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STUDY THE EFFECT OF VITAMIN D3 IN TYPE 2 DIABETIC IRAQI PATIENTS WITH CHRONIC KIDNEY DISEASES

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Abstract: *Low vitamin D levels are associated with mortality in hemodialysis (HD) patients; however, the serum vitamin D thresholds are unclear. This study aimed to identify the vitamin D level below which mortality increases in HD patients. This study was designed to evaluate the vitamin D3 levels in Iraqi patients with chronic kidney disease and type 2 diabetes for both genders. Sixty Iraqi patients with chronic kidney disease and type 2 diabetes depended the hemodialysis duration less than 1 year; their age ranged between (33-60) years and compared with 30 healthy subjects as control group; their age ranged between (30-55) years, who were attending Al-Yarmok Teaching Hospital through September 2019 to March 2020. Anthropometric and biochemical parameters were measured for patients and controls. The baseline characteristics of study population are shown in Table 1. There were significant increases ($p < 0.05$) in glycemic test, urea, total cholesterol, triacylglycerol, low density lipoprotein cholesterol. While, there were significant decreases ($p < 0.05$) in high density lipoprotein cholesterol, glomerular filtration rate, and vitamin D3 in patients group as compared to the controls. Moreover, there were elevations in age and body mass index in patients group as compared to the controls. There were significant increases ($p < 0.05$) in fasting serum glucose, serum total cholesterol, triacylglycerol, and low-density lipoprotein cholesterol. While, there were significant decreases in high density lipoprotein cholesterol, glomerular filtration rate, and vitamin D3 in female patients as compared to the males. Moreover, there were elevations in body mass index, urea, and creatinine in female patients as compared to the males. Hypovitaminosis D was seen in Chronic Kidney disease (CKD) patients in this study, which encourage further work to assess whether the reference vitamin D level currently used in the general population is applicable to HD patients.*

Keywords: *Chronic kidney disease, Diabetes mellitus, Hemodialysis, Vitamin D3, Lipid profile, Renal function test*

INTRODUCTION

Diabetes mellitus (DM) is metabolic disease that has serious impact on human health. Diabetes mellitus complications include cardiovascular diseases, retinopathy and diabetic nephropathy (DN), which is the most common and serious complication of DM [1]. It has become the leading cause of chronic kidney failure, starting with norm-, micro-, and macroalbumin¬uria and ultimately leading to end stage renal disease (ESRD) [2].

The glomerular filtration rate (GFR) test is a skillful way to measure your level of kidney function and determine your stage of kidney disease. When the GFR level is less than 60 ml/min/1.73 m^2 for ≥ 3 months is referring to renal disease or in another term called Chronic Kidney disease (CKD). Other cardinal signs that imply abnormalities of blood or urine test or imaging studies have a strong link with (CKD) [3], even low

levels of vitamin D have main associated with (CKD) [4]. Vitamin D plays an important role in the regulation of approximately 3% of the human genome, as it is involved in this regulation through its cellular bile receptor and its distinct hormonal system. It also works to enhance the absorption of calcium and phosphate from the small intestine and raise their concentration in the teeth and bones. New research topics confirm the association of a range of diseases and symptoms with vitamin D deficiency, such as kidney disease, autoimmune diseases, tuberculosis, cardiovascular disease, diabetes, cancer and, of course, fractures [5]. In CKD, the mineral metabolism is progressively altered. Serum calcium (Ca+2) and phosphorus remain normal until estimated glomerular filtration rate (eGFR) declines below 40 ml/min. There is a body of opinion that supports the higher mortality rate in CKD due to altered mineral metabolism [6].

MATERIALS AND METHODS

Sixty Iraqi patient with CKD and type 2 DM depended the hemodialysis duration less than 1 year encompassed 30 males and 30 females; age ranged between (33-60) years and compared with30 healthy subjects as control group (12 males and 18 females); age ranged between (30-55) years, who were attending Al-Yarmok Teaching Hospital through September 2019 to March 2020. Anthropometric and biochemical parameters were measured for patients and controls.

2.1. Laboratory measurements

Venous blood was sampled from patients following the admission day after 10-12 hours fasting. Fasting serum glucose (FSG), serum lipid profile encompassing: [total cholesterol (TC), triacylglycerol (TAG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), and very lowdensity lipoprotein (VLDL)], serum urea, creatininie, and were determined using standard biochemical techniques by automated Kenza TX 240 instrumental. Serum urea, and creatinine were evaluated using auto-analyzer (Hitachi, China). Glomerular filtration rate (GFR) was determination on equation depended on sex patients. Furthermore, vitamin D3 was measured by (Minividas, Biomerux kit, France).

2.2. Inclusion criteria

Criteria of CKD cases undergoing HD: Adequate hemodialysis for 2 hours/ 2 times weekly during 1st year.

2.3. Exclusion criteria

Patients with ischemic heart disease (IHD), hypothyroidism, nephrotic syndrome, hypertension, familial hypercholesterolemia, hepatic diseases, and recurrent myocardial infarction were excluded from the study.

2.4. Statistical analysis

Study analysis of Results are expressed as mean ± SD. Student-t test was used to compare the significance of the difference in the mean values of any two groups. The p value of less than 0.05 was considered significant.

RESULTS AND DISCUSSION

Approximately 10% in people deaths with type 2 DM are attributable to kidney failure. It is well-established that most diabetic patients develop diabetic kidney disease resulting in persistent albuminuria, a reduced eGFR, or both. The rates of diabetes complications such as CVD significantly decreased in the past two decades, it has not translated nearly as well as kidney complications [9]. The baseline characteristics of study population are shown in Table 1. There were significant increases ($p < 0.05$) in FSG, HbA1c, urea, TC, TAG, LDL-C, SBP, and DBP. While, there were significant decreases ($p < 0.05$) in HDL-C, GFR, and vitamin D3 in patients group as compared to the controls. Moreover, the patients in this study had lower BMI as compared to the controls. Also, (Jitraknatee et al., 2000) manifested their patients were underweighted which is in agreement with our data [10].

The current study showed that CKD patients had hypercholesterolemia and hypertriglyceridemia [11]. Numerous studies demonstrated that the main deviation of lipid in patients with CRF is the dramatic increase in the level of triglycerides [12, 13]. The enzyme (LPL) lipoprotein lipase plays the most prominent role in the decomposition of the TAG coming from the diet, and then the creation of a new TAG in the liver resulting from the breakdown of adipose tissue and muscles. Hence when LPL activity decreases it causes TAG level to rise. Many enzymes and receptors involved in lipoprotein metabolism are disorganized and dysfunctional, especially lipoproteins HLD and TAG, when chronic renal failure occurs. Chronic kidney patients undergoing hemodialysis should have their LCAT, apoA-1, and hepatic lipase regulated in parallel with the regulation of cholesterol-converting protein (CETP) as the largely responsible for reducing HDL-C

and increasing HDL and TAG. [14]. Excessive elevation of TG, LDL, VLDL, IDL and chylomicron residues in blood plasma is caused by disruption of skeletal muscle, LDL adipose tissue enzymes, hepatic lipase, and VLDL receptors. Our data observed increasing levels in VLDL and decreasing levels in HDL-C for CRF patients with hemodialysis as (HD) against controls; these outputs are conformed to results of another pre-research [15].

Table 1: The baseline characteristics of study population

Parameters	Means ± SD		*p* value
	CKD Patients (n=60)	**Controls (n=30)**	
Gender (Male/Female)	(30/30)	(12/18)	-
Age (Years)	54.4±6.21	48.20±5.17	0.81
BMI (Kg/m^2)	21.52±3.74	24.13±2.51	0.63
FSG (mg/dl)	228.6±9.31	92.1±4.55	0.001
HbA1c (%)	10.71±2.11	4.84±0.83	0.04
Urea (mg/dl)	62.7±8.21	28.56±2.52	0.001
Creatinine (mg/dl)	2.17±0.98	0.78±0.24	0.05
TC (mg/dl)	236.11±11.90	159.1±7.50	0.001
TAG (mg/dl)	223.2±3.71	120.22±12.20	0.001
HDL-C (mg/dl)	35.31±3.71	52.52±3.64	0.03
LDL-C (mg/dl)	148.21±12.31	84.63±9.14	0.001
GFR (ml/min)	35.22±4.01	95.13±5.01	0.001
SBP (mmHg)	165±3.41	120.0±1.23	0.01
DBP (mmHg)	105.0±2.51	71.40±1.56	0.01
Vitamin D3 (ng/ml)	12.98±1.81	33.6±3.51	0.01

There were significant increases ($p < 0.05$) in FSG, serum TC, TAG, and LDL-C. While, there were significant decreases in HDL-C, GFR, and vitamin D3 in female patients as compared to the males. Moreover, there was elevation in BMI, urea, creatinine, SBP, and DBP in female patients as compared to the males (Table 2). There was significant increase in the levels of serum urea observed in CRF group. On balance, unhealthy foods full of fats and proteins, especially red meat, lead to a deterioration of the kidneys' condition and cause the accumulation of urea in the blood serum [16]. Raise values of urea in the blood performs to serious complications in the body unless it is removed quickly by the kidneys [17]. Thru hemodialysis, the amount of excess urea is removed from the patient's blood a little to prevent its accumulation. Eating a balanced amount of protein consumed is also a critical step to confine excessive urea production [18]. Waste removal during hemodialysis also depends on the appropriate timing of dialysis, patient education, hemodialysis machine and appropriate dietary habits of patients [19]. The process of diagnosing and monitoring kidney failure can be done by measuring urea and creatinine levels they are important vital sign [20].

The urea molecule which is a bad sub-product of protein metabolism is accumulated in the blood of patients with renal failure causing hematuria [21] [22]. The high level of creatinine in the blood is considered an indication of the occurrence of kidney diseases and thus the difficulty of getting rid of this molecule that is generated as an unwanted product during the metabolic processes of the muscles.

Serum creatinine level was significantly higher than normal range (up to 1.4 mg/dl) in CKD patients undergoing dialysis. Increasing level of creatinine in serum may cause itching and damage to nerve endings [23]. Moreover, CKD patients are at a higher risk of hospitalization and CVD and the risk increases with a decline in GFR [24].

The reasons that may lead to a reduction in the levels of 25 (OH) D in patients with chronic renal failure have been mentioned previously. It is possible to raise the levels of the active vitamin D by eating foods rich in vitamin D and nutritional supplements containing vitamin D [25], despite these conflicting results of research on the extent to which patients with chronic kidney failure benefit from taking these supplements as well as the extent of their impact on deaths [26].

Table (2) Comparison of biochemical characteristic between male and female patients

Parameters	CKD Patients (Means ± SD)		*p* value
	Male (n= 30)	**Female (n= 30)**	
Age (Years)	56.23±2.68	52.27±2.82	0.623
BMI (Kg/m^2)	22.80±2.64	23.45±1.22	0.412
FSG (mg/dl)	278.0±15.61	290.0±17.80	0.05
HbA1c (%)	8.79±2.40	9.31±1.99	0.302
Urea (mg/dl)	63.93±8.81	68.91±7.14	0.05
Creatinine (mg/dl)	2.08±0.23	2.24±0.69	0.158
TC (mg/dl)	252.90±10.05	286.28±8.40	0.01
TG (mg/dl)	208.11±11.32	263.66±10.12	0.01
HDL-C (mg/dl)	43.90±5.06	30.12±4.04	0.01
LDL-C (mg/dl)	138.86±12.40	168.31±14.60	0.01
GFR (ml/min)	43.31±4.81	30.31±3.45	0.01
SBP (mmHg)	168.12±3.11	175.10±2.15	0.146
DBP (mmHg)	91.20±1.23	105.60±2.12	0.178
Vitamin D3 (ng/ml)	18.28±4.50	10.80±1.48	0.01

Additionally, Correlation coefficients between serum vitamin D3 and other parameters in patients' group are shown in Table 3. There were significant positive correlations between seum vitamin D3 and BMI, HDL-C, and GFR in CKD patients. While, there were significant negative correlations between serum vitamin D3 and FSG, TC, TAG, and LDL-C in CKD patients. Vitamin D deficiency may be due to a decrease in the concentration of the enzyme hydroxylase in the kidneys, or due to a decrease in the rate of skin formation of a substance such as cholecalciferol as a result of a lack of physical activities such as walking and morning sports and lack of exposure to beneficial sunlight. In addition, the decrease in calcidiol in chronic kidney disease indicates a decrease in the revivify of vitamin D form they have. The inverse correlation between 25(OH)-VD levels and parathyroid hormone (PTH) has been demonstrated across virtually all stages of CKD [27, 28].

Table (3) Correlation coefficient between serum vitamin D3 and other parameters in patients' group

Parameters	Vitamin D3 (ng/ml)	
	r	***p***
Age (Years)	0.178	0.08
BMI (Kg/m^2)	0.629	0.01
FSG (mg/dl)	-0.367	0.04
HbA1c (%)	-0.337	0.05
Urea (mg/dl)	-0.340	0.05
Creatinine (mg/dl)	-0.254	0.05
TC (mg/dl)	-0.278	0.03
TAG (mg/dl)	-0.461	0.01
HDL-C (mg/dl)	0.263	0.04
LDL-C (mg/dl)	-0.548	0.01
GFR (ml/min)	0.278	0.03

Adults suffer from soft and lax bones in the event of a lack of vitamin D stores in the body, while this decrease causes rickets in children. Different subgroups such as race, geographic latitude, sun exposure, skin pigmentation rate, and dietary vitamin D intake are a classification that is adopted for the normal population when they develop a vitamin D deficiency, but the classification range is wider in chronic kidney patients who need dialysis [29]. The evidence of calcidiol hormone turbulence or low is indicated if its rate in the blood less than (25-25) nmol/liter [30]. Recent investigations have evidenced the insufficiency and deficiency of 25 (OH) D in patients with stage 5 CKD. While, other conditions such as gender, a high BMI

level, and a low rate of sun exposure can exacerbate serum levels of 25 (OH) D as well [31]. Moreover, there were multiple researches used as a guide for distinguishing the decline of both 25(OH)D and 1,25(OH)2D in hemodialysis patients. This lack in both forms of vitamin D is an unrelated reason to death in these patients along with other factors such as residual kidney function which is known as mortality predictor in dialysis patients [20, 21].

CONCLUSIONS AND RECOMMENDATIONS

Our study was marked a steady relationship between serum urea and creatinine levels among CRF patients presenting information on renal function among these populations. Kidney function is evaluated by measuring certain components in the blood plasma, such as the level of urea and creatinine. Dialysis is the best way to get rid of unwanted waste in patients with chronic kidney failure. Spreading health awareness to reduce the spread of obesity and diabetes by advising individuals to eat healthy, fat-free meals or reduce red meat and to provide modern techniques for early detection of diabetes complications that usually end in kidney failure would reduce this problem globally.
Hypovitaminosis D was seen in CKD patients in this study, which assess whether in more activities to the reference level of vitamin D the same for all people in HD patients. A study that includes the administration of various concentrations of vitamin D is needed to estimate its role in the rate of death.

References

[1] B.P Tabaei, A.S Al-Kassab, L.L Ilag, C.M Zawacki, and W.H Herman, Does microalbuminuria predict diabetic nephropathy? Diabetes Care. 2001; 24: 1560-6.
[2] KDIGO. Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention,and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKDMBD).Kidney Int Suppl. 2017; 7: 1–59.
[3] A. Ganguli. Uddanam nephropathy/regional nephropathy in India: preliminary findings and a plea for further research. Am J Kidney Dis. 2016; 68(3):344–8.
[4] J.J Filipov, B.K Zlatkov, E.P. Dimitrov, and D. Svinarov, Biotechnol. Biotechnol. Equip. 2015;29: 331–335.
[5] L.A. Plum, and H.F. DeLuca . Vitamin D, disease and therapeutic opportunities. Nat. Rev. Drug Discov. 2010; 9:941–955.
[6] M. Wolf. Mineral (Mal) Adaptation to KidneyDisease – Young Investigator Award Address:American Society of Nephrology KidneyWeek 2014.Clin J Am SocNephrol. 2015; 10(10) :1875–85.
[7] F. Ahmadi, S. Damghani, M. Lessan-Pezeshki, E. Razeghi, S. Maziar and M. Mahdavi-Mazdeh. Association oflow vitamin D levels with metabolic syndrome in hemodialysis patients. Hemodial. Int. 2015; 20(2):261–269.
[8] Y.C. Li. Renoprotective effects of vitamin D analogs. Kidney Int. 2010; 78(2):134–139.
[9] R. Saran, et al. US Renal Data System 2018 Annual Data Report: Epidemiology of Kidney Disease in the United States: Volume 1 - Chapter 1: CKD in the General Population. Am J Kidney Dis. 2019; 73: S1–S2 8.
[10] J. Jitraknatee, C. Ruengorn and S. Nochaiwong. Prevalence and Risk Factors of Chronic Kidney Disease among Type 2 Diabetes Patients: A CrossSectional Study in Primary Care Practice Scientific Reports. 2020; 10:6205.
[11] W. T. Friedewald, R. I. Levy, and D. S. Fredrickson, et al. Estimation of the Concentration of Low-Density Lipoprotein Cholesterol in Plasma, Without Use of the Preparative Ultracentrifuge. Clinical Chemistry. 1972; 18(6).
[12] R.R. Ravichandran, S.V . Nerurkar, and V.N. Acharya . Hyperlipidemia in patients with chronic renal failure. Journal of Post Graduate Medicine . 1983; 29(4):212–17.
[13] B. Shah, S. Nair, R.A. Sirsat et al. Dyslipidemia in Patients of CRF and in renal transplant patients. J post Grad Med . 1994; 40(2):57–60.
[14] K. Janicki, G. Molas, J. Furmaga, et al. Abnormal lipoprotein metabolism in hemodialysis patients, AnnalesUniversitatisMariae Curie–Sklodowska Lublin Polonia. 2007; 62: 311–14.
[15] N.D Vaziri. Dyslipidemia of chronic renal failure: the nature, mechanisms, and consequences. Am J Physiol Renal Physiol. 2006; 290(2): F262–72.
[16] M.D Khaled, A. Faiz, A.T. Abdelgader. Effect ofhaemodialysis on some metabolic products of CKD patientsin Libya. WJPPS. 2015; 4: 45-54.
[17] C. Felix, C.V .Stefan, R .Dan. Hemodialysis- induced electrolyte variation (serum calcium, magnesium, andbicarbonate) and intradialytic heart rhythm disorders. Int JBioflux Society. 2016; 6: 11-14
[18] G.M .Gonella. Effect of dialysis on certain biochemicalparameters in chronic renal failure patients. InternationalJournal of Contemporary Medical Research. 2016; 3: 2454-7379.
[19] K.S .Merzah, and S.F. Hasson. The biochemical changes inpatients with chronic renal failure. Int J Pharma Med BioSci. 2015; 4: 75-79.

[20] R.S. Entedhar, and A.M. Nawal. Biochemical changes in chronicrenal failure pre and posthemodilysis. J Environ SciEngTechnol. 2016; 5: 190-195.
[21] M. Suresh, R,N. Mallikarjuna, B.S. Sharan. Hematological changes in chronic renal failure. IJSRP. 2012; 2: 2250-3153.
[22] B. N. Shivananda. Manipal manual of clinical biochemistry. Jay Pee Brothers' Medical Publishers (p) Ltd, New Delhi. 2002: 98-99.
[23] K. Attika and Z. Lubna. Effect of hemodialysis on mean prothrombin time and activated partial thromboplastin time in patients of end stage renal disease. Journal RMC. 2015; 19: 247-249.
[24] S.S. Khan, W.H. Kazmi, R. Abichandani, H .Tighiouart, B.J .Pereira, and A. T .Kausz. Health care utilization among patients with chronic kidney disease. Kidney Int. 2002; 62(1): 229-36.
[25] W.C .Liu, C.C .Wu, Y.M .Hung. Pleiotropic effects of vitamin D in chronic kidney disease. ClinChimActa. 2016; 453: 1–12.
[26] M.J .Damasiewicz, N.D. Toussaint. Is nutritional vitamin D supplementation beneficial in dialysis patients? ClinJ Am SocNephrol. 2015; 10: 544–546.
[27] I. Mucsi, C. Almási, G. Deák, A. Marton, C. Ambrus, K. Berta, P. Lakatos, A. Szabó, and C. Horváth, . Serum25(OH)-vitamin D levels and bone metabolism in patients on maintenance hemodialysis. Clin. Nephrol. 2005; 64: 288–294.
[28] N.L. Milinkovic, N.T. Majkic-Singh, D.D. Mirkovic, A.D. Beletic, S.D. Pejanovic, and S.T. Vujanic, . Relation between 25(OH)-vitamin D deficiency and markers of bone formation and resorption in haemodialysispatients. Clin. Lab. 2009; 55: 333–339.
[29] D.R .Mager, S.T. Jackson. M. R. Hoffmann, K. Jindal , and P.A. Senior. Vitamin D3 supplementation, bone health and quality of life in adults with diabetes and chronic kidney disease: Results of an open label randomized clinical trial. Clin Nutr. 2017; 36: 686- 696.
[30] A.B. Korkor, D. Eastwood , and C. Bretzmann**.** Effects of gender, alcohol, smoking, and dairy consumption on bone mass in Wisconsin adolescents. WMJ. 2009; 108: 181-8.
[31] F. Hayati, M. A .Nasouti, S. Shayanpour, S. AhmadiHalili , H. Karimpourian, and Z.B. Mousavi. Vitamin D and chronic kidneydisease. J Parathyr Dis. 2016; 4: 25-30.
[32] D. Vanderschueren, G. Gevers, J .Dequeker, P. Geusens, J. Nijs , P. Devos, et al. Seasonal variation in bone metabolism inyoung healthy subjects. Calcif Tissue Int. 1991; 49: 84-9.