

## REVIEW ARTICLE



# A salty symphony: unraveling the tale of uromodulin and sodium sensitivity

Artemios G. Karagiannidis <sup>1</sup>, Marieta P. Theodorakopoulou <sup>1</sup>, Fotini Iatridi <sup>1</sup>, Alberto Ortiz <sup>2</sup> and Pantelis Sarafidis <sup>1</sup>✉

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Uromodulin is a kidney-specific glycoprotein which is uniquely synthesized by the epithelial cells lining the thick ascending limb and early distal convoluted tubule. Among multiple roles in complex physiological and pathological processes, uromodulin mediates renal sodium handling through modulating tubular sodium transporters that reabsorb sodium and therefore is putatively linked to hypertension through generating sodium sensitivity of blood pressure. This review aims to present an updated overview of the role of uromodulin in sodium renal handling and summarize the existing evidence originating from preclinical, genetic, and clinical studies that support a relationship between uromodulin and sodium-sensitive hypertension.

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## INTRODUCTION

Uromodulin is a 85-kDa kidney-specific glycoprotein uniquely expressed by the kidney epithelial cells lining the thick ascending limb (TAL) and early distal convoluted tubule (DCT1) [1, 2] and represents more than 50% of urinary protein excretion in healthy individuals [3]. It was firstly described during the late 19th century as a waxy material (“cilindrina”) found in the tubular lumen [4]. In 1950 Dr. Tamm and Horsfall isolated a urinary mucoprotein inhibiting viral hemagglutination and since then the molecule was known as Tamm-Horsfall protein [5]. It was not until the mid-1980s that a protein purified from the urine of pregnant women showed immunomodulatory activity in vitro and thus the term uromodulin was proposed [6, 7]. Subsequent genomic analyses verified the equivalence of Tamm Horsfall protein and uromodulin [8], allowing the latter term to generally prevail.

Although its history is quite long, the exact role of uromodulin remained unclear for many years [9]. During the past two decades, uromodulin gained extensive scientific interest [10] and was recognized as a multifaceted player in various, both physiological and pathological processes [11–13]. Several different uromodulin forms co-exist (intracellular, urinary, interstitial and serum/circulating), as uromodulin shows a bilateral secretion from kidney epithelial cells (apical and basolateral) [2, 14]. Of note, these different forms possess discrete roles [1]. Intracellular uromodulin regulates protein trafficking, kinases cascades and sodium renal handling [15–18]. Urinary uromodulin (uUMOD) modulates magnesium and calcium renal handling [19, 20] and prevents nephrolithiasis [21] and urinary tract infections [22–24]. Interstitial uromodulin shows immunoregulatory actions [25–27] and serum uromodulin (sUMOD) is an antioxidant [28] and anticarcinogenic agent [29] and acts as a biomarker for renal, cardiovascular and mortality outcomes [30–32]. In addition, the human uromodulin gene (*UMOD*) has been also extensively investigated. Gain-of-function *UMOD* variants cause autosomal dominant tubulointerstitial

kidney disease (ADTKD) [33], while specific *UMOD* variants are associated with incident chronic kidney disease (CKD) [34–36] and hypertension [17, 37].

Recently, uromodulin has been widely recognized as a pivotal factor accounting for sodium homeostasis and thus is proposedly involved in sodium-sensitive hypertension. The aim of this review is to present an updated overview of the role of uromodulin in sodium renal handling and summarize all existing evidence originating from preclinical, genetic, and clinical studies that support a link between uromodulin and sodium-sensitive hypertension.

## SODIUM SENSITIVITY – DEFINITIONS, MECHANISMS AND DIAGNOSIS

The magnitude of the effects of dietary sodium on blood pressure (BP) levels is heterogeneous and varies among populations with different characteristics. Sodium sensitivity is a physiological characteristic of rodents and mammals, including humans, in which changes in BP of some members of the population follow parallel changes in sodium intake [38]. Sodium-sensitive animals experience BP increase with acute sodium loading and BP drop with sodium depletion, whereas the sodium-resistant animals do not. In humans, the trait is normally distributed and the differentiation between sodium-sensitive and sodium-resistant individuals is made by selecting an arbitrary threshold for sodium-induced BP changes [39]. Although the criteria and assessment methods for sodium sensitivity are not standardized, approximately 25% of normotensive and 30–50% of hypertensive patients are sodium-sensitive [39, 40]. In recent years, inverse sodium sensitivity, a new entity concerning 15% of the general population and defined as a paradoxical BP decrease in response to high sodium intake, has been discovered as masquerading within the broad spectrum of sodium resistance [41, 42].

<sup>1</sup>First Department of Nephrology, Hippokraton Hospital, Aristotle University of Thessaloniki, Thessaloniki, Greece. <sup>2</sup>Department of Nephrology and Hypertension, IIS-Fundacion Jimenez Diaz UAM, Madrid, Spain. ✉email: psarafidis1@yahoo.gr

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Based on the Guytonian model of pressure-natriuresis, any increase in BP increases renal perfusion pressure and renal interstitial hydrostatic pressure, decreases sodium reabsorption by the proximal tubules and increases natriuresis leading to the reduction of systemic BP [43]. In response to high sodium intake, kidneys activate the natriuretic [atrial natriuretic peptide (ANP), nitric oxide (NO)] and suppress the anti-natriuretic systems [renin-angiotensin-aldosterone system (RAAS), sympathetic nervous system (SNS)] [44]. In sodium-sensitive individuals, pressure-natriuresis is impaired, with natriuretic and antinatriuretic systems being ineffectively activated and suppressed respectively. Therefore, pressure-natriuresis curve shifts to the right and the slope is declined, as higher BP is required to maintain sodium equilibrium. In contrast, in sodium-resistant individuals, pressure-natriuresis curve shifts to the right without change in slope.

The putative pathophysiological defect leading to sodium sensitivity may involve several mechanisms, the common denominator of which is a natriuretic handicap [39]. Firstly, attenuated stimulation of RAAS by salt restriction [45, 46] and/or blunted suppression of renin in response to a salt load [47] have been manifested. Furthermore, impaired renal circulation [i.e., increased renal vasoconstriction due to reduced levels of endogenous NO [48] and renal kallikrein [49]] and sympathetic nervous system overactivation [50] are common in sodium-sensitive subjects. Lastly, paradoxically reduced levels of atrial natriuretic peptide in response to high-salt intake [51], oxidative stress [52, 53] and hyperinsulinemia [54] also represent fundamental interrelated mechanisms. Our traditional view of sodium sensitivity being a result of kidney malfunction has been lately challenged by recent seminal studies. It seems that nonosmotic sodium accumulation in the skin interstitium bound to negatively charged glycosaminoglycans [55] and endothelial dysfunction due to alterations of endothelial surface layer characteristics [56] also have a pivotal role in sodium homeostasis and sodium sensitivity.

Existing protocols for the diagnosis of sodium sensitivity are roughly divided into outpatient multiday dietary protocols (i.e., diets of specific low and high sodium content given sequentially for a given period, typically ~1 week each) and inpatient acute protocols (i.e., a 3-day protocol consisting of a rapid volume expansion with intravenous normal saline loading on the first day followed by sodium and volume depletion with dietary sodium restriction and diuretic administration upon the second day) [40]. All of these protocols are inherent to limitations, cannot be easily applied in clinical everyday settings, while BP responses to sodium challenge are poorly reproducible [57]. In parallel, dietary protocols lack standardization regarding the sodium content of diets, the order, the exposure duration, and subsequent washout periods between diets [58]. Moreover, given that a subject is classified as sodium-sensitive if the protocol achieves a BP change (either absolute or percentage) by more than an arbitrary threshold predefined by the investigators, the cutoff levels for sodium-sensitive BP responses vary enormously among studies [59]. Consequently, no consensus has been reached on which protocols should be universally used for diagnosing sodium sensitivity.

#### UROMODULIN AND SODIUM TUBULAR TRANSPORTERS – THE LINK TO SODIUM SENSITIVITY

As previously mentioned, uromodulin is synthesized in TAL and shows a bilateral secretion (apical and basolateral). This results in several uromodulin forms, i.e., intracellular, urinary (uUMOD), interstitial and serum uromodulin (sUMOD), each of which possesses a discrete biological role [1]. Mounting evidence has proposed that uromodulin holds a pivotal role in the development of sodium-sensitive hypertension. The physiologic substrate lies in the tight functional connection of intracellular uromodulin with Na<sup>+</sup> tubular handling through modulation of Na<sup>+</sup> transporters' activity.

Firstly, uromodulin increases the distal Na<sup>+</sup> reabsorption by activating the furosemide-sensitive Na<sup>+</sup>-K<sup>+</sup>-2Cl<sup>-</sup> cotransporter type 2 (NKCC2), located in the apical membrane of TAL cells [60]. Uromodulin induces NKCC2 phosphorylation by increasing activated SPAK (STE20/SPS1-related proline/alanine rich kinase) and OSR1 (oxidative stress response 1) kinases levels [17]. This is proposedly performed via up-regulating the full-length SPAK (FL-SPAK) isoform, through activating phosphorylation by members of the with-no-lysine[K] (WNK) kinase family, and down-regulating the kidney-specific SPAK isoform (KS-SPAK), which lacks the catalytic kinase domain and physiologically inhibits the FL-SPAK/OSR1 pathway and hence acts as a negative regulator of NKCC2 activity [17, 61]. This action seems to be facilitated by a chloride-sensing mechanism, as uromodulin promotes NKCC2 phosphorylation under low chloride hypotonic conditions [16]. In parallel, uromodulin opposes the effects of TNF-α [29, 62], which include inhibition of NKCC2 expression and phosphorylation [63–65]. Finally, uromodulin mediates the vesicular translocation of NKCC2 from the endoplasmic reticulum to the apical membrane and thus increases its abundance [66, 67].

Additionally, uromodulin activates another important Na<sup>+</sup> transporter, the thiazide-sensitive, apical Na<sup>+</sup> / Cl<sup>-</sup> cotransporter (NCC) in DCT1; this is achieved by enhancing its SPAK/OSR1-mediated phosphorylation in a similar way with NKCC2 [18].

Apart from these targets, uromodulin upregulates the membrane expression of ROMK apical channels, which physiologically mediate K<sup>+</sup> efflux [68]. These voltage-dependent K<sup>+</sup> channels are functionally coupled with other tubular cation transporters (including NKCC2 and NCC) via creating the required K<sup>+</sup> conductance for the proper function of the latter [69]. Additionally, intraluminal uUMOD (secreted from TAL) reaches and adheres to the apical surface of the downstream collecting duct (CD) cells and thus increases the activity of the vasopressin-regulated water-channel, i.e., aquaporin-2 (AQP2) [70]. This happens by enhancing AQP2 phosphorylation and apical trafficking, possibly through inhibition of AQP2 endocytosis [70]. This effect reveals that uromodulin mediates an effective crosstalk between TAL and CD in order to synergistically retain Na<sup>+</sup> and water.

Recently, Chen et al. proposed that uromodulin could potentially mediate the activity of aldosterone-induced epithelial Na<sup>+</sup> channels (ENaC); this hypothesis was based on the fact that SPAK/OSR1 pathway activates NKCC2, NCC and ENaC in a common way [71]. However, given that uromodulin is exclusively expressed in TAL and DCT1, but not in late distal convoluted tubule (DCT2) and CD, where ENaCs are actually located, it seems rather unlikely that uromodulin could activate these transporters via this pathway, as this would demand the intracellular presence of the protein. In any case, as alternative mechanisms may be entailed (e.g., increase of ENaC apical abundance by intraluminal uUMOD, similarly to AQP2), the potential link between uromodulin and ENaC should be investigated by future studies.

#### STUDIES LINKING UROMODULIN TO SODIUM-SENSITIVE HYPERTENSION

During the last decades, accumulated evidence indicates that uromodulin is crucial in the development of sodium-sensitive hypertension. The following sections outline the key preclinical, genetic, and clinical studies linking uromodulin to hypertension and sodium sensitivity.

##### Preclinical studies

Our current understanding of the connection of uromodulin with sodium sensitivity and hypertension originates largely from preclinical studies, mainly conducted on animal models with uromodulin deficiency or overexpression.

**Animal models under-expressing uromodulin (Uromodulin deficiency).** These studies are based on comparisons between knock-out (*Umod*<sup>-/-</sup> or *UMOD* KO) and wild type (WT) animals. *Umod*<sup>-/-</sup> mice present with urine concentration impairment, polyuria, salt wasting, reduced BP and eGFR [15, 72]. As a compensatory mechanism for Na<sup>+</sup> loss, upregulation of distal tubular sodium transporters (some of which misplaced in the cytoplasm rather than in the apical membrane, e.g., NKCC2 and NCC) occurs [15, 72]. High NaCl load reaching the macula densa activates the tubuloglomerular feedback loop thus decreasing GFR; consequently, GFR increases upon salt loading [72]. Aged *Umod*<sup>-/-</sup> mice presents with kidney calcification, hypertension and oliguria. Of importance, they are unresponsive to furosemide, but display a suboptimal response to metolazone, which like thiazides targets NCC. However, they are hyperresponsive to acetazolamide, which blocks carbonic anhydrase in proximal tubules. The inactivity of NKCC2 and NCC would explain both the lacking or low response to furosemide and metolazone and the hyperresponsiveness to proximal diuretics, given the inability of the distal nephron to compensate by increasing Na<sup>+</sup> reabsorption [67, 73]. However, findings in elderly mice are difficult to interpret in view of the anatomical defect and the lack of information on kidney function [67, 73]. In young mice, defective cell membrane NKCC2 resulting from uromodulin absence is likely responsible for polyuria and salt wasting, since furosemide only instigate a partial diuretic and natriuretic response as compared to the full response manifested in WT mice [67].

As long as BP levels are concerned, young *Umod*<sup>-/-</sup> mice have lower baseline BP levels compared to WT mice under basal salt conditions. However, their low BP is resistant to dietary salt, as it does not increase upon chronic load with 2% NaCl in drinking water, while WT mice exhibit ~33% BP rise [72]. The failure to increase BP was attributed to a urinary salt-wasting phenotype, with higher urinary excretion of Na<sup>+</sup>, K<sup>+</sup> and Cl<sup>-</sup> (2- to 3-fold higher levels than in WT mice) in response to salt loading. Consequently, uromodulin deficiency causes a leftward shift of pressure-natriuresis curve compared to WT mice when exposed to salt loading, a fact suggesting that uromodulin deficiency results in the loss of the sodium sensitivity of BP [72].

**Animal models with defective uromodulin processing.** In hepsin-deficient mice, uromodulin cannot be properly cleaved and excreted in urine; therefore, in these animals uMOD levels are low and instead intracellular uromodulin accumulates; the latter event initiates endoplasmic reticulum stress response resulting in tubular damage and abnormal regulation of Na<sup>+</sup> handling and BP [74]. Salt loading (2% NaCl in drinking water) further increases intracellular uromodulin accumulation and cytotoxicity, causing evident histological tubular injury, salt wasting and unchanged BP, while WT mice display sodium-sensitive BP increments. Thus, these models seem to recapitulate findings from *Umod*<sup>-/-</sup> models [72].

**Animal models overexpressing uromodulin (Uromodulin excess).** Transgenic mice harboring one (heterozygous) or two (homozygous) risk *UMOD* variants overexpress uromodulin [17]. Compared to control mice, they have higher NKCC2 activity and notably there is a positive correlation between activated NKCC2 and *UMOD* gene dosage [17]. This leads to increased tubular Na<sup>+</sup> reabsorption and hypertension, left ventricular hypertrophy, and histological findings of CKD with apparently preserved kidney function [17]. Regarding their response to loop diuretics, furosemide leads to increased natriuresis and significantly lower BP levels in hypertensive transgenic than in normotensive control mice [17]. Hypertension is *Umod* dosage-dependent and sodium-sensitive, as after an extremely salt-depleted diet (>20-fold decrease in dietary NaCl) BP is normalized in transgenic mice, while in normotensive WT mice no change on BP is evident under

these experimental conditions [17]. Consequently, uromodulin excess causes a rightward shift of pressure-natriuresis curve compared to WT mice when exposed to salt restriction, indicating that uromodulin excess results in the acquisition of the sodium sensitivity of BP [1].

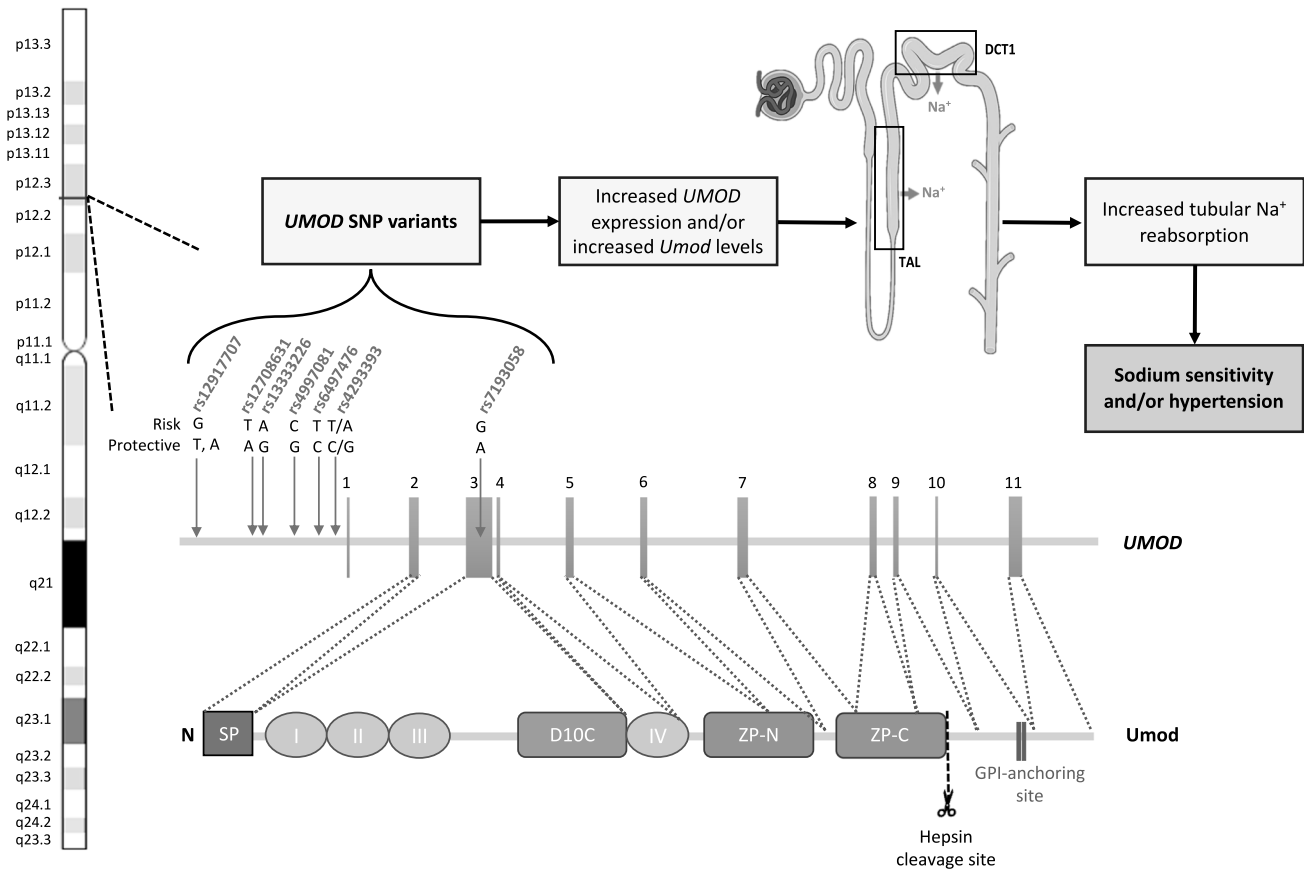
**Animal studies assessing the impact of dietary salt on uromodulin levels.** Studies on normotensive and hypertensive rats provide data regarding the uromodulin's relation to salt intake and sodium sensitivity. Salt loading seems to increase uromodulin mRNA and medullary protein in normotensive Sprague-Dawley rats [75] and lead to intracellular uromodulin retention in hypertensive [stroke-prone spontaneously hypertensive rat (SHRSP)] and normotensive rats (Wistar-Kyoto) [76]. In the latter study, 24-h uMOD excretion was studied and decreased irrespective of BP changes upon salt loading in both rat strains [76]. However, some discrepancies were noted, as in the latter study total kidney (as opposed to medullary) uromodulin protein was unaltered by salt loading in both groups and mRNA was unchanged or even decreased. On the other hand, administration of furosemide -but not chlorothiazide- in normotensive rats on high salt diet instigate greater increments in kidney uromodulin's mRNA levels than high or low salt diet alone [75]. These preliminary results imply that high dietary sodium intake per se is capable of increasing uromodulin levels, thus setting the scenario for unwanted tubular Na<sup>+</sup> retention. However, conflicting results from clinical studies in humans [77, 78] necessitate further research to shed light on the interplay between sodium and uromodulin.

### Genetic human studies

Genetic human studies of the past two decades have largely proposed a strong association of uromodulin with sodium sensitivity. These studies have investigated the link of specific *UMOD* variants with risk for sodium-sensitive hypertension, mostly of single nucleotide polymorphisms (SNPs) in the *UMOD* promoter region. From a pathophysiological point of view, *UMOD* risk variants are thought to result in sodium sensitivity through increased *UMOD* expression and increased uMOD levels, leading subsequently to increased tubular Na<sup>+</sup> reabsorption via activation of tubular sodium transporters (Fig. 1).

**Genome wide association studies (GWAS).** The first and one of the most important studies was conducted by Padmanabhan et al. and examined a common variation rs1333226 in the *UMOD* promoter region [37]. They used an extreme case-control design on a large sample of 21,466 hypertensive cases and 18,240 controls and found that minor G allele was associated with lower uMOD, lower BP levels and lower risk for hypertension incidence (crude OR = 0.87, 95% CI: 0.84–0.91). Of note, this association remained significant after adjustment for age, sex, BMI and eGFR (adjusted OR = 0.893, 95% CI: 0.81–0.89) [37]. However, a smaller (n = 910) Chinese cross-sectional study in the general population had opposite results, showing slightly higher DBP for the G allele carriers of the same variant (83.1 ± 10.7 vs. 81.2 ± 10.2; p = 0.046) [79]. These findings seem inconsistent with the fact that minor G allele encodes for lower uMOD and therefore lower BP levels would be anticipated. However, this discrepancy may be explained by different studied populations and by the fact that the latter study did not directly examine the association with hypertension risk.

Furthermore, rs4293393 represents another variant of interest, with T being the risk allele. In a cohort of 471 untreated hypertensive patients, though baseline BP levels did not differ, administration of furosemide led to increased natriuresis and larger BP decrease in patients homozygous for the T risk allele compared to carriers of the C protective allele ( $\Delta$ SBP:  $-4.3 \pm 0.95$  vs  $-0.9 \pm 1.61$ , p = 0.06;  $\Delta$ DBP:  $-2.0 \pm 0.64$  vs  $0.47 \pm 1.00$ ,



### Chr 16

**Fig. 1** *UMOD* SNP variants associated with sodium-sensitive hypertension.

$p = 0.037$ ) [17]. The relation of this variant with hypertension was further confirmed by a recent study in ~650,000 veterans showing that T (or A) major allele increased the risk for hypertension incidence compared to G (or C) minor allele (OR = 1.03, 95% CI: 1.02–1.05) [80].

Additionally, the minor T allele of the rs12917707 *UMOD* promoter variant was linked to lower hypertension risk in type 2 diabetic patients compared to the major G allele (OR = 0.86;  $p = 0.04$ ) [81]. In parallel, this variant was significantly associated with longitudinal SBP changes over a 8-year follow-up period in a large Chinese cohort ( $\beta = 0.023$ ;  $p < 0.05$ ) [82]. Similar results indicative of a relationship with BP levels have been also reported for rs12708631 [82], rs4997081 [83], rs6497476 [79] and rs7193058 [83].

**Mendelian randomization (MR) studies.** Solid evidence has been recently gained by large genetic studies conducted with the MR analysis (Table 1). This method investigates a putative causality between exposure to specific gene variants and an outcome of interest by implementing Mendel's law; thus, principles of a randomized controlled trial are applied to observational data [84]. The concept that gene variants are randomly inherited leads to random allocation in the population. Given that these genetic variants serve as unconfounded indicators, differences in the outcome between variant carriers and non-carriers suggest differences in exposure [85]. Lately, this method has been widely utilized due to the extended availability of published GWAS and biorepository resources.

By testing the causal effect of a phenotype (exposure) on another phenotype (outcome), MR analysis uses the principles of instrumental variable analysis with the genotype of a genetic

variant serving as the instrument (instrumental variable) [86]. Each MR analysis should meet three core assumptions to obtain valid evaluations: (a) relevance, i.e., the variant should be closely associated with the outcome; (b) independence, i.e., the variant should not be associated with any potential confounders; and (c) exclusion restriction, i.e., the variant should be associated with the outcome through the exposure and not through the confounders [87]. Violation of the exclusion restriction assumption will occur in the case of a direct, not solely dependent on the exposure, causal effect of the variant on the outcome or a causal effect of the outcome on the exposure (reverse causation) [86].

Firstly, Ponte et al. performed a two-sample MR study on four GWAS consortia including ~750,000 Europeans, in order to investigate the causal association between BP and uUMOD levels, as predicted by the *UMOD* promoter variant rs12917707 and the *PDILT* intronic variant rs4494548 (located upstream of *UMOD*) [88]. Higher predicted uUMOD levels were significantly associated with lower eGFR, higher odds for eGFR decline or CKD, and higher SBP or DBP. SNPs associated with each 1-SD higher predicted uUMOD were linked to an increase in SBP by 0.06 SD ( $\beta = 0.06$ , 95% CI: 0.032–0.088;  $p = 2.64 \times 10^{-5}$ ) and DBP by 0.082 SD ( $\beta = 0.082$ , 95% CI: 0.045–0.12;  $p = 1.34 \times 10^{-5}$ ), but no reverse causal effect was detected. Of note, the effect of uUMOD on BP was mediated by eGFR ( $\beta_{\text{indirect}} = 0.02$ ;  $p = 0.014$ ; mediation proportion = 28%), suggesting that it was not a direct consequence of uUMOD itself, but of CKD [88].

A study with similar design including over 1,000,000 participants revealed that hypertension incidence is linked to the same SNPs as in the prior study encoding for high uUMOD (OR = 1.036, 95% CI: 1.029–1.044;  $p < 0.001$ ) and to 16 SNPs encoding for high sUMOD levels (OR = 1.013, 95% CI: 1.009–1.018;  $p < 0.001$ ) [89].

**Table 1.** Major Mendelian randomization (MR) studies linking *UMOD* SNP variants to sodium-sensitive hypertension.

Author, Year	MR design type	Applied methods for evaluating MR assumptions	SNPs in the MR analysis	Participants	Main Results
Ponte et al., 2021 [88]	Two sample MR	<ul style="list-style-type: none"> <li>Inverse-variance weighted MR method</li> <li>MR-Egger regression analysis</li> <li>Weighted median estimation</li> <li>Weighted mode-based estimation</li> </ul>	<ul style="list-style-type: none"> <li>rs12917707</li> <li>rs4494548</li> </ul>	757,601 Europeans (4 genome wide association studies consortia)	<ul style="list-style-type: none"> <li>Causality <i>uUMOD</i> → BP: Confirmed</li> <li>↑ 1 SD <i>uUMOD</i>: ↑ SBP/DBP by 0.06/0.082 SD (<math>\beta = 0.06</math>; 95% CI: 0.032–0.088 and <math>\beta = 0.082</math>; 95% CI: 0.045–0.12, respectively)</li> <li>Causality BP → <i>uUMOD</i>: Not detected.</li> <li><i>uUMOD</i>: ↔ SBP (<math>\beta = 0.033</math>, SE = 0.042, <math>p = 0.44</math>), ↔ DBP (<math>\beta = 0.016</math>, SE = 0.041, <math>p = 0.7</math>)</li> <li><i>uUMOD</i> effect on BP mediated by eGFR.</li> <li><math>\beta_{\text{indirect}} = 0.02</math> (<math>p = 0.014</math>), mediation proportion = 28%</li> </ul>
You et al., 2021 [89]	Two sample MR	<ul style="list-style-type: none"> <li>Inverse variance-weighted MR method</li> <li>MR-Egger regression analysis</li> <li>Weighted median estimation</li> <li>MR-PRESSO</li> </ul>	<ul style="list-style-type: none"> <li><b>For <i>uUMOD</i>:</b></li> <li>rs12917707</li> <li>rs4494548</li> <li><b>For <i>sUMOD</i>:</b></li> <li>rs1155876</li> <li>rs12446492</li> <li>rs12708631</li> <li>rs12917707</li> <li>rs12920537</li> <li>rs12920708</li> <li>rs12930599</li> <li>rs4380062</li> <li>rs4462596</li> <li>rs4558425</li> <li>rs6497445</li> <li>rs7187470</li> <li>rs7192921</li> <li>rs7198000</li> <li>rs7499304</li> <li>rs8060932</li> <li>rs7498776</li> </ul>	1,194,020 participants (6 datasets from UK Biobank, International Consortium for Blood Pressure)	<ul style="list-style-type: none"> <li><i>uUMOD</i> → BP: Confirmed</li> <li>↑ <i>uUMOD</i>: ↑ hypertension incidence (OR = 1.04; 95% CI: 1.03–1.04)</li> <li>↑ 1-unit <i>uUMOD</i>: ↑ SBP (<math>\beta = 1.1</math> mmHg, SE = 0.25, <math>p = 8.92 \times 10^{-6}</math>) and ↑ DBP (<math>\beta = 0.88</math>, SE = 0.19, <math>p = 4.38 \times 10^{-6}</math>)</li> <li><i>sUMOD</i> → BP: Confirmed</li> <li>↑ <i>sUMOD</i>: ↑ hypertension risk (OR 1.01; 95% CI: 1.01–1.02).</li> <li>↑ 1-unit <i>sUMOD</i>: ↑ SBP (<math>\beta = 0.37</math>, SE = 0.07, <math>p = 1.26 \times 10^{-7}</math>) and ↑ DBP (<math>\beta = 0.31</math>, SE = 0.05, <math>p = 3.43 \times 10^{-7}</math>)</li> </ul>
Jian et al., 2022 [90]	Two sample bidirectional MR Multivariable MR	<ul style="list-style-type: none"> <li>Inverse variance-weighted MR method</li> <li>MR-Egger regression analysis</li> <li>Weighted median estimation</li> <li>Weighted mode-based estimation</li> <li>MR-PRESSO</li> </ul>	<ul style="list-style-type: none"> <li>rs13335818</li> <li>rs77924615</li> <li>rs9672398</li> <li>rs12917707</li> <li>rs4494548</li> </ul>	757,601 individuals (UK Biobank, International Consortium of Blood Pressure)	<ul style="list-style-type: none"> <li><i>uUMOD/UCr</i> → BP: Confirmed</li> <li>↑ 1 SD <i>uUMOD</i>: ↑ 0.08 SD in SBP (<math>\beta = 0.08</math>, 95% CI: 0.07–0.10) and ↑ 0.12 SD in DBP (<math>\beta = 0.12</math>, 95% CI: 0.11–0.13)</li> <li>BP → <i>uUMOD/UCr</i>: Not Confirmed</li> <li><i>uUMOD</i> → CVD: Confirmed</li> <li>OR = 1.08 (95% CI: 1.02–1.14) in univariable model</li> <li><i>uUMOD</i> effect on CVD mediated by SBP and DBP</li> <li>OR = 0.98 (95% CI, 0.92–1.05) and OR = 0.99 (95% CI, 0.92–1.06) after adjusting for SBP and DBP respectively</li> <li>Mediation analysis: for SBP (<math>\beta = 1.05</math>, 95% CI: 1.04–1.06, mediation proportion = 69%) and DBP (<math>\beta = 1.07</math>, 95% CI: 1.05–1.08, mediation proportion = 87%)</li> </ul>

95% CI, 95% Confidence Interval; BP blood pressure, CVD cardiovascular disease, DBP diastolic blood pressure, eGFR estimated glomerular filtration rate, MR-PRESSO mendelian randomization pleiotropy residual sum and outlier, OR odds ratio, SBP systolic blood pressure, SD standard deviation, SE standard error, *sUMOD* serum uromodulin, *UCr* urinary creatinine, *uUMOD* urinary uromodulin.

In this analysis, higher predicted uUMOD and sUMOD levels were causally associated with higher SBP and DBP (Table 1); nonetheless, this study did not report on the influence of eGFR [89].

Finally, a third study assessing the relationship of cardiovascular events with the synonymous UMOD rs13335818 and the PDILT rs77924615 variants linked to uUMOD levels, revealed that an increase in uUMOD/UCr ratio was associated with increases in SBP/DBP ( $\beta = 0.08$ , 95% CI: 0.07–0.10 and  $\beta = 0.12$ , 95% CI: 0.11–0.13, respectively) but no reverse relation was manifested [90]. Notably, the increased risk for myocardial infarction due to higher uUMOD in univariable model (crude OR = 1.08, 95% CI: 1.02–1.14) was attenuated after adding BP in the model (SBP adjusted OR = 0.98, 95% CI: 0.92–1.05 and DBP adjusted OR = 0.99, 95% CI: 0.92–1.06) [90]. The above observations were explained by the mediation analysis revealing that the effect of uUMOD on myocardial infarction was mainly mediated by SBP ( $\beta = 1.05$ , 95% CI: 1.04–1.06, mediation proportion = 69%) and DBP ( $\beta = 1.07$ , 95% CI: 1.05–1.08, mediation proportion = 87%) [90].

### Clinical studies

Table 2 summarizes the existing evidence originating from clinical studies that have investigated the relationship between uromodulin and sodium sensitivity and/or sodium-sensitive hypertension.

*Studies in general population.* In general population, only two studies have investigated the association of uromodulin and BP response to salt intake. In an interventional study in 30 healthy individuals who were genetically predisposed to hypertension, 1 week of low-salt (10 mmol sodium/day) was followed by 1 week of high-salt diet (240 mmol sodium/day) [77]. The study showed that 12-h nighttime uUMOD excretion rate during low salt diet was lower than baseline and during high-salt intake; however, 24-h uUMOD excretion rate did not differ between the three time-points, meaning that daytime uUMOD excretion differences occurred in the opposite direction than nighttime ones [77]. After high-salt diet, subjects with sodium sensitivity of BP above the median compared to those below the median displayed higher 24-h uUMOD; in parallel, sodium sensitivity correlated moderately with uUMOD/uCr ratio ( $r = 0.37$ ,  $p < 0.05$ ), but apparently not to 24-h uUMOD which is a more relevant variable [77].

The above association of uromodulin with sodium sensitivity was further supported by a recent study in a large cohort of 948 European adults [91]. Individuals classified in the highest uUMOD strata (i.e., with 24-h uUMOD above the sex-specific median) showed a significant adjusted association of higher 24-h SBP ( $\beta = 0.78$ , 95% CI: 0.28–1.28) and a non-significant trend of higher DBP levels in parallel with an increase in 24-h urinary  $\text{Na}^+$  excretion [91]. Conversely, participants in the lowest uUMOD strata (i.e., 24-h uUMOD below the median) presented a significant association of lower 24-h ambulatory DBP levels ( $\beta = -0.30$ , 95% CI: -0.60, -0.01) and a non-significant trend for lower 24-h SBP in parallel to an increase in 24-h urinary  $\text{Na}^+$  excretion [91]. These results were the first to reveal that uromodulin may have a differential impact on the development of either sodium sensitivity or inverse sodium sensitivity, depending on uUMOD levels. The association of 24-h uUMOD levels with both UMOD rs12917707 variants (i.e., G and T alleles) was confirmed, while subjects with higher uUMOD exhibited higher eGFR [91]. Interestingly, not only  $\text{Na}^+$  excretion, but also higher urine volume (e.g., following water loading) leads to increased 24-h uUMOD excretion without altering uUMOD concentration [92].

*Studies in hypertensive patients.* Evidence proposing a link between uromodulin and sodium sensitivity in hypertensive patients are abundant. A preliminary Polish interventional study in 65 hypertensive and 23 normotensive patients showed no difference in baseline 24-h uUMOD levels between the two groups

[93]. However, after allocating hypertensive patients to receive furosemide ( $n = 24$ ), nifedipine ( $n = 21$ ) or propranolol ( $n = 20$ ) for 10 days, a significant increase in uUMOD was noted only in the furosemide group [93]. In a subsequent study of the same group, the authors tried to investigate the relationship between uUMOD levels and age in healthy (normotensive) and hypertensive patients. To this purpose, 15 young (<60 years) normotensive, 15 young hypertensive, 15 older (>60 year) normotensive and 31 older hypertensive patients were enrolled [94]. uUMOD levels were significantly lower in elderly normotensive patients compared to all other groups, but not in elderly hypertensive ones [94]. The fact that uUMOD was higher in elderly hypertensive compared to normotensive subjects could be either the cause or the consequence of hypertension through a renal adaptation to the chronic hypertensive state; the latter hypothesis seems more likely as a significant positive correlation between uUMOD and mean arterial pressure ( $r = 0.40$ ,  $p < 0.05$ ) was evident only in elderly hypertensive patients [94].

In newly diagnosed, treatment-naïve males with mild hypertension (19 sodium-sensitive, i.e., >4 mmHg increase in mean BP after an acute 2 L saline infusion, vs 37 sodium-resistant), uUMOD levels assessed via Western blot in spot urine samples were significantly higher in both hypertensive groups than in healthy controls (both  $p < 0.001$ ); however, no difference was evident when sodium-sensitive were compared to sodium-resistant patients [95]. ROC curves for predicting sodium-sensitive and sodium-resistant hypertension based on uUMOD levels showed AUC of 0.804 (95% CI: 0.696–0.904) and 0.793 (95% CI: 0.679–0.879) respectively [95]. Urinary samples with lower uUMOD levels had higher urinary  $\text{Na}^+$  concentration [95]. In a subsequent analysis of this study, urinary proteome changes during the salt load test were investigated among a subgroup of these patients (6 sodium-sensitive, 10 sodium-resistant). uUMOD was measured in spot urine samples collected in the 2 h of equilibration (T0), during the 2 h of saline infusion (T120) and along the 2 h of recovery (T240) [96]. Both sodium-sensitive and sodium-resistant patients exhibited comparable increases in uUMOD at T120 as compared to T0 ( $0.01 < p < 0.05$ ) with restoration to basal levels at T240 [96]. Unfortunately, in both analyses, the methods (Western blot in spot urine samples) are suboptimal.

In another interventional study [83], 24-h uUMOD, and sUMOD levels were determined in a Chinese cohort of 16 hypertensive and 64 normotensive adults that followed consecutively a normal, a low-salt (50 mmol  $\text{Na}^+$ /day, actual mean urinary excretion 91 mmol/day) and a high-salt diet (300 mmol  $\text{Na}^+$ /day, urinary excretion 266 mmol/day) lasting for 1 week each. Overall, patients behaved as sodium-sensitive. Both uUMOD and sUMOD levels were significantly reduced during high salt diet compared to baseline. uUMOD, but not sUMOD, correlated inversely with 24-h urinary  $\text{Na}^+$  excretion. During both intervention phases, sUMOD levels were positively correlated with SBP ( $r = 0.184$ ,  $p = 0.037$ ) and DBP ( $r = 0.209$ ,  $p = 0.018$ ) [83]. However, this study has several major issues, ranging from the ~50% decrease in uUMOD in low-salt diet versus baseline, which further decreases on high-salt diet, to the extremely low 24-h uUMOD excretion (mean value < 3 mg/24 h in the three conditions). Therefore, given also that the findings regarding uUMOD were inconsistent with those presented earlier by Torffvit et al. [77], the results of this study should be interpreted with caution.

Bakhom et al. [97], in their ad hoc analysis of 157 participants in the Dietary Approaches to Stop Hypertension (DASH)-Sodium Trial, showed no associations between baseline 24-h uUMOD and change in office BP levels as a response to diets of different salt intake (high: 150 mmol  $\text{Na}^+$ /day, moderate: 100 mmol  $\text{Na}^+$ /day, low: 50 mmol  $\text{Na}^+$ /day). There was no interaction between baseline uUMOD and dietary  $\text{Na}^+$  contents on end-of-intervention SBP levels; similarly, both crude and adjusted (for age, sex, race and BMI) regression models yielded non-significant

**Table 2.** Clinical studies investigating the relation between uromodulin and sodium-sensitive hypertension.

Author, Year	Study design	Participants	Uromodulin form or uMOD variant assessed	Main Results
<b>General population</b>				
Torffvit et al., 2004 [77]	Interventional	30 genetically hypertension-prone individuals ( $\geq 1$ first-degree HT relative)	uUMOD (24-h and 12-h nighttime)	<ul style="list-style-type: none"> <li>• ↓ nighttime uUMOD excretion rate after low-salt (10 mmol Na<sup>+</sup>/day) intake [11.7 <math>\mu</math>g/min (range:1.3–80.1) vs baseline [19.5 (5.1–56.2), <math>p &lt; 0.05</math>] and vs high-salt (230 mmol Na<sup>+</sup>/day) [23.1 (2.5–82.7), <math>p &lt; 0.01</math>].</li> <li>• No change in 24-h uUMOD excretion ratio in low [16.6 (1.0–56.5)] vs baseline [19.8 (1.1–83.7)] and vs high-salt [15.0 (0.6–47.8)]; <math>p &gt; 0.05</math> for both comparisons].</li> <li>• Patients with high vs low sodium sensitivity after 1 week of high salt intake: 124-h uUMOD excretion rate [23.5 <math>\mu</math>g/min (5.3–47.8) vs. 10.3 (0.6–46.9); <math>p &lt; 0.05</math>]</li> <li>• Moderate correlation between sodium sensitivity and uUMOD/uCr after high salt intake (<math>r = 0.37</math>, <math>p &lt; 0.05</math>).</li> </ul>
Ponte et al., 2021 [91]	Cross-sectional	948 European adults [Swiss Kidney Project on Genes in Hypertension (SKIPOGH) cohort study]	uUMOD (24-h)	<ul style="list-style-type: none"> <li>• High uUMOD strata: positive association between urinary Na<sup>+</sup> and 24-h SBP (<math>\beta = 0.78</math>, 95% CI: 0.28,1.28)</li> <li>• Low uUMOD strata: negative association between urinary Na<sup>+</sup> and 24-h DBP (<math>\beta = -0.30</math>, 95% CI: -0.60, -0.01)</li> <li>• A trend for positive association between urinary Na<sup>+</sup> and 24-h DBP in the highest uromodulin strata and negative association between urinary Na<sup>+</sup> and 24-h SBP in the lowest one.</li> </ul>
<b>Hypertensive patients</b>				
Dulawa et al., 1992 [93]	Interventional	65 HT patients and 23 normotensive controls	uUMOD (24-h)	<ul style="list-style-type: none"> <li>• No difference in baseline uUMOD levels between HT and controls</li> <li>• In HT patients: significant increase in uUMOD in furosemide group</li> <li>• In HT patients: no significant change in uUMOD in nifedipine or propranolol groups</li> </ul>
Dulawa et al., 1998 [94]	Cross-sectional	15 young (YC) and 15 older (>60yo) healthy control (OC), 15 young HT (YHT) and 31 older (>60yo) HT patients (OHT)	uUMOD (24-h)	<ul style="list-style-type: none"> <li>• No difference in uUMOD levels between YHT and YC (28.9 <math>\pm</math> 5.7 vs 27.8 <math>\pm</math> 5 mg/24 h, <math>p = \text{ns}</math>)</li> <li>• ↓ uUMOD levels in OC compared to YC (15.1 <math>\pm</math> 2.3 vs 27.8 <math>\pm</math> 5 mg/24 h, <math>p &lt; 0.01</math>), YHT (15.1 <math>\pm</math> 2.3 vs 28.9 <math>\pm</math> 5.7 mg/24 h, <math>p &lt; 0.01</math>), and OHT (15.1 <math>\pm</math> 2.3 vs 24.1 <math>\pm</math> 1.9, <math>p &lt; 0.05</math>)</li> <li>• No difference in uUMOD in OHT vs YC and vs YHT</li> <li>• Significant positive correlation between uUMOD and MAP only in OHT (<math>r = 0.40</math>, <math>p &lt; 0.05</math>)</li> </ul>
Matafora et al., 2014 [95]	Cross-sectional	56 newly diagnosed, untreated, mild HT patients [classified after acute load salt test as sodium-sensitive, $n = 19$ and sodium-resistant, $n = 37$ ] and 19 healthy controls	uUMOD (spot urine specimen)	<ul style="list-style-type: none"> <li>• Sodium-sensitive and sodium-resistant patients vs. controls: ↑ uUMOD by Western blot (for both <math>p &lt; 0.001</math>)</li> <li>• Sodium-sensitive vs. sodium-resistant patients: no difference in uUMOD (<math>p = \text{ns}</math>)</li> <li>• ROC curves for predicting sodium-sensitive and sodium-resistant hypertension based on uUMOD levels: AUC = 0.804 (95% CI: 0.696–0.904) and AUC = 0.793 (95% CI: 0.679–0.879)</li> <li>• BP levels in high vs. low uUMOD group: no difference in SBP/DBP (<math>p = \text{ns}</math> for both).</li> <li>• ↑ urinary Na<sup>+</sup> excretion in low vs. high uUMOD group (<math>p &lt; 0.001</math>).</li> </ul>

Table 2. continued

Author, Year	Study design	Participants	Uromodulin form or uMOD variant assessed	Main Results
Bakhoum et al., 2021 [97]	Ad hoc analysis of randomized controlled trial	157 participants from DASH-Sodium trial	uUMOD (24-h)	<ul style="list-style-type: none"> <li>No interaction between dietary Na<sup>+</sup> level and uUMOD in <math>\Delta</math>SBP in end-of-intervention from low (50 mmol/day) to high Na<sup>+</sup> (150 mmol/day) intake (<math>p = 0.86</math>).</li> <li>No association between <math>\Delta</math>SBP in end-of-intervention from low to high Na<sup>+</sup> and uUMOD in the unadjusted (<math>\beta = -0.86</math>, <math>p = 0.28</math>) and adjusted (<math>\beta = -0.68</math>, <math>p = 0.42</math>) models.</li> <li>No significant difference in <math>\Delta</math>SBP within intervention groups from baseline to end-of-intervention based on uUMOD tertiles (high Na<sup>+</sup> intake, <math>p = 0.85</math>; moderate Na<sup>+</sup> intake, <math>p = 0.81</math>; low Na<sup>+</sup> intake, <math>p = 0.96</math>).</li> </ul>
Du et al., 2021 [83]	Interventional	16 HT patients and 64 normotensive controls	uUMOD (24-h), sUMOD	<ul style="list-style-type: none"> <li>No correlation between sUMOD and 24-h urinary Na<sup>+</sup> (<math>r = -0.140</math>, <math>p = 0.113</math>)</li> <li>↓ uUMOD approximately 50% in low salt vs baseline (<math>p</math> ns), and on high-salt vs. low-salt diet (<math>28.7 \pm 6.7</math> vs. <math>157.2 \pm 21.7</math> ng/ml, <math>p = 0.001</math>)</li> </ul>
Matafora et al., 2021 [96]	Cross-sectional	16 newly diagnosed, untreated, mild HT patients classified after acute load salt test as sodium-sensitive ( $n = 6$ ) and sodium-resistant ( $n = 10$ ).	uUMOD (spot urine specimens)	<ul style="list-style-type: none"> <li>In both sodium-sensitive and sodium-resistant patients: ↑ uUMOD at T120 as compared to T0 (<math>0.01 &lt; p &lt; 0.05</math>) with restoration to basal levels at T240 (<math>p = ns</math>)</li> </ul>
Josipović et al., 2023 [100]	Cross-sectional	326 young untreated middle-aged (18–45yo) subjects: 103 with optimal BP (OBP), 140 with prehypertension (PHT) and 80 with HT	uUMOD (spot urine specimens)	<ul style="list-style-type: none"> <li>No difference in nonindexed and indexed uUMOD levels between groups.</li> <li>In PHT, positive correlation between indexed uUMOD and FENa (<math>r = 0.208</math>, <math>p = 0.02</math>) and negative correlation between indexed uUMOD and 24-h Na<sup>+</sup> excretion (<math>r = -0.188</math>, <math>p = 0.03</math>)</li> <li>In HT, negative correlation between indexed uUMOD and 24-h Na<sup>+</sup> excretion (<math>r = -0.301</math>, <math>p = 0.03</math>)</li> <li>In OBP, positive correlation between nonindexed uromodulin and SBP sleep-through surge (<math>r = 0.372</math>, <math>p = 0.03</math>).</li> <li>In PHT, negative correlation between nonindexed uUMOD and DBP dip (<math>r = -0.287</math>; <math>p = 0.03</math>) and between indexed uUMOD and 24-h PP (<math>r = -0.28</math>, <math>p = 0.04</math>) and nighttime PP (<math>r = -0.311</math>, <math>p = 0.02</math>)</li> <li>In HT, negative correlation between nonindexed uUMOD and MAP (<math>r = -0.289</math>, <math>p = 0.04</math>) and between indexed uUMOD and 24-h DBP (<math>r = -0.289</math>, <math>p = 0.04</math>), daytime DBP (<math>r = -0.273</math>, <math>p = 0.04</math>), nighttime SBP (<math>r = -0.293</math>, <math>p = 0.04</math>) and daytime MAP (<math>r = -0.294</math>, <math>p = 0.03</math>)</li> </ul>

Table 2. continued

Author, Year	Study design	Participants	Uromodulin form or UMOD variant assessed	Main Results
McCallum et al., 2024 [99]	Interventional / genotype-blinded, non-randomized clinical trial	174 subjects with uncontrolled HT, receiving ≥1 nondiuretic antihypertensives for >3 months	rs13333226 UMOD variant	<ul style="list-style-type: none"> <li>• Significant reductions in 24-h ambulatory SBP after 16 weeks in both AA (−6.57 mmHg, 95% CI, −8.44 to −4.69, <math>p &lt; 0.0001</math>) and AG/GG groups (−3.22 mmHg, 95% CI, −5.93 to −0.51, <math>p = 0.021</math>).</li> <li>• Significant reductions in 24-h DBP after 16 weeks in both AA and AG/GG groups</li> <li>• AA vs AG/GG: ↑ change in 24-h ambulatory SBP (difference between groups from baseline to 16 weeks: −3.35 mmHg, 95% CI, −6.64 to −0.05, <math>p = 0.048</math>) and daytime SBP (difference: −4.62 mmHg, 95% CI, −8.21 to −1.02, <math>p = 0.0126</math>)</li> <li>• Trajectories of 24-h SBP over 16 weeks:               <ul style="list-style-type: none"> <li>○ AA: consistent decrease over the whole study period (from baseline to week 8: −4.34, 95% CI, −6.32 to −2.36, <math>p &lt; 0.0001</math>; from weeks 8 to 16: −2.22, 95% CI, −4.24 to −0.21, <math>p = 0.0320</math>)</li> <li>○ AG/GG: more marked decrease at 8 weeks (−7.03, 95% CI, −9.85 to −4.19, <math>p &lt; 0.0001</math>), followed by a rebound between 8 and 16 weeks (+3.81, 95% CI, 0.92 to 6.69, <math>p = 0.0104</math>)</li> </ul> </li> <li>• Similar trajectories for 24-h DBP</li> </ul>
<b>CKD patients</b>				
Bakhoum et al., 2022 [101]	Cross-sectional	436 children from CKID cohort	uUMOD (spot urine samples)	<ul style="list-style-type: none"> <li>• Significant associations of uUMOD/uCr ratio with 24-h SBP/DBP and cSBP/DBP in univariate but not in multivariate models.</li> <li>• No interaction between uUMOD and <math>\text{Na}^+</math> intake in their effect on 24-h BP [24-h SBP: −0.04 (−0.41, 0.32) and 24-h DBP: −0.15 (−0.43, 0.14)] or cBP [cSBP: 0.12 (−0.28 to 0.53) and cDBP: 0.03 (−0.38 to 0.43)].</li> </ul>
Bullen et al., 2024 [102]	Cross-sectional	52 CKD patients undergoing kidney native (n = 33) or allograft kidney biopsies (n = 19)	uUMOD (spot urine samples)	<ul style="list-style-type: none"> <li>• Association of uUMOD with urine output response to furosemide stress test: significant in multivariate models adjusting for age, sex, urine creatinine (<math>\beta = -81</math> [−144, −18], <math>p = 0.01</math> for each halving of uUMOD) and for age, sex, urinary creatinine, furosemide dose (<math>\beta = -72</math> [−134, −10], <math>p = 0.02</math>) but non-significant after adding baseline eGFR and urinary albumin to latter model (<math>\beta = -55</math> [−125, 14], <math>p = 0.11</math>).</li> <li>• Similar results when stratifying the association of uUMOD with diuretic response to furosemide stress test based on kidney transplant status.</li> </ul>

95%CI, 95% Confidence Interval; BP blood pressure, CVD cardiovascular disease, DBP diastolic blood pressure, eGFR estimated glomerular filtration rate, OR odds ratio, SBP systolic blood pressure, SD standard deviation, SE standard error, sUMOD serum uromodulin, UCr urinary creatinine, uUMOD urinary uromodulin.

association between baseline uMOD and SBP change from low to high Na<sup>+</sup> diet [97]. However, this study has some limitations. Given that patients were randomized to diets with different Na<sup>+</sup> content and acknowledging that dietary sodium influences uMOD levels, uMOD levels at the end of study should have been significantly changed compared to baseline; nonetheless, uMOD was only calculated at baseline (during screening period) and not at the end of study. Additionally, the range of allocated dietary sodium diets was narrow and possibly not enough to investigate associations between uMOD and salt-related BP changes.

Clinical studies in hypertensive patients that examine BP responses to loop diuretics according to *UMOD* genotype provide corroborating evidence. Following results in transgenic mice [17], Trudu et al. retrospectively analyzed a cohort of 471 treatment-naïve hypertensive patients stratified a posteriori for a *UMOD* risk variant (rs4293393T>C). For a subgroup of these patients (n = 165), data from furosemide tests were available; furosemide administration in patients homozygous for the risk allele (TT) led to greater natriuretic response (i.e., higher natriuresis over baseline and greater BP reduction) as compared to other hypertensive patients (CC + CT). Thus, the hypothesis that patients with risk *UMOD* alleles will respond better to loop diuretics was introduced. In this regard, a prospective genotype-directed clinical trial (BHF *UMOD* Trial) was designed to examine whether hypertensive patients present differential BP response to torsemide based on their *UMOD* genotype (i.e., rs13333226 *UMOD* variant) [98]. The study showed that both patients homozygous and heterozygous for the risk A allele had significant reductions in 24-h ambulatory SBP (AA: -6.57 mmHg, 95% CI, -8.44 to -4.69, p < 0.0001; AG/GG: -3.22 mmHg, 95% CI, -5.93 to -0.51, p = 0.021) and DBP after 16 weeks treatment with torsemide [99]. However, the change in 24-h ambulatory SBP was greater in the AA group (difference between groups from baseline to 16 weeks: -3.35 mmHg, 95% CI, -6.64 to -0.05, p = 0.048) [99]. Interestingly, the two groups presented different trajectories of 24-h SBP and DBP over the 16 weeks interval. The AG/GG group had a more marked decrease of BP at 8 weeks followed by a rebound between 8 and 16 weeks, differing from the consistent decrease over the whole study period in AA group [99]. These results confirmed that hypertensive patients homozygous for the *Umod*-increasing alleles exhibit enhanced responsiveness to loop diuretics. These findings bear clinical significance, underscoring the potential for incorporating *UMOD* genotype-guided use of loop diuretics into personalized hypertension treatment algorithms.

Lastly, a recent cross-sectional study in 326 young untreated middle-aged (18–45 yo) Croatian subjects tried to investigate the relationship between uMOD, salt intake and BP [100]. Patients were classified based on JNC-7 criteria as having optimal BP (n = 103), prehypertension (n = 140) or hypertension (n = 80) and uMOD was measured from spot urine samples. There was no difference in nonindexed and indexed uMOD levels between groups [100]. However, in subjects with prehypertension, indexed uMOD was positively correlated with fractional Na<sup>+</sup> excretion and negatively correlated with 24-h Na<sup>+</sup> excretion [100]. Importantly, uMOD was positively associated with SBP sleep-through surge in the optimal BP group, and negatively associated with DBP dip in the prehypertension group [100]. The lowest morning BP surge was observed in the first tertile of indexed uMOD in the optimal BP group and the highest DBP dip in the first tertile of nonindexed uMOD in the prehypertension group. This study was the first to show that uMOD levels influence per se the circadian BP patterns and are linked to circadian BP alterations in prehypertensive subjects as a precursor of sustained hypertension.

**Studies in CKD patients.** Data regarding the relation between sodium-sensitive hypertension and uromodulin in the setting of

CKD originate solely from two studies. In a pediatric study including 436 children (age 6 months to 16 years, eGFR = 30–90 mL/min/1.73 m<sup>2</sup>), although doubling of the uMOD/Cr ratio was associated with a decrease in 24-h SPB/DBP [-1.66 (95% CI: -2.31, -1.00) / -1.71 mmHg (-2.45, -0.97)] respectively] and office SBP/DBP in univariable analyses, no significant associations between uMOD/Cr and either 24-h or office SB/DBP were evident in multivariable models [101]. Of note, the relationship between uMOD and BP levels was not modified after adding estimated Na<sup>+</sup> intake in multivariable models [101]. Among major limitations, Na<sup>+</sup> intake was subjectively estimated through a food frequency questionnaire completed by the parents and urinary Na<sup>+</sup> excretion was not measured. Furthermore, uMOD was measured in spot urine samples and indexed to urinary creatinine. This practice adjusts for glomerular filtration of small molecules, limiting the impact of the magnitude of urine concentration. However, adjusting for filtered small molecules is not justified for tubule-secreted proteins, such as uromodulin, and thus this method introduces a source of systematic error, since urinary creatinine is influenced by muscle mass [78].

A recent cross-sectional study in 52 participants with a wide range of kidney function (mean eGFR 56 mL/min/1.73m<sup>2</sup>) that underwent native or allograft kidney biopsy for clinical indications (CKD patients n = 33; kidney transplant recipients, n = 19), tested whether uMOD levels are related to diuretic response to loop diuretics [102]. uMOD was measured from spot urine samples at the beginning of the study in duplicate and patients underwent furosemide stress test with strict urine output quantification done for the first 6 h [102]. Each halving of uMOD levels was significantly associated with decreased urine output response to the furosemide stress test in multivariable models adjusting for several covariates (age, sex, urinary creatinine, furosemide dose), but this association was no longer significant after adjusting for baseline eGFR and albuminuria [102]. Similar results were evident when the association of uMOD with diuretic response was stratified based on kidney transplant status [102].

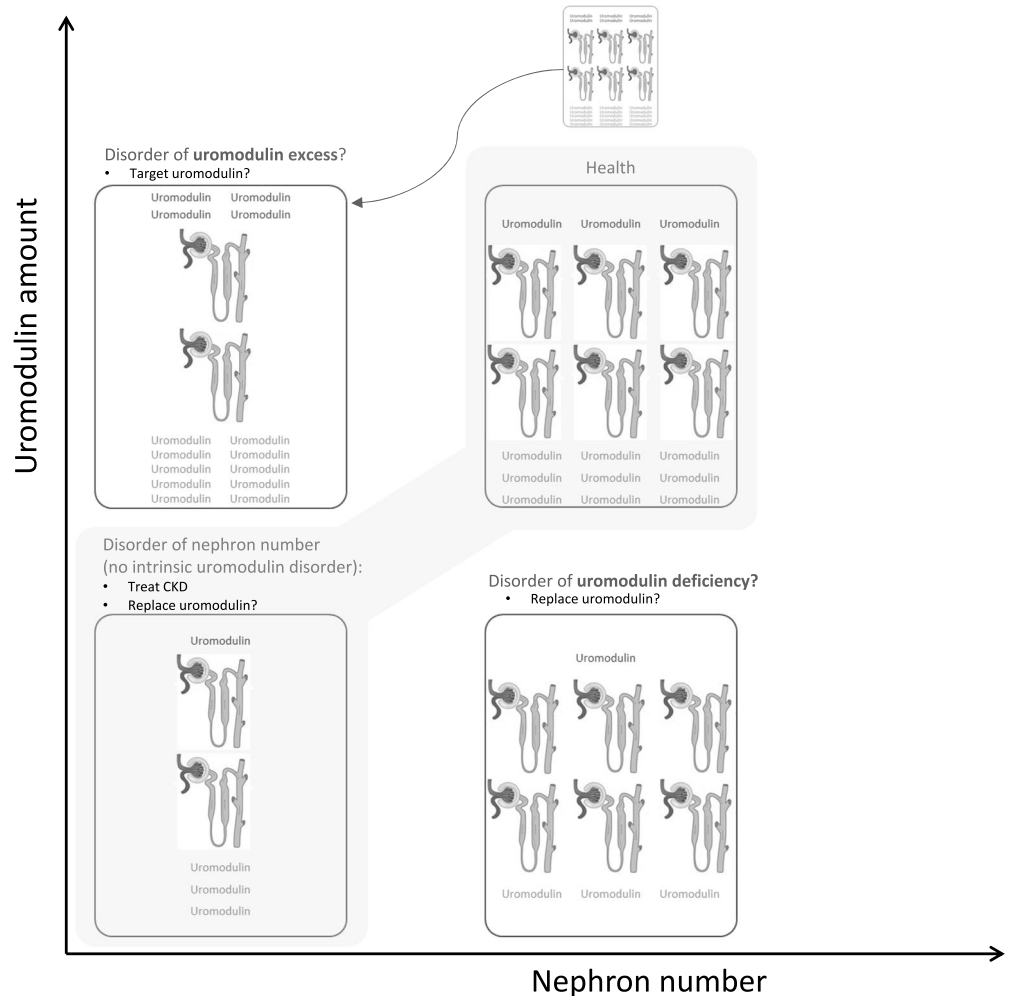
#### GAPS AND NEEDS FOR FURTHER RESEARCH

Although current evidence on the link of uromodulin with sodium sensitivity is intriguing, preclinical and clinical studies are highly heterogeneous and thus additional research efforts are needed to address several issues. Given that protocols for defining sodium sensitivity or sodium-sensitive BP responses greatly vary between existing studies, the results are not easily compared with each other nor reproducible when applying different research settings, rendering the clinical translation cumbersome. Therefore, a consensus should be ideally reached on which protocols should be utilized.

In parallel, with regards to the CKD population, solid data on the link of uromodulin with sodium sensitivity are currently missing. The confirmation of such an association in the context of CKD is rather important, as these patients significantly differ from the ones studied so far (e.g., general population, hypertensive patients). CKD patients show decreasing uromodulin levels mirroring decreasing nephron and tubular mass with progression to ESKD [103], while eGFR seems to significantly mediate the effects of uromodulin on BP.

In addition to the above, interventional studies assessing the impact of uromodulin levels and/or *UMOD* genotype on the antihypertensive effect of NKCC2/NCC blockade and sodium restriction are highly anticipated. This perspective is supported by the recent results from McCallum et al. [99] showing that guided use of loop diuretics based on *UMOD* genotyping can be useful in hypertension management. In case future studies applying these interventions confirm the therapeutic benefit and generalizability to diverse groups and reveal strong associations with morbidity and mortality outcomes, they are expected to

## Conceptual framework for uromodulin disorders



**Fig. 2 Conceptual framework for uromodulin disorders.** On the one hand, sUMOD and uUMOD may reflect the mass of healthy TAL cells able to produce uromodulin and this may underlie the association of higher uromodulin levels with better kidney outcomes (lower left and upper right corners). On the other hand, genetic defects (e.g., *Umod* deficiency) or variants of the *UMOD* gene may result in insufficient (or simply lower) uromodulin levels even in presence of a healthy normal TAL mass (lower right corner). There is preclinical evidence that uromodulin administration may improve some features of uromodulin deficiency, but increasing uUMOD may not be feasible. Finally, genetic predisposition may result in higher uromodulin levels than expected for kidney mass or even than desirable, resulting in disease, such as hypertension with end-organ damage in *Umod* overexpressing mice. This may be the situation for humans with certain genetic variants in the *UMOD* or adjacent genes, but whether any intervention aimed at uromodulin or tubular sodium transporters will benefit patients remains unclear. An association between genetically predicted excess uromodulin and CKD or low eGFR has been described in humans and mice (panel above the “health” panel). The figure represents theoretical possibilities. Currently, there is not sufficient evidence in humans to consider any of these situations a pathological entity requiring intervention over uromodulin, except for ADTKD, in which decreasing production (and accumulation) of abnormal uromodulin is currently considered to be desirable and potentially therapeutic.

change current diagnostic and/or therapeutic hypertension algorithms by incorporating the determination of uromodulin levels and/or *UMOD* variant genotyping as both a prognostic factor and a therapeutic target, as a part of individualization therapies.

Lastly, given the extended research around uromodulin disorders and the physiological role of uromodulin, field experts should agree upon the dichotomy between uromodulin levels as a reflection of healthy kidney mass or of individual genetics or environment. To this purpose, when discussing uromodulin levels and disorders, one should always compare its levels to nephron mass. A conceptual framework for uromodulin disorders is displayed on Fig. 2.

### DATA AVAILABILITY

This is a review paper with no new data generated or analysed in support of it.

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## AUTHOR CONTRIBUTIONS

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**ADDITIONAL INFORMATION**

**Correspondence** and requests for materials should be addressed to Pantelis Sarafidis.

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