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LIFESTYLE MEDICINE

Alleviation of thirst in hemodialysis patients – relief or belief?

A Systematic Review on therapeutic strategies in Randomized Controlled Trials

by

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Author's Contribution Statement

I certify that I am the author of this thesis and that any assistance I have had in its preparation is fully acknowledged and referenced in the following text. I have also cited any sources from which I have used data, ideas or words, whether they are quoted exactly or paraphrased. I also certify that this thesis was prepared by me personally specifically for the requirements of obtaining a Master's degree in Lifestyle Medicine by the University of Thessaly. I declare that I will respect co-authorship rights in any linked scientific publication and/or presentation stemming from this thesis, in accordance to my signed affirmation, and in respect of the principles of ethics in research. Likewise, I declare I will recognize any funding sources and will acknowledge my affiliation to the University of Thessaly during the preparation of this work in any future presentation.

Stefanie DUCHEK

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Abstract

Introduction: 850 million people suffer from chronic kidney disease (CKD) worldwide, 3,9 million of people with end stage kidney disease (ESKD) need renal replacement therapy (RRT) – most of them treated by hemodialysis (HD). Though HD and concomitant medical therapy replace some of the kidneys' functions people still suffer from various symptoms, including thirst and xerostomia.

Thirst is a complex physiological reaction to various changes of the body's homeostasis in healthy individuals and is even more complicated in patients with ESKD requiring hemodialysis (HD). Little is known about the changes in regulatory mechanisms and hormonal messengers of thirst and its satiation in these patients. Even though the majority of hemodialysis patients suffer from thirst or xerostomia and its influence on their daily life and lifestyle there is a lack of evidence-based relief for this specific population.

Aims: This thesis aims to give an insight into the existing knowledge in physiological theory, analyze the strongest available evidence of therapeutic treatments, compare these with eminence-based advice and patients' behavioral lifestyle strategies and highlight concepts to target in future.

Methodology: Systematic review of randomized controlled trials.

Results: Oropharyngeal remedies like sugar free chewing gum and mouthwash, as well as saliva-stimulating acupressure techniques and allotting the fluid allowance with a timetable provide beneficial effects for the alleviation of thirst without noteworthy side-effects. Pilocarpine also increased saliva and thus decreased dipsogenic sensations but showed major adverse effects. RAAS-blockage medication and lowering sodium dialysate have produced ambiguous results, while a psychological intervention showed no improvement of thirst. No studies for low sodium diet or cold remedies were available for analysis.

Discussion/Conclusion: There is an urgent need for deeper understanding of the pathological changes in thirst regulations in the ESKD cohort. More RCTs, either further investigating known strategies to reduce the heterogeneity of results or exploring innovative treatment concepts, are of great importance for improving hemodialysis patients' lives by relieving them from suffering from thirst and easing the burden of individual, medical and financial consequences.

Keywords: dipsogenic, xerostomia, dry mouth, hyposalivation, end-stage kidney disease

Abstract in German

Einleitung: Weltweit leiden circa 850 Millionen Menschen an chronischer Nierenerkrankung, 3,9 Millionen davon benötigen aufgrund terminaler Niereninsuffizienz eine Nierenersatztherapie – meistens Hämodialyse. Obwohl durch Dialyse und begleitende Therapien einige der Funktionsverluste ersetzt werden können, ist der Leidensdruck bei diesen Patientinnen und Patienten sehr hoch. Viele Symptome, unter anderem Durst, schränken die Lebensqualität deutlich ein.

Hinter der Empfindung von Durst steckt ein komplexes Netzwerk, dass durch Veränderungen der physiologischen Balance des Körpers aktiviert wird. Über Ausmaß und Art der Veränderungen aufgrund einer Hämodialysebehandlung ist noch wenig bekannt. Obwohl die meisten Patientinnen und Patienten an Durst oder Mundtrockenheit leiden und dies massive Auswirkungen auf Leben und Alltag hat, gibt es wenig evidenzbasierte Therapien dagegen.

Zielsetzung: Ziel dieser Masterarbeit ist es, einen Einblick in bekannte physiologische Grundlagen zu geben, die besten wissenschaftlich bewiesenen Therapien zu analysieren und mit Empfehlungen von medizinischem Personal sowie den Strategien von Patientinnen und Patienten zu vergleichen und neue Ansatzpunkte für die Zukunft aufzuzeigen.

Methodik: Systematische Übersichtsarbeit (“Systematic review“) von randomisiert kontrollierten Studien

Ergebnisse: Orale Anwendungen wie zuckerfreier Kaugummi oder Mundwasser, sowie Anregung der Speichelproduktion durch Akupressur und tägliche Einteilung der erlaubten Flüssigkeitsmenge mittels Tabelle konnten ohne wesentliche Nebenwirkungen erfolgreich Durstgefühle reduzieren. Pilocarpin erhöht ebenfalls die Speichelmenge und mildert dadurch Mundtrockenheit aber mit teils intensiven Begleitreaktionen. Studien zu Medikamenten mit Wirkung auf das RAAS und Senkung des Natriumgehaltes im Dialysat brachten gegensätzliche Ergebnisse, während eine psychologische Intervention keinen Effekt hatte. Zu natriumarmer Ernährung oder kalten Lokaltherapien gab es keine passenden Studien zur Analyse.

Diskussion/Schlussfolgerung: Tiefergehendes Verständnis der Veränderungen im Netzwerk der Durstregulierung von terminal niereninsuffizienten ist dringend notwendig. Es ist äußerst wichtig, mehr randomisiert kontrollierte Studien durchzuführen, einerseits

um bekannte Strategien zu erforschen und dadurch die Heterogenität der Ergebnisse zu reduzieren, und andererseits, um innovative Therapieansätze zu entdecken, damit dadurch das Leben von Hämodialysepatientinnen und -patienten verbessert werden kann. Durch die Befreiung vom Leidensdruck durch Durst werden individuelle, medizinische und finanzielle Folgen verringert.

Stichwörter: Durst, Hämodialyse, Mundtrockenheit, chronische Nierenerkrankung, terminale Niereninsuffizienz

Περίληψη [in Greek]

[same structure]

Εισαγωγή:

Σκοπός:

Μεθοδολογία:

Αποτελέσματα:

Συζήτηση:

Λέξεις -κλειδιά: [up to 5]

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List of abbreviations

ACE/ACE-I:	Angiotensin-Converting Enzyme/ACE-Inhibitor
ADA:	American Diabetes Association
ADH:	AntiDiuretic Hormone = AVP
ADPKP:	Autosomal Dominant Polycystic Kidney Disease
ARB:	Angiotensin II Receptor Blocker
ASN:	American Society of Nephrology
AVP:	(Arginin-)Vasopressin = ADH = AntiDiuretic Hormone
BP:	Blood Pressure
CKD:	Chronic Kidney Disease
CVD:	Cardiovascular Disease
DASH-diet:	Dietary Approaches to Stop Hypertension
DM:	Diabetes mellitus
DTI:	Dialysis Thirst Inventory
ECV:	Extracellular Volume
ERA:	European Renal Association
ESKD:	End-Stage Kidney Disease
FU:	Follow-Up
GFR:	Glomerular Filtration Rate
HD:	H(a)emodialysis
IDWG:	InterDialytic Weight Gain
ISN:	International Society of Nephrology
KDIGO:	Kidney Disease Improving Global Outcomes
KDOQI:	Kidney Disease Outcomes Quality Initiative
KTx:	Kidney Transplant
LM:	Lifestyle Medicine
NA:	Not Available
$[Na^+]$:	Latin: Natrium = Sodium
NKF:	National Kidney Foundation

OVLT:	Organum Vasculosum Laminae Terminalis
PC-SWS:	Paraffin/Parafilm-Chewing Stimulated Whole Saliva
PD:	Peritoneal Dialysis
PICOS:	Population, Intervention, Comparison, Outcomes and Study design
RAAS:	Renin-Angiotensin-Aldosterone System
RCT:	Randomized Controlled Trial
RRT:	Renal Replacement Therapy
SFO:	Subfornical Organ
SR:	Systematic Review
SXI:	Summated Xerostomia Inventory
TCM:	Traditional Chinese Medicine
TRPM8:	Transient Receptor Potential cation channel subfamily M (melastatin) member 8
TENS:	Transcutaneous Electrical Nerve Stimulation
USRDS:	United States Renal Data System
UWS:	Unstimulated Whole Saliva
VAS:	Visual Analogue Scale
VRS:	Verbal Rating Scale
WHO:	World Health Organization
XI:	Xerostomia Inventory
YLD:	Years lived with disability

1. Introduction

More than 850 million people worldwide suffer from chronic kidney disease (CKD) and about 3.9 million people currently need renal replacement therapy (RRT). Equally alarming as these numbers is the fact that CKD is rapidly rising in the rankings of causes of death and estimated to be number 5 in 2040. Lifestyle diseases diabetes mellitus and hypertension are not only the most common causes but also fuel for progression of CKD. Even with prime medical therapy and patients' commitment to changing their lifestyle, a lot of them advance to end-stage renal disease (ESRD) and require some form of RRT, globally hemodialysis (HD) is still the most wide-spread technique. ESRD itself and HD treatment have mayor impact on the quality of life of these patients since even with the best supportive therapy they suffer from a myriad of symptoms. Thirst, being not only very common but highly excruciating, often leads to a fluid intake higher than individually recommended. In consequence, this causes volume overload in patients and creates or perpetuates multiple consequences like pulmonary and peripheral edema and cardiovascular disease.

The network of causes, messengers and feedback-mechanisms behind the subjective perception of thirst and -alleviation is extraordinarily complex and to a great content still underexplored. Homeostatic, more precisely natremic, thirst seems to be the main trigger in the general population and in ESRD patients, but little is known regarding changes of dipsogenic regulation in the HD cohort. As a nephrologist I've had countless conversations with patients about the importance of following fluid restrictions and – to the best of my knowledge - gave them tips on how to tackle their thirst and dry mouth. But most of the times this felt like a Sisyphean task, a tiny drop in the ocean of their suffering from the sensation of thirst. There are many strategies that are advised by medical experts and/or popular in the HD population, but since there are no clear guidelines, there is need to analyze their true effectiveness.

Empowering patients in improving their lifestyle has led me to enroll in this Master of Lifestyle Medicine course, while simultaneously nephrology is still at the heart of my medical focus. So, for my thesis, I chose to dig deep into the topic of thirst and -alleviation in HD patients to support them with the best evidence-based advice in cultivating prime remedies for their suffering.

2. Aims – Significance

The first aim of this thesis was a comprehensive literature review by giving an insight into prevalence, etiology and course of CKD and influences on life and lifestyle of patients suffering from this disease. Additionally, existing knowledge in physiological theory behind thirst in general and the known differences in hemodialysis patients were explored, as well as interventions for alleviation from thirst, their mechanisms, obstacles or (potential) adverse effects.

Comparing if nephrology-eminence-based advice and patient's own lifestyle strategies in the battle against dipsogenic feelings correspond with the strongest available evidence of therapeutic treatments was of prime significance to this thesis.

This thesis intended showing if a true remedy against unquenchable thirst of HD patients with fluid restrictions really existed, explaining which scientifically proven strategies provide said relief and highlighting concepts to target in the future.

There was need for an analysis of trials with highest scientific power and significance, since most prior reviews had either focused on interdialytic weight gain (IDWG) as outcome or allowed a broader variety of types of trials including observational data. So, to the best of my knowledge, the systematic review, that was basis for this thesis, represented the first effort to discuss only randomized controlled trials (RCTs) investigating interventions for the alleviation of thirst or xerostomia in the hemodialysis cohort as primary or secondary outcomes. By following the PRISMA 2020 checklist[99] as closely as possible and including Cochrane's RoB 2[98] as risk of bias judgement tool, this thesis aimed to produce reliable, accurate and reproducible results of great significance. The outcome of this work intended to empower and support patients by improving their quality of life when being faced with living with end-stage kidney disease and suffering from thirst, thereby easing the resulting individual, medical and financial burdens.

3. Literature Review

3.1. Chronic Kidney Disease

Chronic kidney disease (CKD) is defined as damage of the kidneys in structure or function being present for > 3 months and has a major impact on the health of patients.[1] CKD is classified based on cause, reduction in glomerular filtration rate (GFR), a parameter calculated through blood tests (ml/min/1,73 m²), and/or measurement of protein in the urine, also called albuminuria (mg/g or mg/mmol).[1]

CKD is then categorized by GFR in stages G1–G5 with G5 or end-stage-kidney-disease (ESKD) being most severe requiring some form of kidney replacement therapy and albuminuria ranging from A1–A3 with A3 defined as highest level of proteinuria.[1]

Prognosis of CKD by GFR and albuminuria categories: KDIGO 2012				Persistent albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30–300 mg/g 3–30 mg/mmol	>300 mg/g >30 mg/mmol
GFR categories (ml/min per 1.73 m²) Description and range	G1	Normal or high	≥90			
	G2	Mildly decreased	60–89			
	G3a	Mildly to moderately decreased	45–59			
	G3b	Moderately to severely decreased	30–44			
	G4	Severely decreased	15–29			
	G5	Kidney failure	<15			

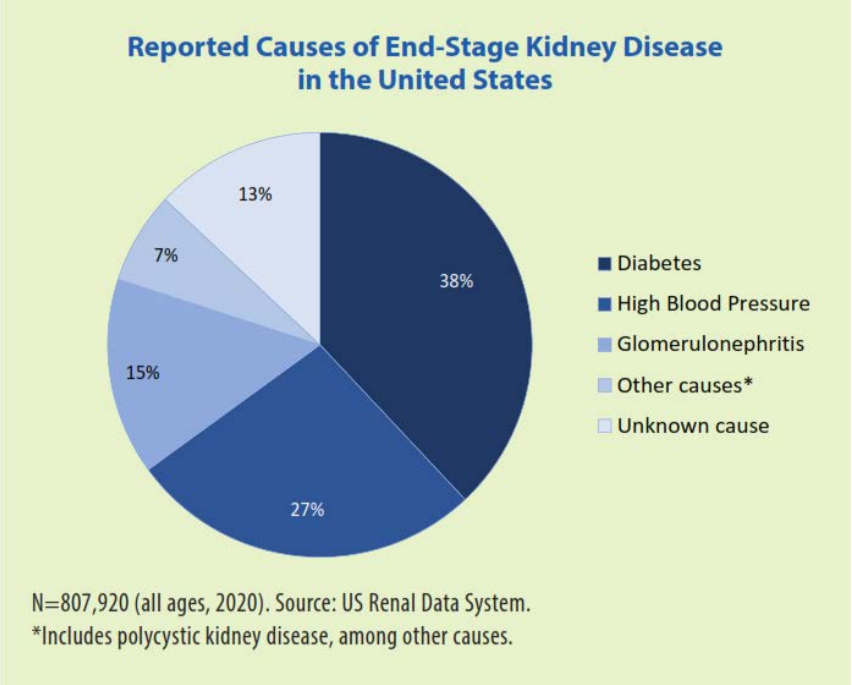
Green, low risk (if no other markers of kidney disease, no CKD); yellow, moderately increased risk; orange, high risk; red, very high risk.

Graph 1: KDIGO 2020 Clinical Practice Guideline for Diabetes management in Chronic Kidney Disease [2]

Global estimations of people suffering from CKD (all stages) range from 697,5 million - resulting in a prevalence of 9.1% in 2017 [3] - to 850 million in 2019, twice as much as persons living with diabetes (422 million) and 20 times more than individuals diagnosed with cancer (42 million) at that time [4], and most recently an increase in the prevalence to

9,5% in 2024 has been observed. [5] What is especially alarming is the growth rate of 29,3% in all-age groups between 1990 and 2017 [3] as well as the trend in quickly ascending the ranks in the list of leading causes of death, from number 16 in 2016 to an estimation to be number 5 in 2040. [6]

Lifestyle diseases have a major impact in the etiology of CKD with diabetes mellitus (DM) and hypertension being the two most common reasons, causing so called diabetic and hypertensive nephropathy. [7] Other forms of glomerular diseases, named after "glomerulus"- the tiny capillary filter unit that each kidney has about one million of, are primary glomerulonephritides (that target the kidneys first like IgA or membranous glomerulonephritis), inherited conditions e.g. autosomal-dominant polycystic kidney disease (ADPKP), autoimmune-disorders, side-effects of medication (mostly painkillers – non-steroid-anti-inflammatory drugs or NSAIDs), infections and primarily structural damages vascular diseases/damages or malformations, heart disease, kidney cancer, stones or urinary tract infections. [8,12]



Graph 2: Centers for Disease Control and Prevention. *Chronic Kidney Disease in the United States, 2019*. [8]

Diabetes mellitus and hypertension are not only the main culprits for CKD but – if not managed well by both patients and their medical caregivers – also fuel for further worsening the damage of the kidneys. Apart from the non-modifiable risk factors old age (>65 years) and female gender, other lifestyle influences like smoking, hyperlipidemia,

obesity and hyperuricemia also contribute to further reducing healthy kidney tissue and function. Hence essential parts of lifestyle medicine (LM) like regular (here: mostly aerobic) exercise, mediterranean and salt-reduced diet, maintaining a healthy weight and cessation of smoking are the biggest cornerstones of the patients' involvement in CKD therapy. [9]

When CKD progresses the kidneys more or less lose all of their functions, including but not limited to the ability to filter and excrete toxins from blood, maintain a healthy fluid balance, manage salt or other electrolyte levels and acid-base-metabolism, produce Erythropoietin for a stable red-blood-cell count, activate Vitamin D for a healthy bone structure and regulate blood-pressure. [10] The amount of loss in each function has great interpersonal variability and patients need to be monitored regularly by healthcare professionals to slow down the course of renal insufficiency by reducing or treating concomitant factors and/or providing targeted therapy.

CKD stages 1-4 are mostly asymptomatic, but when despite all efforts the damage progresses to stage 5 or ESKD patients will eventually develop symptoms of so-called uremia (from Latin: urina – urine and Greek: αἷμα – blood) referring to a high level of urea in the blood and meaning the accumulation of toxins that are normally excreted through urine. Patients then develop an abundance of symptoms: anorexia or vomiting or other gastrointestinal issues; neurologic signs like fatigue, confusion and muscle weakness; peripheral and pulmonary edema or fluid accumulation around lungs, heart or intestine; itchiness and even their breath might smell like urine. [10] Apart from these manifestations on patients' side there are some alarm signs that also force nephrologists to start renal replacement therapy (RRT): hyperkalemia endangering the heart's proper function, fluid overload threatening lung insufficiency or pericardial effusion and acid base imbalances that cannot be managed with medication. [10]

There are four different methods of kidney replacement therapy: kidney transplantation (KTx), hemodialysis (HD), peritoneal dialysis (PD) or supportive/palliative management.[10,11,12] Despite developments in modern nephrology in the last decades, though transplant is the gold standard of RRT, hemodialysis remains to be the main form of therapy with >85% of ESKD patients in the United States of America. [10] It is important to mention that there are large international differences – e.g. in Hong Kong and El

Salvador >50% are treated by PD and Scandinavian states are among the top 10 of highest incidence of kidney transplant (KTx) recipients. [7]

Among the different stages of CKD, stage G5 (ESKD) has the smallest prevalence with 0,07% and only 0,041% = 3,9 million requiring renal replacement therapy (RRT) in form of dialysis[4], but calculations for years lived with disability (YLD) are largest in these stages, summing up to 40% and 22% of YLDs for CKD, respectively, in 2017. [3]

Though all variations of dialysis save and prolong CKD patient's lives both the disease itself and its therapy have a major impact not only on the lifespan but even more on the quality of life. Dialysis patients experience numerous symptoms, some serious in terms of medical outcomes and all serious in terms of potential reductions in functioning and well-being. [13]

The most common signs of ESKD, even when well-treated with RRT, are fatigue and drowsiness (prevalence of 70% resp. 53%), musculoskeletal complaints like bone/joint pain, muscle cramps, weakness or soreness (55, 46, 43, 36% each) and poor mobility (56%), sleep disturbances (49%) or sleep apnea (40%), pruritus (46%), sexual dysfunction (48%), various mental-health disorders (30-44%), gastrointestinal symptoms from thirst (see chapter 3.2.4.) to constipation (35%), neurological diseases like restless legs syndrome (27%) or paresthesia (34%) and signs of fluid-overload like dyspnea, peripheral or pulmonary edema (up to 45%). [14]

An objective measurement of fluid overload in HD patients is interdialytic weight gain (IDWG), referring to the difference in weight between the end of one HD session and the beginning of the next, though the impact of the relationship between thirst and IDWG is hard to declare due to a multitude of measurement techniques for both parameters. [15] Maintaining an euvolemic status within the recommended range of weight gain (4-4.5%) is of great importance, since a relative IDWG > 5,7% of patients estimated so-called dry weight, the "normal" weight when fluid volume is optimal, has shown to be associated with a higher risk for mortality and even at already >4% IDWG with increased numbers of hospitalizations for symptoms of fluid overload. [16]

A possible cause for high IDWG is the intake of more fluids than individually recommended by medical caregivers mostly due to the feeling of thirst. Since each patient has a different residual kidney function regarding urine volume, a personalized amount of

daily liquid allowance is calculated, usually the amount of urine the patient produces in 24h and an additional 500 ml. In case of complete anuria, the daily fluid intake should not exceed 500 ml. [17]

Apart from the impact that CKD has on the lives of the individual persons suffering from it and their immediate surroundings, there are also huge financial consequences. According to the United States Renal Data System (USRDS) in 2020 the total inflation-adjusted Medicare expenditures for patients with ESRD in the US were $50,8 billion, on average $94 532 per person per year (dual Medicare/Medicaid coverage). [7] Additionally, for every episode of symptomatic fluid overload leading to emergency department visits, outpatient assessments or hospital admissions, average costs of $6,300 per event or $266 million in total for HD patients on Medicare health insurance were reported in 2010. [18] These findings endorse the need for guidelines and good clinical practice for decreasing not only fluid overload but also one of its main reasons – thirst.

3.2.Thirst, Xerostomia and Hyposalivation

First and foremost, it is important to distinguish between the central drive of thirst, the subjective feeling of xerostomia and the objective symptom of hyposalivation.

3.2.1. Thirst

Thirst is defined as "specific, central motivational state of readiness to consume water"[19], a highly sensitive phenomenon since just a 1% change in the osmolarity in the blood (number of osmotically active substances per liter of solution, osm/l) already triggers this state. [20] The complex regulations behind the urges to drink fluid, actions following these dipsogenic perceptions and pleasure of alleviation will be discussed in the following chapter.

A primary distinction between homeostatic thirst as response to an existing deficit, as opposed to anticipatory thirst occurring before the actual deficit can be made. [21]

Looking closer on **homeostatic causes** first, the foremost reason is assumed to be osmotic, also called natremic thirst, triggered by osmoreceptor cells in the brain, more precisely the subfornical organ (SFO) and organum vasculosum of the lamina terminalis (OVLT) in the forebrain, reacting to high osmolarity. This occurs due to relatively high salt levels or low extracellular fluid amount in the blood and can be caused for example by excessive sweating or high salt intake. [20, 22]

The other homeostatic dipsogenic drive is volumetric**.** Due to hypovolemia (= low circulating volume of blood/plasma) baroreceptors in the heart's atria and blood vessels sense low cardiac return volume inducing thirst (the detailed signaling in this cascade is still unclear), while at the same time the kidneys also detect the low blood pressure and activate the renin-angiotensin-aldosterone system (RAAS) so the level of Angiotensin II rises, triggering the aforementioned SFO in the brain, these mechanisms seem to be important especially immediately post dialysis. [20,22]

Both osmotic and volumetric triggers activating SFO +/- OVLT lead to responses on behavioral, autonomic and neuroendocrine levels. While, apart from the subjective feeling of thirst, a reduced sensation of hunger follows as behavioral consequence, autonomic reactions are increases in heart rate and blood pressure and via kidneys a change in the regulation of urine leading to more natriuresis (loss of [Na^+] through urine) and less urine volume. Neuroendocrine effects are the production of the hormones vasopressin (AVP) and oxytocin also reenforcing water retention through the kidneys including the RAAS.[20]

Apart from salt- or volume driven thirst it is important to mention **other osmoregulatory factors** that induce the urge to drink fluids like hyperglycemia and especially in HD patients changes in serum urea and possibly potassium depletion (though this is unlikely and hypokalemia uncommon in HD patients). [23]

Once enough fluid has been consumed and blood osmolarity is restored a (postabsorptive) satiety ceases further drinking urges. [19]

Coming back to **anticipatory thirst** or relief from this sensation, the SFO in the forebrain is also receiving signals directly from the oral cavity. On one hand this causes prandial or meal-associated thirst leading to the urge to simultaneously drink while eating, the body seems to anticipate results of food consumption. Aspects of these learned associations are expected absorption of osmotic active substances like salt and glucose and foreseen usage and redistribution of fluids (e.g. saliva, bile, increased blood flow to the intestines) though exact mechanisms behind this are yet unclear. [20] Other theories regarding preabsorptive alleviation are oropharyngeal stimuli including thermosensors being triggered by cold temperatures (Transient receptor potential cation channel subfamily M (melastatin) member 8 = TRPM8 or cold and menthol receptor 1 = CMR1), osmoreceptors that measure the level of mucosal hydration, mechanoreceptors detecting the sheer forces that occur during swallowing or moving of the tongue with dry mucosa[19],

or stretch- or osmoreceptors in the stomach. [20] These mechanisms could also explain the quick quenching of thirst directly after taking a sip – especially of cold - fluid, long before the ingestion of water reaches the bloodstream.

Finally, hyperthermia or heat exposure and circadian regulations – for instance preventing us from being thirsty when sleeping – also fall into the category of anticipatory causes. [21]

Other aspects apart from these truly regulatory dipsogenic drives include **habitual, cultural and psychogenic triggers**[24], these happen due to specific internal or external cues without an actual physical deficit happening or impending – examples include circadian influences that always occur at the same time of the day every day, certain social locations or situations like being in a café/bar or meeting friends, routines as taking a break from work, or moods e.g. boredom. [25]

3.2.2. Xerostomia and Hyposalivation

Another strong stimulus for water intake is xerostomia (Greek: ξηρός [xeros] = dry and στόμα [stoma] = mouth), the subjective feeling of a dry mouth. [26] Both cause and an objective measurement of xerostomia is Hyposalivation (unstimulated saliva flow rate <0.1 ml/min or not measurable), due to salivary gland fibrosis and atrophy, medication (e.g. antidepressants, antipsychotics, benzodiazepines, antihistamines, antihypertensives, diuretics, aspirin, opioids, bronchodilators and proton pump inhibitors), old age and fluid restriction (perpetuating a vicious circle). Other reasons for dry mouth sensations are changes in the composition of saliva (viscosity, concentrations of urea, electrolytes, pH), mouth breathing or diabetes mellitus. [27, 28]

Xerostomia influences patients' daily lifestyle because of resulting difficulties in chewing, swallowing (esp. dry food) and speaking, different taste perceptions, risk for oral infections (e.g. caries and periodontal disease, candida infections, lesions of gingiva, tongue or oral mucosa) and halitosis and reduced quality of life in general. [28,29]

3.2.3. The role of salt and sodium

The main trigger for osmometric/natremic thirst is high salt/sodium intake. [22] Although a tight relationship between salt and hypertension has been demonstrated by plenty of epidemiological, experimental and interventional trials since before the 1990ies, 40 years

later details and objections are still topics of heated discussions among experts and scientists. [30, 31]

The WHO has been recommending a sodium intake of <2g/<87 mmol of [Na^+] – equivalent to < 5g of salt a day (less than a teaspoon) for adults[32], in CKD patients KDIGO endorses limiting sodium intake to < 100mmol/d or < 2,3g/d as an adjunctive lifestyle modification to reduce blood pressure as well as proteinuria and improve volume control[33] possibly slowing CKD progression and limiting cardiovascular events. [34] Only 13-19% of patients seem to be achieving this target[35], and in the dialysis cohort 7,9 to 14.1 g are consumed every day. [36]

Causal for the great impact of salt on CKD patients are well demonstrated effects of increased oxidative stress and inflammation and damaged vascular function[37] from excessive salt/[Na^+] intake leading to higher albuminuria and cardiovascular burden. [38,39]

Another known fact is that sodium excretion is impaired and sodium sensitivity increased in kidney disease[10,40,41] causing excess fluid, more precisely extracellular volume (ECV) overload and contributing to hypertension, but the actual mechanisms interfering with thirst regulation remain obscured. [36]

3.2.4. Thirst and xerostomia in the hemodialysis patient cohort

Both Thirst and Xerostomia have a high prevalence in HD patients with 31 to 86% and 28 to 74,2% respectively, while hyposalivation is present in 20-55% but there are broad ranges due to different measurement methods. [23,26,27,29,42,43,44]

In hemodialysis patients, where osmotic thirst is also expected to be the primary trigger, excessive salt – i.e. sodium - can come from their diet, especially fast-food and pre-cooked meals (since up to 75% of salt in these foods are added during manufacturing[45]) a high dialysate sodium concentration, or saline infusions to treat hypotensive episodes or cramps during HD sessions. [15]

Little is known about the specific changes in thirst sensation or satiation in the CKD or dialysis population, apart from observations that patients with higher intradialytic weight gain (IDWG) seem to have a stronger reaction to dipsogenic factors. [46] Other than that it remains mostly unclear how kidney damage influences the complex network around the perception of thirst, Bossola Maurizio was summarizing the uncertainty in a few questions: are there differences in dipsogenic perceptions and fluid consumption during days

with/without dialysis? Do changes in prandial drinking cues due to different taste and dietary restrictions have an impact or might HD patients have disturbed circadian thirst trigger changes due to sleep disorders and is thirst-satiation impaired or altered? [36]

It has been postulated since the 1980s that in some cases in ESKD changes in the RAAS leading to higher Angiotensin II concentrations could act as a powerful dipsogen and cause high IDWG (while sodium levels were stable/not associated) or as a possible augmentation of osmotic triggers. [47]

In hemodialysis patients suffering from a dry mouth[27] and thirst sensation, the perception itself and the resulting discomfort[15] also led to increased fluid intake and IDWG thus increasing morbidity and mortality (see chapter 3.1).

Apart from a higher incidence of salivary gland fibrosis, two reasons for a higher prevalence of xerostomia in the HD cohort need to be highlighted, a high incidence of sleeping disorders and an especially high pharmacological burden since they need to take approx. 12 different meds per day. [28]

Subgroup analyses of CKD patients, women are shown to have higher scores for dry mouth [26] while people > 65 have lower XI and DTI scores[26] and CKD-patients with residual urine output also have less thirst & xerostomia (DTI, XI, VAS)[29] so, according to observational data, these populations could benefit the most from alleviation of dipsogenic sensations.

All definitions of thirst emphasize the subjectivity of this sensation hence self-reported questionnaires seem to be the appropriate tool for measurement. [48] Or to quote Mistiaen Patriek: “Thirst is a subjective feeling that exists when a person says it exists and cannot be measured other than by asking people.” [49]

In the hemodialysis population several indices and techniques are used, this thesis includes the Dialysis Thirst Inventory (DTI) in the original, 7 question format and the short 5 question version as well as versions of visual analogue scales (VAS) for thirst. [26,50] For dry mouth the Xerostomia Inventory (XI) and the short version called Summated Xerostomia Inventory (SXI) and VAS or VRS (Verbal Rating Scale) are featured as validated measurements. [51,52] Saliva amounts were calculated by saliva flow (ml/min) with either unstimulated whole saliva (UWS), following specific instructions before spitting in a tube every 30 sec (except SUNG et al[44] and IBRAHIM et al[63], who provided no info on the

frequency, and OZEN et al[84] whose participants spat every 2 minutes), and weighing the total amount with a high precision scale. PC-SWS used the same technique after a chewing a paraffin/parafilm stripe. CHEN et al[82] used the Schirmer tear test and placed the test filter paper on the floor of patients' mouths for 3 minutes then interpreted the length of the discoloration.

Dialysis Thirst Inventory (7) [26]	**DTI (5)**[50]	**Never =1**	**Hardly ever =2**	**Occasionally =3**	**Fairly often =4**	**Very often =5**
Thirst is a problem for me						
I am thirsty during the day						
I am thirsty during the night						
My social life is influenced because of my thirst feelings						
I am thirsty before dialysis						
I am thirsty during dialysis						
I am thirsty after dialysis						
Xerostomia Inventory [51]	**SXI** [52]					
I sip liquid to aid in swallowing food						
My mouth feels dry when eating a meal						
I get up at night to drink						
My mouth feels dry						
I have difficulty in eating dry foods						
I suck sweets or cough drops to relieve dry mouth						
I have difficulties swallowing certain foods						
The skin of my face feels dry						
My eyes feel dry						
My lips feel dry						
The inside of my nose feels dry						

Table 1: Dialysis Thirst Inventory[26,50] and (Summated) Xerostomia Inventory[51,52]

3.3. Interventions for reducing thirst or xerostomia

In literature a broad spectrum of strategies for alleviating thirst can be found and sorted into five major categories:

1) intra-oral or saliva-augmenting techniques

2) psychological or behavioral methods

3) pharmaceutical interventions

4) alterations of dialysate

5) dietary approaches

Anecdotally nephrologists and dialysis nurses are most frequently advising ESRD patients to allot fluids, suck ice cubes, use lemon juice or slices and sugar free chewing gum or lozenges while observational data are providing the preferred interventions among patients:

Ad 1) Intra-oral or saliva-augmenting techniques for improving xerostomia like consuming ice chips or cold food, drinking ice-cold drinks, performing mouth care, sucking on hard candies or chewing gum, eating lemon peel, lemony foods or juicy fruit, and wetting only the lips. [53, 54,55]

Ad 2) Behavioral approaches as measuring daily allotment[55,56] or taking medication only with mealtime fluid, limiting sun-exposure, staying busy, avoiding fast food restaurants[56] and only drinking small sips when thirsty. [54]

Ad 5) Dietary approaches like limiting salt intake or eating raw fruits and vegetables [55]

During the research for this thesis, the following strategies were mentioned in the literature, special emphasis is put on the interventions utilized in the RCTs that were part of the SR. Their mechanisms, and side-effects will be described in the following chapters.

Ad 1) topical oral therapies or saliva-stimulating: chewing gum, artificial saliva, use of straw and mouthwashes and acupressure devices/TENS for increasing saliva flow; ice and menthol

Ad 2) cognitive-behavioral strategies

Ad 3) pharmaceutical interventions: RAAS-blockage medication and pilocarpine

Ad 4) dialysate alteration: lowering dialysate sodium

Ad 5) dietary approaches: low salt diet

3.3.1. Intra-oral or saliva-stimulating techniques

Topical or salivary enhancing therapies target hyposalivation and/or dry mouth as triggers of thirst and through creating fluid in the oral cavity possibly also activate receptors of anticipatory thirst alleviation. [19,20]

Chewing gum and Lozenges

Mechanism: Sugar free chewing gum is claimed to mechanically stimulate salivary glands to enhance saliva production and improve oral health[57,58] and it also contributes to stress relief. Most chewing gums used in the literature also contain menthol, that stimulates TRPM8 receptors (in this case in the oropharynx) as much as the sensation of cold and contribute to thirst alleviation. [19]

Side-effects: Adverse reactions are very minimal, but patients should be warned not to chew excessively to prevent temporomandibular joint strain[82], fructose-intolerant persons need to use sorbitol and xylitol free gum and patients who wear full dentures might not be able to chew gum. [50]

Artificial saliva

Mechanism: Artificial saliva substitutes the lack of spit in patients with hyposalivation and xerostomia to lubricate the mouth and aid for example in swallowing food. Modes of delivery include liquids, sprays, lozenges, gels or oils.

Side-effects: Due to great differences in composition and/or active ingredients no general statement on adverse reactions can be stated, though taste can be impaired and gastrointestinal symptoms may occur. [59]

Straw

Mechanism: Using a straw is thought to reduce the amount of fluid consumed in one act of drinking

Regarding side-effects no scientific data was available.

Mouthwash

Mechanism: Mouthwash with antibacterial agents is commonly used to reduce halitosis and promote oral health. [60]

Thyme honey oral rinse

Mechanism: Honey has a long history of medicinal use, powerful antibacterial and antifungal, antioxidant, and immunomodulatory effects and due to the high sugar content, it stimulates the salivary glands to secrete more saliva. [61,62]

Side-effects: Even though this rinse should not be swallowed, patients with diabetes mellitus need to be cautious and people who are fructose intolerant should refrain from using honey products, apart from these contraindications no adverse were reported in the literature. [63]

Licorice mouthwash

Mechanism: Licorice root (Radix Glycyrrhizae) was medically used in various ancient cultures and continues to be of great importance in Traditional Chinese Medicine (TCM), possibly due to its approximately 300 active components. Anticancer, antibacterial, cardio- and hepatoprotective effects have been described as well as use as treatments for respiratory tract diseases and – important for this review - for improving dry throat and relieving throat pain. [64,65,66,83]

Side-effects: People who suffer from arterial hypertension or are at risk for it are recommended to minimize licorice consumption because of its blood pressure rising effects. Scientists also advise against long-term intake due to pseudo-hyperaldosteronism - mimicking of aldosterone actions leading to hypokalemia and metabolic alkalosis, edema, and renal failure. Cases of rhabdomyolysis as adverse reaction have been documented. The dosing of licorice is very challenging not only for medical uses but also because a lot of candy or over-the-counter products containing the substance can lead to added effects.[64,65,66,83]

Acupressure points

Mechanism: Acupressure is a form of acupuncture and part of TCM. By physically activating acupoints (trigger points) on so called meridians Qi (energy of life) imbalances can be improved thus leading to physical effects by complex neuro-hormonal responses. [67] Transcutaneous electrical nerve stimulation (TENS) is a method that uses adhesive electrodes on the skin to exert pulsed electrical stimuli of different frequencies. [68] Usage of TENS at Jiache and Yifeng acupoints is claimed to stimulate the auriculotemporal nerve to induce a secretomotor drive to the parotid gland leading to increased salivary flow[69], TENS also is claimed to induce endogenous analgetic effects. [68]

Adverse effects: For TENS local reactions to electrodes appear to be the only true side effect, while local paresthesia, discomfort, pain or twitching of muscles during the treatment are known to be part of the operating principle but can be quite troubling for patients. Generally, adverse events were hardly reported in detail across literature. [68,42]

Ice and menthol

Mechanism: Cold substances and menthol in any phase of matter trigger oropharyngeal TRPM8 receptors. Observations in healthy humans found that gargling with cold fluid for 2 min quickly reduced thirst (in 5 min') but only for 15 min - 30 min. [19] Details regarding this pattern have been discussed in chapter 3.2.1.

Side-effects: Apart from the possibility of sudden headache while consuming ice-cold substances, when the temperature from the roof of the mouth drops too quicky probably triggering the trigeminal nerve, no major adverse reactions have been described. [70]

3.3.2. Pharmaceutical interventions

RAAS-blockage medication

Mechanism: RAAS and especially Angiotensin II serve important roles in the regulation of thirst and drinking behavior [28] and patients with ESRD have higher levels of Angiotensin II. [47] Details on this mechanism have been discussed in chapters 3.2.1 and 3.2.4.

Side-effects: Most common adverse reactions are allergic events including angioedema, chronic cough (mostly ACE-I), hyperkalemia or acute renal failure and low blood pressure. [10,71]

Pilocarpine

Mechanism: This plant alkaloid (pilocarpus jaborandi) is a cholinergic parasympathomimetic drug and due to a demonstrated increase salivary flow it has been used for xerostomia caused by radiation-damage or Sjögren syndrome. [44,72,73]

Side-effects: prolonged use of pilocarpine causes sweating, urinary frequency, lacrimation, flushing, chest tightness, shortness of breath, gastrointestinal disorders, and visual disturbances. [74,83]

3.3.3. Cognitive-behavioral approaches

Mechanism: Self-managing the fluid allowance requires cognitive and behavioral skills and is related to personal beliefs, social and cultural customs and the ability to counteract the drives for drinking fluids. A vast number of educational and cognitive-behavioral interventions, alone and in combination, were designed for promoting adherence to said regimes. [75] Individual differences due to age, gender and especially health literacy and comorbidities need to be integrated in this approach as well as the experts delivering the intervention. [75]

Obstacles: Frequent boosters are needed to help maintaining the effects of psychological education[75] and patients with lower general education usually benefit less from psychotherapy. [76] Furthermore, though patients perceived allotting fluids into a one pitcher per day as most effective, it seems to be relatively seldomly used, because it appears neither practical nor appealing. [53]

3.3.4. Dialysate alteration - dialysate sodium

Mechanism: As mentioned earlier in chapter 3.2.3., a high dialysate sodium concentration or saline infusions to treat symptoms during HD have a dipsogenic effect through rising serum [Na^+] levels. [15] Hence reducing the sodium level of dialysate to <138 140 mEq/L vs the current standard of 138-140 140 mEq/L dialysate has been of interest for nephrologists.

Side-effects: It is important to note that intradialytic hypotension is more common with this technique and might worsen the already fragile cardiovascular stability of HD patients.[77]

3.3.5. Dietary approaches – low salt diet

Mechanism: Large oral salt intake is the main culprit for relatively high levels of sodium in the extracellular fluid hence the main trigger for osmotic thirst. A diet low in salt aims to counteract this cascade. (See also chapters 3.2.1 and 3.2.3)

Side-effects and obstacles: Following a salt reduced diet has been described as boring in taste from patients accustomed to high salt as gustatory ingredient. It is important to address social aspects like dining out or the possible impact on family meals. Hyponatremia (too low [Na^+] concentration in the blood) is possible from a very law salt

diet, but since HD patients' blood is monitored at every dialysis session this seems highly unlikely.

4. Methodology

4.1. Searching and Selection process

For this thesis the database PUBMED was searched before March 6, 2024, for eligible studies available in English language using the following strategy:

Search words:

[thirst OR dry mouth OR dipsogenic OR xerostomia OR hyperdips* OR oral dryness OR hyposalivation OR salivary flow OR fluid restriction OR chronic fluid overload] AND [dialy* OR hemodialy* OR haemodialy* OR end-stage renal disease OR end-stage kidney insufficiency OR end-stage kidney disease OR end-stage renal insufficiency OR renal dialysis OR interdial*]

Filter:

A filter for only RCTs was used.

Selection process:

Out of 99 records found through the search on PUBMED 18 reports were selected for retrieval based on the PICOS criteria, these were assessed for eligibility. On taking a closer look the decision was made to exclude 3 trials, DURUK, N. et al "The Null Effect of Chewing Gum During Hemodialysis on Dry Mouth"[78] because the intervention of chewing gum only took place on a single day while BOTS, CP et al. "The management of xerostomia in patients on haemodialysis: comparison of artificial saliva and chewing gum"[79] and OLIVER, Matthew J et al: "Impact of Sodium and Ultrafiltration Profiling on Hemodialysis-Related Symptoms"[80] were not accepted because the results did not match the desired outcome (thirst/xerostomia/saliva indexes). Hence finally 15 studies were included in this thesis.

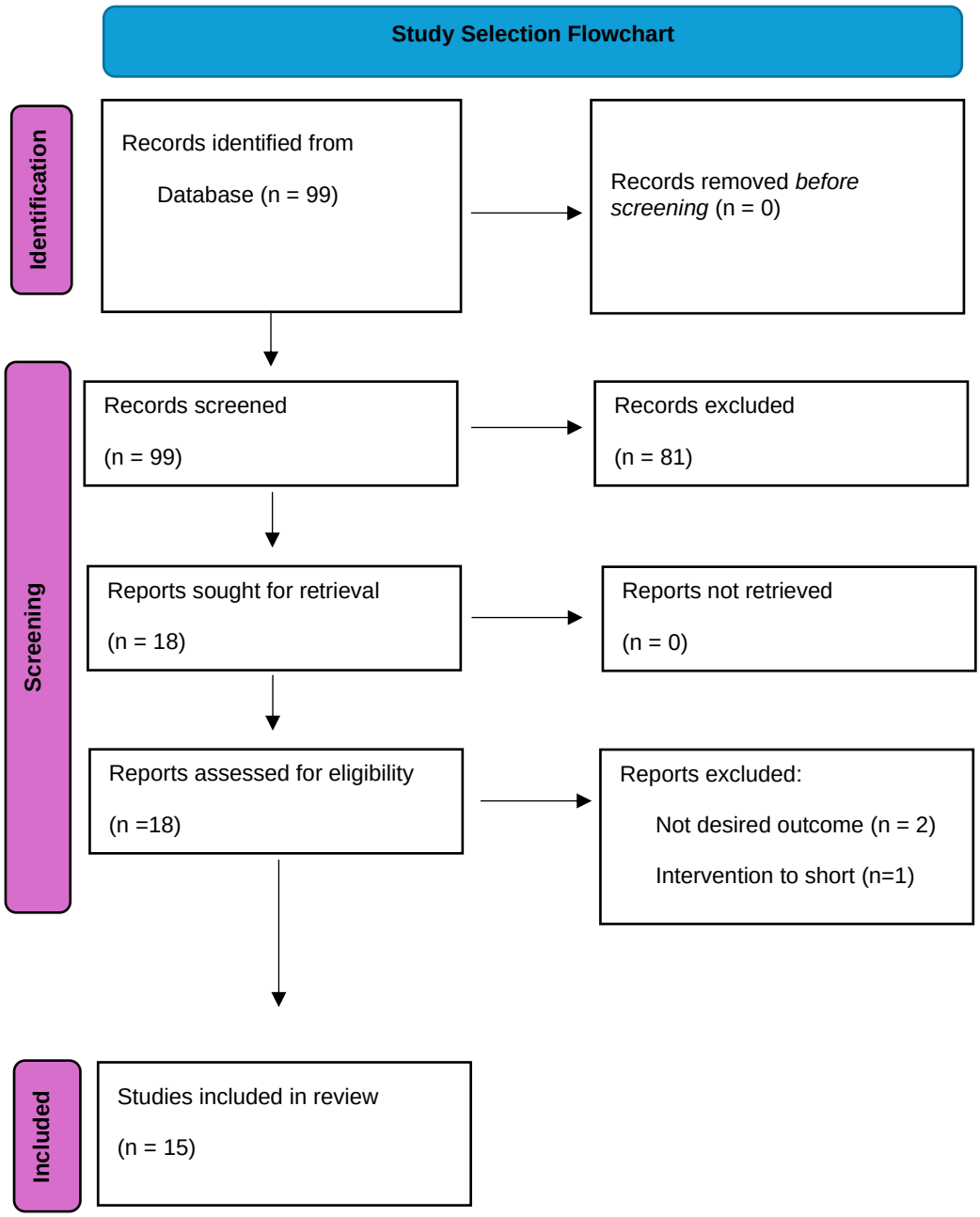


Table 2: Study Selection Flowchart

4.2. Inclusion criteria

Eligibility criteria according to PICOS[101] (Population, Intervention, Comparison, Outcomes and Study design):

P Adult (≥18 years) patients with end-stage-kidney-disease on hemodialysis treatment were included.

I It was planned to evaluate all methods decreasing the intensity of thirst or xerostomia, not limited to certain types of treatments. Interventions were required to continue for at least 7 days. Finally analyzed methods: chewing gum, straw, saliva substitute, thyme honey rinse, (licorice) mouthwash, losartan (as in dual RAAS-blockage), enalapril, pilocarpine, psychological intervention, timetable, Acupressure (TENS and electrical device), low ± profiled sodium dialysate.

C The following varieties of control were accepted: standard treatment (reg. sodium dialysate concentration, dietician counseling, nurse teaching), placebo, saline rinse, mock TENS, mock acupressure, no intervention (chewing gum, mouthwash) and comparison of two interventions [29,50]

O RCTs that had less thirst, less dry mouth or more saliva as primary or secondary outcome, measured by the following inventories and scales were included.

Thirst: DTI[26,50] – Dialysis Thirst Inventory (5 or 7 questions), VAS (Visual Analogue Scales 1-10: cm, mm, numerical)
Xerostomia: XI[51] – xerostomia Inventory or SXI[52] – Summated Xerostomia Inventory, VAS, VRS (Verbal Rating Scale, all: 1-10: cm, mm, numerical)
Self-developed VAS-scales and questionnaires explicitly targeting thirst and xerostomia
Saliva: UWS – Unstimulated Whole Saliva, PC-SWS – Paraffin/Parafilm chewing Stimulated Whole Saliva, Schirmer tear test

S Only RCT and quasi RCT were eligible for our systematic review.

4.3. Exclusion criteria

Excluded were studies on animals, pregnant women and children, on patients treated only with peritoneal dialysis or having received a kidney transplant and conservative treatment of ESKD or CKD 1-5 patients without hemodialysis and articles not available in English language.

4.4. Study design

This thesis was written based on a systematic review (SR) of (quasi) randomized controlled trials (RCT).

4.5. Materials

Risk of bias was assessed using the Cochrane "risk of bias" tool for Systematic Reviews (RoB 2, 22 August 2019 version or Higgins 2016)[98]. This tool judges the bias arising from the following components: 1) Randomization process, 2) Intended assignment, 3) Missing data, 4) Outcome and 5) Reported results grading them into low (bias), some concerns or high (bias). Then an overall summarizing judgment was made based on the recommendations of Cochrane Training.[100]

5. Results

#	Author Date	Country	Participants Male DM Mean Age Anuric	Duration (D) Intervention (I)[a] Control (C)	Measurements: THIRST (T) [26,50] XEROSTOMIA (X) [51,52] SALIVA (S)	Outcome	Conclusion
1	**FAN** et al[29] 2013	CN	11/NA[b] NA NA NA NA	D: 6 weeks cross-over (I: 2 weeks) I **a**: Chewing gum I **b**: straw	T: DTI5, VAS X: XI11, VAS S: UWS (5 min), PC-SWS	POS a: T & X ↓ b: T ↓ NEG S =	Both gum and straw decrease thirst, but only gum also reduces xerostomia. When compared directly: only VAS (X) sign more reduced through gum, no influence on saliva Good options for decreasing thirst, gum for xerostomia, straw good for allotting fluid. Psychological effect since saliva same or no relation of thirst and hyposalivation?
2	**BOTS** et al[50] 2005	NL	89/65 64,6% 15,4% 54,6y 72,3%	D: 6 weeks cross-over (I: 2 weeks) I **a**: Chewing gum I **b**: Saliva substitute	T: DTI5 X: XI11 S: UWS (5 min), PC-SWS	POS a: T & X modest ↓ b: T ↓ NEG S =	Both effective against thirst, gum also for xerostomia. Saliva not influenced. Interesting subgroup analyses: Especially when anuric, high suffering from thirst and/or hyposalivation benefit from gum (XI, not DTI)
3	**CHEN** et al[82] 2023	TW	37/37 48,6% 62,2% 68,11y NA	D: 1 week I: Chewing gum C: No chewing gum, usual routine	T: VAS X: SXI S: Schirmer tear test	POS T VAS & SXI ↓ NEG S =	Gum reduces Thirst and Xerostomia; saliva amount is equal. Gum against psychological motivated thirst?
4	**OZEN** et al[84] 2021	TR	56/44 50% 25% 61,56y NA	D: 12 weeks I: Chewing gum C: no chewing gum	X: VAS S: UWS (6 min)	POS X ↓, S ↑	Shows less xerostomia after 2 months, more saliva after 3 months - time effect? + Fluid control better 3rd month
5	**IBRAHIM** et al[63] 2023	EG	28/28[c] 64% 0% 69,7y NA	D: 4 weeks I: Thyme Honey Oral Rinse C: Saline Rinse	T: Subj. + obj. scores [d] S: UWS (5 min)	POS T Subj & Obj ↓ S ↑	Efficient for reducing subj & obj thirst and increasing saliva - Only geriatric, no DM

6	**YU** et al[83] 2016	TW	129/122 50% NA 60,8y NA	D: ~ 1,5 weeks (10 days) I: Mouthwash I **a**: licorice I **b**: pure water C: no mouthwash	X: SXI S: UWS (5 min)	POS a: X ↓ a + b: UWS ↑ (a >> b)	Good reduction of feelings of dry mouth after 20-30 min for 2-3h with licorice. Both interventions stimulated saliva flow, licorice a lot more than pure water gargling. => licorice a good aid against xerostomia
7	**OLDENBURG** et al [85] 1988	AU	25/20[e] 60% NA 40y NA	D: 18 weeks (I: 4 weeks) I: Enalapril C: Placebo	T: VAS X: VAS	POS T and X ↓	No change in perceptions, but a trend in lower fluid intake (special scale) Possible: angiotensin breakthrough phenomenon? (takes some weeks)
8	**MASAJTIS-ZAGAJEWSKA** et al[81] 2009	PL	21/NA 76% NA 54y 100%	D: 9 weeks cross-over (I: 4 weeks) I: Dual Blockage of RAAS Losartan on top of ACE-I C: Placebo	T: DTI7 X: XI S: PC-SWS	NEG T & X = POS S slight but sign ↑	Not effective for thirst and xerostomia despite saliva increase. Is saliva flow less important for thirst/xerostomia?
9	**SUNG** et al[44] 2005	TW	60/35/35 NA NA NA 100%	D: **a:** short: 7 weeks (I: 2 weeks) **b:** long: + 3 months I: Pilocarpine solution C: Placebo solution	T: VAS X: VAS[f] S: UWS (10 min)	POS Short and long: T ↓ X 3 of 5 ↓ (oral dryness, oral comfort, speaking) Short: S ↑ long: S ↑ modestly	For patients who don't mind the taste – possible alleviation, but a lot of side-effects.
10	**BELLOMO** et al[76] 2015	IT	54/53, 68,5% 34,5% 65,65y 92,5%	D: 5 weeks + follow up 6 months I: Psychological Intervention + standard treatment C: Standard treatment only (renal dietician counseling on nutrition and fluids)	T: DTI7, VAS X: XI11	NEG T & X =	Though thirst and xerostomia remain on same level, IDWG change without thirst change – increasing patient confidence, control over their disease – biopsychosocial health = helpful in improving adherence
11	**MINA** et al[86] 2019	PH	24/24 62,5% NA 50,4y 100%	D: 4 weeks I: Fluid Distribution Timetable (additional to standard care) C: Standard care	T: DTI7	POS DTI ↓	Adjunct strategy to promote fluid restriction adherence, significant decrease of thirst at week 4
12	**YANG** et al[42] 2019	TW	83/80 43,8% 36,3% 57,7y 67,5%	D: 3 weeks + 1 week FU I: TENS C: mock TENS	X: VRS S: UWS (5 min cotton roll weight)	POS X ↓ (I>C but C also) S ↑	TENS reduces xerostomia and increases saliva, but control also less X – psychological effect?

13	**YILDIRIM KESKIN** et al[54] 2021	TR	67/60, 58,4% NA NA NA	D: 6 weeks I: Acupressure device C: Scam Acupressure	X: VAS S: UWS (3 min)	POS X ↓ S ↑	Positive effect on X and S but only anuric < 0,5 kg above dry weight target admitted and high difference btw groups in fluid intake.
14	**DOMINIC** et al[87] 1996	IN	22/22 86% NA 46,6y NA	D: ~ 4 weeks cross over (I: ~2 weeks) [g] I: Low Sodium Dialysate/Profiled Sodium + step-linear reduced UF C: Standard Sodium Dialysate + steady UF	T: VAS [h]	POS T ↓	Thirst decreased a lot and fluid intake decreased; well-being increased while UF same. Only IDWG >2,5kg, 46,6 y mean age in the study
15	**MARSHALL** et al[88] 2020	NZ	99/86 67% 31% 51y 20%	D: 48 weeks I: Low sodium dialysate C: Standard sodium dialysate	T: DTI7 X: SXI	NEG T & X =	No effect reg thirst Young, healthy participants (many 0 bp med) – not representative for standard HD population. More intradialytic hypotension

Key	
a	For details on interventions and their administration see table 6 in "Appendices"
b	Baseline data was only available for the initial – observational – part of the study
c	Not 100% clear but indicated all 28 patients finished the study
d	Subjective symptoms of oral dryness: Q1 does your mouth feel dry? Q2 Do you sip liquids to aid in swallowing dry food? Q3 Does your mouth feel dry when eating a meal? Q4 Does the amount of saliva in your mouth seem to be too little? Answers: Y/N, 1 p for each Y -> scores 0-5; Objective dry mouth score, examination for signs: S1 Loss of pooled saliva. S2 Mouth mirror stickiness, S3. Stringy or foamy appearance. S4 Labial dehydration. S5 Irresponsiveness to parotid stimulation, 1 p for each observed sign -> scores 0-5 [63]
e	2 PD Patients
f	VAS Xerostomia subdivided in categories of 1) oral dryness 2) oral comfort 3) requirement of liquid to speak 4) requirement of liquid to sleep 5) requirement of liquid to chew/swallow + VAS: stress of fluid restriction
g	7 sessions each in a thrice weekly hemodialysis-session schedule
h	VAS self-developed scale: nil, mild, moderate, severe
↑	increase
↓	decrease
=	no effect
NA	not available

Table 3: Summary of results

Author	DTI (5,7) [26,50]	VAS (T)	(S)XI [51,52]	VAS/VRS (X)	Saliva	Other scores	IDWG
FAN et al[29] 2013 **a**	↓	↓	↓	↓	=		2d, 3d ↓
FAN et al[29] 2013 **b**	↓	↓	=	=	=		3d ↓
BOTS et al[50] 2005 **a**	↓		↓		=		=
BOTS et al[50] 2005 **b**	↓		=		=		=
CHEN et al[82] 2023		↓	↓		=		
OZEN et al[84] 2021				↓	↑		=
IBRAHIM et al[63] 2023					↑	Thirst ↓	
YU et al[83] 2016 **a**			↓		↑		
OLDENBURG et al [85] 1988		↓		↓		drinking scale ↓ trend	
MASAJTIS-ZAGAJEWSKA et al[81] 2009	=		=		↑		=
SUNG et al[44] 2005 **a+b**		↓		↓	↑		**a** 2d ↓ modest **b** 2,3d ↓
BELLOMO et al[76] 2015	=	=	=				Small ↓
MINA et al[86] 2019	↓						=
YANG et al[42] 2019				↓	↑		
YILDIRIM KESKIN et al[54] 2021				↓	↑		
DOMINIC et al[87] 1996		↓				Fluid intake ↓ Wellbeing ↑	NS ↓
MARSHALL et al[88] 2020	=		=				↓

Key		
Positive effect ↓ less thirst/xerostomia ↑ more saliva	No effect	Not studied

Table 4: Summary of effects

Study	Randomization Process	Intended Assignment	Missing Data	Outcome	Reported Results	Overall risk of bias
FAN et al[29], 2013	?	-	+	-	+	-
BOTS et al[50], 2005	?	-	-	-	+	-
CHEN et al[82], 2023	?	-	+	-	+	-
OZEN et al[84], 2021	+	+	?	-	+	-
IBRAHIM et al[63], 2023	+	+	+	-	+	-
YU et al[83], 2016	?	+	+	+	+	?
OLDENBURG et al [85], 1988	+	+	+	+	+	+
MASAJTIS-ZAGAJEWSKA et al[81], 2009	?	-	-	+	+	-
SUNG et al[44], 2005	+	+	-	+	-	-
BELLOMO et al[76], 2015	?	+	+	-	+	-
MINA et al[86], 2019	+	-	+	-	+	-
YANG et al[42], 2019	-	+	+	+	+	-
YILDIRIM KESKIN et al[54], 2021	?	+	-	+	+	-
DOMINIC et al[87], 1996	?	-	+	-	+	-
MARSHALL et al[88], 2020	+	+	+	+	+	+

Key:		
+ low	? some concerns	- high

Table 5: Risk of bias assessment, according to RoB 2 tool[98]

A high number of studies - 12 of 15 - were judged to have an overall high risk of bias, due to several factors: the majority of trials failed to report details for randomization and concealment of allocation (8/15 each), additionally two trials had major baseline differences between groups while four did not share this information. Six studies did not use analyses to estimate the effects of the assignments. A third of the trials was highly biased due to high dropout rates and/or possible influences of these withdrawals to the outcome. And most importantly eight studies were not able to totally blind participants.

For this thesis 15 studies were reviewed, where a total of 805 participants had been randomized. The results of 708 participants were available to analyze. FAN et al[29], MASAJTIS-ZAGAJEWSKA et al[81] IBRAHIM et al[63] failed to report the drop-out-rate and so for the analysis an assumption of no dropouts was made. All the studies were randomized or quasi-randomized controlled trials.

Four trials were conducted in Taiwan (CHEN et al[82], YU et al[83], SUNG et al[44], YANG et al[42]), two studies in Turkey (OZEN et al[84] and YILDIRIM KESKIN et al[54]) and one study each was from China (FAN et al[29]), the Netherlands (BOTS et al[50]), Egypt (IBRAHIM et al[63]), Poland (MASAJTIS-ZAGAJEWSKA et al[81]), Australia (OLDENBURG et al[85]), Italy (BELLOMO et al[76]), the Philippines (MINA et al[86]), India (DOMINIC et al[87]) and New Zealand (MARSHALL et al[88]).

Though this thesis was primarily focused on thirst and xerostomia, additional measurements of IDWG, fluid intake or quality of life were added to the results as they provide additional interesting details and findings.

5.1.Intra-oral or saliva-stimulating techniques

Eight out of the fifteen examined studies were conducted using topical interventions in the oral cavity or targeting the increase of salivary flow by other means.

Chewing gum was part of four investigations, that all showed less perceptions of thirst respectively dry mouth. FAN et al[29] showed that gum reduced all measurements of thirst and xerostomia (DTI(5) from 19.3 ± 3.4 to 14.3 ± 4.8, p = 0.000 (sic!), VAS(T) from 70.7 ± 17.1 to 61.1 ± 22.0, p = 0.038, XI from 32.2 ± 9.4 to 27.3 ± 11.7, p = 0.001 and VAS (X) (from 54.6 ± 19.6 to 44.6 ± 20.0, p = 0.001, 100 mm VAS scales) in eleven patients when compared against using a straw for 2 weeks each, while using a straw aided only against thirst (DTI(5) to 15,6 ± 5.3, p = 0.03, VAS(T) to 59.4 ± 21,7, p = 0.016). It is important to note that in direct comparison of both techniques the only significant superiority of gum was a stronger reduction in the measurement of VAS thirst. The second study by BOTS et al[50] controlled against artificial saliva, each intervention also lasting for 2 weeks and found that, for the 65 patients analyzed, chewing gum alleviated both thirst and xerostomia (DTI(5) from 16,6 ± 5,1 to 15.4 ± 4,8, p <0,05, XI from 29.9 ± 9.5 to 28.1 ± 9.1 p < 0.05), while the saliva only reduced thirst (DTI(5) to 15,5 ± 5,0, p < 0,05). Patients in this cohort notably preferred gum over saliva especially due to the unpleasant taste of the artificial spit. Subgroup analyses in the study of BOTS et al[50] of anuric patients,

those who were suffering a lot from thirst at baseline and who had hyposalivation especially benefit from gum, not saliva in reducing the XI. Thirdly CHEN et al[82] also demonstrated a significant lowering of both subjective sensations in 37 patients when testing against standard control for 1 week (VAS(T), 100 mm scale converted to numbers from 1-10, 5.16 ± 1.64 vs. 7.37 ± 2.34, $p < 0.0001$ and SXI 13.89 ± 3.16 vs. 16.79 ± 3.19, $p = 0.004$) and finally OZEN et al[84] tested chewing gum (compared with usual care) for the significantly longer period of 12 weeks and showed a significant reduction in xerostomia (VAS(X), 1-10 numerical scale, from 3,89 ± 3,17 to 1,73 ± 2,07, group*time $p < 0,01$) for the 44 patients who finished the trial. None of the shorter trials showed any sialagogic effect while OZEN et al[84] demonstrated a rise in saliva amount (UWS from 0,12 ± 0,05 to 0,17 ± 0,04, group*time $p < 0,01$) after 3 months. Furthermore, it is important to note that three studies looking at associated effects on IDWG reported contrasting results, FAN et al[29] showed an improvement (2d 2.78 ± 0.66 kg to 2.43 ± 0.70 kg, $p = 0.009$ + 3d 3.17 ± 0.89 kg to 2.88 ± 0.65 kg, $p = 0.017$) while BOTS et al[50] and OZEN et al[84] reported no significant effects.

Regarding mouthwashes, the study IBRAHIM et al[63] rinsing the mouth with thyme honey for 4 weeks showed great efficiency for reducing thirst ($p < 0,05$ no absolute numbers available) and improving saliva flow ($p < 0,01$ no absolute numbers available). Since they were utilizing a self-developed scale evaluating subjective and objective symptoms of thirst and specifically investigated 28 geriatric HD patients without diabetes it is hard to truly compare or extrapolate these findings. YU et al[83] investigated the effect of a licorice mouthwash against gargling with pure water and no intervention in 122 patients for 10 days and concluded that licorice was very effective in the reduction of xerostomia (SXI from 14.1 ± 5.8 to 12,0 ± 4,7, $p < 0,001$), the improvement started 20-30 minutes after usage and lasted for 2-3 hours. In terms of saliva flow both gargling fluids showed improvements, but at the end of the study UWS in the licorice group was increased by 250% while only by 30% in the water gurgling patients (UWS licorice from 0,07 ± 0,07 to 0,19 ± 0,13 $p < 0,001$, water from 0,08 ± 0,06 $p < 0,05$).

Acupressure points were the chosen interventional approach by 2 studies. YANG et al[42] used TENS at Jiache and Yifeng points in 83 patients for 3 weeks and concluded a significant improvement in subjective feelings of dry mouth (VRS numerical scale, 1-10, from 4,7 ± 2,3 to 2,2 ± 0,9, $p < 0,01$) and objective levels of saliva (UWS 0,09 ± 0,08 to 0,36 ± 0,10, $p < 0,001$). Since the control group, who received mock TENS, also reported

less xerostomia (VRS from 3,5 ± 2,2 to 2,2 ± 1,2, $p < 0,05$) the true size of the effect is unknown. A similar study using an electric acupressure device was used on 67 participants by YILDIRIM KESKIN et al[54] for 6 weeks on Lianquan, Yifeng and Yongqua/Jing-well points and reported similar results in reduction of xerostomia (VAS 10 cm scale from 5,22 ± 1,29 before 1st to 3,86 ± 1,12 after 6th session) and increase of saliva amount (UWS 0,86 ± 0,56 to 1,35 ± 0,82). In this trial only anuric patients on target weight were admitted and the intervention group had significantly higher fluid intake at baseline.

5.2. Pharmaceutical interventions

Three RCTs had investigated the effects of medication, two trials targeted the RAAS while a single study used pilocarpine.

Already in 1988 OLDENBURG et al[85] used Enalapril in 25 patients who were naïve to any drugs with effect on the RAAS, showing a reduction in both parameters assessed by VAS (100 mm scales, T: from 62 ± 20 to 36 ± 19/67 ± 19 to 47 ± 17, $p < 0,05$ and X: from 56 ± 24 to 39 ± 20/63 ± 23 to 48 ± 12) after a total duration of 18 weeks and a downward trend in fluid intake was reported (from 853 ± 295 to 698 ± 232/1009 ± 302 to 78 ± 253 ml). MASAJTIS-ZAGAJEWSKA et al[81] even used a double RAAS-blockage with an intervention of Losartan on top of any already established ACE-I of anuric 21 HD patients. This proved to be ineffective regarding thirst and xerostomia despite a small but significant increase in stimulated saliva amount at the end of the 9-week study period (PC-SWS from 1,2 ± 0,7 to 1,5 ± 1, $p = 0,03$), additionally, there was no effect on IDWG.

SUNG et al[44] studied the outcomes of pilocarpine on thirst and xerostomia in 60 HD patients, after an initial short period of 14 days continuing for another 5 weeks for 35 patients. They concluded that both parameters were significantly improved (VAS(T) in mm, Short 74,8 ± 3,5 to 55,4 ± 4,8/67,9 ± 2,9 to 34,4 ± 2,0, $p = 0,001$; Long 78,1 ± 2,8 to 49,1 ± 3,4, $p = 0,07$); VAS (X = oral dryness: Short 71,8 ± 3,7 to 46,2 ± 3,0/65,2 ± 2,8 to 31,5 ± 2,1, $p < 0$ 001, long 67,8 ± 3,9 to 48,8 ± 3,1, $p < 0,001$). They also reported betterment VAS of requiring liquid to speak and stress of fluid restriction. Though saliva rate was also higher after both durations (UWS: Long: 0,11 ± 0,03 to 0,15 ± 0,02, $p = 0,08$) and IDWG decreased, especially during the long period (3d, in kg, 4,38 ± 0,22 to 3,31 ± 0,45, $p = 0,07$) a very high dropout rate of almost 60 percent in the first, short trial phase, mostly due to exceptionally frequent adverse effects or dislike of the taste of the pilocarpine solution, needs to be noted.

5.3. Cognitive-behavioral approaches

Of the two studies targeting psychological and behavioral aspects of thirst, BELLOMO et al[76] studied the effect of a psychological intervention in group sessions for 54 participants for a duration of 5 weeks. They were following the "Carl Roger's Person-Centered Approach" [103], a form of person-centered counseling with "encounter groups" that is aimed at solving a specific problem. No change in perception of dipsogenic sensations or dry mouth was observed, but since they found a small but significant decline in IDWG (1332 ± 338 to 1203 ±284 $p < 0,001$), this biopsychosocial approach might be useful for empowering patients to control psychological triggers of thirst or generally improve their adherence to treatment and recommendations.

Targeting behavioral forms of fluid intake, MINA et al[86] conducted a 4-week trial comparing the use of a personalized timetable against standard care in 24 patients. Inspired by the Health Promotion Model by Pender et al [94] they aimed to modify three cognitions: perceived benefits, barriers and self-efficacy by providing an exact prescription for each patient on how much fluid was provided for meals, taking medication, physical activity and urgent onset of dipsogenic sensations. Additionally, both groups received measuring cups. At the end of the trial participants experienced less thirst shown by a significant decrease in DTI (7) (from 17,77 ± 2,95 to 12,62 ± 1,33, $p = 0,0001$, when compared to standard care p 0,003). IDWG significantly decreased in both groups, so the timetable might have resulted in a different perception of thirst while the standard care including a standardized cup, that both groups received, possibly caused the IDWG reduction. (in kg: intervention: 3,15 ± 1,49 to 1,65 ± 1,05, $p = 0,0001$ and control from 2,61 ± 0,87 to 1,93 ± 0,19, $p = 0.009$, direct comparison $p = 0,561$)

5.4. Dialysate alteration – dialysate sodium

Last but not least only two RCTs focused on the main dipsogenic culprit – salt - were conducted until March 2024. Both these studies were using a lower than (at that time) usual sodium dialysate to prevent natremic thirst. Even though in 1996 a beneficial effect of the combined setting of gradually decreasing sodium in dialysate and a parallel reduction of ultrafiltration was shown for 22 patients by DOMINIC et al[87] (VAS nil-mild-moderate-severe, from 12% nil, 18% mild, 19% mod, 6% severe to 93% nil, 7% mod), additionally accompanied by reduced fluid intake and higher scores of well-being but without much of an effect on IDWG, a longer study in 2020 by MARSHALL et al[88] with linear low sodium dialysate showed no effect on thirst or xerostomia despite a good

reduction in IDWG (-0,57 kg ± 0,29, p = 0.05) for the analyzed 86 patients. Since both studies included relatively young participants with mean ages of 46,6 and 51 years these results are not representative for a standard HD population.

6. Discussion

First, this thesis provided knowledge about CKD and explained the network of thirst and satiation including the scarce information available on known differences in dialysis population.

Second aim of this thesis was to compare if advice provided by medical caregivers in nephrology and patients' strategies for the alleviation from thirst and xerostomia were popular myths or based on evidence. Intra-oral topical therapies, low sodium nutrition and planned distribution of the recommended fluid amount were frequently recommended by nephrologists and used by patients most often. While some of the stated strategies, especially gum and mouthwashes as well as fluid allotment through a timetable, showed significant alleviation from thirst, for others - ice-cold remedies, low salt diet or lemon – no RCTs were available for analysis. Some HD patients also reported that they follow the tactics of only taking small sips when thirsty, scientific proof corroborated this theory when a straw was used.

Third objective was analyzing the best available evidence for unburdening hemodialysis patients from thirst. In addition to the above-mentioned strategies of chewing gum and mouthwash, acupressure was shown to be advisable, but regarding all other strategies, no clear conclusions could be drawn due to conflicting results of the analyzed RCTs, thus this objective could not be fulfilled.

There were several factors impairing the comparison of the results and making it difficult to draw conclusions for answering the main research questions of this thesis. First, there were mainly small sizes of participants namely between 11 and 129 per study, study populations had heterogenous characteristics – mean ages between ~46 and 69 years, male participants from 43 to 67% and anuria from 20 to 100%. Additionally, study periods were short: between 1 and 12 weeks, only one trial lasted 48 weeks, various measurement techniques (four different standardized inventories, several scales and self-developed questionnaires) and to a great content overall high risk of bias (12/15 studies).

Summarizing oropharyngeal strategies, this thesis showed that chewing gum provides good effectiveness on perception of thirst and xerostomia but since only one trial increased saliva, this cannot be the major reason behind the mode of action. Strong psychological bias need to be assumed since both blinding of participants and use of placebo are impossible for the intervention of chewing gum. Patients themselves report easy use and

pleasant taste. It was furthermore shown that using a straw for taking small sips was good for restricting fluid and also for decreasing thirst, while direct moisturizing of the mouth is induced by artificial saliva, though interestingly this resulted only in a reduction in thirst and not in xerostomia. Mouthwash containing thyme honey or licorice and saliva-increasing techniques, namely acupressure via device and TENS also alleviate xerostomia. These findings are in accordance with the opinion of Bossola[27,28,36], who conducted several reviews on thirst and xerostomia in the hemodialysis cohort. Until March 2024, no interventional trial has investigated the effect of cold or mentholated substances in any form on the dipsogenic perceptions of HD patients. It was observed that those who already consumed cold water or ice chips did not have lower thirst perception[95], but in other populations (perioperative or intubated) low temperature agents (ice, ice chips, cold water or gauze including one bundle of cold water, oral swabs and mentholated lip hydration) proved to be very effective in alleviating thirst. [96] Notably, intra-oral strategies are only targeting oropharyngeal receptors i.e. perceptions and not true causes of thirst and, because their effect is significant, but not long-lasting, they might be a good interim solution.

Though explored since the 1980s, pharmaceutical methods targeting RAAS have produced ambiguous results. Not only in this thesis but according to opinions of Bossola[27,28,36] and Mistiaen[49], who were looking at a greater variety of interventional trials. Therefore, no recommendation regarding ACEI or ARB concerning thirst can be drawn.

Pilocarpine on the other hand plays a role in Sjögren's syndrome or after oropharyngeal radiation[102], but results for HD come from a single trial, where the substance proved to be beneficial when tolerated but with high rates of adverse effects a wide or long-term use is questionable.

Of the two trials using cognitive-behavioral approaches psychological counseling did not influence thirst but decreased IDWG, probably by empowering patients to control their dipsogenic-triggered actions by increasing knowledge, while a timetable as a mainly behavioral strategy led to lower dipsogenic feelings but standard care in this trial seemed to be responsible for most of the effect on IDWG since both groups showed a significant decrease. Similar conclusions come from investigating forms of behavioral therapies in observational studies[89], trials of self-monitoring combined with other psychological strategies like transtheoretical model of change (TTM)[90] or health belief model (HBM)[91] or behavior modification using rewards showing reduced IDWG to a smaller or greater

magnitude. [92] Overall, psychoeducational interventions are hard to compare, as not only are there an abundance of different techniques and ways to convey them like group vs. individual etc., but studies also vary regarding the qualifications of persons delivering said therapies. In conclusion they should only be utilized as an adjunct strategy for controlling psychological, social and behavioral aspects of dipsogenic factors by aiding patients to recognize said triggers, distribute their fluid requirements and encourage them to actively watch their fluid intake or for enhancing adherence to dialysis and concomitant therapy recommendations.

Lowering sodium in dialysate has produced conflicting results across literature. Though KDOQI guidelines[93] recommend "adequate sodium/water removal with hemodialysis to manage hypertension, hypervolemia, and left ventricular hypertrophy" but since there so few RCTs investigating this topic, no firm guideline for generally lowering the standard (138 to 140 mEq/L dialysate) were made. Though beneficial effects regarding lowering IDWG and BP have been reported, regarding thirst attempts have been challenging and produced beneficial as well as none and even negative effects due to for example higher rates of intradialytic hypotension amplifying cardiovascular instability. This is shown not only in the two trials analyzed in this thesis, but also in reviews from Bossola[27,28,36,] Ashrafi[15] and Mistiaen[49]. They share the opinion of this thesis that there is not enough evidence for the use of this technique for alleviation of thirst or other patient-centered outcomes.[12]

Although unfortunately no RCT of a low sodium diet was available for analysis, this topic was of great importance for this thesis. The NKF states in their KDOQI clinical practice guideline for hemodialysis[93] that they recommend "reducing dietary sodium" to support less fluid intake and thus lower blood pressure and volume overload but also emphasize the paucity in studies of the highest level of evidence. Data from studies looking at BP and IDWG reduction have shown mostly positive results, though it is pointed out that conventional dietitian teaching or simple prescription of a diet with low salt content are inferior to multifactorial interventions and intensive nutritional guidance. Obstacles including lack of knowledge and tight food restrictions in HD patients (pre-existing limitations to foods high in phosphorus and potassium), the social impact on family meals or dining out and flavorless taste perception need to be overcome with additional strategies. [15,36] RCTs should be conducted in the HD patients with focus on thirst as an outcome.

7. Strengths & Weaknesses of this work

The biggest strength of this thesis was that only results from the best available level of evidence, namely randomized controlled trials of remedies against thirst in hemodialysis patients, were evaluated. Additionally, a clear structure, categorization and assessment of these interventions were provided. Furthermore, the comprehensive literature review adds to the understanding of underlying mechanisms for medical specialists in nephrology.

Large limitations of this work were the small quantities of studies for each type of intervention and that for one very important strategy, namely reducing the burden of salt intake, only 2 investigations for low sodium dialysate and no RCTs at all for low salt diet were available. Moreover, due to predominantly short durations of the trials and because most studies had to be rated “high” in the risk of bias analysis the impact of this thesis was restricted.

In the future, not only is there urgent need for (more) RCTs to reduce the heterogeneity of results, especially when investigating the effects of lowering sodium in dialysate or nutrition, but also for development of new strategies to relieve HD patients from suffering from thirst and ease the burden of individual, medical and financial consequences.

8. Conclusions

Small sizes of participants, heterogenous characteristics of study populations, mostly short study periods, high risk of bias for 12 of 15 studies analyzed and a multitude of different measurement techniques made it very difficult to compare results and decide on a general overall conclusion.

Oropharyngeal remedies like sugar free chewing gum and mouthwashes, that are popular among nephrology experts and patients, provide short time relief from thirst without noteworthy side-effects and can be emphasized for a quick interim alleviation.

Saliva-stimulation via acupressure (TENS and electronic device) and Pilocarpine significantly increased the amount of saliva and thus reduce dipsogenic sensations. Though acupressure was well-tolerated and could potentially be part of clinical practice, pilocarpine showed major adverse effects thus cannot be recommended for broad or long-term use.

Allotting the fluid allowance with a timetable provide beneficial effects for the alleviation of thirst by addressing behavioral triggers and could be of great importance as an adjunct strategy.

RAAS-blockage medication and lowering sodium dialysate have produced ambiguous results, while a psychological intervention showed no improvement of thirst.

Two important interventions have not been studied in RCTs in the HD cohort. All aggregates of cold remedies, favored by patients and medical specialists, have produced beneficial effects in perioperative situations and low-salt diet proved to significantly decrease BP and IDWG, so there is great demand to further investigate these strategies.

There is an urgent need for deeper understanding of the pathological changes in thirst regulations in the ESRD cohort. More RCTs, either further investigating known strategies to reduce the heterogeneity of results or exploring innovative treatment concepts, are of great importance for improving hemodialysis patients' lives by relieving them from suffering from thirst and easing the burden of individual, medical and financial consequences.

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Appendices

Appendix I:

Study	Details of intervention	Administration
FAN et al[29] 2013 **a**	Sugar free chewing gum	6x/d >10 min + as desired (thirsty/dry mouth);
FAN et al[29] 2013 **b**	straw	take a little water when thirsty
BOTS et al[50] 2005 **a**	Sugar free chewing gum	6x/d > 10 min + as desired (thirsty/dry mouth);
BOTS et al[50] 2005 **b**	Saliva substitute	sprayed > 6x/d + as desired (thirsty/dry mouth)
CHEN et al[82] 2023	Sugar free chewing gum	6x/d > 10 min + 2 gums when thirsty
OZEN et al[84] 2021	Sugar free chewing gum	6x/d 10 min, after each meal + when thirsty/dry mouth
IBRAHIM et al[63] 2023	Thyme honey rinse (20 ml in 100 ml water)	3/day no swallowing
YU et al[83] 2016	Licorice mouthwash 8,34g of licorice concentrate in 500 ml of pure water	1 min 30-60 min after each main meal or: 9 am, 1 pm, 7 pm when frequent small meals no swallowing
OLDENBURG et al [85] 1988	Enalapril	2x5mg per week
MASAJTIS-ZAGAJEWSKA et al[81] 2009	Losartan on top of ACE-I	50 mg/day in a single morning dose
SUNG et al[44] 2005 **a + b**	Pilocarpine 1% ophthalmic solution (3:7 saline:Milli-Q* Water)	10 drops 4/d, 30min before each main meal + at bedtime
BELLOMO et al[76] 2015	psychological intervention: group sessions, Carl Roger's Person-Centered Approach[103]	a 45 min, 1/w for 5 weeks
MINA et al[86] 2019	Fluid Distribution Timetable + calibrated cup for measured fluid intake on top of nurse teaching at every HD session	
YANG et al[42] 2019	TENS (Transcutaneous electrical nerve stimulation) 250 μs/50 Hz Placebo: mock TENS 50 μs/ 2Hz Jiache point and Yifeng point	20 min, 1/week during HD
YILDIRIM KESKIN et al[54] 2021	Acupressure device (massaging with low frequency waves) Lianquan, Yifeng and Yongqua/ Jing-well points	15min, 3/week, during HD
DOMINIC et al[87] 1996	Low Sodium Dialysate/Profiled Sodium (gradual decrease 137 to 128 mEq/l) + step-linear reduced UF Control: Standard Sodium Dialysate (137 mEq/l) + constant UF	Every dialysis session
MARSHALL et al[88] 2020	Low sodium dialysate (135 mmol/l) Control: Standard sodium dialysate (140 mmol/l)	Every dialysis session

Key	
*	Milli-Q Water is simply water purified using a Millipore Milli-Q lab water system[97]

Table 6: Detailed description of interventions

Appendix II: Copyright Statement

Affirmation

The undersigned DUCHEK, Stefanie, postgraduate student of the Postgraduate Program "LIFESTYLE MEDICINE" of the University of Thessaly

I declare responsibly that I accept the following terms concerning:

(a) the copyright of my Master's Thesis entitled " Alleviation of thirst in hemodialysis patients – relief or belief? A Systematic Review on therapeutic strategies in randomized controlled trials"

(b) the management of the research data I will collect in the course of its elaboration:

1. The copyright of the resulting volume of the master's thesis will belong to me. I will follow the instructions for writing, printing and depositing copies of the dissertation in the relevant repositories (in printed and/or electronic form).
2. The management of the dissertation data belongs jointly to me and the Director of Studies/Main Supervisor.
3. Any scientific publication or announcement (posted or oral), or reference derived from the material/data of this work will be made with authors myself, the main supervisor and/or other researchers (such as a member of the three-member advisory committee), depending on their contribution to the research or the writing of the research paper(s).
4. The order of names in scientific publications or scientific announcements will be decided jointly by me and the main supervisor (DOS) of the project before it begins. This decision will be certified in writing between myself and the main supervisor.

Finally, I declare that I am aware of the rules on plagiarism and intellectual property and that I will strictly follow them throughout my studies, I will attend to the educational obligations arising from this MSc, as well as will attend the publication procedures that will arise after the completion of my studies.

JUNE 18, 2024

DUCHEK, Stefanie