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Medicine

Evaluation of Therapeutic Effectiveness of Vitamin D in Proteinuria Regression in Diabetic Nephropathy

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Abstract: Albuminuria in diabetes mellitus (DM) is common and ushers the onset of systemic micro and macrovascular complications. Various metabolic and hemodynamic factors involve in the pathogenesis of albuminuria and by interacting through molecular and signaling pathways, these produce inflammatory changes and activate renin angiotensin aldosterone system (RAAS). Vitamin D has been shown to modulate both inflammation and RAAS, and hence found to be Reno protective. This study is to examine, whether vitamin D levels and albuminuria correlates inversely and how much albuminuria correction can be achieved if vitamin D is added as therapeutic adjuvant.
Keywords: Proteinuria, Vitamin D, Diabetic Kidney Disease.

INTRODUCTION

Low serum 25 (OH) Vitamin D (VD) level is associated with impaired glucose tolerance (IGT) and diabetes [1]. Hyperglycemia blunts the vitamin D receptor (VDR) [2]. Loss of VDR is also associated with reduced renal tissue in long standing diabetic kidney disease (DKD). VD has been reported to negatively regulate RAAS. In VD deficiency, hyperglycemia and renal tissue loss induced VDR dysfunction, RAAS is upregulated and angiotensin II synthesis is increased. These changes, angiotensin II in particular, produce podocytes effacement and glomerular basement thickening. Hyperglycemia stimulates cytokines, growth factors and transforming growth factor – β (TGF-β). These Inflammatory responses and activation of RAAS generated by various metabolic and hemodynamic factors in diabetic patients, play a role in the pathogenesis Of DKD - albuminuria.

High dose VD therapy, by modulating these changes, is found to have renoprotection and antiproteinuric effect [3]. VD therapy also decreases insulin resistance and blood pressure [2, 4] augmenting renoprotection and antiproteinuric effect.

Though renin decreases proteinuria in diabetics, yet efficacy of angiotensin converting enzyme inhibitors (ACE – I) is reduced by the reactive renin increase due to disruption of the renin feed- back inhibition [5]. Even angiotensin receptor blocker (ARB) [6-7] and new renin inhibitor aliskiren [6] are not effective in complete inhibition of renin secretion. The finding that apart from modulating RAAS and inflammatory process, VD also represses renin gene transcription [9], so it forms the basis of its use as an adjuvant to RAAS inhibitors.

MATERIALS AND METHODS

This study was conducted in M.M. Medical College & Hospital Kumarhatti – Solan (Himachal Pardesh). It was a prospective, randomized and Pharmaco-interventional study. Study was aimed to include about 100 diabetic patients, both sexes, with pathological proteinuria to find out VD induced regression in proteinuria Vis – a – vis improvement in DKD.

Duration of study

From Nov 2016 for about one and half year

Inclusion criteria

- Diabetic patients with pathological proteinuria irrespective of age, sex, weight, height, ethnicity, region and economic factors.
- Patients taking antidiabetic medicines.
- Diabetic patients with associated comorbidities.

Exclusion criteria

- Malabsorption syndrome, Chronic intestinal diseases and intestinal resection
- Serum calcium > 12mg/dl
- Patients taking steroids and phenytoin
- Hepatic insufficiency including cirrhosis
- Terminally ill

Ethical Issue

The research was approved by the Ethical Committee of the institution and conducted as per its laid down norms.

Participants

On enrolment in study each participant was informed about the nature of study and, if agreed, consent was taken and allotted a Participation Number. Patients were assessed clinically on first and subsequent visits. Following parameters were recorded: Age & sex; symptomatology suggestive of DM, hormonal therapy / drugs (influencing proteinuria); family history of endocrinopathy; weight, height, BMI and associated comorbidity and organ damage, if any.

Biochemical parameters: Following relevant laboratory tests were carried out: Hemoglobin (Hb), blood sugar, Glycosylated hemoglobin (HbA1c), lipid profile, ECG, serum Calcium & Phosphate, serum Vitamin D and 24 hours urinary protein.

Estimated Glomerular Filtration Rate (e GFR) was calculated by the abbreviated MDRD equation: 186 x (Creat / 88.4)$^{-1.154}$ x (Age)$^{-0.203}$ x (0.742 if female) x (1.210 if black).

DKD was classified according to Kidney Disease Outcomes Quality Initiative (KDOQI) 2002, and subsequently adopted with minor modifications by Kidney Disease Improving Global Outcomes (KDIGO) guidelines based on the eGFR [10].

Study groups: Patients grouped as:

Group - I (Gp – I): patients already taking / prescribed antidiabetic medication and in addition were given ACE – I / ARB and VD 60,000 units/week till completion of study.

Group – II (Gp-II): Same criteria as in Gp – 1 except VD.

Patients in both groups were allowed to continue therapy for associated comorbidities. Patients were reviewed three monthly till the conclusion of the study.

End Point: Based on study results.

RESULTS

173 diabetic patients [83 Male (M) and 90 Female (F)] with biochemically confirmed pathological proteinuria were included in the study. In Gp – I, participants were (M = 40 & F = 46) and in Gp – II (M = 43 & F = 44). During study period, 43 patients (M = 21 and F = 22) were excluded from the study due to compliance reasons. Participants excluded were: 2 died (M = 1 & F = 1), 5 (M = 3 & F = 2) referred to higher nephrology centers, 17 (M = 9 & F = 8) preferred alternate discipline of medicine and 19 (M = 8& F = 11) did not cooperate / report after first visit.

Remaining 130 patients (M = 62 & F = 68), completing the duration of the study, included: Gp – I (M = 29 & F = 36) and Gp – II (M = 33 & F = 32). Mean age for male and female patients was 55.05 ± 12.39 (P=0.96) and 53.24 ± 12.81 (P=0.85) years respectively. Age and sex wise distribution of patients depicted in Table – 1. Apart from diabetes mellitus patients were having associated co - morbidities as shown in Table – 2.

Table-1: Age and sex wise distribution of patients

Age groups	Male			Female		
(Years)	Gp – 1	Gp – II	Total	Gp – 1	Gp – II	Total
< 30	2	-	2	1	-	1
31 – 40	4	3	7	6	7	13
41 – 50	6	6	12	4	10	14
51 – 60	9	12	21	14	6	20
>60	8	12	20	11	9	20
Total	29	33	62	36	32	68

Systolic blood pressure (BP) >130 mm Hg was found in 42 males (17 in Gp – I & 25 in Gp – II) and 44 females (25 in Gp – I & 19 in Gp – II), whereas diastolic BP > 90 mm Hg in 48 males (21 in Gp –I & 27 in Gp – II) and 51 females (28 in Gp – I & 23 in Gp – II).

Various biochemical abnormalities found during initial evaluation shown in Table – 3. VD deficiency was detected in 88.70% males (Mean 17.913 ± 9.83 ng/ml) and 79.42% in females (Mean 21.484 ± 17.995 ng/ml) (Fig – 1). (On inquiry, almost all patients, with normal serum VD level, accepted that they were taking combination of calcium and VD supplements as prescribed by health care worker or at

their own). At the time of recruitment, based on blood glucose level and HbA1c, diabetes mellitus was poorly controlled in 118 (90.76%) patients [54 (87%) males and 64 (94%) females], Mean blood glucose level in male and female being 273.258 ± 81.34 and 294.779 ± 84 mg/dl respectively. All diabetic patients were detected to have significant pathological proteinuria (Mean urinary protein in males 492.55 ± 957.87 mg and in female 471.29 ± 943.36 mg/24 hours).

Table-2: Associated co – morbidities in diabetic patients

Comorbidities with diabetes mellitus	Male	Female
Diabetes mellitus without other co – morbidity	37	46
Hypertension	6	13
Coronary Artery Disease	2	3
Obesity*	13	26
More than two co-morbidities**	25	32
Cerebrovascular Accident	1	-
Diabetic foot	1	-
Cholelithiasis	-	3
Xanthoma	-	1
Nephrolithiasis	-	2
Recurrent Infections***	3	4
Miscellaneous	3	2

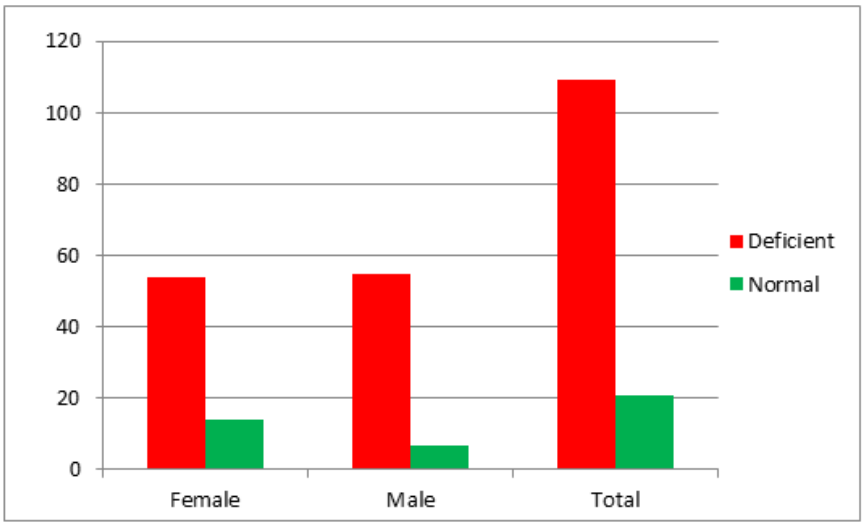
* Asian guidelines for BMI were considered for Obesity.

**Diabetes mellitus associated with 2 or more than 2 co – morbidities e.g. HTN, CAD, Obesity, dyslipidemia, CVA, diabetic foot

***Recurrent infections usually pulmonary, cutaneous or urinary tract

Abbreviations: BMI (Body Mass Index); HTN (Hypertension), CAD (Coronary Artery Disease), CVA (Cerebrovascular Accident)]

Serum triglyceride levels more than 100 mg/dl were present in 82.26% male and 89.71% female, serum low density lipoprotein (LDL) more than 70 mg/dl in 54.84/dl males and in 75mg/dl in females, serum high density lipoprotein (HDL) 45.16 mg/d in male and 64.71 mg/dl in female. HbA1c more than 6.5 g/dl was found in 74.19% & 95.59% males and females respectively.



Fig–1: level showing vitamin D deficiency in study group. Red and Green bars show deficient and normal level respectively)

Table-3: Biochemical abnormalities

Biochemical abnormalities	Male		Female	
	Gp– I	Gp – II	Gp– I	Gp - II
S. Vitamin D (<30 ng/ml)	28 (96.55%)	27 (81.81%)	28(77.77%)	26 (81.25%)
S. Triglyceride (>100 mg/dl)	25 (86.21%)	26 (78.79%)	32 (88.89%)	29 (90.63%)
S. LDL (>70 mg/dl)	14 (48.28%)	20 (60.61%)	24 (66.67%)	27 (84.36%)
S. HDL (<40 mg/dl in male & <50 mg/dl in female)	12 (41.38%)	16 (48.48%)	22 (61.11%)	22 (68.75%)
HbA1c (g/dl)	21 (72.41%)	25 (75.76%)	34 (94.44%)	31 (96.88%)

After calculation of e-GFR as per abbreviated MDRD equation, DKD staging was done according to the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation– 2002[10] as given in Table - 4.

Table-4: Staging of DKD based on eGFR

Stage of CKD BEFORE therapy	Male	Female	Total	Stage of DKD AFTER therapy	Male	Female	Total
1	45	47	92	1	48	47	95
2	4	10	14	2	4	11	15
3	10	8	18	3	7	7	14
4	2	2	4	4	2	2	4
5	1	1	2	5	1	1	2
Total	62	68	130	Total	62	68	130

(Table – 4 shows one step up improvement in DKD level in Stages 2 to 3. Proteinuria worsened in Stage – 1. There is no improvement in Stage 4 & 5.)

Patients were started medication as per respective group protocol and followed three monthly or four monthly depending on the inclement weather conditions of Himachal Pradesh. ACE – I /ARB was discontinued in stage 4 and 5 diabetic nephropathy irrespective of the study group. Results were recorded and compiled for analysis. Diabetes mellitus was controlled 127 (97.69%) patients with addition of insulin, if needed. Whereas, 3 patients (2 female in stage– 1, 1 male in stage - 3 CKD) refused to accept insulin for diabetic control. BP was well controlled in all subjects within acceptable limit [11]. Other associated co-morbidities remained stable during study period.

At the end of the study, 6 patients (5 females and 1 male) showed deterioration in stage - 1, improvement in DKD was evident in stage 2 & 3 with or without associated other co-morbidities, no change was noticed in stage 4 & 5 despite achieving diabetic control. Results, both improvement / deterioration, were statistically not significant as depicted in Table – 6 and Table - 7.

Table-6: (DKD - Stage wise breakdown of patients depicting effect of therapy)

Stage of DKD	Male	Female	Total
Stage - 1			
No Change	44 (*P = 0.8765*)	42 (*P = 0.8643*)	86
Worsened	1	5	6
Stage - 2			
Improved	1	4	5
No Change	2 (*P = 0.39503*)	4 (*P= 0.2021*)	6
Worsened	1	2	3
Stage - 3			
Improved	4 (*P =0.80542*)	4 (*P = 0.81921*)	8
No Change	6	4	10
Stage - 4			
No Change	2 Not calculated	2 Not calculated	4
Stage - 5			
No Change	1 Not calculated	1 Not calculated	2
Grand Total	62	68	130

Table-7: Stage – 1 of DKD depicting improvement / deterioration in renal function:Group and Sex wise

Groups	Patients in group	Stage – I	Improvement / Deterioration
Male			
Gp – I	29	23 (*P = 0.7962*)	No Change
Gp – II	33	22 (*P = 0.7912*)	1 deteriorated
Female			
Gp – I	32	26 (*P = 0.7984*)	2 deteriorated
Gp –II	36	26 (*P = 0.8035*)	2 deteriorated

DISCUSSION

As the life expectancy of diabetics is increasing, so are the diabetic related complications. Forerunner of these complications is the DKD, and emerging as the main cause of end stage renal disease (ESRD). At molecular level, hyperglycemia, glycated proteins, hemodynamic and oxidative stress play an important role in the pathogenesis of DKD. Microalbuminuria being the earlies feature suggesting development of DKD, its reversal was attempted to salvage kidney from damage by various studies. These studies based on to achieve and maintain strict diabetic control [12, 13], to minimize glycemic variabilities [14], renoprotection by ACE – Is [5, 15, 16], ARBs [17, 18], apart from antihypertensive drugs, diltiazem and allopurinol [3].

In this study, diabetic patients were VD deficient / insufficient, same reported in other studies also [19-23]. VD, acting on VDRs, regulates via autocrine pathway, cell differentiating and ant proliferative actions, in different tissues, i.e. renal, cardiovascular, and immune systems. In DKD, VDRs are markedly deficient because of renal tissue loss and hence VD effect proves to be ineffective. VD also regulates RAAS and nuclear factor (NF) κB pathway. In DKD, regulation of RAAS undergoes dysregulation because of hyperglycemia and hypovitaminosis D and results in excessive angiotensin II activation, which is one of the main causes of proteinuria. Evidences have shown an inverse relationship between VD levels and degree of albuminuria, which is an important diagnostic hallmark of DKD [24].

We have observed that despite VD therapy, condition of DKD deteriorated in stage – 1, particularly in female. There was statistically insignificant improvement in stage 2 & 3 in both sexes and no improvement in stage 4 & 5, may due to severe loss of renal tissue, RAAS activity and substantial loss of VDRs and burnt out inflammatory changes. Deterioration in stage – 1 DKD seems to be due to persistent hyperglycemia for some time before diabetic control is achieved and replenishment of generalized deficient VD stores in other tissues and hence less availability to renal tissues. VD effect may become apparent later on as it modulates inflammation, RAAS and prevents glomerulosclerosis [2, 4]. The initial deterioration of DKD was also reported in some studies [25, 26]. It seems, VD related modulation and replenishment is sex dependent. Subsequently, there was, though statistically insignificant, improvement in proteinuria in DKD, especially in stage 2 & 3. Many studies have substantiated reno- protective.

And anti-proteinuric effect of VD in man [2, 4, 26-30], including animal studies [31]. In this study, Gp – I diabetic patients were taking VD, whereas ACE – Is and/or ARBs was added to both groups. In our study female patients in both groups did not show improvement in stage – 1, despite Reno protective agents V D with or without ACE – Is and/or ARBs. This observation is not in accordance with a study where it was demonstrated moderate reduction of proteinuria by losartan or paricalcitol alone and synergistic action of losartan and paricalcitol by completely blocking the development of proteinuria in diabetic mice [32]. The interpolation of animal study in human being needs further exploration. We have documented there was improvement, though statsically insignificant, in stage 2 & 3 DKD and no change in end stages. We recommend therapeutic supplementation of VD in diabetics at the earliest stage, as it apart from correcting their vitamin D deficiency (common in DKD), may also prevent or retard to some extent the development and progression of DKD.

Limitation of the Study

(1). Small number of the patients. (2). we estimated only 1, 25 (OH) 2D and not the 25(OH) D which is important for its autocrine effects. Mainly, it is the plasma 25(OH) D, which determines the possible progression of DKD and coexisting CVD, HTN and DM

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