INTRODUCTION

Patients with chronic kidney disease (CKD) have a high prevalence of vascular calcification (VC), and cardio-vascular disease (CVD) is the leading cause of death in this population. However, the molecular mechanisms of vascular calcification, which are multifactorial, cell-mediated and dynamic, are not yet fully understood ***(Francisco and Rodríguez, 2013).***

The cardiovascular mortality of patients on maintenance hemodialysis is more than 10-fold higher compared with the normal population ***(Nemcsi et al., 2012).***

Understanding the pathogenesis of vascular calcification is essential, as it is a frequent cause of morbidity and mortality for patients with CKD. Indeed, vascular calcification occurs in all ages and stages of CKD ***(Shroff et al., 2011)***.

Interestingly, not all dialysis patients develop arterial calcification, and importantly, do not develop calcification with increased duration of dialysis. These findings imply that there are protective factors, either in the blood vessels or in the circulation, or both ***(Oliveira et al., 2013).***

Magnesium (Mg) is one of the major intracellular cations. It is a vital element in human metabolism and general body function. Developments in methods to monitor this element have provided an improved understanding of its role in various diseases, particularly in CVD ***(Covic, 2010).***

Magnesium is considered to be ‘a natural calcium antagonist’, as one of its major functions in biological systems is to modulate the neuromuscular activity of calcium ions. Thus, contractility of all types of muscles is dependent upon the actions and interactions of these two divalent cations. The magnesium ion can block calcium movement across vascular smooth muscle cell (VSMC) membranes and lower peripheral and cerebral vascular resistance ***(Massy and Drüeke, 2012).***

Although, the mechanism of VC is multifactorial, it is now evident that Mg depletion is involved in the pathogenesis of VC. It seems that Mg depletion may be the missing link between multiple cardiovascular risk factors and the development of atherosclerosis ***(Nassiri and Hakemi, 2013)*.**

Mg, in the form of magnesium carbonate ($MgCO_3$), is a promising oral phosphate binder for the treatment of hyperphosphatemia in patients with stage 5 CKD who are receiving haemodialysis ***(Covic, 2010).***

AIM OF THE WORK

The aim of this work was to assess the relationship between serum magnesium levels, and vascular stiffness in children with CKD on regular hemodialysis.

CHRONIC KIDNEY DISEASE

Background

Chronic kidney disease (CKD) is a life-threatening condition characterized by progressive and irreversible loss of renal functions that progresses to end-stage renal disease (ESRD). The increasing inability of the kidneys to properly clear the blood of waste products eventually results in the implementation of dialysis (or kidney transplant) in order to prevent azotemia, systemic organ damage and death ***(Gheissari et al., 2013).***

Definition

CKD is defined by a presence of kidney damage (for example, any structural or functional abnormality involving pathological, laboratory or imaging findings) for ≥ 3 months or a glomerular filtration rate (GFR) <60 ml /min / 1.73 m^2 for ≥ 3 months ***(Collins et al., 2011).***

Note that the above definition is not applicable to children younger than 2 years, because they normally have a low GFR, even when corrected for body surface area. In these patients, calculated GFR can be compared with normative age-appropriate values to detect renal impairment ***(Eddy, 2009).***

Etiology of CKD

In a recent report from the North American Pediatric Renal Transplant Cooperative Study (NAPRTCS) congenital causes, including congenital anomalies of the kidney and urinary tract (CAKUT) (48%) and hereditary nephropathies (10%), were the most common causes of CKD. Glomerulonephritis accounted for 14% of cases of CKD ***(Harambat et al., 2012).***

The distribution of causes varied with age. Whereas CAKUT predominate in younger patients, glomerulonephritis is the leading cause of CKD in children older than 12 years of age. Causes of CKD vary across races, for example, focal segmental glomerulosclerosis, the main cause of glomerular disease, was three times more common in blacks than in whites (19 vs 6%) and especially among black adolescents (35%) ***(Harambat et al., 2012).***

Table (1): Etiology of chronic kidney disease

1. Glomerular diseases	• Primary Glomerular disease such as: ➢ Glomerulonephritis. ➢ Focal segmental glomerulosclerosis. ➢ Alport syndrome. • Secondary Glomerular disease such as: ➢ Diabetic nephropathy. ➢ Lupus nephritis.
2. Obstructive diseases	• Posterior uretheral valves (PUV). • Pelvi-ureteric junction obstruction (PUJ). • Uretheral strictures. • Bilateral kidney stones.
3. Vascular diseases	• Large vessel disease such as: ➢ Bilateral renal artery stenosis. • Small vessel disease such as: ➢ Ischemic nephropathy. ➢ Hemolytic-uremic syndrome. ➢ Vasculitis.
4. Tubulointerstitial diseases	• Polycystic kidney disease. • Drug and toxin-induced chronic tubulointerstitial nephritis. • Reflux nephropathy.

(Collins et al., 2011)

Incidence and prevalence of CKD:

The prevalence of CKD in the pediatric population is approximately 18 per 1 million. The rate of ESRD incidence increases with age such that approximately 75 % of pediatric patients with ESRD are between the ages of 10-19 ***(Harambat et al., 2012)*.**

The higher prevalence of childhood CKD in the Middle-East can be attributed to the high rate of consanguineous

marriage that is culturally acceptable in this region. Besides, some predisposing genetic risk factors may also exist in this ethnic group. The socio-economic effects of the disease are greater in low and middle-income countries compared with the developed world ***(Gheissari et al., 2013).***

CKD staging

It is important to note that the CKD stages only apply to children 2 years old and above, because children younger than 2 years normally have a low GFR, even when corrected for body surface area. In these patients, calculated GFR based on serum creatinine can be compared with normative age-appropriate values to detect renal impairment. The following table shows staging of CKD into 5 stages, based on the level of estimated GFR (eGFR) ***(Harambat et al., 2012).***

Table (2): Classification of chronic kidney disease

Stage	eGFR (mL/min/1.73 m^2)	Description
1	90 or greater	Normal or increased eGFR, with evidence of kidney damage.
2	60–89	Slight decrease in eGFR, with evidence of kidney damage.
3A	45–59	Moderate decrease in eGFR, with or without other evidence of kidney disease.
3B	30–44	
4	15–29	Severe decrease in eGFR, with or without other evidence of kidney disease.
5	Less than 15	Established renal failure (end-stage renal disease).

(Harambat et al., 2012)

Table (3): Normal GFR in children and adolescents

Age	Mean GFR ± SD (mL/min/1.73 m^2)
1 week (males and females)	41±15
2–8 weeks (males and females)	66±25
>8 weeks (males and females)	96±22
2–12 years (males and females)	133±27
13–21 years (males)	140±30
13–21 years (females)	126±22

(Warady and Chadha, 2007)

Manifestations of CKD

CKD is asymptomatic in its earliest stages, although urinalysis findings or blood pressure may be abnormal. As CKD progresses to more advanced stages, signs and symptoms greatly increase ***(Eddy, 2009).***

Table (4): Clinical manifestations of CKD

1	Hematological abnormalities: • Anemia. • Bleeding.
2	Growth failure.
3	Renal osteodystrophy.
4	Gastrointestinal manifestations.
5	Nervous system abnormalities: • Peripheral neuropathy. • Encephalopathy.
6	Cardiovascular abnormalities: • Hypertension. • Myocardial dysfunction. • Pericardial disease.
7	Infections.
8	Acid-base disturbances.
9	Fluid and electrolyte disorders.
10	Nutritional disorders.
11	Psychological disorders.

(López-Novoa et al., 2010)

The most common manifestations of CKD will be discussed:

1. Hematological Manifestations

a) Anemia:

Table (5): Pathogenic factors of anemia of CKD

Decreased erythropoiesis.
Reduced availability of erythropoietin.
Inhibitor(s) of erythropoiesis.
Bone marrow fibrosis.
Shortened red blood corpuscles (RBCs) survival due to chronic uremia.
Hemolysis due to extracorpuscullar factor(s).
Chronic blood loss from frequent laboratory testing and from the gastrointestinal tract.
Deficiency • Iron deficiency. • Folic acid deficiency. • Vitamin B12 deficiency. • Vitamin C deficiency which could interfere with the production of healthy RBCs. • Carnitine deficiency might also decrease the survival of RBCs as it increases the membrane fragility of RBCs.
These factors seem to be exacerbated by: • Hyperparathyroidism. • Infection. • Malnutrition. • Oxidant substances or drugs. • Microangiopathy. • Hypersplenism.

(Greenbaum et al., 2009)

b) Bleeding disorders:

Renal failure is associated with severe haemorrahgic complications. The bleeding tendency is characterized by prolonged bleeding time, and it is rarely of clinical consequence before the GFR falls below 15% ***(Shroff et al., 2011).***

The pathogenesis of uremic bleeding is multifactorial, the platelet count in uremia is usually normal, whereas platelet function is impaired, and the major defects involve platelet-vessel wall and platelet-platelet interactions ***(Navaneethan et al., 2009).***

2. Cardiovascular Manifestations:

Cardiovascular disease (CVD) is a significant cause of morbidity and mortality in children with ESRD ***(Chavers et al., 2011).***

a) Hypertension (HTN):

Hypertension is one of the most common sequelae of CKD in children. Blood pressure is one of the most critical determinants of the progression rate of renal failure in children, and cardiovascular mortality in childhood onset renal failure. Therefore, good antihypertensive management can substantially contribute to better patient survival of adults with childhood-onset CKD ***(Hadtstein and Schaefer, 2008).***

Table (6): Causes of hypertension in dialyzed children

• Extracellular volume overload and sodium retention**.**
• Inappropriate high renin–angiotensin system (RAS) in relationship to high volume and sodium body content leading to increased vasoconstriction.
• Sympathetic overactivity.
• Impaired endothelium-dependent vasodilatation with reduced synthesis of nitric oxide (NO) and increased levels of vasoconstrictors.
• Genetic factors.
• Iatrogenic factors (e.g. steroids for primary disease).
• Secondary hyperparathyroidism.
• High dialysate sodium concentration.
• Inadequate dialysis regimen.

(Narchi, 2011)

b) Cardiac Problems:

Although thought to be subclinical, alterations in cardiac structure and function are present in the early stages of pediatric CKD and progress over time ***(Shroff et al., 2011).***

i- Uremic cardiomyopathy

Uremic cardiomyopathy often involves cardiac dysfunction, which may be associated with congestive heart failure. Heart failure may be caused by uncontrolled sodium retention and aggravated by anemia, hypertension and other metabolic derangements associated with uremia, such as chronic elevation of parathyroid hormone ***(Tonelli et al., 2011).***

ii- Pericardial disease

Pericarditis has generally been considered to be an uncommon complication of CKD. Clinical manifestations of uremic pericarditis include: fever, pain, friction rub, leucocytosis, cardiomegaly, cardiac arrhythmias and cardiac failure ***(Hemmelgarn et al., 2010).***

3. Neurological manifestations:

- ***Uremic polyneuropathy:***

Clinical findings

- Commonly begins with the "restless legs syndrome" with sensations of creeping, crawling, prickling, or itching in the lower extremities.
- Burning paresthesias, tenderness, and swelling of the feet may also be seen and is known as "burning foot syndrome".
- Progression to sensory-motor loss in the legs.
- Loss of sensation distally and diminution of deep tendon reflexes.
- In rare cases, the polyneuropathy exhibits a more acute clinical course and may present similar to Guillain-Barre syndrome.

(Palmer, 2007)

- ***Hypertensive encephalopathy:***

A sudden and severe elevation of blood pressure can result in intracranial arteriolar necrosis and cerebral edema, causing headache and seizures. Such hypertensive crises often occur in patients with advanced CKD and can be aggravated by corticosteroid therapy ***(Van Buren and Inrig, 2012).***

- ***Uremic encephalopathy:***

Uremic encephalopathy presents with manifold symptoms ranging from headache, visual abnormalities, tremors, asterixis, multifocal myoclonus, chorea and seizures to clouding of consciousness and coma. The pathophysiology of uremic encephalopathy is poorly understood and the name 'uremic' is historical and does not depict the cause of the disease ***(Tonelli et al., 2011).***

4. Infections:

Children with ESRD who receive chronic hemodialysis (HD) are at increasing risk of serious infections as a result of: uremia, inadequate nutrition, impaired immunologic defenses. Furthermore, the presence of an indwelling venous catheter or an arteriovenous shunt adds an additional risk to the patient receiving HD ***(Greenbaum et al., 2009).***

5. Acid - base disturbances:

Metabolic acidosis is always present in patients with CKD due to retention of acid metabolites such as sulfate, phosphate and other organic acid anions that are retained due to decreased GFR. Metabolic acidosis is inevitable once the reduction of GFR exceeds 50% ***(Hemmelgarn et al., 2010).***

6. Electrolytes disturbances:

a) Sodium:

Most children with CKD maintain normal sodium and water balance. However, infants and children whose renal failure is a consequence of renal dysplasia may be polyuric with significant urinary sodium losses. These children may benefit from high volume, low caloric density feeding with sodium supplementation. On the other hand, children with high blood pressure, edema, or heart failure may require sodium restriction and diuretic therapy ***(Moysés et al., 2010).***

b) Potassium:

In most children with CKD, potassium (K) balance is maintained until renal function deteriorates to the level at which dialysis is initiated. Hyperkalemia may develop, however, in patients with moderate renal insufficiency who have excessive dietary potassium intake, severe acidosis, tissue damage (e.g. haemolysis, sepsis) or hyporeninemic hypoaldosteronism ***(Tonelli et al., 2011).***

c) Calcium:

Both dietary calcium (Ca) uptake and urinary calcium excretion are decreased in children with CKD. Net gastrointestinal calcium absorption is low as a result of decreased circulating 1,25-dihydroxy vitamin D_3 levels. Increased secretion of parathyroid hormone (PTH) augments both bone calcium release and renal calcium reabsorption ***(Moysés et al., 2010).***

d) Phosphorus:

Normal serum phosphorus levels are usually maintained in patients with mild to moderate CKD by increasing urinary phosphate excretion. However, hyperphosphatemia develops when the GFR declines to 25 to 30% of normal. Hyperphosphatemia promotes the secretion of PTH ***(Mejia et al., 2011).***

7. Psychological disorders:

Pediatric patients with CKD are liable to mental disorders. Additionally; their quality of life is significantly impaired when compared to the general population. This fact is due to the demands and restrictions brought on by the clinical condition, the disruptions in the family dynamics, and the troublesome treatment ***(Hooper et al., 2011).***

8. Mineral and bone disorder (MBD):

Disturbances in mineral and bone metabolism in children with CKD lead to specific abnormalities of skeletal homeostasis called CKD–mineral and bone disorder (CKD-