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Evolution of Scientific Paradigms in Understanding Water Balance

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Highlights

Shifts in the scientific paradigms of understanding body water balance: historical reflections and the development of modern concepts, seminal contributions by Homer Smith, the Theory of the Countercurrent Mechanism by Berliner and Bennett, mathematical descriptions of urine concentration, quantitative nephrology and the concept of clearance, the revolutionary discovery of aquaporins, identification of CHIP28/AQP1 by Peter Agre, 2003 Nobel Prize in Chemistry, structural-functional analyses of Preston et al., expression in Xenopus laevis oocytes, paradigmatic shifts in understanding water homeostasis, limitations of classical binary models, critiques of dichotomous approach by robertson, complexity of clinical syndromes (as SIADH and CSWS), and need for an integrative understanding, systems biology and network appoach, principles of network biology as given by Barabási and Oltvai, emergent properties of biological systems, robustness, modularity and hierarchy (as described by Kitano), and their relevance to water homeostasis.

The evolutionary path of scientific paradigms regarding understanding water balance and homeostasis is reviewed herein. It highlights the importance of foundational principles, such as the countercurrent mechanism and quantitative nephrology, and the revolutionary finding of aquaporins. The challenge to classical binary models highlights the complex nature of fluid disorders and opportunities for integrative systems biology approaches. Network biology also describes emergent properties that are essential for increasing knowledge about water homeostasis.

Abstract
Background: This review is a historical synthesis of research on the "Development of Scientific Paradigms in the Study of Water Balance: A Retrospective View and the Shaping of Current Notions." It includes seminal work by Homer Smith, the Berliner and Bennett hypothesis of the countercurrent mechanism, mathematical models of urine concentration, quantitative nephrology, and the clearance concept. It also emphasizes the groundbreaking aquaporins, especially CHIP28/AQP1 by Peter Agre, which won him the Nobel prize in Chemistry in 2003. Structural–functional analysis by Preston et al., together with expression studies in Xenopus laevis oocytes, identify paradigmatic transformations in water homeostasis. This argument critiques traditional dualities and engages with Robertson's challenge to the dichotomous approach in consideration of the complexities of clinical disorders such as SIADH and CSWS. It highlights the need for a holistic perspective through systems biology and a network methodology, inspired by the tenets of network biology proposed by Barabási and Oltvai and by the systemic properties of biological systems exemplified by robustness, modularity and hierarchy put forward by Kitano. These principles are analyzed in relation to water homeostasis.
Objectives: The review seeks to taxonomize the historical evolution of paradigms, evaluate foundational physiological and molecular contributions, compare quantitative nephrology models, and explore systems biology approaches to elucidate the intricacies of water homeostasis.
Methods: A systematic analysis of interdisciplinary literature was conducted, encompassing classical physiology, molecular biology, mathematical modeling, and network theory.
Results: Key findings elucidate the pivotal role of Homer Smith's clearance concept and the countercurrent mechanism in establishing the foundations of quantitative renal physiology; the transformative impact of aquaporin discovery alongside structural-functional characterization on the molecular comprehension of water transport; and the significant advancements achieved through mathematical and systems biology models that integrate signaling pathways and cellular dynamics to encapsulate regulatory complexity. Furthermore, a critical reassessment of traditional binary models is warranted in the context of clinical syndromes such as SIADH and CSWS, accentuating the necessity for integrative frameworks.
Conclusions: These findings converge to underscore the evolution from reductionist to holistic paradigms, accentuating emergent properties and network robustness in water homeostasis. This synthesis highlights the essential need for multi-scale systems-level approaches to bridge molecular mechanisms with clinical phenotypes, thereby informing future research and therapeutic strategies.

Keywords: Water balance, aquaporins, systems biology, homeostasis, nephrology, countercurrent mechanism, network biology

Анотація
Передумови: У цьому огляді ми синтезуємо дослідження еволюції наукових парадигм у розумінні водного балансу: історична ретроспектива та формування сучасних концепцій фундаментальні роботи Гомера Сміта, теорія протитечійного механізму Берлінера та Беннета, математичні моделі концентрування сечі, кількісна нефрологія та концепція кліренсу, революційне відкриття аквапоринів, Пітер Агре та ідентифікація CHIP28/AQP1, Нобелівська премія з хімії 2003 року, структурно-функціональні дослідження Престона та співавторів, експресія в ооцитах Xenopus laevis, парадигмальні зсуви у розумінні водного гомеостазу, обмеження традиційної бінарної моделі, критика дихотомічного підходу Робертсона, складність клінічних синдромів SIADH, CSWS, необхідність інтегративного розуміння, системна біологія та мережевий підхід, принципи мережевої біології Барабасі та Ольтваї, емерджентні властивості біологічних систем, робастність, модульність, ієрархічність Кітано, застосування до водного гомеостазу для усунення фрагментованих уявлень про нього та клінічних труднощів його регуляції.
Цілі: Огляд мав на меті систематизувати розвиток історичних парадигм, оцінити фундаментальний фізіологічний та молекулярний внесок, порівняти кількісні моделі нефрології та дослідити підходи системної біології для з'ясування водного гомеостазу.
Методи: Було проведено систематичний аналіз міждисциплінарної літератури, що охоплює класичну фізіологію, молекулярну біологію, математичне моделювання та теорію мереж.
Результати: Ключові висновки включають вирішальну роль концепції кліренсу Гомера Сміта та протитечійного механізму у встановленні кількісної фізіології нирок; трансформаційний вплив відкриття аквапоринів та структурно-функціональної характеристики на молекулярне розуміння транспорту води; досягнення математичних та системно-біологічних моделей, які інтегрують сигнальні шляхи та клітинну динаміку для відображення регуляторної складності; та критичну переоцінку традиційних бінарних моделей у світлі клінічних синдромів, таких як SIADH та CSWS, підкреслюючи необхідність інтегративних підходів.
Висновки: Ці висновки сходяться, щоб підкреслити еволюцію від редукціоністських до цілісних парадигм, акцентуючи емерджентні властивості та мережеву робастність у водному гомеостазі. Синтез підкреслює необхідність багатомасштабних підходів системного рівня для поєднання молекулярних механізмів з клінічними фенотипами, інформуючи майбутні дослідження та терапевтичні стратегії.

Ключові слова: Водний баланс, аквапорини, системна біологія, гомеостаз, нефрологія, протитечійний механізм, мережева біологія

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1. Introduction

The exploration of the evolution of scientific paradigms in comprehending water balance has emerged as an exceedingly vital domain of inquiry, given its fundamental significance in physiology and clinical medicine. Early anatomical and physiological investigations established the groundwork for concepts pertaining to renal function, with pivotal contributions from luminaries such as Homer Smith, who enhanced clearance methodologies and mechanistic insights into renal water and electrolyte management (Giebisch, 2004; Navar, 2004). The elucidation of the countercurrent mechanism by Berliner and Bennett further illuminated the processes of urine concentration (Schafer, 2004; Thomas, 2001), while the subsequent emergence of mathematical models profoundly enriched our understanding of renal transport and urine concentration dynamics (Edwards, 2010; Layton, 2013). The identification of aquaporins, particularly through the groundbreaking research of Peter Agre and his colleagues, represented a revolutionary advancement in this field, unveiling molecular water channels that are indispensable for preserving water homeostasis (Fenton, 2024; Brown, 2017). This trajectory bears significant clinical ramifications, as disorders of water balance, including nephrogenic diabetes insipidus and hyponatremia, afflict millions globally (Schrier, 2006; Nielsen et al., 2002). Contemporary investigations into osmoregulatory mechanisms (Gozhenko et al., 2003) and the regulation of sodium ion homeostasis (Filipets et al., 2022) augment classical concepts with novel data on adaptive mechanisms.

Despite these advancements, significant lacunae persist in comprehensively elucidating the intricate regulation of water homeostasis. Traditional binary paradigms of water balance have been called into question for their propensity to oversimplify physiological processes (Schrier, 2006; Acher, 2002), and this dichotomous framework has faced scrutiny for its inability to capture the subtleties of clinical syndromes such as SIADH and cerebral salt wasting (Schrier, 2006; Schlanger & Sands, 2018). Furthermore, the synthesis of molecular revelations, including aquaporin transport and vasopressin signaling, with overarching physiological models remains inadequate (Chen et al., 2022; Olesen & Fenton, 2021). Persistent debates revolve around the mechanisms governing urine concentration, the multifaceted roles of aquaporins beyond mere water transport, and the applicability of reductionist models to complex biological systems (Thomas, 2001; Hillyard, 2015). These deficiencies impede the formulation of comprehensive therapeutic strategies for disorders of water balance (Vrettou et al., 2024).

The conceptual framework of this review synthesizes historical and contemporary paradigms that encompass renal physiology, the molecular biology of aquaporins, and principles of systems biology. Central concepts include the countercurrent multiplication mechanism, aquaporin-mediated water transport, and attributes of network biology such as robustness and modularity (Koulouridis & Koulouridis, 2014; D'Acierno et al., 2024; Acher, 2002). This framework fosters a comprehensive understanding of water homeostasis, interlinking molecular mechanisms with emergent physiological properties and clinical phenotypes (Chen et al., 2022; Knepper, 2012).

The objective of this systematic review is to critically evaluate the evolution of scientific paradigms in water balance research, illuminating foundational works, paradigm shifts, and the integration of systems biology approaches. By addressing identified deficiencies, this review aspires to furnish a thorough synthesis that enhances theoretical comprehension and informs clinical practice. This endeavor adds value by intertwining historical perspectives with contemporary molecular and computational concepts, thereby promoting an integrative approach to water homeostasis. The physiological underpinnings of regulating the mineral composition of body fluids (Gozhenko & Lebedeva, 2013) serve as the bedrock for understanding this evolution.

The review methodology encompasses comprehensive literature surveys that traverse classical studies to recent advancements, with inclusion criteria accentuating pivotal contributions and contemporary systems biology research. The analytical framework integrates historical retrospectives, molecular biology, mathematical modeling, and network theory. Results are systematically organized thematically to delineate the evolution of paradigms, molecular discoveries, and system-level integration.

2. Aims and Scope of the Review

The purpose of this report is to scrutinize the extant research on "Evolution of Scientific Paradigms in Understanding Water Balance: Historical Retrospective and Formation of Modern Concepts." It encompasses seminal works by Homer Smith, the countercurrent mechanism theory proposed by Berliner and Bennett, mathematical models pertaining to urine concentration, the quantitative nephrology framework, and the concept of clearance. Furthermore, it delves into the groundbreaking discovery of aquaporins, notably the identification of CHIP28/AQP1 by Peter Agre, which earned him the Nobel Prize in Chemistry in 2003. The report also highlights structural-functional studies conducted by Preston et al., including their expression in Xenopus laevis oocytes.

This synthesis aims to illuminate the paradigmatic shifts in our comprehension of water homeostasis, addressing the limitations inherent in traditional binary models. It critically examines the dichotomous approach articulated by Robertson, as well as the intricate nature of clinical syndromes such as SIADH and CSWS. There is an imperative need for an integrative understanding, which can be achieved through the lens of systems biology and a network approach, as delineated by Barabási and Oltvai. This perspective emphasizes the emergent properties of biological systems, including robustness, modularity, and hierarchy, as discussed by Kitano.

By weaving together insights from classical nephrology, molecular discoveries, and systems-level analysis, this report endeavors to identify deficiencies and opportunities for a more holistic understanding of water homeostasis and its clinical ramifications. The methodological aspects of determining functional kidney reserve, as elucidated by Kravchuk et al. (2016), underscore the practical significance of an integrative approach within contemporary nephrology.

Objectives:

Taxonomize the historical evolution of scientific paradigms pertaining to renal water balance and mechanisms of urine concentration. Evaluate the seminal contributions of Homer Smith's foundational works alongside the countercurrent mechanism theory posited by Berliner and Bennett. Compare the mathematical and quantitative nephrology models that have propelled the conceptualization of urine concentration and clearance. Identify and synthesize the ramifications of aquaporin discovery, structural-functional investigations, and expression systems on contemporary paradigms of water homeostasis. Contrast systems biology and network biology methodologies for elucidating the intricacies and regulation of water balance in both health and disease.

Research Problems

Integration Problem: How can classical physiological concepts of water balance with contemporary molecular and systems biology approaches to create a holistic paradigm for understanding water homeostasis?
Mechanistic Problem: What molecular mechanisms regulate aquaporin function in the kidneys, and how do they influence urine concentration and water balance?
Complexity Modeling Problem: How effective are existing mathematical models in capturing the multi-level regulation of water homeostasis from molecular to systemic levels?
Clinical Problem: Why are traditional binary models of water balance unable to fully explain complex clinical syndromes such as SIADH and CSWS?
Translational Problem: How can molecular discoveries regarding aquaporins into effective therapeutic strategies for treating water balance disorders?
Evolutionary Problem: How do evolutionary adaptations of renal structures and aquaporins influence contemporary understanding of water balance regulation mechanisms?

Research Hypotheses

Integration Hypothesis: Application of systems biology approaches and network analysis will allow integration of molecular mechanisms of aquaporins with classical physiological concepts, creating a more complete understanding of water homeostasis.
Mechanistic Hypothesis: Regulation of aquaporins, especially AQP2, occurs through the complex interaction of multiple signaling pathways, involving not only phosphorylation but also other post-translational modifications and protein-protein interactions.
Modeling Hypothesis: Multi-scale computational models that integrate molecular, cellular, and systemic levels of regulation will be able to predict physiological and pathological states of water balance than traditional single-scale models.
Clinical Hypothesis: Clinical syndromes associated with water balance disorders result from complex interactions between multiple regulatory pathways, requiring an integrative approach for accurate diagnosis and treatment.
Translational Hypothesis: Targeted modulation of aquaporin expression and function through specific signaling pathways can provide effective treatment for nephrogenic diabetes insipidus and other water balance disorders.
Evolutionary Hypothesis: Conserved evolutionary mechanisms of aquaporin regulation between species may reveal new therapeutic targets for treating water balance disorders in humans.
Emergent Properties Hypothesis: Water homeostasis demonstrates emergent properties at the system level that cannot be fully explained by the simple summation of molecular components, requiring the application of principles of robustness, modularity, and hierarchy from network theory.

Statistical Hypotheses

Hypothesis 1 H_0: There is no statistically significant difference between traditional binary water balance models and integrative systems biology approaches in explaining clinical syndromes of water homeostasis disorders. H_1: Integrative systems biology approaches demonstrate statistically significant improvement in explaining clinical syndromes of water homeostasis disorders compared to traditional binary models ($p < 0.05$).
Hypothesis 2 H_0: The discovery of aquaporins did not lead to statistically significant changes in understanding the molecular mechanisms of water transport in the kidneys. H_1: The discovery of aquaporins led to a statistically significant increase in the number of publications and citations in the field of molecular mechanisms of water transport in the kidneys ($p < 0.01$).
Hypothesis 3 H_0: Mathematical models of urine concentration do not demonstrate statistically significant improvement in prediction accuracy compared to classical descriptive models. H_1: Contemporary mathematical models of urine concentration demonstrate statistically significant improvement in prediction accuracy (30% or more) compared to classical descriptive models.
Hypothesis 4 H_0: There is no statistically significant correlation between aquaporin expression levels and urine osmolality in experimental models. H_1: There is a statistically significant positive correlation ($r > 0.7$) between AQP2 aquaporin expression levels and urine osmolality in experimental models.
Hypothesis 5 H_0: Network biology principles (robustness, modularity, hierarchy) do not have a statistically significant impact on water homeostasis modeling. H_1: Application of network biology principles leads to statistically significant improvement ($p < 0.05$) in the predictive value of water homeostasis models.

Statistical Analysis Methods
For testing the formulated hypotheses, the following statistical methods will be used:
Bibliometric Analysis: Analysis of publication and citation numbers before and after key discoveries using a t-test for comparing mean values.
Correlation Analysis: Determination of Pearson or Spearman correlation coefficients between aquaporin expression levels and physiological parameters.
Regression Analysis: Construction of multiple regression models to assess the impact of various factors on water balance parameters.
Meta-Analysis: Integration of results from different studies to evaluate the effectiveness of various models in explaining clinical syndromes.

Time Series Analysis: Investigation of the dynamics of scientific paradigm changes over time.
Network Analysis: Application of complex network analysis methods to assess relationships between components of the water balance regulation system.
For all statistical tests, a significance level of α = 0.05 will be used, corresponding to a 95% confidence interval. When conducting multiple statistical tests, the Bonferroni correction will be applied to control the level of type I errors.

3. Materials and Methods

Literature Selection Methodology

The systematic literature review was executed in accordance with established guidelines for a comprehensive analysis of the evolution of scientific paradigms concerning water balance comprehension. The conceptual framework encompassed: Evolution of scientific paradigms in the understanding of water balance: a historical retrospective and the formation of contemporary concepts, seminal contributions by Homer Smith, the countercurrent mechanism theory proposed by Berliner and Bennett, mathematical models pertaining to urine concentration, quantitative nephrology, and the clearance concept, the groundbreaking discovery of aquaporins, Peter Agre's identification of CHIP28/AQP1, the Nobel Prize in Chemistry awarded in 2003, structural-functional investigations conducted by Preston et al. and expression studies in Xenopus laevis oocytes. Paradigmatic shifts in the comprehension of water homeostasis, addressing the limitations of traditional binary models and critiques of the dichotomous approach by Robertson, alongside the complexities of clinical syndromes such as SIADH and CSWS, highlight the necessity for an integrative understanding. Systems biology and the network approach, including the principles of network biology articulated by Barabási and Oltvai, and the emergent properties of biological systems, such as robustness, modularity, and hierarchy as discussed by Kitano, with applications to water homeostasis. Regulatory mechanisms governing renal water and solute balance: historical perspectives and contemporary advancements in renal physiology, emphasizing the role of aquaporins, systems biology methodologies, and integrative models to elucidate water homeostasis. An exploration of regulatory mechanisms and the pivotal role of aquaporins in renal function and water balance disorders, accentuating their expression patterns, implications for chronic kidney disease, and potential therapeutic applications. Exploration of clinical implications of aquaporins in water balance disorders, focusing on novel therapeutic approaches for conditions such as nephrogenic diabetes insipidus, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and chronic kidney disease. Integration of aquaporin research with systems biology approaches enhances understanding of renal water homeostasis and implications for disorders such as nephrogenic diabetes insipidus and syndrome of inappropriate antidiuretic hormone secretion. Interdisciplinary approaches in health sciences (Zukow et al., 2018) provide the methodological foundation for comprehensive literature analysis.

Literature Search Strategy

Electronic Databases

The following electronic databases were used for searching relevant literature:
PubMed/MEDLINE
Scopus
Web of Science
Google Scholar
EMBASE
Cochrane Library
Ukrainian Scientific Medical Library
Polish Medical Bibliography

Keywords and Search Queries

Literature search was conducted using the following keywords and their combinations in Ukrainian, English, Polish, and Russian languages:
"water balance", "водний баланс", "równowaga wodna", "водный баланс"
"aquaporins", "аквапорини", "akwaporyny", "аквапорины"
"Homer Smith", "Berliner", "Bennett", "Peter Agre", "Preston"
"countercurrent mechanism", "протитечійний механізм", "mechanizm przeciwprądowy", "противоточный механизм"
"urine concentration", "концентрування сечі", "koncentracja moczu", "концентрирование мочи"
"clearance", "кліренс", "klirens", "клиренс"
"systems biology", "системна біологія", "biologia systemów", "системная биология"
"network biology", "мережева біологія", "biologia sieci", "сетевая биология"
"SIADH", "CSWS", "diabetes insipidus", "нецукровий діабет", "moczówka prosta", "несахарный диабет"
Boolean operators (AND, OR, NOT) and special search filters were used to improve search accuracy.

Document Screening Process

Inclusion and exclusion criteria were applied to obtain a targeted set of candidate papers for the database of 493 articles.

Primary Screening

Primary screening of publications was conducted by analyzing titles and abstracts according to established inclusion and exclusion criteria. Two independent researchers conducted the screening, with disagreements resolved through consensus or the involvement of a third researcher.

Full-Text Analysis

Publications that passed primary screening were evaluated through full-text analysis. At this stage, more detailed criteria for assessing study quality and relevance were applied.

Citation Analysis

To identify additional relevant publications, citation analysis was conducted using the "snowball" method - examining reference lists of key publications and searching for works citing these publications.

Inclusion Criteria

Study Type:

Original research, systematic reviews, and meta-analyses.
Fundamental works on renal physiology and water balance.
Studies of molecular mechanisms of aquaporins.
Mathematical models of urine concentration and water balance.
Systems biology research related to water homeostasis.

Time Frame:
Classical fundamental works (Homer Smith, Berliner, Bennett) without time restrictions.
Contemporary research published in the last 30 years (from 1991, when aquaporins were discovered).
Latest systems biology research from the last 10 years.
Thematic Focus:
Studies concerning urine concentration mechanisms.
Structure, function, and regulation of aquaporins in the kidneys.
Molecular mechanisms of vasopressin action.
Mathematical modeling of kidney function.
Systems biology of water homeostasis.
Clinical studies of water balance disorders (SIADH, CSWS, nephrogenic diabetes insipidus).
Methodological Criteria:
Studies with clearly described methodologies.
Experimental studies with appropriate controls.
Mathematical models validated on experimental data.
Clinical studies with well-characterized patient groups.
Publication Language:
Publications in English, Ukrainian, Polish, and Russian languages.
Exclusion Criteria
Publication Type:
Unpublished materials and conference abstracts.
Editorial articles and letters to editors without original data.
Popular articles without scientific peer review.
Studies with methodological flaws or inadequate method descriptions.
Thematic Limitations:
Studies not directly related to water balance or kidney function.
Studies of aquaporins in tissues unrelated to kidneys or osmoregulation.
General reviews of renal physiology without a specific focus on water balance.
Methodological Limitations:
Studies with small sample sizes without proper justification.
Mathematical models without experimental validation.
Clinical studies without clear diagnostic criteria.
Time Limitations:
For molecular and systems biology studies - publications older than 30 years (before 1991), except for classical fundamental works.
For clinical studies - publications older than 20 years, if their results were refuted or significantly supplemented by newer studies.
Availability:
Studies whose full texts are unavailable for analysis.
Publications with incomplete descriptions of methodology or results.
Relevance assessment and ranking.
A pool of 493 candidate papers was collected (359 from search queries + 134 from citation chains) and relevance ranking was established so that the most relevant studies rose to the top of the summary work table. 482 articles were found to be relevant to the research query. Of the 482 articles, 50 were highly relevant.

Artificial Intelligence Usage Clause - Extended Declaration on the Use of Artificial Intelligence in Scientific Research:
The authors of this scientific work declare partial use of artificial intelligence (AI) tools in the process of preparation, analysis, and formatting of the presented work. AI use was conducted in accordance with principles of scientific ethics, transparency, and academic integrity according to international standards of scientific publications and recommendations of leading publishers.
Types of AI Systems Used:
Large language models (LLM) for literature analysis and text structuring.
Automatic translation tools for processing international sources.
Grammar and stylistic text correction systems.
AI analytical platforms for systematizing bibliographic data.
Specific Tasks Performed with AI Assistance:
Primary analysis and categorization of scientific literature (approximately 15% of the total analytical volume).
Structuring and formatting bibliographic references.
Grammatical and stylistic correction of text.
Generation of initial versions of certain sections with subsequent substantial author revisions.
Creation of schemes and diagrams for the visualization of conceptual models.
Tasks NOT Using AI:
Forming main scientific hypotheses and conclusions.
Interpreting research results and clinical data.
Creating original conceptual models.
Critical analysis and synthesis of scientific evidence.
Developing methodological approaches and research designs.
Scientific Reliability Control:
Verification of all scientific statements through primary sources.
Independent verification of statistical data and illustrations.
Basing clinical recommendations exclusively on peer-reviewed publications.
Methodological approaches developed and approved by the authors personally.
Ethical Aspects:
All used sources are properly cited, regardless of the identification method.
AI was not used for copying or paraphrasing copyrighted materials.
Full transparency regarding information sources is ensured.

Documentation and Reproducibility:
Detailed records of AI usage stages are preserved.
Text versions before and after AI processing are documented.
Documentation of all queries and prompts to AI systems.
AI usage methodology can be reproduced by other researchers.

4. Results

Descriptive Summary of Studies

The research landscape of literature on "Evolution of Scientific Paradigms in Understanding Water Balance: Historical Retrospective and Formation of Modern Concepts" encompasses a broad historical and scientific spectrum, from fundamental physiological theories and experimental discoveries to advanced molecular characterizations and integrative systems biology models. Noteworthy contributions include the seminal works of Homer Smith, the countercurrent mechanism theory proposed by Berliner and Bennett, the mathematical models elucidating urine concentration, the quantitative nephrology framework, and the clearance concept. The revolutionary discovery of aquaporins, particularly the identification of CHIP28/AQP1 by Peter Agre, which earned him the Nobel Prize in Chemistry in 2003, marked a significant milestone. Structural-functional studies conducted by Preston et al., alongside their expression in Xenopus laevis oocytes, have significantly influenced paradigmatic shifts in the comprehension of water homeostasis.
Additionally, the limitations of the traditional binary model have been highlighted, particularly through the critiques of the dichotomous approach by Robertson, which underscore the complexity of clinical syndromes such as SIADH and CSWS. This complexity necessitates an integrative understanding that transcends simplistic categorizations. The principles of systems biology and network approaches, articulated by Barabási and Oltvai, reveal the emergent properties of biological systems, including robustness, modularity, and hierarchy as delineated by Kitano, and their application to the domain of water homeostasis.
Contemporary studies examining osmoregulatory kidney function across various age demographics (Gozhenko et al., 2003) further enrich these classical concepts, illuminating age-related features of adaptive mechanisms. The methodologies employed span a diverse array—from classical physiological experiments and mathematical modeling to cutting-edge molecular biology, proteomics, and computational systems biology—reflecting the interdisciplinary nature of nephrology, biophysics, and systems science. This comparative synthesis is pivotal for addressing research inquiries concerning paradigm evolution, molecular mechanisms, modeling strategies, and the clinical implications associated with water homeostasis.

Detailed Comparative Analysis Table of Studies

Table 1. Summary of Studies

Study	Historical Paradigm Development	Molecular Mechanism Elucidation	Mathematical Modeling Approaches	Systems Biology Integration	Clinical Relevance and Model Limitations
(Fenton, 2024)	Traces aquaporin discovery and evolution over 30 years.	Detailed AQP structure, function, and regulation, including phosphorylation.	Highlights AQP2 trafficking modeling and water permeability.	Discusses signaling networks and therapeutic targeting.	Links AQP dysfunction to diseases like diabetes insipidus and heart failure.
(Keogh et al., 2021)	Reviews kidney evolution from fish to mammals, critiques Smith's ideas.	Focuses on anatomical and genetic factors in kidney development.	Limited modeling focus, more evolutionary narrative.	Not emphasized.	Discusses evolutionary adaptations relevant to kidney function.
(Koulouridis & Koulouridis, 2014)	Chronicles the discovery of the loop of Henle and countercurrent multiplication theory.	Describes the physiological basis of urine concentration.	Reviews experimental validation of countercurrent models.	Minimal systems biology content.	Addresses historical acceptance and refinement of urine concentration models.
(Giebisch, 2004)	Highlights Homer Smith's fundamental contribution to renal physiology.	Emphasizes clearance methods and renal function analysis.	Introduces the clearance concept as a quantitative tool.	Not highlighted.	Notes Smith's impact on clinical and experimental nephrology.
(Navar, 2004)	Details Smith's mechanistic insights and clearance technique development.	Focus on clearance as a method for analyzing intrarenal functions.	Clearance technique as a quantitative model.	Not addressed.	Emphasizes clinical and research utility of the clearance method.
(Schafer,	Discusses	Supports the	Experimental	Not	Validates

Study	Historical Paradigm Development	Molecular Mechanism Elucidation	Mathematical Modeling Approaches	Systems Biology Integration	Clinical Relevance and Model Limitations
2004)	experimental validation of countercurrent urine concentration.	physiological basis of the countercurrent mechanism.	data underlying theoretical models.	included.	classical models explaining urine concentration
(Thomas, 2001)	Reviews historical theories of the urine concentration mechanism	Explores metabolic contributions to the medullary osmotic gradient	Reviews the theoretical and experimental interplay	Limited systems biology discussion	Highlights ongoing debates and model limitations
(Edwards, 2010)	Summarizes modeling achievements in renal transport and dysfunction	Integrates molecular transport data into models	Comprehensive review of multi-scale kidney models	Addresses model relevance to physiological questions	Discusses model applications and gaps in understanding kidney pathophysiology
(Fröhlich et al., 2010)	Not historical; focuses on AQP2 trafficking modeling	Models the molecular regulation of AQP2 trafficking	Uses ODE-based mathematical models for signaling pathways	Applies systems biology to AQP2 regulation	Provides mechanistic insights relevant to water balance disorders
(Mioni et al., 2017)	Mathematically reviews renal tubular transport concepts	Formalizes transport kinetics and tubular reabsorption/secretion	Proposes fundamental transport equations	Not focused on systems biology	Suggests clinical diagnostic and therapeutic implications
(Thomas et al., 2006)	Reviews the status and perspectives of kidney modeling	Covers nephron segment models and renal cell types	Discusses detailed physiological and hemodynamic models	Introduces the concept of renal physiome	Highlights integration challenges and clinical significance
(Sweatha et al., 2023)	Describes renal physiology control systems for fluid and acid-base balance	Details sensor feedback mechanisms in renal regulation	Presents Simulink models for renal control systems	Emphasizes control theory and systems integration	Model references pathological state prediction
(Chen et al., 2022)	Not historical; focuses on the vasopressin V2 receptor system biology	Explores the molecular actions of GPCR in water balance	Uses large-scale data integration and Bayesian modeling	Strong systems biology approach to signaling networks	Links molecular insights to water balance disorders
(Yang et al., 2022)	Not historical; proteomics of AQP2 regulation	Uses mass spectrometry for quantitative AQP2 phosphorylation	Quantitative proteomics integrated with signaling models	Supports systems biology understanding of AQP2 regulation	Provides a molecular basis for water balance disorder mechanisms
(Salhadar et al., 2021)	Not historical; phosphoproteomics of vasopressin signaling	Identifies PKA-dependent phosphorylation sites regulating AQP2	Phosphoproteomic data used for signaling pathway modeling	Integrates signaling data into systems biology frameworks	Enhances understanding of vasopressin-related water disorders
(D'Acierno et al., 2024)	Reviews contemporary understanding of water	Discusses novel AQP2 regulators and osmoregulation	Not focused on mathematical modeling	Highlights integrative molecular and	Links basic science to water balance disorder treatment

Study	Historical Paradigm Development	Molecular Mechanism Elucidation	Mathematical Modeling Approaches	Systems Biology Integration	Clinical Relevance and Model Limitations
	homeostasis biology			physiological regulation	
(Knepper, 2012)	Historical trend from reductionism to systems biology in physiology	Focus on the vasopressin signaling network in the kidneys	Discusses signaling pathway modeling	Emphasizes systems biology in renal physiology	Addresses complexity beyond traditional models
(Hillyard, 2015)	Reviews comparative and evolutionary physiology of water channels	Details aquaporin diversity and evolutionary genomics	Limited modeling focus	Discusses evolutionary systems perspectives	Highlights physiological and clinical implications of aquaporin diversity
(Lieburg et al., 1995)	Early discovery of renal water channels	Molecular identification of AQP1, AQP2 and others	Functional expression in Xenopus oocytes	Not focused on systems biology	Links mutations to nephrogenic diabetes insipidus
(Deen et al., 1994)	Demonstrates AQP2 requirement for vasopressin-dependent urine concentration	Functional expression studies in Xenopus oocytes	Experimental validation of AQP2 function	Not addressed.	Establishes the molecular basis of nephrogenic diabetes insipidus
(Sabolić et al., 1992)	Localization of CHIP28 (AQP1) in rat kidney tubules	Immunocytochemistry and western blotting of water channels	Not modeling-oriented	Not included.	Provides anatomical basis for water permeability in kidneys
(Schrier, 2006)	Discusses the impact of aquaporin discovery on body water regulation	Reviews AQP1 and other renal water channels	Not modeling-oriented	Not included.	Highlights clinical significance of aquaporins in water balance
(Kuchel, 2006)	Historical analysis of aquaporin discovery controversies	Details early experimental evidence and naming history	Not modeling-oriented	Not included.	Addresses recognition and credit in aquaporin research
(Gade & Robinson, 2006)	Survey of aquaporins and renal physiology implications	Discusses AQP family and clinical laboratory relevance	Not modeling-oriented	Not included.	Links aquaporin dysfunction to clinical syndromes
(Acher, 2002)	Molecular organization and evolution of osmoregulatory reflexes	Describes vasopressin signaling and aquaporin regulation	Not modeling-oriented	Not included.	Integrates molecular and physiological osmoregulation
(Hoenig & Zeidel, 2014)	Historical and contemporary perspectives on homeostasis and nephron function	Summarizes nephron role in maintaining the internal environment	Not modeling-oriented	Not included.	Provides clinical foundation for renal physiology
(Vrettou et al., 2024)	Reviews aquaporins in critical illness and clinical implications	Discusses AQP role in inflammation, edema, and organ function	Not modeling-oriented	Not included.	Highlights therapeutic potential in critical care settings

Study	Historical Paradigm Development	Molecular Mechanism Elucidation	Mathematical Modeling Approaches	Systems Biology Integration	Clinical Relevance and Model Limitations
(Sands et al., 2013)	Physiology of water homeostasis and urine concentration	Details vasopressin and countercurrent multiplication mechanisms	Reviews experimental and modeling approaches	Not focused on systems biology	Discusses pathophysiology of water balance disorders
(Leberecht et al., 2022)	Multi-scale computational model of AQP2 recycling	Integrates vesicular transport and signaling pathways	Combines multiple models for cellular regulation	Strong systems biology and computational modeling	Provides insights into diabetes insipidus mechanisms
(Wirz, 1968)	Historical transition to quantitative renal physiology	Emphasizes clearance methods and filtration theory	Early quantitative approaches to kidney function	Not included.	Highlights fundamental physiological concepts
(DeHaven & Shapiro, 1967)	Mathematical and physicochemical models of urine formation control	Uses Jacobian matrices to predict water and electrolyte changes	Early mathematical modeling of renal control	Not included.	Discusses model utility and limitations
(Tymofyychuk et al., 2020)	Historical development of urine formation physiology	Reviews concepts from 17th to 20th centuries	Not modeling-oriented	Not included.	Provides historical context for renal physiology
(Hillyard, 2011)	Historical and functional review of water transport across membranes	Describes aquaporin discovery and physiological roles	Not modeling-oriented	Not included.	Synthesizes knowledge about water transport mechanisms
(Pitts, 1960)	Early intrarenal sites and mechanisms of salt and water exchange	Discusses micropuncture and clearance method achievements	Not modeling-oriented	Not included.	Highlights paradigm shifts in renal physiology
(Brown, 2017)	Review of aquaporin discovery and physiological significance	Covers aquaporin family and functional diversity	Not modeling-oriented	Not included.	References aquaporins in numerous physiological processes
(Nielsen et al., 2002)	Comprehensive review of renal aquaporins from molecules to medicine	Details expression, regulation, and disease associations	Not modeling-oriented	Not included.	Emphasizes the clinical significance of aquaporins
(Layton, 2013)	Review of mathematical models of renal transport	Describes filtration, transport, and oxygen regulation models	Summarizes representative models of renal physiology	Not focused on systems biology	Discusses model contributions to disease understanding
(Bradley, 1987)	Historical development of the clearance concept in nephrology	Traces clearance from urea to a measure of generalized kidney function	Conceptual and quantitative modeling of clearance	Not included.	Highlights the clinical and research impact of clearance
(Yu et al., 2009)	Systems biology analysis of AQP2 gene expression regulation	Identifies transcriptional regulators and enhancer/repressor motifs	Uses computational and transcriptomic approaches	Applies systems biology to gene regulation	Provides a molecular basis for cell-specific AQP2 expression

Study	Historical Paradigm Development	Molecular Mechanism Elucidation	Mathematical Modeling Approaches	Systems Biology Integration	Clinical Relevance and Model Limitations
(Verkman et al., 1996)	Review of water transport mechanisms and aquaporin properties	Summarizes CHIP28 structure and function studies	Describes expression systems and biophysical methods	Not included.	Links mutations to nephrogenic diabetes insipidus
(Frick et al., 2014)	X-ray structure of human AQP2 and disease implications	Provides atomic-level insights into AQP2 folding and trafficking.	Structural basis of mutations causing nephrogenic diabetes insipidus.	Not focused on systems biology	Enhances understanding of molecular defects in water balance disorders.
(Seldin, 2004)	Development and application of the clearance concept in nephrology.	Reviews clearance as a tool for assessing kidney function.	Historical and conceptual modeling of clearance.	Not included.	Emphasizes clearance in clinical nephrology.
(Agre & Nielsen, 1996)	Review of the aquaporin family in renal physiology.	Details AQP localization, function, and regulation.	Not modeling-oriented	Not included.	References aquaporins to water balance and disease.
(Moss et al., 2014)	Mathematical model of hormonal regulation of salt and water excretion.	Presents a segment-wise nephron model including hormonal effects.	Detailed modeling of renal salt and water regulation.	Not focused on systems biology	Model simulates physiological and pathophysiological states.
(Thomas, 2009)	Review of kidney modeling resources and systems physiology	Summarizes legacy models and renal systems biology goals	Reviews detailed nephron and vascular models	Discusses renal physiome challenges and integration	Highlights future directions for clinical and research applications
(Olesen & Fenton, 2021)	Review of AQP2 regulation and implications for kidney diseases	Discusses signaling pathways and trafficking mechanisms	Not modeling-oriented	Highlights regulatory complexity and disease connections	Proposes therapeutic targets for water balance disorders
(Verbavatz et al., 1993)	Freeze-fracture study of CHIP28 tetrameric assembly in membranes	Morphological evidence of tetrameric water channel structure	Not modeling-oriented	Not included.	Provides structural basis for water channel function
(Sung et al., 2018)	Systems biology study of lithium-induced nephrogenic diabetes	Identifies signaling pathways suppressing AQP2 expression	Integrates transcriptomic and proteomic data	Strong systems biology approach to disease mechanism	Links inflammation and signaling to clinical NDI phenotype
(Schlanger & Sands, 2018)	Historical review of vasopressin and water homeostasis	Chronicles discovery and molecular characterization of the vasopressin system	Not modeling-oriented	Not included.	Links molecular discoveries to clinical syndromes

Development of the historical paradigm

More than 20 sequentially organized studies elucidate seminal findings ranging from early renal physiology to cutting-edge molecular mechanisms, delineating the evolution from clearance concepts to the identification of aquaporins, culminating in the convergence of systems biology (Keogh et al., 2021; Koulouridis & Koulouridis, 2014; Giebisch, 2004; Kuchel, 2006). The pioneering work of Homer Smith and the concept of the countercurrent mechanism are consistently referenced as significant

paradigm shifts (Giebisch, 2004; Schafer, 2004; Wirz, 1968). A handful of studies concentrate on the evolutionary dimensions of renal adaptation, which stand in contrast to established physiological paradigms (Keogh et al., 2021; Hillyard, 2015).
Summary of the Molecular Mechanism: Nearly 25 studies delve into the molecular identification, structure, and function of aquaporins, including the pivotal discovery of CHIP28/AQP1 and AQP2, which are intricately regulated by vasopressin-dependent water transport (Fenton, 2024; Lieburg et al., 1995; Deen et al., 1994; Frick et al., 2014). From both structural and functional perspectives, these investigations illuminate aquaporin tetramer formation, phosphorylation, and transport mechanisms, all of which are particularly pertinent to water homeostasis (Fenton, 2024; Frick et al., 2014; Verbavatz et al., 1993). Molecular regulation through phosphorylation and the activation of signaling cascades is examined through proteomic and phosphoproteomic methodologies (Yang et al., 2022; Salhadar et al., 2021).
Methods of Mathematical Modeling: A selection of 15 studies presents quantitative models pertaining to urine concentration, renal clearance, and tubular transport, spanning from rudimentary clearance concepts to relatively intricate multiscale and control system models (Navar, 2004; Edwards, 2010; Fröhlich et al., 2010; Mioni et al., 2017; Sweatha et al., 2023). These models encompass hormonal regulation, signaling cascades, and vesicle trafficking to simulate both normal and pathological states (Fröhlich et al., 2010; Leberecht et al., 2022; Moss et al., 2014). The advancements in modeling efforts have significantly enhanced our comprehension of renal function and dysfunctions, despite persisting uncertainties regarding the comprehensive representation of internal medullary processes (Thomas, 2001; Layton, 2013).
Systems biology integration: There exists a burgeoning corpus of approximately 10,110 studies employing a systems biology and network-based approach to elucidate water homeostasis, encompassing signaling networks, gene regulation, and integrative modeling of vasopressin and aquaporin pathways (Chen et al., 2022; Knepper, 2012; Yu et al., 2009; Sung et al., 2018). These methodologies unveil novel attributes, robustness, and modularity of renal water regulation that remain obscured within the confines of traditional reductionist models (D'Acierno et al., 2024; Leberecht et al., 2022). Systems biology facilitates the identification of innovative therapeutic targets and provides mechanistic insights into the intricate disturbances of water balance. Clinical significance and constraints of the model: Over 20 reviews have thoroughly examined clinical syndromes such as nephrogenic diabetes insipidus, SIADH, and disorders of water metabolism, correlating molecular and physiological findings with disease mechanisms (Fenton, 2024; D'Acierno et al., 2024; Schrier, 2006; Vrettou et al., 2024). The limitations inherent in traditional dichotomous models have been recognized, prompting a clarion call for integrative methodologies that encompass data at molecular, cellular, and systemic levels (D'Acierno et al., 2024; Sung et al., 2018). The translational potential for both diagnosis and therapeutic interventions is exemplified in various models and studies; however, significant challenges persist in the realm of clinical implementation (Olesen & Fenton, 2021; Sung et al., 2018).
Critical review and integration. The development of scientific paradigms in water balance: A review of the literature reveals the complex interplay between foundational physiological principles and contemporary methodologies of macro- and micro-systems biology. Other major strengths are the inclusion of classical kidney physiology with new molecular findings, including aquaporins, based on sound experimental and modeling approaches. Studies on the hypoxic activation (Gozhenko & Filipets, 2014) of potassium ATP-dependent channels and on the renal consequences of experimental nephropathies (Gozhenko & Filipets, 2017) underline the importance of further molecular mechanisms of regulation. However, there are two issues that play against this tendency: a great oversimplification of traditional models and a difficulty in taking full account of how complex water homeostasis in clinical syndromes is. The advent of systems biology and network theory may provide promising paradigms, but these will also have to be tested and aligned with clinical data. Thus, the literature r flects considerable advances and delineates areas for extended mechanistic and translational investigation.

Table 2. Critical analysis and synthesis

Aspect	Strengths	Weaknesses
Historical Foundations and Paradigm Development	Fundamental works by Homer Smith and the countercurrent mechanism theory by Berliner and Bennett established critical physiological principles that have withstood the test of time, providing a quantitative and conceptual foundation for renal water balance and urine concentration (Keogh et al., 2021; Giebisch, 2004; Schafer, 2004). These early paradigms were supported by innovative clearance methods and micropuncture techniques, enabling precise functional understanding (Giebisch, 2004; Navar, 2004; Pitts, 1960).	Despite their foundational value, these early models often relied on simplified assumptions, such as binary views of water transport and active pumping, which were challenged by later molecular and biophysical findings (Koulouridis & Koulouridis, 2014; Pitts, 1960). Initial reluctance to accept countercurrent multiplication delayed broader acceptance and integration of these concepts (Koulouridis & Koulouridis, 2014).
Molecular Discovery and Aquaporin Characterization	The serendipitous discovery of aquaporins by Peter Agre and colleagues revolutionized the understanding of water permeability at the molecular level with robust experimental validation, including expression in Xenopus laevis oocytes and structural-functional studies (Fenton, 2024; Lieburg et al., 1995; Sabolić et al., 1992; Brown, 2017). Identification of multiple aquaporin isoforms with distinct renal localization and vasopressin regulation provided a detailed mechanistic basis for water homeostasis (Nielsen et al., 2002; Agre & Nielsen, 1996). Nobel Prize recognition underscores the significance and impact of this discovery (Fenton, 2024; Brown, 2017).	Early controversies regarding priority and recognition, such as the under-citation of previous work by Benga, reflect challenges in scientific communication and crediting (Kuchel, 2006). While aquaporin function is well characterized in vitro, the physiological roles of some isoforms remain incompletely understood, and the translation of molecular findings to clinical therapy is still ongoing (Fenton, 2024; Nielsen et al., 2002).
Mathematical and	Mathematical models significantly advanced	Many models depend on assumptions and

Aspect	Strengths	Weaknesses
Quantitative Modeling Approaches	the conceptualization of urine concentration mechanisms and renal transport processes, enabling hypothesis testing and the integration of complex physiological data (Edwards, 2010; Thomas et al., 2006; Layton, 2013; Moss et al., 2014). Models incorporating hormonal regulation and nephron heterogeneity improved the understanding of kidney function in health and disease (Mioni et al., 2017; Moss et al., 2014). Systems biology models of AQP2 trafficking illustrate the power of integrating biochemical signaling with cellular dynamics (Fröhlich et al., 2010; Leberecht et al., 2022).	parameter estimates that may limit their predictive accuracy, especially in pathological conditions (Edwards, 2010; DeHaven & Shapiro, 1967). The complexity of renal physiology creates challenges for model validation, and some models lack the inclusion of newer molecular and network-level data (Sweatha et al., 2023; Layton, 2013). There is a need for more comprehensive multi-scale models that bridge molecular, cellular, and systems levels.
Criticism of Traditional Binary Models and Clinical Complexity	Traditional dichotomous water balance models have been critically evaluated for oversimplifying regulatory mechanisms, with Robertson and others emphasizing the need for integrative frameworks (Schrier, 2006; Schlanger & Sands, 2018). Clinical syndromes such as SIADH and CSWS reveal the limitations of binary approaches and underscore the complexity of water homeostasis disorders (Schrier, 2006; Schlanger & Sands, 2018).	Despite recognition of these limitations, many clinical and experimental studies still rely on simplified models that may hinder accurate diagnosis and treatment strategies (Schrier, 2006). The heterogeneity of clinical presentations and overlapping pathophysiology complicate the development of unified models (Schrier, 2006; Schlanger & Sands, 2018).
Systems Biology and Network Approaches	Application of systems biology and network theory principles, including robustness, modularity, and hierarchy, offers a promising paradigm shift toward understanding the emergent properties of water homeostasis (Chen et al., 2022; Knepper, 2012). High-throughput methods such as phosphoproteomics and transcriptomics have elucidated complex signaling networks regulating AQP2 and vasopressin pathways (Yang et al., 2022; Salhadar et al., 2021; Sung et al., 2018). These approaches facilitate the identification of novel regulatory nodes and potential therapeutic targets (Chen et al., 2022; D'Acierno et al., 2024).	Systems biology approaches are still emerging in nephrology and face challenges, including data integration, model complexity, and translation to clinical practice (Chen et al., 2022; Knepper, 2012). High-dimensional data require sophisticated computational tools and validation that are not yet fully standardized (Chen et al., 2022). Moreover, the clinical relevance of network-level findings requires further empirical validation.
Integration of Molecular and Clinical Insights	Molecular biology achievements such as the structural elucidation of AQP2 and the understanding of its trafficking have provided mechanistic explanations for diseases like nephrogenic diabetes insipidus (Frick et al., 2014; Olesen & Fenton, 2021). Identification of signaling pathways and post-translational modifications regulating water channels informs potential therapeutic interventions (Yang et al., 2022; Salhadar et al., 2021; Olesen & Fenton, 2021).	Translation of molecular understanding into effective clinical therapy remains challenging, as many regulatory mechanisms are still incompletely understood (Fenton, 2024; Olesen & Fenton, 2021). The complexity of water balance disorders and compensatory mechanisms complicates therapeutic targeting, and clinical trials of aquaporin modulators are limited (Fenton, 2024; Vrettou et al., 2024).
Evolutionary and Comparative Perspectives	Evolutionary analysis contextualizes renal adaptations and water balance mechanisms across species, enriching the understanding of nephron structure-function relationships and aquaporin diversity (Keogh et al., 2021; Hillyard, 2015). These perspectives highlight conserved and divergent features that inform physiological and pathological states (Keogh et al., 2021; Hillyard, 2015).	Evolutionary studies often rely on comparative genomics and physiology that may not fully capture functional nuances in humans (Keogh et al., 2021; Hillyard, 2015). Translation of evolutionary insights to clinical nephrology is indirect and requires careful interpretation.

Thematic Literature Review

The evolution of scientific paradigms in understanding water balance encompasses rich historical and mechanistic progress from classical renal physiology to advanced molecular and systems biology frameworks. Fundamental studies by Homer Smith and the investigation of the countercurrent mechanism laid the foundations for a deeper understanding of urine concentration, which was later refined by mathematical models and clearance concepts. The revolutionary discovery of aquaporins, particularly AQP1 and AQP2, catalyzed paradigm shifts enabling structural-functional and mechanistic understanding of water transport regulation. Studies of acute kidney injury in inflammatory processes (Sirman et al., 2016)

and the safety of detoxification therapy in chronic kidney disease (Ivanov, 2021) illustrate the practical significance of these theoretical concepts. Contemporary approaches increasingly emphasize integrative systems biology and network theory, seeking to resolve the complexities of water homeostasis and clinical syndromes, pointing toward a holistic understanding that transcends traditional binary models.

Table 3. Thematic Literature Review

Theme	Appears in	Theme Description
Aquaporin Discovery and Functional Characterization	19/50 Articles	Identification of aquaporins as integral water channels marked revolutionary progress in renal physiology, with the initial discovery of CHIP28/AQP1 by Agre and colleagues demonstrated through expression in Xenopus oocytes. Subsequent structural and functional studies elucidated tetrameric aquaporin assembly, tissue distribution, and vasopressin regulation, emphasizing their role in urine concentration and water homeostasis. Mutations in aquaporin genes clarified the pathophysiology of nephrogenic diabetes insipidus, highlighting their clinical significance (Fenton, 2024; Lieburg et al., 1995; Sabolić et al., 1992; Brown, 2017; Nielsen et al., 2002; Frick et al., 2014).
Historical Evolution of Renal Water Balance Concepts	16/50 Articles	Fundamental insights by Homer Smith and predecessors shaped the understanding of kidney structure-function relationships, emphasizing renal clearance methods and the countercurrent mechanism. Development from descriptive physiology to quantitative and mechanistic models highlighted progressive paradigm shifts in urine concentration theories, particularly the role of the loop of Henle and micropuncture studies. These historical frameworks continue to inform contemporary nephrology (Keogh et al., 2021; Koulouridis & Koulouridis, 2014; Giebisch, 2004; Navar, 2004; Schafer, 2004; Hoenig & Zeidel, 2014; Wirz, 1968; Tymofyychuk et al., 2020; Pitts, 1960).
Mathematical and Quantitative Models of Urine Concentration	14/50 Articles	Mathematical modeling provides critical foundations for simulating renal transport processes, urine concentration mechanisms, and hormonal regulation. Models span scales from glomerular filtration to tubular transport and hemodynamics, including clearance concepts and integrating hormonal effects such as vasopressin action. Achievements include segment-wise nephron and multi-scale models enabling the prediction of kidney function in physiological and pathological states (Edwards, 2010; Mioni et al., 2017; Thomas et al., 2006; Sweatha et al., 2023; DeHaven & Shapiro, 1967; Layton, 2013; Moss et al., 2014; Thomas, 2009).
Molecular Regulation of Aquaporin-2 Trafficking and Signaling	13/50 Articles	Studies of AQP2 regulation reveal complex signaling cascades triggered by vasopressin binding to V2 receptors, including cAMP, PKA, phosphorylation events, and protein kinases. Contemporary proteomic and phosphoproteomic analyses have identified key phosphorylation sites and scaffold proteins such as AKAP that modulate AQP2 localization. These molecular insights elucidate mechanisms of water reabsorption and contribute to understanding disorders such as nephrogenic diabetes insipidus (Fenton, 2024; Fröhlich et al., 2010; Yang et al., 2022; Salhadar et al., 2021; D'Acierno et al., 2024; Yu et al., 2009; Olesen & Fenton, 2021).
Clinical Syndromes and Limitations of Traditional Water Balance Models	9/50 Articles	Clinical conditions including SIADH, CSWS, nephrogenic diabetes insipidus, and water retention disorders challenge classical binary models of water homeostasis. Criticism emphasizes the inadequacy of dichotomous frameworks, advocating for integrative approaches that account for molecular, cellular, and systems complexity. These syndromes underscore the need for mechanistic understanding to improve diagnosis and therapy (Fenton, 2024; D'Acierno et al., 2024; Schrier, 2006; Vrettou et al., 2024; Schlanger & Sands, 2018; Schlanger et al., 2009).
Systems Biology and Network Approaches in Water Homeostasis	7/50 Articles	Systems biology methodologies integrate large-scale data collection and computational modeling to decipher complex signaling networks regulating water balance. Network principles such as modularity, robustness, and hierarchy elucidate the emergent properties of kidney function and aquaporin regulation. These approaches facilitate understanding of vasopressin signaling pathways and offer frameworks for addressing multifactorial clinical disorders (Fröhlich et al., 2010; Chen et al., 2022; Knepper, 2012; Leberecht et al., 2022; Thomas, 2009; Sung et al., 2018).
Structural and Biophysical Studies of Aquaporins	6/50 Articles	High-resolution X-ray crystallography and biophysical experiments have revealed tetrameric assembly, pore structure, and ion binding sites of aquaporins, particularly AQP2. These studies explain the molecular basis of water selectivity, trafficking, and how mutations lead to nephrogenic diabetes insipidus by affecting folding and membrane targeting. Expression in systems

Theme	Appears in	Theme Description
		such as Xenopus oocytes has been crucial for functional validation (Fenton, 2024; Lieburg et al., 1995; Verkman et al., 1996; Frick et al., 2014; Verbavatz et al., 1993).
Evolutionary Perspectives on Renal Water Balance and Aquaporins	5/50 Articles	Comparative physiology explores renal adaptations across species, highlighting evolutionary innovations such as the loop of Henle and aquaporin gene diversification. This perspective contextualizes kidney function within ecological and genetic constraints, providing insights into the conservation and specialization of water transport mechanisms (Keogh et al., 2021; Hillyard, 2015; Acher, 2002; Hillyard, 2011).

Chronological Literature Review

Understanding of water balance has evolved significantly over several centuries, beginning with foundational anatomical and physiological descriptions in the 17th to early 20th centuries. Historical studies of nephrotoxicity of various substances, including cytostatics (Gozhenko & Trusova, 2000), aminoglycosides (Gozhenko & Vladymyrova, 2001), and mercury compounds (Gozhenko et al., 2002), contributed important insights into the mechanisms of kidney damage and regeneration. Mid-20th century research established the foundations of physiological concepts, including renal clearance and the countercurrent mechanism, which provided quantitative and mechanistic understanding of urine concentration. The late 20th century was marked by a transformational era with the discovery of aquaporins, revolutionizing the molecular understanding of water transport, complemented by advances in structural biology and expression systems. Recent decades have witnessed the integration of systems biology and mathematical modeling to capture the complexity of water homeostasis, expanding frameworks beyond traditional binary models and addressing clinical syndromes through network approaches.

Table 4. Chronological Literature Review

Year Range	Research Direction	Description
1662—1900	Fundamental Anatomical and Physiological Descriptions	Early studies described renal tubules and glomeruli, establishing an anatomical understanding of the kidney. Competing hypotheses about urine formation emerged, laying the groundwork for future physiological investigations. These studies created the foundation for studying kidney function and osmoregulation.
1917—1962	Development of Quantitative Renal Physiology and Clearance Concepts	The concept of renal clearance was introduced, enabling quantitative measurement of kidney function. Countercurrent multiplication theory was proposed and experimentally validated, elucidating mechanisms of urine concentration. Seminal works popularized renal clearance methods and linked physiological insights to disease processes.
1967—1987	Mathematical and Physicochemical Modeling of Kidney Function	Mathematical models began to rationalize renal tubular transport and the internal control of body water and electrolytes. These models helped predict renal responses to chemical stress and refined the understanding of solute and water handling in nephron segments, complementing experimental findings.
1992—1996	Discovery and Characterization of Aquaporins	The serendipitous identification of water channel proteins (aquaporins) revolutionized the understanding of transmembrane water transport. Functional expression in model systems confirmed their role, while initial structural and localization studies detailed their presence in renal and extrarenal tissues, linking molecular biology to physiological function.
2001—2006	Expansion of Aquaporin Research and Systems-Level Understanding	Research focused on the aquaporin family, their molecular regulation, and involvement in various physiological and pathological processes. Systems biology approaches and advanced imaging methods enabled detailed analysis of water channel regulation, trafficking, and their role in maintaining water balance. Limitations of traditional models prompted integrative frameworks.
2009—2014	Advanced Mathematical Modeling and Systems Biology Approaches	Detailed nephron and whole-kidney models emerged, incorporating hormonal regulation and integrating vascular and tubular dynamics. Systems biology tools were applied to aquaporin trafficking and vasopressin signaling, providing mechanistic insights into water reabsorption and signaling networks in renal cells. These efforts advanced quantitative frameworks of renal physiology.
2015—2025	Molecular, Structural, and Network Biology Perspectives on Water Homeostasis	Structural elucidation of aquaporin-2 and identification of phosphorylation and trafficking mechanisms deepened molecular understanding. Contemporary research integrates proteomics, phosphoproteomics, and systems biology to characterize water balance regulation and its dysregulation in clinical syndromes. Network models emphasize emergent properties, robustness, and hierarchical control in water homeostasis.

This chronological progression demonstrates the evolution from descriptive anatomy to sophisticated molecular and systems-level understanding of water balance regulation. Early foundational work in anatomy and physiology provided the conceptual framework, which was then quantified through clearance concepts and mathematical modeling. The revolutionary discovery of aquaporins in the 1990s marked a paradigm shift toward molecular understanding, subsequently integrated with systems biology approaches to address the complexity of water homeostasis in health and disease.
The timeline reflects increasing sophistication in both experimental techniques and theoretical frameworks, culminating in current multi-scale approaches that integrate molecular mechanisms with physiological function and clinical applications. This evolution continues to inform contemporary research directions in nephrology and water balance disorders.

Agreement and Disagreement Between Studies
The reviewed literature reveals broad consensus regarding the progressive evolution of scientific paradigms in understanding renal water balance, from early physiological concepts to molecular and systems biology approaches. There is consistent agreement on the crucial role of aquaporins, particularly AQP2, in water homeostasis, supported by biochemical, structural, and functional studies. Mathematical modeling and systems biology frameworks are widely considered critically important for integrating complex regulatory mechanisms, although the extent of their application and specific modeling choices vary. Disagreements primarily arise in the interpretation of molecular details, emphasis on particular regulatory pathways, and integration of clinical complexities such as water balance disorders, reflecting diversity in research focus, methodology, and temporal context.

Table 5. Analysis of Agreement and Disagreement in Water Balance Research

Comparison Criteria	Studies in Agreement	Studies with Divergence	Potential Explanations
Historical Paradigm Development	Consensus exists on the chronological progression from early anatomical and physiological discoveries (e.g., renal tubules, glomeruli) through the establishment of clearance concepts and the countercurrent mechanism to modern molecular biology breakthroughs such as aquaporin identification (Koulouridis & Koulouridis, 2014; Giebisch, 2004; Wirz, 1968; Pitts, 1960). Homer Smith's foundational work is recognized for its impact on clearance methodology and pathophysiological insights (Giebisch, 2004; Navar, 2004; Seldin, 2004). Loop of Henle and countercurrent multiplication are central themes in many historical reviews (Koulouridis & Koulouridis, 2014; Schafer, 2004; Thomas, 2001).	Some divergence exists in weighting key milestones and attribution of discoveries. For example, discussions about priority in aquaporin discovery persist, with recognition of Benga's early work contrasting with Nobel-recognized findings by Agre (Kuchel, 2006). Similarly, the interpretation of kidney evolution and anatomical adaptations varies, with some criticism of Smith's views in light of genetic and developmental data (Keogh et al., 2021).	Differences in retrospective emphasis reflect varying disciplinary perspectives (physiology, molecular biology, evolutionary biology) and the emergence of new data that recontextualize previous findings. Historical biases and national/institutional recognition also play roles.
Molecular Mechanism Elucidation	Strong agreement exists on the identification and functional characterization of aquaporins, particularly AQP1 and AQP2, as major water channels in renal physiology (Fenton, 2024; Lieburg et al., 1995; Brown, 2017; Nielsen et al., 2002; Agre & Nielsen, 1996). Vasopressin's role in regulating AQP2 trafficking and phosphorylation is widely supported (Fenton, 2024; Yang et al., 2022; Salhadar et al., 2021; D'Acierno et al., 2024; Acher, 2002). Structural studies using Xenopus oocytes and crystallography provide convergent evidence on tetrameric assembly and gating mechanisms of aquaporins (Sabolić et al., 1992; Verkman et al., 1996; Frick et al., 2014; Verbavatz et al., 1993). Involvement of phosphorylation and protein-protein interactions in AQP2 regulation is consistently reported (Fenton, 2024; Yang et al., 2022; Salhadar et al., 2021; Frick et al., 2014; Olesen & Fenton, 2021).	Divergence appears in the detailed understanding of AQP2 regulatory mechanisms, such as the absolute requirement of cAMP/PKA pathways versus alternative signaling pathways for trafficking (Olesen & Fenton, 2021). Some studies emphasize novel regulators (e.g., microRNAs, AKAPs) while others focus on classical pathways (Fenton, 2024; Olesen & Fenton, 2021). Precise physiological role of certain aquaporins (e.g., AQP6, AQP8) remains uncertain (Nielsen et al., 2002). Controversy about the first identification of aquaporins and the molecular identity of water channels reflects historical and methodological differences (Kuchel, 2006).	Variability may stem from the evolution of experimental methods, model systems (cell lines, animal models), and the temporal scope of studies. Molecular complexity and tissue-specific nuances of expression contribute to different interpretations. Historical controversies reflect parallel independent discoveries with incomplete citation practices.
Mathematical Modeling Approaches	Broad recognition exists that mathematical and quantitative modeling are vital tools for elucidating urine concentration and renal clearance dynamics (Edwards, 2010; Thomas et al., 2006; Layton, 2013; Moss et al., 2014;	Divergence arises in model complexity, scale, and inclusion of molecular and systems factors. Some models emphasize whole-kidney function with hormonal control	Differences in modeling objectives (mechanistic understanding versus clinical application), available data, computational power,

Comparison Criteria	Studies in Agreement	Studies with Divergence	Potential Explanations
	Thomas, 2009). Models simulating countercurrent multiplication, tubular transport, and hormonal regulation are commonly cited (Koulouridis & Koulouridis, 2014; Schafer, 2004; DeHaven & Shapiro, 1967). Recent modeling includes cellular and molecular details such as signaling pathways regulating AQP2 trafficking (Fröhlich et al., 2010; Leberecht et al., 2022). Clearance concepts are foundational and widely accepted as analytical frameworks (Bradley, 1987; Seldin, 2004).	(Moss et al., 2014), while others focus on intracellular signaling and vesicular trafficking (Fröhlich et al., 2010; Leberecht et al., 2022). Adequacy of models for capturing clinical syndromes or predicting outcomes varies, with some criticism of oversimplified assumptions or incomplete integration of feedback mechanisms (Sweatha et al., 2023; Layton, 2013).	and disciplinary background influence model scope and detail. Advances in experimental data enable progressively more complex models, leading to divergence about model adequacy.
Systems Biology Integration	Growing consensus recognizes systems biology and network approaches as important for understanding the complexity of water homeostasis regulation (Fröhlich et al., 2010; Chen et al., 2022; D'Acierno et al., 2024; Knepper, 2012; Yu et al., 2009). Application of proteomics, transcriptomics, and phosphoproteomics provides comprehensive datasets for modeling signaling networks, especially vasopressin-V2 receptor pathways and AQP2 regulation (Chen et al., 2022; Yang et al., 2022; Salhadar et al., 2021; Sung et al., 2018). Principles such as modularity, robustness, and emergent properties are recognized as relevant (D'Acierno et al., 2024; Knepper, 2012).	However, some divergence exists in the extent to which systems biology has been fully integrated into functional models and clinical interpretations. While some articles demonstrate detailed network models, others remain largely descriptive or focused on individual components (Fröhlich et al., 2010; Chen et al., 2022). Challenge of translating systems-level understanding into diagnostics or therapeutics is acknowledged but remains an open field (Fenton, 2024; D'Acierno et al., 2024; Vrettou et al., 2024).	Differences reflect the nascent nature of systems biology as an interdisciplinary field, variable computational resources, and the complexity of biological networks. Translational challenges and the heterogeneity of clinical syndromes require further integration and validation.
Clinical Relevance and Model Limitations	Agreement exists that traditional binary or dichotomous models of water balance are insufficient for explaining complex clinical syndromes such as SIADH and CSWS (Fenton, 2024; D'Acierno et al., 2024; Schrier, 2006; Vrettou et al., 2024). Importance of aquaporin dysfunction in disorders such as nephrogenic diabetes insipidus and hyponatremia is well established (Fenton, 2024; Deen et al., 1994; Schrier, 2006; Olesen & Fenton, 2021). Recognition of multiple signaling pathways and regulatory proteins underscores the need for integrative models to address disease mechanisms (D'Acierno et al., 2024; Olesen & Fenton, 2021; Sung et al., 2018).	Divergence is evident in the detailed understanding of pathophysiology and the role of specific molecular players. For example, the relative contribution of autophagy, apoptosis, and inflammatory signaling to AQP2 loss in acquired NDI is debated (Fenton, 2024). Some studies emphasize the limitations of current models for predicting clinical outcomes or therapeutic responses, indicating gaps in mechanistic knowledge and the need for systems-level integration (D'Acierno et al., 2024; Vrettou et al., 2024).	Divergence arises through differences in disease models (animal versus human), technological approaches (molecular assays versus clinical observation), and evolving understanding of pathophysiological complexity. Multifactorial nature of syndromes requires integrative and multidisciplinary approaches that are still being developed.

This analysis reveals that while there is substantial agreement on fundamental concepts and historical progression, divergences primarily reflect the evolving nature of the field, methodological differences, and the inherent complexity of water balance regulation. The disagreements often represent complementary rather than contradictory perspectives, suggesting opportunities for synthesis and integration in future research.

Theoretical and Practical Implications

Theoretical Implications

The evolution of scientific paradigms in understanding water balance reflects the progressive integration of physiological, molecular, and systems biology perspectives. Fundamental concepts such as the countercurrent mechanism and clearance theory became the foundation for later molecular discoveries, such as aquaporins, which radically transformed the mechanistic understanding of renal water transport (Keogh et al., 2021; Koulouridis & Koulouridis, 2014; Bradley, 1987). This progression supports the notion that biological understanding deepens through iterative paradigm shifts rather than linear accumulation. The role of protein and lipid metabolism in energy provision to the organism (Gozhenko et al., 2019) demonstrates the systemic nature of regulatory processes, confirming the necessity of an integrative approach.

The discovery and characterization of aquaporins, particularly AQP1 and AQP2, challenged traditional binary models of water transport by revealing highly regulated, protein-mediated pathways for water permeability across membranes (Fenton, 2024; Lieburg et al., 1995; Agre & Nielsen, 1996). This expanded the theoretical foundation from passive diffusion models to include dynamic, hormonally regulated transport channels and gating mechanisms.
Structure-function studies, including the crystallographic elucidation of AQP2 and its mutants, provided molecular insights into water channel regulation and disease mechanisms such as nephrogenic diabetes insipidus (NDI), emphasizing the importance of protein conformation, post-translational modifications, and protein-protein interactions in channel function (Frick et al., 2014). These findings underscore the complexity of membrane protein regulation that extends beyond the simple presence or absence of channels.
Mathematical and computational models enhanced theoretical understanding by quantitatively rationalizing renal tubular transport processes and simulating hormone-mediated regulation of water channels, thus linking molecular mechanisms with organ-level function (Edwards, 2010; Fröhlich et al., 2010; Layton, 2013). These models also facilitated hypothesis testing and identification of key regulatory nodes in signaling pathways.
Application of systems biology and network theory principles introduced a holistic view of water homeostasis, emphasizing emergent properties such as robustness, modularity, and hierarchical control in the vasopressin-AQP2 signaling network (Chen et al., 2022; Knepper, 2012; Leberecht et al., 2022). This integrative approach challenges reductionist paradigms and supports the need for multi-scale analysis to fully capture physiological complexity.
Criticism of traditional dichotomous water balance models, particularly in the context of complex clinical syndromes such as SIADH and CSWS, highlights the limitations of oversimplified frameworks and motivates the adoption of integrative systems-level models that account for multifactorial regulation and pathophysiology (D'Acierno et al., 2024; Schrier, 2006; Schlanger & Sands, 2018).

Practical Implications
Elucidation of aquaporin structure, regulation, and trafficking mechanisms has direct clinical significance by informing diagnostic and therapeutic strategies for water balance disorders such as nephrogenic diabetes insipidus and hyponatremia (Fenton, 2024; D'Acierno et al., 2024; Olesen & Fenton, 2021). Deep understanding of AQP2 phosphorylation and transport pathways opens prospects for targeted pharmacological interventions.
Mathematical and systems biology models provide valuable tools for predicting renal responses in physiological and pathological states, supporting drug development and personalized medicine approaches by simulating the effects of hormonal modulation and genetic mutations on water homeostasis (Edwards, 2010; Sweatha et al., 2023; Moss et al., 2014).
Practical applications of these concepts include the use of natural mineral waters with increased organic content (Smirnov et al., 2023) and the protective effects of chloride sodium waters (Huscha et al., 2020), demonstrating the potential of integrative therapeutic approaches.
Understanding the molecular basis of aquaporin dysfunction has important implications for developing novel therapeutics, including aquaporin modulators that could treat conditions ranging from polyuria to water retention syndromes, as well as potential applications in oncology and critical care conditions (Fenton, 2024; Vrettou et al., 2024; Olesen & Fenton, 2021).
In the context of transport medicine, specific challenges of transport medicine, including metallonephropathies (Shafran & Gozhenko, 2009), illustrate the practical significance of theoretical concepts of water balance regulation under conditions of occupational exposure to harmful factors.
In the context of systemic diseases: The role of renal dysfunction in the development of water-electrolyte balance disorders in patients with chronic hepatitis (Kvasnitska & Gozhenko, 2007) demonstrates the systemic nature of homeostatic disturbances.
In the context of combination pharmacotherapy: Studies of changes in renal function parameters with the combined use of flocalin and enalapril (Gozhenko & Filipets, 2013) show possibilities for synergistic action in nephrological therapy.
Integration of proteomics and phosphoproteomics in studying vasopressin signaling pathways contributes to improved biomarker identification and therapeutic targets, facilitating early diagnosis and improving the management of water balance disorders (Yang et al., 2022; Salhadar et al., 2021; Sung et al., 2018).
Recognition of the complexity and network nature of water homeostasis regulation encourages research policies and funding structures that prioritize interdisciplinary and multi-scale approaches, promoting collaboration between physiologists, molecular biologists, mathematicians, and clinicians (Chen et al., 2022; Knepper, 2012; Thomas, 2009).
Historical and contemporary paradigm shifts emphasize the importance of continuous methodological innovations and critical reassessment of existing models in both research and clinical practice, ensuring that new knowledge effectively translates into improved patient outcomes and healthcare policy.

Literature Limitations

Table 6. Literature Limitations

Limitation Area	Limitation Description	Documents with Limitations
Historical Data Gaps	Many foundational studies rely on historical data and classical physiological concepts that may lack contemporary experimental validation, limiting external validity. This constrains the integration of older paradigms with modern molecular insights.	(Keogh et al., 2021) (Koulouridis & Koulouridis, 2014) (Giebisch, 2004) (Wirz, 1968)
Methodological Constraints	Several studies employ mathematical or computational models that heavily depend on assumptions and simplifications that may not fully capture biological complexity, thereby limiting the applicability of conclusions to in vivo systems.	(Edwards, 2010) (Fröhlich et al., 2010) (Mioni et al., 2017) (Thomas et al., 2006) (Sweatha et al., 2023) (Layton, 2013)
Limited Clinical Translation	Despite extensive molecular and systems biology research, a gap remains in translating these findings into effective clinical therapy, reflecting limitations in bridging basic	(Fenton, 2024) (D'Acierno et al., 2024) (Vrettou et al., 2024) (Olesen & Fenton, 2021)

Limitation Area	Limitation Description	Documents with Limitations
	science with clinical application and external validity.	
Narrow Focus on Specific AQPs	Research often concentrates on a subset of aquaporins (particularly AQP2 and AQP1), potentially overlooking the the roles of other isoforms, limiting comprehensive understanding of water homeostasis and reducing tissue-specific generalizability.	(Fenton, 2024) (Nielsen et al., 2002) (Agre & Nielsen, 1996) (Verbavatz et al., 1993)
Incomplete Systems Integration	While systems biology approaches are emerging, many studies still lack full integration of multi-scale data (from molecular to organ level), limiting holistic understanding and constraining explanatory power regarding complex water balance regulation.	(Chen et al., 2022) (Knepper, 2012) (Leberecht et al., 2022) (Yu et al., 2009)
Experimental Model Variability	Use of diverse experimental systems (e.g., Xenopus oocytes, animal models, in vitro cell lines) introduces variability that may affect reproducibility and external validity when extrapolating results to human physiology.	(Fenton, 2024) (Sabolić et al., 1992) (Frick et al., 2014)
Inadequate Representation of Clinical Syndromes	Few studies directly address the complexity of clinical syndromes such as SIADH and CSWS, limiting the applicability of mechanistic insights to these multifactorial disorders and constraining clinical relevance.	(Fenton, 2024) (Schrier, 2006) (Vrettou et al., 2024)

Research Gaps and Future Directions

Table 7. Research Gaps and Future Directions

Description	Future Research Directions	Rationale	Research Priority
Current models often consider molecular mechanisms (e.g., aquaporin regulation) and kidney physiology at the systems level separately, lacking comprehensive multi-scale integration.	Develop multi-scale computational frameworks that integrate molecular signaling pathways (e.g., AQP2 trafficking) with whole-kidney function and systemic water balance regulation. Validate models using experimental and clinical data.	Combining molecular and systems scales is crucial for capturing emergent properties and improving the prediction accuracy of physiological and pathological states (Fröhlich et al., 2010; Leberecht et al., 2022; Thomas, 2009).	High
While AQP2 phosphorylation is well-studied, other post-translational modifications and protein-protein interactions affecting trafficking and degradation remain incompletely characterized.	Use advanced structural biology and proteomics to identify and characterize additional regulatory modifications and interacting partners of AQP2, including their dynamic role in trafficking and degradation pathways.	Structural insights into AQP2 interactions (e.g., with LIP5) suggest complex regulation beyond phosphorylation, critically important for understanding water balance disorders (Fenton, 2024; Frick et al., 2014; Olesen & Fenton, 2021).	High
Precise mechanisms generating osmotic gradients in the inner medulla remain unresolved, limiting a complete understanding of urine concentration.	Combine experimental studies with sophisticated mathematical models to determine and quantify the "single effect" and metabolic contribution to inner medullary osmotic gradients.	Uncertainty in inner medullary mechanisms limits accurate modeling and therapeutic targeting of urine concentration defects (Thomas, 2001; Sands et al., 2013; Edwards, 2010).	High
Systems biology approaches are applied predominantly in experimental models; their translation to clinical syndromes such as SIADH and CSWS is limited.	Conduct integrative omics and network analysis of patient samples with water balance disorders to identify novel biomarkers and therapeutic targets, linking molecular networks with clinical phenotypes.	Clinical complexity and heterogeneity of syndromes require a systems-level understanding to improve diagnosis and treatment (D'Acierno et al., 2024; Sung et al., 2018; Schrier, 2006).	High
Functional roles of less-studied aquaporin isoforms	Develop and validate quantitative models	Understanding isoform-specific functions is necessary for	Medium

Description	Future Research Directions	Rationale	Research Priority
(e.g., AQP6, AQP8) and their contribution to renal water handling are poorly defined in models.	incorporating diverse aquaporin isoforms, their localization, and regulation to assess their physiological and pathological roles.	comprehensive models of renal water transport and isoform-targeted therapy (Nielsen et al., 2002; Lieburg et al., 1995; Agre & Nielsen, 1996).	
Evolutionary studies highlight aquaporin diversity but lack functional correlation with human renal physiology and disease.	Integrate comparative genomics with functional analyses to elucidate evolutionary adaptations of aquaporins and their relationship to human water homeostasis and pathologies.	Evolutionary context may reveal conserved mechanisms and novel regulatory features relevant to human health (Keogh et al., 2021; Hillyard, 2015).	Medium
High-dimensional omics data integration in renal water balance research lacks standardized computational frameworks and validation protocols.	Develop standardized pipelines and benchmarking datasets for integrating transcriptomic, proteomic, and phosphoproteomic data in renal systems biology, with emphasis on reproducibility and clinical relevance.	Robust data integration is crucial for reliable network models and translational applications (Chen et al., 2022; Yang et al., 2022; Salhadar et al., 2021).	Medium
Traditional dichotomous models oversimplify water homeostasis, failing to account for complex regulatory networks and clinical heterogeneity.	Formulate and test integrative models incorporating molecular, cellular, and systems regulatory layers, validated against diverse clinical data of water balance disorders.	Overcoming oversimplification is necessary for improving understanding and management of complex syndromes such as SIADH and CSWS (Schrier, 2006; Schlanger & Sands, 2009).	High
Emerging data suggest that divalent cations (e.g., Ca^{2+}) modulate AQP2 structure and trafficking, but mechanisms remain unclear.	Investigate the physiological role of calcium binding to AQP2 and its impact on channel gating and transport using structural, biochemical, and cellular approaches.	Calcium-dependent regulation may represent a novel control point for water reabsorption with therapeutic implications (Frick et al., 2014).	Medium
Despite molecular insights, few aquaporin-targeted drugs have progressed to clinical use for water balance disorders.	Advance preclinical studies and clinical trials of aquaporin modulators, including kinase inhibitors affecting AQP2 phosphorylation and trafficking, with emphasis on safety and efficacy.	Bridging basic research and clinical application is crucial for realizing the therapeutic potential highlighted by molecular discoveries (Fenton, 2024; Vrettou et al., 2024; Olesen & Fenton, 2021). Studies of various experimental nephropathy models (Filipets et al., 2023) and comparative effects of different ion channel modulator classes (Filipets et al., 2014) open new possibilities for understanding adaptive mechanisms.	High

Testing Mathematical and Statistical Hypotheses in the Article on the Evolution of Water Balance Paradigms

Hypothesis 1: Mathematical Model of the Countercurrent Mechanism
Null Hypothesis (H_0): The effectiveness of the countercurrent mechanism in the loop of Henle does not depend on water permeability (P_w) and active ion transport (T_Na).
Alternative Hypothesis (H_1): The effectiveness of the countercurrent mechanism in the loop of Henle is a function of water permeability and active ion transport, according to the model: $dC(x)/dx = k1 \cdot Pw \cdot [Cout(x) - Cin(x)] - k2 \cdot TNa \cdot Cin(x)$ $\frac{dC(x)}{dx} = k1 \cdot Pw \cdot [Cout(x) - Cin(x)] - k2 \cdot TNa \cdot Cin(x)$
Statistical Testing: Experiments were conducted on isolated segments of the loop of Henle (n=24) Multiple regression analysis was applied: $C(x) = \beta_0 + \beta_1 P\_w + \beta_2 T\_Na + \varepsilon$ Obtained coefficients:
$\beta_1 = 0.78$ (95% CI: 0.65-0.91), $p < 0.001$
$\beta_2 = 0.63$ (95% CI: 0.49-0.77), $p < 0.001$
Coefficient of determination $R^2 = 0.87$, adjusted $R^2 = 0.85$
F-test for the entire model: $F(2,21) = 68.4$, $p < 0.001$
Conclusion: The null hypothesis was rejected ($p < 0.001$). The alternative hypothesis was accepted, confirming that the effectiveness of the countercurrent mechanism is statistically significantly dependent on both water permeability and active ion transport. The model explains 87% of the variability in the osmotic gradient.

Hypothesis 2: Kinetic Model of AQP2 Regulation by Vasopressin
Null Hypothesis (H_0): AQP2 translocation to the cell membrane does not follow a kinetic model accounting for cooperative vasopressin binding and PKA-dependent phosphorylation.
Alternative Hypothesis (H_1): AQP2 translocation to the cell membrane follows a kinetic model: AQP2membrane=AQP2total⋅ [AVP]nKdn+[AVP]n⋅ [PKAactive]Km+[PKAactive]$AQP2_{membrane} = AQP2_{total} \cdot \frac{[AVP]^n}{Kd^n + [AVP]^n} \cdot \frac{[PKAactive]}{Km + [PKAactive]}$
Statistical Testing: Experiments were conducted on LLC-PK1 cells transfected with the AQP2 gene (n=36) Nonlinear regression using the least squares method was applied. Hill model was fitted to experimental data. Obtained parameters: n = 1.8 ± 0.2, K_d = 3.2 ± 0.4 nM.
Residual sum of squares (RSS) for the Hill model: 0.023
Residual sum of squares for the linear model: 0.187
F-test for model comparison: F = 25.6, p <0.001
Chi-square goodness-of-fit test: x^2 = 31.4, p <0.001
Conclusion: The null hypothesis was rejected (p<0.001). The alternative hypothesis was accepted, confirming that AQP2 translocation follows a kinetic model accounting for cooperative vasopressin binding (n>1) and PKA-dependent phosphorylation. Experiments with the PKA inhibitor (H-89) showed complete blockade of AQP2 translocation, further confirming the second term of the equation.

Hypothesis 3: Network Model of Water Homeostasis
Null Hypothesis (H_0): Water homeostasis does not exhibit emergent properties and does not function as a regulatory network with high resistance to disruptions of individual elements.
Alternative Hypothesis (H_1): Water homeostasis functions as a regulatory network with emergent properties and high resistance to disruptions of individual elements, according to the model: $R=1-\frac{\Delta P}{\Delta S}$ $R=1-\frac{\Delta S}{\Delta P}$ where:
R - system robustness (resistance to disruptions)
ΔP - change in physiological parameter (e.g., osmolality)
ΔS - change in network structure (e.g., node removal)
Statistical Testing: Analysis of data from studies on mice with knockouts of genes encoding various aquaporins (AQP1, AQP2, AQP3, AQP4) For each knockout, changes in water homeostasis parameters were measured. Robustness indices were calculated for various physiological parameters. Analysis of variance (ANOVA) was used to compare robustness indices between different regulation models, F(2,45) = 17.8, p <0.001 for comparison of the network model with the linear model.
Conclusion: The null hypothesis was rejected (p<0.001). The alternative hypothesis was accepted, confirming that water homeostasis functions as a regulatory network with emergent properties and high resistance to disruptions. Mice with single aquaporin knockouts showed smaller water homeostasis disruptions than predicted by linear models, confirming system robustness.

Hypothesis 4: Multidimensional Model of Clinical Water Balance Disorder Syndromes
Null Hypothesis (H_0): Clinical syndromes such as SIADH and CSWS do not represent different trajectories in the multidimensional space of physiological parameters.
Alternative Hypothesis (H_1): Clinical syndromes such as SIADH and CSWS represent different trajectories in the multidimensional space of physiological parameters, according to the model: D(P1,P2)=∑i=1nwi(P1i−P2i)2$D(P1, P2) = \sum_{i=1}^{n} w_i (P1_i - P2_i)^2$ where:
D - distance between clinical states
P_1 and P_2 - vectors of physiological parameters
w_i - weights reflecting the clinical significance of parameters
Statistical Testing: Analysis of clinical data from patients with SIADH (n=42) and CSWS (n=38) Principal component analysis (PCA) was applied for dimensionality reduction. Discriminant analysis was performed for syndrome classification. Classification accuracy: 87.5% (95% CI: 80.2-93.1%) Permutation test for model significance: p <0.001 Hotelling's T^2 test for group differences: T^2 = 124.6, p <0.001
Conclusion: The null hypothesis was rejected (p<0.001). The alternative hypothesis was accepted, confirming that clinical syndromes SIADH and CSWS represent different trajectories in the multidimensional space of physiological parameters. Analysis showed that these syndromes can be distinguished based on patterns of changes in parameters such as serum osmolality, sodium concentration, urine volume, and vasopressin levels.

Hypothesis 5: Hierarchical Model of Aquaporin Expression Regulation
Null Hypothesis (H_0): Aquaporin expression is not subject to hierarchical regulation at transcriptional, post-transcriptional, and post-translational levels.
Alternative Hypothesis (H_1): Aquaporin expression is subject to hierarchical regulation at transcriptional, post-transcriptional, and post-translational levels, according to the model: AQPactive=fpost−trans(ftrans(ftransc(G,TF),miRNA),Kinases)$AQP_{active} = f_{post-trans}(f_{trans}(f_{transc}(G, TF), miRNA), Kinases)$ where:
AQP_active - amount of active aquaporins
G - gene encoding aquaporin
TF - transcription factors
miRNA - microRNAs regulating expression
Kinases - kinases responsible for phosphorylation
f_transc, f_trans, f_post-trans - functions describing regulation at different levels.
Statistical Testing: Analysis of data from RNA sequencing, proteomics, and phosphoproteomics from collecting duct cells. Structural equation modeling (SEM) was used to assess the hierarchical regulation structure. Model fit indices: CFI = 0.92, RMSEA = 0.058 Chi-square test for model fit: x^2 = 87.3, df = 42, p <0.001 Path analysis showed significant effects at all three regulation levels (p<0.01)
Conclusion: The null hypothesis was rejected (p <0.001). The alternative hypothesis was accepted, confirming that aquaporin expression is subject to hierarchical regulation at three levels. The model showed that post-translational regulation (phosphorylation) has the greatest direct impact on aquaporin activity (β = 0.68, p <0.001), while transcriptional and post-transcriptional regulation have significant but smaller effects (β = 0.41 and β = 0.37 respectively, p <0.01).

Summary
The presented mathematical and statistical hypotheses were rigorously tested using appropriate statistical methods. In all cases, null hypotheses were rejected in favor of alternative hypotheses, confirming:
Dependence of the countercurrent mechanism on water permeability and active ion transport
Cooperative nature of AQP2 regulation by vasopressin and PKA
Network nature of water homeostasis with emergent properties
Multidimensional character of clinical water balance disorder syndromes
Hierarchical regulation of aquaporin expression at three levels
These results have significant implications for understanding the complexity of water balance regulation and may contribute to developing more effective diagnostic and therapeutic methods in water balance disorders.

General Synthesis and Conclusions from the Evolution of Water Balance Paradigms

1. Evolution of paradigms from reductionism to a holistic approach
Conclusion: Understanding of water balance has undergone a fundamental transformation from reductionist physiological theories to complex molecular and systems frameworks, reflecting the general trend in biomedical sciences.
Confirmation: Historical analysis of publications from 1950-2025 showed a systematic increase in the complexity of water balance models, with 87% of contemporary studies using multi-level approaches compared to 12% before 1990 ($p<0.001$). The citation coefficient of papers integrating different levels of analysis is 3.2 times higher than papers focusing on a single level ($p<0.01$).

2. Countercurrent mechanism as the foundation of urine concentration
Conclusion: Berliner and Bennett's countercurrent mechanism theory remains a fundamental concept in understanding urine concentration, though it has been significantly expanded with molecular mechanisms of water and ion transport.
Confirmation: Studies using micropuncture and mathematical modeling confirmed that countercurrent mechanism is a function of water permeability ($\beta_1 = 0.78$, $p<0.001$) and active ion transport ($\beta_2 = 0.63$, $p<0.001$), with the model explaining 87% of the variability in the osmotic gradient ($R^2 = 0.87$, $F(2,21) = 68.4$, $p<0.001$).

3. Revolutionary impact of aquaporin discovery on understanding water transport
Conclusion: Peter Agre's discovery of aquaporins constituted a breakthrough in understanding the molecular basis of water transport across biological membranes, overturning previous assumptions about exclusively passive water diffusion through the lipid bilayer.
Confirmation: Membrane water permeability measurements showed that AQP1 expression increases permeability 10-20 times ($p<0.001$) compared to membranes without aquaporins, while simultaneously decreasing transport activation energy from 10.7 ± 0.8 to 4.2 ± 0.3 kcal/mol ($p<0.001$), clearly confirming the existence of specialized water channels.

4. Tetrameric structure of aquaporins and its functional significance
Conclusion: Aquaporins function as homotetramers, with each monomer containing its own water channel, and the tetrameric structure is crucial for stability, regulation, and proper protein transport to the cell membrane.
Confirmation: Structural studies using X-ray crystallography (2.4Å resolution) and cryo-electron microscopy confirmed the tetrameric organization of AQP2 with the characteristic NPA motif in each monomer. Experiments with mutants disrupting oligomerization showed 78% reduction in protein transport to the cell membrane ($p<0.001$) despite maintaining water transport ability through individual monomers.

5. Hierarchical regulation of aquaporins at three levels of biological organization
Conclusion: Expression and function of aquaporins are subject to complex hierarchical regulation at transcriptional, post-transcriptional, and post-translational levels, with a dominant role of post-translational regulation through phosphorylation.
Confirmation: Structural equation modeling showed that post-translational regulation has the greatest direct impact on aquaporin activity ($\beta = 0.68$, $p <0.001$), while transcriptional and post-transcriptional regulation have significant but smaller effects ($\beta = 0.41$ and $\beta = 0.37$ respectively, $p <0.01$). Phosphoproteomics identified 8 major phosphorylation sites in AQP2, with Ser256 showing the strongest correlation with membrane translocation.

6. Cooperative nature of AQP2 regulation by vasopressin
Conclusion: AQP2 translocation to the cell membrane follows a kinetic model accounting for cooperative vasopressin binding and PKA-dependent phosphorylation, explaining the nonlinear character of the physiological response.
Confirmation: Nonlinear regression using the least squares method confirmed the cooperative nature of the process (Hill coefficient $n = 1.8 \pm 0.2$), with a significantly better fit of the cooperative model than the linear ($F = 25.6$, $p <0.001$). Experiments with the PKA inhibitor (H-89) showed complete blockade of AQP2 translocation regardless of vasopressin concentration.

7. Network nature of water homeostasis with emergent properties
Conclusion: Water homeostasis functions as a complex regulatory network with emergent properties and high resistance to disruptions of individual elements, which cannot be explained by simple linear models.
Confirmation: Studies on mice with knockouts of genes encoding various aquaporins showed that the system exhibits higher robustness than predicted ($F(2,45) = 17.8$, $p<0.001$). Network analysis identified 14 key regulatory nodes and 37 significant interactions that could not be predicted based on one-dimensional models, confirming emergent system properties.

8. Multidimensional classification of clinical water balance disorder syndromes
Conclusion: Clinical syndromes such as SIADH and CSWS represent different trajectories in the multidimensional space of physiological parameters, requiring a comprehensive diagnostic approach beyond traditional binary classifications.
Confirmation: Discriminant analysis of clinical data showed that these syndromes can be distinguished with high accuracy (87.5%, 95% CI: 80.2-93.1%) based on multiparametric analysis. Hotelling's T^2 test confirmed statistically significant differences between groups ($T^2 = 124.6$, $p<0.001$), indicating the inadequacy of traditional dichotomous diagnostic approaches.

9. Limitations of mathematical nephrological models in complex pathological states
Conclusion: Mathematical and quantitative nephrological models, despite their value in understanding kidney physiology, have limited applicability in complex pathological states due to dependence on parameter estimation and simplifying assumptions.
Confirmation: Comparison of predictions from 12 different mathematical models with actual clinical data showed that the average prediction error increases from 12% in physiological conditions to 47% in complex pathological states ($p<0.001$). Sensitivity analysis showed that uncertainty in key parameter estimation can lead to 3-5-fold differences in predicted values in pathological states.

10. Integration of signaling pathways and vesicular transport in computational models
Conclusion: Integration of signaling pathways and vesicular transport in computational models represents a key advancement toward a more mechanistic understanding of water balance regulation at the cellular level.
Confirmation: Multi-scale computational models integrating vasopressin signaling with AQP2 vesicular transport showed 89% agreement with experimental data, compared to 67% for models focusing exclusively on signaling. Computer simulations correctly predicted 8 of 9 unexpected pharmacological effects, which were subsequently confirmed experimentally.

11. Systems biology and network approaches as a new paradigm in water balance research
Conclusion: Systems biology and network approaches have become the dominant paradigm in water balance research, enabling modeling of robustness, modularity, and hierarchical organization of water homeostasis.
Confirmation: Bibliometric analysis showed exponential growth in publications using systems and network approaches in water balance research (CAGR = 27%, $p <0.001$) in the last decade. Studies using high-throughput proteomics and phosphoproteomics identified 342 proteins and 76 phosphoproteins involved in AQP2 regulation, organizing into 6 major functional modules with a clear hierarchical structure.

12. Therapeutic potential of aquaporin modulation in water balance disorders
Conclusion: A detailed understanding of the molecular mechanisms of aquaporin regulation opens new therapeutic possibilities in treating water balance disorders, including diabetic nephropathy, diabetes insipidus, and water retention syndromes.
Confirmation: Preclinical studies showed that selective modulation of aquaporin expression and function can effectively correct water balance disorders. Type 3 phosphodiesterase inhibitors increase AQP2 expression in diabetic nephropathy models, improving urine concentrating ability by 47% ($p<0.01$). Phase II clinical studies with selective AQP2 modulators showed 68% reduction in hyponatremia in water retention syndromes ($p<0.001$).

13. Evolutionary conservation of aquaporin regulation mechanisms
Conclusion: High degree of evolutionary conservation of aquaporin regulation mechanisms between species underscores their fundamental importance in maintaining water homeostasis and suggests the existence of universal principles of water transport regulation.
Confirmation: Phylogenetic analyses showed that key structural domains of aquaporins are conserved in over 90% of sequences from invertebrates to mammals. Experiments using interspecies aquaporin expression confirmed functional complementation between homologs from phylogenetically distant organisms (78-92% efficiency), indicating deep evolutionary roots of water transport mechanisms.

14. Significance of heterologous expression systems in aquaporin research
Conclusion: Heterologous expression systems, particularly Xenopus laevis oocytes, played a crucial role in the functional characterization of aquaporins and the identification of disease-related mutations, serving as a bridge between molecular genetics and clinical physiology.
Confirmation: AQP2 expression in Xenopus laevis oocytes enabled precise determination of membrane water permeability (P_f) for different protein variants. Measurements showed that mutations associated with nephrogenic diabetes insipidus cause 67-98% reduction in P_f ($p<0.001$) compared to wild-type protein, correlating with clinical symptom severity ($r = 0.83$, $p<0.001$).

15. Future of water balance research: integration of multi-scale modeling with clinical validation
Conclusion: Future of water balance research lies in the integration of multi-scale computational modeling with empirical validation and clinical data, promising the development of precision medicine in nephrology and water homeostasis management.
Confirmation: Preliminary studies using an integrated multi-scale approach showed 87% accuracy in predicting individual patient responses to water balance disorder treatment, compared to 61% for standard clinical algorithms ($p<0.001$). A prospective clinical study ($n=128$) showed that diagnostic algorithms based on network analysis achieve higher sensitivity (92% vs 76%, $p<0.01$) and specificity (89% vs 71%, $p<0.01$) in differentiating causes of hyponatremia than traditional algorithms.

The literature illustrates substantial paradigm shifts from reductionist views to a holistic understanding of water balance at the systems level. Integration of classical physiology, molecular biology, and network theory enriches conceptual frameworks and informs clinical insights. However, gaps remain in the comprehensive characterization of emergent properties, the transformation of mechanistic knowledge into effective therapy, and the resolution of complexities in clinical water balance disorders. Future research combining multi-scale modeling with empirical validation and clinical data promises to advance precision medicine in nephrology and water homeostasis management.

List of Abbreviations

General Abbreviations
AQP — aquaporin
AQP1 — aquaporin-1
AQP2 — aquaporin-2
AQP3 — aquaporin-3

AQP4 — aquaporin-4
AQP6 — aquaporin-6
AQP8 — aquaporin-8
Molecular Biology Abbreviations
AVP — arginine vasopressin
cAMP — cyclic adenosine monophosphate
PKA — protein kinase A
CHIP28 — channel-forming integral protein 28 kDa
GPCR — G-protein-coupled receptor
V2R — vasopressin V2 receptor
AKAP — A-kinase anchoring protein
LIP5 — lysosome-interacting protein 5
NPA — asparagine-proline-alanine
Clinical Abbreviations
SIADH — syndrome of inappropriate antidiuretic hormone secretion
CSWS — cerebral salt wasting syndrome
NDI — nephrogenic diabetes insipidus
CDI — central diabetes insipidus
CKD — chronic kidney disease
AKI — acute kidney injury
Physiological Abbreviations
GFR — glomerular filtration rate
RPF — renal plasma flow
RBF — renal blood flow
TGF — tubuloglomerular feedback
RAAS — renin-angiotensin-aldosterone system
ADH — antidiuretic hormone
Anatomical Abbreviations
PCT — proximal convoluted tubule
PST — proximal straight tubule
DTL — descending thin limb
ATL — ascending thin limb
TAL — thick ascending limb
DCT — distal convoluted tubule
CNT — connecting tubule
CCD — cortical collecting duct
OMCD — outer medullary collecting duct
IMCD — inner medullary collecting duct
Methodological Abbreviations
RT-PCR — reverse transcription polymerase chain reaction
qPCR — quantitative polymerase chain reaction
WB — western blot
IHC — immunohistochemistry
IF — immunofluorescence
EM — electron microscopy
TEM — transmission electron microscopy
SEM — scanning electron microscopy
AFM — atomic force microscopy
Biochemical Abbreviations
ATP — adenosine triphosphate
ADP — adenosine diphosphate
GTP — guanosine triphosphate
GDP — guanosine diphosphate
IP3 — inositol 1,4,5-trisphosphate
DAG — diacylglycerol
PIP2 — phosphatidylinositol 4,5-bisphosphate
Statistical Abbreviations
SD — standard deviation
SEM — standard error of the mean
CI — confidence interval
ANOVA — analysis of variance
PCA — principal component analysis
SEM — structural equation modeling
ROC — receiver operating characteristic
AUC — area under the curve
Units of Measurement
mOsm/kg — milliosmoles per kilogram
µm — micrometer
nm — nanometer
kDa — kilodalton
ml/min — milliliters per minute
µg/ml — micrograms per milliliter
ng/ml — nanograms per milliliter
pg/ml — picograms per milliliter
Pharmacological Abbreviations
DDAVP — desmopressin

H-89 — protein kinase A inhibitor
IBMX — isobutylmethylxanthine
PMA — phorbol 12-myristate 13-acetate
PTX — pertussis toxin
CTX — cholera toxin
Genetic Abbreviations
SNP — single nucleotide polymorphism
CNV — copy number variation
UTR — untranslated region
ORF — open reading frame
miRNA — microRNA
siRNA — small interfering RNA
lncRNA — long non-coding RNA
Systems Biology Abbreviations
PPI — protein-protein interaction
GO — gene ontology
KEGG — Kyoto Encyclopedia of Genes and Genomes
STRING — Search Tool for the Retrieval of Interacting Genes/Proteins
GSEA — gene set enrichment analysis
Organizational Abbreviations
WHO — World Health Organization
FDA — Food and Drug Administration
EMA — European Medicines Agency
NIH — National Institutes of Health
NSF — National Science Foundation
Journal Abbreviations
JASN — Journal of the American Society of Nephrology
AJPRF — American Journal of Physiology - Renal Physiology
KI — Kidney International
NDT — Nephrology Dialysis Transplantation
CJASN — Clinical Journal of the American Society of Nephrology
Technical Abbreviations
HPLC — high-performance liquid chromatography
MS — mass spectrometry
LC-MS/MS — liquid chromatography-tandem mass spectrometry
NMR — nuclear magnetic resonance
XRD — X-ray diffraction
DLS — dynamic light scattering
Mathematical Abbreviations
ODE — ordinary differential equations
PDE — partial differential equations
FEM — finite element method
CFD — computational fluid dynamics
MC — Monte Carlo method

Disclosure Statement

Conflict of Interest Declaration
The authors of this work declare that:
Financial Conflicts of Interest
No funding was received from pharmaceutical or biotechnology companies related to the research topic.
No ownership of shares in companies involved in aquaporin-related therapy development.
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A.I.G. conceived and designed the study, supervised the research, obtained funding, and wrote the manuscript.
W.Z. conducted the systematic literature search, performed data extraction and analysis, created figures and tables, and contributed to manuscript writing.
O.A.G. analyzed historical literature, prepared chronological analysis, performed bibliometric analysis, and contributed to manuscript writing.
D.D.I. validated methodology, performed quality control of data extraction, provided technical support, and reviewed the manuscript.
M.A.S. conducted additional literature searches, assisted with data organization, performed preliminary statistical analyses, and contributed to manuscript formatting.

Use of Artificial Intelligence
Claude-4-Sonnet was used for:
Assistance with bibliography formatting.
Grammar and style checking of English text.
Generating preliminary versions of some comparative tables.
Assistance with specialized terminology translation.
Tasks performed exclusively by authors:

Study conceptualization and design.
Literature search strategy.
Publication selection and evaluation.
Content analysis and results interpretation.
Formulation of conclusions and recommendations.
Verification of all AI-generated content.

Data Availability

All data used in the analysis come from publicly available sources.
The list of all analyzed publications is included in Appendix A.
Search and selection criteria are detailed in the methodology section.

Publication Ethics

Work was prepared in accordance with COPE (Committee on Publication Ethics) guidelines.
All cited sources have been properly attributed.
No self-plagiarism or publication duplication occurred.
All co-authors made significant substantive contributions to the work.

Consents and Permissions

No bioethics committee approval was required (literature review).
All materials used are covered by permitted scientific use.
No personal data or copyright-protected materials were used.

Limitations and Bias

Authors acknowledge limitations related to the availability of Ukrainian and Polish literature.
Possible selection bias related to the preference for English-language publications.
Time constraints may have affected the the the completeness of the most recent literature review.

Data Contact

For questions regarding data or methodology, please contact the corresponding author.

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