INTRODUCTION

Worldwide, the prevalence of vitamin D deficiency is as high as almost 50% among the elderly. A recent meta-analysis showing that vitamin D supplementation significantly decreased all-cause mortality raised the public health interest in vitamin D. the classic role of vitamin D for maintaining bone health was recently extended by reports linking vitamin D deficiency to various other diseases, including arterial hypertension and diabetes mellitus ***(Foramen et al., 2007).*** It also turned out that the myocardium is an important target tissue for vitamin D-mediated effects on a genomic and non-genomic level ***(Nibbelink et al., 2007)***. Cardiomyocytes express the vitamin D receptor, and studies in rodents have shown that vitamin D protects against cardiac hypertrophy and myocardial dysfunction ***(Mosekilde et al., 2005).***

Heart failure is a complex clinical syndrome characterized by impaired myocardial performance and progressive activation of the neuroendocrine system leading to circulatory insufficiency and congestion. The major pathophysiologic process in the progression of heart failure appears to be cardiac remodeling, often referred to as progressive chamber enlargement over time and obligatory reduction in Ejection Fraction ***(McMurray et al., 2013)***. It is important to accurately define prognostic factors in patients with heart failure to identify the high-risk individuals who require closer follow-up and more intensive intervention.

Although many studies have reported that renal insufficiency is associated with adverse cardiovascular outcomes, renal dysfunction is still an underappreciated prognostic factor in heart failure and renal insufficiency is commonly viewed as a relative contraindication to some proven efficacious therapies ***(Dries et al., 2000*)**. The mechanisms by which decreased renal function is correlated with cardiovascular disease are unknown. It is unclear if cardiac pump failure secondarily leads to diminished renal function or if mild renal dysfunction leads to progression of functional cardiac deterioration. The term cardiorenal syndrome (CRS) is used to describe a condition characterized by kidney failure and heart failure. The primarily failing organ may be either the heart or the kidney. The cardiorenal syndrome is divided by *Ronco et al.* into five subtypes**:**

- Type 1 describes acute decompensated heart failure leads to acute kidney injury.
- Type 2 is characterized by chronic heart failure that leads to chronic kidney disease.
- Type 3 describes acute kidney injury that leads to acute cardiac dysfunction or heart failure.
- Type 4 is characterized by primary chronic kidney disease that contributes to cardiac dysfunction.
- Type 5 is combined heart and kidney dysfunction due to systemic disorders such as sepsis.

(Ronco et al., 2008)

The association between vitamin D and cardiovascular disease events is widely debated and analyzed in the recent literature. In a very recent cross-sectional study, *Pilz et al* measured 25(OH)D [25(OH)Vitamin D] levels in 3,299 Caucasian patients who were routinely referred for coronary angiography. They found that vitamin D is associated with prevalent myocardial dysfunction, heart failure, and sudden cardiac death ***(Pilz et al., 2008*).** Although the link between vitamin D deficiency and cardiovascular disease may be, in part, mediated through elevated PTH and calcium-phosphate metabolism, recent scientific evidence showed that vitamin D has 3 major potential protective mechanisms First, experimental studies indicate that 1,25 (OH) vitamin D could directly suppress renin gene expression ***(Li et al., 2003).*** Second, the presence in the cardiac muscle cells of a vitamin D receptors, a calcitriol-dependent Calcium binding protein and a calcitriol-mediated rapid activation of voltage-dependent calcium channels ***(Nibbelink at al., 2007; Tiskoff et al., 2008).*** Third, vitamin D deficiency triggers secondary hyperparathyroidism, which then directly promotes cardiac hypertrophy ***(Simpson et al., 2007).***

However, despite the suggested relation between vitamin D deficiency and cardiac function, the relation between vitamin D deficiency and the echocardiographic predictors of cardiac functions in patients with heart failure, to the best of our knowledge, has not been studied yet.

Aim of the Work

Accordingly, we aim to study the relation between serum 25-hydroxy vitamin D levels and parameters of cardiac systolic and diastolic function in patients with cardio renal syndrome.

PHYSIOLOGY OF VITAMIN D

Introduction:

Vitamins are chemically unrelated families of organic compounds that are essential in small amounts for normal metabolism. Because vitamins (with the exception of vitamin D) cannot be synthesized by humans, they need to be ingested in the diet to prevent disorders of metabolism ***(Wolf et al., 2004).***

Vitamins are divided into water-soluble and fat-soluble, vitamin D is a fat-soluble vitamin, vitamin D is unique because it can be ingested as cholecalciferol (vitamin D_3) or ergocalciferol (vitamin D_2) and also the body can also synthesize it (from cholesterol) when sun exposure is adequate (hence its nickname, the "sunshine vitamin") ***(Wolf et al., 2004).*** Vitamin D works like a hormone because it is produced primarily in one organ (the kidney) before circulating through the blood stream to organs where it has wide-ranging effects ***(Holick et al., 2007).***

Actually it's a pro hormone that is synthesized in the skin after exposure to ultraviolet radiation. Less than 10% of vitamin D comes from dietary sources in the absence of food fortification or use of supplements. The pro hormone is then converted to the metabolically active form in the liver and kidneys ***(Wolf et al., 2004).***

Vitamin D has received a great deal of attention late in the scientific literature. Scores of mostly observational studies have investigated the possible role of vitamin D in the prevention of chronic diseases ranging from cancer to CVD to autoimmune disorders & infections. No one doubts that vitamin D is essential to the health of older adults; the abundance of vitamin D receptor binding sites throughout the human genome highlight the pleiotropic nature of vitamin D in the human body ***(Ramagopalan et al., 2010).***

Deficiency of vitamin D (commonly referred to as "rickets" when it occurs in children) is of unique historical value. Rickets was first described in the mid **1600s** by Whistler and Glisson ***(Fraser and Scriver, 1979).***

But for decades thereafter, no progress was made in identifying the cause. In **1918**, Sir Edward Mellanby described the deficiency of a fat-soluble nutrient as the cause for rickets ***(Mellanby et al., 1918).***

Shortly thereafter, Goldblatt and Soames demonstrated that skin exposed to sunlight or ultraviolet light produced a substance with similar properties to this fat-soluble nutrient ***(Goldblatt and Soames, 1923).***

This ultimately led to the discovery of the chemical structure of vitamin D by Windaus ***(Windaus et al., 1936).***

Vitamin D and its metabolites have a significant clinical role because of their interrelationship with Calcium homeostasis and bone metabolism. Rickets due to vitamin D deficiency is now rare except in populations with unusually low sun exposure and lack of vitamin D in fortified foods ***(Das et al., 2006).***

Subclinical vitamin D deficiency, as measured by low levels of 25(OH)D, has been described among adolescents**,** and the elderly**,** and may contribute to the development of osteoporosis and an increased risk of fractures and falls in the elderly ***(Lips et al., 2006).***

Moreover, sufficient concentrations of vitamin D may be important in reducing the occurrence of autoimmune diseases, such as multiple sclerosis**,** rheumatoid arthritis, diabetes and some cancers ***(Garland et al., 2009).***

Adequate vitamin D may also allow for a normal innate immune response to pathogens, improve cardiovascular function and mortality and increase insulin responsiveness ***(Mason et al., 2011).***

Forms & structure:

1- Vitamin D2 (Ergocalciferol).

2- Vitamin D3 (Cholecalciferol).

3- Calcidiol, 25-hydroxycholecalciferol.

4- Calcitriol, 1, 25-hydroxycholecalciferol.

Vitamin D_2 has low affinity for the vitamin D-binding protein makes it nearly **ten times** less effective than Vitamin D_3 at raising long-term vitamin D levels ***(Laura et al., 2004).***

Sources of vitamin D:

1. Sun exposure:

The major source of vitamin D is sunlight exposure. It contributes **80%** to **90%** of vitamin D supply in free-living persons ***(Wolf et al., 2004).***

Exposure to **one** minimal erythemal dose (**MED**) in a bathing suit is equivalent to **~20,000** international unit **(**IU) vitamin D. Thus, exposure of arms and legs to **0.5** MED is equivalent to ingesting **~3,000** IU vitamin D ***(Holick et al., 2007).***

Ultraviolet (UV) B radiation with a wavelength of **290–315** nanometers penetrates uncovered skin and converts cutaneous **7**-dehydrocholesterol to pre-vitamin D_3, which in turn becomes vitamin D_3 ***(Wolf et al., 2004).***

2. Food:

Dietary vitamin D intake is usually below **5** µg daily ***(Zittermann et al., 2003),*** and **1** µg vitamin D increases circulating 25(OH) D concentrations by approximately **1-3**nmol/L ***(Vieth et al., 2009).***

Very few foods in nature contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources ***(Sidbury et al., 2008)***

Table (1): Dietary Sources of Vitamin D3 ***(Sidbury et al., 2008):***

Food	Cholesterol per 100g	Vitamin D per 100 g
Cod liver oil	570 mg	10,000 IU (up to 25,555 IU)
Herring	12.9 mg	680 IU
Oysters	54 mg	642 IU
Catfish	81 mg	500 IU
Sardines	142 mg	480 IU
Mackerel	95 mg	450 IU
Salmon	87 mg	320 IU
Caviar	588 mg	232 IU
Shrimp	173 mg	172 IU
Butter	218 mg	56 IU
Whole Egg (contained in Yolk only)	424 mg	49 IU

Metabolism and Feed Back Regulation:

Endogenously produced D3 can travel to the liver via D-binding protein (**VDBP**), while supplemented D2 or D3 is incorporated into micelles with dietary fats and the assistance of bile salts and primarily absorbed in the duodenum. D2 and D3 are transported in lymph via chylomicrons to the liver ***(Sidbury et al., 2008).***

- **Hepatic metabolism:**

Within the liver, the mono-oxygenase enzymes of the cytochrome P450 (**CYP**) family, and particularly CYP27A1 (25–hydroxylase), add a hydroxyl group to C-25, resulting in the formation of 25(OH)D or calcidiol.

There is some feedback regulation of the hepatic 25-hydroxylase, but it is insufficient to prevent vitamin D intoxication following the ingestion of large amounts of vitamin D. The liver is the usual storage system for vitamin D. When large amounts of vitamin D are ingested, much of the excess vitamin D is stored in adipose tissue.

The liver has the capacity to metabolize 25(OH)D to inactive metabolites. This is accomplished by the P-450 system and is enhanced by alcohol, barbiturates, and phenytoin ***(DeLuca et al., 2004).***

- **Renal metabolism:**

25Hydroxy vitamin (25OH) D2 and D3 produced by the liver enters the circulation and travels to the kidney, again bound to vitamin D binding protein. It is activated in the Kidney to 1, 25(OH) 2 vitamin D this protein has a single binding site, which binds vitamin D and all of its metabolites. Only **3** to **5%** of the total circulating binding sites are normally occupied; as a result, this protein is not rate-limiting in vitamin D metabolism unless large amounts are lost in the urine as in the nephrotic syndrome ***(DeLuca et al., 2004).***

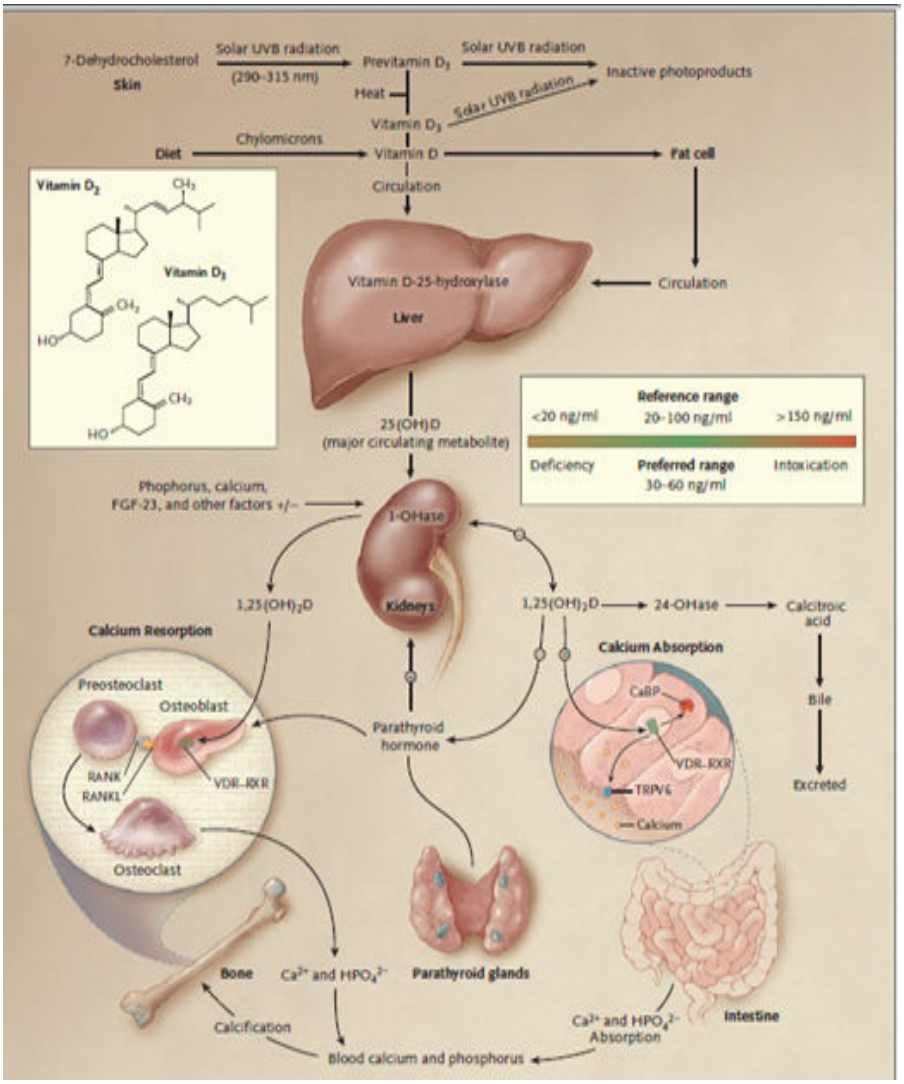

Figure (1): Synthesis and Metabolism of Vitamin D in the Regulation of Calcium, Phosphorus, and Bone metabolism ***(Holick et al., 2007).***

Mechanism of Action:

The circulating hormone 1, 25(OH) $_2$ D_3 crosses the cell membrane and cytoplasm and reaches the nucleus of the cell ***(Holick et al., 2007).***

Receptors for 1, 25(OH) $_2$ D_3 are situated in the nuclei of cells of multiple organs and activation of these receptors results in an increased expression of more than **200** genes, all of which increase the expression of CYP27B1. This can also be increased by immune inputs, such as those from Toll-like receptors (**TLRs**) signaling. The result of CYP27B1 expression, whether due to active vitamin D or an immune input, is the production of the intracellular proteins, which are ultimately responsible for the protean actions of vitamin D ***(Nibbelink et al., 2007).***

Functions of Vitamin D:

A. Skeletal function:

Calcium and Phosphorus balance:

It acts to increase the concentration of Calcium (Ca2+) in the blood, by acting upon parathyroid hormone receptor in **three** parts of the body:

A. It enhances the release of Calcium from the large reservoir contained in the **bones**. Bone resorption is the normal destruction of bone by osteoclasts, which are indirectly stimulated by PTH.

B. It enhances active reabsorption of Calcium and magnesium from distal tubules and the thick ascending limb of loop of Henell in the **kidney.**

C. It enhances the absorption of Calcium in the **intestine** by increasing action of intestinal plasma membrane pump.

(Deluca et al., 2004)

B. Non skeletal functions:

(1) Regulation of Proliferation and Differentiation:

Cells that are dividing rapidly are said to be proliferating. Differentiation results in the specialization of cells for specific functions. In general, differentiation of cells leads to a decrease in proliferation ***(Holick et al., 2003).***

While cellular proliferation is essential for growth and wound healing, uncontrolled proliferation of cells with certain mutations may lead to diseases like cancer. The active form of vitamin D inhibits proliferation and stimulates the differentiation of cells ***(Holick et al., 2003).***

(2) Regulation of Hormone Secretion:

Parathyroid hormone (PTH): Circulating PTH levels are better correlated with 25(OH) D levels than with 1, 25(OH) 2D, even though it is 1, 25(OH) 2D that inhibits the synthesis and secretion of PTH and prevents the proliferation of the parathyroid gland ***(Deluca et al., 2004).***

Insulin: In vitro and in vivo studies suggest that vitamin D can prevent pancreatic beta-cell destruction and reduces the

incidence of autoimmune diabetes. This may at least in part be due to a suppression of pro-inflammatory cytokines such as tumor necrosis factor (**TNF**)-α. ***(Liu et al., 2009).***

Fibroblast Growth Factor 23 (FGF23): FGF23 is produced primarily by bone, in particular by osteoblasts and osteocytes, 1, 25(OH) 2 D stimulates this process, but the mechanism is not clear ***((Liu et al., 2007).***

(3) Regulation of Immune Function:

Vitamin D in the form of 1, 25-dihydroxyvitamin D is a potent immune system modulator. The vitamin D receptor (**VDR**) is expressed by most cells of the immune system, including T cells and antigen-presenting cells, such as dendritic cells and macrophages ***(Liu et al., 2005).***

(4) Blood Pressure Regulation:

The renin-angiotensin system (RAS) plays an important role in the regulation of blood pressure.

Renin is an enzyme that catalyzes the cleavage (splitting) of a small peptide (Angiotensin **I**) from a larger protein (angiotensinogen) produced in the liver. Angiotensin converting enzyme (**ACE**) catalyzes the cleavage of angiotensin I to form angiotensin II, a peptide that can increase blood pressure by inducing the constriction of small arteries and by increasing Sodium and water retention. The rate of angiotensin **II** synthesis is dependent on renin ***(Li et al., 2002).***

Research in mice lacking the gene encoding the VDR indicates that 1,25-dihydroxyvitamin D decreases the expression of the gene encoding renin through its interaction with the VDR ***(Li et al., 2002).***

Since inappropriate activation of the renin-angiotensin system is thought to play a role in some forms of human hypertension, adequate vitamin D levels may be important to reduce the risk of high blood pressure ***(Foramen et al., 2007).***

Assessment of Vitamin D Status:

A working group of U.S. and Canadian government scientists from the U.S. Department of Agriculture, the U.S. Army Medical Research and Material Command, Health Canada, the U.S. Food and Drug Administration, the U.S. National Institutes of Health, the U.S. Department of Health and Human Services, and the Public Health Agency of Canada has endorsed the need to evaluate vitamin D intakes in the context of the changes they produce in serum concentrations of the vitamin D metabolites, 25-hydroxyer-gocalciferol (25-OHD2) and 25-hydroxycholecalciferol (25-OHD3) ***(Yetley et al., 2009).***

This endorsement is consistent with that of the Food and Nutrition Board of the Institute of Medicine (**IOM**), which concluded that the serum 25-OHD concentration is the best indicator of total vitamin D exposure because: