Review Article

Beyond Blood: Investigating the Clinical Potential of Electrolyte Detection in Tears: A Systematic Review

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ABSTRACT

Aim and Background: Tears have emerged as a promising medium for non-invasive biomarker research, providing valuable insights into overall health through their rich biochemical composition. This systematic review delves into the clinical potential of measuring electrolytes in tears compared to blood, addressing the benefits and challenges of tear-based diagnostics. **Materials and Methods:** From an initial identification of 1,134 articles, four (4) studies from 2014 to the present were analyzed to evaluate the clinical significance of tear electrolyte analysis and their clinical implications. Literature research was conducted using reputable academic databases like Google Scholar, PubMed, ScienceDirect, JSTOR, and Cochrane Library. **Results:** The review found that tear electrolyte analysis holds potential as a non-invasive diagnostic tool, offering insights into personalized health monitoring and disease detection. However, a significant disadvantage is the variability in tear volume and variability, which can lead to inconsistent results and complicate the interpretation of data. **Conclusion and Recommendations:** Standardization of tear collection procedures is crucial for accurate biomarker analysis, emphasizing the need for consistent protocols in tear-based diagnostics. With advancements in wearable technologies, tear analysis presents a practical and convenient option for long-term health monitoring and early disease detection.

Keywords: Tear Electrolyte, Tear Electrolyte Value, Blood Values, and Electrolyte Values.

INTRODUCTION

In the early 21st century, the medical field is increasingly focused on developing diagnostic tests that are not only easily accessible to patients but also align with the World Health Organization's criteria for point-of-care testing, which include being affordable, sensitive, selective, user-friendly, rapid, equipment-free, and deliverable to end-users.[1]

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This push towards innovation is supported by study advancements in proteins, metabolites, and genetic technologies, emphasizing the importance of discovering potential biological markers for systemic diseases. Such markers are crucial for enhancing early diagnosis, monitoring therapeutic intervention efficacy, and advancing toward predictive, preventive, and personalized medicine.[2]

Extensive studies have been conducted on biofluids such as urine, sweat, saliva, and tears in an attempt to find a compatible and alternative source that shows comparable biomarker profiles, given the standard blood collection approach is invasive. In this context, tears have emerged as a promising medium due to their noninvasive collection method and their potential for biochemical information.[3]

Though traditionally regarded for its role in protecting and lubricating the eyes, tears have since come to contain an abundance of biochemical information indicative of overall health.[4] The composition of tear fluid, reflecting the body's physiological state, is controlled by a complex interplay of systemic and ocular factors, making it a valuable instrument for health assessment.[5] Collecting and analyzing tear samples poses challenges due to their small volume and rapid chemical composition changes. Since standard clinical assays for proteins and other indicators are insufficient for identifying ion concentrations in tears, assessing tear electrolyte levels can be complex.[6]

The practicality of incorporating tear-based diagnostics into routine health examinations is demonstrated by the development of technologies such as smart contact lenses, which are intended to analyze biomarkers in tears.[7] The Intra Ocular Pressure (IOP), the amount of glucose in tears, and certain biomarkers linked to specific disorders are all possible to measure by these sensors.[8] Although tears and blood glucose levels are known to be correlated,[9] there hasn't been much research done on the electrolyte content of tears.[10]

Electrolytes, which are charged atoms or ions present in body fluids, are crucial for bodily functions. For example, sodium (Na^+) and potassium (K^+) are important for the nervous system, while calcium (Ca^+) and magnesium (Mg^+) support heart health. Electrolyte abnormalities can be brought on by illnesses like cirrhosis, heart disease, kidney disease, and alcoholism.[11] Additionally, measuring electrolytes is an ideal diagnostic technique because they aid in maintaining the pH balance of bodily fluids. Although tears are primarily composed of electrolytes and can be considered an ultrafiltrate of plasma,[12] standardization of this technique is essential to ensure its accuracy and reliability. Once established, tear electrolyte analysis may provide an efficient way to identify early health problems and modify treatments to each patient's requirements, improving patient compliance and comfort.[13]

Furthermore, the use of tears as a diagnostic tool is a novel and intriguing development in medical research which offers continuous condition monitoring and early detection of health problems using non-invasive techniques. This approach may redefine the way diseases are identified and managed. Through utilizing tears as a detection tool, this systematic review intends to investigate the potential of tears as a robust and non-invasive strategy for medical research, opening up new possibilities for improved patient care and diagnostics.

Objective

This review will explore the diagnostic capabilities of tears as a non-invasive source for electrolyte biomarkers. It will systematically evaluate the importance of detecting electrolytes in tears compared to blood, highlighting the *clinical benefits and implications* of analyzing tear electrolytes. By doing so, this aims to review the potential of tear electrolyte analysis in health monitoring, offering insights into its unique advantages.

MATERIALS AND METHODOLOGY

Literature Research

Relevant literature was sourced from reputable academic databases, such as Google Scholar, PubMed, ScienceDirect, JSTOR, and Cochrane Library. Google Scholar and ScienceDirect are large databases; to narrow down the studies the researchers use these systematic combinations of search terms, specifically "Tear Electrolyte" OR "Tear Electrolyte Value" OR 'COMPOSITION" AND "Blood Values" OR "Electrolyte Values,". These are the terms used to identify studies that focus on investigating the tears used as analytes in differentiating their normal values from blood glucose normal values in determining underlying conditions or monitoring health status.

Table 1: PICO Framework for Tear Electrolyte Analysis as a Non-Invasive Diagnosis Tool

Patient, Population or Problem	Intervention	Comparison Intervention	Outcome
Patients or individuals who may benefit from non-invasive diagnostic testing, particularly those with conditions that can be monitored through electrolyte levels in tears (e.g., dry eye syndrome, diabetes, etc.).	The use of tear sample collection and analysis to measure electrolyte levels as a non-invasive diagnostic tool.	Traditional diagnostic methods, such as blood tests, that measure electrolyte levels and other biomarkers to assess whether these have similarities in values.	The accuracy, reliability, and clinical utility of tear electrolyte analysis in diagnosing and monitoring health conditions compared to blood tests.

Eligibility Criteria

This review examines the significance of tear electrolyte analysis by limiting the included studies and articles to

those published between 2014 and the present. Full-text articles or abstracts containing statistically significant data on the composition of tears and blood electrolytes are included in the publications. Furthermore, research that investigates the clinical relevance of tear electrolyte assessment in diagnosing or monitoring physiological or pathological conditions is eligible for consideration. The inclusion criteria include (a) publications from 2014 to the present, (b) studies reporting on electrolyte levels in tears, (c) studies reporting on electrolyte levels in blood, (d) investigations into the clinical implications of tear electrolyte analysis, and (d) full-text articles or abstracts presenting statistically significant data. The eligibility of these selected articles was determined using specific exclusion criteria. Exclusions included (a) publications before 2014, (b) research that do not report on tear electrolyte levels, (c) Investigations with little clinical relevance to tear electrolyte analysis, and (d) articles from predatory journals. The selection process entails a thorough evaluation of titles and abstracts to identify relevant publications.

Notable restrictions to study eligibility in a systematic review on tear electrolyte analysis are essential for ensuring the quality and relevance of included research. Limiting studies to those published from 2014 onward ensures that findings reflect the most current methodologies and technologies. Excluding studies with little clinical relevance and those from predatory journals helps maintain the integrity of the review. Overall, these restrictions contribute to a robust understanding of the clinical potential of tear electrolyte analysis.

Table 1 guided the literature search on tear electrolyte analysis's impact on health outcomes, using the PICO framework to define the research focus: Patient/Population (individuals with health conditions), Intervention (tear electrolyte analysis), Comparison (with and without specific conditions), and Outcome (effects on electrolyte composition and health indicators). This structured approach aimed to systematically identify relevant studies and highlight areas for further research.

Selection Strategy

The researchers meticulously reviewed the eligibility and discrepancies of the selected studies that were identified for inclusion. Articles that appeared relevant were screened by two (2) researchers for full-text screening and final inclusion in the review. With guidance from the research adviser, any disputes or arguments were carefully addressed, ensuring that a comprehensive and unbiased analysis was carried out.

The articles underwent a thorough review process, with regard to contradictions and eligibility criteria. Prior to in-depth evaluation, the titles and abstracts of the study were thoroughly reviewed to streamline the selection process and ascertain that only pertinent research was taken into consideration.

Risk of Bias and Quality Assessment

For the risk of bias and quality assessment of the included studies, the authors carefully selected and extracted studies and articles based on their relevance to the research topic beginning with the screening of its title, abstract, and full text. Two (2) authors utilized the CASP (Critical Appraisal Skills Programme) Systematic Review Checklist to eliminate the risk of bias and ensure study quality. Using this checklist, the studies have been assessed for their results, validity, and significance. Additionally, the authors also used RobVis's Risk of Bias Tracking Media to obtain the Risk of Bias extraction results with most of the studies having low risk (Figure 1). Two (2) other independent reviewers and the research adviser validated the data and resolved any conflict or discrepancy during data collection and extraction.

The CASP Checklist results indicate that the study effectively addressed a clear research question and compared the diagnostic test with an appropriate reference standard. However, there is room for improvement, as two studies lacked sufficient methodological detail, and the use of different instrumentations may result in varied outcomes. Overall, while the findings suggest applicability to the relevant patient population and consideration of all important outcomes, the inconsistencies highlight the need for standardization in future studies.

Data Extraction

The authors extracted the study characteristics of the eligible articles such as: (1) the first author's name, (2) the year of publication, (3) the title, (4) electrolytes tears concentration, (5) methods, (6) key findings of each study. Detailed data extraction of articles is outlined in Table 2.

Details from relevant journals were extracted, including the author's name, title, year of publication, and attributes. The publications' abstracts and discussion sections were examined to further gather and extract significant information. Table 2 presents a list of the eligible articles along with their respective details.

RESULTS

The initial search yielded 1,134 articles. Duplicate research studies were identified using ZOTERO, open-source management software designed to organize

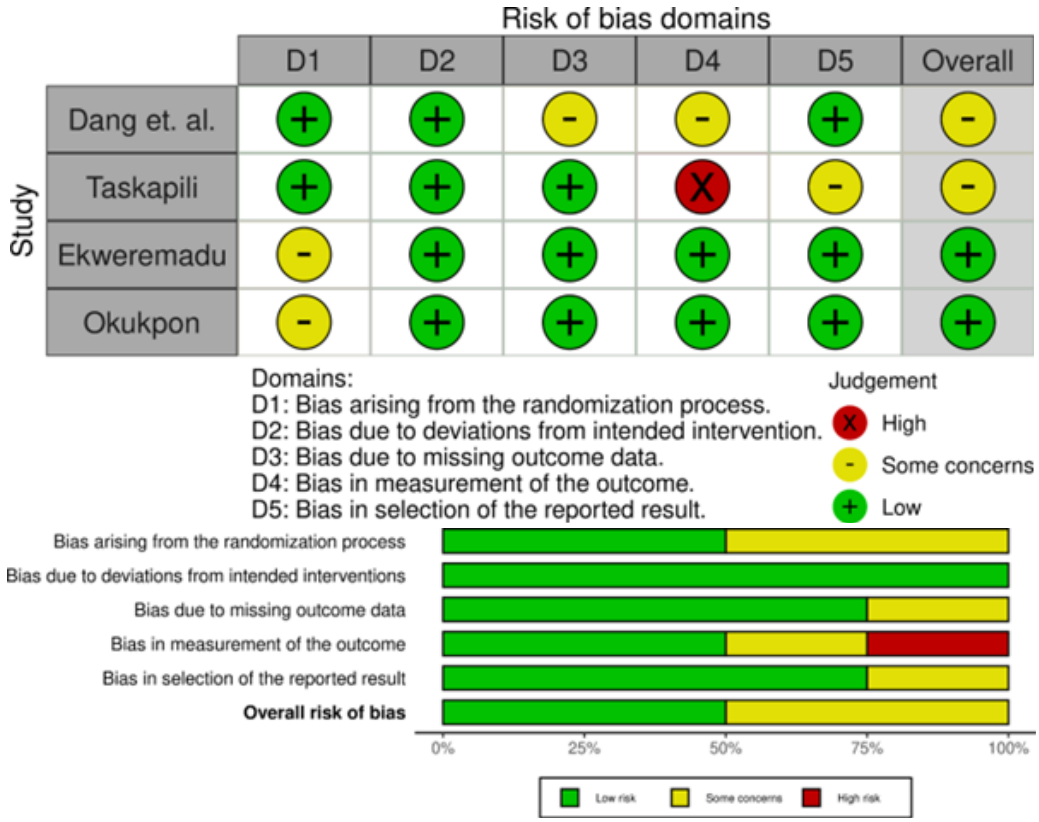

Figure 1: Risk-of-bias VISualization (Robvis).

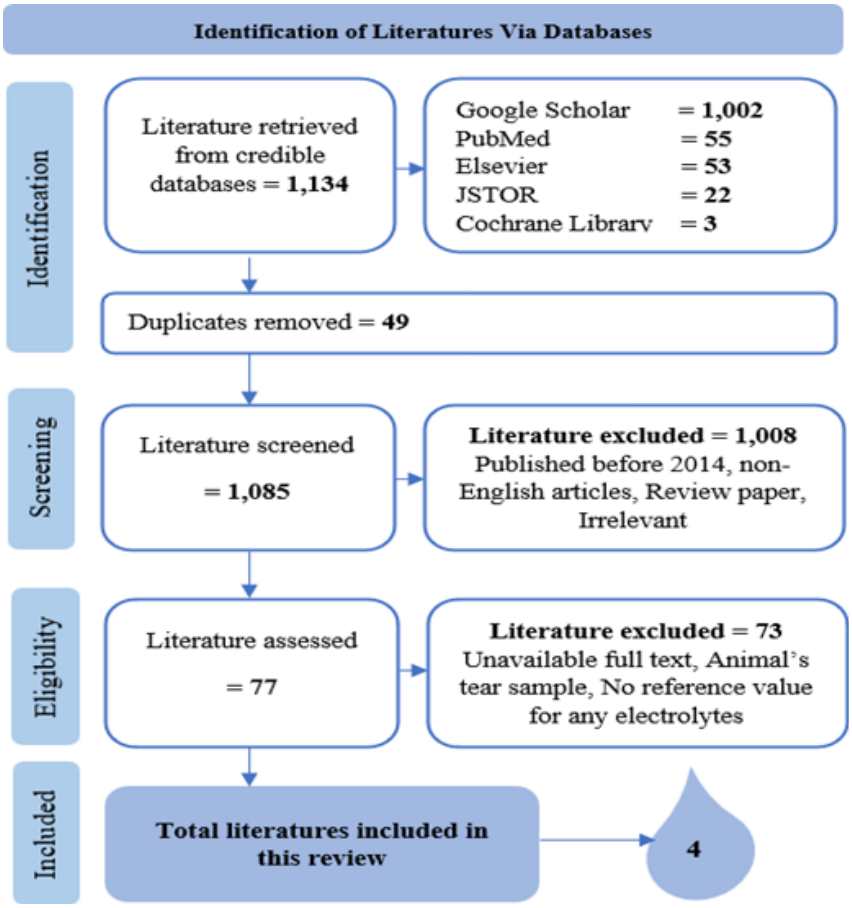

Figure 2: Schematic diagram of the literature selection process.

Table 2: Studies Discuss the Electrolyte Values from Tear Fluid

Reference	Author	Title	Electrolyte Tears Concentration	Methods	Findings
[15]	Dang W., et.al. (2018)	Stretchable Wireless System for Swear pH Monitoring Biosensors and Bioelectronics	Na 120 - 165 mM K 20 - 42 mM Cl 118 - 135 mM Ca 20 – 42 mM Mg 0.5 – 0.9 mM	Not mentioned.	Tear electrolytes, including sodium, potassium, chloride, calcium, and magnesium, play crucial roles in maintaining ocular health and function. Abnormal level of these electrolytes in tears can indicate underlying ocular diseases or systemic conditions. Monitoring tear electrolytes provides valuable insights for diagnosing and managing ocular and systemic health issues.
[16]	Taskapili M., et.al. (2015)	The Effects of Hemodialysis on Tears Osmolarity	Na 120 - 170 mmol/kg K 6 - 42 mmol/kg Cl 106 - 135 mmol/kg HCO3 26 mmol/kg	Not mentioned.	Tear electrolytes, like sodium and potassium, help maintain the proper balance and osmolarity of tears, crucial for clear vision and eye comfort. Imbalances in tear electrolytes can contribute to conditions like dry eye syndrome, affecting the stability of the tear electrolyte levels provides valuable insights into ocular health conditions and guides targeted treatment approaches for maintaining a healthy tear film.
[14]	Ekweremadu E., Ezeh C., & Kamah J. (2021)	Tear and Serum Electrolyte Concentrations as a Biomarker in Primary Glaucoma Subjects	Na 131.06 ± 6.39 K 1.40 ± 1.57 Cl 122.86 ± 7.12	Tilting the head allowed for tear collection from the lateral canthal area using a sterile 50 ul plane capillary tube. Both serum and tear samples were analyzed using Sensa Core R's ST-100 B electrolyte analyzer that uses direct ion-selective electrode method. All results are included and there is no measurement removed as an outliner during analysis.	Potassium and chloride concentrations were significantly higher in tear samples compared to serum samples, while sodium concentration in tears was not statistically significantly different. Age and sex did not have a significant effect on tear electrolytes. The study highlighted the potential protective role of high potassium concentration in tears against ocular tissue injury.
[10]	Okukpon J., et.al. (2019)	Tear Electrolyte Assessment of Diabetic Patients in Southern Nigeria	Ca: Male 2.51 ± 1.46, Female 2.38 ± 0.97 Mg: Male 0.69 ± 0.33, Female 0.99 ± 0.63 PO4: Male 0.12 ± 0.058, Female 0.11 ± 0.082	Tear samples were collected using 75mm micro-point glass capillary tubes and stored at 4°C for analysis. Magnesium, calcium, and phosphorous were measured using Bulk Scientific Atomic Absorption Spectrophotometer 210 VGP and 6715 Visible Spectrophotometer.	Tear electrolytes, such as calcium, magnesium, and phosphate, play a crucial role in maintaining the health of the ocular system. Imbalances in these electrolytes can contribute to complications like neuropathy, nephropathy, and vascular issues in diabetic patients.

research materials and references. After removing duplicates, 49 articles remained. Titles and abstracts were screened, resulting in 77 articles. These were then evaluated for eligibility. Thus, the final number of articles included in this review is 4. The selection process for this study is illustrated in Figure 2.

As shown in Table 2, two studies have available methodologies for tear electrolyte concentration that were fully discussed to enhance credibility. Focused on diabetic patients in Southern Nigeria, collecting tear samples using cotton wool soaked in methylated spirit to clean the skin around the eyes before collection. This step, combined with the use of specific glass capillary tubes, minimized the risk of contamination. The samples were then stored at 4°C to preserve electrolyte stability until analysis[10] On the other hand, Ekweremadu *et al.* (2021)[14] investigated tear electrolytes in African hospital subjects, using a distinct approach for sample collection and analysis. Tears were gathered from the lower lateral tear meniscus using sterile capillary tubes to maintain sample consistency. The samples were analyzed with an automated electrolyte analyzer that employed direct ion-selective electrode (ISE) technology, accurately measuring sodium, potassium, and chloride ions. Both studies utilized meticulous methods to ensure the integrity and accuracy of their findings.

DISCUSSION

Tear Structure

The precorneal tear film consists of three layers, totaling a thickness ranging from 2-5.5 µm.[17] A research conducted by Xianquan, Z., *et al.* in 2021[18] provides insights that the tear film is a complex and dynamic fluid that protects and lubricates the ocular surface. It has a three-layered structure, including an inner mucus layer, an intermediate aqueous layer, and an outer lipid layer which is shown in Figure 3. The aqueous layer contains several proteins like lactotransferrin, lysozyme, zinc-alpha-2 glycoprotein, cystatin S, and cystatin SN, identified through methods like two-Dimensional Gel Electrophoresis (2DGE) and Mass Spectrometry (MS). Studies have found a small set of proteins-lipocalin, lysozyme, lactoferrin, sIgA, and serum albumin-that make up 80–90% of tear protein content. According to Mukamal (2023),[19] tears are not entirely saline. Similar in composition to saliva, they also contain enzymes, metabolites, lipids, and electrolytes. The tear film consists of three layers as shown in Figure 3:

- Inner mucus layer-maintains tear adhesion to the eye.
- Middle watery layer-thickest layer, hydrates the eye, repels bacteria, and protects the cornea.
- Outer oily layer-smooths the surface and prevents evaporation of other layers.

In addition, Bruszel, B., *et al.* 2024[20] stated that the tear film also contains electrolytes, metabolites, and other substances that vary in concentration of which varies based on the individual's emotional state, environmental factors, and health status.

The electrolytes in the tear film, along with other components, contribute to the structure and functionality of tears, playing a vital role in protecting the eye, lubricating the ocular surface, and maintaining ocular health. The addition of electrolyte solutions, such as sodium or potassium chloride, to human tears has been shown to significantly improve tear ferning grades, particularly in dry-eye subjects.[21]

The tear film coats the eye's surface, crucial for shielding it from the environment, lubricating, maintaining smoothness for light refraction, and ensuring conjunctiva and corneal health. It spans about 3 to 10 µL in volume, 3 µm thick, secreted at a rate of 1 to 2 µL/min. Tear pH averages 7.45, fluctuating between 7.14 to 7.82 due to diurnal and seasonal variations.[22]

Meibomian glands are vital for producing the oily layer of tear film, which prevents excessive tear fluid evaporation. Gland dysfunction contributes to both evaporative dry eye and general dry eye.[23] Changes in lipid composition, as highlighted by Badugu *et al.* (2021),[6] can also impact the total electrolyte concentration in tears. Such alterations, often stemming from Meibomian gland dysfunction, can accelerate water evaporation from tears, leading to elevated electrolyte concentrations. According to Mukamal (2023),[19] tears are crucial in maintaining both visual clarity and ocular health. Additionally, tears serve as a means of emotional expression. Tears comprise three main types:

- Basal tears: These tears are always in the eyes, lubricating, nourishing, and protecting the cornea. Basal tears continuously shield the eye from dirt and debris.
- Reflex tears: Triggered by irritants like smoke, foreign particles, or onion fumes, reflex tears are produced in larger quantities than basal tears. They may contain increased levels of antibodies, helping combat bacteria and other harmful substances.

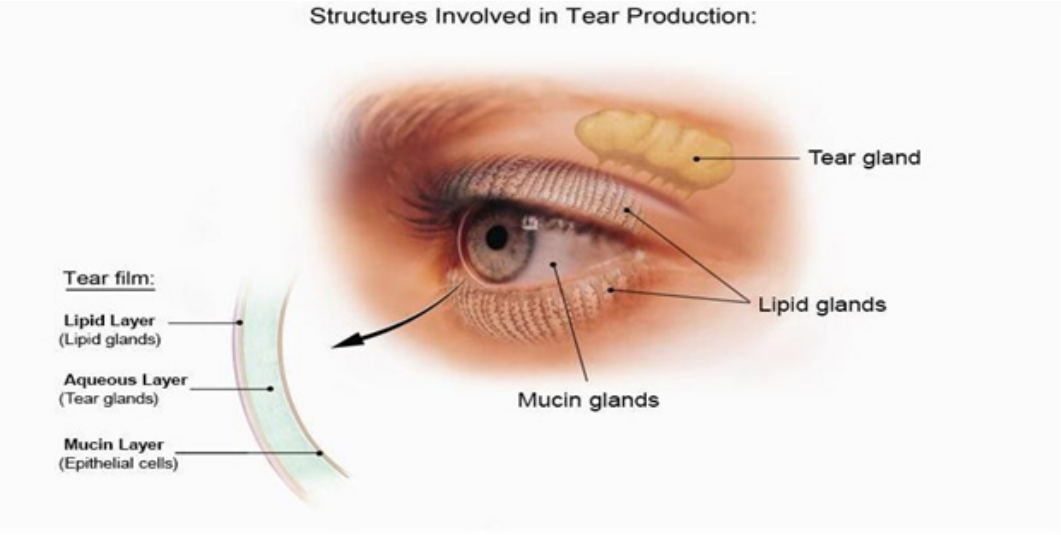

Figure 3: Structures Involved in Tear Production.

- Emotional tears: Triggered by feelings like joy, sadness, or fear, emotional tears differ from basal and reflex tears. Some researchers suggest emotional tears contain extra hormones and proteins, showing the link between emotions and tear production

Tear Collection Methods

The research on tear fluid holds an intriguing avenue to discovering novel biomarkers due to its non-invasive sampling method and high protein content. Consequently, this has sparked a lot of interest in studying tear fluid, particularly in ocular surface diseases.[24] Tear fluid biomarkers show potential for diagnosing various ocular conditions, but they require reliable collection methods. The continued expansion of interest in tear fluid research is linked to its ease of access and collection compared to serum or plasma, which makes it a viable option for biomarker discovery.[13] Because various factors affect the molecular composition of tear fluid samples, it's important to study different collection techniques and their impact on sample quality and composition. However, due to the inadequate volume of tear fluid as well as the instability of its components, influenced by ambient conditions, emotional state, and medical conditions, significant challenges arise.[25] Hence, the need to develop and improve methods for tear sample collection and analysis is crucial to overcome these challenges and provide accurate and reliable results.

Emphasize how crucial it is to standardize tear fluid collection and processing methods. Among the widely used methods of tear collection are the capillary tubes and Schirmer strips. Capillary tubes made of either glass or plastic are narrow tubes that are placed near the lower eyelid of an individual in order to collect tears through capillary action. These tubes aim to collect approximately 10 µl of sample in less than 10 min, thereby facilitating a direct assessment of tear electrolyte concentrations.[13] Schirmer strips, on the other hand, consist of small paper strips with marked measurements indicated on them and they are placed beneath the individual's lower eyelids to absorb tears for a definite period of time, usually ranging 5 min.[26]

Recent studies have provided insight into the advantages and disadvantages of both capillary tube and Schirmer strip methods for tear collection, emphasizing the need for further research to improve tear collection for electrolyte analysis. While these methods were deemed safe and well-received, they exhibit disparities in comfort and ease of use.[13] The Capillary Tube method, which is often perceived as more comfortable by the participants, offers convenience in sample collection as it minimizes foreign body sensations, thereby increasing the volume of tear samples collected. Additionally, this method allows direct measurement of electrolytes. It does, however, require more effort and expertise during the tear collection process which might affect both the overall experience of the patient and collector. In contrast, it becomes apparent that the simple application of the Schirmer strips saves time and guarantees that patients find them convenient to use. Yet, this method might as well induce potential discomfort through direct ocular contact, hence changing sample composition by mechanically contact with the corneal and conjunctival surfaces. Consequently, the difficulties in collecting tear fluid along with alterations in sample composition during the tear collection process further impede the

effectiveness of the method and limit its applicability. For instance, when a patient comes into contact with Schirmer strips and the ocular surface, he may feel mechanical irritation leading to discomfort. Therefore, if there is any mechanical stimulation on the eye, it may potentially influence tear flow dynamics. Despite its limitations, the Schirmer strip method remains valuable in measuring tear flow rates and various tear components that would be useful in determining the patient's dry eye status. Discrepancies in results are due to the variation in findings in sample collection procedures and how these affect the rates of tear flow. A less invasive method is provided by the capillary tubes, minimizing the risk of mechanical irritation and potential protein loss in the course of collection. Conversely, mechanical irritation and changes in protein composition could be initiated by Schirmer strips by directly contacting the ocular surface. This variation contributes to differences in the ocular flow rates of tears, where the IgG concentrations are moderately correlated with capillary tubes; Schirmer stripes may yield higher tear flow rates due to mechanical stimulation. Moreover, lower total protein concentrations can be due to minimal interference from capillary tubes during collection, while higher IgG concentrations may be due to direct contact-induced mechanical irritation of Schirmer strips. Understanding these variations is crucial to precisely interpreting tear fluid composition and its importance in diagnostic biomarkers and research applications. It is noteworthy that the method of tear collection greatly affects the sample composition, thus, it should comply with the objectives of the study, to ensure that the biomarker studies on tear fluid are reliable and consistent.

Table 3: Advantages and Disadvantages of Using Tears as Electrolyte Biomarker.

	Advantages	Disadvantages
Accessibility and Non-invasiveness	Easily collected with no discomfort to patients. Low risk of infection. High acceptability among patients.[29]	Difficulty in obtaining consistent findings.[28], [31] Challenges in tear collection due to small volume.[33]
Consistency and Sustainability	Consistent and sustainable supply of analytes. [29] Repeatable collection method for constant monitoring. [30] Long-term preservation without sample damage.	Risk of evaporation and variability in tear production. [33]
Cost-effectiveness	Cost-effective collection and analysis.[29]	[26]Impact of variation in collection techniques and storage on accuracy.

Table 3 outlines the advantages and disadvantages of utilizing tears for the analysis of electrolyte biomarkers which are discussed in terms of the concepts provided in the first column. Advantages include non-invasive tear collection, high acceptability among patients, and the potential for a consistent supply of analytes. On the other hand, the disadvantages include challenges such as the limited volume of tear fluid, variability in tear production, and the influence of collection techniques on the accuracy of results. This overview emphasizes the clinical relevance of tear electrolytes in health monitoring and diagnostic applications.

The use of tears as a specimen for testing offers several advantages, as highlighted in a seminal study by Makaram et al. (2014).[27] The accessibility and non-invasiveness of tears present significant advantages in clinical practice. Tear fluid presents a promising path for biomarker discovery, disease prediction, diagnosis, and monitoring given that it is easily collected with no discomfort to the patient. Its ease of collection is in line with individualized medical care based on each patient's specific health risks, offering a comfortable, non-invasive testing approach that patient can use for routine check-ups without experiencing significant inconvenience. This accessibility lowers barriers to entry for patients, encouraging regular testing and monitoring, particularly among individuals who may be hesitant or unable to undergo more invasive procedures. As tears are highly accessible compared to other bodily fluids, such as blood or cerebral fluid, tear fluid analysis holds the potential to revolutionize healthcare delivery by offering a less burdensome and more patient-friendly approach to disease detection and management.[28]

Due to its non-invasiveness, tear collection via methods such as the capillary tube or Schirmer strip ensures there is no risk of infection, which is a notable advantage over other bodily fluids like blood. Unlike blood samples, which may change over time or require frequent replenishment to maintain analyte stability, tears offer a consistent and sustainable supply of analytes for testing. This is attributed to the absence of invasive procedures or the introduction of foreign substances into the body during tear collection. Consequently, the potential for contamination is minimized, ensuring a safe and reliable collection process. Quah *et al.* (2014)[29] conducted a study wherein patients were asked about their opinions regarding blood collection methods such as finger prick

testing and antecubital venipuncture in comparison to tear collection. A pain-sensing questionnaire on a 0-10 scale was also filled out by participants. The pain score for the Schirmer strip tear collection was found to be greater than that of the finger puncture but much lower than those of the antecubital venipuncture. According to the study, 74% of participants would rather provide tears than blood for testing, demonstrating the high acceptability of using Schirmer strips for tear collection during primary health screening.

On top of that, since biomarkers are simple to collect, the method is repeatable, which allows for constant monitoring of biomarker variations over time and yields important information about the course of the disease and the effectiveness of treatment. Tears are also a great resource for long-term studies and personalized treatment techniques since they can be preserved for lengthy periods of time without damaging the integrity of the sample.[30]

Moreover, using tears as a specimen for testing is cost-effective, as tear collection and analysis typically require less resource consumption compared to blood sampling. This is attributed to the fact that minimal expertise and equipment are needed for tear collection which limits the demand for highly trained staff and strict storage requirements. Such cost-effectiveness can be particularly beneficial in large-scale screening initiatives or resource-limited settings.

As tears offer advantages as a specimen for testing, several notable disadvantages also exist. Research on tears in medicine emphasizes how difficult it is to obtain consistent findings from more extensive, multicenter, and longitudinal studies. For instance, studies of Sambandam SN, et al. (2015)[31] on rotator cuff tears highlight the limited understanding of asymptomatic tears due to scarce longitudinal data. Similarly, the research of Mordecai SC et al. (2014)[32] on meniscal tears emphasizes the reliance on a few multicentre studies, raising concerns about generalizability. The complexity of conducting a long-term study of tears may be complicated by participant attrition and data management issues, which ultimately limit the availability of robust evidence.

The limited volume of tear fluid poses challenges in collection and analysis. Kim et al. (2018)[33] also discussed that using tears for laboratory diagnoses comes with challenges, including: the small volume of tear samples, the risk of evaporation during collection, differences in how much individuals produce tears, and changes in this production throughout the day, and difficulties in collecting tears that might alter the concentrations of substances being measured.

Standardization in tear collection procedures, pre-processing, and sample storage is crucial for consistent biomarker research using tears. Variations in techniques and storage impact accuracy.[26] Lacking standardized protocols, variations in collection techniques, and storage conditions may substantially affect the accuracy and interpretation of biomarker levels. Thus, a major drawback that impedes the ability to produce consistent and dependable results in biomarker research.

Tear Electrolytes and their Clinical Significance

Tear collection is a non-invasive method for patients, especially those who may be averse to blood draws or other invasive procedures. It is a quick and easy technique, making it practical and convenient for screening and monitoring diseases. Changes in tear composition can also be used to predict some disease information using specific analytes,[34] which can contribute to long-term monitoring of human health. Recent advances in wearable electronics have been pivotal in enhancing medical applications through continuous health monitoring. For example, current developments in smart contact lenses allow for the ongoing monitoring of eye function and tear fluid, providing immediate medical diagnostics. These lenses focus on ocular diseases, glucose levels, intraocular pressure, and cancer detection (Kazanskiy et al., 2023).[35] The exploration of tear biomarkers for diverse medical applications is also gaining popularity in the scientific community, who are examining its potential in the diagnosis and monitoring of conditions such as systemic disorders, and neurological disorders.[3] However, despite the presence of valuable electrolytes in tears, current wearable technologies do not yet have the capability to detect them. Therefore, there is potential for developing technology that analyzes electrolytes in tears to monitor various health conditions by analyzing their values.

The table below (Table 4) will explore various electrolytes found in tears, compare their concentrations with those in blood, and identify their relevance to associated health issues. This analysis emphasizes the importance of tears as a non-invasive method for understanding health, demonstrating their significant potential in disease diagnosis and management.

Tears often contain analytes including glucose, Na^+, and K^+,[40] $Mg2^+$, $Ca2^+$, Cl^-, and urea are correlated with their counterparts in the blood.[41] Over the years, tear-based sensors have primarily targeted glucose monitoring but show significant potential for non-invasive detection of other crucial biomarkers. Kim (2018)[33] stated that the range of analytes in tears can be broadened to include additional metabolites and essential electrolytes that

Table 4: Tear and Blood Electrolyte Values and their Possible Implications.

Electrolytes	Normal Tear Values	Normal Blood Values		Possible Implications
Sodium (Na)	120-160 mM[15]	135-145 mmol/L[36]	Hyponatremia	Muscular Weakness, Seizures,[37]
			(↓Na)	Coma
	120-170 mmol/kg[16]			
	131.06±6.39[14]		Hypernatremia (↑Na)	Lethargy, Difficult Respiration, Increased Thirst[37]
Potassium (K)	20-42 mM[15]	3.6-5.5 mmol/L[36]	Hypokalemia	Muscle Weakness or Paralysis,[36]
			(↓K)	Increased Risk of Arrhythmia
	6-42 mM[16]			
	1.40±1.57[14]		Hyperkalemia (↑K)	Numbness, Mental Confusion, Cardiac Arrhythmia[36]
Chloride (Cl)	118-135 mM[15]	96-107 mmol/L[37]	Hypochloremia (↓Cl)	Diabetic Ketoacidosis, Aldosterone Deficiency, Pyelonephritis[36]
	106-135 mM[16]			
	122.86-7.12 mM[14]		Hyperchloremia (↑Cl)	GI Losses, Renal Tubular Acidosis, Metabolic Acidosis[36]
Calcium (Ca)	Male-2.51±1.46 Female-2.38±0.97[10]	Male - 8.6-10.3mg/dL Female-8.6-10.2 mg/dL	Hypocalcemia (↓Ca)	Neuromuscular Irritability, Cardiac Irregularities[37]
	20-42 mM[15]	8.8-10.7 mg/dL[36]	Hypercalcemia (↑Ca)	Anorexia, Peptic Ulcer Disease, Nephrolithiasis[37]
Magnesium (Mg)	0.5-0.9 mM[15]	1.46-2.68 mg/dL[36]	Hypomagnesemia	Arrhythmia, Hypertension,[36]
			(↓Mg)	Hypocalcemia
			Hypermagnesemia	Bradycardia, Hypertension,[36]
			(↑Mg)	Hypocalcemia
Phosphate (PO_4)	Male-0.12±0.058[10]	3.4-4.5 mg/dL[36]	Hypophosphatemia	Osteopenia, Osteoporosis,[41]
	Female-0.11±0.082		(↓PO4)	Metabolic Encephalopathy
			Hyperphosphatemia	Conjunctivitis, Vascular[39]
			(↑PO4)	Calcification, Arteriosclerosis[38]

Table 5: Normal Values of Tear and Blood Electrolytes.

Electrolytes	Normal Tear Values	Mean Tear Values	Normal Blood Values	Interpretation
Sodium (Na)	[15] 120-160 mM [16] 120-170 mmol/kg [14] 131.06±6.39	121.6-157.5 mM	[36]135-145 mmol/L	Similar
Potassium (K)	[15] 20-42 mM [16] 6-42 mM [14] 1.40±1.57	8.7-28.9 mM	[36] 3.6-5.5 mmol/L	Higher
Chloride (Cl)	[15] 118-135 mM [16] 106-135 mM [14] 122.86-7.12 mM	113.2-133.3mM	[37] 96-107 mmol/L	Higher
Calcium (Ca)	[10] Male-2.51±1.46	Male-1.05-3.97	Male - 8.6-10.3mg/dL	Male-Lower
		Female-1.96-3.35	Female-8.6-10.2	Female-Lower
	Female-2.38±0.97	----------	mg/dL	----------
	[15] 20-42 mM	20-42 mM	----------	Higher
			[36] 8.8-10.7 mg/dL	
Magnesium (Mg)	[15] 0.5-0.9 mM	0.5-0.9 mM	[36] 1.46-2.68 mg/dL	Similar
Phosphate (PO_4)	[10] Male-0.12±0.058 Female-0.11±0.082	Male-0.062-0.178 Female-0.028-0.192	[36] 3.4-4.5 mg/dL	Lower

exhibit close correlations with blood. Tears are essential in maintaining health, with a correlation existing between the concentrations of glucose, sodium, potassium, and other analytes in blood and tears.[42] Additional studies, such as those by Gilbard and Pardo (2005),[43] have noted that an imbalance in tear fluid electrolytes could lead to electrolyte imbalance toxicity.

The studies summarized in Table 5 show that sodium levels in tears are comparable to those in blood, suggesting that sodium is naturally secreted into tear fluid. Notably, potassium levels in tears are significantly higher than in blood plasma, a phenomenon attributed to the active transport of potassium and chloride ions into the tear fluid. High potassium levels play a crucial role in maintaining the proper thickness of the cornea's outer layer, thus protecting it from certain types of cell damage induced by UV light, as noted by Ekweremadu (2021).[14] Chloride, which is essential for fluid balance and tissue function, is present in slightly higher concentrations in tears than in blood serum. Moreover, the concentration of calcium in tears is generally lower than in blood plasma and remains constant regardless of tear production rates. Similarly, magnesium levels in tears are also somewhat lower than those in blood serum, reflecting the fraction of magnesium that is not protein-bound. Both calcium and magnesium are crucial for regulating the transport of substances across cell membranes. Bicarbonate levels in tears help maintain the nearly neutral pH of the tear film, which is why they are similar in blood.

CONCLUSION AND RECOMMENDATIONS

Limited studies have consistently shown a connection between electrolyte levels in tears and blood. Moreover, the field remains partially unexplored, with current research articles largely based on a limited number of studies, some of which date back to the late 1980s. This inconsistency may be attributed to the diverse methods used for collecting and analyzing tear samples. Necessarily, the implementation of standardized collection methods is crucial for ensuring reliable and accurate analysis of tear samples, as it reduces variability and enhances reproducibility across studies. Additionally, the challenge of accurately diagnosing conditions from reflex tears, which are produced in response to emotional or physical stimuli, is a critical area for further investigation. Ensuring that the sensors attain the necessary accuracy and precision for detecting specific analytes in tears is a crucial challenge in developing these devices. Given the significant potential of research in non-invasive biosensors, advancements are anticipated in the near future. Current trends involve the advancement of minimally invasive and continuous testing methods, miniaturized technologies, and the use of telemedicine for remote monitoring. The advancements for wearable sensors are continuous, thereby transforming and enhancing people's lives through innovative health monitoring solutions. The authors recommend noting the sensitive nature of the human eye, which requires utmost care during the sample collection process to avoid discomfort or damage. Based on current literature, contact lenses are comfortable to wear and

maintain constant contact with tear fluid. This offers a promising solution for efficient tear collection that researchers may consider. However, there is still room for improvement because most contact lens sensors can only identify one analyte at a time, making people with multiple disorders unable to meet their needs. The contact lens sensors are anticipated to detect numerous analytes simultaneously due to the rapid advancement of biosensor technology. Such innovations could revolutionize the field of diagnostics and personalized medicine, where monitoring and treatment are tailored to individual physiological profiles.

This has encouraged a search for an appropriate and alternative biofluid source that exhibits comparable biomarker profiles, with several studies being done on biofluids such as tears, sweat, urine, and saliva.

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AUTHOR'S CONTRIBUTIONS

This study was initiated and conceptualized by Mheizeli Pantanilla and Mikaela Calimon. Author Elriel Bernardino led the group and set the cadence that resulted in the development and completion of the study. Authors Mheizeli Pantanilla, Mikaela Calimon, and Nathalie Lopez composed the abstract of the study. Authors Mikaela Calimon, Mheizeli Pantanilla, Edsel Trinidad, and Mary Lou Nogales constructed the initial draft of the introduction. As for the Methodology, authors Elriel Bernardino and Carlo Basilan conducted screening and assessment of each article included in the study, with all authors contributing to the analysis and interpretation of the gathered data. Authors Carlo Basilan and Mikaela Calimon provided the conclusion of the study. Author Bernardino Hagosojos provided invaluable feedback, guidance, and support throughout the manuscript development process. Through collaborative efforts, all authors rigorously reviewed and approved the final manuscript version.

ETHICAL STATEMENT

The authors adhere to the ethical guidelines for conducting and collecting data from secondary sources. All references were appropriately cited and acknowledged.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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