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Study Ceramide Kinase Enzyme in Pediatric with Acute Kidney Disease

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Abstract: Acute Kidney Injury (AKI) is very common and its absolute incidence has increased in over the last years. AKI has been reported to complicate 1–7% of all hospital admissions and 1–25% of Intensive Care Unit (ICU) admissions 1. Over the past 50 years, mortality rates of patients with AKI in ICUs have remained high approximately 50–70%. In ICU, between 5–20% of critically ill patients have at least one episode of AKI 2. Altered lipid metabolism is a characteristic feature and potential driving factor of acute kidney injury (AKI). Of the lipids that accumulate in injured renal tissues, ceramides are potent regulators of metabolism and cell fate. Up-regulation of ceramide synthesis is a common feature shared across several AKI etiologies in vitro and in vivo. Furthermore, ceramide accumulation is an early event in the natural history of AKI that precedes cell death and organ dysfunction. Emerging evidence suggests that inhibition of ceramide accumulation may improve renal outcomes in several models of AKI. This review examines the landscape of ceramide metabolism and regulation in the healthy and injured kidney. Furthermore, we discuss the body of literature regarding ceramides as therapeutic targets for AKI and consider potential mechanisms by which ceramides drive kidney pathogenesis.

ألخلاصه

الإصابة الكلوية الحادة شائعة جدًا وقد زاد معدل حدوثها المطلق على مدار السنوات الأخيرة. وقد تم الإبلاغ عن أن الإصابة الكلوية الحادة تعقد ما بين 1-7% من جميع حالات الدخول إلى المستشفيات و1-25% من حالات الدخول إلى وحدة العناية المركزة 1. وعلى مدار الخمسين عامًا الماضية، ظلت معدلات الوفيات بين المرضى المصابين بالإصابة الكلوية الحادة في وحدات العناية المركزة مرتفعة بنسبة تقارب 50-70%. وفي وحدة العناية المركزة، يعاني ما بين 5-20% من المرضى المصابين بأمراض خطيرة من نوبة واحدة على الأقل من الإصابة الكلوية الحادة 2. يعد تغيير التمثيل الغذائي للدهون سمة مميزة وعاملًا محتملًا لإصابة الكلى الحادة. من بين الدهون التي تتراكم في أنسجة الكلى المصابة، تعد السيراميدات منظمات قوية لعملية التمثيل الغذائي ومصير الخلايا. يعد زيادة تنظيم تخليق السيراميد سمة مشتركة بين العديد من مسببات الإصابة الكلوية الحادة في المختبر وفي الجسم الحي. علاوة على ذلك، يعد تراكم السيراميد حدثًا مبكرًا في التاريخ الطبيعي للإصابة الكلوية الحادة يسبق موت الخلايا وخلل وظائف الأعضاء. تشير الأدلة الناشئة إلى أن تثبيط تراكم السيراميد قد يحسن النتائج الكلوية في العديد من نماذج الفشل الكلوي الحاد. تدرس هذه المراجعة المشهد الخاص باستقلاب السيراميد وتنظيمه في الكلى السليمة والمصابة. علاوة على ذلك، نناقش مجموعة التحاليل المتعلقة بالسيراميد كأهداف علاجية للفشل الكلوي الحاد وننظر في الآليات المحتملة التي من خلالها يدفع السيراميد تطور أمراض الكلى.

Keywords: Health, Disease, Normativism, Georges Canguilhem, Value Judgments, Socio-Cultural Preferences, Deviant Behaviors, إصابة الكلى الحادة، السيراميدات، السفينجوليبيدات

INTRODUCTION

The prevalence and costs associated with acute kidney injury (AKI) are increasing in the United States and global populations.[1,2] Despite a significant clinical need, no therapies are currently available to prevent or treat AKI or its transition to chronic kidney disease. Development and validation of candidate therapeutic strategies will require a better understanding of the primary effectors and molecular processes necessary for AKI pathogenesis. Increasing evidence suggests that the proximal tubular epithelium is the primary site affected during AKI and that tubule-specific molecular insults are sufficient to induce kidney pathology. In particular, the form and function of the proximal tubule is tightly coupled to its metabolism. Because of the high energy demand and reliance on aerobic oxidation of fatty acids required to support active solute reabsorption, the proximal tubule is especially vulnerable to metabolic injury. Altered lipid metabolism, characterized by mitochondrial impairments and lipid accumulation, is a shared feature common to diverse AKI etiologies.

This study was conducted on children who suffer from acute kidney failure between the ages of one and 15 years in the Central Child Teaching Hospital and Child Protection in the Medical City, Al Karama Teaching Hospital, and they were suffering from high levels of urea and creatinine, high cholesterol, low levels of protein and albumin, decreased immunity, and decreased Hemoglobin and iron levels, in addition to low calcium and vitamin D3, high potassium, and low sodium levels in the blood.

From the ER, dihydroceramides and ceramides can be shuttled to the Golgi apparatus or mitochondria for the formation of more complex sphingolipids, such as (dihydro)sphingomyelin, via the addition of various head-groups (eg, choline, phosphate, carbohydrate moieties) to the first-position oxygen molecule.[5] Hydrolysis of the choline headgroup from sphingomyelin (SM), mediated by a family of sphingomyelinases (SMase), is the second mechanism contributing to ceramide synthesis (Fig. 1).[6]

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Lastly, dihydroceramides and ceramides are degraded by the removal of the variable acyl chain to form (dihydro)sphingosine and a free fatty acid via a group of ceramidases (CDase)[7] or the ligand-gated ceramidase activity of the adiponectin receptors.[8] The liberated sphingoid backbone can be phosphorylated by sphingosine kinase to form (dihydro)sphingosine-1-phosphate, which has unique bioactivity relevant to kidney diseases, and was recently reviewed elsewhere.[9,10] Re-acylation of (dihydro)sphingosine by CERS to form (dihydro)ceramide is the third and final mechanism of ceramide production, termed the *salvage pathway* .

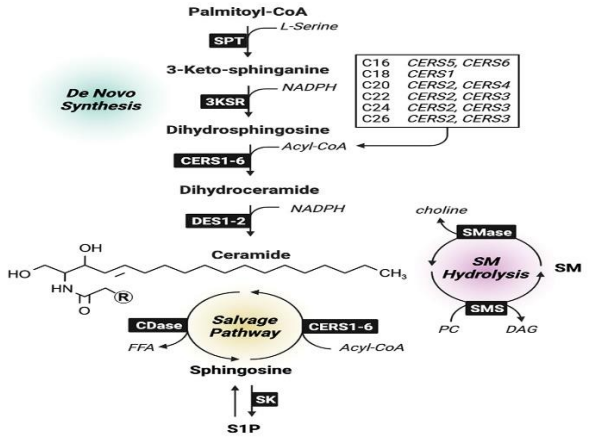

Figure 1: Ceramide synthesis. Ceramides are produced via de novo biosynthesis, sphingomyelin hydrolysis, or salvage of sphingoid bases. The ubiquitous de novo pathway is characterized by the transfer of serine to palmitoyl CoA, producing a sphingoid backbone that subsequently is acylated and desaturated to form ceramide. Alternatively, cleavage of a choline headgroup by a family of sphingomyelinase enzymes rapidly converts sphingomyelin to ceramide. Lastly, re-acylation of liberated (dihydro)sphingosine by the (dihydro)ceramide synthase enzymes regenerates ceramides in the salvage pathway. The length of acyl chain incorporated into a ceramide molecule is dependent on the substrate specificity of the (dihydro)ceramide synthases. Abbreviations: CDase, ceramidase; CERS, (dihydro)ceramide synthase; DAG, diacylglycerol; DES, dihydroceramide desaturase; FFA, free fatty acid; SK, sphingosine kinase; PC, phosphatidylcholine; R, accessory acyl chain; SK, sphingosine kinase; SM, sphingomyelin; SMase, sphingomyelinase; SMS, sphingomyelin synthase; SPT, serine palmitoyltransferase; S1P, sphingosine 1-phosphate; 3KSR, 3-ketosphinganine reductase. Figure was created with BioRender.com.

METHODOLOGY

These study was done in 30 children patients' comparison with 30 healthy children. The concentration of the ceramide enzyme in the blood was measured using the ELISA technique. The measurement of urea, creatine, protein, albumin, calcium, cholesterol, as well as the iron level in the clinical chemistry unit was through the self-analysis technique, and the salt elements sodium, potassium, and chloride were measured using the Ion Selective device. As for measuring the blood level and taking a picture of the blood and knowing The hemoglobin level was in the hematology unit, and a high level of inflammation was observed by analyzing the CRP, as well as a high level of cells lymphocytes (pus cells) in urine analysis.

RESULTS

In this study, the results were monitored for patients and healthy children, and it was noted that the sick children had higher ceramide enzyme results compared to healthy children.

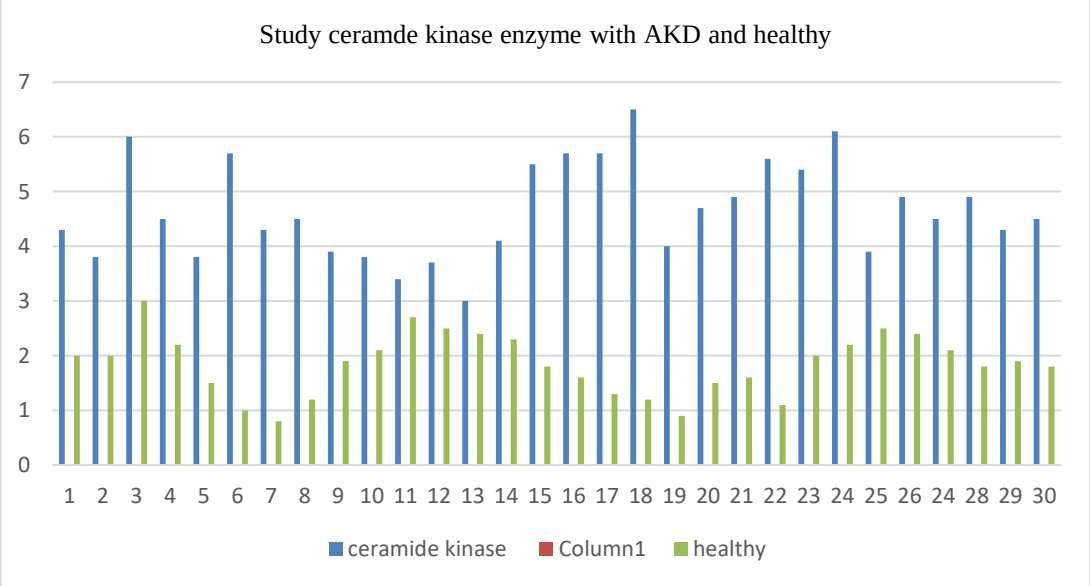

Figure 2: Comparison ceramide kinase between ACK and healthy.

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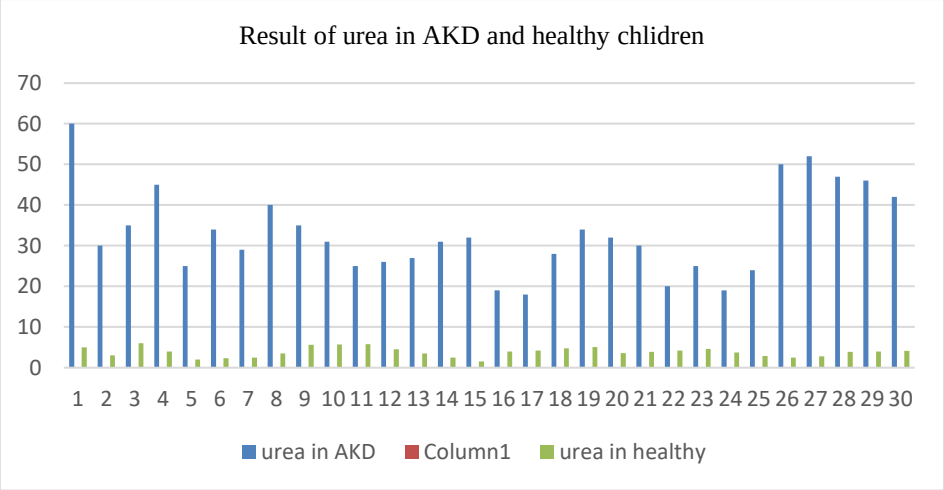

Figure 3: The result of urea in AKD comparison with healthy children.

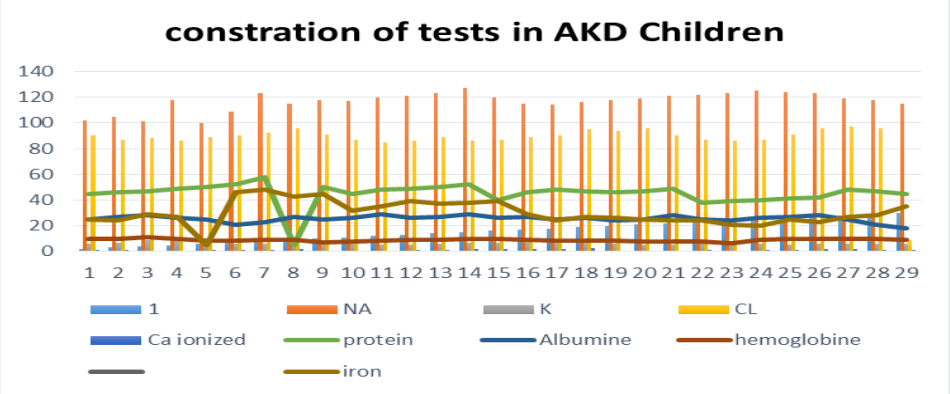

Figure 4: Concentration of urea, creatinine, albumin, protein, sodium potassium chloride and calcium ionized, iron, hemoglobin in AKD with healthy

DISCUSSION

In this result we shown that high concentration of ceramide kinase, creatinine, urea, protein, albumin, sodium, potassium, chloride, calcium ionized, hemoglobin and iron in AKD children that mean the low affinity of kidney nephron and can work well as the healthy kidney in children in same ages.

Although ceramides play a well-documented role in membrane structure and organization, we believe that their pleiotropic effects on cellular metabolism and survival serve an evolutionarily conserved purpose of sensing and responding to increasing intracellular free fatty acid levels. The injured kidney is subject to damage related to fatty acid (FA) overload,[80–83] secondary to both increased tubular uptake and impaired FA oxidation. This imbalance in lipid availability and utilization provokes a shift toward increased storage of FAs as inert triglyceride, which is likely not pathogenic.[84,85] However, insufficient storage or oxidation of amphipathic free FAs subjects cells to increased risk of membrane lysis and tissue injury. In response, modest increases in ceramides elicit a coordinated metabolic program to alleviate the FA burden by 1) enhancing FA esterification and storage as triglyceride and 2) decreasing mitochondrial efficiency, requiring consumption of a larger number of FA substrates to maintain the mitochondrial membrane potential (reviewed by Nicholson et al[86]). Further increases in ceramide levels stimulate a pivot toward programmed cell death and fibrosis processes to minimize overall damage to the tissue or organism caused by uncontrolled cell lysis.[86] The actions of ceramide to promote lipid accumulation and storage may not be pathogenic per se in the setting of kidney injury. Instead, more evidence suggests that mechanisms of ceramides inciting mitochondrial dysfunction and cell death may be influential features of AKI.

CONCLUSIONS

Thus far, the frontier of research exploring the metabolism and mechanisms of ceramides within the kidney remains minimally explored. Preliminary evidence points to complex cellular and spatial organization regulating ceramide metabolism in the kidney. Yet, significant challenges in the fields of sphingolipid and renal metabolism have stalled scientific advancements in this area. For example, progress in spatial and single-cellular proteomic and lipidomic profiling has lagged behind transcriptomic methods. Development and optimization of these technologies will allow for in-depth characterization of ceramide

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distribution within healthy kidneys and their relation to injured cell signatures. Furthermore, many proposed actions of ceramides are likely related to post-translational, rather than transcriptional, mechanisms. Methodologies to probe for lipid-protein interactions on the molecular level and within subcellular compartments will provide valuable context to ceramide-driven pathology in AKI. Lastly, interventional studies using pharmacologic inhibitors of ceramide-metabolizing enzymes often are complicated by direct renal toxicity of the compound (eg, fumonisin B1, amitriptyline) or its dependence on renal clearance (eg, cycloserine). Development of more specific and potent inhibitors will rely on ongoing characterization of target enzymes' high-resolution structural information. Lastly, genetic manipulation of ceramide metabolism within the kidney has been minimally exercised. Because of the established roles of sphingolipids in development, these studies will require inducible transgenic manipulations of ceramides within specific kidney cell types.

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