	Urinary biomarkers NGAL and KIM-1; AKI by KDIGO criteria
NCT05374759	NGAL and Renal Resistive Index in the Diagnosis and Prognosis of Sepsis-associated AKI	Not yet recruiting	Sepsis; acute kidney injury	Diagnostic test: neutrophil gelatinase-associated lipocalin; diagnostic test: renal resistive index	NGAL; renal resistive index
NCT05290077	Role of NGAL in Vitiligo	Not yet recruiting	Vitiligo	Diagnostic test: NGAL	Serum neutrophil gelatinase–associated lipocalin in patients with vitiligo
NCT04574024	HFP (High-Fiber Supplement) in MS (Multiple Sclerosis)	Enrolling by invitation	Multiple sclerosis	Drug: NBT-NM108 (60 g/day); other: NBT-NM108 (0 g/day)	Effect of high-fiber supplement (HFS) on (1) composition of gut microbiota and (2) production of short-chain fatty acids (SCFAs) and Foxp3 regulatory T cells (Tregs); examine fecal Lcn-2 levels before/after MS relapse
NCT05101746	Nitric Oxide Effect on Brain and Kidney in Pediatric Patients Undergoing Cardiopulmonary Bypass	Enrolling by invitation	Congenital heart disease; congenital heart defect; congenital heart malformations	Drug: nitric oxide (NO) 20 parts per million (ppm); other: standard of care cardiopulmonary bypass	Level of glial fibrillary acid protein (GFAP); level of neutrophil gelatinase–associated lipocalin (NGAL); daily prevalence of delirium as measured by preschool confusion assessment method for the ICU (psCAM-ICU); length of ICU stay; duration of mechanical ventilation; length of hospital stay; mortality; organ dysfunction as measured by the pediatric sequential organ failure assessment; functional status
NCT05388643	Early Detection of Gestational Diabetes Mellitus in Pregnancy	Not yet recruiting	Gestational diabetes mellitus in pregnancy; pregnancy, high risk	Diagnostic test: enhanced first trimester GDM screening; diagnostic test: routine gestational diabetes screening	Gestational diabetes mellitus; mode of delivery; neonatal birthweight; number of participants with shoulder dystocia; number of participants with brachial plexus injury; APGAR score; neonatal intensive care unit admission; gestational age at delivery; patient satisfaction with diabetes screening method
NCT05350423	Trial Comparing Renal Damage of Thulium to Holmium Laser	Recruiting	Nephrolithiasis	Device: thulium fiber laser; device: holmium:yttrium–aluminum-garnet	Change in kidney injury molecule-1 (KIM-1); change in neutrophil gelatinase–associated lipocalin (NGAL); change in $\hat{I}^2$2-microglobulin ($\hat{I}^2$2M); operative time
NCT03830450	Biomarkers of Acute Kidney Injury in Cardiac Surgery	Not yet recruiting	Acute kidney injury (nontraumatic)		Consecutive values of neutrophil gelatinase-associated lipocalin (NGAL); consecutive values of growth differentiation factor 15 (GDF-15); consecutive values of glomerular filtration rate (GFR)

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT04991376	Specific miRNAs in Sepsis and Nephrotoxic Antibiotic Treatment	Active, not recruiting	Sepsis; septic shock; acute kidney injury	Diagnostic test: blood-specific miRNA levels	miRNA expression over 7 days of treatment; association between circulating miRNA expression and serum neutrophil gelatinase–associated lipocalin (NGAL) and other renal or inflammatory markers
NCT04917718	Renal Tubular Injury and Transplant Outcomes in Cardiac Recipients Converting From IR Tacrolimus to XR Tacrolimus	Recruiting	Chronic kidney diseases; heart transplant	Drug: conversion from IR tacrolimus to XR tacrolimus	Urinary neutrophil gelatinase–associated lipocalin (NGAL); estimated glomerular filtration rate (eGFR); microalbuminuria; CYP3A5 expressor category; heart transplant rejection; cardiac allograft vasculopathy; blood pressure; serum glucose; LDL cholesterol
NCT03534141	Mild Hypothermia and Acute Kidney Injury in Liver Transplantation	Recruiting	Cirrhosis; end-stage liver disease; acute kidney injury; liver transplant; complications; chronic kidney diseases; hepatitis C; hepatitis B; NASH—nonalcoholic steatohepatitis; alcoholic cirrhosis; hepatocellular carcinoma	Device: esophageal cooling/warming device; other: mild hypothermia; other: normothermia	Incidence of acute kidney injury (AKI); distribution of the stages of acute kidney injury (AKI); duration of intensive care unit (ICU) stay; duration of hospital stay; patient survival; need for renal replacement therapy; persistent renal dysfunction; serum neutrophil gelatinase-associated lipocalin (NGAL); urine neutrophil gelatinase-associated lipocalin (NGAL)
NCT02911714	Contrast-Enhanced Ultrasound for Kidney Transplant	Recruiting	Kidney transplantation	Drug: Lumason contrast-enhanced ultrasound	Biomarker-defined delayed graft function; biopsy-proven acute rejection; dialysis-defined delayed graft function
NCT04705766	KIDney Injury in Times of COVID-19 (KIDCOV)	Recruiting	SARS-CoV infection; Covid19; corona virus infection; acute kidney injury; kidney injury	Other: urine collection	Continuous, quantitative KIT Score; Number of participants with a level of Kidney Injury Molecule-1 (KIM1) above 1 ng/mL; number of participants with a level of neutrophil gelatinase–associated lipocalin (NGAL) above 1 ng/mL; number of participants with a level of soluble urokinase-type plasminogen activator receptor (suPAR) above 1 ng/mL
NCT04346290	Effects of Dexmedetomidine on Microcirculation and Residual Kidney Function in Kidney Donors	Recruiting	Kidney transplant; microcirculation	Drug: dexmedetomidine	Change of perfused vessel density; change of creatinine level
NCT04195126	Early Haemadsorption in Major Burns	Not yet recruiting	Burns; multiple organ failure; shock; organ dysfunction syndrome, multiple; renal dysfunction; cytokine storm	Device: CytoSorb hemadsorption device	7-day mortality; 28-day mortality; levels of inflammatory and anti-inflammatory cytokines during treatment; markers of oxidative stress (ROS production, MDA levels, tyrosine isomers); intensive care unit length of stay; volume resuscitation fluid need of our patients; vasopressor need of our patients; length of mechanical ventilation (if needed); severity of organ failures according to SOFA point system
NCT04902846	Immune Checkpoint Inhibitors Nephrotoxicity	Recruiting	Kidney injury; antineoplastics toxicity	Diagnostic test: early kidney damage biomarkers; diagnostic test: predisposition to kidney injury biomarkers	Change of urinary albumin; change of urinary N-Acetyl-Î²-D-glucosaminidase (NAG); change of urinary Kidney Injury Molecule-1 (KIM-1); change of urinary neutrophil gelatinase-associated lipocalin (NGAL); change of urinary biomarkers of predisposition to kidney injury; body weight; height; body mass index (BMI); age; gender; concentration of plasma creatinine
NCT05299970	Fermented Millet Porridge, Gut Microbiota and Inflammation Status in Women	Recruiting	Inflammation; microbiome, human	Other: fermented porridge	Gut microbiota diversity; concentration of inflammation markers in blood and stool; concentration of short-chain fatty acid in stool; concentration of macronutrients in millet dough and porridge; relative abundance of bacterial and fungal micro-organisms in millet dough and porridge; concentration of ferritin in plasma; number of participant with anemia
NCT05612802	A New Marker for Early Diagnosis of Pneumoperitoneum-Related Acute Kidney Injury: Insulin-Like Growth Factor-1 (IGF-1)	Not yet recruiting	Acute kidney injury (nontraumatic); pneumoperitoneum	Diagnostic test: IGF-1	Diagnosis of acute kidney injury in the early postoperative period with IGF-1 (insulin-like growth factor-1)

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT04269486	A Multicenter Observational Study on Safety of the Herbal Medicines at Inpatient Setting	Recruiting	Drug-induced liver injury; drug-induced kidney injury; herbal medicine adverse reaction		Alanine aminotransferase (ALT) (U/L), if ALT > 3 upper normal limits, Roussel Uclaf casualty assessment method scoring; blood urea nitrogen (BUN) (mg/dL); liver function tests: AST (U/L), ALP (U/L), Î³-GT (U/L), total bilirubin (mg/dL). Drug-induced liver injury biomarkers: microRNA-122 (miR122), glutamate dehydrogenase (GLDH); kidney function tests: urine creatinine (mg/dL), serum creatinine (mg/dL). Drug-induced kidney injury biomarkers: neutrophil gelatinase–associated lipocalin, kidney injury molecule-1
NCT04344769	Characterization of the Nrf2 Response in Patients With Autosomal Dominant Polycystic Kidney Disease (ADPKD)	Recruiting	Autosomal dominant polycystic kidney disease		Assessment of oxidative status; assessment of antioxidant response; total kidney volume (TKV); assessment of kidney injury
NCT05321277	Response of Cardiometabolic Biomarkers and Gut Microbiota to Walnut Consumption	Recruiting	Cardiovascular diseases	Dietary supplement: walnuts; dietary supplement: no-nut diet	Assessing the influence of walnut consumption on blood lipid measurements; assessing the influence of walnut consumption on circulating inflammatory markers: PAI-1, VCAM-1, and ICAM-1. Assessing the influence of walnut consumption on blood pressure; assessing the influence of walnut consumption on fecal pH; assessing the influence of walnut consumption on stool consistency; assessing the influence of walnut consumption on fecal moisture; assessing the influence of walnut consumption on the levels of gut inflammatory markers: Lipocalin-2 and calprotectin; assessing the influence of walnut consumption on plasma and urine levels of walnut-derived metabolites—urolithins
NCT04702958	TRANSFORM-HF Ancillary Mechanistic Study	Enrolling by invitation	Heart failure		Differences in proteomic protein clusters between treatment groups; differences in trajectories of protein clusters between treatment groups; differences in single biomarkers and biomarker trajectories between treatment groups; differences in urinary protein levels between treatment groups
NCT04520048	Vascular Biomarkers Predictive of the Progression From Gestational Hypertension to Preeclampsia in Pregnant Women	Not yet recruiting	Gestational hypertension; pre-eclampsia	Procedure: laser Doppler–coupled with acetylcholine iontophoresis; procedure: aortic central pressure and the carotid-femoral pulse wave velocity; other: vascular biomarker assay	Change in endothelium-dependent vasodilatation between 26 and 34 weeks of pregnancy; change in circulating levels of soluble Fms-like tyrosine kinase (sFlt-1) between 26 and 34 weeks of pregnancy; change in circulating placental growth factor (PlGF) between 26 and 34 weeks of pregnancy; change in circulating levels of vascular endothelial growth factors (VEGF) between 26 and 34 weeks of pregnancy; change in circulating levels of soluble endogline (sEng) between 26 and 34 weeks of pregnancy; change in anti-angiotensin II receptor (AT1) between 26 and 34 weeks of pregnancy; change in circulating Copetid between 26 and 34 weeks of pregnancy; change in circulating levels of interleukin IL-17 between 26 and 34 weeks of pregnancy; change in urinary levels of Neutrophil Gelatinase–Associated Lipocalin (NGAL) between 26 and 34 weeks of pregnancy; change in urinary endothelial microparticle levels between 26 and 34 weeks of pregnancy; change in central aortic blood pressure between 26 and 34 weeks of pregnancy; change in carotid-femoral pulse wave velocity between 26 and 34 weeks of pregnancy
NCT04941625	Risk of Acute Kidney Injury in Patients Undergoing Cytoreductive Surgery and Hyperthermic Intra-peritoneal Chemotherapy	Recruiting	Acute kidney injury	Diagnostic test: serum cystatin C; diagnostic test: serum beta-microglobulin; diagnostic test: urine	Acute kidney injury

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT04767711	Prevention of Glucocorticoid-Induced Impairment of Bone Metabolism	Recruiting	Bone loss	Dietary supplement: *Lactobacillus reuteri* ATCC PTA 6475 (*L. reuteri* 6475); drug: prednisolone	Change in bone turnover marker serum osteocalcin; change in bone turnover marker serum PINP; change in bone turnover marker serum CTX; change in blood glucose levels; change in serum marker of intestinal permeability—endotoxin levels; change in feces marker lipocalin-2 of intestinal inflammation; change in feces marker calprotectin of intestinal inflammation; change in serum marker lipocalin-2 of intestinal inflammation; change in serum marker calprotectin of intestinal inflammation; change in the gut microbiota composition
NCT02375854	Outcomes of Neonatal Acute Kidney Injury In Premature Infants	Recruiting	Acute kidney injury; chronic kidney disease	Other: observation	Chronic kidney disease (incidence of chronic renal insufficiency in childhood); acute kidney injury (incidence of acute kidney injury in preterm infants); assessment of serum biomarkers—cystatin C; assessment of urinary biomarkers—urinary neutrophil gelatinase-associated lipocalin, interleukin 18 and kidney-injury molecule-1
NCT03782610	Early Prediction of Spontaneous Patent Ductus Arteriosus (PDA) Closure and PDA-Associated Outcomes	Recruiting	Patent ductus arteriosus; preterm infant; bronchopulmonary dysplasia; neurodevelopmental abnormality		Patent ductus arteriosus (PDA) closure documented via echocardiogram by 36-weeks postmenstrual age (PMA) (binary); mortality or supplemental oxygen or positive-pressure respiratory support at 36-weeks PMA (binary); composite Bayley III Motor Score at 22–26 months corrected age (continuous); mortality by 36 weeks PMA (binary); Bayley III Gross Motor Development Scaled Standard Score at 22–26 months corrected age (continuous); Bayley III Fine Motor Development Scaled Standard Score postnatal age at 22–26 months corrected age (continuous); Bayley III Cognitive Composite Score at 22–26 months corrected age (continuous); Bayley III Language Composite Score at 22–26 months corrected age (continuous)
NCT02299921	Effect of Alcohol and Drugs of Abuse on Immune Function in Critically Ill Patients With Respiratory Failure	Active, not recruiting	Infection; alcohol abuse; drugs of abuse; lung injury	Other: characterize alcohol and drug use	Prevalence of alcohol use disorders (AUDs); incidence and etiology of respiratory failure, stratified by AUD/DUD/both/neither; incidence and etiology of respiratory failure, stratified by AUD/DUD/both/neither: month 3; incidence and etiology of respiratory failure, stratified by AUD/DUD/both/neither: month 6
NCT04508049	A Study to Evaluate Renal Fibrosis Using MRI Techniques	Recruiting	Hypertension; renovascular	Device: qMT-MRI to detect fibrosis	Fibrosis assessed by qMT-MRI in the stenotic kidney and contralateral kidneys; fibrosis assessed by qMT-MRI compared to stenotic kidney function; fibrosis assessed by qMT-MRI compared to stenotic kidney injury markers
NCT04900688	Prospective Evaluation of the LithoVue Elite Ureteroscope	Not yet recruiting	Kidney stone	Device: LithoVue Elite	WISQOL; BPI; stone free rate; infectious complications; complications; change in neutrophil gelatinase-associated lipocalin (NGAL) from baseline

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT05348694	OsteoPreP: Food Supplements for Postmenopausal Bone Health	Recruiting	Postmenopausal osteopenia; bone loss, age-related; age-related sarcopenia; glucose metabolism disorders; age-related cognitive decline	Dietary supplement: Pendulum WBF-038; dietary supplement: pendulum placebo	Total volumetric bone mineral density of the distal tibia; bone mineral density of the lumbar spine; bone mineral density of the hip; tibia and radius trabecular bone volume; tibia and radius cortical area; tibia and radius cortical volumetric bone mineral density; total volumetric bone mineral density of the distal radius; serum C-terminal cross-linking telopeptide of type I collagen (ÃŸCTX-I)—bone turnover marker; serum procollagen type 1 N-terminal propeptide (P1NP)—bone turnover marker; serum osteocalcin (OC)—bone turnover marker; short-chain fatty acids (SCFAs); 16 s rRNA genetic sequencing of the gut microbiota; fasting blood glucose; glycated hemoglobin (HbA1c); lower leg muscle area; lean body mass; grip strength; high-sensitivity C-reactive protein (hs-CRP); regulatory T lymphocytes (Tregs); oral glucose tolerance test (OGTT); muscle tissue glycogen content; muscle tissue triglyceride content; muscle tissue type 1 fiber composition; lipocalin2; Cogstate One back Test Cognitive performance test; Cogstate Groton Maze Learning Test Cognitive performance test; Cogstate Continuous Paired Associate Learning Test Cognitive performance test; Cogstate Social Emotional Cognition Test Cognitive performance test; Depression, Anxiety and Stress Scale 21; Gastrointestinal Symptom Rating Scale; plasma glucagon-like peptide 1; plasma peptide tyrosine-tyrosine; Plasma adiponectin; EuroQol Five Dimensions Quality of life Medical Outcome Survey; Social Interaction Anxiety Scale; The Warwick-Edinburgh Mental Wellbeing Scale; continuous blood glucose level monitoring for 10 days; fasting blood insulin; fat mass; blood metabolomics; office blood pressure; the visual analog scale pain intensity; calprotectin; muscle mass
NCT05434286	Point-of-Care Echocardiography to Assess Impact of Dynamic Cardiac Function, Renal and Cardiac Biomarkers in Cirrhosis With Hepatorenal Syndrome-Acute Kidney Injury	Recruiting	Hepatorenal syndrome; cirrhosis, liver; acute-on-chronic liver failure; AKI; refractory ascites	Diagnostic test: echocardiographic assessment	Cardiac output measurement by echocardiography; IVC size and collapsibility changes; number of patients with complete response in HRS-AKI; number of patients with partial response in HRS-AKI; number of patients with non-response in HRS-AKI; change in cystatin C and neutrophil gelatinase–associated lipocalin (NGAL) level; change in NT pro brain natriuretic peptide (BNP) level; change in plasma renin activity level; change in galectin-3 level
NCT04118010	Vitamin D and Prebiotics for Intestinal Health in Cystic Fibrosis	Recruiting	Cystic fibrosis; dysbiosis	Drug: vitamin D_3; drug: placebo vitamin D_3; drug: inulin; drug: placebo inulin	Change in GI microbiota composition; change in GI microbiota diversity; change in GI microbiota richness; change in calprotectin level in the stool; change in lipocalin-2 blood level; change in serum C-reactive protein blood level; change in tumor necrosis factor (TNF) blood level; change in interleukin-6 blood level; change in interleukin-8 blood level
NCT05540678	The FibreGum Study—Changing the Course of Obesity in Children	Not yet recruiting	Nutritional and metabolic diseases; child obesity; adolescent obesity	Dietary supplement: FibreGum; dietary supplement: placebo	Reduction in the body mass index (BMI) Z-score; fasting blood glucose change; fasting insulin change; HOmeostatic Model Assessment of Insulin Resistance (HOMA-IR) index change; hemoglobin A1c (HbA1c) change; lipid-profiles change; systolic and diastolic blood pressures changes; differential blood count change; Calprotectin and lipocalin-2 change in stool; oral health; intestinal health; descriptive analysis of treatment adherence using data from an adherence-tracking app

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT05032937	The Accuracy and Safety of Coronary Artery Contrast-enhanced Magnetic Resonance Imaging With Polysaccharide Superparamagnetic Iron Oxide Nanoparticle	Recruiting	Coronary heart disease	Drug: domestic polysaccharide superparamagnetic iron oxide nanoparticle	The degree of coronary artery stenosis; plaque stability of coronary atherosclerotic plaques; blood routine; blood biochemistry; urine routine; 24-h urine biochemistry; retinol binding protein; neutrophil gelatinase-associated lipocalin; serum iron; ferritin; transferrin; change of iron content in tissues between different time points
NCT03874338	CLEAR SYNERGY Neutrophil Substudy	Recruiting	Neutrophils hypersegmented	Bld-Ser-Plas; STEMI—ST elevation myocardial infarction	Drug: colchicine pill	Soluble L-selectin; other soluble markers of neutrophil activity; markers of systemic inflammation; neutrophil-driven responses that may further propagate injury
NCT04557540	Weight Loss Interventions for Black Adults of Faith	Recruiting	Obesity-related malignant neoplasm	Behavioral: lifestyle therapy; other: quality-of-life assessment; other: questionnaire administration; other: short-term fasting	Change in body weight; changes in body composition; change in height; change in heart rate; change in blood pressure; change in waist circumference; change in hip circumference; dietary intake; obesity-related biomarker analysis; glucose metabolism; changes in adipokine levels; C-peptide level
NCT04391608	TDF Dose Adjustment VS. Switching to TAF in TDF-experienced CHB Patients With Renal Impairment	Recruiting	Renal insufficiency; tenofovir	Drug: switching to tenofovir alafenamide	Renal safety assessed by changes in eGFR; renal safety assessed by changes in urine sugar (0 to 4 +); renal safety assessed by changes in urine protein creatinine ratio; renal safety assessed by changes in urine ÃŸ2-microglobulin (Âµg/mL); renal safety assessed by changes in urine phosphate (mg/dL); renal safety assessed by changes in urine neutrophil gelatinase-associated lipocalin (NGAL) (ng/mL); efficacy of viral suppression assessed by the amount of hepatitis B (HBV DNA) (IU/mL)
NCT05477030	Effect of Automated Insulin Delivery on Early-stage Diabetic Complications	Recruiting	Type 1 diabetes	Device: Medtronic MiniMed 780G with SmartGuard activation; device: Medtronic MiniMed 780G without SmartGuard activation	Time in glycemic range 70–180 mg/dL; glycated hemoglobin (HbA1c); early microangiopathic damage markers: sTNFR-1/2; early microangiopathic damage markers: B-2 microglobulin; early microangiopathic damage markers: cystatin C; early microangiopathic damage markers: neutrophil gelatinase–associated lipocalin; early microangiopathic damage markers: osteopontin; early microangiopathic damage markers: vWF levels; endothelial disfunction
NCT05295784	PK and Safety of Caffeine in Neonates With Hypoxic Ischemic Encephalopathy Receiving Therapeutic Hypothermia	Not yet recruiting	Acute kidney injury; hypoxic-ischemic encephalopathy; caffeine	Drug: caffeine citrate	Clearance of caffeine; volume of distribution of caffeine; peak plasma concentration (Cmax) of caffeine; area under the plasma concentration–time curve of caffeine; seizure incidence; seizure burden; acute kidney injury; renal near-infrared spectroscopy (NIRS); urine neutrophil gelatinase-associated lipocalin (NGAL) (ng/mL); urine kidney injury molecule-1 (KIM-1) (pg/mL); urine interleukin-18 (IL-18) (pg/mL)
NCT05487755	Investigational and Comparative Study in the Management of Diabetic Nephropathy	Not yet recruiting	Diabetic nephropathy type 2	Drug: tadalafil 20 mg oral tablet; drug: pentoxifylline 400 mg oral tablet	Change in urinary albumin/creatinine ratio (ACR); change in hemoglobin A1C (HbA1c); change in Sr Cr; change in fasting blood glucose; change in serum (TNF-Î±); change in serum malondialdehyde (MDA); change in BUN (blood urea nitrogen); change in 2-h postprandial blood glucose; change in urinary NGAL (uNGAL); change in lipid profile (TC, TG, LDL, and HDL); change in creatinine clearance
NCT05420753	Body Composition Changes After TIPS and Associated Clinical Outcomes	Recruiting	Cirrhosis, liver; sarcopenia	Procedure: transjugular intrahepatic portosystemic shunt (TIPS) creation	Body composition changes; short performance physical battery test; liver frailty test; Chronic Liver Disease Quality of Life Questionnaire; overall survival; transplant complications; cardiac function; liver function tests; cardiac mass; serum ammonia; serum glucose

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT04353752	Observational Trial of the Longitudinal Effects of CFTR Modulator Drugs	Active, not recruiting	Cystic fibrosis		Change in blood inflammatory markers; change in sputum microbiology; changes in lung function; changes in urine inflammatory marker; changes in quality of life; changes in hospitalizations
NCT05600452	Comparison of a Novel Condensed Heat Acclimation Programme With a Traditional Longer-term Heat Acclimation Programme	Recruiting	Heat stress	Other: heat acclimation	Reduction in the peak deep body temperature; reduction in the resting deep body temperature; reduction in the peak mean body temperature; reduction in the resting mean body temperature; increased plasma volume; increased sweating rate; reduced sweat sodium concentration; reduced exercise heart rate; increased resting intracellular heat shock protein 70 content; increased post heat stress intracellular heat shock protein 70 content; increased resting intracellular heat shock protein 90 alpha content; increased post heat stress intracellular heat shock protein 90 alpha content; maximal oxygen uptake; lactate threshold; gross mechanical efficiency; peak power output; peripheral oxygen saturation during exposure to hypoxia; heart rate during exposure to hypoxia; minute ventilation during exposure to hypoxia; plasma neutrophil gelatinase-associated lipocalin; urine neutrophil gelatinase–associated lipocalin; plasma kidney injury molecule-1; urine kidney injury molecule-1; tissue inhibitor of metalloproteinase 2; insulin-like growth factor-binding protein 7; intestinal fatty acid binding protein; soluble cluster of differentiation 14; lipopolysaccharide binding protein; interleukin-6; cortisol
NCT04948918	Distal Renal Denervation to Prevent Renal Function Decline in Patients With T2DM and Hypertension	Recruiting	Type 2 diabetes mellitus; hypertension	Procedure: anatomically optimized distal renal denervation	Change in estimated glomerular filtration rate renal function (eGFR); change in eGFR; change in office blood pressure levels (systolic/diastolic); change in ambulatory 24-h blood pressure levels (24-h mean, daytime, nighttime; systolic/diastolic); change in cystatin C levels; change in lipocalin 2 (NGAL) levels; change in 24-h urinary albumin excretion; change in the cortical and medullary volume of the kidneys and their ratio according to MRI; prognostic significance of baseline HbA1c value with regard to change in eGFR; change in the renal resistive index in a trunk; change in peak linear blood flow velocity in the trunk and in segmental renal arteries

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT05359263	Effects of Dapagliflozin on EChOcardiographic Measures of CarDiac StructurE and Function in Patients With CKD	Not yet recruiting	Chronic kidney diseases	Drug: dapagliflozin 10 mg; drug: placebo	Change in LV mass index assessed by echocardiography at 6 months; change in LV dimensions assessed by echocardiography at 6 months; change in LVEF assessed by echocardiography at 6 months; change in E-wave assessed by echocardiography at 6 months; change in A-wave assessed by echocardiography at 6 months; change in E/e' assessed by echocardiography at 6 months; change in E/A ratio assessed by echocardiography at 6 months; change in LA volume assessed by echocardiography at 6 months; change in GLS assessed by echocardiography at 6 months; change in LA strain assessed by echocardiography at 6 months; change in RV strain assessed by echocardiography at 6 months; change in high sensitivity troponin I (hs-TNI) at 6 months; change in soluble suppression of tumorigenicity 2 (sST2) at 6 months; change in N-terminal pro B-type natriuretic peptide (NT-pro-BNP) at 6 months; change in necrosis factor Î±(TNF-Î±) at 6 months; change in copeptin at 6 months; change in high sensitivity C-reactive protein (hs-CRP) at 6 months; change in estimated glomerular filtration rate (eGFR) 6 months; change in serum potassium at 6 months; change in serum neutrophil gelatinase-associated lipocalin (sNGAL) at 6 months; change in urinary neutrophil gelatinase-associated lipocalin (uNGAL) at 6 months; change in urinary kidney injury molecule-1 (KIM-1) at 6 months; change in insulin growth factor-binding protein-7 (IGFBP7) at 6 months; change in serum cystatin C at 6 months; change in uric acid at 6 months; change in urinary albumin-to-creatinine ratio (UACR) at 6 months; change in erythropoietin (EPO) at 6 months; change in estimated plasma volume at 6 months; change in hemoglobin at 6 months; change in hemotocrit at 6 months; change in ferritin at 6 months; change in transferrin at 6 months; change in iron at 6 months; change in calcium at 6 months; change in phosphate at 6 months; change in magnesium at 6 months; change in PTH at 6 months; change in fibroblast growth factor 23 (FGF-23) at 6 months; change in calcification propensity (T50) at 6 months; change in fetuin-A (fetA) at 6 months; change in bicarbonate at 6 months; change in klotho at 6 months; change in urine sodium at 6 months; change in urine glucose at 6 months; change in hemoglobin A1C at 6 months; change in central blood pressure assessed by pulse wave analysis at 6 months; augmentation index assessed by pulse wave analysis at 6 months
NCT05309785	Safety and Efficacy of Canagliflozin in Advanced CKD	Not yet recruiting	ESRD; CKD stage 4; CKD stage 5	Drug: Invokana 300 mg and 100 mg tablet	The 26-week change in albuminuria compared to baseline, as assessed by the UACR; the drug exposure at steady state with 100 mg, as expressed by the AUC0-24, compared to published estimates with the 300 mg dose in patients with preserved renal function; change in UACR with 300 mg (at 26 weeks) vs. 100 mg dose (at 12 weeks) vs. baseline; change in 24-h ambulatory blood pressure (BP); area under the plasma concentration versus time curve (AUC); change in 6-min walk distance from baseline; change in urinary excretion of sodium from baseline; neutrophil gelatinase–associated lipocalin (NGAL) levels

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT03904277	Does Patent Foramen Ovale Size Matter in Men and Women	Recruiting	Patent foramen ovale		Alveolar-arterial difference in oxygen; aerobic exercise capacity; 6-min walk test; minute flow of intrapulmonary areterio-venous anastomoses (QIPAVA); core body temperature; level of tumor necrosis factor-alpha; level of C–C motif cytokine 2; level of interferon-alpha 2; level of interferon-gamma; level of interleukin 1 beta; level of interleukin 6; level of interleukin 8; level of interleukin 10; level of interleukin 12p70; level of interleukin 17 alpha; level of interleukin 18; level of interleukin 23; level of interleukin 33; level of myoglobin; level of myeloid-related protein 8/14; level of neutrophil gelatinase-associated lipocalin; level of c-reactive protein; matrix metallopeptidase 2; level of osteopontin; level of myeloperoxidase; level of Serum amyloid A; level of insulin-like growth factor binding protein 4; level of intracellular adhesion molecule 1; level of vascular cell adhesion protein 1; level of metallopeptidase 9; level of cystatin C
NCT05208788	Urinary Biomarkers in Paediatric Kidney Transplantation (pKTx)	Recruiting	Renal transplantation; chronic kidney insufficiency; healthy controls	Diagnostic test: biomarker test	Change of serum creatinine level [mg/dL]; change of serum urea level [mg/dL]; change of serum cystatin C level [mg/L]; measurement of urine creatinine level [g/L]; change of urine alpha-1-microglobulin (A1M); change of urine aquaporin 2 (AQP2) [ng/mL]; change of urine Caldesmon [ng/mL]; change of urine clusterin [ng/mL]; change of urine cystatin C [ng/mL]; change of urine interleukin 9 (IL-9) [ng/mL]; change of urine kidney injury molecule 1 (Kim-1) [ng/mL]; change of urine nephrin [ng/mL]; change of urine neutrophil gelatinase–associated lipocalin (NGAL) [ng/mL]; change of urine osteopontin (OPN) [ng/mL]; change of urine P-selectin (SELP) [ng/mL]; change of urine podocin [ng/mL]; change of urine retinol-binding protein 4 (RBP4) [ng/mL]; change of urine smoothelin [ng/mL]; change of urine synaptopodin [ng/mL]; change of urine tumor necrosis factor alpha (TNF-Î±) [ng/mL]; change of urine vascular cell adhesion molecule-1 (VCAM-1)
NCT04482920	Effect of Hormone Therapy on Renal Function	Recruiting	Transgenderism; kidney diseases; kidney injury	Diagnostic test: p-aminohippurate clearance study; diagnostic test: iohexol infusion	Change in measured glomerular filtration rate (GFR); Change in effective renal plasma flow; Change in biomarkers of tubular injury and repair (Neutrophil gelatinase-associated lipocalin [NGAL], Kidney injury molecule-1 [KIM-1], Chitinase-3-like protein 1 [YKL-40]); Change in fat mass; Change in fat-free mass; Change in intracellular fluid; Change in extracellular fluid

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT05145283	Recombinant Human C1 Esterase Inhibitor (Conestat Alfa) in the Prevention of Acute Ischemic Cerebral and Renal Events After Transcatheter Aortic Valve Implantation	Recruiting	Acute ischemic stroke; acute renal injury	Drug: Conestat alfa (RuconestÂ®); drug: NaCl 0.9%	Total volume of new cerebral ischemic lesions as evaluated by magnetic resonance imaging (MRI); maximum new lesion volume as measured by MRI (i.e., volume of the largest new lesion); number of new cerebral ischemic lesions as measured by MRI; number (incidence) of clinically manifest ischemic stroke; change in secondary brain atrophy at 3-months follow-up; change in secondary infarct growth at 3-months follow-up (defined as the difference between the infarct volumes); total brain damage (defined as the sum of secondary brain atrophy and final infarct volume); change in National Institutes of Health Stroke Scale Score (NIHSS); change in modified Rankin scale; change in trail making test; change in Montreal Cognitive Assessment test (MOCA); incidence of acute kidney injury (AKI) defined according to the Kidney Disease: Improving Global Outcomes criteria (any stage); peak increase of urinary neutrophil gelatinase–associated lipocalin (NGAL); incidence of significant increase in serum cystatin C (> 10%)
NCT04614064	London Underground Study—Health Effects of Particulate Matter	Recruiting	Chronic obstructive pulmonary disease	Other: exposure to London underground ambient particulate matter; other: exposure to London air ambient particulate matter	The difference (London underground vs control exposure) in post-exposure pulse wave velocity in healthy vs COPD participants; other clinical responses on the London underground vs control exposure; circulating inflammatory and oxidative responses after the exposure on the London underground vs control exposure
NCT05358171	Ultra-processed Food Consumption, Gut Microbiota, and Glucose Homeostasis	Not yet recruiting	Insulin sensitivity; 24-h glucose control	Other: high UPF-controlled diet; other: no UPF-controlled diet	Change in insulin sensitivity from baseline to 6-weeks post high or no UPF diet; change in 24-h glucose control (24-h mean) from baseline to 6 weeks post high or no UPF diet; change in 24-h glucose control (AUC) from baseline to 6 weeks post high or no UPF diet; change in 24-h glucose control (time in range) from baseline to 6 weeks post high or no UPF diet; change in 24-h glucose control (glycemic variability [GV]) from baseline to 6 weeks post high or no UPF diet; change in 24-h glucose control (postprandial glucose) from baseline to 6 weeks post high or no UPF diet; change in inflammatory cytokines from baseline to post 6-weeks high or no UPF diet; change in endotoxin from baseline to post 6 weeks high or no UPF diet; change in gut microbial composition from baseline to post 6 weeks high or no UPF diet; change in gut microbial function from baseline to post 6 weeks high or no UPF diet; change in intestinal inflammation from baseline to post 6 weeks high or no UPF diet; change in intestinal permeability from baseline to post 6 weeks high or no UPF diet

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT03841981	Body Fat as Determinant of Female Gonadal Dysfunction	Recruiting	Polycystic ovary syndrome; hypothalamic amenorrhea	Diagnostic test: anthropometric and physical examination; diagnostic test: indirect calorimetry, accelerometer, and seven-day dietary recall; diagnostic test: biochemical, hormonal, and metabolic phenotyping; diagnostic test: sonographic studies; diagnostic test: 24-h ambulatory blood pressure monitoring; procedure: percutaneous biopsy; diagnostic test: cardiovascular autonomic function studies; diagnostic test: oral smear and feces specimen	Adipokine and myokine signaling identification; circulating adipokine profile; Appetite regulation hormonal profile; association between body mass index and sex steroids; association between the percentage of fat mass with respect to total body weight and sex steroids; association between the percentage of lean mass with respect to total body weight and sex steroids; association between body fat depots and sex steroids; association between body composition, sex steroids, and insulin resistance; association between body composition, sex steroids, and lipids; association between body composition, sex steroids, and office blood pressure; association between body composition, sex steroids, and ambulatory blood pressure monitoring parameters; association between body composition, sex steroids, and cardiovascular autonomic function tests; association between body composition, sex steroids, and carotid intima-media thickness; association between body composition, sex steroids, and oxidative stress; association between body composition, sex steroids, and microbiome
NCT04962594	Safety and Efficacy of Infant Formulas Supplemented With Pre- and Probiotic(s)	Recruiting	Healthy infants	Other: experimental formulas (EF); other: control formulas (CF); other: breastfeeding (BF)	Weight; bifidobacteria abundance; fecal microbiome; fecal metabolic profile: fecal pH; fecal metabolic profile: fecal organic acids; fecal markers of immune health and gut barrier; fecal cytokine profile; blood markers of immune health; GI-related behavior: stool frequency; GI-related behavior: stool consistency; GI-related behavior: incidence of spitting; GI-related behavior: incidence of flatulence; GI-related behavior: crying time; GI-related behavior: sleep time; GI-related behavior: volume of formula consumed; Infant Gastrointestinal Symptom Index; bone index; additional growth parameters: weight; additional growth parameters: length; additional growth parameters: head circumference; additional growth parameters: body mass index; dietary pattern; absenteeism (infant and parent)
NCT05310396	Efficacy of a Nutrient Blend in Improving Neurocognitive and Behavioral Outcomes in Infants: a Randomized, Controlled, Intervention Study	Not yet recruiting	Infant nutrition; cognitive development	Other: experimental formula; other: control formula	Scores on the cognitive subscale of the Bayley Scale of Infant Development, 4th Edition; infant global developmental status in all domains of the Bayley Scale of Infant Development, 4th Edition; infant visual attention; infant visual learning; early language development; working memory and inhibitory control; behavioral manifestations of executive function; infant temperament; child temperament; infant sleep; infant fecal microbiota; infant immune and gut health biomarkers

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT04610476	Impact of Tapering Immunosuppressants on Maintaining Minimal Disease Activity in Adult Subjects With Psoriatic Arthritis	Recruiting	psoriatic arthritis; withdrawal; reduction	Drug: prednisolone; drug: sulfasalazine; drug: leflunomide; drug: methotrexate; drug: tofacitinib; drug: apremilast; drug: etanercept; drug: adalimumab; drug: infliximab; drug: certolizumab pegol; drug: golimumab; drug: abatacept; drug: secukinumab; drug: ixekizumab; drug: ustekinumab	Presence of MDA (minimal disease activity) 12 months after baseline; key secondary endpoint: PASDAS (Psoriatic Arthritis Disease Activity Score); key secondary endpoint: DAPSA (Disease Activity in PSoriatic Arthritis); key secondary endpoint: CPDAI (Composite Psoriatic Disease Activity Index); number of swollen and tender joints; number of tender entheseal points: SPARCC (Spondyloarthritis Consortium of Canada); number of tender entheseal Points: LEI (Leeds Enthesitis Index); number of tender entheseal Points: MASES (Maastricht Ankylosing Spondylitis Enthesitis Score); dactylitis counts; activity of psoriasis: PASI (Psoriasis Area and Severity Index); activity of psoriasis: BSA (body surface area); activity of axial involvement: BASDAI (Disease Activity of Ankylosing Spondylitis); quality of life and health/disability: PsAID-12 (Psoriatic Arthritis Impact of Disease); quality of life and health/disability: HAQ-DI (Stanford Health Assessment Questionnaire Disability Index); quality of life and health/disability: DLQI (Dermatology Life Quality Index); quality of life and health/disability: ASQoL (Ankylosing Spondylitis Quality of Life); quality of life and health/disability: SF-36 (Short Form Health); pain (VAS); proportion of patients with loss of MDA within 12 months after baseline; proportion of patients with loss of MDA within 24 months after baseline; time to loss of MDA; time needed to restore MDA after readjustment of the DMARD therapy in subjects who lost MDA within the intervention period; biomarker levels; intervention-related events within the observation period of 24 months after baseline; AE (adverse event); AR (adverse reaction); SAE (serious adverse event); SAR (serious adverse reaction); SUSAR (suspected unexpected serious adverse reaction)
NCT03914157	Ultrasound Wave Therapy for Post-stenotic Microvascular Remodeling	Not yet recruiting	Renal artery stenosis	Device: low-energy extracorporeal ultrasound shockwave therapy (SWT)	Change in kidney perfusion assessed by computed tomography; change in renal function assessed by GFR; change in blood oxygen in kidney assessed by MRI; change in renal fibrosis assessed by MRI; change in urinary levels of biomarkers and extracellular vehicles; change in labs collected from right and left renal veins and/or inferior vena cava; change in mean arterial pressure assessed by oscillometry; change in peripheral microvascular endothelial function assessed in the fingertip
NCT04407481	PErfusioN, OxyGen ConsUmptIon and ENergetics in ADPKD (PENGUIN)	Recruiting	Polycystic kidney disease, adult; polycystic kidney, autosomal dominant	Drug: aminohippurate sodium inj 20%; drug: iohexol inj 300 mg/mL; radiation: PET/CT scan	Renal oxygen consumption; insulin sensitivity; mitochondrial function; glomerular filtration rate (GFR); effective renal plasma flow (ERPF); renin–angiotensin–aldosterone-system activity; kidney injury biomarkers
NCT04216927	NO During CPB in Neonates to Reduce Risk of AKI	Not yet recruiting	AKI; CHD—congenital heart disease; surgery	Drug: nitric oxide; drug: oxygen	AKI; biomarker evidence of AKI—NGAL; biomarker evidence of AKI—KIM-1; biomarker evidence of AKI—IL-18; biomarker evidence of AKI—L-FABP; biomarker evidence of AKI—urinary nitrite; impact on GFR; low cardiac output
NCT04012177	Nutritional Support and Prophylaxis Doses of Azithromycin for Pregnant Women—Mumta Pregnant Women Trial	Active, not recruiting	Undernutrition	Dietary supplement: balanced-energy protein (BEP); drug: azithromycin tablets; drug: choline bitartrate; drug: nicotinamide	Birth weight of newborn; birth length of the newborn

Table 2 (continued)

NCT number	Title	Status	Conditions	Interventions	Outcome measures
NCT03955445	OL Extension Study of LNP023 in C3G	Recruiting	C3 glomerulopathy	Drug: LNP023	Number of participants with composite renal response; number of participants with adverse events; change in urine protein/creatinine ratio (UPCR); change in urine albumin/creatinine ratio (UACR); change in serum creatinine; change in estimated glomerular filtration rate (eGFR); status of C3G disease progression; levels of complement component C3; levels of complement component Bb; levels of complement component sC5b-9; urine markers of renal damage; longer-term effect on the composite renal response endpoint, renal function, renal histopathology, and specific components of the complement pathway; pharmacokinetics of LNP023 in subjects under prolonged treatment by determining plasma LNP023 concentration up to 12 months at trough; change from baseline in log-transformed urine protein/creatinine ratio (UPCR); change from baseline in log-transformed urine albumin/creatinine
NCT04352231	Luxembourgish Fiber Cohort	Recruiting	Dietary fiber; gastrointestinal microbiome; healthy volunteers	Dietary supplement: high-fiber diet intervention; dietary supplement: low-fiber diet intervention	Change in gut microbiota composition across study periods; change in gut microbiota CAZyme abundance across study periods; change in gut microbiota mucolytic enzyme activity across study periods
NCT04428190	Prebiotic Therapy to Improve Outcomes of Renal Transplant	Recruiting	Kidney transplant; complications	Dietary supplement: human milk oligosaccharides (HMO); other: placebo	Short Form Health Survey (SF-36); adverse events; microbiome changes from baseline to end of treatment; microbiome changes post-intervention
NCT03897335	Preventing Acute Kidney Injury (AKI) in Pediatric Patients	Recruiting	Acute kidney injury	Drug: aminophylline; drug: placebo	Acute kidney injury state II/III by AKIN criteria; urine output during post-op; concentration of delta serum cystatin C; acute kidney injury stage

detection of impending acute myocardial infarction, heart failure, or stroke [58].

Other functions of Lcn2

Lcn-2 is prominent for its contribution as a prominent biomarker during inflammation, ischemia, infection, and AKI. While its role is protective in infections and IBD, it has both beneficial and determining functions in cancer, neurodegenerative diseases, metabolic syndrome, skin, and other renal disorders. Paradoxical effects of Lcn2 on insulin resistance are observed. Iron dysregulation is involved in the development of insulin resistance and suggests the potential adverse role of Lcn2 in obesity. Almost 1/3rd of patients with obesity and metabolic syndrome suffer from iron dysregulation; the condition is known as dysmetabolic iron overload syndrome (DIOS). Lcn2 may be used as a potential therapeutic target for DIOS [59].

Skin epithelial cells and neutrophils are able to upregulate or release their Lcn2 to prevent potential microbial invasion. Lcn2 has a protective role as it facilitates the process of cutaneous wound healing [60]. However, it has a paradoxical detrimental role as it promotes dysregulated keratinocyte differentiation in several skin disorders, primarily psoriasis. Serum and tissue Lcn2 were observed to be elevated in patients with psoriasis. Anti-Lcn2 antibody treatment was shown to alleviate the disease in a mouse model of psoriasis. Molecular analysis may be conducted to isolate Lcn2 protein expression and levels of mRNA expression encoding for Lcn2 [15]. Lcn2 protein levels are measurable by detecting levels in serum, blood, or feces and by quantifying Lcn2 mRNA transcription or translation. Assays may include the identification of lipocalin-2 mRNA expression, protein expression, or protein activity. Determinants of Lcn2 transcription or translation include levels of mRNA, stability of mRNA, degradation of mRNA, and rates of transcription and translation [15].

Therapeutic potential

Breast

Inhibition of Lcn2 may be able to prevent breast cancer tumorigenesis and invasiveness by acting as an inhibitory monoclonal antibody in certain aggressive breast tumors [24].

Kidney

The role of 4-phenyl butyric acid (PBA) in preventing the toxic effects of proteinuria in CKD progression is closely related to increasing proteinuria. Kidney function may

Table 3 Study designs, enrollment, and locations

NCT number	Enrollment	Funded by	Study type	Study designs	Completion date	Locations
NCT04573998	500	Other	Observational	Observational model: other; time perspective: retrospective	30 May 2024	Department of Endocrinology, Shanghai Tenth People's Hospital, Shanghai, Shanghai, China
NCT05450523	220	Industry	Observational	Observational model: case–control; time perspective: prospective	Jul 2022	The first affiliated hospital of Nangchang University, Nanchang, Jiangxi, China
NCT05439538	60	Other	Observational	Observational model: cohort; time perspective: prospective	1 Jan 2025	Not available
NCT04354467	100	Other	Observational	Observational model: cohort; time perspective: prospective	30 Dec 2022	Children's of Alabama, Birmingham, AL, USA; Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
NCT04191785	50	Other	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: diagnostic	Feb 2023	HÃ´pital La Fontonne, Antibes, France; Fondation Lenval Hopitaux Pediatriques de Nice Chu Lenval, Nice, France
NCT05349292	50	Other	Observational	Observational model: cohort; time perspective: prospective	Dec 2023	Not available
NCT05374759	100	Other	Observational	Observational model: cohort; time perspective: prospective	11 Dec 2022	Ayse Belin B OZER, Malatya, Turkey
NCT05290077	90	Other	Interventional	Allocation: non-randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: screening	15 Dec 2022	Sohag faculty, Sohag, Egypt
NCT04574024	50	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: triple (participant, care provider, outcomes assessor); primary purpose: basic science	30 Sep 2023	Robert Wood Johnson University Hospital, New Brunswick, NJ, USA
NCT05101746	50	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: treatment	Nov 2024	Vanderbilt University Medical Center, Nashville, TN, USA
NCT05388643	80	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: single (outcomes assessor); primary purpose: screening	1 Dec 2024	University of Massachusetts Memorial Medical Center, Worcester, MA, USA
NCT05350423	108	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: single (participant); primary purpose: treatment	Dec 2022	Mount Sinai West, New York, NY, USA
NCT03830450	50	Other	Observational	Observational model: cohort; time perspective: prospective	31 Dec 2022	Not available
NCT04991376	53	Other	Observational	Observational model: case-only; time perspective: prospective	31 Dec 2022	University Hospital Ostrava, Ostrava, Moravian-Silesian Region, Czechia
NCT04917718	42	Other; industry	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: other	31 Dec 2024	Loyola University Medical Center, Maywood, IL, USA

Table 3 (continued)

NCT number	Enrollment	Funded by	Study type	Study designs	Completion date	Locations
NCT03534141	230	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: double (participant, outcomes assessor); primary purpose: prevention	31 Dec 2023	University of California, San Francisco, San Francisco, CA, USA; University of Colorado Anschutz Medical Campus, Aurora, CO, USA; Houston Methodist Hospital, Houston, TX, USA
NCT02911714	55	Other	Interventional	Allocation: non-randomized; intervention model: single group assignment; masking: none (open label); primary purpose: diagnostic	Sep 2024	The University of Utah Hospital, Salt Lake City, UT, USA
NCT04705766	2000	Other	Observational	Observational model: cohort; time perspective: prospective	Mar 2024	Dane Munar, San Francisco, CA, USA; Rush University, Chicago, IL, USA; University of Michigan, Ann Arbor, MI, USA
NCT04346290	120	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: treatment	Jun 2024	National Taiwan University Hospital, Taipei, Taiwan
NCT04195126	20	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: double (participant, outcomes assessor); primary purpose: treatment	1 Jul 2023	University of PÃ©cs, Dept. of Anaesthesia and Intensive Care, PÃ©cs, Baranya County, Hungary
NCT04902846	220	Other	Observational	Observational model: case–control; time perspective: prospective	30 Dec 2023	Servicio de OncologÃa del CAUSA, Salamanca, Spain; Servicio de oncologÃa del Hospital Universitario de Valladolid, Valladolid, Spain
NCT05299970	80	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: screening	31 Mar 2024	IRSS-DRO, Bobo-Dioulasso, Houet, RÃ©gion Des hauts-Bassins, Burkina Faso
NCT05612802	25	Other	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: diagnostic	30 May 2023	Not available
NCT04269486	500	Other	Observational	Observational model: case-only; time perspective: prospective	31 Dec 2022	Five tertiary Korean Medicine Hospitals (Jecheon, Yangsan, Gwangju, Seoul, Bundang), Seoul, Korea, Republic of
NCT04344769	40	Other; NIH	Observational	Observational model: case–control; time perspective: prospective	Jul 2023	Mayo Clinic in Rochester, Rochester, MN, USA
NCT05321277	30	Other	Interventional	Allocation: randomized; intervention model: crossover assignment; masking: none (open label); primary purpose: basic science	Mar 2023	Ragle Human Nutrition Center, Davis, CA, USA
NCT04702958	250	Other; NIH	Observational	Observational model: cohort; time perspective: prospective	1 Dec 2023	Yale University School of Medicine, New Haven, CT, USA; Ochsner Clinic Foundation, New Orleans, LA, USA; Baltimore VA, Baltimore, MD, USA; University of Minnesota, Minneapolis, MN, USA; Northwell Health, Manhasset, NY, USA; Duke University Hospital, Durham, NC, USA; Inova Health System, Falls Church, VA, USA; Sentara Norfolk, Norfolk, VA, USA

Table 3 (continued)

NCT number	Enrollment	Funded by	Study type	Study designs	Completion date	Locations
NCT04520048	154	Other	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: prevention	Sep 2024	AP-HP Avicenne Hospital, Department of internal medicine, Bobigny, Seine Saint-Denis, France; AP-HP Jean Verdier Hospital, Gynecology and obstetrics Department, Bondy, Seine Saint Denis, France
NCT04941625	150	Other	Observational	Observational model: cohort; time perspective: prospective	31 Dec 2021	Chang Gung Memorial Hospital, Chiayi, Taipei, Taiwan
NCT04767711	46	Other; industry	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: quadruple (participant, care provider, investigator, outcomes assessor); primary purpose: treatment	1 Mar 2023	Geriatric Medicine, Sahlgrenska University Hospital, MÃ¶lndal, Sweden
NCT02375854	200	Other	Observational	Observational model: cohort; time perspective: prospective	Dec 2030	Jack D. Weiler Hospital, Bronx, NY, USA
NCT03782610	675	Other; NIH	Observational	Observational model: cohort; time perspective: prospective	Dec 2025	Nationwide Children's Hospital Main Campus Neonatal Intensive Care Unit, Columbus, OH, USA; Nationwide Children's Neonatal Intensive Care Unit at The Ohio State University Wexner Medical Center, Columbus, OH, USA; Nationwide Children's Neonatal Intensive Care Unit at OhioHealth Riverside Methodist Hospital, Columbus, OH, USA; Nationwide Children's Hospital Neonatal Intensive Care Unit at OhioHealth Grant Medical Center, Columbus, OH, USA
NCT02299921	100	Other; NIH	Observational	Observational model: cohort; time perspective: prospective	30 Apr 2024	The University of Colorado Hospital, Aurora, CO, USA
NCT04508049	27	Other; NIH	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: screening	Sep 2023	Mayo Clinic in Rochester, Rochester, MN, USA
NCT04900688	150	Other	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: treatment	15 Aug 2025	Vancouver General Hospital, Vancouver, British Columbia, Canada; Western University, London, Ontario, Canada; HÃ´pital Maisonneuve-Rosemont (HMR), MontrÃ©al-Est, Quebec, Canada; Centre Hospitalier de l'UniversitÃ© de MontrÃ©al (CHUM), MontrÃ©al, Quebec, Canada; CHU de QuÃ©bec-UniversitÃ© Laval, QuÃ©bec, Quebec, Canada; University of Saskatchewan, Saskatoon, Saskatchewan, Canada
NCT05348694	160	Other; industry	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: triple (participant, investigator, outcomes assessor); primary purpose: prevention	May 2025	Australian Catholic University, Melbourne, Victoria, Australia

Table 3 (continued)

NCT number	Enrollment	Funded by	Study type	Study designs	Completion date	Locations
NCT05434286	75	Other	Observational	Observational model: cohort; time perspective: prospective	15 Jun 2023	PGIMER, Chandigarh, Delhi, India
NCT04118010	40	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: double (participant, investigator); primary purpose: treatment	Dec 2022	Emory Clinic, Atlanta, GA, USA
NCT05540678	96	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: quadruple (participant, care provider, investigator, outcomes assessor); primary purpose: treatment	Nov 2024	Kinderklinik Bern, Berne, Switzerland
NCT05032937	11	Other; industry	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: diagnostic	1 Jul 2023	First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu, China
NCT03874338	670	Other; NIH	Observational	Observational model: other; time perspective: prospective	1 Feb 2024	NYU School of Medicine, New York, NY, USA
NCT04557540	60	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: prevention	15 Sep 2023	Roswell Park Cancer Institute, Buffalo, NY, USA
NCT04391608	80	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: treatment	31 Jul 2022	Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok Noi, Bangkok, Thailand
NCT05477030	52	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: other	23 Feb 2024	ASST FBF Sacco, Milan, Italy
NCT05295784	18	Other	Interventional	Allocation: non-randomized; intervention model: sequential assignment; masking: none (open label); primary purpose: treatment	Jul 2024	Arkansas Children's Hospital, Little Rock, AR, USA; the University of Arkansas for Medical Sciences, Little Rock, AR, USA
NCT05487755	90	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: treatment	Dec 2023	Not available
NCT05420753	22	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: treatment	Feb 2025	Oregon Health and Science University, Portland, OR, USA
NCT04353752	80	Other	Observational	Observational model: cohort; time perspective: prospective	Dec 2025	National Jewish Health, Denver, CO, USA
NCT05600452	30	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: prevention	1 Sep 2024	University of Portsmouth, Portsmouth, Hampshire, UK
NCT04948918	30	Other	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: treatment	20 Sep 2023	Cardiology Research Institute, Tomsk National Research Medical Centre, Russian Academy of Sciences, Tomsk, Russian Federation

Table 3 (continued)

NCT number	Enrollment	Funded by	Study type	Study designs	Completion date	Locations
NCT05359263	222	Other	Interventional	allocation: randomized; intervention model: parallel assignment; masking: triple (participant, care provider, investigator); primary purpose: treatment	15 Apr 2025	Not available
NCT05309785	44	Other	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: treatment	1 Feb 2025	McGill University Health Center Research Institute, Montreal, Quebec, Canada
NCT03904277	28	Other	Observational	Observational model: case–control; time perspective: cross-sectional	31 Dec 2022	Cardiorespiratory and Pulmonary Physiology Lab, Eugene, OR, USA
NCT05208788	135	Other	Observational	Observational model: case–control; time perspective: prospective	31 May 2024	University Children's Hospital Tuebingen, Tuebingen, Germany
NCT04482920	20	Other	Observational	Observational model: cohort; time perspective: prospective	30 Jul 2023	Children's Hospital Colorado, Aurora, CO, USA
NCT05145283	250	Other; industry	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: double (participant, investigator); primary purpose: prevention	Jan 2024	University Hospital Basel, Division of Internal Medicine, Basel, Switzerland
NCT04614064	120	Other	Interventional	Allocation: randomized; intervention model: crossover assignment; masking: none (open label); primary purpose: basic science	May 2023	Imperial Clinical Research Facility, London, UK
NCT05358171	42	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: single (outcomes assessor); primary purpose: prevention	Jun 2024	Virginia Tech, Blacksburg, VA, USA
NCT03841981	50	Other	Observational	Observational model: case–control; time perspective: cross-sectional	31 Dec 2022	Endocrinology and Nutrition, Madrid, Spain
NCT04962594	326	Industry	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: quadruple (participant, care provider, investigator, outcomes assessor); primary purpose: other	Jun 2024	HÃ´pital de la Croix Rousse, Lyon, France
NCT05310396	240	Industry	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: quadruple (participant, care provider, investigator, outcomes assessor); primary purpose: other	Jun 2025	Not available
NCT04610476	270	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: treatment	19 Oct 2025	UniversitÃ¤tsklinikum Erlangen, Erlangen, Bavaria, Germany
NCT03914157	30	Other; NIH	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: none (open label); primary purpose: treatment	1 Dec 2029	Mayo Clinic in Rochester, Rochester, MN, USA
NCT04407481	20	Other	Observational	Observational model: cohort; time perspective: cross-sectional	31 Dec 2023	Children's Hospital Colorado, Aurora, CO, USA

Table 3 (continued)

NCT number	Enrollment	Funded by	Study type	Study designs	Completion date	Locations
NCT04216927	40	Other; industry	Interventional	Allocation: randomized; intervention model: sequential assignment; masking: triple (participant, care provider, investigator); primary purpose: prevention	1 Jun 2025	Cincinnati Children's Hospital Medical Center, Cincinnati, OH, USA
NCT04012177	1884	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: single (outcomes assessor); primary purpose: treatment	31 Dec 2023	Peri-urban slum (Rehri Goth), Karachi, Sindh, Pakistan
NCT03955445	95	Industry	Interventional	Allocation: N/A; intervention model: single group assignment; masking: none (open label); primary purpose: treatment	1 Dec 2028	Novartis Investigative Site, Iowa City, IA, USA; Novartis Investigative Site, Montpellier, France; Novartis Investigative Site, Paris, France; Novartis Investigative Site, Essen, Germany; Novartis Investigative Site, Ranica, BG, Italy; Novartis Investigative Site, Barcelona, Catalunya, Spain; Novartis Investigative Site, Madrid, Spain; Novartis Investigative Site, London, UK; Novartis Investigative Site, Newcastle Upon Tyne, UK
NCT04352231	40	Other	Interventional	Allocation: randomized; intervention model: crossover assignment; masking: none (open label); primary purpose: basic science	Jan 2025	Luxembourg Institute of Health, Esch-sur-Alzette, Luxembourg; Luxembourg Institute of Health, Strassen, Luxembourg
NCT04428190	60	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: double (participant, investigator); primary purpose: treatment	15 Dec 2022	London Health Sciences Centre, London, Ontario, Canada
NCT03897335	80	Other	Interventional	Allocation: randomized; intervention model: parallel assignment; masking: triple (participant, care provider, investigator); primary purpose: treatment	1 Feb 2024	LeBonheur Children's Hospital, Memphis, TN, USA; LeBonheur Children's Hospital, Memphis, TN, USA

be restored following ischemia-induced tissue injury by employing the macrophage-dependent sphingosine-1-phosphate (S1P)–induced downstream release of Lcn2 [61].

Gut

Experimental models lacking Lcn2 exhibited greater sensitivity to bacterial infections including *Escherichia coli* and endotoxin-induced sepsis [62, 63]. It may be possible to treat the conditions with exogenous administration of recombinant Lcn2, but the therapeutic roles of Lcn2 in critically ill patients are yet to be established.

Systematic findings of current clinical trials

In total, 70 current clinical trials were included in this synthesis, with a total enrollment of 12,185 participants. The trials were to be completed between December 2022 and December 2030, spanning 8 years in total. The various conditions of the clinical trials comprised acute kidney injury, acute ischemic stroke, other heart diseases, chronic kidney disease, chronic obstructive pulmonary disease, diabetes, liver injury, heat stress, pregnancy-induced diabetes mellitus, obesity, endocrine disorders, and also SARS-CoV-2. Lcn2 was assessed in all outcomes with interventions and diagnostics comprising devices for hypothermia, extracorporeal shockwave therapy, biomarker testing, aminophylline, caffeine citrate, dapagliflozin, nitric oxide, vitamin D_3, tadalafil, and heat acclimation. The full summary is enlisted in Tables 2 and 3.

Conclusion

Lcn2 has become increasingly relevant in the last few years given its association with many diseases as a prognostic biomarker. As an acute-phase response, Lcn2 modulates cell physiological responses, acting as the bridge between physiology and pathology. Currently, available data for Lcn2 in organs across the body demonstrates its role in physiological and pathological conditions. Importantly, the levels of Lcn2 having a correlation with the severity of disease demonstrate its use as a prognostic biomarker. However, there are gaps in the understanding of Lcn2's contribution to the underlying pathophysiology of the disease. Further mice models and translational studies exploring functional roles are required to understand the contribution of Lcn2 beyond its biomarker potential. Exploring Lcn2 as a therapeutic target in inflammatory and malignant conditions will require further studies, and research is currently underway.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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