Vitamin D and Human Health: Insights from Local Studies in Nepalese Population

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By

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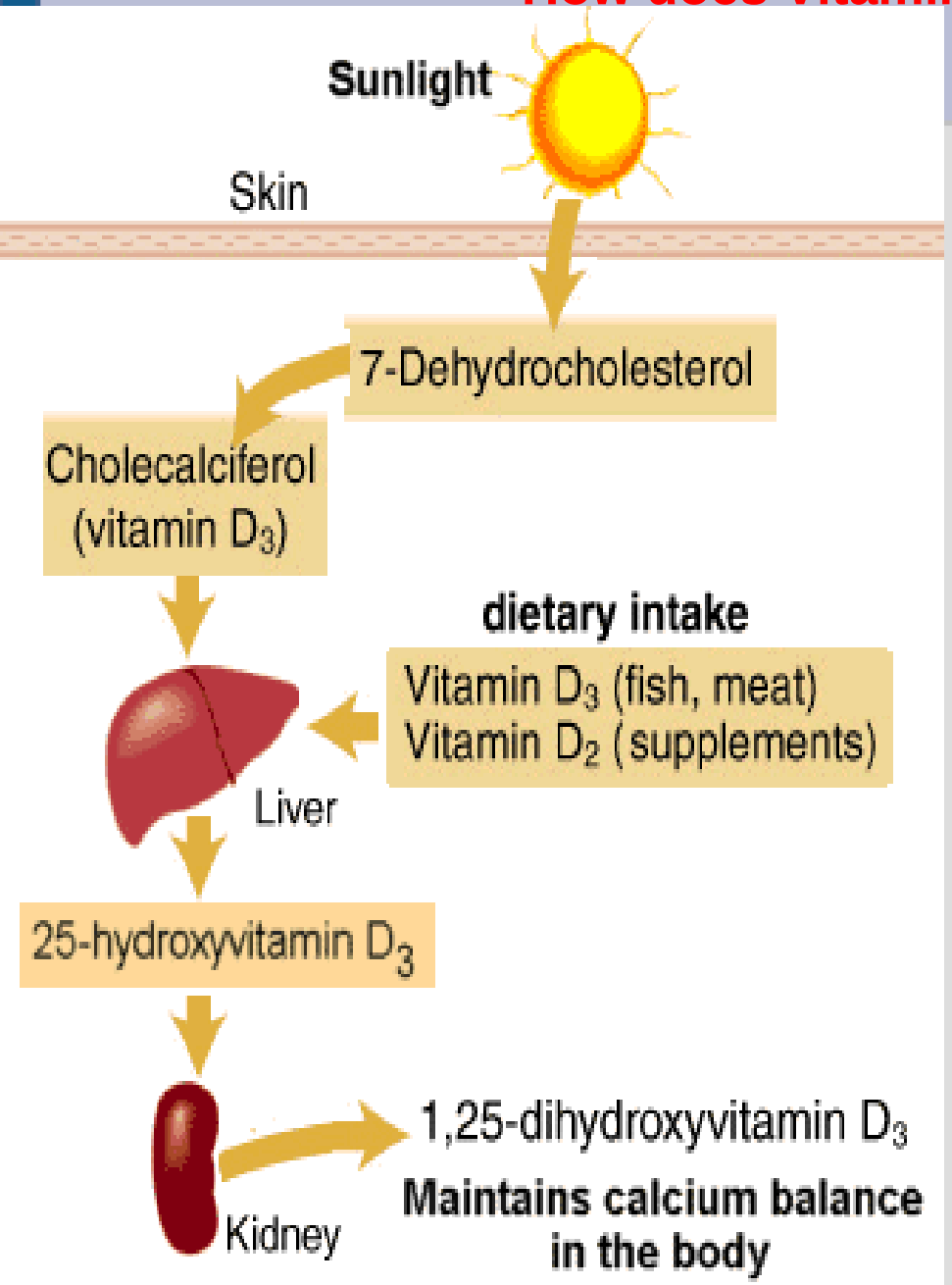
Vitamin D

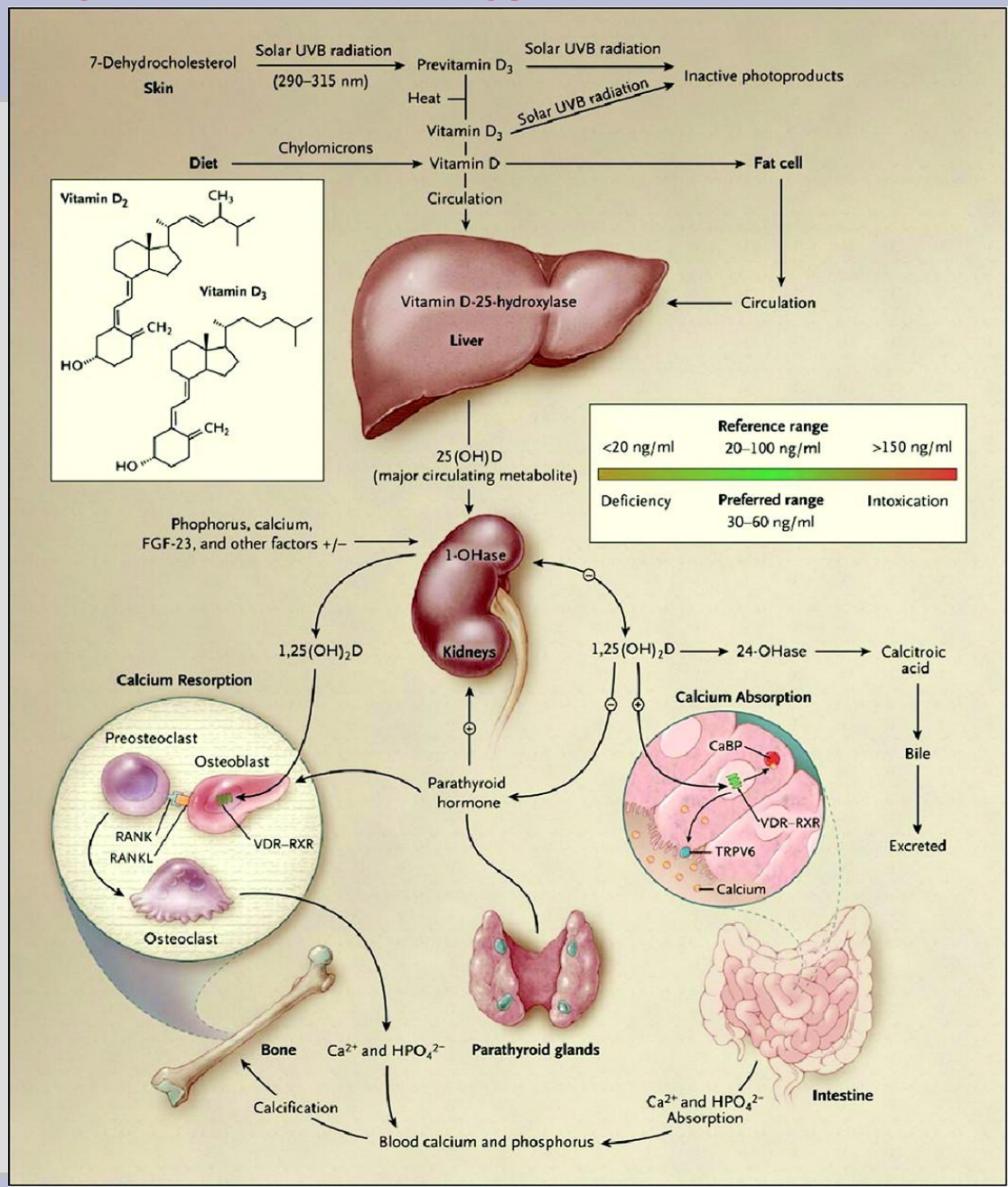
- Vitamin D is a steroid hormone ,playing important role in calcium in mineral metabolism and bone growth and maintenance.

- Most cells in the body have been found to have receptors for vitamin D, and is therefore now seen as an important nutrient in preventing many chronic diseases.

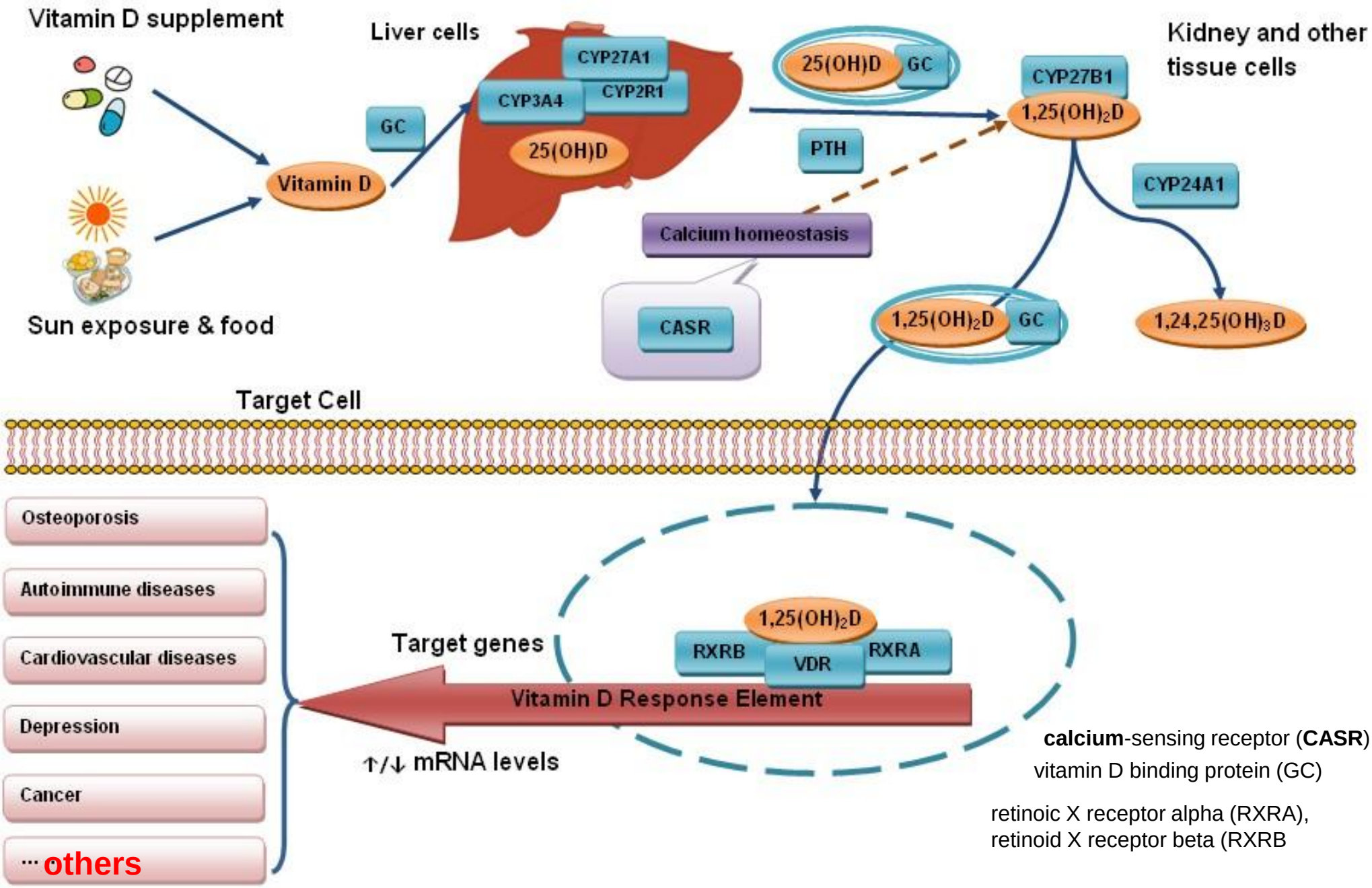
Vitamin D Metabolism

How does Vitamin D synthesized in body)





How does Vit-D work

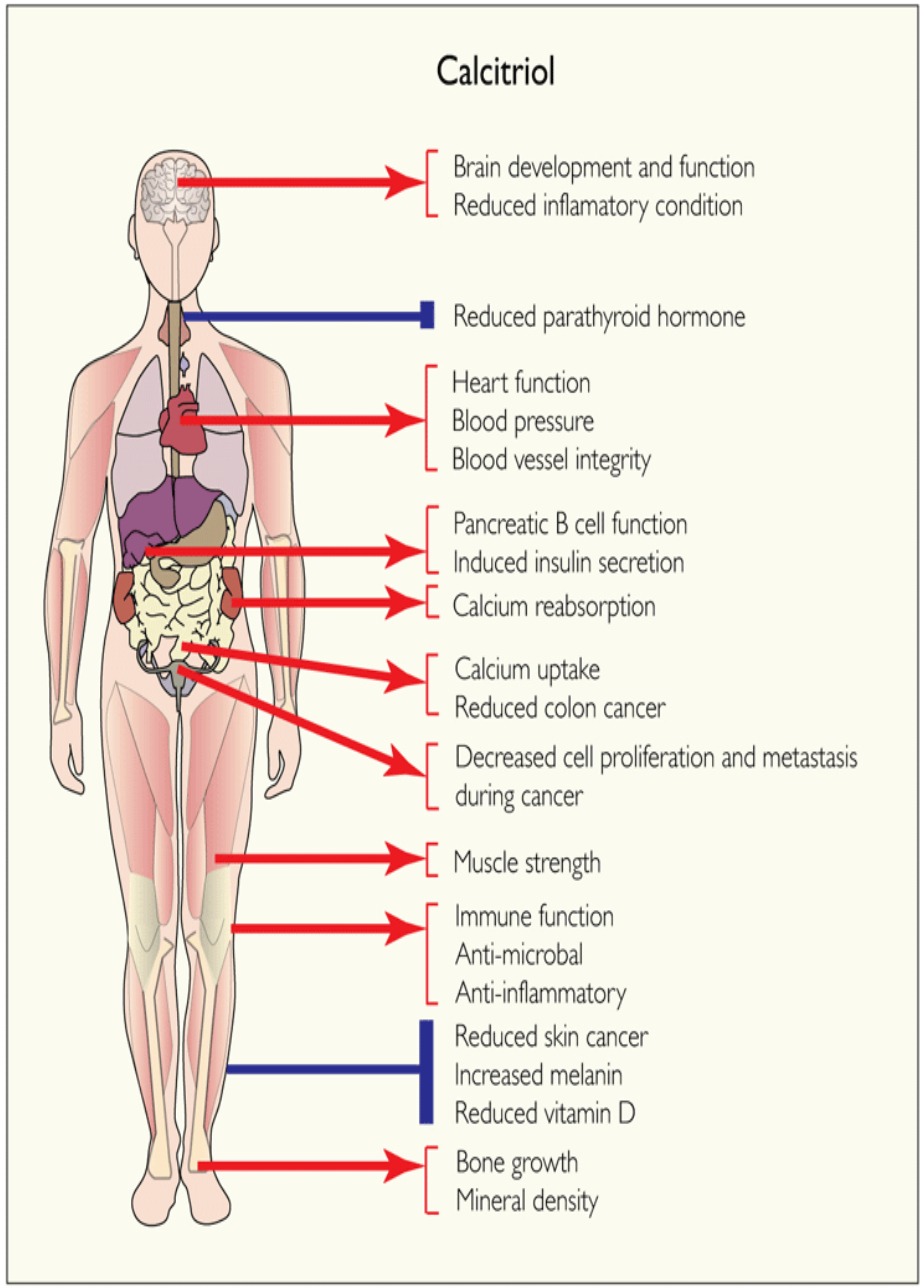


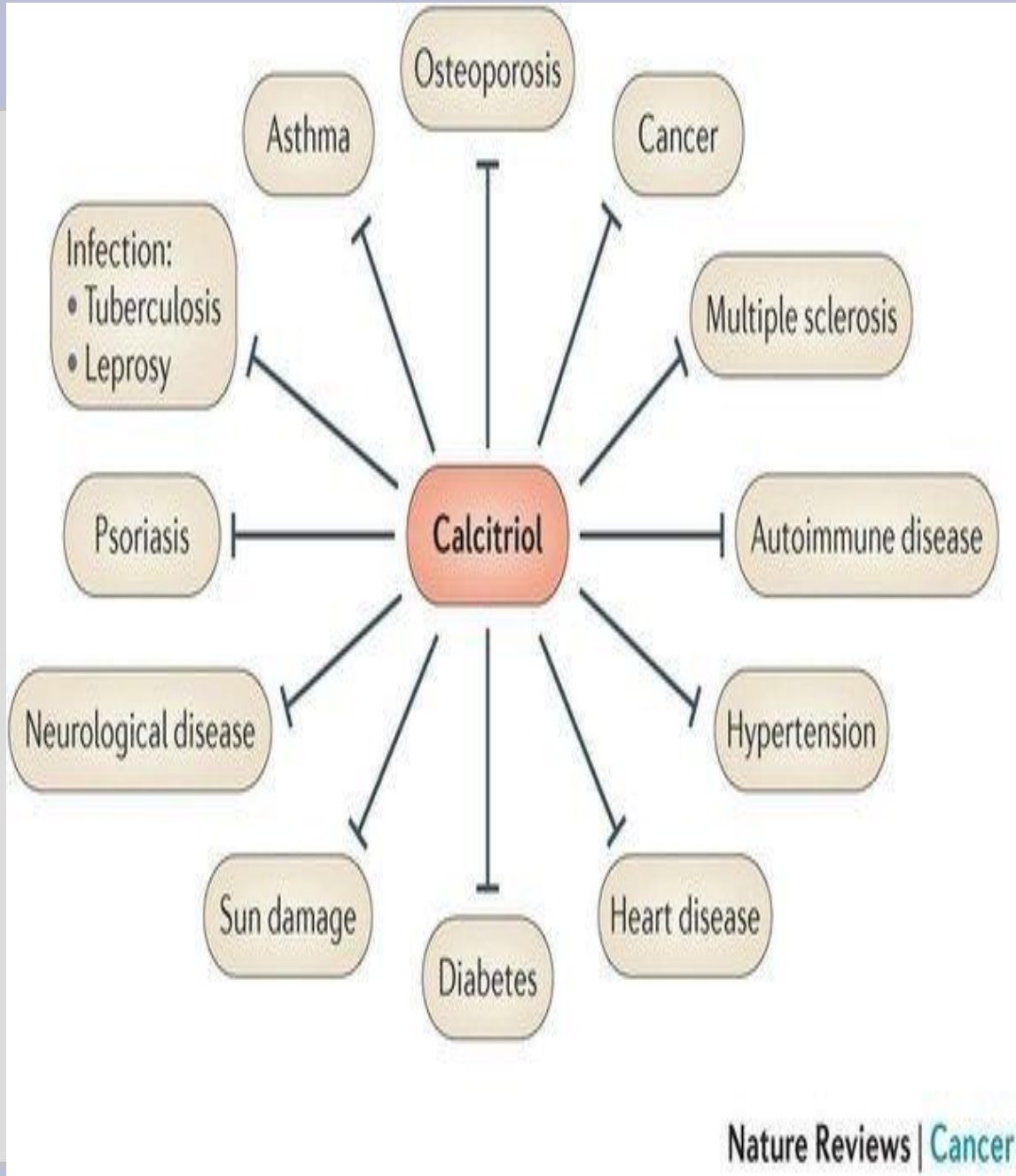
calcium-sensing receptor (**CASR**)

vitamin D binding protein (GC)

retinoic X receptor alpha (RXRA),
retinoid X receptor beta (RXRB

Vitamin D in health and disease





Vitamin D status:

(as per guidelines set by US Endocrine Society)

- **Vitamin D sufficiency: >30 ng/ml**
- **Vitamin D deficiency: <30 ng/ml**
- **Vitamin D insufficiency: 10-29 ng/ml and**
- **Severe vitamin D deficiency: <10 ng/ml**

Prevalence of Vitamin-D Deficiency in Nepal: Some Fact

- **Diana Avagyan et al in 2013 in Nepalese children : Hypovitaminosis D identified in 91.1% of children.**
- **Pokharel BR et al 2015,Vit-D in stroke found 61.92% of stroke pts had Vit-D deficiency**
- **Study done by Bhatta MP et al (2016) in western region: 73.68% had Vitamin-D deficiency and Female were more deficient than male By 5.29%. (laboratory based data)**
- **Study done by *Shanti Regmi et al, 2016 at CMC,* 74.1% (80) patients had 25(OH) D levels lower than 30 ng/ml.**
- **Laxmi RC** et al in 2018 in Lalitpur found 91.2% had Vitamin D deficiency.
- **Tirtha Narayan Shah** et al (2021) in Rupandehi, 14.9% had deficient, 42.8% had insufficient, 35.3% had sufficient and 7% had high level of serum vitamin D.
- **Chandra Yogal** et al in 2022 , Bhaktpur, VDD and VDI were observed in **6.3 and 42.4%** of the participants, respectively, and the prevalence increased by age.

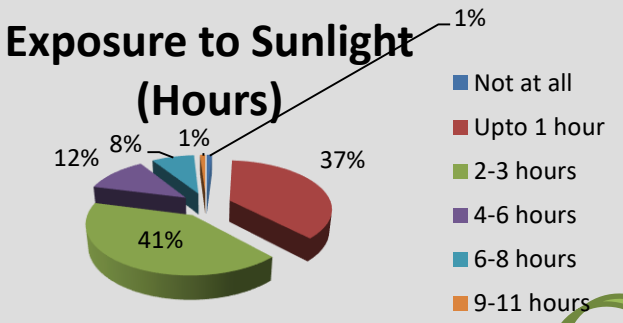
Our Study at TUTH

In Diabetes mellitus by Pradhan S et al , found that around 85% diabetic patients had Vit-D insufficiency

Vitamin D Status in Healthy Population Visiting for General Health Checkup in Tribhuvan University Teaching Hospital found 46.7% had Vit-D deficiency while 13.7 % had severe Vit-D deficiency(2017).

Louis et al (Sweden) at TUTH in 2015

Mean Vitamin D Levels Distribution Across Gender (ng/ml)		
	Mean Serum 25(OH)D Levels	p-value
Male	18.08 ± 6.8	0.029
Female	15.03 ± 6.9	



serum 25(OH)D			
How many hours do you normally spend outside during the day?	Mean	N	Std. Deviation
Not at all	20.9	1	
Upto 1 hour	15.925	37	8.7503
2-3 hours	15.908	41	4.9361
4-6 hours	18.982	12	8.3023
6-8 hours	18.613	8	4.8407

Autoimmune Thyroiditis Among Hypothyroid Individual And Its Association With Vitamin D (Jyoti et al, 2018 at TUTH)

Parameters	Case (Hypothyroid patient with AIT(n = 60)		Control (Apparently healthy euthyroid individual(n = 40)		p-value
	Mean	SD	Mean	SD	
Age	35.22	7.72	36.08	9.15	0.6
TSH	76.2	25.6	2.1	0.8	<0.001 *
FT_4	3.6	2.1	14.4	2.1	<0.001 *
FT_3	3.3	1.3	5.9	0.5	<0.001 *
Vitamin D	13.6	2.8	26.8	2.3	<0.001 *

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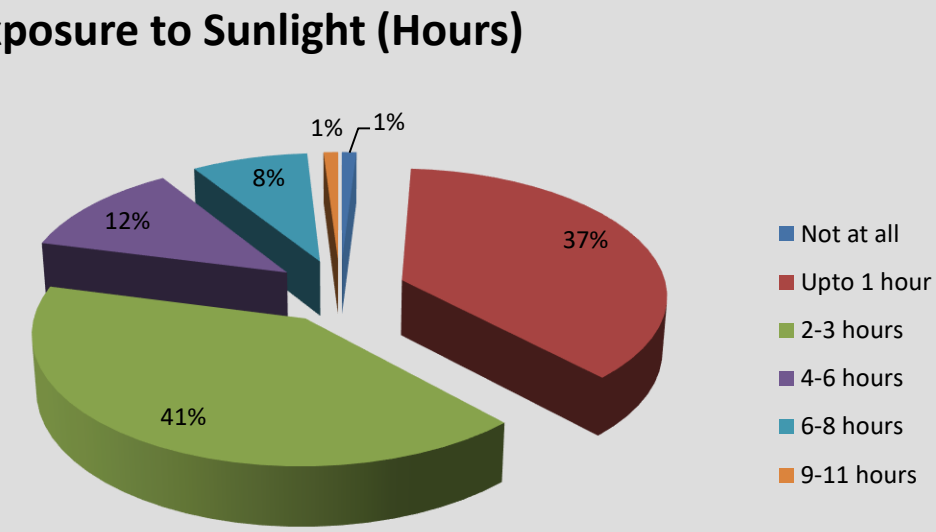

serum 25(OH)D				
How many hours do you normally spend outside during the day?	Mean	N	Std. Deviation	Range
Not at all	20.9	1	.	0
Upto 1 hour	15.925	37	8.7503	35.1
2-3 hours	15.908	41	4.9361	20.8
4-6 hours	18.982	12	8.3023	26.6
6-8 hours	18.613	8	4.8407	16
9-11 hours	8	1	.	0
Total	16.47	100	7.0216	35.1

Autoimmune Thyroiditis Among Hypothyroid Individual And Its Association With Vitamin D (Jyoti et al, 2018 at TUTH)

Parameters	Case (Hypothyroid patient with AIT) n = 60		Control (Apparently healthy euthyroid individual) n = 40		p-value
	Mean	SD	Mean	SD	
Age	35.22	7.72	36.08	9.15	0.6
TSH	76.2	25.6	2.1	0.8	<0.001*
FT_4	3.6	2.1	14.4	2.1	<0.001*
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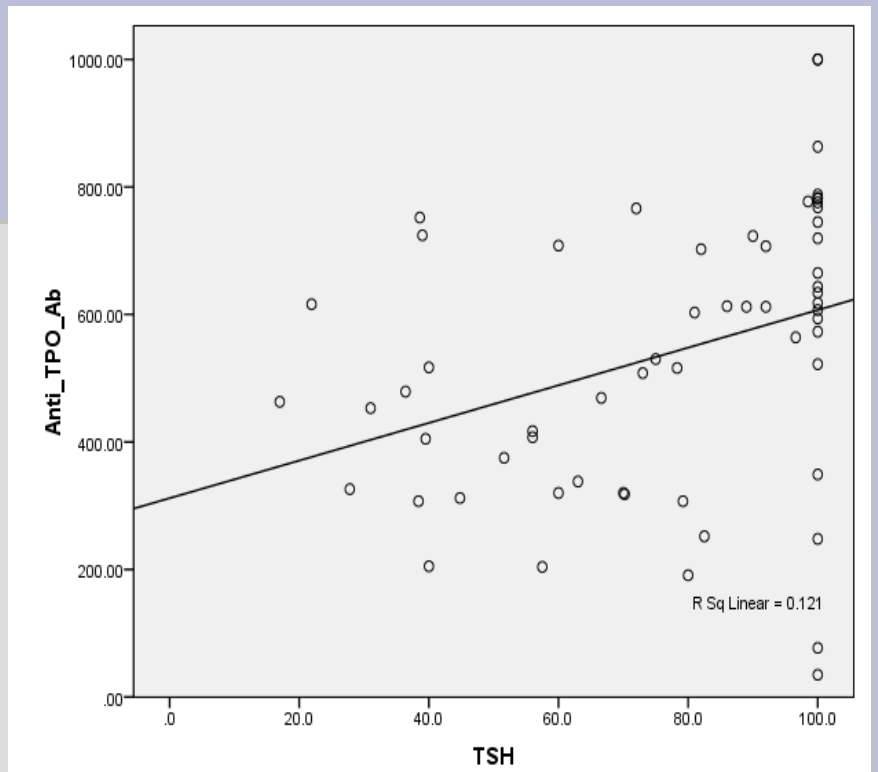
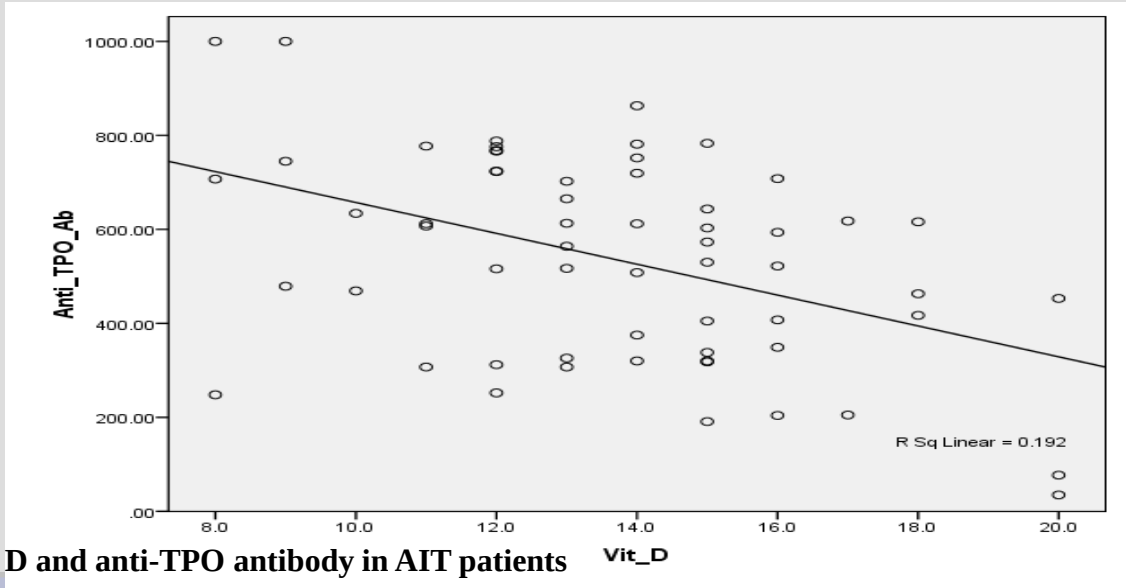


Correlation between TSH and anti-TPO antibody in AIT patients

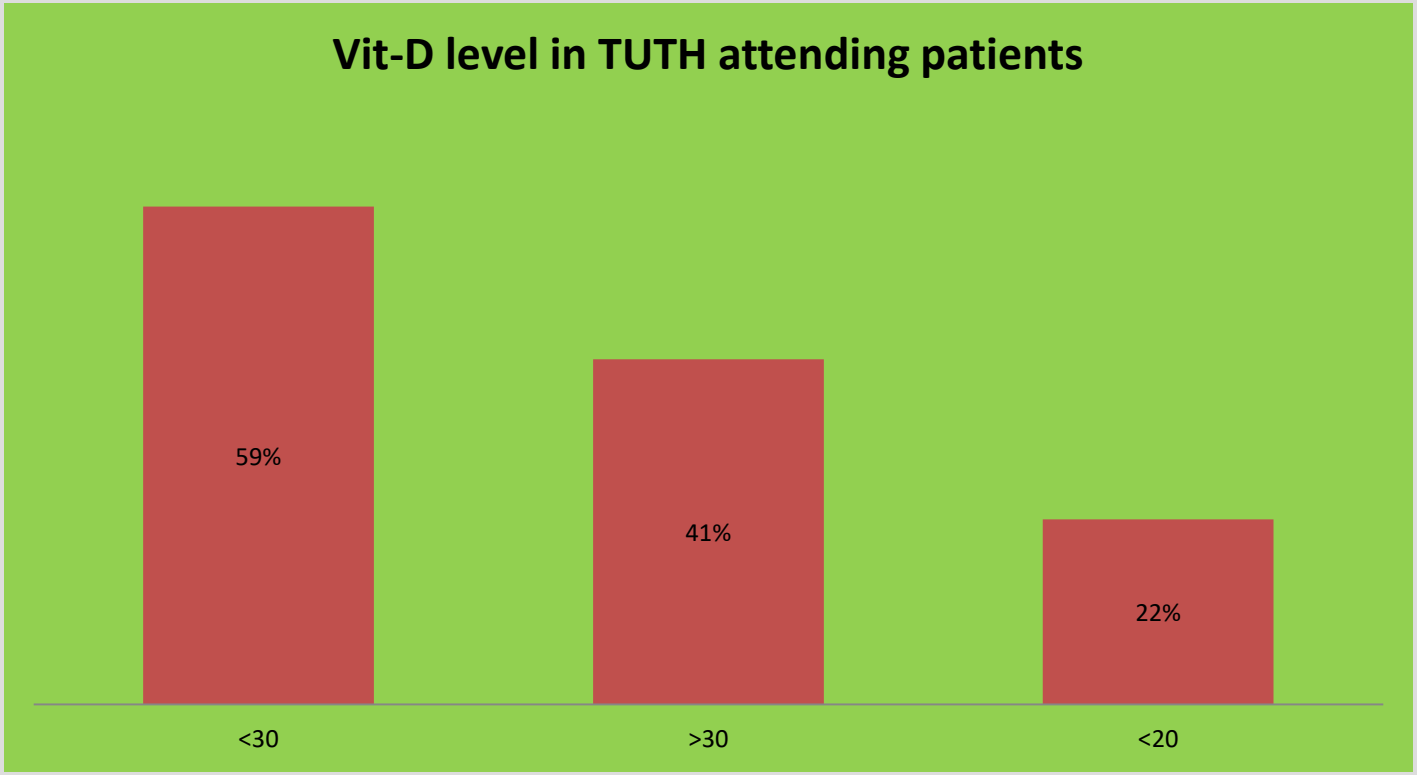


Correlation between vitamin D and anti-TPO antibody in AIT patients

Vit-D level in TUTH attending patients

Binita et al, 2017, TUTH

Vitamin-D	Mean	Std. Deviation
Female(1460)	31.05	31.10
Male(930)	35.45	35.71



Introductory Conclusion

From theses several study,

- Nepal is also suffering from hypovitaminosis-D, instead of having a very good amount of sunlight exposure.

- More research are needed to rule out the major cause for the same.

➢ **Probable cause for hypovitaminosis are:**

- Nutritional deficiency
- Food habit
- **Genetics**

Population based study has not been done yet so it will be better to study Vitamin-D level in general population and factors responsible for the same .

Two Population based study in Nepal

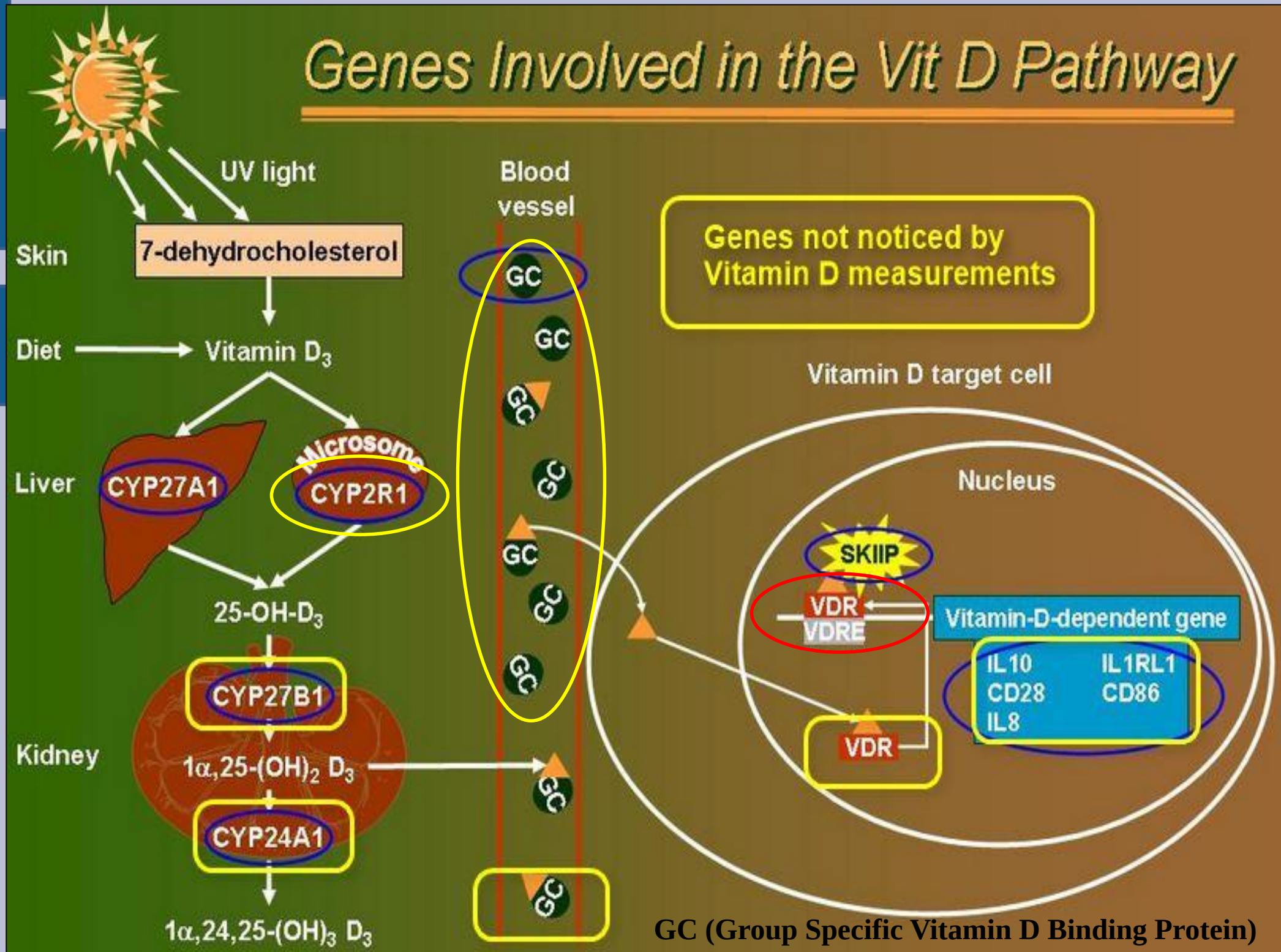
- **Bajrachray A and Yadav BK et al 2023 in Bagmati Pradesh (NAST Academician Grant)**

The values of reference interval obtained for age-groups 18 – 30 years, 31 – 50 years and 51 – 65 years were (13.97 – 39.79)ng/ml, (15.18 – 39.68)ng/ml and (15.48 – 51.13)ng/ml, respectively.
The overall value of reference interval for vitamin D obtained in this study was **15 ng/ml to 40 ng/ml.**

- **Yadav BK and Pandit R et al , 2023 in Madhesh Pradesh (NHRC Provincial Grant)**
  - The reference values for age-groups 18 – 30 years, 31 – 50 years and 51 – 65 years were (12.71 – 46.38) ng/ml, (13.45 – 52.61) ng/ml and (14.50 – 55.00) ng/ml, respectively.
  - The overall reference interval values for vitamin D obtained in this study ranges from **13 ng/ml to 50 ng/ml.**

Age grp(yrs)	Bagmati Pradesh	Madhesh Pradesh
18-30	13.97 – 39.79 ng/ml	12.71 – 46.38ng/m
31-50	15.18 – 39.68 ng/ml	13.45 – 52.61ng/ml
51-65	15.48 – 51.13 ng/ml	14.50 – 55.00 ng/ml
Overall	**15 - 40 ng/ml.**	**13 -50 ng/ml.**

What may be the cause of Hypovitaminosis -D???????


Genes Involved in the Vit D Pathway
UV light
Skin
7-dehydrocholesterol
Diet
Vitamin D_3
Liver
CYP27A1
Microsome
CYP2R1
25-OH-D_3
CYP27B1
Kidney
1α,25-$(OH)_2$ D_3
CYP24A1
1α,24,25-$(OH)_3$ D_3
Blood vessel
GC
Genes not noticed by Vitamin D measurements
Vitamin D target cell
Nucleus
SKIIP
VDR
VDRE
Vitamin-D-dependent gene
IL10
IL1RL1
CD28
CD86
IL8
VDR
GC (Group Specific Vitamin D Binding Protein)

Research Questions:

Is there a association between genetic polymorphism and vitamin D in individual visiting TUTH for general Health Checkup?

Objectives:

General: To find out the association between genetic polymorphism and vitamin-D- level in individual visiting TUTH hospital

Specific:

1. To screen Nepalese individuals for CYP2R1 (vitamin D 25 hydroxylase) associated single nucleotide polymorphisms (rs10741657, rs12794714) related to Vitamin D metabolism.

2. To screen Nepalese individuals for GC (Group Specific Vitamin D Binding Protein) associated single nucleotide polymorphisms (rs4588, rs7041) related to Vitamin D metabolism.

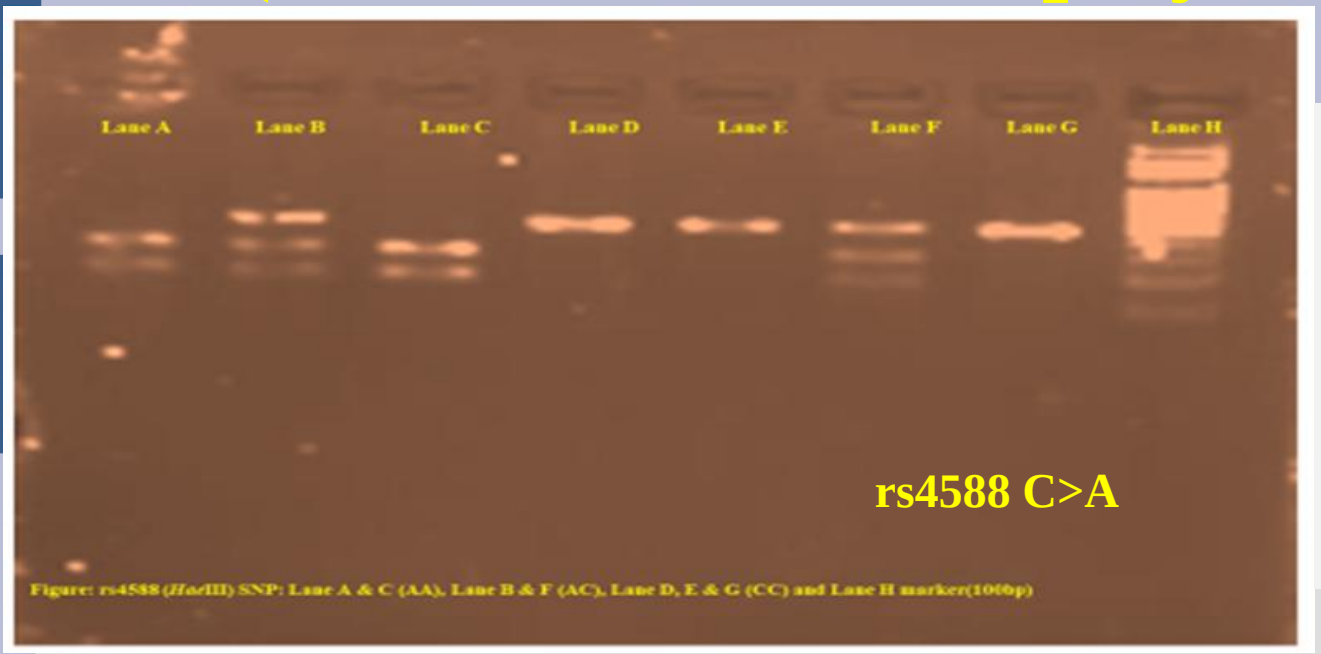
3. To screen Nepalese individuals for VDR (Vitamin D Receptor) associated single nucleotide polymorphisms (rs2238136, rs731236) related to Vitamin D metabolism.

4. To study the association of genetic polymorphisms and hypovitaminosis D in the study group.

Gene (SNP ID), Base change, PCR products, Restriction sites and RFLP fragment

Gene (SNP ID)	Base change	PCR product (bp)	Restriction enzyme (Temp.)	Allele: RFLP fragment (bp)
GC (rs4588)	C/A	483	HaeIII, 37˚C	C: 483 A: 297 + 186
GC (rs7041)	T/G	483	StyI, 37˚C	T: 483 G: 305 + 178
CYP2R1 (rs10741657)	G/A	288	MnlI, 37˚C	G: 151 + 105 + 32 A: 256 +32
CYP2R1 (rs12794714)	G/A	181	FokI, 37˚C	A: 181 G: <181
VDR (rs731236)	T/C	716	TaqI, 65˚C	T: 512 + 204 C: 716
VDR (rs2238136)	G/A	135	Bpu10I, 37˚C	A: 135 G: 72 + 63

The polymorphisms of GC (rs4588 and rs7041 polymorphisms)



rs4588 (*Hae*III) SNP: Lane A & C (AA), Lane B & F (AC), Lane D, E & G (CC) and Lane H marker(100bp)

RFLP products for rs4588 C>A (Thr436Lys) were 297 and 186 bp for wildtype homozygous genotype and no restriction (483 bp) for the homozygous mutant genotype.

rs7041 (*Sty*I) SNP: Lane A& F (TT), Lane B, C, D, E & G (TG)

RFLP products for rs7041 T>G (Asp432Glu) SNP were 305 and 178 bp for the mutant homozygous and no restriction for the wild-type homozygous genotype.

Polymorphism of rs10741657 (CYP2R1 gene)

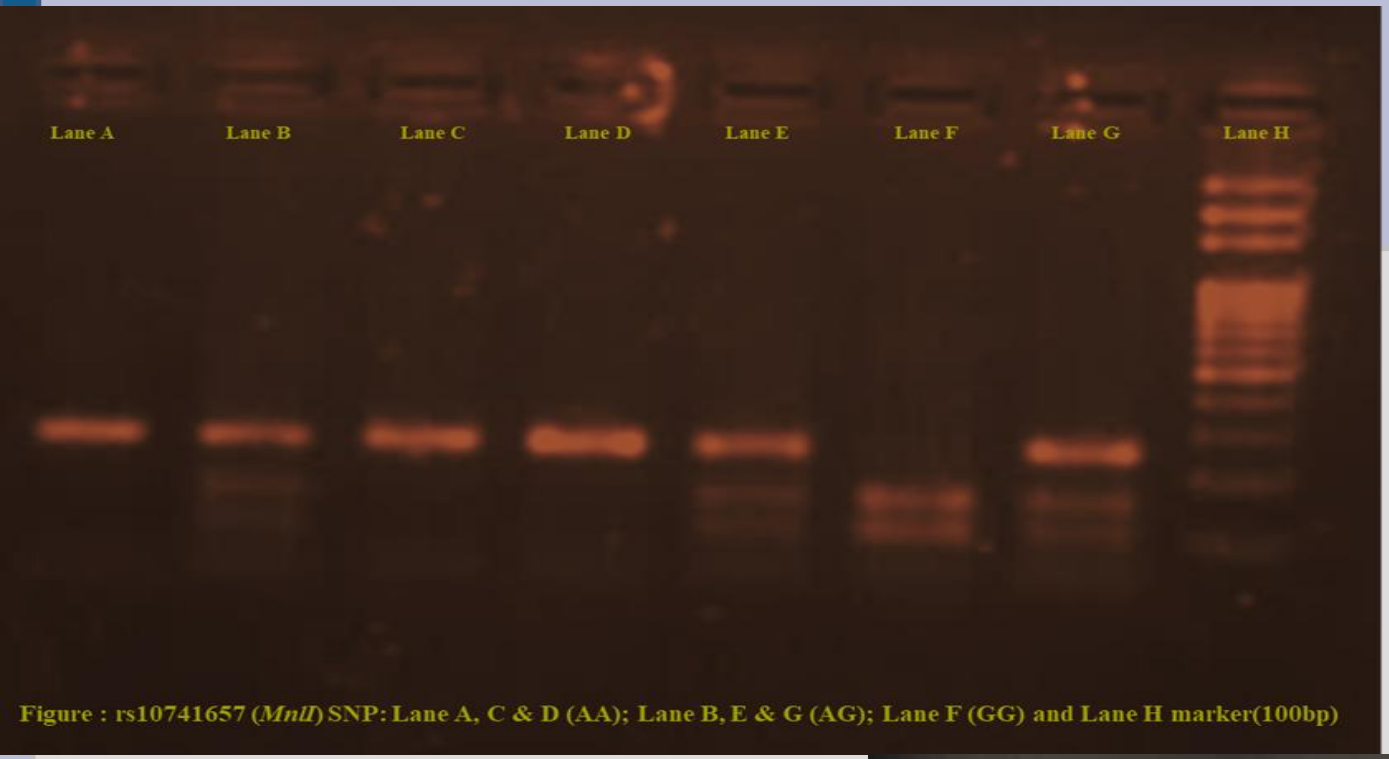


Figure : rs10741657 (*MnlI*) SNP: Lane A, C & D (AA); Lane B, E & G (AG); Lane F (GG) and Lane H marker(100bp)

rs10741657(*MnlI*) SNP:Lane A,C &D(AA), Lane B, E& G (AG), Lane F(GG)

After RFLP, the 288-bp PCR product was cleaved into 3 bands of 151 bp, 105 bp and 32 bp fragment size in homozygous GG genotype while infrequent AA genotype produced 2 bands of 256 bp and 32 bp fragment size and the heterogygous genotype AG yielded 4 bands of 256 bp, 151 bp, 105 bp and 32 bp fragment size

Genotyping for rs12794714(CYP2R1)

rs12794714 (*Fok*I) SNP: Lane A, C, D, F & G (AG), Lane B (GG) and Lane H marker (100bp)

After Restriction digestion, the 181-bp PCR product was cleaved into two fragments.

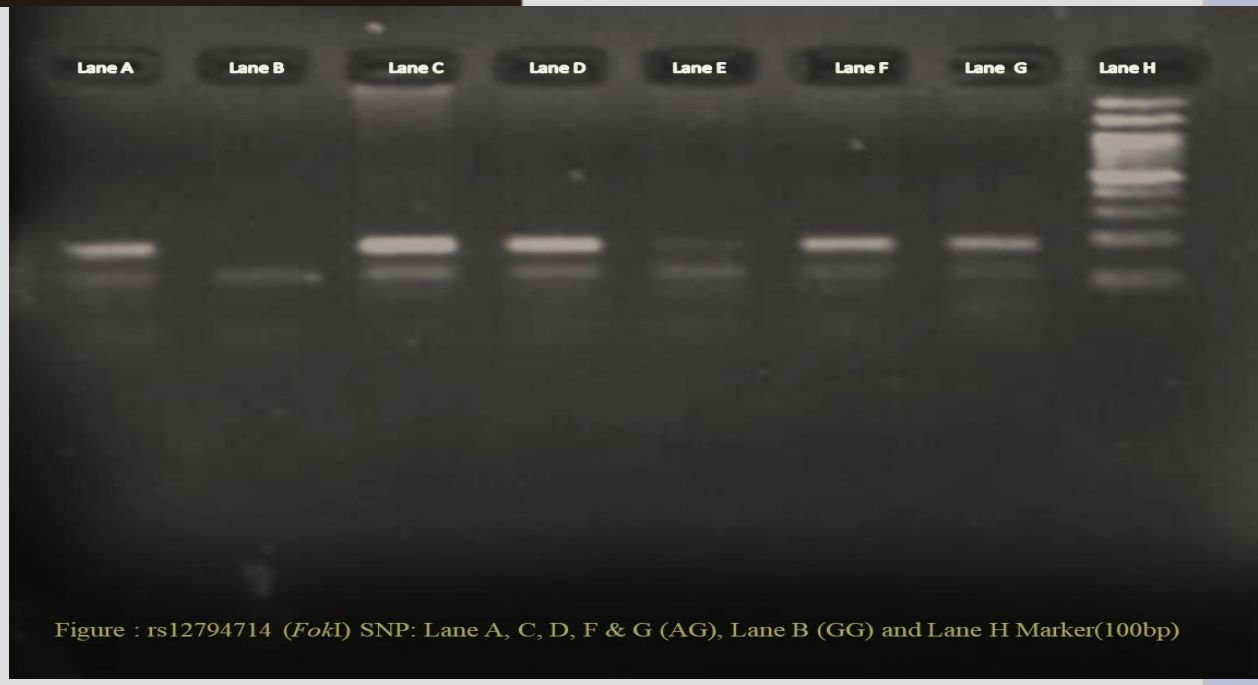


Figure : rs12794714 (*Fok*I) SNP: Lane A, C, D, F & G (AG), Lane B (GG) and Lane H Marker(100bp)

Genotyping of VDR rs2238136 (VDR) G/A SNP

Figure : rs2238136 (*Bpu*10I) SNP: Lane A, C, F & G (GG), Lane B & D (AG), Lane E (AA) and Lane H marker(100bp)

rs2238136 (*Bpu*10I) SNP: Lane A, C, F & G (GG), Lane B & D (AG), Lane E (AA)
With A allele 135 bp product was left intact while G allele produced two fragments of 72 and 63 bp.

Genotyping of TaqI rs731236 (VDR) SNP

rs731236 SNP (*Taq*I); Lane A & E (TC variant), Lane B & D (CC), Lane C & F (TT)
The wild type genotype TT produced 512 and 204 bp fragment while mutant CC only 716 bp fragment

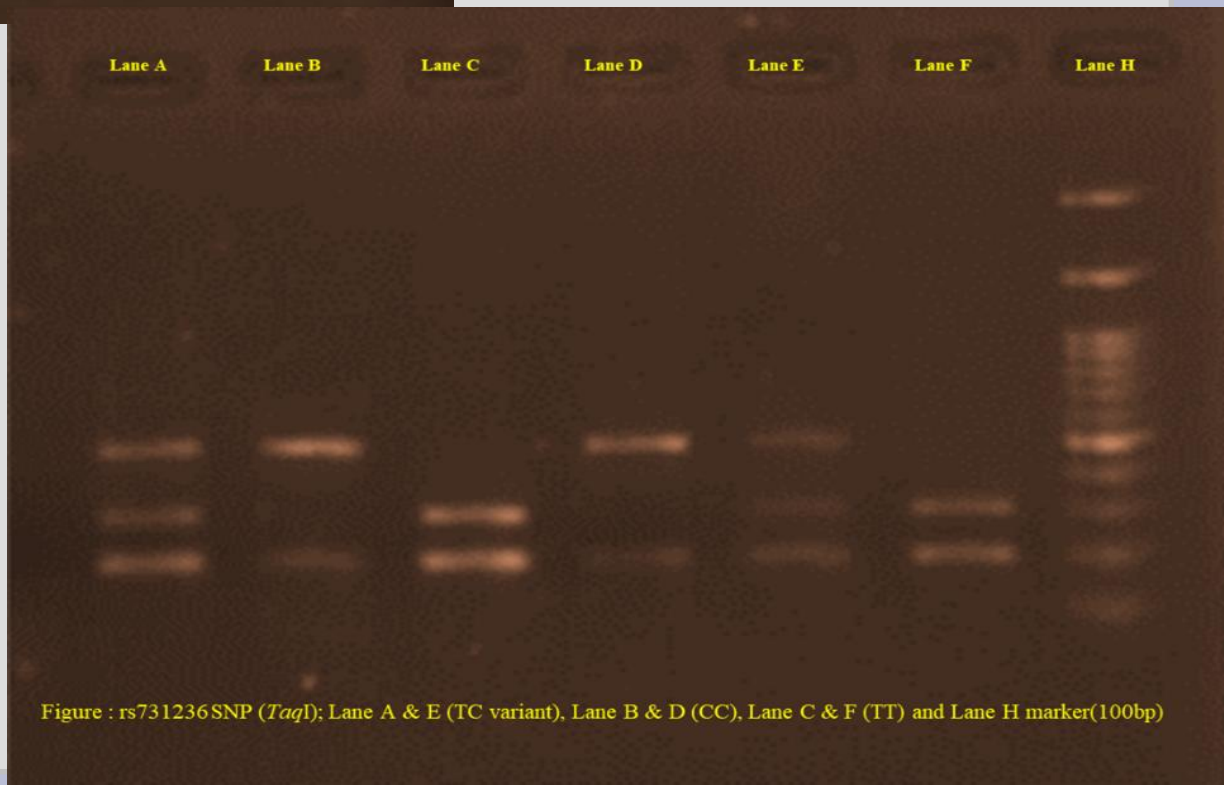
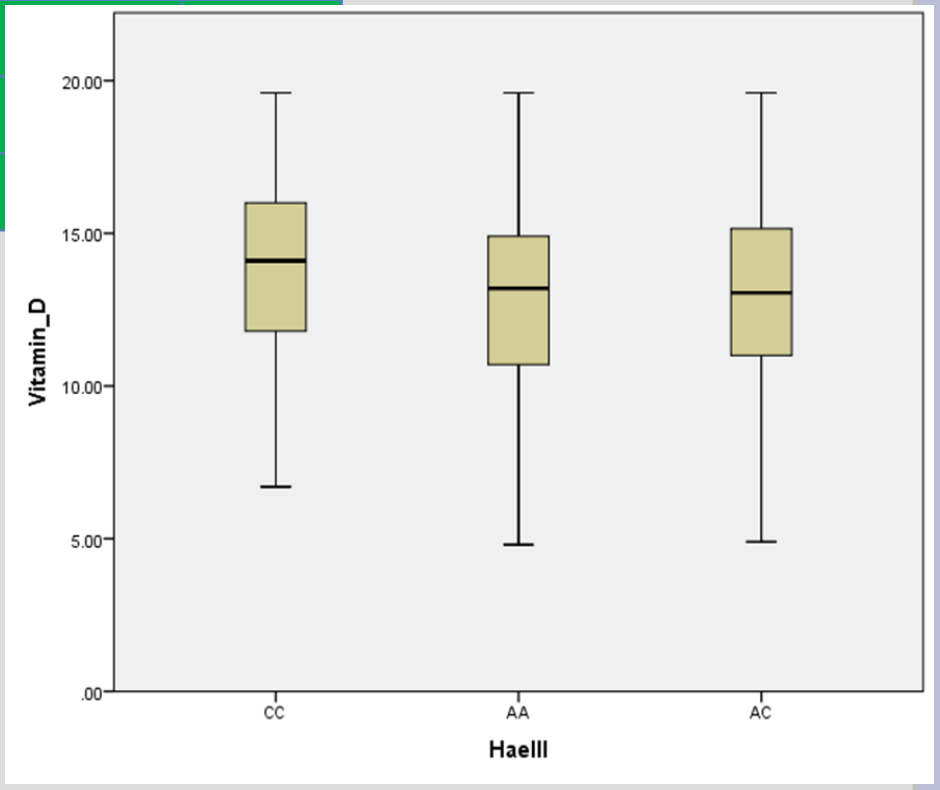


Figure : rs731236 SNP (*Taq*I); Lane A & E (TC variant), Lane B & D (CC), Lane C & F (TT) and Lane H marker(100bp)

Table 1: Allelic frequency and vitamin D levels in rs4588 polymorphism

HaeIII (rs4588) genotype (C>A) Thr436Lys	Genotype	Frequency n(%)	Vitamin D nmol/L	p-value
483(CC)	Wild-type	86 (21.5)	13.73 ± 3.04	0.063
297+186(AA)	Mutant	134 (33.5)	12.92 ± 3.09	
483+297+186(AC)	Mutant	180 (45.0)	12.72 ± 3.34	
Total		400		
Allele		Frequency (%)		
C		44.0		
A		56.0		



Box-plot showing vitamin D levels in different allelic distribution of rs4588 polymorphism

Table 2: Allelic frequency and vitamin D levels in rs7041 polymorphism

StyI (rs7041) genotype (T>G) Asp432Glu	Genotype	Frequency, n (%)	Vitamin D nmol/L	p-value
483(TT)	Wild-type	232 (58.0)	12.8 ± 3.15	0.181
305+178(GG)	Mutant	12 (3.0)	13.28 ± 3.76	
483+305+178(TG)	Mutant	156 (39.0)	13.29 ± 3.25	
Total		400		
Allele		Frequency (%)		
T		77.5		
G		22.5		

Box-plot showing vitamin D levels in different allelic distribution of rs7041 polymorphism

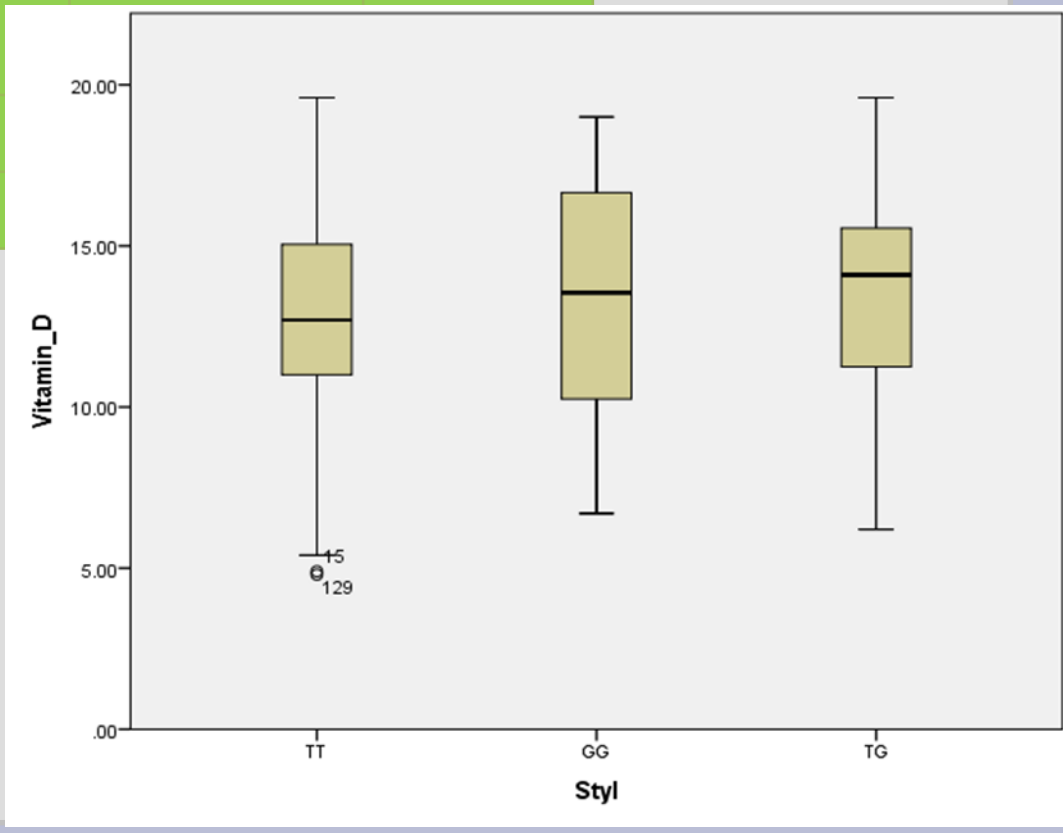
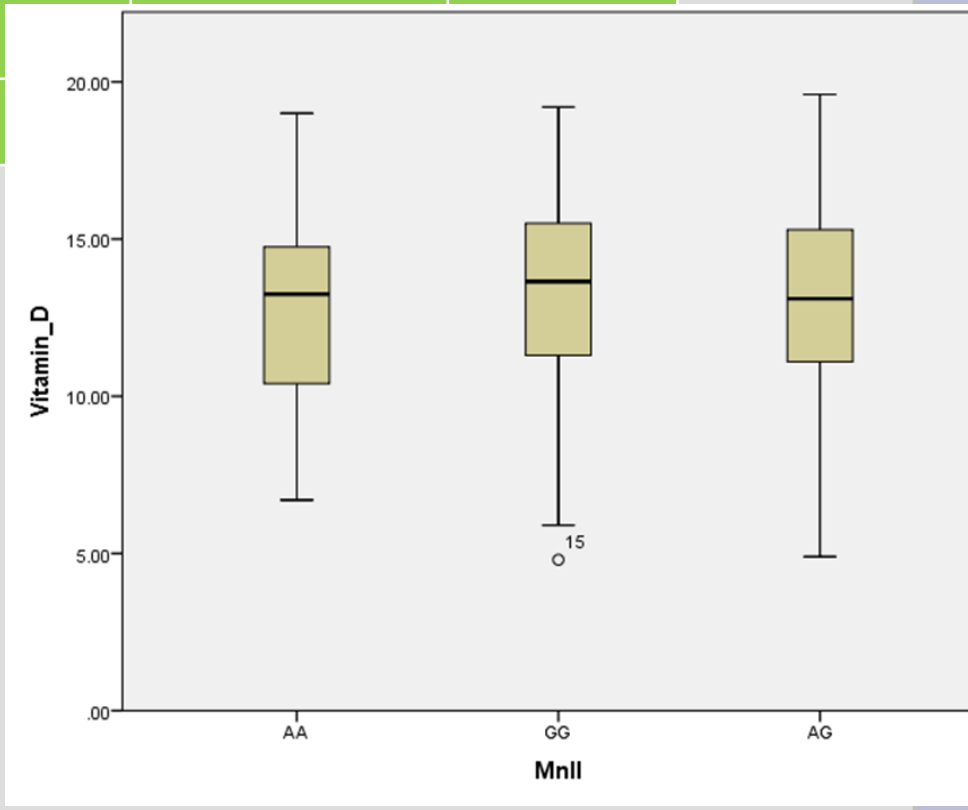


Table 3: Allelic frequency and vitamin D levels in rs10741657 polymorphism

MnlI (rs10741657) genotype (G > A)	Genotype	Frequency, n, (%)	Vitamin D nmol/L	p-value
151+105+32(GG)	Wild-type	150 (37.5)	13.23 ± 3.28	0.314
256+32 (AA)	Variant	84 (21.0)	12.71 ± 3.03	
256+151+105+32(AG)	Variant	166 (41.5)	12.94 ± 3.24	
Total		400		
Allele		Frequency (%)		
A		41.75		
G		58.25		



Box-plot showing vitamin D levels in different allelic distribution of rs10741657 polymorphism

Table 4: Allelic frequency and vitamin D levels in rs2238136 polymorphism

Bpu10I (rs2238136) genotype A>G	Genotype	Frequency n(%)	Vitamin D nmol/L	p-value
135 (AA)	Wild	24 (6.0)	14.5 ± 3.75	0.035
72+63 (GG)	variant	238 (59.5)	13.13 ± 3.03	
135+72+63 (AG)	variant	138 (34.5)	12.52 ± 3.34	
Total		400		
Allele		Frequency (%)		
A		23.25		
G		76.75		

Box-plot showing vitamin D levels in different allelic distribution of rs2238136 polymorphism

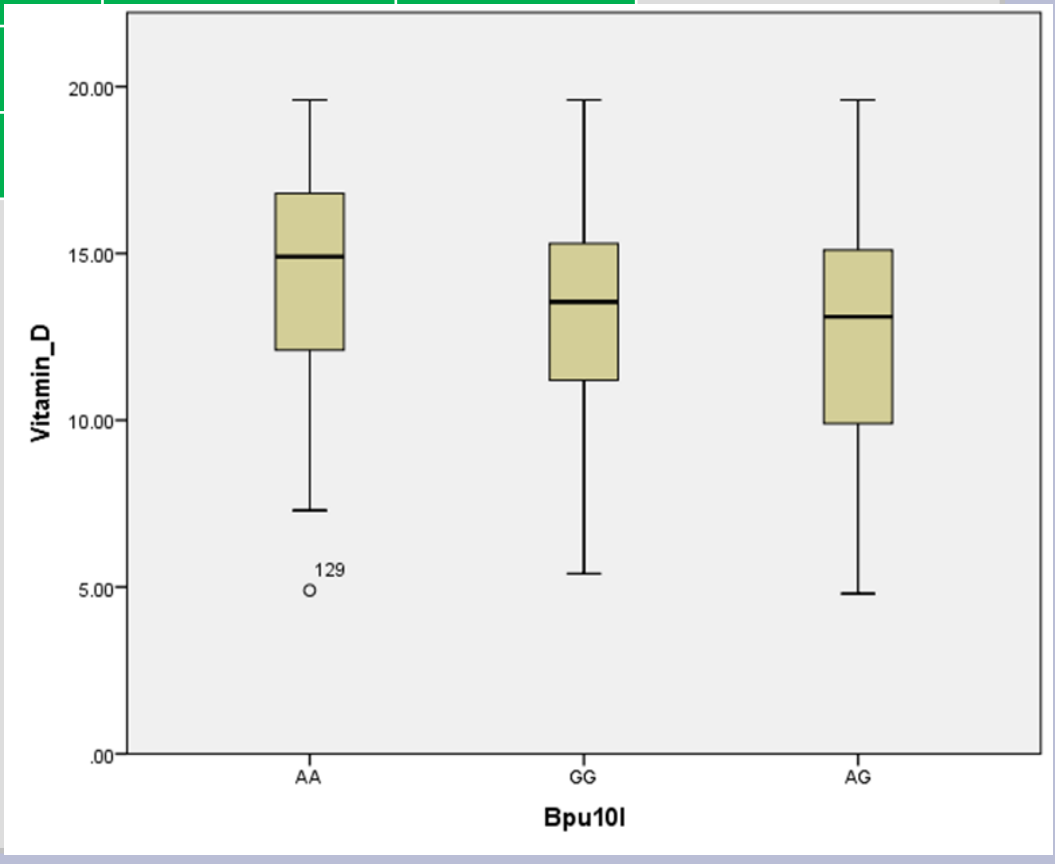


Table 5: Allelic frequency and vitamin D levels in rs12794714 polymorphism

FokI (rs12794714) genotype (G > A)	Genotype	Frequency, n(%)	Vitamin D nmol/L	p-value
GG	Wild	126 (31.5)	12.40 ± 3.19	0.013
AA	Variant	78 (19.5)	12.99 ± 3.31	
AG	Variant	196 (49.0)	13.39 ± 3.14	
Total		400		
Allele		Frequency (%)		
A		44.0		
G		56.0		

Box-plot showing vitamin D levels in different allelic distribution of rs12794714 polymorphism

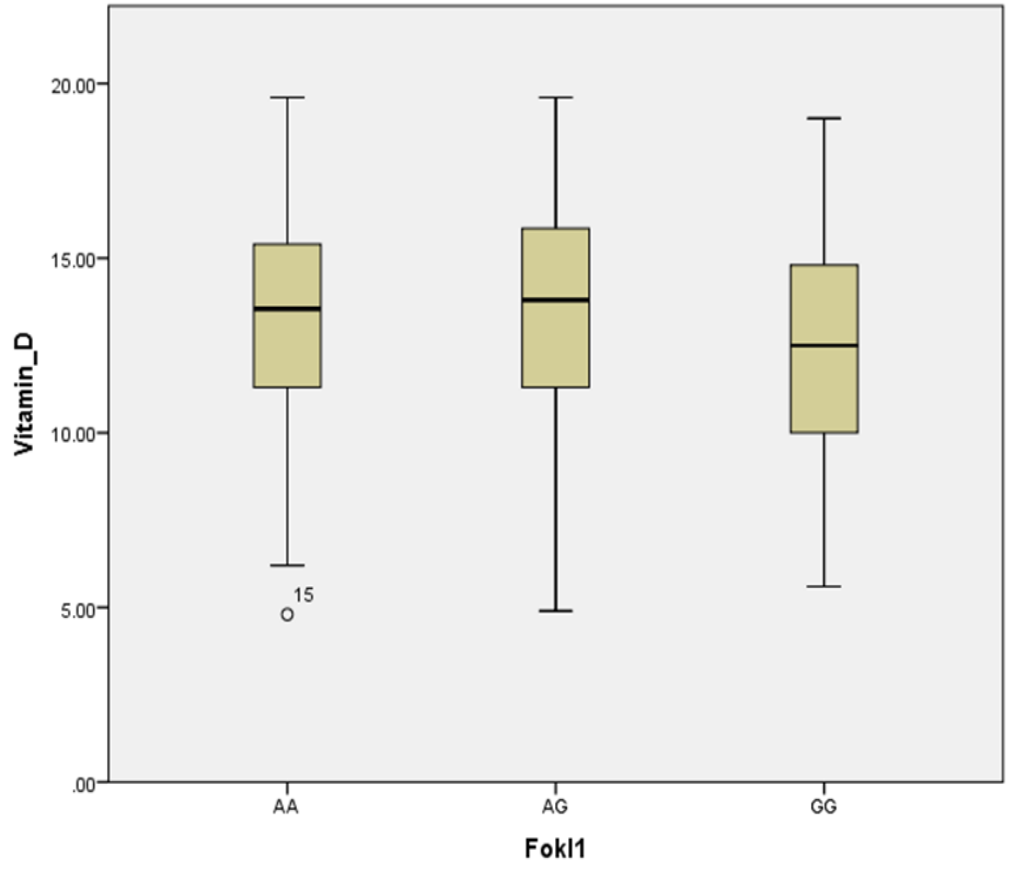
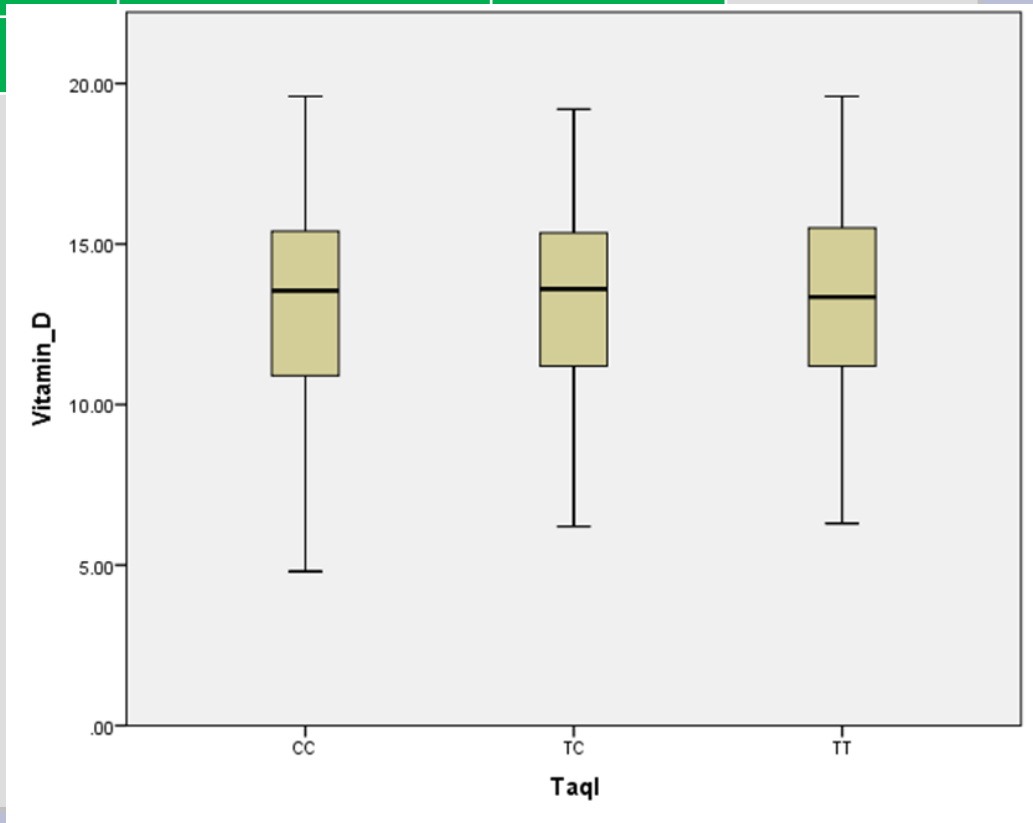


Table 6: Allelic frequency and vitamin D levels in rs731236 polymorphism

TaqI (rs731236) genotype c.1056T>C	Genotype	Frequency, n(%)	Vitamin D nmol/L	p-value
512 + 204 (TT)	Wild	140 (35.0)	13.16 ± 3.09	0.537
716 (CC)	Mutant	226 (56.5)	12.84 ± 3.27	
716+512+204 (TC)	Mutant	34 (8.5)	13.49 ± 3.28	
Total		400		
Allele		Frequency (%)		
T		39.25		
C		60.75		

Box-plot showing vitamin D levels in different allelic distribution of rs731236 polymorphism



Discussion

- In a study by Dogan et al., individuals with **rs4588-A** allele in GC gene had lower vitamin D levels(26). It coincides with the findings of our study in which individuals with A allele had comparatively lower vitamin D. In concordance to Lafi et al.(21), the levels of vitamin D was higher in wild-type genotypes (GG and CC), respectively **for rs4588 and rs7041**.
- Our findings were in concord with those of Das et al. (28) in which vitamin D deficiency was comparatively higher in individuals with TT genotype **(rs7041)** and AA genotype **(rs4588)** respectively though, statistically insignificant in our case.
- In contrast to the findings of Lafi et al(21) showing higher vitamin D levels among the genotype containing A allele in rs10743657, our study iterate comparatively lower vitamin D levels in the individuals with A allele.
- The allele frequency for rs2238136 in our study was similar to that reported by Xiong et al.(31) in American population with A allele 28.1% while G allele accounting for 71.9%.The genotypic distribution of FokI (rs12794714) SNP coincides with the distribution in German population with coronary artery disease

Recommendation

- This study recommends the use of local finding of Vitamin D level in healthy individuals and concept of genetic polymorphism of gene related to Vitamin D related metabolism while interpreting the value of Vitamin D and taking any clinical decision.

- Because of some limitations, this study also strongly recommend a nation-wide study in large number of population covering wide geographical area in correlation with the parathyroid hormone level, calcium level and bone mineral density status for the better result of Association of genetic polymorphism of gene related to vitamin D metabolism.

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Pratibha Kandel ,
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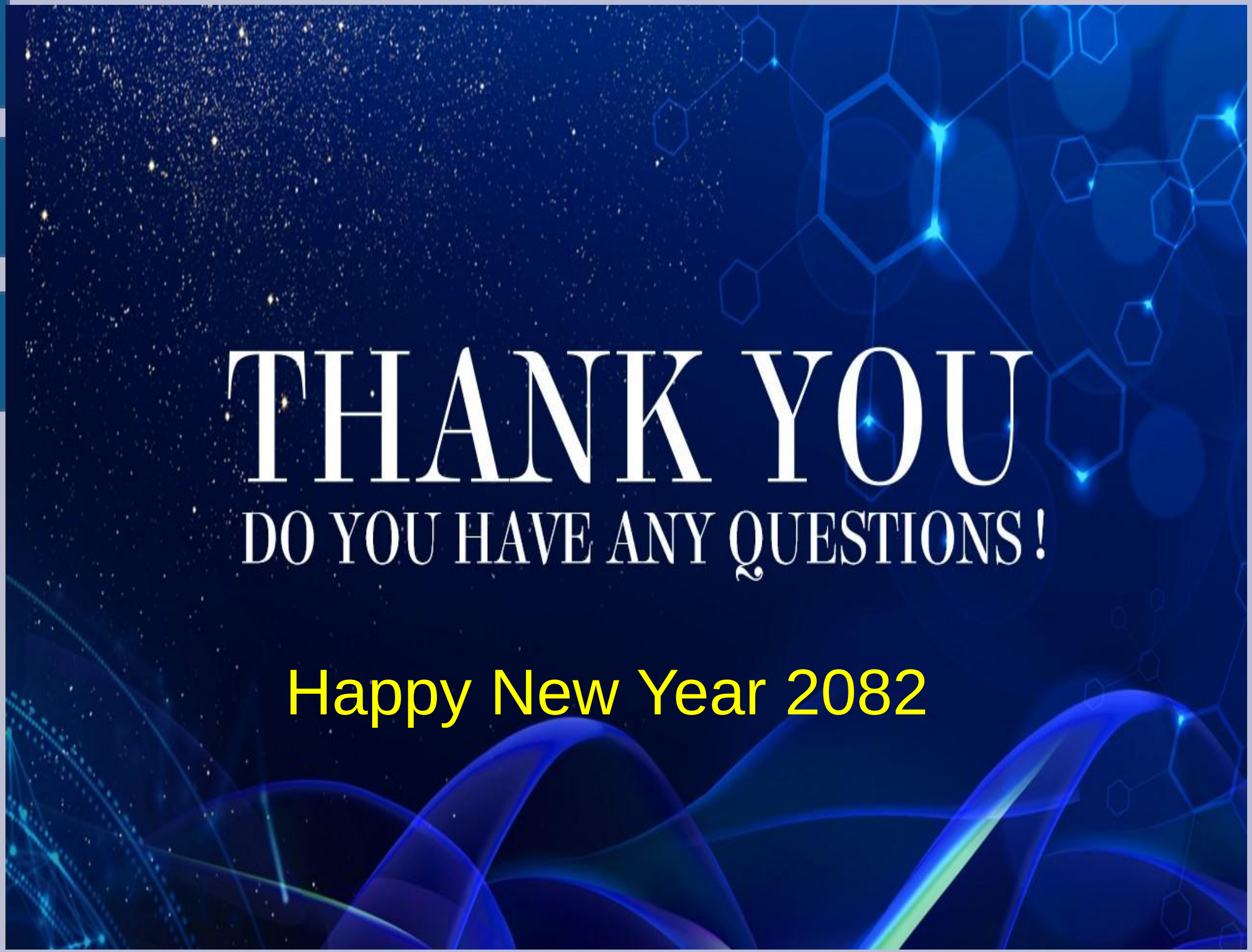
THANK YOU
DO YOU HAVE ANY QUESTIONS !
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