

## “Evaluation of Vitamin D Supplementation In Management of Diabetic Retinopathy”

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### Abstract

#### AIM & OBJECTIVES OF THE STUDY:

- To evaluate the role of vitamin-D supplementation in management of diabetic retinopathy.
- To assess retinal vascular changes in diabetic retinopathy patients taking vitamin-D supplementation.

#### PATIENTS & METHODS:

In the present study, role of vitamin D supplementation in management of diabetic retinopathy was analysed. 47 diabetic retinopathy patients were taken according to inclusion criteria. After base line investigations 47 patients of either sex between 35-75 years were enrolled for the study and divided into two groups (group A and B). Patients with normal serum levels of vitamin D were kept under Group A (controls) & patients with low levels were kept under Group B (test subjects). After grouping, 25 patients were in group 'A' and 22 patients were in group 'B'. The base line parameters of the study population like age, sex, height, weight, FBS, PLBS, HbA1c and serum vitamin D levels were estimated before initiating the study. Vitamin D supplementation given in group B. Other modalities of treatment for diabetes and diabetic retinopathy maintained constant in both the groups. Parameters like weight, height, FBS, PLBS, HbA1c levels were tested at 0 day, end of 6<sup>th</sup> and 12<sup>th</sup> months. Serum vitamin D levels were tested at 0 day and end of 12<sup>th</sup> month. Results were analysed with p value calculated by t-test and chisquare test.

#### RESULTS:

Results of the study demonstrated that BMI varied from 0 day to 12<sup>th</sup> month in each group but they did not vary much when compared between the two groups, both the therapies are showing similar effect on BMI.

The % reduction in BMI was 0.78% in group A and 1.52% in group B. The difference in percentage is 0.74% which is insignificant.

The reduction in FBS was significant in Group A and Group B at the end of 12<sup>th</sup> month showing percentage reduction as 9.54% & 15.43% respectively. The difference in the percentage is 5.89%. Vitamin D supplementation is effective upto some extent in reducing FBS as there is little difference in both the groups.

The reduction in PLBS was significant in both the test groups showing percentage reduction of 18.79% and 19.74% in Group A & Group B respectively at the end of 12<sup>th</sup> month. The difference in percentage is 0.95% which is very small.

The reduction in HbA1c was insignificant in group A with a % reduction was 16.31% from 0 day to the end of 12<sup>th</sup> month. But in group B it was showing significant reduction with a % reduction was 13.99% from 0 day to the end of 12<sup>th</sup> month. The difference in percentage is 2.34%

The % increment in serum vitamin D levels in group A was 2.08% at 12<sup>th</sup> month and in group B it was increased very significantly with a % increment of 58.67% at the end of 12<sup>th</sup> month. The difference in percentage is 56.59%.

Serum levels of vitamin D in all the patients in group B raised above 30ng/ml at the end of 12<sup>th</sup> month. Above study supported the guidelines of endocrine society i.e., treatment for vitamin D deficiency is vitamin D supplementation of 50,000IU once a week for 8 weeks to achieve a blood level of 25(OH)D above 30ng/ml, followed by maintenance therapy of 1500IU/day.

The progression of disease from mild or moderate or severe NPDR to PDR in group A increased upto 16% at the end of 12<sup>th</sup> month. But in group B, progression from NPDR to PDR was not seen at the end of 12<sup>th</sup> month. The difference in percentage is 16%.

**Conclusion:** The results show that supplementation of vitamin D in diabetic retinopathy who are vitamin D deficient, decreases proliferation and neovascularisation in retina, improving glycemic control and also various other benefits without causing any side effects in cost effective manner.

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## **I. Introduction**

Diabetes mellitus is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period. If it is untreated, it causes many acute and chronic complications. Diabetic retinopathy is one of the chronic complications of diabetes. Diabetic retinopathy is called when damage occurs to the retina due to diabetes. It can eventually lead to blindness.<sup>(1)</sup> It is an ocular manifestation of diabetes, a systemic disease, which affects up to 80 percent of all patients who have had diabetes for 20 years or more.<sup>(2)</sup> Despite these intimidating statistics, research indicates that at least 90% of these new cases could be reduced if there were proper and vigilant treatment and monitoring of the eyes.<sup>(3)</sup> The longer a person has diabetes, the higher his or her chances of developing diabetic retinopathy.<sup>(4)</sup> It is also the leading cause of blindness for people aged 20 to 64 years.<sup>(5)</sup>

Diabetic retinopathy is a highly specific vascular complication and a sight-threatening problem related to diabetes. Diabetic retinopathy is characterised by gradually progressive alterations in the retinal microvasculature, leading to retinal non-perfusion, increased vascular permeability and pathologically intraocular proliferation of retinal vessels.

## **II. Epidemiology**

A recent pooled analysis from 35 population-based studies estimated that 93 million people worldwide have diabetic retinopathy, of whom 17 million (~18%) have proliferative DR, 21 million (~23%) have diabetic macular edema (DME), and 28 million (~20%) have sight-threatening DR<sup>[6]</sup>.

Among people with diabetes, this translates to an overall prevalence of 34.6% for any DR, 7.0% for proliferative DR, 6.8% for DME, and 10.2% for sight-threatening DR<sup>[6]</sup>. Pooled analyses showed no difference in prevalence between men and women. Asians had the lowest prevalence and African Americans the highest.

The prevalence of retinopathy is higher in people with long duration of diabetes, those with type 1 diabetes, and those with increased levels of HbA1c, blood pressure, or cholesterol<sup>[6]</sup>. Historically, DR was considered to be relatively infrequent in developing countries such as India and China; however changes in economies, diet, and longevity mean these nations now have as much, or more, DR than fully developed countries<sup>[7]</sup>.

India is set to emerge as the diabetic capital of the world. According to the WHO, 31.7 million people were affected by diabetes mellitus (DM) in India in the year 2000. This figure is estimated to rise to 79.4 million by 2030, the largest number in any nation in the world. Almost two-third of all Type 2 and almost all Type 1 diabetics are expected to develop diabetic retinopathy (DR) over a period of time.<sup>[8],[9],[10]</sup>

WESDR investigators reported a 10-year incidence of retinopathy of 74%. Of those with DR at baseline, 64% developed more severe DR and 17% progressed to proliferative DR<sup>[11]</sup>. Information from the 25-year follow-up of this cohort showed that virtually everyone eventually developed DR (97%), with up to half progressing to sight-threatening disease<sup>[12],[13]</sup>.

Vitamin D is essential for a vast number of physiologic processes and vitamin D insufficiency has reached pandemic proportions, with more than half the world's population at risk.<sup>(14)</sup> Vitamin D insufficiency has been implicated in the development of diabetes and also correlated with an elevated risk of cardiovascular disease, cancer, and mortality.<sup>(14-16)</sup> Additionally, vitamin D insufficiency has been associated with neurologic conditions, such as multiple sclerosis and Parkinson's disease.<sup>(17-18)</sup>

Vitamin D may play a role in the pathogenesis of diabetic retinopathy through its effects on the immune system and on angiogenesis. Vitamin D exerts an anti-inflammatory effect by decreasing the proliferation of lymphocytes, natural killer cells, and several pro-inflammatory cytokines.<sup>(19)</sup> Additionally, it has been shown that the active metabolite of vitamin D, calcitriol, is a potent inhibitor of retinal neovascularization in a mouse oxygen-induced ischemic retinopathy model.<sup>(20)</sup>

Vitamin-D deficiency is also one of the important risk factor for diabetic retinopathy as vitamin-D deficiency causes inflammatory and angiogenic effects in retina.

Hence the present study is undertaken to explore whether supplementing vitamin D preparations causes a reduction in changes of retinal vessels in treatment of diabetic retinopathy in a cost effective manner.

## **III. Aim of The Study**

- To evaluate the role of vitamin-D supplementation in management of diabetic retinopathy.

### **OBJECTIVES:**

- To assess retinal vascular changes in diabetic retinopathy patients taking vitamin-D supplementation.
- To determine relationship between vitamin-D supplementation and retinal changes in diabetic retinopathy.

#### **IV. Review of Literature**

##### **DIABETES MELLITUS**

**Diabetes mellitus (DM)**, commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period.<sup>[21]</sup> Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger.

Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced.<sup>[22]</sup> There are three main types of diabetes mellitus:

- Type 1 DM results from the pancreas's failure to produce enough insulin. This form was previously referred to as "insulin-dependent diabetes mellitus" (IDDM) or "juvenile diabetes". The cause is unknown.<sup>[23]</sup>
- Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly.<sup>[23]</sup> As the disease progresses a lack of insulin may also develop.<sup>[24]</sup> This form was previously referred to as "non insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The primary cause is excessive body weight and not enough exercise.<sup>[23]</sup>
- If left untreated, diabetes can cause many complications.<sup>[23]</sup> Acute complications can include diabetic ketoacidosis, nonketotic hyperosmolar coma, or death.<sup>[25]</sup> Serious long-term complications include heart disease, stroke, chronic kidney failure, foot ulcers, and damage to the eyes.<sup>[23]</sup>

#### **V. Diabetic Retinopathy**

**Diabetic retinopathy** affects blood vessels in the light-sensitive tissue called the retina that lines the back of the eye. The longer a person has diabetes, the more likely they will develop diabetic retinopathy. It is the most common cause of vision loss among people with diabetes and the leading cause of vision impairment and blindness among working-age adults.

##### **Signs and symptoms:**

Diabetic retinopathy often has no early warning signs. Even macular edema, which can cause rapid vision loss, may not have any warning signs for some time. In general, however, a person with macular edema is likely to have blurred vision, making it hard to do things like read or drive. In some cases, the vision will get better or worse during the day.

In the initial stages of diabetic retinopathy, patients are generally asymptomatic; in the more advanced stages of the disease, however, patients may experience symptoms that include floaters, blurred vision, distortion, and progressive visual acuity loss. Signs of diabetic retinopathy include the following:

- **Microaneurysms:** The earliest clinical sign of diabetic retinopathy; these occur secondary to capillary wall outpouching due to pericyte loss; they appear as small, red dots in the superficial retinal layers
- **Dot and blot hemorrhages:** Appear similar to microaneurysms if they are small; they occur as microaneurysms rupture in the deeper layers of the retina, such as the inner nuclear and outer plexiform layers
- **Flame-shaped hemorrhages:** Splinter hemorrhages that occur in the more superficial nerve fiber layer
- **Retinal edema and hard exudates:** Caused by the breakdown of the blood-retina barrier, allowing leakage of serum proteins, lipids, and protein from the vessels
- **Cotton-wool spots:** Nerve fiber layer infarctions from occlusion of precapillary arterioles; they are frequently bordered by microaneurysms and vascular hyperpermeability
- **Venous loops and venous beading:** Frequently occur adjacent to areas of nonperfusion; they reflect increasing retinal ischemia, and their occurrence is the most significant predictor of progression to proliferative diabetic retinopathy (PDR).
- **Intraretinal microvascular abnormalities:** Remodeled capillary beds without proliferative changes; can usually be found on the borders of the nonperfused retina
- **Macular edema:** Leading cause of visual impairment in patients with diabetes
- **Diabetic retinopathy may progress through four stages:**

**1. Mild Nonproliferative diabetic retinopathy:** Indicated by the presence of at least 1 microaneurysm

**2. Moderate Nonproliferative diabetic retinopathy:** Includes the presence of hemorrhages, microaneurysms, and hard exudates. As the disease progresses, blood vessels that nourish the retina may swell and distort. They may also lose their ability to transport blood. Both conditions cause characteristic changes to the appearance of the retina and may contribute to DME.

**3. Severe Nonproliferative diabetic retinopathy:** (4-2-1) Characterized by hemorrhages and microaneurysms in 4 quadrants, with venous beading in at least 2 quadrants and intraretinal microvascular abnormalities in at

least 1 quadrant. Many more blood vessels are blocked, depriving blood supply to areas of the retina. These areas secrete growth factors that signal the retina to grow new blood vessels.

**4.Proliferative diabetic retinopathy:** At this advanced stage, growth factors secreted by the retina trigger the proliferation of new blood vessels, which grow along the inside surface of the retina and into the vitreous gel, the fluid that fills the eye. The new blood vessels are fragile, which makes them more likely to leak and bleed. Accompanying scar tissue can contract and cause retinal detachment—the pulling away of the retina from underlying tissue, like wallpaper peeling away from a wall. Retinal detachment can lead to permanent vision loss

- Neovascularization: Hallmark of PDR
- Preretinal hemorrhages: Appear as pockets of blood within the potential space between the retina and the posterior hyaloid face; as blood pools within this space, the hemorrhages may appear boat shaped
- Hemorrhage into the vitreous: May appear as a diffuse haze or as clumps of blood clots within the gel
- Fibrovascular tissue proliferation: Usually seen associated with the neovascular complex; may appear avascular when the vessels have already regressed
- Traction retinal detachments: Usually appear tented up, immobile, and concave
- Macular edema

In non-proliferative diabetic retinopathy (NPDR) there are no symptoms, the signs are not visible to the eye and patients will have 20/20 vision. The only way to detect NPDR is by fundus photography, in which microaneurysms (microscopic blood-filled bulges in the artery walls) can be seen. If there is reduced vision, fluorescein angiography can be done to see the back of the eye. Narrowing or blocked retinal blood vessels can be seen clearly and this is called retinal ischemia (lack of blood flow).

Macular edema in which blood vessels leak their contents into the macular region can occur at any stage of NPDR. The symptoms of macular edema are blurred vision and darkened or distorted images that are not the same in both eyes. Ten percent (10%) of diabetic patients will have vision loss related to macular edema. Optical Coherence Tomography can show the areas of retinal thickening (due to fluid accumulation) of macular edema.<sup>[26]</sup>

In proliferative diabetic retinopathy (PDR), abnormal new blood vessels (neovascularisation) form at the back of the eye as part of *proliferative diabetic retinopathy* (PDR); these can burst and bleed (vitreous hemorrhage) and blur the vision, because these new blood vessels are fragile. The first time this bleeding occurs, it may not be very severe. In most cases, it will leave just a few specks of blood, or spots floating in a person's visual field, though the spots often go away after few hours.

These spots are often followed within a few days or weeks by a much greater leakage of blood, which blurs the vision. In extreme cases, a person may only be able to tell light from dark in that eye. It may take the blood anywhere from a few days to months or even years to clear from the inside of the eye, and in some cases the blood will not clear. These types of large hemorrhages tend to happen more than once, often during sleep.

On funduscopic exam, a doctor will see cotton wool spots, flame hemorrhages (similar lesions are also caused by the alpha-toxin of *Clostridium novyi*), and dot-blot hemorrhages.

#### **Risk factors:**

All people with diabetes mellitus are at risk – those with Type I diabetes and those with Type II diabetes. The longer a person has diabetes, the higher their risk of developing some ocular problem. Between 40 and 45 percent of Americans diagnosed with diabetes have some stage of diabetic retinopathy.<sup>[27]</sup> After 20 years of diabetes, nearly all patients with Type I diabetes and >60% of patients with Type II diabetes have some degree of retinopathy.

Anyone who has diabetes can develop diabetic retinopathy. Risk of developing the eye condition can increase as a result of:

- Duration of diabetes — the longer you have diabetes, the greater your risk of developing diabetic retinopathy
- Poor control of your blood sugar level
- High blood pressure
- Pregnancy
- Tobacco use
- Being black, Hispanic or Native American

Prior studies had also assumed a clear glycemic threshold between people at high and low risk of diabetic retinopathy.<sup>[28]</sup>

However, it has been shown that the widely accepted WHO and American Diabetes Association diagnostic cutoff for diabetes of a fasting plasma glucose  $\geq 7.0$  mmol/l (126 mg/dl) does not accurately identify diabetic retinopathy among patients.<sup>[29]</sup>

During pregnancy, diabetic retinopathy may also be a problem for women with diabetes. It is recommended that all pregnant women with diabetes have dilated eye examinations each trimester to protect their vision.

#### **Pathophysiology:**

The exact mechanism by which diabetes causes retinopathy remains unclear, but several theories have been postulated to explain the typical course and history of the disease.<sup>[30,31]</sup>

#### **Growth hormone**

Growth hormone appears to play a causative role in the development and progression of diabetic retinopathy. Diabetic retinopathy has been shown to be reversible in women who had postpartum hemorrhagic necrosis of the pituitary gland (Sheehan syndrome). This led to the controversial practice of pituitary ablation to treat or prevent diabetic retinopathy in the 1950s. This technique has since been abandoned because of numerous systemic complications and the discovery of the effectiveness of laser treatment. It should be noted that diabetic retinopathy has been reported in patients with hypopituitarism as well.

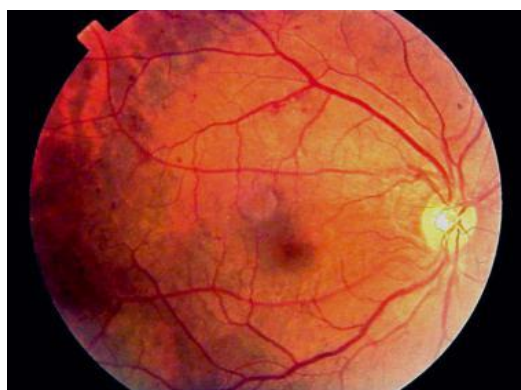
#### **Platelets and blood viscosity**

The variety of hematologic abnormalities seen in diabetes, such as increased erythrocyte aggregation, decreased red blood cell deformability, increased platelet aggregation, and adhesion, predispose the patient to sluggish circulation, endothelial damage, and focal capillary occlusion. This leads to retinal ischemia, which, in turn, contributes to the development of diabetic retinopathy.

#### **Aldose reductase and vasoproliferative factors**

Fundamentally, diabetes mellitus (DM) causes abnormal glucose metabolism as a result of decreased levels or activity of insulin. Increased levels of blood glucose are thought to have a structural and physiologic effect on retinal capillaries causing them to be both functionally and anatomically incompetent.

A persistent increase in blood glucose levels shunts excess glucose into the aldose reductase pathway in certain tissues, which converts sugars into alcohol (eg, glucose into sorbitol, galactose to dulcitol). Intramural pericytes of retinal capillaries seem to be affected by this increased level of sorbitol, eventually leading to the loss of their primary function (ie, autoregulation of retinal capillaries). This results in weakness and eventual saccular outpouching of capillary walls. These microaneurysms are the earliest detectable signs of DM retinopathy. (See the image below.)



Fundus photograph of early background diabetic retinopathy showing multiple microaneurysms.

Using nailfold video capillaroscopy, a high prevalence of capillary changes is detected in patients with diabetes, particularly those with retinal damage. This reflects a generalized microvessel involvement in both type 1 and type 2 diabetes.<sup>[32]</sup>

Ruptured microaneurysms result in retinal hemorrhages either superficially (flame-shaped hemorrhages) or in deeper layers of the retina (blot and dot hemorrhages). (See the image below.)

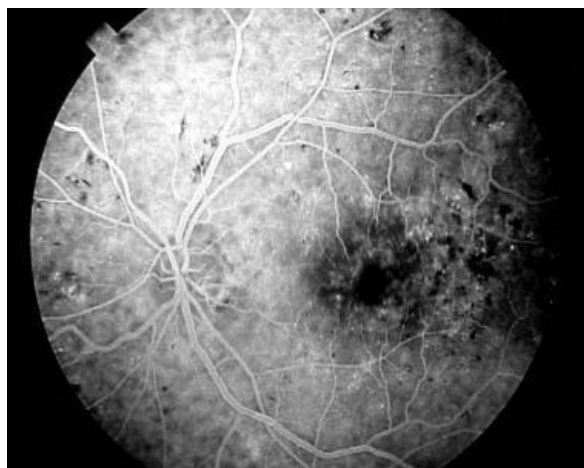


Retinal findings in background diabetic retinopathy, including blot hemorrhages (long arrow), microaneurysms (short arrow), and hard exudates (arrowhead).

Increased permeability of these vessels results in leakage of fluid and proteinaceous material, which clinically appears as retinal thickening and exudates. If the swelling and exudation involve the macula, a diminution in central vision may be experienced. An experimental study suggests that the pericyte death is caused when by blood glucose persistently activating protein kinase C and mitogen-activated protein kinase (MAPK), which through a series of intermediates inhibits signaling through platelet-derived growth factor receptors — signaling that supports cellular survival, proliferation, and growth. The resulting withdrawal of this signaling leads to the programmed cell death (apoptosis) of the cells in this experimental model.<sup>[33]</sup>

#### **Macular edema**

Macular edema is the most common cause of vision loss in patients with nonproliferative diabetic retinopathy (NPDR). However, it is not exclusively seen in patients with NPDR; it may also complicate cases of proliferative diabetic retinopathy.



Fluoresceinangiogram demonstrating foveal dye leakage caused by macular edema.



Fundus photograph of clinically significant macular edema demonstrating retinal exudates within the fovea.

Another theory to explain the development of macular edema focuses on the increased levels of diacylglycerol from the shunting of excess glucose. This is thought to activate protein kinase C, which, in turn, affects retinal blood dynamics, especially permeability and flow, leading to fluid leakage and retinal thickening.

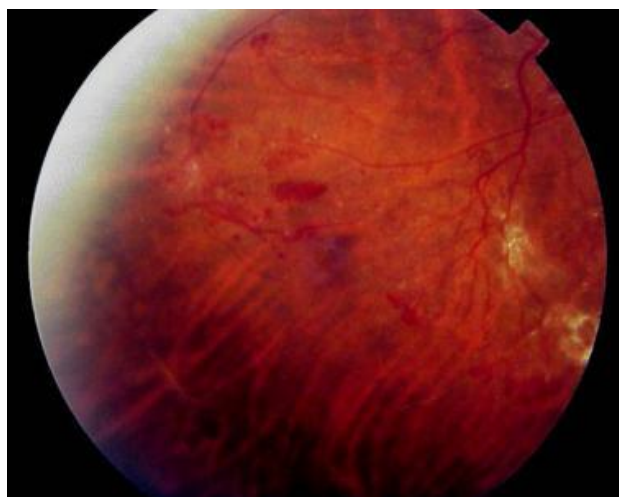
### **Hypoxia**

As the disease progresses, eventual closure of the retinal capillaries occurs, leading to hypoxia. Infarction of the nerve fiber layer leads to the formation of cotton-wool spots, with associated stasis in axoplasmic flow.

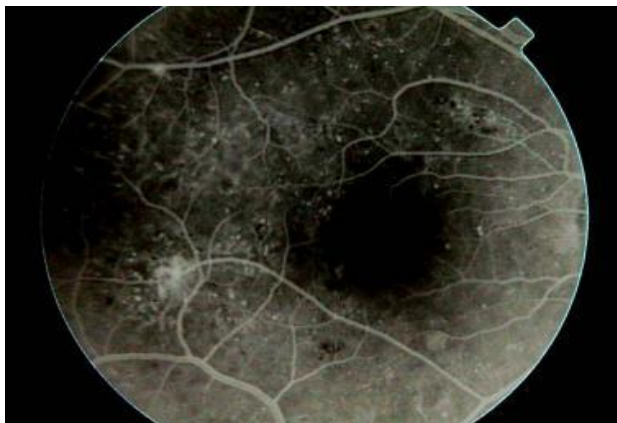
More extensive retinal hypoxia triggers compensatory mechanisms in the eye to provide enough oxygen to tissues. Venous caliber abnormalities, such as venous beading, loops, and dilation, signify increasing hypoxia and almost always are seen bordering the areas of capillary nonperfusion. Intraretinal microvascular abnormalities represent either new vessel growth or remodeling of preexisting vessels through endothelial cell proliferation within the retinal tissues to act as shunts through areas of nonperfusion.

### **Neovascularization**

Further increases in retinal ischemia trigger the production of vasoproliferative factors that stimulate new vessel formation. The extracellular matrix is broken down first by proteases, and new vessels arising mainly from the retinal venules penetrate the internal limiting membrane and form capillary networks between the inner surface of the retina and the posterior hyaloid face. (See the images below.)



New vessel formation on the surface of the retina (neovascularization elsewhere)



An area of neovascularization that leaks fluorescein on angiography



Boat-shaped preretinal hemorrhage associated with neovascularization elsewhere.

In patients with proliferative diabetic retinopathy (PDR), nocturnal intermittent hypoxia/reoxygenation that results from sleep-disordered breathing may be a risk factor for iris and/or angle neovascularization.<sup>[34]</sup>

Neovascularization is most commonly observed at the borders of perfused and nonperfused retina and most commonly occurs along the vascular arcades and at the optic nerve head. The new vessels break through and grow along the surface of the retina and into the scaffold of the posterior hyaloid face. By themselves, these vessels rarely cause visual compromise, but they are fragile and highly permeable. These delicate vessels are disrupted easily by vitreous traction, which leads to hemorrhage into the vitreous cavity or the preretinal space.

These new blood vessels initially are associated with a small amount of fibroglial tissue formation. However, as the density of the neovascular frond increases, so does the degree of fibrous tissue formation.

In later stages, the vessels may regress, leaving only networks of avascular fibrous tissue adherent to both the retina and the posterior hyaloid face. As the vitreous contracts, it may exert tractional forces on the retina via these fibroglial connections. Traction may cause retinal edema, retinal heterotopia, and both tractional retinal detachments and retinal tear formation with subsequent detachment.

#### Diagnosis:

- *Visual acuity test:* This test uses an eye chart to measure how well a person sees at various distances (*i.e.*, visual acuity).
- *Pupil dilation:* The eye care professional places drops into the eye to dilate the pupil. This allows him or her to see more of the retina and look for signs of diabetic retinopathy. After the examination, close-up vision may remain blurred for several hours.
- *Ophthalmoscopy or fundus photography:* Ophthalmoscopy is an examination of the retina in which the eye care professional: (1) looks through a slit lamp biomicroscope with a special magnifying lens that provides a narrow view of the retina, or (2) wearing a headset (indirect ophthalmoscope) with a bright light, looks through a special magnifying glass and gains a wide view of the retina. Hand-held ophthalmoscopy is insufficient to rule out significant and treatable diabetic retinopathy. Fundus photography generally recreate considerably larger areas of the fundus, and has the advantage of photo documentation for future reference, as well as availing the image to be examined by a specialist at another location and/or time.



- *Fundus Fluorescein angiography (FFA)*: This is an imaging technique which relies on the circulation of Fluorescein dye to show staining, leakage, or non-perfusion of the retinal and choroidal vasculature.
- *Optical coherence tomography (OCT)*: This is an optical imaging modality based upon interference, and analogous to ultrasound. It produces cross-sectional images of the retina (B-scans) which can be used to measure the thickness of the retina and to resolve its major layers, allowing the observation of swelling.
- *Digital Retinal Screening Programs*: Systematic programs for the early detection of eye disease including diabetic retinopathy are becoming more common, such as in the UK, where all people over 12 years old with diabetes are offered retinal screening at least annually. This involves digital image capture and transmission of the images to a digital reading center for evaluation and treatment referral. See Vanderbilt Ophthalmic Imaging Center<sup>[35]</sup> and the NHS Diabetic Eye Screening Programme<sup>[36]</sup> The name Diabetic Retinopathy Screening Service (DRSS), or more recently - Diabetic Eye Screening Service (DESP) is also used.<sup>[37]</sup>
- *Computer Vision Approach*: It is a System developed by Researchers at IIT Kharagpur in collaboration with IBM India. It uses data analytics capabilities to automatically compare and analyse retina images of the patient. It can tell if the patient has DR and also provides risk categorisation ranging from low to medium and high.<sup>[38]</sup>

The eye care professional will look at the retina for early signs of the disease, such as:

1. leaking blood vessels,
2. retinal swelling, such as macular edema,
3. pale, fatty deposits on the retina (exudates) – signs of leaking blood vessels,
4. damaged nerve tissue (neuropathy), and
5. any changes in the blood vessels.

If macular edema is suspected, FFA and sometimes OCT may be performed.

#### **Prevention:**

Diabetic retinopathy usually takes years to develop, which is why it is important to have regular eye exams. Because people with Type 2 diabetes may have been living with the disease for some time before they are diagnosed, it is important that they see an ophthalmologist without delay.

The American Academy of Ophthalmology recommends the following diabetic eye screening schedule for people with diabetes:

**Type 1 Diabetes:** Within five years of being diagnosed and then yearly.

**Type 2 Diabetes:** At the time of diabetes diagnosis and then yearly.

**During pregnancy:** Pregnant women with diabetes should schedule an appointment with their ophthalmologist in the first trimester because retinopathy can progress quickly during pregnancy.

Vision lost to diabetic retinopathy is sometimes irreversible. However, early detection and treatment can reduce the risk of blindness by 95%. Because diabetic retinopathy often lacks early symptoms, people with diabetes should get a comprehensive dilated eye exam at least once a year. People with diabetic retinopathy may need eye exams more frequently. Women with diabetes who become pregnant should have a comprehensive dilated eye exam as soon as possible. Additional exams during pregnancy may be needed.

Studies such as the Diabetes Control and Complications Trial (DCCT) have shown that controlling diabetes slows the onset and worsening of diabetic retinopathy. DCCT study participants who kept their blood glucose level as close to normal as possible were significantly less likely than those without optimal glucose control to develop diabetic retinopathy, as well as kidney and nerve diseases. Other trials have shown that controlling elevated blood pressure and cholesterol can reduce the risk of vision loss among people with diabetes.

Treatment for diabetic retinopathy is often delayed until it starts to progress to PDR, or when DME occurs. Comprehensive dilated eye exams are needed more frequently as diabetic retinopathy becomes more severe. People with severe nonproliferative diabetic retinopathy have a high risk of developing PDR and may need a comprehensive dilated eye exam as often as every 2 to 4 months.

#### **Management:**

There are three major treatments for diabetic retinopathy, which are very effective in reducing vision loss from this disease.<sup>[39]</sup> In fact, even people with advanced retinopathy have a 95 percent chance of keeping their vision when they get treatment before the retina is severely damaged.<sup>[40]</sup> These three treatments are laser surgery, injection of corticosteroids or anti-VEGF agents into the eye, and vitrectomy.

Although these treatments are very successful (in slowing or stopping further vision loss), they do not cure diabetic retinopathy. Caution should be exercised in treatment with laser surgery since it causes a loss of

retinal tissue. It is often more prudent to inject triamcinolone or anti-VEGF drugs. In some patients it results in a marked increase of vision, especially if there is an edema of the macula.<sup>[41]</sup>

Avoiding tobacco use and correction of associated hypertension are important therapeutic measures in the management of diabetic retinopathy.<sup>[42]</sup>

The best way of preventing the onset and delaying the progression of diabetic retinopathy is to monitor it vigilantly and achieve optimal glycaemic control.<sup>[43]</sup>

Since 2008 there have been other therapies (e.g. kinase inhibitors and anti-VEGF) drugs available.<sup>[44]</sup>

### **Laser photocoagulation**

Laser photocoagulation can be used in two scenarios for the treatment of diabetic retinopathy. It can be used to treat macular edema by creating a Modified Grid at the posterior pole and it can be used for panretinal coagulation for controlling neovascularization. It is widely used for early stages of proliferative retinopathy. Laser treatment:

- involves shining a laser into patient's eyes – patient will be given local anaesthetic drops to numb his eyes; eye drops are used to widen his pupils and special contact lenses are used to hold his eyelids open and focus the laser onto his retina
- normally takes around 20-40 minutes
- is usually carried out on an outpatient basis, which means no need to stay in hospital overnight
- may require more than one visit to a laser treatment clinic
- isn't usually painful, although patient may feel a sharp pricking sensation when certain areas of eye are being treated

### **Side effects**

After treatment, patient may have some side effects for a few hours. These can include:

- blurred vision – patient won't be able to drive until this passes
- increased sensitivity to light – it might help to wear sunglasses until eyes have adjusted
- aching or discomfort – over-the-counter painkillers, such as paracetamol, should help

### **Possible complications**

Patient should be told about the risks of treatment in advance. Potential complications include:

- reduced night or peripheral (side) vision
- bleeding into the eye or objects floating in vision (floaters)
- being able to "see" the pattern made by the laser on the back of eye for a few months
- a small, but permanent, blind spot close to the centre of vision

Need to get medical advice if sight gets worse after treatment.

### **Modified Grid Laser photocoagulation:**

A 'C' shaped area around the macula is treated with low intensity small burns. This helps in clearing the macular edema.

### **Panretinal photocoagulation:**

Panretinal photocoagulation, or PRP (also called scatter laser treatment), is used to treat proliferative diabetic retinopathy (PDR). The goal is to create 1,600 - 2,000 burns in the retina with the hope of reducing the retina's oxygen demand, and hence the possibility of ischemia. It is done in multiple sittings.

In treating advanced diabetic retinopathy, the burns are used to destroy the abnormal blood vessels that form in the retina. This has been shown to reduce the risk of severe vision loss for eyes at risk by 50%.

Before using the laser, the ophthalmologist dilates the pupil and applies anaesthetic drops to numb the eye. In some cases, the doctor also may numb the area behind the eye to reduce discomfort. The patient sits facing the laser machine while the doctor holds a special lens on the eye. The physician can use a single spot laser or a pattern scan laser for two dimensional patterns such as squares, rings and arcs. During the procedure, the patient will see flashes of light. These flashes often create an uncomfortable stinging sensation for the patient. After the laser treatment, patients should be advised not to drive for a few hours while the pupils are still dilated. Vision will most likely remain blurry for the rest of the day. Though there should not be much pain in the eye itself, an ice-cream headache like pain may last for hours afterwards.

Patients will lose some of their peripheral vision after this surgery although it may be barely noticeable by the patient. The procedure does however save the center of the patient's sight. Laser surgery may also slightly reduce colour and night vision.

### **Intravitreal triamcinolone acetonide:**

Triamcinolone is a long acting steroid preparation. When injected in the vitreous cavity, it decreases the macular edema (thickening of the retina at the macula) caused due to diabetic maculopathy, and results in an increase in visual acuity. The effect of triamcinolone is transient, lasting up to three months, which necessitates repeated injections for maintaining the beneficial effect. Best results of intravitreal Triamcinolone have been found in eyes that have already undergone cataract surgery. Complications of intravitreal injection of triamcinolone include cataract, steroid-induced glaucoma and endophthalmitis.

#### **Intravitreal anti-VEGF drugs:**

There are good results from multiple doses of intravitreal injections of anti-VEGF drugs such as bevacizumab.<sup>[46]</sup> Present recommended treatment for diabetic macular edema is Modified Grid laser photocoagulation combined with multiple injections of anti-VEGF drugs.

Anti-VEGF drugs are injected into the vitreous gel to block a protein called vascular endothelial growth factor (VEGF), which can stimulate abnormal blood vessels to grow and leak fluid. Blocking VEGF can reverse abnormal blood vessel growth and decrease fluid in the retina. Available anti-VEGF drugs include Avastin (bevacizumab), Lucentis (ranibizumab), and Eylea (aflibercept). Lucentis and Eylea are approved by the U.S. Food and Drug Administration (FDA) for treating DME. Avastin was approved by the FDA to treat cancer, but is commonly used to treat eye conditions, including DME.

The NEI-sponsored Diabetic Retinopathy Clinical Research Network compared Avastin, Lucentis, and Eylea in a clinical trial. The study found all three drugs to be safe and effective for treating most people with DME. Patients who started the trial with 20/40 or better vision experienced similar improvements in vision no matter which of the three drugs they were given. However, patients who started the trial with 20/50 or worse vision had greater improvements in vision with Eylea.

Most people require monthly anti-VEGF injections for the first six months of treatment. Thereafter, injections are needed less often: typically three to four during the second six months of treatment, about four during the second year of treatment, two in the third year, one in the fourth year, and none in the fifth year. Dilated eye exams may be needed less often as the disease stabilizes.

The injections are usually given once a month to begin with. Once your vision starts to stabilise, they'll be stopped or given less frequently.

Injections of steroid medication may sometimes be given instead of anti-VEGF injections, or if the anti-VEGF injections don't help.

#### **Risks and side effects**

Possible risks and side effects of anti-VEGF injections include:

- eye irritation or discomfort
- bleeding inside the eye
- floaters or a feeling of having something in your eye
- watery or dry, itchy eyes

There's also a risk that the injections could cause blood clots to form, which could lead to a heart attack or stroke. This risk is small, but it should be discussed with patient before taking consent to treatment.

The main risk with steroid injections is increased pressure inside the eye.

#### **Vitrectomy:**

Instead of laser surgery, some people require a vitrectomy to restore vision. A vitrectomy is performed when there is a lot of blood in the vitreous. It involves removing the cloudy vitreous and replacing it with a saline solution. Studies show that people who have a vitrectomy soon after a large hemorrhage are more likely to protect their vision than someone who waits to have the operation. Early vitrectomy is especially effective in people with insulin-dependent diabetes, who may be at greater risk of blindness from a hemorrhage into the eye.

Vitrectomy is often done under local anesthesia. The doctor makes a tiny incision in the sclera, or white of the eye. Next, a small instrument is placed into the eye to remove the vitreous and insert the saline solution into the eye. Vitrectomy is frequently combined with other modalities of treatment.

#### **Cryotherapy:**

When laser photocoagulation is precluded in the presence of an opaque media, such as in cases of cataracts and vitreous hemorrhage, cryotherapy may be applied instead. The principles behind the treatment are basically the same—that is, to ablate retinal tissue for oxygen demand to be decreased and to induce a chorioretinal adhesion, which could increase oxygen supply to the retina in the hope of preventing or down-regulating the vasoproliferative response.

#### **Patient Education:**

One of the most important aspects in the management of diabetic retinopathy is patient education. Inform patients that they play an integral role in their own eye care.

Excellent glucose control is beneficial in any stage of diabetic retinopathy. It delays the onset and slows down the progression of the diabetic complications in the eye.

The following symptoms and/or health concerns must be addressed in any patient education program for those with diabetic retinopathy:

- Systemic problems (eg, hypertension, renal disease, and hyperlipidemia) may contribute to disease progression.
- Smoking, although not directly proven to affect the course of the retinopathy, may further compromise oxygen delivery to the retina. Therefore, all efforts should be made in the reduction, if not outright cessation, of smoking.
- Visual symptoms (eg, vision changes, floaters, distortion, redness, pain) could be manifestations of disease progression and should be reported immediately.

Diabetes mellitus, in general, and diabetic retinopathy, in particular, are progressive conditions, and regular follow-up care with a physician is crucial for detection of any changes that may benefit from treatment.

#### **Prognosis:**

Prognostic factors that are favorable for visual loss include the following:

- Circinate exudates of recent onset
- Well-defined leakage
- Good perifoveal perfusion

Prognostic factors that are unfavorable for visual loss include the following:

- Diffuse edema/multiple leaks
- Lipid deposition in the fovea
- Macular ischemia
- Cystoid macular edema
- Preoperative vision of less than 20/200
- Hypertension

Approximately 8,000 eyes become blind yearly because of diabetes. The treatment of diabetic retinopathy entails tremendous costs, but it has been estimated that this represents only one eighth of the costs of Social Security payments for vision loss. This cost does not compare to the cost in terms of loss of productivity and quality of life. The Early Treatment for Diabetic Retinopathy Study has found that laser surgery for macular edema reduces the incidence of moderate visual loss (doubling of visual angle or roughly a 2-line visual loss) from 30% to 15% over a 3-year period. The Diabetic Retinopathy Study has found that adequate scatter laser panretinal photocoagulation reduces the risk of severe visual loss (< 5/200) by more than 50%.<sup>[45, 46]</sup>

#### **Complications:**

Diabetic retinopathy involves the abnormal growth of blood vessels in the retina. Complications can lead to serious vision problems:

- **Vitreous hemorrhage.** The new blood vessels may bleed into the clear, jelly-like substance that fills the center of eye. If the amount of bleeding is small, patient might see only a few dark spots (floaters). In more-severe cases, blood can fill the vitreous cavity and completely block his vision.
- Vitreous hemorrhage by itself usually doesn't cause permanent vision loss. The blood often clears from the eye within a few weeks or months. Unless patient's retina is damaged, his vision may return to its previous clarity.
- **Retinal detachment.** The abnormal blood vessels associated with diabetic retinopathy stimulate the growth of scar tissue, which can pull the retina away from the back of the eye. This may cause spots floating in vision, flashes of light or severe vision loss.
- **Glaucoma.** New blood vessels may grow in the front part of eye and interfere with the normal flow of fluid out of the eye, causing pressure in the eye to build up (glaucoma). This pressure can damage the nerve that carries images from eye to brain (optic nerve).
- **Blindness.** Eventually, diabetic retinopathy, glaucoma or both can lead to complete vision loss.

#### **Diabetic retinopathy and vitamin D:**

"Patients with diabetes and low vitamin D levels may develop earlier or more severe diabetic retinopathy," Dr Sanguankeo told *Medscape Medical News* in an interview.

The mechanism could be twofold, he said. Studies suggest that vitamin D might improve insulin secretion in type 2 diabetes and may also directly reduce vascular endothelial growth factors. (Thus, deficiency would have the opposite effects.)

Animal studies have demonstrated vitamin D receptors in the retina, and when given vitamin D, vascularization was reduced in animal models.

"But in humans, there are very few studies that assess how vitamin D supplementation affects diabetic retinopathy," Dr Sanguankeo commented.

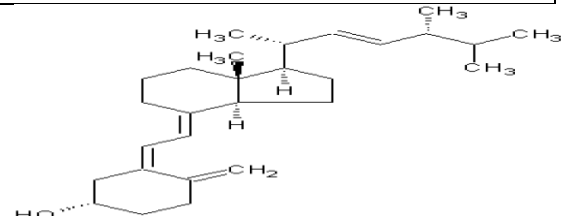
Mantel et al.11 recently showed that calcitriol inhibits angiogenesis in vivo in a xenograft breast cancer model and EC proliferation and morphogenesis in vitro by inhibiting EC proliferation and induction of apoptosis. However, the effect of calcitriol on EC proliferation mediated by VEGF was small.

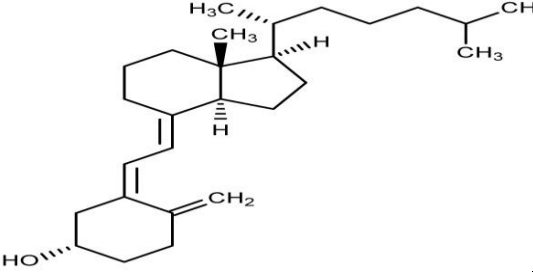
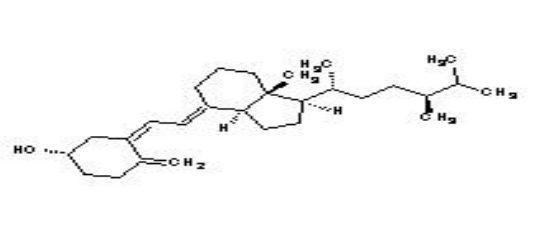
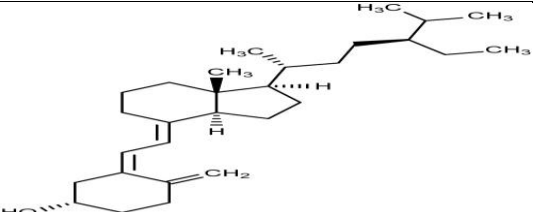
Vitamin D probably has little role in the prevention of diabetes in people with normoglycemia. It has been suggested that in individuals with prediabetes, low serum 25(OH)D levels can promote further deterioration in glucose tolerance. Hence, the role of Vitamin D supplementation in progression of prediabetes to overt diabetes is being explored.

Vitamin D's ability to inhibit neovascularization also has led researchers to examine the hormone's involvement in diabetic retinopathy (DR) development. In an epidemiological study, Aksoy et al. (2000) found that serum vitamin D concentrations were inversely related to the severity of retinopathy in diabetic patients, with the lowest concentrations of the hormone measured in patients with proliferative DR (Aksoy et al., 2000). Patients without associated retinopathy had the highest serum vitamin D concentrations. A similar study classified patients into diabetic groups based on disease severity and also found that patients with proliferative DR had the lowest mean 25D3 levels (21.1 ng/mL) (Payne et al., 2012). In addition, vitamin D deficiency was associated with increased risk of retinopathy in an adolescent population with type 1 diabetes (Kaur et al., 2011), however it was not associated with changes in retinal geometric parameters such as vascular branching angle, length-diameter ratio, or tortuosity (Poon et al., 2013). Genetic variations in VDR have also been associated with diabetic retinopathy. In a cohort of Caucasian patients with type 1 diabetes, patients with the FokI VDR polymorphism (FF genotype), had a lower incidence of advanced diabetic retinopathy, particularly in those patients whose duration of diabetes was less than 25 years (Taverna et al., 2005). The FokI substitution is a functional polymorphism which has been reported to increase immune cell activity (van Etten et al., 2007) and therefore could have a protective effect on DR development. In other studies, the VDR BsmI gene polymorphism was also associated with risk of DR (Bucan et al., 2009) and the Taq I polymorphism with severe DR (Taverna et al., 2002). Looking to an animal model to study vitamin D's ability to protect against retinopathy, Ren et al. used a rat model of type 2 diabetes (Ren et al., 2012). They found that animals treated with vitamin D had decreased retinal expression of VEGF and TGF- $\beta$ 1. Histological examination also suggested that vitamin D had a protective effect in the retinas of these rats. These combined studies suggest that vitamin D status could be important in the prevention of DR, particularly proliferative retinopathy. Further studies are needed to determine the mechanism of vitamin D protection and if it can directly inhibit neovascularization in this sight-threatening condition.

## VI. Vitamin D

**Vitamin D** refers to a group of fat-soluble secosteroids responsible for increasing intestinal absorption of calcium, iron, magnesium, phosphate, and zinc. In humans, the most important compounds in this group are vitamin D<sub>3</sub> (also known as cholecalciferol) and vitamin D<sub>2</sub> (ergocalciferol).<sup>[47]</sup> Cholecalciferol and ergocalciferol can be ingested from the diet and from supplements.<sup>[47][48][49]</sup>

Types		
Name	Chemical composition	Structure
Vitamin D <sub>1</sub>	Mixture of molecular compounds of ergocalciferol with lumisterol, 1:1	
Vitamin D <sub>2</sub>	ergocalciferol (made from ergosterol)	

<b>Vitamin D<sub>3</sub></b>	cholecalciferol (made from 7-dehydrocholesterol in the skin).	
<b>Vitamin D<sub>4</sub></b>	22-dihydroergocalciferol	
<b>Vitamin D<sub>5</sub></b>	sitocalciferol (made from 7-dehydrositosterol)	

Several forms (vitamers) of vitamin D exist. The two major forms are vitamin D<sub>2</sub> or ergocalciferol, and vitamin D<sub>3</sub> or cholecalciferol; vitamin D without a subscript refers to either D<sub>2</sub> or D<sub>3</sub> or both. These are known collectively as calciferol. Vitamin D<sub>2</sub> was chemically characterized in 1931. In 1935, the chemical structure of vitamin D<sub>3</sub> was established and proven to result from the ultraviolet irradiation of 7-dehydrocholesterol.

Chemically, the various forms of vitamin D are secosteroids, i.e., steroids in which one of the bonds in the steroid rings is broken. The structural difference between vitamin D<sub>2</sub> and vitamin D<sub>3</sub> is the side chain of D<sub>2</sub> contains a double bond between carbons 22 and 23, and a methyl group on carbon 24.

**History:**

American researchers Elmer McCollum and Marguerite Davis in 1914 discovered a substance in cod liver oil which later was called "vitamin A". British doctor Edward Mellanby noticed dogs that were fed cod liver oil did not develop rickets and concluded vitamin A, or a closely associated factor, could prevent the disease. In 1922, Elmer McCollum tested modified cod liver oil in which the vitamin A had been destroyed. The modified oil cured the sick dogs, so McCollum concluded the factor in cod liver oil which cured rickets was distinct from vitamin A. He called it vitamin D because it was the fourth vitamin to be named.

In 1925, it was established that when 7-dehydrocholesterol is irradiated with light, a form of a fat-soluble vitamin is produced (now known as D<sub>3</sub>). Alfred Fabian Hess stated: "Light equals vitamin D. Adolf Windaus, at the University of Göttingen in Germany, received the Nobel Prize in Chemistry in 1928 for his work on the constitution of sterols and their connection with vitamins. In 1929, a group at NIMR in Hampstead, London, were working on the structure of vitamin D, which was still unknown, as well as the structure of steroids.

In 1932, Otto Rosenheim and Harold King published a paper putting forward structures for sterols and bile acids which found immediate acceptance. In the 1930s, Windaus clarified further the chemical structure of vitamin D.

In 1923, American biochemist Harry Steenbock at the University of Wisconsin demonstrated that irradiation by ultraviolet light increased the vitamin D content of foods and other organic materials. After irradiating rodent food, Steenbock discovered the rodents were cured of rickets. A vitamin D deficiency is a known cause of rickets. Using \$300 of his own money, Steenbock patented his invention. His irradiation technique was used for foodstuffs, most memorably for milk. By the expiration of his patent in 1945, rickets had been all but eliminated in the US.

In 1971–72, the further metabolism of vitamin D to active forms was discovered. In the liver, vitamin D was found to be converted to calcidiol. Calcidiol is then converted by the kidneys to calcitriol, the biologically active form of vitamin D. Calcitriol circulates as a hormone in the blood, regulating the concentration of calcium and phosphate in the bloodstream and promoting the healthy growth and remodeling of

bone. The vitamin D metabolites, calcidiol and calcitriol, were identified by competing teams led by Michael F. Holick in the laboratory of Hector DeLuca and by Tony Norman and colleagues.

**Dietary sources:** Vitamin D is found in few dietary sources. Sunlight exposure is the primary source of vitamin D for the majority of people, other than supplements.<sup>[48]</sup>

<b>Table : Selected Food Sources of Vitamin D</b>		
<b>Food</b>	<b>IUs per serving*</b>	<b>Percent DV**</b>
Cod liver oil, 1 tablespoon	1,360	340
Swordfish, cooked, 3 ounces	566	142
Salmon (sockeye), cooked, 3 ounces	447	112
Tuna fish, canned in water, drained, 3 ounces	154	39
Orange juice fortified with vitamin D, 1 cup (check product labels, as amount of added vitamin D varies)	137	34
Milk, nonfat, reduced fat, and whole, vitamin D-fortified, 1 cup	115-124	29-31
Yogurt, fortified with 20% of the DV for vitamin D, 6 ounces (more heavily fortified yogurts provide more of the DV)	80	20
Margarine, fortified, 1 tablespoon	60	15
Sardines, canned in oil, drained, 2 sardines	46	12
Liver, beef, cooked, 3 ounces	42	11
Egg, 1 large (vitamin D is found in yolk)	41	10
Ready-to-eat cereal, fortified with 10% of the DV for vitamin D, 0.75-1 cup (more heavily fortified cereals might provide more of the DV)	40	10
Cheese, Swiss, 1 ounce	6	2

\*IUs=InternationalUnits.

\*\* DV = Daily Value. DVs were developed by the U.S. Food and Drug Administration to help consumers compare the nutrient contents among products within the context of a total daily diet. The DV for vitamin D is currently set at 400 IU for adults and children age 4 and older.

**Dietary reference intakes:**

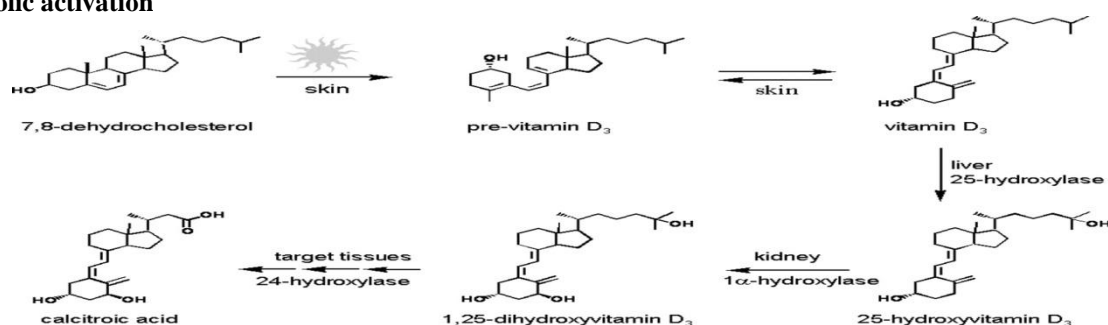
Different institutions propose different recommendations concerning daily amounts of the vitamin. The recommended daily intake of vitamin D *may* not be sufficient if sunlight exposure is limited.<sup>[50]</sup>

<b>SUGGESTED VITAMIN D INTAKE</b>				
<b>Age</b>	<b>General Population (Institute of Medicine Recommendations)</b>		<b>At Risk of Vitamin D Deficiency (The Endocrine Society Suggestions)</b>	
	<b>RDA (IU/day)</b>	<b>Upper Limit (IU/day)</b>	<b>Daily Recommendation (IU/day)</b>	<b>Upper Limit (IU/day)</b>
<b>Infants and children</b>				
0-6 months	—	1,000	400-1,000	2,000
6-12 months	—	1,500	400-1,000	2,000
1-3 years	600	2,500	600-1,000	4,000
4-8 years	600	3,000	600-1,000	4,000
9-18 years	600	4,000	600-1,000	4,000
<b>Adults</b>				
19-70 years	600	4,000	1,500-2,000	10,000
>70 years	800	4,000	1,500-2,000	10,000
<b>Pregnant or breast-feeding</b>				
14-18 years	600	4,000	600-1,000	4,000
19-50 years	600	4,000	1,500-2,000	10,000

IU = International Units

**Mechanism of action:**

### Metabolic activation



Vitamin D is carried in the bloodstream to the liver, where it is converted into the prohormone calcidiol (25-hydroxyvitamin D<sub>3</sub>). Circulating calcidiol may then be converted into calcitriol (1,25-dihydroxyvitamin D<sub>3</sub>), the biologically active form of vitamin D, in the kidneys. Following the final converting step in the kidney, calcitriol is released into the circulation. By binding to vitamin D-binding protein, a carrier protein in the plasma, calcitriol is transported to various target organs. In addition to the kidneys, calcitriol is also synthesized by monocyte-macrophages in the immune system. When synthesized by monocyte-macrophages, calcitriol acts locally as a cytokine, defending the body against microbial invaders by stimulating the innate immune system.

Whether it is made in the skin or ingested, cholecalciferol is hydroxylated in the liver at position 25 (upper right of the molecule) to form 25-hydroxycholecalciferol (calcidiol or 25(OH)D). This reaction is catalyzed by the microsomal enzyme vitamin D 25-hydroxylase, which is produced by hepatocytes. Once made, the product is released into the plasma, where it is bound to an  $\alpha$ -globulin, vitamin D-binding protein.

Calcidiol is transported to the proximal tubules of the kidneys, where it is hydroxylated at the 1- $\alpha$  position (lower right of the molecule) to form calcitriol (1,25-dihydroxycholecalciferol or 1,25(OH)<sub>2</sub>D). This product is a potent ligand of the vitamin D receptor, which mediates most of the physiological actions of the vitamin. The conversion of calcidiol to calcitriol is catalyzed by the enzyme 25-hydroxyvitamin D<sub>3</sub> 1- $\alpha$ -hydroxylase, the levels of which are increased by parathyroid hormone (and additionally by low calcium or phosphate).

### Biosynthesis

In the presence of UV radiation, many animals synthesize vitamin D<sub>3</sub> from 7-dehydrocholesterol, and many fungi synthesize vitamin D<sub>2</sub> from ergosterol.

### Photochemistry

The transformation that converts 7-dehydrocholesterol to vitamin D<sub>3</sub> occurs in two steps. First, 7-dehydrocholesterol is photolyzed by ultraviolet light in a 6-electron conrotatory ring-opening electrocyclic reaction; the product is previtamin D<sub>3</sub>. Second, previtamin D<sub>3</sub> spontaneously isomerizes to vitamin D<sub>3</sub> (cholecalciferol) in an antarafacial sigmatropic hydride shift. At room temperature, the transformation of previtamin D<sub>3</sub> to vitamin D<sub>3</sub> in an organic solvent takes about 12 days to complete. The conversion of previtamin D<sub>3</sub> to vitamin D<sub>3</sub> in the skin is about 10 times faster than in an organic solvent.

### Evolution

Photosynthesis of vitamin D in the ocean by phytoplankton (such as coccolithophore and *Emiliania huxleyi*) has existed for more than 500 million years and continues to the present. Although primitive vertebrates in the ocean could absorb calcium from the ocean into their skeletons and eat plankton rich in vitamin D, land animals required another way to satisfy their vitamin D requirement for a calcified skeleton without relying on plants. Land vertebrates have been making their own vitamin D for more than 350 million years.

Vitamin D can be synthesized only by a photochemical process, so land vertebrates had to ingest foods that contained vitamin D or had to be exposed to sunlight to photosynthesize vitamin D in their skin to satisfy their vitamin D requirements.

### Synthesis in the skin

In the epidermal strata of the skin, production is greatest in the stratum basale and stratum spinosum. Vitamin D<sub>3</sub> is produced photochemically from 7-dehydrocholesterol in the skin of most vertebrate animals, including humans. The precursor of vitamin D<sub>3</sub>, 7-dehydrocholesterol is produced in relatively large quantities. 7-Dehydrocholesterol reacts with UVB light at wavelengths between 270 and 300 nm, with peak synthesis occurring between 295 and 297 nm. These wavelengths are present in sunlight, as well as in the light emitted by the UV lamps in tanning beds (which produce ultraviolet primarily in the UVA spectrum, but typically produce



4% to 10% of the total UV emissions as UVB). Exposure to light through windows is insufficient because glass almost completely blocks UVB light.

Adequate amounts of vitamin D can be produced with moderate sun exposure to the face, arms and legs, averaging 5–30 minutes twice per week, or approximately 25% of the time for minimal sunburn. The darker the skin, and the weaker the sunlight, the more minutes of exposure are needed. Vitamin D overdose is impossible from UV exposure; the skin reaches an equilibrium where the vitamin degrades as fast as it is created.

Sunscreen absorbs or reflects ultraviolet light and prevents much of it from reaching the skin. Sunscreen with a sun protection factor (SPF) of 8 based on the UVB spectrum decreases vitamin D synthetic capacity by 95%, and SPF 15 decreases it by 98%.<sup>[51]</sup>

The skin consists of two primary layers: the inner layer called the dermis, composed largely of connective tissue, and the outer, thinner epidermis. Thick epidermis in the soles and palms consists of five strata; from outer to inner, they are: the stratum corneum, stratum lucidum, stratum granulosum, stratum spinosum, and stratum basale. Vitamin D is produced in the two innermost strata, the stratum basale and stratum spinosum.

The naked mole-rat appears to be naturally cholecalciferol-deficient, as serum 25-OH vitamin D levels are undetectable. In some animals, the presence of fur or feathers blocks the UV rays from reaching the skin. In birds and fur-bearing mammals, vitamin D is generated from the oily secretions of the skin deposited onto the feathers or fur and is obtained orally during grooming.

### **Biological activity:**

#### **Synthesis of vitamin D**

The active vitamin D metabolite calcitriol mediates its biological effects by binding to the vitamin D receptor (VDR), which is principally located in the nuclei of target cells.<sup>[52]</sup> The binding of calcitriol to the VDR allows the VDR to act as a transcription factor that modulates the gene expression of transport proteins (such as TRPV6 and calbindin), which are involved in calcium absorption in the intestine. The vitamin D receptor belongs to the nuclear receptor superfamily of steroid/thyroid hormone receptors, and VDRs are expressed by cells in most organs, including the brain, heart, skin, gonads, prostate, and breast. VDR activation in the intestine, bone, kidney, and parathyroid gland cells leads to the maintenance of calcium and phosphorus levels in the blood (with the assistance of parathyroid hormone and calcitonin) and to the maintenance of bone content.

One of the most important roles of vitamin D is to maintain skeletal calcium balance by promoting calcium absorption in the intestines, promoting bone resorption by increasing osteoclast number, maintaining calcium and phosphate levels for bone formation, and allowing proper functioning of parathyroid hormone to maintain serum calcium levels. Vitamin D deficiency can result in lower bone mineral density and an increased risk of reduced bone density (osteoporosis) or bone fracture because a lack of vitamin D alters mineral metabolism in the body. Thus, although this may initially appear paradoxical, vitamin D is also critical for bone remodeling through its role as a potent stimulator of bone resorption.

The VDR may be involved in cell proliferation and differentiation. Vitamin D also affects the immune system, and VDRs are expressed in several white blood cells, including monocytes and activated T and B cells. In vitro, vitamin D increases expression of the tyrosine hydroxylase gene in adrenal medullary cells, and affects the synthesis of neurotrophic factors, nitric oxide synthase, and glutathione.

Apart from VDR activation, various alternative mechanisms of action are under study, such as inhibition of signal transduction by hedgehog, a hormone involved in morphogenesis.

### **ROUTE OF ADMINISTRATION OF VITAMIN D SUPPLEMENTS:**

Oral and intramuscular routes can be given.

**ROUTE OF ELIMINATION:** urine

### **HEALTH ASPECTS OF SUPPLEMENTATION:**

#### **Mortality**

Vitamin D<sub>3</sub> supplementation has been tentatively found to lead to a reduced risk of death in the elderly, but the effect has not been deemed pronounced or certain enough to make taking supplements recommendable.

Other forms (Vitamin D<sub>2</sub>, alfalcidol, and calcitriol) do not appear to have any beneficial effects with regard to the risk of death. High blood levels appear to be associated with a lower risk of death, but it is unclear if supplementation can result in this benefit. Both an excess and a deficiency in vitamin D appear to cause abnormal functioning and premature aging. The relationship between serum calcidiol level and all-cause mortality is parabolic. Harm from vitamin D appears to occur at a lower vitamin D level in the black population than in the white population.

### **Bone health**

In general, no good evidence supports the commonly held belief that vitamin D supplements can help prevent osteoporosis. Its general use for prevention of this disease in those without vitamin D deficiency is thus likely not needed.

For older people with osteoporosis, taking vitamin D with calcium may help prevent hip fractures, but it also slightly increases the risk of stomach and kidney problems. Supplementation with higher doses of vitamin D, in those older than 65 years, may decrease fracture risk. This appears to apply more to people in institutions than those living independently.

Vitamin D deficiency causes osteomalacia (called rickets when it occurs in children). Use of vitamin D in children with normal vitamin D levels does not appear to improve bone density. Beyond that, low serum vitamin D levels have been associated with falls, and low bone mineral density. Taking extra vitamin D, however, does not appear to change the risk.

Because it found mounting evidence for a benefit to bone health, though it had not found good evidence of other benefits, the Food and Drug Administration of the United States has proposed requiring manufacturers to declare the amount of vitamin D on nutrition facts labels, as "nutrients of public health significance". As of August 2015, this is currently still open for public comment.

Athletes who are vitamin D deficient are at an increased risk of stress fractures and/or major breaks, particularly those engaging in contact sports. The greatest benefit with supplementation is seen in athletes who are deficient (25(OH)D serum levels <30 ng/ml), or severely deficient (25(OH)D serum levels <25 ng/ml). Incremental decreases in risks are observed with rising serum 25(OH)D concentrations plateauing at 50 ng/ml with no additional benefits seen in levels beyond this point.

### **Cancer**

Vitamin D supplements have been widely marketed for their claimed anticancer properties. Associations have been shown in observational studies between low vitamin D levels and the risk of development of certain cancers including colon cancer.

It is unclear, however, if taking additional vitamin D in the diet or as supplements affects the risk of cancer. Reviews have described the evidence as being "inconsistent, inconclusive as to causality, and insufficient to inform nutritional requirements" and "not sufficiently robust to draw conclusions".

A 2014 review found that supplements had no significant effect on cancer risk. Another review suggested that vitamin D<sub>3</sub> may slightly decrease the risk of death from cancer (one fewer death in 150 people over 5 years), but concerns with the quality of the data were noted.

Insufficient evidence exists to recommend vitamin D supplements for people with cancer, although some evidence suggests hypovitaminosis D may be associated with a worse outcome for some cancers, and that higher 25-hydroxy vitamin D levels at the time of diagnosis are associated with better outcomes.

### **Cardiovascular disease**

Taking vitamin D supplements does not meaningfully reduce the risk of stroke, cerebrovascular disease, cardiac infarction, or ischaemic heart disease. Supplementation has no effect on blood pressure.

### **Depression**

Clinical trials of vitamin D supplementation for depressive symptoms have generally been of low quality and show no overall effect, although subgroup analysis showed supplementation for participants with clinically significant depressive symptoms or depressive disorder had a moderate effect.

### **Cognition and dementia**

A systematic review of clinical studies shows an association between low vitamin D levels, cognitive impairment, and a higher risk of developing Alzheimer's disease. However, lower vitamin D concentrations is also associated with poor nutrition and spending less time outdoors. Therefore, alternative explanations for the increase in cognitive impairment exist and hence a direct causal relationship between vitamin D levels and cognition could not be established.

### **Infectious disease**

In general, vitamin D functions to activate the innate and dampen the adaptive immune systems. Deficiency has been linked to increased risk of viral infections, including HIV and influenza. Low levels of vitamin D appear to be a risk factor for tuberculosis, and historically it was used as a treatment.

### **Autoimmune disease**

Although tentative data link low levels of vitamin D to asthma, evidence to support a beneficial effect from supplementation is inconclusive. Accordingly, supplementation is not currently recommended for treatment or prevention of asthma. Vitamin D hypovitaminosis may be a risk factor for multiple sclerosis, but no evidence indicates vitamin D has any clinically significant benefit as a treatment. Further research is needed to determine if the association represents a cause and effect relationship. Low levels of vitamin D are associated with Crohn's disease and ulcerative colitis.

### **Pregnancy**

Low levels of vitamin D in pregnancy are associated with gestational diabetes, pre-eclampsia, and small infants. The benefit of supplements, however, is unclear. Pregnant women who take an adequate amount of vitamin D during gestation may experience positive immune effects. Pregnant women often do not take the recommended amount of vitamin D.

### **Weight Loss**

Though hypothesized that supplementation of Vitamin D may be an effective treatment for obesity, studies do not support this.

### **VITAMIN D SIDE EFFECTS & SAFETY:**

Vitamin D is likely safe when taken by mouth or given as a shot into the muscle in recommended amounts. Most people do not commonly experience side effects with vitamin D, unless too much is taken. Some side effects of taking too much vitamin D include weakness, fatigue, sleepiness, headache, loss of appetite, dry mouth, metallic taste, nausea, vomiting, and others. Taking vitamin D for long periods of time in doses higher than 4000 units daily is possibly unsafe and may cause excessively high levels of calcium in the blood. However, much higher doses are often needed for the short-term treatment of vitamin D deficiency. This type of treatment should be done under the supervision of a healthcare provider.

### **Special Precautions & Warnings:**

- **Pregnancy and breast-feeding:** Vitamin D is likely safe during pregnancy and breast-feeding when used in daily amounts below 4000 units. Do not use higher doses. Vitamin D is possibly unsafe when used in higher amounts during pregnancy or while breast-feeding. Using higher doses might cause serious harm to the infant
- **Kidney disease:** Vitamin D may increase calcium levels and increase the risk of “hardening of the arteries” in people with serious kidney disease. This must be balanced with the need to prevent renal osteodystrophy, a bone disease that occurs when the kidneys fail to maintain the proper levels of calcium and phosphorus in the blood. Calcium levels should be monitored carefully in people with kidney disease.
- **High levels of calcium in the blood:** Taking vitamin D could make this condition worse.
- **“Hardening of the arteries” (atherosclerosis):** Taking vitamin D could make this condition worse, especially in people with kidney disease.
- **Sarcoidosis:** Vitamin D may increase calcium levels in people with sarcoidosis. This could lead to kidney stones and other problems. Use vitamin D cautiously.
- **Histoplasmosis:** Vitamin D may increase calcium levels in people with histoplasmosis. This could lead to kidney stones and other problems. Use vitamin D cautiously.
- **Over-active parathyroid gland (hyperparathyroidism):** Vitamin D may increase calcium levels in people with hyperparathyroidism. Use vitamin D cautiously.
- **Lymphoma:** Vitamin D may increase calcium levels in people with lymphoma. This could lead to kidney stones and other problems. Use vitamin D cautiously.
- **Tuberculosis:** Vitamin D might increase calcium levels in people with tuberculosis. This might result in complications such as kidney stones.

### **DRUG INTERACTIONS:**

- **Aluminium** is found in most antacids. Vitamin D can increase how much aluminium the body absorbs. This interaction might be a problem for people with kidney disease. Take vitamin D two hours before, or four hours after antacids.
- **Calcipotriene** is a drug that is similar to vitamin D. Taking vitamin D along with calcipotriene (Dovonex) might increase the effects and side effects of calcipotriene (Dovonex). Avoid taking vitamin D supplements with calcipotriene (Dovonex).

- Vitamin D helps your body absorb calcium. Calcium can affect the heart. Digoxin (Lanoxin) is used to help your heart beat stronger. Taking vitamin D along with digoxin (Lanoxin) might increase the effects of digoxin (Lanoxin) and lead to an irregular heartbeat.
- Vitamin D helps in absorbing calcium. Taking large amounts of vitamin D along with diltiazem and verapamil, might decrease the effectiveness of diltiazem and verapamil.
- Water pills (Thiazide diuretics) interacts with vitamin D. Some "water pills" increase the amount of calcium in the body. Taking large amounts of vitamin D along with some "water pills" might cause to be too much calcium in the body. This could cause serious side effects including kidney problems.

### **RECOMMENDED SERUM LEVELS**

Recommendations on recommended 25(OH)D serum levels vary. A 2014 review concluded that the most advantageous serum levels for 25(OH)D appeared to be close to 75 nmol/l.<sup>[53]</sup> A 2015 review reported that regarding optimal levels, a review of 2004 had recommended that at least 70 nmol/L should be maintained in order to avoid negative health effects, that desirable 25(OH)D levels between 90-120 nmol/l have been reported by another review, but that optimal vitamin D levels are still controversial. The review concluded that ranges from 75 to 100 nmol/L were to be recommended for athletes. Part of the controversy stems from that numerous studies have found differences in serum levels of 25(OH)D between ethnic groups and studies point to genetical as well as environmental to be the reasons behind these variations. Supplementation to achieve these standard levels could cause harmful vascular calcification.

US labs generally report 25(OH)D levels as ng/ml. Other countries often use nmol/l.

An IOM committee concluded a serum 25-hydroxyvitamin D level of 20 ng/ml (50 nmol/l) is desirable for bone and overall health. The dietary reference intakes for vitamin D are chosen with a margin of safety and 'overshoot' the targeted serum value to ensure the specified levels of intake achieve the desired serum 25-hydroxyvitamin D levels in almost all persons. No contributions to serum 25-hydroxyvitamin D level are assumed from sun exposure and the recommendations are fully applicable to people with dark skin or negligible exposure to sunlight.

The Institute found serum 25-hydroxyvitamin D concentrations above 30 ng/ml (75 nmol/l) are "not consistently associated with increased benefit". Serum 25-hydroxyvitamin D levels above 50 ng/ml (125 nmol/l) may be cause for concern. However, the desired range of serum 25-hydroxyvitamin D is between 20 and 50 ng/ml.

	IOM Guidelines	Endocrine Society Guidelines
Deficiency	Below 12 ng/mL	Below 20 ng/ml
Insufficiency	12 to 20 ng/mL	21-29 ng/ml
Adequate	Over 20 ng/mL	30-60 ng/ml
Excessive	Over 60 ng/mL	

The risk of cardiovascular disease is lower when vitamin D ranged from 8 to 24 ng/ml (20 to 60 nmol/l). A "threshold effect" appears to occur once a level of 24 ng/ml (60 nmol/l) has been reached i.e., levels of vitamin D over 24 ng/ml (60 nmol/l) did not show added benefit.

### **VITAMIN D DEFICIENCY:**

A diet deficient in vitamin D in conjunction with inadequate sun exposure causes osteomalacia (or rickets when it occurs in children), which is a softening of the bones. In the developed world, this is a rare disease. However, vitamin D deficiency has become a worldwide problem in the elderly and remains common in children and adults. Low blood calcidiol (25-hydroxy-vitamin D) can result from avoiding the sun.

#### **Groups at Risk of Vitamin D Inadequacy**

- Breastfed infants
- Older adults
- People with limited sun exposure
- People with dark skin
- People with inflammatory bowel disease and other conditions causing fat malabsorption
- People who are obese or who have undergone gastric bypass surgery

Deficiency results in impaired bone mineralization and bone damage which leads to bone-softening diseases, including:

### **Rickets**

Rickets, a childhood disease, is characterized by impeded growth and soft, weak, deformed long bones that bend and bow under their weight as children start to walk. This condition is characterized by bow legs, which can be caused by calcium or phosphorus deficiency, as well as a lack of vitamin D; today, it is largely found in low-income countries in Africa, Asia, or the Middle East and in those with genetic disorders such as pseudovitamin D deficiency rickets. Maternal vitamin D deficiency may cause overt bone disease from before birth and impairment of bone quality after birth. Nutritional rickets exists in countries with intense year-round sunlight such as Nigeria and can occur without vitamin D deficiency. Although rickets and osteomalacia are now rare in Britain, outbreaks have happened in some immigrant communities in which osteomalacia sufferers included women with seemingly adequate daylight outdoor exposure wearing Western clothing. Having darker skin and reduced exposure to sunshine did not produce rickets unless the diet deviated from a Western omnivore pattern characterized by high intakes of meat, fish, and eggs, and low intakes of high-extraction cereals. The dietary risk factors for rickets include abstaining from animal foods. Vitamin D deficiency remains the main cause of rickets among young infants in most countries, because breast milk is low in vitamin D and social customs and climatic conditions can prevent adequate sun exposure. In sunny countries such as Nigeria, South Africa, and Bangladesh, where the disease occurs among older toddlers and children, it has been attributed to low dietary calcium intakes, which are characteristic of cereal-based diets with limited access to dairy products. Rickets was formerly a major public health problem among the US population; In the United States and Canada, vitamin D-fortified milk, infant vitamin supplements, and vitamin supplements have helped to eradicate the majority of cases of rickets for children with fat malabsorption conditions.

### **Osteomalacia**

Osteomalacia is a disease in adults that results from vitamin D deficiency. Characteristics of this disease are softening of the bones, leading to bending of the spine, bowing of the legs, proximal muscle weakness, bone fragility, and increased risk for fractures. Osteomalacia reduces calcium absorption and increases calcium loss from bone, which increases the risk for bone fractures. Osteomalacia is usually present when 25-hydroxyvitamin D levels are less than about 10 ng/mL. Although the effects of osteomalacia are thought to contribute to chronic musculoskeletal pain, there is no persuasive evidence of lower vitamin D levels in chronic pain sufferers or that supplementation alleviates chronic nonspecific musculoskeletal pain.

### **Diabetes**

A systematic review of 2014 concluded that the available studies show no evidence of vitamin D3 supplementation having an effect on glucose homeostasis or diabetes prevention. A review article of 2016 reported that while there is increasing evidence that Vitamin D deficiency may be a risk factor for diabetes mellitus, over-all evidence regarding vitamin D levels and diabetes mellitus is contradictory, requiring further studies.

### **Skin pigmentation**

Some research shows dark-skinned people living in temperate climates have lower vitamin D levels. Dark-skinned people may be less efficient at making vitamin D because melanin in the skin hinders vitamin D synthesis; however, a recent study has found novel evidence that low vitamin D levels among Africans may be due to other reasons. Recent evidence implicates parathyroid hormone in adverse cardiovascular outcomes. Black women have an increase in serum parathyroid hormone at a lower 25(OH)D level than white women. A large-scale association study of the genetic determinants of vitamin D insufficiency in Caucasians found no links to pigmentation.

## **VII. Vitamin D Toxicity**

Vitamin D toxicity is rare. It is caused by supplementing with high doses of vitamin D rather than sunlight. The threshold for vitamin D toxicity has not been established; however, the tolerable upper intake level (UL), according to some research, is 4,000 IU/day for ages 9–71. Whereas another research concludes that in healthy adults, sustained intake of more than 1250 µg/day (50,000 IU) can produce overt toxicity after several months and can increase serum 25-hydroxyvitamin D levels to 150 ng/ml and greater; those with certain medical conditions, such as primary hyperparathyroidism, are far more sensitive to vitamin D and develop hypercalcemia in response to any increase in vitamin D nutrition, while maternal hypercalcemia during pregnancy may increase fetal sensitivity to effects of vitamin D and lead to a syndrome of mental retardation and facial deformities.

Hypercalcemia is a strong indication of vitamin D toxicity, noted with an increase in urination and thirst. If hypercalcemia is not treated, it results in excess deposits of calcium in soft tissues and organs such as the kidneys, liver, and heart, resulting in pain and organ damage. Pregnant or breastfeeding women should

consult a doctor before taking a vitamin D supplement. The FDA advised manufacturers of liquid vitamin D supplements that droppers accompanying these products should be clearly and accurately marked for 400 international units (IU). In addition, for products intended for infants, the FDA recommends the dropper hold no more than 400 IU. For infants (birth to 12 months), the tolerable upper limit (maximum amount that can be tolerated without harm) is set at 25 µg/day (1,000 IU). One thousand micrograms per day in infants has produced toxicity within one month. After being commissioned by the Canadian and American governments, the Institute of Medicine (IOM) as of 30 November 2010, has increased the tolerable upper limit (UL) to 2,500 IU per day for ages 1–3 years, 3,000 IU per day for ages 4–8 years and 4,000 IU per day for ages 9–71+ years (including pregnant or lactating women).<sup>[54]</sup>

Vitamin D overdose causes hypercalcemia, and the main symptoms of vitamin D overdose are those of hypercalcemia: anorexia, nausea, and vomiting can occur, frequently followed by polyuria, polydipsia, weakness, insomnia, nervousness, pruritus, and, ultimately, renal failure. Proteinuria, urinary casts, azotemia, and metastatic calcification (especially in the kidneys) may develop. Other symptoms of vitamin D toxicity include mental retardation in young children, abnormal bone growth and formation, diarrhea, irritability, weight loss, and severe depression. Vitamin D toxicity is treated by discontinuing vitamin D supplementation and restricting calcium intake. Kidney damage may be irreversible. Exposure to sunlight for extended periods of time does not normally cause vitamin D toxicity. The concentrations of vitamin D precursors produced in the skin reach an equilibrium, and any further vitamin D produced is degraded.

A review published in 2015 noted that adverse effects have been reported only at 25(OH)D serum concentrations above 200 nmol/L.

Published cases of toxicity involving hypercalcemia in which the vitamin D dose and the 25-hydroxy-vitamin D levels are known all involve an intake of  $\geq 40,000$  IU (1,000 µg) per day.

Research has indicated that Vitamin D toxicity is closely related to a depletion of Vitamin K and that repletion of Vitamin K allows individuals to supplement with higher doses of Vitamin D without the negative calcium-related side effects.

### **VIII. Vitamin-D Treatment**

Endocrine society suggest that all adults who are vitamin D deficient be treated with 50,000 IU of vitamin D2 or vitamin D3 once a week for 8 wk or its equivalent of 6000 IU of vitamin D2 or vitamin D3 daily to achieve a

blood level of 25(OH)D above 30 ng/ml, followed by maintenance therapy of 1500–2000 IU/d. Endocrine Society recommended<sup>[55]</sup> higher amounts of vitamin D for the treatment and prevention of vitamin D deficiency. For example, studies in adults revealed that 1,000 IUs of vitamin D daily during the winter in Boston was incapable of raising their blood levels of 25(OH)D above 30 ng/mL.<sup>[56]</sup> It is estimated that for every 100 IUs of vitamin D ingested, blood levels of 25(OH)D increase on average by 0.5–1.0 ng/mL. To treat vitamin D deficiency in children 2,000 IUs of vitamin D daily for 6–8 weeks or 50,000 IUs of vitamin D once a week for 8 weeks is both effective and safe.<sup>[57]</sup> In adults, 50,000 IUs of vitamin D once a week for 8 weeks (equivalent to approximately 6,500 IUs of vitamin D daily) is often adequate to treat vitamin D deficiency and fill the empty vitamin D tank.<sup>[58]</sup> To maintain vitamin D sufficiency, i.e. to keep the vitamin D tank full, adults can take 50,000 IUs of vitamin D once every 2 weeks (equivalent to approximately 3,300 IUs of vitamin D daily) for at least 6

years without any concern for vitamin D toxicity

Vitamin D toxicity has been of great concern especially for children. However, it is now recognized even by the IOM that vitamin D is not as toxic as once thought.<sup>[59]</sup> They recommended that up to 4,000 IUs of vitamin D daily for most children and adults was safe. A study in healthy adult males receiving 10,000 IUs of vitamin D3 daily for 5 months did not cause any untoward toxicity.<sup>[60]</sup> The IOM and the Endocrine Society also recognize that patients with kidney stones or with primary hyperparathyroidism can receive vitamin D supplementation without concern for increased risk for developing kidney stones or increased blood calcium respectively.<sup>[55,59]</sup>

### **IX. Patients And Methods**

- This was a prospective open label study conducted at Sarojini Devi Eye Hospital and department of Pharmacology, Gandhi Medical College with 50 diabetic retinopathy patients who were previously diagnosed by experienced retinologist were selected according to the inclusion criteria. Approval from Institutional Ethics Committee (DCGI Regd No. ECR/180/Inst/AP/2013, dt. 20-04-2013) was taken before commencing the study. Duration of study was 1 year. 47 patients have completed the study for 1 year. Three patients were dropped out. The reasons were one patient with noncompliance of vitamin D supplementation, one patient with change of hospital and one patient with transfer of place.

- Patients with normal serum levels of vitamin D were kept under Group A (controls) & patients with serum vitamin D level <20ng/ml were kept under Group B (test subjects).Numbering of the patients done from 1-25 in each group.
- Vitamin D<sub>3</sub> supplements used in this study are:

	LOADING DOSE	MAINTENANCE DOSE
Dose	50,000IU	1500IU
Brand name	D3-50 CHOLECALCIFEROL	VITAMIN D <sub>3</sub> 1500IU
Company	Biotech company	Rx health labs

- All participants were advised appropriate diet regimens based on diabetic diet
- Patients were counselled about the probable adverse effects of vitamin D toxicity and all participants were educated to report about the adverse effects of vitamin D toxicity.

### **X. Description Of The Procedure:**

- Prior to participation in the study informed consent was taken from all participants in prescribed format.
- After an overnight fast, a baseline blood sample was obtained; another blood sample for plasma glucose was obtained 2 h following the ingestion of 75 g of anhydrous glucose in water. Plasma glucose concentration was measured by an enzymatic method using glucose oxidase and peroxidase on an automated analyzer.
- Serum Vitamin D level was assessed by the Chemiluminescent Microparticle Immunoassay (CMIA) method
- After base line investigations, Group-A patients (controls) managed conventionally and Group-B patients (test subjects) managed conventionally along with vitamin-D supplementation.
- Patients in Group-B, were given loading dose of vitamin D 50,000IU orally weekly for 8 weeks and maintenance dose of vitamin D 1500IU daily orally for next 10 months and to undergo assessment of their health and vision using standard, nonexperimental clinical devices i.e., fundoscopy, tonometry, visual acuity and if required,fluorescein angiography before starting study and after completion of the study.Results of pre and post vitamin D supplementation were compared and analysed.
- All the subjects in the intervention group who completed 12 months of study took Vitamin D as prescribed as ascertained from the number of tablets or capsules remained in the bottle at each visit. Subjects were reminded each month by telephone to take the medication.
- Complete medical history with concurrent medication use was taken.In physical examination height, weight and vitals (PR, RR, TEMP & BP) were recorded.

### **BASE LINE INVESTIGATIONS:**

- Fasting and Postprandial Blood Sugar
- Glycated hemoglobin (HbA1c)
- Lipid profile
- Blood urea
- Serum creatinine
- Serum vitamin-D test
- Best corrected visual acuity
- Intraocular pressure (IOP) by tonometry
- Fundoscopic examination
- Fundus fluorescein angiography if required.

### **INCLUSION CRITERIA:**

- Age group 35 to 65 years
- Both Sex
- Diabetes mellitus type 2
- Mild,moderate and severe nonproliferative diabetic retinopathy

### **EXCLUSION CRITERIA:**

- Age group <35 and >65 years
- Diabetes mellitus type 1
- Proliferative diabetic retinopathy
- Pregnant women
- Smokers and alcoholics
- Patients on concurrent administration of Thiazide diuretics,Digitoxin &Sucralfate

- Patients with hypertension, dyslipidemia, tuberculosis, diarrheal, or malabsorption state & chronic liver disease
- Patients with serum creatinine >1.5mg/dl in male or >1.4mg/dl in female, patients
- Subjects were seen monthly for the first 3 months and subsequently every 3 months for a total of 1-year. FBS, PLBS, and HbA1c levels were measured at baseline and at 6 and 12 months. HbA1c level was measured with GFR<90ml/min/1.73m<sup>2</sup> with high-performance liquid chromatography standardized to the diabetes control and complications trial assay. Vitamin D was measured at baseline and at 12 months.

**Statistically analysis:**

Statistical analysis was done by using Graph Pad Prism 7 software. Results were expressed as mean±SD and percentages. Comparisons between two groups were made using t-test and Chi- square test. P <0.05 was considered statistically significant.

**Vitamin D supplements used in this study:**



**RESULTS:**

The present study was done to study the “**Evaluation of vitamin D supplementation in management of diabetic retinopathy**”

The patients were grouped into A and B.

GROUP-A= CONTROL GROUP( without vitamin D supplementation)

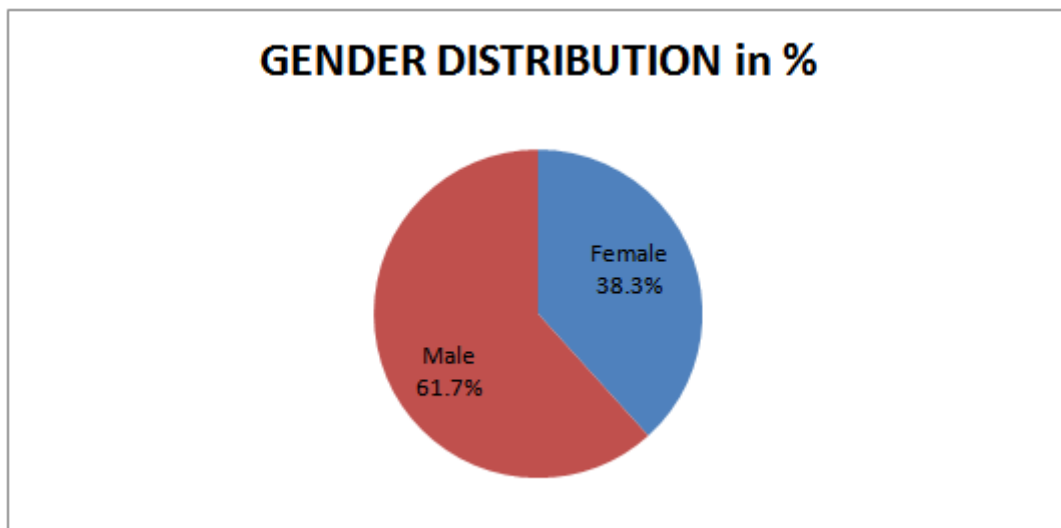
GROUP-B= TEST GROUP(with vitamin D supplementation)

**GENDER DISTRIBUTION:**

Socio demographic distribution of study population.

A total of 47 patients participated in the study and consist of 18 Females(38.3%) and 29 Males(61.7%).All the patients belonged to lower & middle socio economic status.

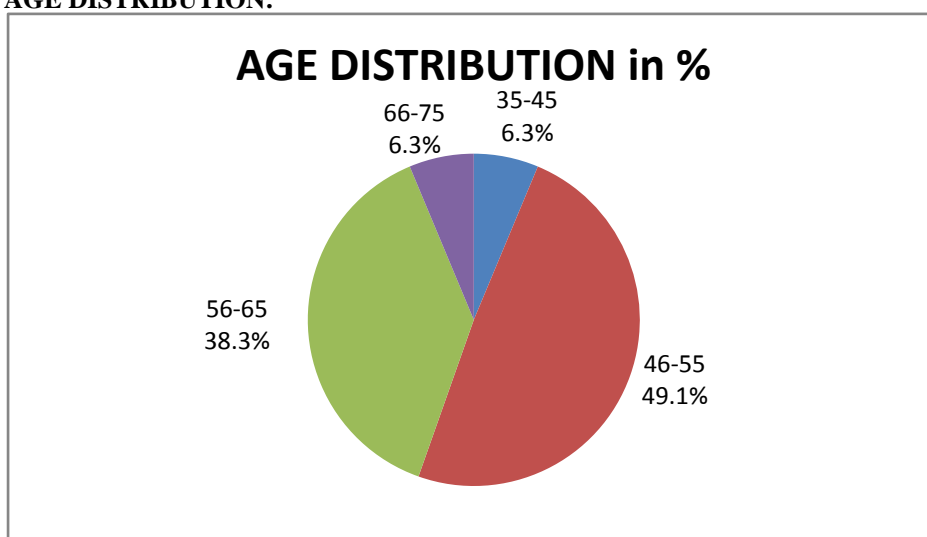




**PIE DIAGRAM 1:** showing gender distribution of patients indicates the percentage distribution of Males 61.7% and females 38.3% in the study.

SEX	PERCENTAGE
MALE	61.7%
FEMALE	38.3%

**AGE DISTRIBUTION:**



**PIE DIAGRAM 2:** showing age distribution of patients, shows in the age group of 35-45 years were 6.3%, with age group of 46-55 years were 49.1%, with age group 56-65 years were 38.3% & with age group 66-75 years were 6.3%.

AGE IN YEARS	PERCENTAGE
35-45	6.3%
46-55	49.1%
56-65	38.3%
66-75	6.3%

**Table 1: BASELINE CHARACTERISTICS:**

*“Evaluation Of Vitamin D Supplementation In Management Of Diabetic Retinopathy”*

<b>BASELINE CHARACTERISTICS</b>	<b>GROUP A</b>	<b>GROUP B</b>
Number of patients	25	22
Age range (in years)	35-75	35-75
Sex (male/female)	18/7	11/11
BMI ( Kg/m <sup>2</sup> )	25.2±3.1	25.9±2.7
FBS (mg/dl)	133.24±25.42	142.22±37.65
PLBS (mg/dl)	202.8±42.56	203.04±43.15
HbA <sub>1c</sub> (%)	7.92±0.59	8.29±1.16
Serum Vitamin D levels (ng/ml)	33.88±3.35	14.08±2.34

Table 2: Variation in parameters in group A at 0 day, 6<sup>th</sup> and 12<sup>th</sup> months

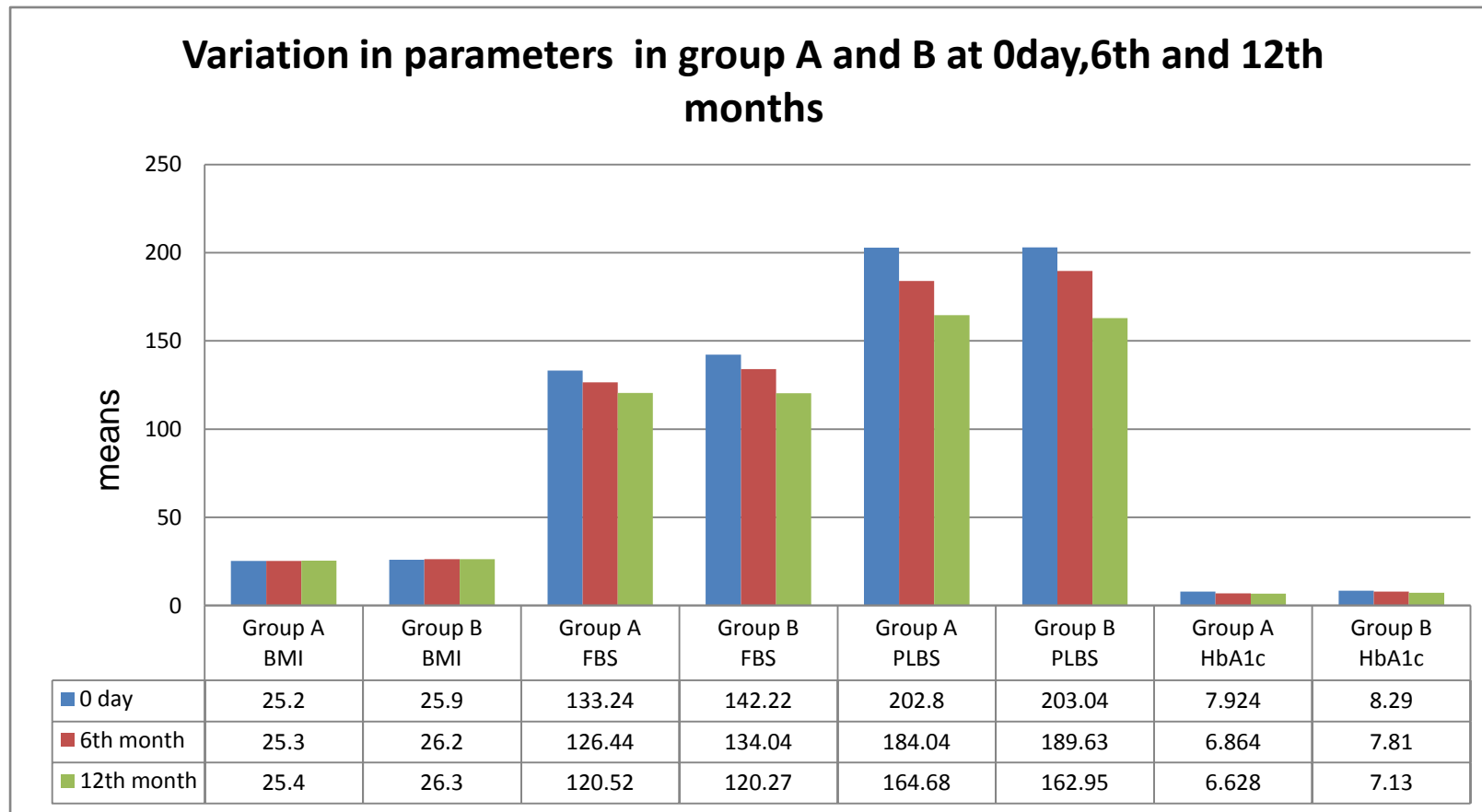
Parameter				P value		
	At 0 day	At 6 <sup>th</sup> month	At 12 <sup>th</sup> month	0d Vs 6m	6m Vs 12m	0d Vs 12m
BMI (kg/m <sup>2</sup> )	25.2±3.1	25.3±2.8	25.4±2.8	P=0.9052 t=0.1197	P=0.9000 t=0.1263	P=0.8118 t=0.2394
FBS(mg/dl)	133.24±25.42	126.44±20.4	120.52±16.56	P=0.3021 t=1.0432	P=0.2655 t=1.1265	P=0.0413* t=2.0964
PLBS(mg/dl)	202.8±42.56	184.04±30.13	164.68±24.32	P=0.0783 t=1.7988	P=0.0159* t=2.5000	P=0.0003** t=3.8883
HbA1c(%)	7.92±0.59	6.86±0.65	6.628±0.566	P=0.0001** t=6.0122	P=0.1792 t=1.3631	P=<0.0001*** t=7.9257
Serum vitamin D levels(ng/ml)	33.88±3.35	-	34.6±2.87	-	-	P=0.4185 t=0.8161
New PDR cases(%)	-	-	16%	-	-	P=0.8941 X <sup>2</sup> = 0.018

Table-3: Variation in parameters in group B at 0 day, 6<sup>th</sup> and 12<sup>th</sup> months

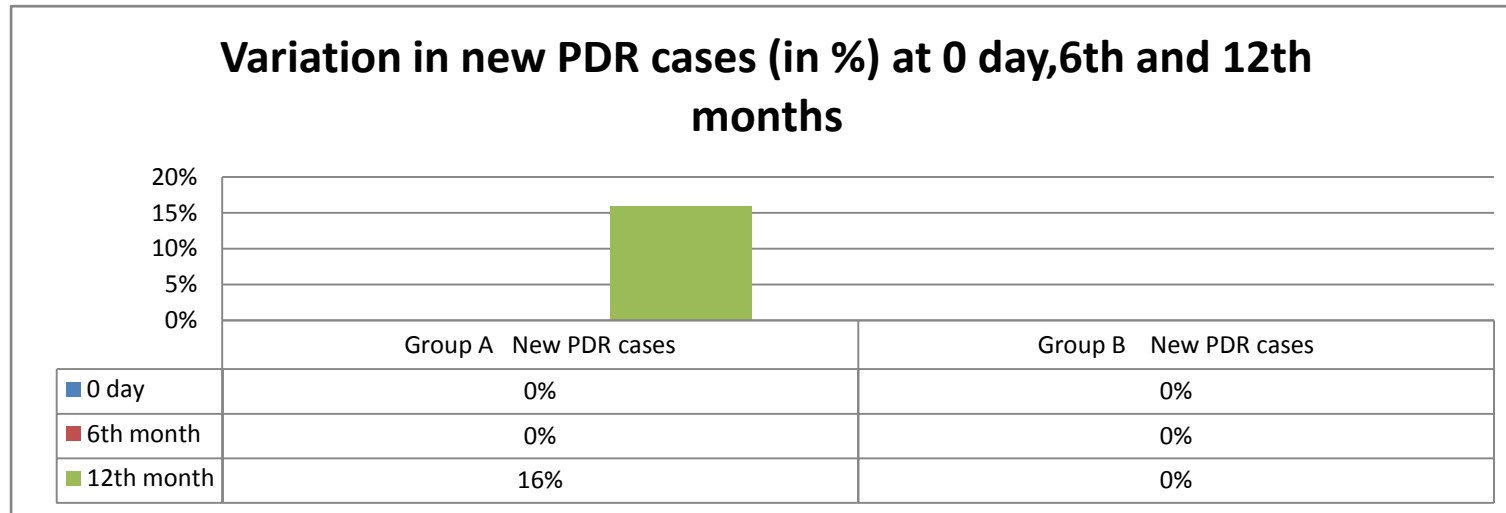
Parameter				P value		
	At 0 day	At 6 <sup>th</sup> month	At 12 <sup>th</sup> month	0d Vs 6m	6m Vs 12m	0d Vs 12m
BMI (kg/m <sup>2</sup> )	25.9±2.7	26.2±2.7	26.3±2.3	P=0.7143 t=0.3685	P=0.8954 t=0.1322	P=0.5996 t=0.5290
FBS(mg/dl)	142.22±37.65	134.04±31.09	120.27±25.09	P=0.4364 t=0.7858	P=0.1134 t=1.6166	P=0.0280* t=2.2755
PLBS(mg/dl)	203.04±43.15	189.63±42.32	162.95±34.21	P=0.3040 t=1.0407	P=0.0265* t=2.2996	P=0.0014* t=3.4148
HbA1c(%)	8.29±1.16	7.81±0.710	7.13±0.66	P=0.1053 t=1.6554	P=0.0020* t=3.2902	P=0.0002** t=4.0767
Serum vitamin D levels(ng/ml)	14.08±2.34	-	34.07±3.86	-	-	P=<0.0001*** t=20.7718
New PDR cases(%)	-	-	0%	-	-	P=0.0338* X <sup>2</sup> = 4.506

**BMI=Body mass index FBS=Fasting blood sugar PLBS=Post lunch blood sugar HbA1c=Glycosylated haemoglobin  
PDR= Proliferative diabetic retinopathy**

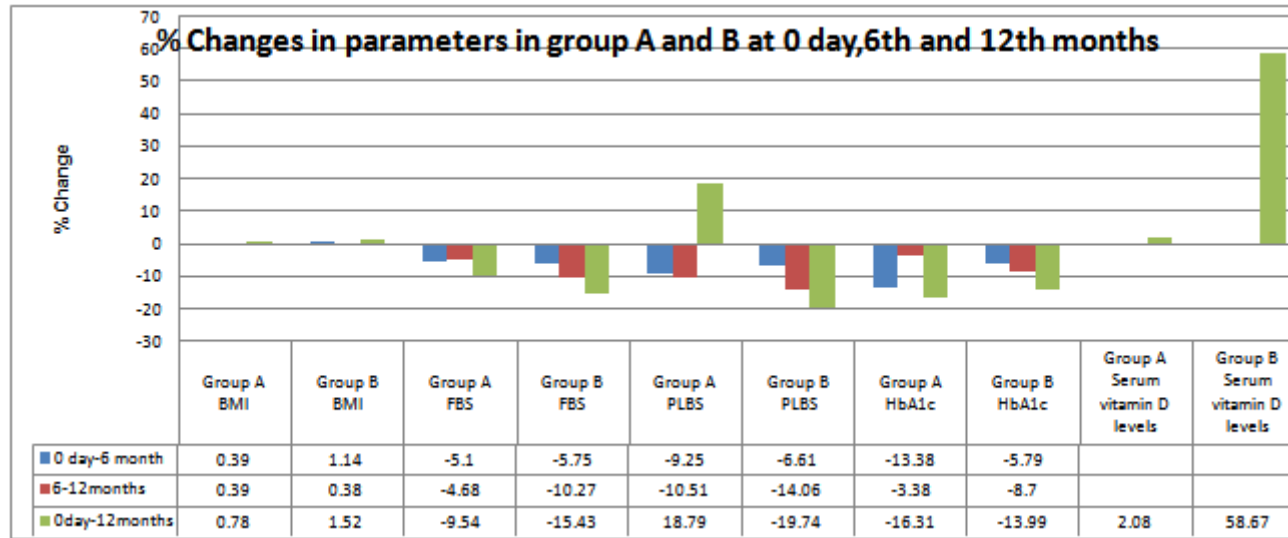
**Bar diagram 1:** Shows variation in parameters in group A and B at 0 day, 6<sup>th</sup> and 12<sup>th</sup> months



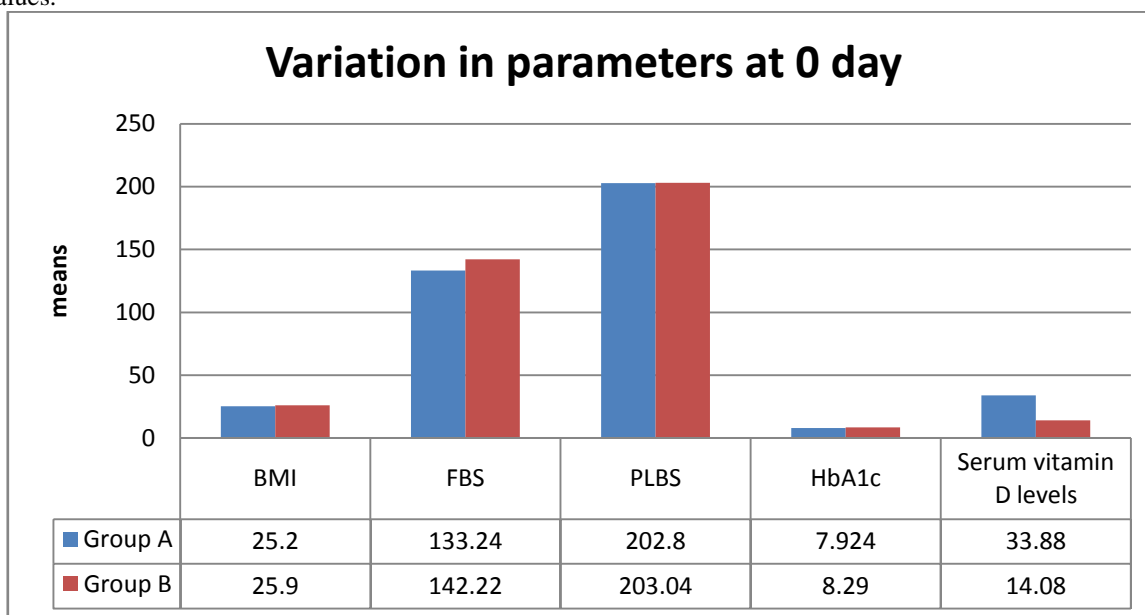
**Bar diagram 2:** Shows variation in new PDR cases in group A and B at 0day,6th and 12th months



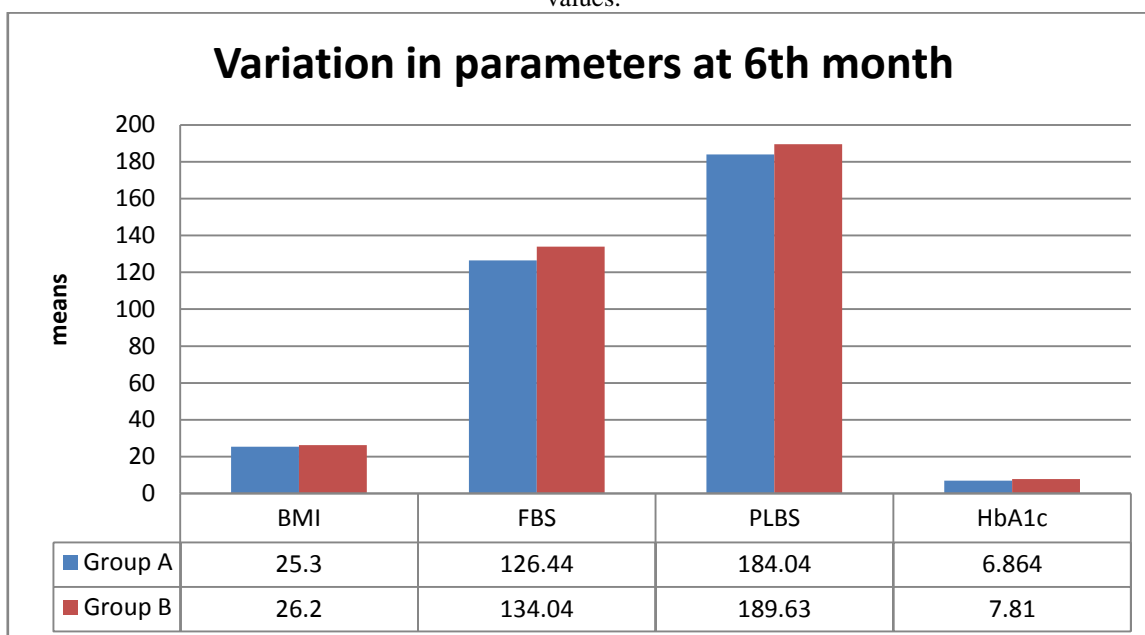
**Bar diagram 3:**Shows % changes in parameters in group A and B at 0day,6<sup>th</sup> month and 12<sup>th</sup> month



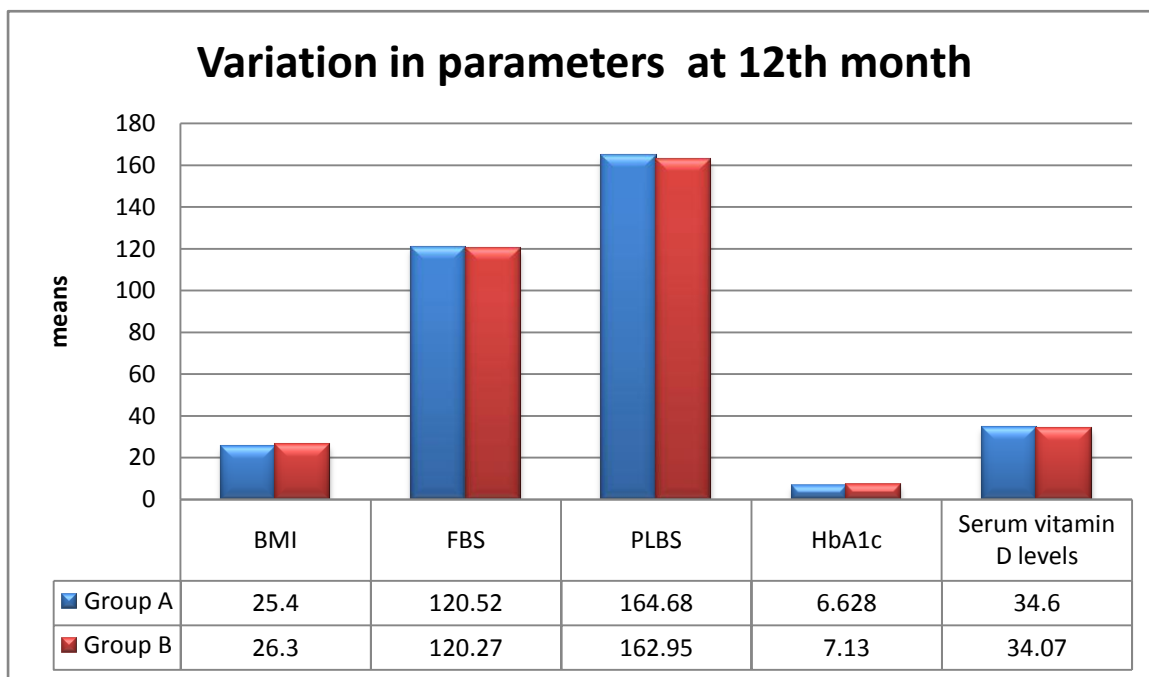
**Bar diagram 4:** Showing variation in parameters in group A and B at 0 day. Y axis represents their mean values.



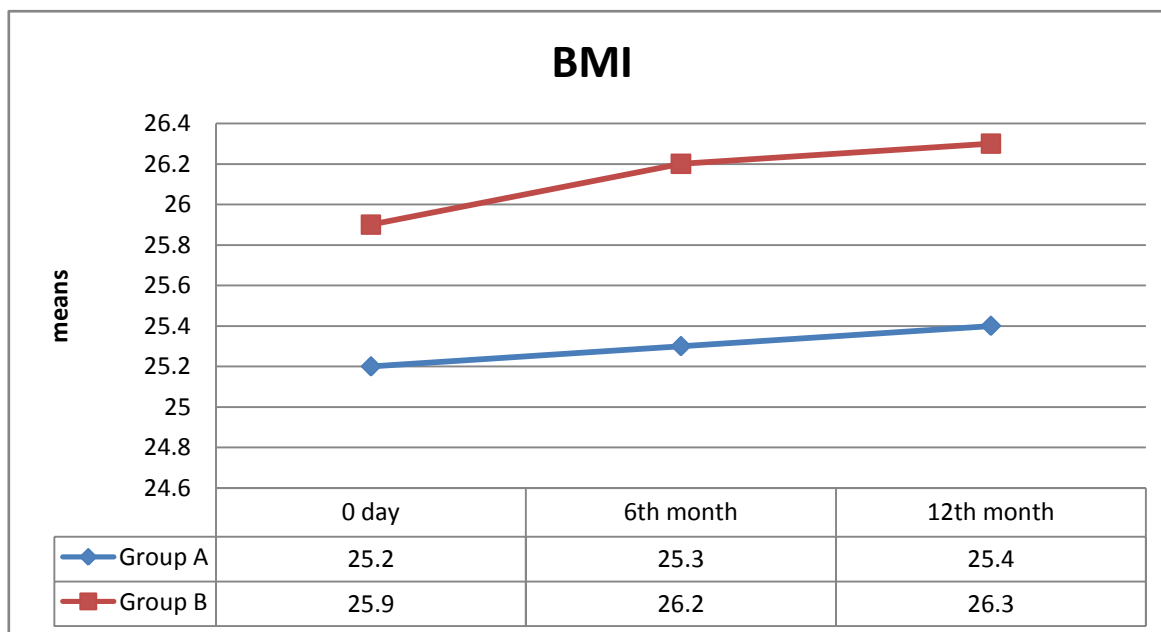
**Bar diagram 5:** Showing variation in parameters in group A and B at 6<sup>th</sup> month. Y axis represents their mean values.



**Bar diagram 6:** Showing variation in parameters in group A and B at 12<sup>th</sup> month. Y axis represents their mean values.

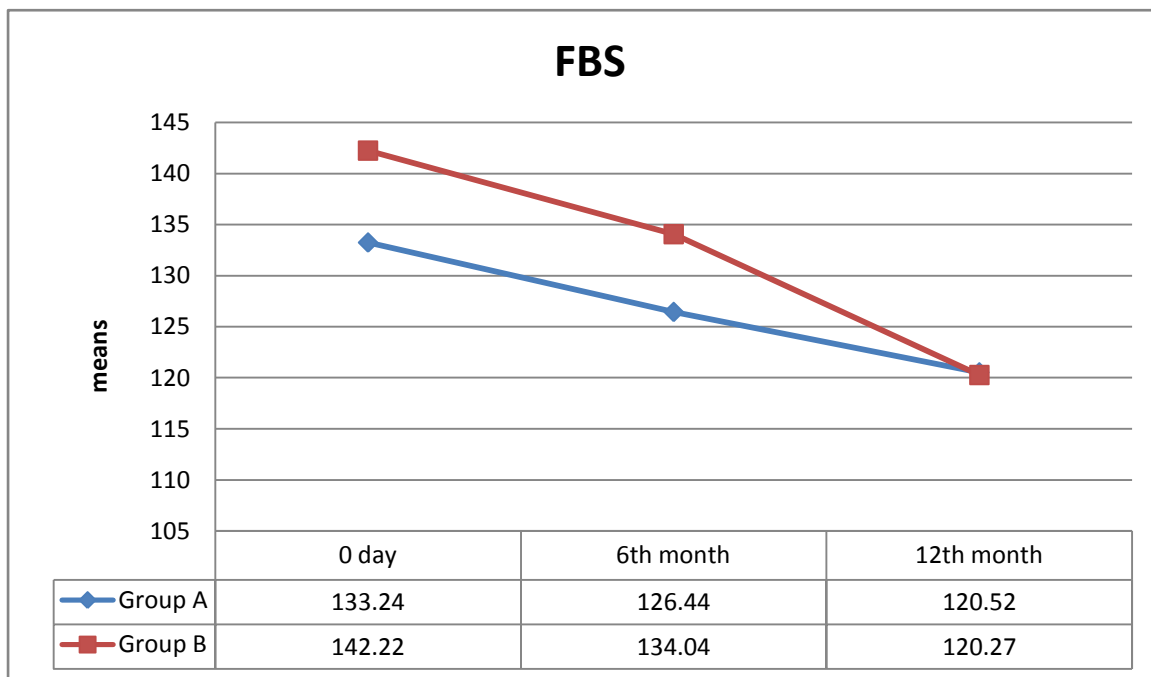


**Line diagram 1:** Variation in BMI in group A and B from 0 day → 6<sup>th</sup> month → 12<sup>th</sup> month.

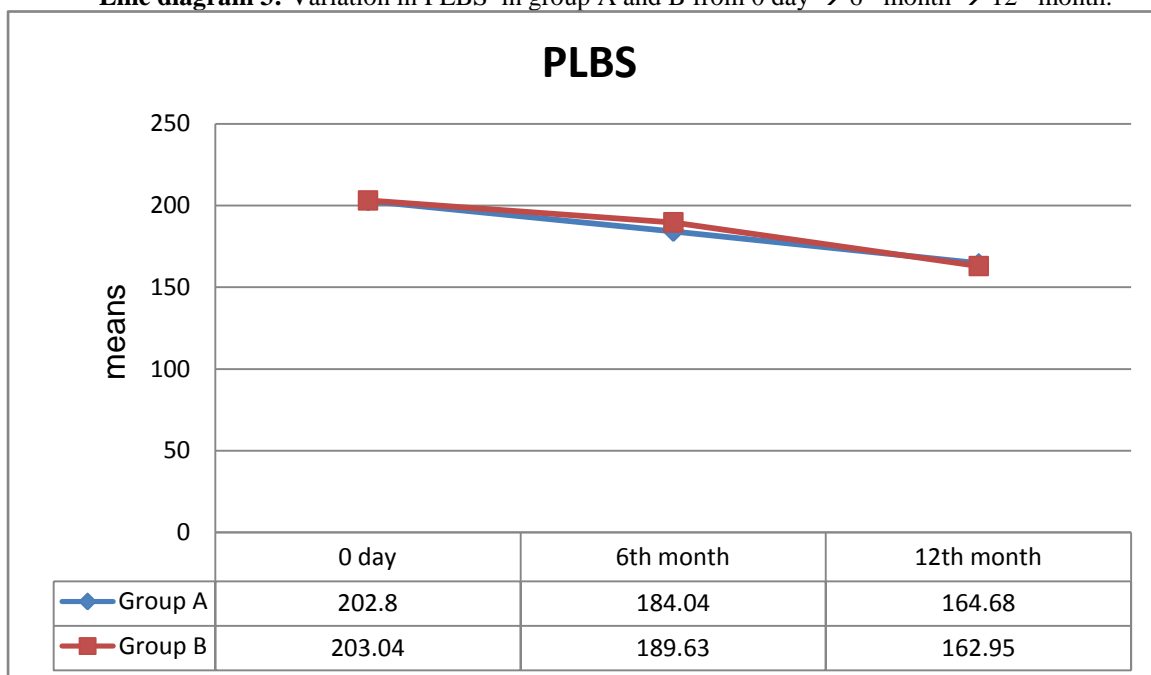


**Line diagram 2:** Variation in FBS in group A and B from 0 day → 6<sup>th</sup> month → 12<sup>th</sup> month.

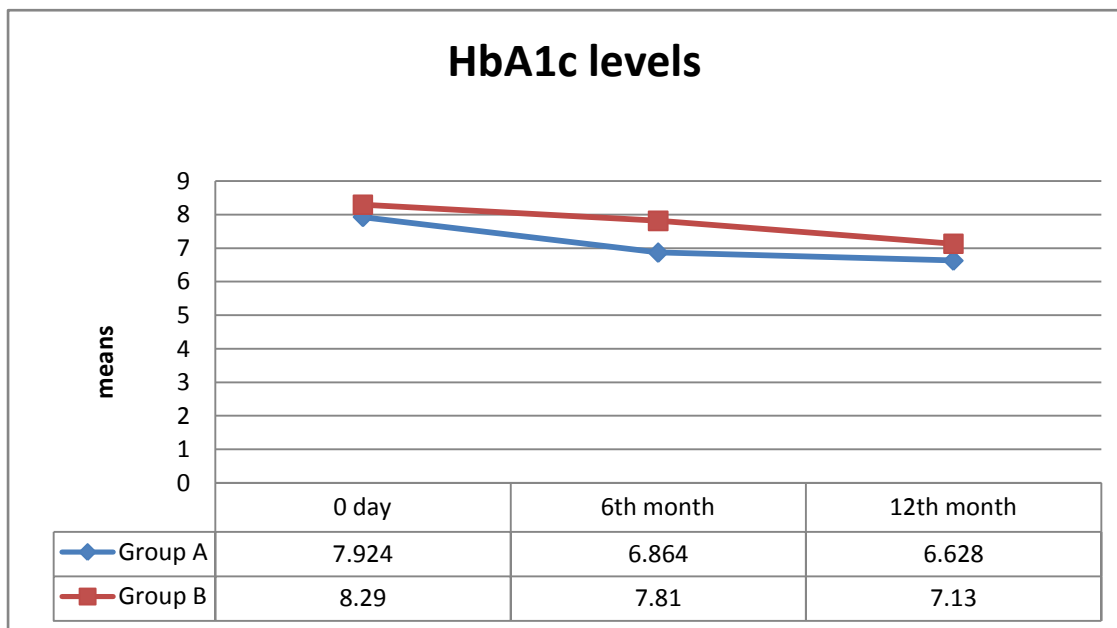




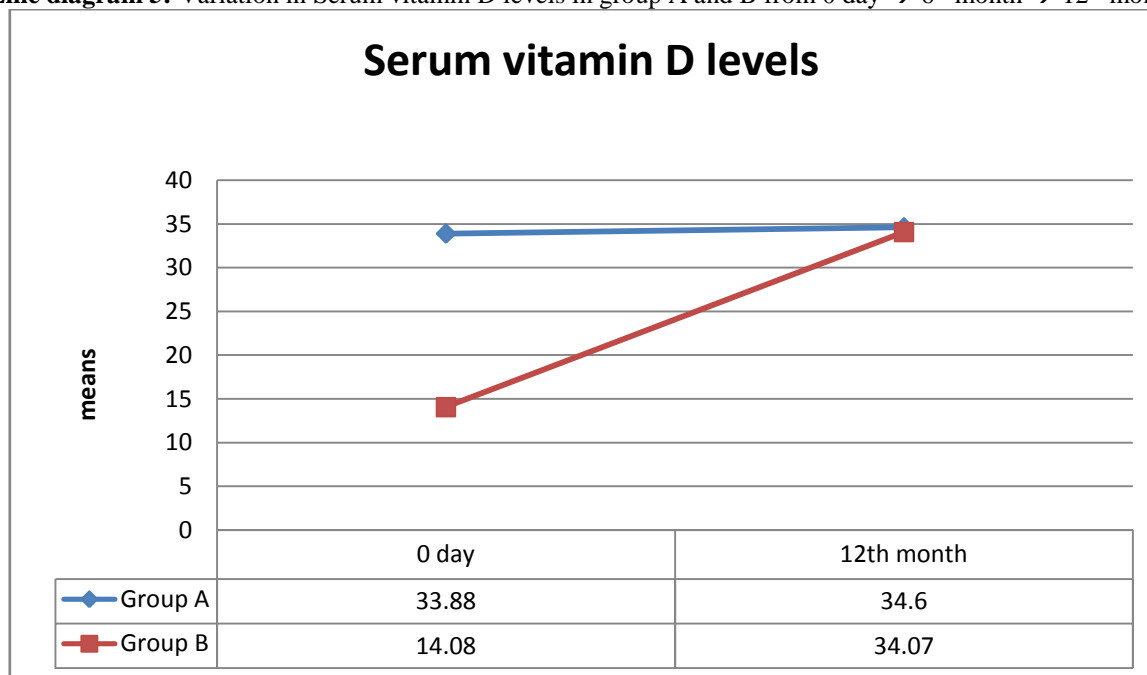
**Line diagram 3:** Variation in PLBS in group A and B from 0 day → 6<sup>th</sup> month → 12<sup>th</sup> month.



**Line diagram 4:** Variation in HbA1c in group A and B from 0 day → 6<sup>th</sup> month → 12<sup>th</sup> month.



**Line diagram 5:** Variation in Serum vitamin D levels in group A and B from 0 day → 6<sup>th</sup> month → 12<sup>th</sup> month.



## XI. Analysis Of Results

Values were expressed as Mean±SD. Statistical difference in mean was analysed using student unpaired t-test and chi-square test. P value less than 0.05 was considered as significant and less than 0.01 is considered as statistically significant.

<b>Significance</b>	<b>P value</b>
Not significant	>0.05
Significant	<0.05 *
Highly significant	<0.001**
Very highly significant	<0.0001***

**PIE DIAGRAM-1** showing gender distribution of the patients, the male percentage distribution was 61.7% while the female percentage distribution was 38.3%.

**PIE DIAGRAM-2** showing age distribution of patients, shows in the age group of 35-45 years were 6.3%, with age group of 46-55 years were 49.1%, with age group 56-65 years were 38.3% and with age group 66-75 years were 6.3%.

**TABLE 1:** Shows baseline characteristics of patients with diabetic retinopathy divided into two groups, one group (n=25) of non-vitamin D supplemented and another group (n=22) of vitamin D deficient, received vitamin D supplementation.

There was no difference in baseline parameters between two groups except serum vitamin D levels.

**TABLE 2&3 and BAR DIAGRAM 1&2:** Shows changes in parameters like BMI, FBS, PLBS, HbA1c, Serum vitamin D levels and new PDR cases at 0 day, 6<sup>th</sup> and 12<sup>th</sup> months in two groups with statistical analysis.

**In group A:**

- The BMI value at 0 day was 25.2±3.1 kg/m<sup>2</sup> increased to 25.3±2.8 kg/m<sup>2</sup> at 6<sup>th</sup> month and 25.4±2.8 at 12<sup>th</sup> month with no statistical significant difference (p>0.05).
- The FBS value on 0 day was 133.24±25.42mg/dl decreased to 126.44±20.4mg/dl at 6<sup>th</sup> month and 120.52±16.56mg/dl at 12<sup>th</sup> month with statistically **significant** difference with p=0.0413.
- The PLBS value on 0 day was 202.8±42.56mg/dl decreased to 184.04±30.13mg/dl at 6<sup>th</sup> month and 164.68±24.32mg/dl at 12<sup>th</sup> month with statistically **highly significant** difference with p=0.003
- The HbA1c value on day 0 was 7.924±0.59% decreased to 6.864±0.655% at 6<sup>th</sup> month and 6.628±0.566% at 12<sup>th</sup> month with statistically **very highly significant** difference p<0.0001
- The serum vitamin D level value on day 0 was 33.88±3.35ng/ml increased to 34.6±2.87ng/ml at 12<sup>th</sup> month with no statistical significant difference (p>0.05)
- The new PDR cases at the end of 12<sup>th</sup> month were 4 in 25 cases (16%) with no statistical significant difference (p>0.05)

**In group B:**

- The BMI value at 0 day was 25.9±2.7 kg/m<sup>2</sup> increased to 26.2±2.7 kg/m<sup>2</sup> at 6<sup>th</sup> month and 26.3±2.3 at 12<sup>th</sup> month with no statistical significant difference (p>0.05).
- The FBS value on 0 day was 142.22±37.65mg/dl decreased to 134.04±31.09mg/dl at 6<sup>th</sup> month and 120.27±20.09mg/dl at 12<sup>th</sup> month with statistically **significant** difference with p=0.0280.
- The PLBS value on 0 day was 203.04±43.15mg/dl decreased to 189.63±42.32mg/dl at 6<sup>th</sup> month and 162.95±34.21mg/dl at 12<sup>th</sup> month with statistically **highly significant** difference with p=0.0014
- The HbA1c value on day 0 was 8.29±1.16% decreased to 7.81±0.710% at 6<sup>th</sup> month and 7.13±0.66% at 12<sup>th</sup> month with statistically **highly significant** difference p=0.0002
- The serum vitamin D level value on day 0 was 14.08±2.34ng/ml increased to 34.07±3.86ng/ml at 12<sup>th</sup> month with statistically **very highly significant** difference (p<0.0001)
- The new PDR cases at the end of 12<sup>th</sup> month were nil in 22 cases with statistical **significant** difference (p=0.0338)

**BAR DIAGRAM 3: SHOWS PERCENTAGE CHANGES**

**Changes in BMI:**

- The percentage increment of BMI from 0 day to 6<sup>th</sup> month was 0.39% in group A & in group B increment was 1.14%.
- The percentage increment of BMI from 6<sup>th</sup> to 12<sup>th</sup> month was 0.39% in group A & in group B increment was 0.38%.
- After 12 months of study, the percentage increment in BMI from 0 day was 0.78% in group A & 1.52% in group B.
- The increment in both the groups was not significant.

**Changes in FBS:**

- The percentage reduction of FBS from 0 day to 6<sup>th</sup> month was 5.1% in group A & in group B reduction was 5.75%.
- The percentage reduction of FBS from 6<sup>th</sup> to 12<sup>th</sup> month was 4.68% in group A & in group B reduction was 10.27%.
- After 12 months of study, the percentage reduction in FBS from 0 day was 9.54% in group A & 15.43% in group B.
- The reduction in both the groups was **significant**.

**Changes in PLBS:**

- The percentage reduction of PLBS from 0 day to 6<sup>th</sup> month was 9.25% in group A & in group B reduction was 6.61%.
- The percentage reduction of PLBS from 6<sup>th</sup> to 12<sup>th</sup> month was 10.51% in group A & in group B reduction was 14.06%.
- After 12 months of study, the percentage reduction in PLBS from 0 day was 18.79% in group A & 19.74% in group B.
- The reduction in both the groups was **significant**.

**Changes in HbA1c:**

- The percentage reduction of HbA1c from 0 day to 6<sup>th</sup> month was 13.38% in group A & in group B reduction was 5.79%.
- The percentage reduction of HbA1c from 6<sup>th</sup> to 12<sup>th</sup> month was 3.38% in group A & in group B reduction was 8.7%.
- After 12 months of study, the percentage reduction in HbA1c from 0 day was 16.31% in group A & 13.99% in group B.
- The reduction in both the groups was **significant**.

**Changes in Serum vitamin D levels:**

- After 12 months of study, the percentage increment in serum vitamin D levels from 0 day was 2.08% in group A & 58.67% in group B.
- The increment in group A was not significant. But in group B, the increment was **very highly significant**.

## **XII. Discussion**

Vitamin D deficiency is associated with hyperglycemia and also associated with development and progression of diabetic retinopathy. Vitamin D supplementation improves glycemic control and prevent severity of diabetic retinopathy. Hence the present was undertaken to see the effect of vitamin D supplementation in treatment of diabetic retinopathy.

In the present study, role of vitamin D supplementation in management of diabetic retinopathy was analysed in 50 diabetic retinopathy patients who were selected according to inclusion criteria. After base line investigations 50 patients of either sex between 35-75 years were enrolled for the study and divided into two groups (group A and B). Patients with normal serum levels of vitamin D were kept under Group A (controls) & patients with low levels were kept under Group B (test subjects). After grouping, 25 patients were in group 'A' and 25 patients were in group 'B'. The base line parameters of the study population like age, sex, height, weight, FBS, PLBS, HbA1c and serum vitamin D levels were estimated before initiating the study. The variations in base line parameters between the two test groups was non-significant ( $p > 0.05$ ).

- Vitamin D supplementation given in group B. Other modalities of treatment for diabetes and diabetic retinopathy maintained constant in both the groups. Parameters like weight, height, FBS, PLBS, HbA1c levels were tested at 0 day, end of 6<sup>th</sup> and 12<sup>th</sup> months. Serum vitamin D levels were tested at 0 day and end of 12<sup>th</sup> month. 47 patients have completed the study for 1 year. Three patients in group-B were dropped out. The reasons were one patient with noncompliance of vitamin D supplementation, one patient with change of hospital and one patient with transfer of place.

Results of the study demonstrated that BMI varied from 0 day to 12<sup>th</sup> month in each group but they did not vary much when compared between the two groups, both the therapies are showing similar effect on BMI.

The % reduction in BMI was 0.78% in group A and 1.52% in group B . The difference in percentage is 0.74% which is insignificant.

The reduction in FBS was significant in Group A and Group B at the end of 12<sup>th</sup> month showing percentage reduction as 9.54% & 15.43% respectively. The difference in the percentage is 5.89%. Vitamin D supplementation is effective upto some extent in reducing FBS as there is little difference in both the groups.

According to the previous study done by Anthony Chinedu Anyanwu et al<sup>(61)</sup> who also supplemented vitamin D in type 2 diabetic patients for glycemic control concluded that vitamin D3 supplementation in persons with T2DM with Vitamin D deficiency and poor glycemic control results in a significant improvement in glycemic control.

The reduction in PLBS was significant in both the test groups showing percentage reduction of 18.79% and 19.74% in Group A & Group B respectively at the end of 12<sup>th</sup> month. The difference in percentage is 0.95% which is very small.

The reduction in HbA1c was insignificant in group A with a % reduction was 16.31% at the end of 12<sup>th</sup> month. But in group B it was showing significant reduction with a % reduction was 13.99% at 12<sup>th</sup> month. The difference in percentage is 2.34%

The % increment in serum vitamin D levels in group A was 2.08% at 12<sup>th</sup> month and in group B it was increased very significantly with a % increment of 58.67% at the end of 12<sup>th</sup> month. The difference in percentage is 56.59%.

Serum levels of vitamin D in all the patients in group B raised above 30ng/ml at the end of 12<sup>th</sup> month. Above study supported the guidelines of endocrine society i.e., treatment for vitamin D deficiency is vitamin D supplementation of 50,000IU once a week for 8 weeks to achieve a blood level of 25(OH)D above 30ng/ml, followed by maintenance therapy of 1500IU/day.

The progression of disease from mild or moderate or severe NPDR to PDR in group A increased upto 16% at the end of 12<sup>th</sup> month. But in group B, progression from NPDR to PDR was not seen at the end of 12<sup>th</sup> month. The difference in percentage is 16%.

Vitamin D may also play a protective role through its effects on glycemic control and hypertension, both significant risk factors for the development and progression of diabetic retinopathy<sup>(62-65)</sup>. There is evidence to suggest that vitamin D plays a role in normal insulin secretion in response to glucose<sup>(66,67,68)</sup>. Additionally, vitamin D supplementation in patients with impaired fasting glucose leads to a reduction in insulin resistance and an attenuation of the rise in fasting glucose levels<sup>(69)</sup>.

It is possible that treating vitamin D insufficiency may lead to an improvement in blood sugar and blood pressure control, which could ultimately slow the progression of retinopathy.

Vitamin D is essential for a vast number of physiologic processes and vitamin D insufficiency has reached pandemic proportions, with more than half the world's population at risk. Vitamin D insufficiency has been implicated in the development of diabetes and also correlated with an elevated risk of cardiovascular disease, cancer, and mortality. Additionally, vitamin D insufficiency has been associated with neurologic conditions, such as multiple sclerosis and Parkinson's disease. So by providing vitamin D supplementation to deficient patients helps in decreasing the risk of development of all above conditions.

No adverse drug reactions were reported in the whole study period.

The results show that supplementation of vitamin D in diabetic retinopathy who are vitamin D deficient, decreases proliferation and neovascularisation in retina, improving glycemic control and also various other benefits without causing any side effects in cost effective manner.

#### **Study limitations:**

- Study participants were assumed to have kept doses of other antidiabetics constant during the intervention period
- The study participants were also assumed not to be taking Vitamin D containing complimentary medicines alongside their medications during the intervention period
- It takes several months to correct Vitamin D deficiency.
- Measurement of response to Vitamin D therapy takes several months (at least 3–4 months)<sup>(62)</sup>. The minimal changes in serum Vitamin D levels noted after supplementation in this study may be due to the reasons above.

Longer periods of follow-up during supplementation would have been more ideal. However, this was not feasible due to time constraints and cost.

The data derived from this study points to a potential relationship between vitamin D deficiency and proliferative retinopathy and can be used in the design of larger studies. Certainly any study examining the relationship between vitamin D and retinopathy prospectively will take years to examine.

While dietary intake and outdoor exposure data were not collected, these limitations would not be expected to have a large effect on the results. Heaney and colleagues have shown that the amount of daily vitamin D obtained from dietary sources have small effects on serum 25(OH)D levels<sup>(70)</sup>. Additionally, effects

from sunlight exposure were minimized in this study as all subjects were enrolled over a three month period in winter.

However further extensive long term studies with larger sample size are recommended.

### **XIII. Conclusion**

Supplementation of vitamin D in diabetic retinopathy who are vitamin D deficient is effective in decreasing proliferation and neovascularisation in retina,

Hence conclusions drawn are:

- Vitamin D supplementation improves serum 25(OH)D levels
- It also helps in improving glycemic control
- It provides benefits without causing any side effects
- Vitamin D supplementation is also cost effective.

### **XIV. Summary**

In the present study, role of vitamin D supplementation in management of diabetic retinopathy was analysed. 47 diabetic retinopathy patients were taken according to inclusion criteria. After base line investigations 47 patients of either sex between 35-75 years were enrolled for the study and divided into two groups (group A and B). Patients with normal serum levels of vitamin D were kept under Group A (controls) & patients with low levels were kept under Group B (test subjects). After grouping, 25 patients were in group 'A' and 22 patients were in group 'B'. The base line parameters of the study population like age, sex, height, weight, FBS, PLBS, HbA1c and serum vitamin D levels were estimated before initiating the study.

Vitamin D supplementation given in group B. Other modalities of treatment for diabetes and diabetic retinopathy maintained constant in both the groups. Parameters like weight, height, FBS, PLBS, HbA1c levels were tested at 0 day, end of 6<sup>th</sup> and 12<sup>th</sup> months. Serum vitamin D levels were tested at 0 day and end of 12<sup>th</sup> month. Results were analysed with p value obtained by t-test and chisquare test.

From the results obtained, it is concluded that:

- Vitamin D supplementation improves serum 25(OH)D levels
- It also helps in improving glycemic control
- It provides benefits without causing any side effects
- Vitamin D supplementation is also cost effective.

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## **INSTITUTIONAL ETHICS COMMITTEE**

GANDHI MEDICAL COLLEGE, SECUNDERABAD - 500 003.  
PHONES: 27502742 / 27508392 FAX: 27502856  
DCGI Regd No. ECR/180/Inst/AP/2013, dt. 20-04-2013

Re.No. IEC/GMC/2015/

Dated: - 16/07/2015

To,  
**Dr. Mohammad Juber**  
PG in Pharmacology  
Gandhi Medical College/Hospital,  
Secunderabad.

**Dr. Mohammad Juber,**

**Sub: “Evaluation of vitamin-D supplementation in management of Diabetic Retinopathy” – by Dr. Mohammad Juber. -Approval- Reg.**

The **XXIV** Institutional Ethical Committee meeting held on 13-07-2015 Monday at 02.30 pm at Medical Education Cell, Gandhi Medical College, Musheerabad, Secunderabad.

### **The following members were present:-**

1	Mr. J. Aswini Kumar	Advocate	Chairman
2	Dr. S. Sreelatha	Principal, GMC, Sec.bad	Member Secretary
3	Dr.D.Mahesh Chander	Vice-Principal (Academic)	Member
4	Dr.K. Indira	Prof. of Pharmacology	Convener
5	Sri. K. V. Subrahmanyam	Common Man	Member- LAYMAN
6	Dr. Vimala Thomas	Prof.& HOD of Community Medicine	Member
7	Dr. T. Usha Sree	Professor & HOD of Pharmacology	Member-LADY
8	Dr. P.V. Chalam	Professor of General Surgery	Member
9	Mrs. Devaki	Project Coordinator, Ashray Akruithi	Member-NGO
10	Dr. B.S.V. Manjula	Professor of Medicine	Member
11	Dr. J. V. Rao	Professor & HOD, Paediatrics	Member

### **The following members were absent:-**

1	Dr.G. Venkateswarlu	Superintendent, Gandhi Hospital	Member
2	Dr. P. Upender Gowd	Vice-Principal(Admn), GMC, Sec.bad	Member
3	Dr. Sundaresh Peri	Technical Officer, Lepra India	Member - NGO
4	Sri. Y. Rama Rao	Advocate	Member

After discussion, the project was put to vote:

Members voted for	:	11
Members voted Against	:	Nil
Members Absent	:	04

The Institutional Ethics Committee, Gandhi Medical College, discussed your application & approved to conduct: “Evaluation of vitamin-D supplementation in management of Diabetic Retinopathy” – by Dr. Mohammad Juber, PG in Pharmacology, Gandhi Medical College/Gandhi Hospital, Secunderabad under the guidance of Dr. T.S. Usha Sree, Prof.&HOD of Pharmacology, GMC, Secunderabad.

The Institutional Ethics Committee expects to be informed about the progress of the study, any changes in the protocol and patient information / informed consent and asks to submit a copy of the final report.

Yours sincerely,

  
MEMBER SECRETARY  
INSTITUTIONAL ETHICS COMMITTEE

### రోగి సమ్మతి పత్రం

మేము మిమ్ములను గాంధీ వైద్యశాలనందుజరుగు ఒక శాస్త్రీయ అధ్యయనంలో పాల్గొనమని కోరడం అయినది. ఈ అధ్యయనంలో మీరు పాల్గొనాలా లేదా అనేది స్వచ్ఛందంగా నిర్ణయించుకోవచ్చు. మీరు ఈ అధ్యయనంలో ఏకణానైనా విరమించుకోనుటకు అధికారము కలదు. ఇలా విరమించుకొనినందున మీకు ఈ వైద్యశాలలో జరుగు వైద్య సదుపాయములకు ఎటువంటి నియంత్రణ కలుగదు. మీకు ఈ వైద్య పరీక్షలు మీ వ్యాధి చికిత్స కొరకు చేయడం జరుగుతుంది. ఇందులో ఎటువంటి వ్యాపార సంబంధమైన ఉద్దేశ్యము లేదు.

ముఖ్య ఉద్దేశ్యము: రక్తంలో అధిక క్రోవు ఉన్న వారికి 1) ప్రతి దినము మరియు 2) దినము తప్పి దినము రోసువోస్టాటిన్ ఇచ్చి దానియొక్క సామర్థ్యాన్ని పోల్చడం జరుగును.

**విధానం:** రక్తంలో అధిక క్రొవ్వు ఉన్న వారికి 10mg రోసువోస్టాటిన్ దినము ఒక గ్రాపు వారికి మరియు 10mg రోసువోస్టాటిన్ దినము తప్పి దినము రెండవ గ్రాపు వారికి నోటి ద్వారా ఒకటి చొప్పున రాత్రి సమయంలో తీసుకోమనడం జరుగుతుంది.

ఈ అధ్యయన కాలం 6 వారములు.

ఈ అధ్యయనంలో 3ml రక్తమును వైద్య పరీక్షల నిమిత్తం మందులు వాడకముందు మరియు మందులు వాడిన తరువాత 4వ వారమున, 6 వారముల తరువాత తీయుట జరుగుతుంది.

**అనుకూల ప్రభావాలు:** ఈ అధ్యయన ఫలితాలు రక్తంలో అధిక క్రొవ్వు ఉన్న వారికి గుండె జబ్బులు నివారించుటకు తోడ్పడును.

**ప్రతికూల ప్రభావాలు:** ఈ ఔషధము తక్కువ మోతాదులో ఎటువంటి దుస్పృభావము చూపదు. అధిక మోతాదులో తీసుకొనిన యడల స్వల్పముగా కండరాలపై ప్రభావము చూపును.

ఈ అధ్యయనము గురించి అన్ని వివరములు నాకు తెలియచేయడమైనది. నేను పైన వివరించిన అధ్యయనంలో పాల్గొనుటకు సమ్మతి తెలియచేయుచున్నాను.

రోగి పేరు: సంతకము:

చిరునామ: తేది:

సాక్షి:

**INFORMED CONSENT PROFORMA**

I \_\_\_\_\_ S/o.w/o. \_\_\_\_\_ do here by give my consent freely, voluntarily, unreservedly & in full sense to participate in the research project entitled **“EVALUATION OF VITAMIN-D SUPPLEMENTATION IN MANAGEMENT OF DIABETIC RETINOPATHY”**

The investigator explained me about the purpose of the study & its benefits without compromising the quality of the treatment in understandable / local languages

As per the advice of the investigator I undergo investigations.

**Signature / Thumb Impression**

**CASE SHEET PROFORMA**

**I.P/O.P no:**

**Name:**

**Age:**

**Sex:**

**Chief complaints:**

**H/O presenting illness:**

**H/O previous ocular disease/ treatment:**

**H/O systemic illnesses:**

**Family History:**

**Personal History:**

**General examination:**

**Ocular Examination:**

	Right eye	Left eye
Visual acuity		
Lids		
Conjunctiva		
Cornea		
Anterior chamber		
Iris		
Pupil		
Lens		

Applanation tonometry		
Gonioscopy		

**Fundus examination:**

**Investigations:**

**Fundus Fluorescein Angiography:**

**Optical Coherence Tomography:**

**Diagnosis:**

**Treatment advised for abnormal systemic parameters:**

**Treatment given:**

**Follow up:**

**Remarks:**

XXXXX "Arrhythmia Classification Approach Based On Features Extracted From 1d and 2d Discrete Cosine Transforms On ECG Signals."IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 3, 2018, pp 01-45