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General Medicine

STUDY OF VITAMIN D LEVELS IN TYPE 2 DIABETES MELLITUS

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ABSTRACT **Background and objectives:** Vitamin D is one of the essential nutrients to sustain the human health. As a member of the steroid hormone family, it has a classic role in absorption of calcium form GI Tract and bone mineralisation and a non-classic role in affecting cell proliferation differentiation and expression of many genes as Vitamin D has receptors in various organs called the Vitamin D nuclear receptors. Epidemiological studies have shown that 25OHD deficiency is closely associated with common chronic diseases such as bone metabolic disorders, tumours, cardiovascular diseases, and diabetes It is therefore necessary to know the adverse health effects of 25OHD deficiency, and to design interventions and early treatments for those who are likely to have low levels of 25OHD.Diabetes is defined as disturbance in intermediary metabolism manifesting as Chronic sustained hyperglycaemia, primarily due to either an absolute or relative lack of insulin. Many epidemiological studies have shown deficiency of Vitamin D as a risk Factor for Diabetes Mellitus. There is evidence suggesting a role of Vitamin D in insulin secretion, which includes the presence of the Vitamin D Receptor in beta cells and the Vitamin D dependent calcium-binding proteins (DBP) in pancreatic tissue. Vitamin D itself is essential for normal insulin release in response to glucose and for maintenance of glucose tolerance. Other studies have found that glucagon hormone release is significantly high in Vitamin D Deficiency. Thus, 25OHD deficiency not only suppresses insulin secretion through weakening the islet β cell function, but also elevates blood sugar through enhancing islet α cell function.Thus various studies have shown that vitamin D deficiency has been implicated in the pathogenesis of type 2 diabetes mellitus and its vascular complications. There is a lack of literature from central India in evaluating and associating the vitamin D levels in general population with type 2 diabetic patients. Hence this study has been undertaken. **Methods:** An observational study undertaken on 153 type 2 diabetes mellitus cases aged 30-70 years and 100 age and sex matched controls attending the outpatient department and inpatients of R D Gardi Medical College and C.R.G.H hospital , Ujjain during the period of one and half year i.e. from January 2018 to June 2019. Patients with type 1 diabetes mellitus and other variants of type 1 diabetes mellitus, Patient of diabetes with history of acute and chronic liver disease ,acute or chronic renal diseases, infectious diseases or malignancies, Patient on Dialysis Patient of diabetes with history of hormone replacement therapy , Patient with history of vitamin D and calcium supplements within 6 weeks of study and Patient of diabetes with thyroid disorders were excluded from the study. Physical and systemic examination of patient were done and baseline vital parameters were recorded as per routine institutional practice. Venous blood samples were taken and were sent for routine investigations like complete blood count, liver function tests, kidney function tests, random blood glucose, fasting blood sugar, post prandial blood sugar and other specific investigations like HBA1C levels, vitamin D levels and urinary microalbumin levels. **Results:** Vitamin D levels were found to be deficient in 75 diabetic cases (49%) while vitamin D levels were found to be deficient in 24 controls (24%) . Vitamin D insufficiency was found more in control group (56%) as compared to cases (34%). There was a statistical significant difference between the two. Vitamin D levels were found to be low in females as compared to males. There was no statistical significant difference between the two. Among the 69 female cases 35 had vitamin D deficiency (50.7%). among the 84 male cases 40 had Vitamin D deficiency (47.6%) . Vitamin D levels were found to be significantly lower in the diabetic cases with long duration of diabetes (>10 years) as compared to recently diagnosed diabetic cases (<1 year). Vitamin D levels were found to be significantly lower in diabetics with poor control of glycemic index as compared to diabetics with good glycemic control . it was found that patients with poor glycemic control i.e HbA1C >8 had more prevalence of Diabetic neuropathy (70.69%), diabetic nephropathy (73.91%) and diabetic retinopathy PDR (82.61%) and NPDR (64.58 %). Vitamin D levels were found to be significantly lower in diabetic cases who had Proliferative diabetic retinopathy as compared to diabetic cases without diabetic retinopathy. **Interpretation:** Vitamin D deficiency is more common among females due to poor exposure to sunlight, poor dietary Vitamin D supplementation, lack of education, dark skin pigmentations, use of sunscreen lotions and excess adiposity. Vitamin D levels are lower in Diabetic patients in comparison to normal individuals. There is an inverse relation between the duration of diabetes mellitus and Vitamin D. As the duration of Diabetes increases, there is more Vitamin D deficiency .Vitamin D has negative correlation with blood HbA1C levels. Patients with poor Glycemic control have much more Vitamin D deficiency. Early detection of Vitamin D deficiency and supplementation may be an effective public health intervention programme to prevent Diabetes Mellitus and prevent long term diabetic complications.

KEYWORDS :

INTRODUCTION

The term diabetes mellitus describes a metabolic syndrome of multiple etiology characterized by chronic hyperglycaemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action,or both. It is a chronic condition with serious morbidity, increased mortality and is rapidly becoming a global pandemic.[1] Based on current trends, the International Diabetes Federation projects that 642 million individuals will have diabetes by the year 2040 worldwide and the prevalence of diabetes in India is 73 million in the year 2019. [2] Vitamin D deficiency is emerging as one of the nutritional risk factors for Insulin Resistance and Type 2 Diabetes Mellitus.[3] As a member of the steroid hormone family, it has a classic role in absorption of calcium form GI Tract and bone mineralisation and a non-classic role in affecting cell proliferation, differentiation and expression of many genes as Vitamin D has receptors in various organs called the Vitamin D nuclear receptors.[4]Epidemiological studies have shown that Vitamin D deficiency is closely associated with common chronic diseases such as bone metabolic disorders, tumours, cardiovascular diseases, and diabetes.[5]Studies have reported that there is an association between poor glycemic control, progression to diabetes mellitus and vitamin D deficiency. Hence, vitamin D is considered as one of the potential modifier of diabetes risk.[6] Although the exact mechanism is not clear, the association of reduced vitamin D levels in T2DM may be mediated through effects on blood glucose homeostasis and direct effect of vitamin D on the betacell function, and thus insulin secretion.[7] Studies found that vitamin D deficiency leads to insulin resistance. Decreased vitamin D level is associated with markers of impaired glucose metabolism, such as (HbA1c).[8]There are limited number of studies available on the vitamin D levels in Type 2 Diabetes Mellitus. In view of increased prevalence of diabetes mellitus, Vitamin D deficiency and association of Vitamin D with Diabetes Mellitus the present study is undertaken to evaluate vitamin

D levels in type 2 diabetes mellitus patients and its correlation with HbA1c.

MATERIAL AND METHODS

This was an observational study which was carried out at RD Gardi medical college and CR Gardi hospital Ujjain after the approval of ethical committee in the department of general medicine on 153 cases of type 2 diabetes mellitus aged 30-70 years and 100 age sex matched controls during the period of one and half year i.e. from January 2018 to June 2019. A well informed consent from all study subjects was taken. Patients with type 1 diabetes mellitus and other variants of type 1 diabetes mellitus, Patient of diabetes with history of acute and chronic liver disease ,acute or chronic renal diseases, infectious diseases or malignancies, Patient on Dialysis Patient of diabetes with history of hormone replacement therapy , Patient with history of vitamin D and calcium supplements within 6 weeks of study and Patient of diabetes with thyroid disorders were excluded from the study. Tools for data collection were structured questionnaire and clinical examination followed by measuring various parameters. Consent of the patient was taken prior to collection of samples. The venous samples were collected with 10 hours of fasting.

Blood sample was immediately transferred to fluoride vial for plasma glucose estimation and EDTA vials for other parameters.**HBA1C -** Measurement of glycated haemoglobin (HbA1c) is the standard method for assessing long-term glycemic control. It reflects the glycemic history over the previous 2-3 months.In our study, HbA1c was estimated by cation exchange HPLC – BIORAD D-10 In our study the cases and controls were divided into three groups according to their control on the glycemic index , those with HbA1C ranging between (5.8-6.9) were considered to have good glycemic control, those with HbA1C (7-8) were considered moderate glycemic control and >8.0 were considered to have poor glycemic control._ **Vitamin D –** Vitamin D levels were measured in serum by enhanced chemiluminescence immunoassay (CLIA) method using Snibe Maglumi 1000.In our study vitamin D levels of <20 ng/ml were considered deficient, 20-30 ng/ml were considered insufficient, 30-100 ng/ml were considered sufficient and 100 ng/ml were considered potentially toxic.**FBS and PPBS –** These were measured by Glucose oxidase peroxidase method (GOD-POD) method. Kits were supplied by Erba diagnostics. The parameters were read using semi auto analyser (STAT FAX 3300). Other routine investigations were done that included CBC, LFT, RFT, Electrolytes, Chest xray, ECG and urine routine microscopy.

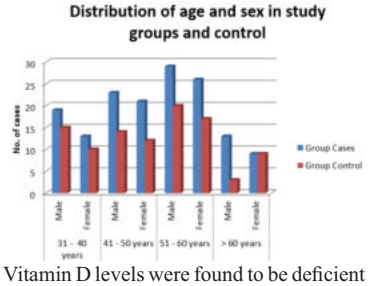
***Tests to check for Complications of Diabetes* - Diabetic Nephropathy** In our study early morning urine samples were collected in two containers. One was sent to microbiology lab for the estimation of urinarymicroalbumin and the other was sent to biochemistry lab for estimation of urinary Creatinine. Urinary microalbumin levels were determined by using fluorescence immunoassay (FIA) by commercial kit. Then the urinary albumin creatinine ratio was calculated to look for Diabetic Nephropathy. A UACR of <30 mg/gm was considered normal. **Diabetic Neuropathy** In our study diabetic neuropathy was checked by detailed clinical examination and monofilament testing.

Monofilament testing was done to assess the loss of protective sensations (LOPS).The Semmes Weinstein 5.07 monofilament was used. 10 different sites were tested in each foot using the monofilament. **Diabetic Retinopathy** It is classified into proliferative or Non proliferative. In our study fundus examination was done in all the Diabetic patients using the Heine Beta 200S 2.5 v LED ophthalmoscope.

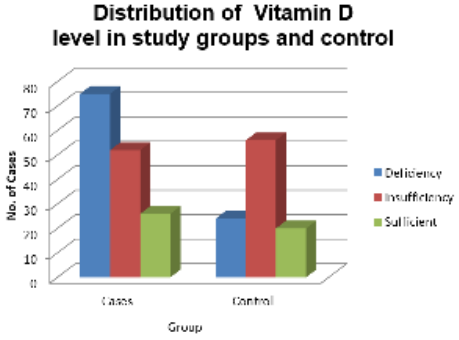
RESULTS

In our study there were a total a 84 male cases (54.9%) and 69 female cases (45.1%). In the age group 31-40 years there were 32 cases out of which 19 were males (59.4%) and 13 were females (40.6%). In the age group 41-50 years there were 44 cases out of which 23 were males (52.3%) and 21 were females(47.7%).in the age group 51-60 years there were 55 cases out of which 29 were males (52.7%) and 26 were females (47.3%).

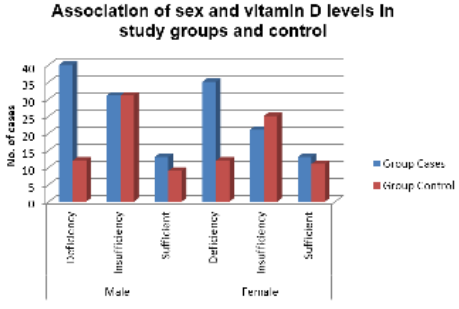
In age group >60 years there were 21 cases out of which 13 were males (59.1%) and 9 were females (40.9%).In control group there were a total of 52 males (52%) and 48 females (48%). In the age group 31-40 years there were 25 individuals out of which 15 were males (60%) and 10 were females (40%). In the age group 41-50 years there were 26 individuals out of which 14 were males (53.6%) and 12 were females (46.2%). In the age group 51-60 years there were 37 individuals out of which 20 were males (54.1%) and 17 were females (45.9%). In the age group >60 years there were 12 individuals out of which 3 were males (25%) and 9 were females (75%).



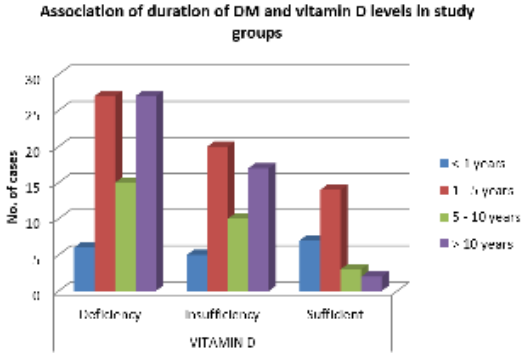
In our study Vitamin D levels were found to be deficient in 75 diabetic cases (49%) while vitamin D levels were found to be deficient in 24 controls (24%) . There was a statistical significant difference between the two. (p value – 0.002) In our study Vitamin D insufficiency was found more in control group (56%) as compared to cases (34%). There was a statistical significant difference between the two. (p- 0.002)



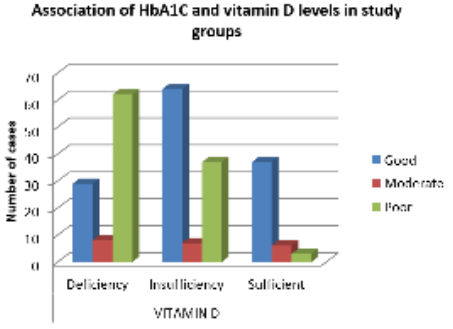
Vitamin D levels were found to be low in females as compared to males. There was no statistical significant difference between the two. Among the 69 female cases 35 had vitamin D deficiency (50.7%). among the 84 male cases 40 had Vitamin D deficiency (47.6%) Amongst the controls Vitamin D levels were also found to be low in females as compared to males. But there was no statistical difference between the two. In control group vitamin D deficiency was found in 25% of females as compared to 23.1% in males



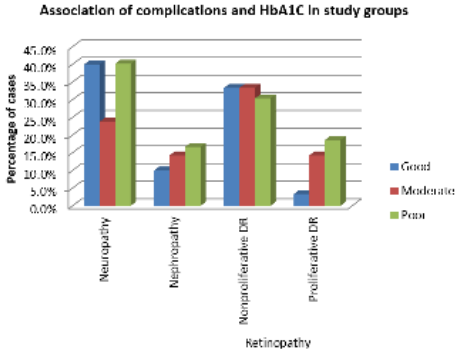
In our study Vitamin D levels were found to be significantly lower in the diabetic cases with long duration of diabetes (>10 years) as compared to recently diagnosed diabetic cases (<1 year). This was statistically significant (p-0.001) There was an inverse relation between duration of diabetes and vitamin D levels .



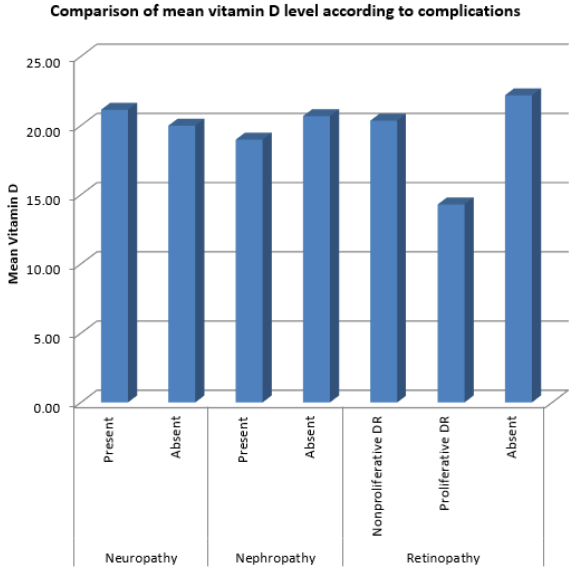
In our study Vitamin D levels were found to be significantly lower in diabetics with poor control of glycemic index as compared to diabetics with good glycemic control. This was statistically significant. (p-0.002). There was an inverse relation between HbA1c and Vitamin D levels



In our study it was found that patients with poor glycemic control i.e HbA1C >8 had more prevalence of Diabetic neuropathy (70.69%), diabetic nephropathy (73.91%) and diabetic retinopathy PDR (82.61%)andNPDR(64.58%)



In our study Vitamin D levels were found to be significantly lower in diabetic cases who had Proliferative diabetic retinopathy as compared to diabetic cases without diabetic retinopathy.(p-0.001) The mean value of Vitamin D in diabetic cases with PDR was 14.30 ng/ml while it was 22.19ng/ml in diabetic cases without diabetic retinopathy. The difference was statistically significant.(p-0.001) There was no statistical significant difference in vitamin D levels among patients with Diabetic Neuropathy and Diabetic nephropathy as compared to diabetic patients without complications.(p-0.425)



DISCUSSION

Diabetes mellitus is one of the most common causes of mortality and morbidity worldwide. Its prevalence has been steadily increasing in India. Vitamin D deficiency is also a common health problem in large population in India. Many studies have pointed towards a potential association of Vitamin D deficiency with Type 2 diabetes Mellitus and its complication. We have taken the study to see the relationship between these two disorders. The present study was aimed to evaluate the Vitamin D levels in Type2 diabetes Mellitus, its correlation with HbA1c levels and duration of Diabetes mellitus. The present study consists of a population of 153 known diabetic patients the mean age of which is 49.88 years. 84 were females (54.9%) 69 were males (45.1%) .Their Vitamin D levels were evaluated and compared to another group of population of 100 healthy age and sex matched controls. The mean age of which is 41.33 years. 52 Were males (52%) and 48 were females (48%).In our study it was found that Vitamin D deficiency was more prevalent among females. 50.7 % diabetic females had Vitamin D deficiency and 25% healthy control females had vitamin D deficiency. Amongst males 47.6 % diabetic males had Vitamin D deficiency while 23.1 % healthy male controls had Vitamin D deficiency. However there was no statistical significant difference between Vitamin D levels between males and females. More profound Vitamin D deficiency in females could be attributed to poor exposure to sunlight, poor dietary Vitamin D supplementation, sedentary lifestyle and and lack of education. It could also be explained on the basis of impaired ultraviolet rays induced cutaneous synthesis of Vitamin D which may be caused by dark skin pigmentations, use of sunscreen lotions, limited time outdoors and excess adiposity. Similar results were observed by Al Zaharani et al who observed Vitamin D deficiency in 53.5% diabetic females and 46.7 % diabetic males. The findings of Al Zaharani are in agreement to the findings of the present study ***Vitamin D levels in Diabetics vs Non Diabetics*** **:** The results of the present study revealed that 49% of the Diabetic study population was deficient in Vitamin D levels while 34% of the diabetic study group was insufficient in Vitamin D levels and remaining 17 % had normal vitamin D levels. However in the control group 24% of the healthy individuals were found to deficient in Vitamin D levels while 56% of the controls were found to be insufficient in Vitamin D levels and remaining 20% had sufficient vitamin D levels. The results of the present study showed that there was a statistical significant difference between Vitamin D levels in diabetic patients and the healthy subjects. Correlating with the result of present study was the study done by Lalitha A et al in Vishakhapatnam who observed 38% of the diabetic subjects being deficient in Vitamin D levels as compared to 22% of the healthy individuals who were found to be Vitamin D deficient [9]. This could be because of difference in dietary patterns of the two populations and different sunshine duration status in Madhyapradesh and Goa. Another possible reason for Low Vitamin D levels in diabetic population could be Obesity. Obese people tend to have a sedentary lifestyle and reduced outside activities and thus lower sunlight exposure. Studies have also shown that there is reduced synthetic capacity of Vitamin D in obese population. Subcutaneous Adipose tissue has also been found to have lower expression of one of the enzymes responsible for 25-hydroxylation of Vitamin D as well as tendency towards a decreased expression of 1 alpha hydroxylase. This suggests that both 25 hydroxylation and 1 alpha hydroxylation are impaired in obese individuals. This suggests that there is a significant reduction in Vitamin D levels in type 2 Diabetes Mellitus patients compared to controls [10].***Vitamin D and its correlation with duration of diabetes*** In the present study the cases were divided into 4 categories on the basis of duration of diabetes i.e. recent onset Diabetes Mellitus (<1 years) , patients having diabetes of (1-5 years), patients having diabetes of (5-10 years) and patients having diabetes of (>10 years).When the Vitamin D levels were measured and compared to the duration of Diabetes mellitus it was found that :-Patients having recent onset diabetes of <1 years had sufficient Vitamin D levels (38.9%) .Patients having Diabetes of >10 years had Maximum Vitamin D deficiency (58.7%) and Vitamin Insufficiency (37%) .With the increasing duration of Diabetes Mellitus, Vitamin D deficiency also increased. This suggests an inverse relation between the duration of diabetes mellitus and Vitamin D. As the duration of Diabetes Increases, there is more Vitamin D deficiency[11]***Co-relation between Vitamin D and HbA1c levels*** In this study the diabetic cases were divided into 3 groups according to their control on the glycemic index , those with HbA1C ranging between (5.8-6.9) were considered to have good glycemic control, those with HbA1C (7-8) were considered moderate glycemic control and >8.0 were considered to have poor glycemic control. In our study it was found that patients with poor glycemic control had maximum Vitamin D deficiency(60.8%) and those with good glycemic control had sufficient Vitamin D levels (56.7%).The mean value of Vitamin D in patients with Good Glycemic control was found to be 27.52 ng/ml, with moderate glycemic control it was 22.88ng/dl and with poor glycemic control it was 17.84ng/dl. This finding is in agreement with Al Timimi et al who reported mean serum Vitamin D value of 20.7 ng/dl in patients with poor glycemic control and 32.4 ng/dl in patients with good glycemic control [12]. This suggests that there was an inverse relationship or a negative co-relation between

Vitamin D and HbA1C [13] ***Vitamin D and its correlation with complications of diabetes***In our study correlation of vitamin D was done with diabetic retinopathy, diabetic neuropathy and diabetic nephropathy. There have been many studies in the past which have made association between VitaminD deficiency and Diabetic retinopathy. The characterstic feature of diabetic retinopathy is the appearance of vascular lesions of increasing severity, ending up in neovascularisation. Vitamin D has anti inflammatory properties and inhibits vascular smooth mucle cell growth. Vitamin D is also an important regulator of cell division and apoptosis [14]. Annwelier et al found that the serum vitamin D levels were associated with optic chiasma volume and vitamin D was found to inhibit neovascularisation in retinal tissue. Therefore low levels of Vitamin D are associated with an increased risk of diabetic retinopathy.The results of the present study revealed that out of 153 diabetic patients 23 diabetic patients (15%) had Diabetic Nephropathy. Then Vitamin D levels were measured in the patients of Diabetic nephropathy it was observed 47.8% had Vitamin D deficiency and out of 130 diabetic patients who did not have diabetic nephropathy 49.2% had vitamin D deficiency. The mean value of Vitamin D among the diabetic nephropathy was 18.68ng/ml and it was 20.98 in patients without diabetic nephropathy There was no statistical significant correlation between Vitamin D deficiency and Diabetic Nephropathy.In our study we found significantly low levels of vitamin D in diabetic population. The levels of Vitamin D were found to be significantly low with long duration of Diabetes and poor glycemic control. Role of Vitamin D in glucose metabolism has been investigated by many workers. There are several studies which support the role for Vitamin D in pancreatic Beta cell function. Vitamin D has an important role in synthesis and secretion of insulin.[15]Patrick et al and co-workers have shown the presence of Vitamin D receptors (VDR) in pancreatic beta cells. Expression of these Vitamin D receptors (VDR) in the beta cells of Pancreas and Polymorphisms in the VDR gene is responsible for the transcription and synthesis of insulin [22]. Pitas et al and co-workers have explained the direct effect of Vitamin D on insulin synthesis and secretion by demonstrating the activation of Vitamin D within the beta cells of pancreas by 1 alpha hydroxylase enzyme which is expressed in beta cells. Studies have shown that , Insulin secretion is a calcium dependant process and there is a crucial role of Vitamin D in maintaining extracellular calcium concentrations and calcium influx into beta cells which is necessary for insulin secretion [24]. In a study by Baynes et al and his co-workers it was found that Vitamin D is very important for maintaining Beta cell mass and deficiency of Vitamin D may cause increased apoptosis of beta cells thereby decreasing the insulin secretion. Apart from insulin secretion , studies have shown that Vitamin D could also affect insulin sensitivity and insulin resistance[16].Karl et al has shown that Vitamin D may also enhance insulin sensitivity by activating peroxisome proliferator activated receptor delta (PPAR-δ) which is a transcription factor that regulates the metabolism of fatty acids in skeletal muscle and adipose tissue [17]. Alex et al explained the role of Vitamin D on insulin sensitivity via its regulatory role in extracellular calcium concentration and flux through cell membranes. Uncontrolled Diabetes is shown to be a state of inflammation . There are increased levels of inflammatory markers like tumor necrosis factor alpha and beta, C reactive protein , plasminogen activator inhibitor and interleukin 6 which is responsible for increased atherosclerosis and end organ damage. It has been shown that Vitamin D acts as an anti-inflammatory hormone and it exerts its beneficial effects on the glycemic control and prevention of complications by repressing cytokines and interleukins [18] .Gagen et al showed that Vitamin D also protects against beta cell cytokine induced apoptosis by directly modulating the expression and activity of cytokines. Studies have suggested that physiological interactions exist between Vitamin D and insulin like growth factor-1 . Variations in circulating IGF-1are associated with variations in glycemia and may interact with Vitamin D status to influence metabolic syndrome risk It has been shown that Vitamin D has an important role in maintaining a large number of cellular processes. It maintains the Wnt/Beta catenin signalling pathway that inhibits adipocyte differentiation during adipogenesis. When Vitamin D is deficient many of these processes begin to decline and this set the stage for the onset of diseases such as diabetes [19]. Studies have shown that Vitamin D has a very significant role in maintaining the epigenome. Epigenetic alterations are a feature of diabetes by which many diabetes related genes are inactivated by hypermethylation [20]. Vitamin D acts to prevent such hypermethylation by increasing the expression of DNA demethylases that act to prevent the hypermethylation of multiple gene promoter regions of many diabetes related genes. In Vitamin D deficiency these processes begin to decline which may be responsible for early onset of diabetes [21]. It has been observed that Patients with chronic hyperglycemia with diabetic nephropathy leads to low Vitamin D levels as there are decreased rate of Vitamin D hydroxylation in the kidney Thus we see an important role of Vitamin D in carbohydrate metabolism with multiple effect on insulin secretion , Beta cell health and peripheral utilisation of insulin. So patients with vitamin D deficiency may lead to deleterious effect on glucose metabolism, poor glycemic control and problems related with chronic hyperglycemia [22].

CONCLUSION

Vitamin D deficiency is more common among females due to poor exposure to sunlight, poor dietary Vitamin D supplementation, lack of education, dark skin pigmentations, use of sunscreen lotions and excess adiposity. Vitamin D levels are lower in Diabetic patients in comparison to normal individuals. There is an inverse relation between the duration of diabetes mellitus and Vitamin D. As the duration of Diabetes increases, there is more Vitamin D deficiency .Vitamin D has negative correlation with blood HbA1C levels. Patients with poor Glycemic control have much more Vitamin D deficiency. Early detection of Vitamin D deficiency and supplementation may be an effective public health intervention programme to prevent Diabetes Mellitus and prevent long term diabetic complications**.**

LIMITATIONS

There are many factors such as occupation, dietary patterns etc whichmay be responsible for Vitamin D deficiency. These act as counfounding factors and they were not taken into consideration.

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CONFLICT OF INTEREST

None

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