بسم الله الرحمن الرحيم

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بقسم التوثيق الإلكتروني بمركز الشبكات وتكنولوجيا المعلومات دون أدنى مسئولية عن محتوى هذه الرسالة.

ملاحظات: ....

The effect of sodium bicarbonate supplementation on serum alpha klotho in chronic kidney disease patients stage 3b to 4

Thesis

Submitted for partial fulfillment of Master Degree in Internal Medicine & Nephrology

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تأثير مكملات بيكربونات الصوديوم على مصل ألفا كلوثو في مرضى أمراض الكلى المزمنة في المرحلة ٣b إلى ٤

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توطئة للحصول علي درجة الماجستير في الطب الباطني وأمراض الكلى

مقدمة من

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Contents

List of Abbreviations

Abb.	Full term
ACE-i	Angiotensin converting enzyme inhibitor
ACR	Albumin creatinine ratio
ADH	Antidiuretic hormone
ADPKD	Autosomal dominant polycystic kidney disease
AKI	Acute kidney injury
ARB	Angiotensin receptor blocker
ATN	Acute tubular necrosis
AVF	Arteriovenous fistula
BUN	Blood urea nitrogen
CKD	Chronic kidney disease
CKD-EPI	Chronic kidney disease epidemic collaboration
CNS	Central nervous system
CrCl	Creatinine clearance
CRIC	Chronic renal insufficiency cohort
CVD	Cardio vascular disease
ECM	Extra cellular matrix
eGFR	Estimated glomerular filtration rate
ESA	Erythropoietin stimulating agent
ESRD	End stage renal disease
FDA	Food drug administration
FGF	Fibroblast growth factor
FGFR	Fibroblast growth factor receptor
GN	Glomerulonephritis
KDIGO	Kidney disease improving global outcomes
KDOQI	Kidney disease outcomes quality initiative
MTHFS	Methenyltetrahydrofolate synthetase
NHE	Na hydrogen exchanger
OPC	Outpatient clinic
PTH	Parathyroid hormone
RAAS	Renin angiotensin aldosterone system
RRT	Renal replacement therapy
SCN	Sickle cell nephropathy
SPSS	Statistical package for social sciences

Abb.	Full term
TRPC	Transient receptor potential channel
TRPV	Transient receptor potential channel of vanilloid subtype
VBG	Venous blood gas

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INTRODUCTION

The Klotho proteins, αKlotho and βKlotho, are essential components of endocrine fibroblast growth factor (FGF) receptor complexes, as they are required for the high-affinity binding of FGF19, FGF21 and FGF23 to their FGF receptors (FGFRs). ***(Dalton et al., 2017)***

Collectively, these proteins form a unique endocrine system that governs multiple metabolic processes in mammals.

FGF23 is secreted by osteocytes in response to phosphate intake and binds to αKlotho–FGFR complexes, which are expressed most abundantly in renal tubules, to regulate mineral metabolism.

The present study is aiming to ascertain the potential significance of oral sodium bicarbonate supplementation on soluble α-Klotho serum levels in chronic kidney disease (stage 3b:4) according to CKD-EPI formula.

Growing evidence suggests that the FGF–Klotho endocrine system also has a crucial role in the pathophysiology of ageing-related disorders, including diabetes, cancer, arteriosclerosis and chronic kidney disease.

Therefore, targeting the FGF–Klotho endocrine axes might have therapeutic benefit in multiple systems; investigation of the crystal structures of FGF–Klotho–FGFR complexes is paving the way for the development of drugs that can regulate these axes. ***(Citterio et al., 2020)***

FGF23 is a phosphaturic hormone; increased FGF23 levels in patients with early-stage chronic kidney disease or elderly individuals is indicative of excess phosphate intake relative to the residual nephron number.

Serum levels of FGF21 increase in patients with CKD, as early as stage 2, and continue to rise with declining renal function.

A few studies have reported that klotho deficiency is associated with hypertension, salt-sensitive hypertension, CKD, arterial stiffness, and cardiomyopathy. ***(Jamal et al., 219)***

Therefore, evaluation of circulating Klotho concentrations or klotho genotypes could help identify patients at higher risk of developing age-related cardiovascular morbidities. ***(Amaro-Gahete et al., 2020)***

Klotho concentration, blood pressure, and arterial stiffness were highly dependent on age and other cardiovascular risk factors, such as diabetes mellitus, cigarette smoking, CKD, and metabolic syndrome. ***(Zoccali et al., 2044)***

CKD is known to be related to cardiac overload, which reconfigures the architecture and physiology of the myocardium, inducing hypertrophy and fibrosis. ***(Dubin et al., 2017)***

These alterations appear in the early stages of the disease and are aggravated with worsening kidney disease, compromising cardiac function and inducing the development of cardiovascular disease (CVD) ***(Xu et al., 2016)***.

Recently, Xie et al. demonstrated that Klotho may inhibit cardiac TRPC6 channels, thereby protecting the myocardium against excessive pathological remodeling . ***(Xie et al., 2012)***

The specific actions of Klotho are still being investigated, but it appears that Klotho relies on its enzymatic properties to act as a major regulator of ion transport and growth factor signaling. ***(Xie et al., 2015)***

For instance, Klotho has been shown to reduce stress-induced cardiac hypertrophy by inhibiting cardiac TRPC6 channels in cardiomyocytes, as well as to stimulate TRPV5 receptors in the renal distal tubules, thus allowing the regulation of phosphate metabolism independently of calcium levels. ***(Wolf et al., 2014; Wu et al., 2016)***

The elucidation of Klotho and FGF-23-mediated functions in CKD paved the way for the development of targeted therapies.

For instance, Di Marco et al. showed that the progression of cardiac hypertrophy and cardiac fibrosis could be reduced by antibody-mediated blockage of the FGF receptor. ***(Di Marco et al., 2014)***

Recently,alarge randomized study providing sodium bicarbonate supplementation slowed the rate of decline of renal function as assessed by CrCl to 1 mL/minute/year as compared with 2.5 mL/minute/year in untreated patients. It also significantly reduced the number of patients who progressed to end-stage renal disease. ***(De Brito-AshurstI et al., 2009; Kalantar-Zadeh and Fouque. 2017)***

The fact that serum a-Klotho is reduced during chronic acidosis might be paralleled with the increased mortality described in CKD patients' clinical reports. ***(Marcais et al., 2017).***

Aim of the work

To evaluate the effect of oral sodium bicarbonate supplementation on soluble α-Klotho serum levels in chronic kidney disease (stage 3b:4) according to CKD-EPI formula.