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

ملاحظات:
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Comparative study evaluating the effect of the administration of vitamin K1 versus placebo on vascular calcification in Haemodialysis patients

Thesis

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Contents

List of Abbreviations

Abb.	Full term
ACS	Acute coronary syndrome
ADMA	Asymmetric dimethyl arginine
CAC	Coronary artery calcification
CARE	Cholesterol and recurrents events
CaRs	Calcium-sensing receptors
CHF	Congestive heart failure
CKD	Chronic kidney disease
CVCs	Cardiovascular calcifications
CVD	Cardiovascular disease
DM	Diabetis mellitus
EBCT	Electron beam computed tomohraphy
EDTA	Ethylene diamine tetraaectic acid
ESRD	End stage renal disease
FGF-23	Fibroblast growth factor 23
GFR	Glomerular filtration rate
HD	Hemodialysis
HTN	Hypertension
ISHD	Ischemic heart disease
LVH	Left ventricular hypertrophy
MGP	Matrix gla protein
MSCT	Multislice comouted tomography
OPN	Osteoprotegerin
PD	Peritoneal dialysis
PTH	Parathyroid hormone
RAAS	Renin angiotensin aldosterone system
RRT	Renal replacement therapy
SCD	Sudden cardiac death
VDRAs	Vitamin d receptor agonists

List of Table

Table No	Subjects	Page

List of Figures

Figure No	Subjects	Page

INTRODUCTION

Cardiovascular calcification is a risk factor and contributor to morbidity and mortality in End stage kidney disease patients. Patients with chronic kidney disease develop accelerated calcification of the intima, media, heart valves and myocardium as well as the rare condition of calcific uremic arteriolopathy (calciphylaxis). Pathomechanistically, Cardiovascular calcification is most likely due to an imbalance of promoters (e.g. Calcium and phosphate) and inhibitors (e.g. fetuin-A and matrix Gla protein) ***(Schlieper et al., 2015).***

Cardiovascular mortality progressively increases with advancing chronic kidney disease (CKD) and loss of renal function.

In dialysis patients, Cardiovascular issues are the most frequent cause of death and most patients starting renal replacement therapy have abnormal cardiovascular function and dimensions. Traditional risk factors such as hypercholesterolemia or arterial hypertension fail to explain these observations, pointing to an added role of non-traditional risk factors such as uremia, disordered mineral-bone disease, premature senescence of cardiovascular tissues, inflammatory and oxidative stress and others ***(Schlieper et al., 2015).***

Here, we review the latest insights on, cardiovascular calcifications in CKD, which become highly prevalent as CKD progresses and which are strong predictors of cardiovascular mortality in CKD patients ***(Ketteler et al., 2006).***

It has been argued that cardiovascular calcification in CKD is mostly a consequence of vascular inflammation and therefore does not constitute a relevant targeted treatment ***(Zoccali et al., 2015).***

However, inflammation is not a major feature of degenerative calcification. In addition, measures that experimentally reduce CKD-associated vascular calcification and do not necessarily involve effects on inflammatory processes ***(Finch et al., 2015).***

We acknowledge that there is currently a variety of data to confirm this in patients with CKD and surely the problem exists that therapeutic measures that affect calcification in CKD patients usually have a broad array of actions and consequences.

Arteriosclerosis is the first cardiovascular change observed in patients with CKD which is characterized by arterial stiffening and calcification, left ventricular diastolic dysfunction, and left ventricular hypertrophy. Atherosclerotic plaque formation often occurs later or simultaneously with initial cardiovascular changes aggravated by CKD ***(Youn et al., 2009).***

Understanding the molecular mechanisms that cause vascular calcification in CKD patients is important to limit vascular calcification and hence mortality. It is known that the extracellular fluid is a mixture of fluids and electrolytes with regard to calcium and phosphate Concentrations and that active inhibitors of calcification must be present, both locally and circulating in blood stream, to prevent the spontaneous formation of apatite which is the main component of the mineral phase: a situation that certainly occurs to the CKD patients. The inhibition process involves vascular smooth muscle cells and a number of proteins, some of which are vitamin K-dependent ***(Nguyen et al., 2012).***

Vitamin K functions as an enzyme cofactor for the carboxylation of vitamin K–dependent proteins involved in many physiological processes, including vascular calcification. Although various vitamin K–dependent proteins have been identified in vascular tissue and have also been implicated in arterial calcification and CVD, the most studied is matrix gla protein (MGP). This is due to the availability of animal models and biochemical assays that can measure the protein in tissue and circulation ***(Tesfamariam 2019).***

Like all vitamin K–dependent proteins, MGP is synthesized in its uncarboxylated form (ucMGP) ***(Barone et al., 1991).***

In the presence of vitamin K, it is carboxylated (cMGP). It is only the cMGP form that inhibits vascular calcification ***(Price et al., 1998).***

Given that MGP is an important protein in the process of inhibition of abnormal calcification in the vessels and that vitamin K is crucial for MGP function, it has been proposed that vitamin K has a role in the complications of CKD that are associated with abnormal calcification, including arterial Calcification, stiffening, and CVD ***(Sedaghat et al., 2015).***

It is also possible vitamin K influences CKD development and progression indirectly through mechanisms linked to abnormal calcification ***(Ford et al., 2010)***.