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Original Research

Study of Serum Vitamin-D and Insulin Resistance in Subjects with Prediabetes

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ABSTRACT:

Background: Vitamin-D plays a pivotal role in regulating homeostasis of bone and mineral metabolism but it also has non skeletal actions since vitamin-D receptors are present in various tissues including the brain, breast, prostate, pancreas, colon and immune cells. Biological functions of vitamin-D includes bone metabolism, immune response modulation and regulation of cell differentiation and cell proliferation. It is believed that vitamin-D might play role in the risk of cardio metabolic outcomes, including diabetes mellitus, hypertension and cardiovascular disease. The magnitude of type 2 diabetes worldwide is on the rise and is either due to lack of insulin or due to inadequate insulin action following increase in insulin resistance. Therefore, it is imperative to think that vitamin-D deficiency might be playing a role in insulin resistance leading to diabetes mellitus. The present study has been planned to study the association of Vitamin-D and insulin resistance in subjects with prediabetes. **Materials & Methods:** This observational cross sectional study was conducted at Sir Sunderlal Hospital, BHU, Varanasi. A total of 60 subjects with IFG (fasting blood sugar of 100-125 mg/dl) and/or IGT (2 hr. post prandial blood sugar of 141- 199 mg/dl) or with HbA1c of 5.7 - 6.4, who fulfilled the inclusion and exclusion criteria were included. Fasting blood sugar, 2-hour post prandial blood sugar, HbA1C, Ser. Vitamin-D and fasting insulin were estimated. Insulin resistance was determined by HOMA-IR. Statistical analysis was done by Chi square test, Student t test, Wilcoxon signed-rank test. P value of <0.05 was taken to be significant. **Results:** Vitamin-D deficiency was found in almost 40% of the study subjects. There was a statistically significant difference and negative correlation between HOMA-IR and HDL of the subjects with vitamin-D deficiency, insufficiency as well as in the sufficiency group (p=0.009 and 0.028 respectively). **Conclusion:** Our study results indicate that low vitamin-D levels are associated with prediabetes. Interventional studies on large sample can help in determining if vitamin-D supplementation can have a beneficial effect on the progression of prediabetes to diabetes.

Key words: prediabetes, insulin resistance, vitamin-D, diabetes mellitus

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INTRODUCTION:

Vitamin-D is known to regulate homeostasis of bone and mineral metabolism but it also has non skeletal actions since vitamin-D receptors are present in various tissues including the brain, breast, prostate, pancreas, colon and immune cells. Biological functions of vitamin-D includes bone metabolism, immune response modulation and regulation of cell differentiation and cell proliferation. It is believed that vitamin-D might play role in the risk of cardio metabolic outcomes, including diabetes mellitus, hypertension and cardiovascular disease. The magnitude of type 2 diabetes worldwide is on the rise and is either due to lack of insulin or due to inadequate insulin action following increase in insulin resistance. Therefore, it is imperative to think that vitamin-D deficiency might be playing a role in insulin resistance leading to diabetes mellitus. The role of vitamin-D deficiency in insulin resistance is thought to be due to inherited gene polymorphisms including that of vitamin-D receptor, vitamin-D- binding protein and vitamin-D 1-alpha-hydroxylase gene. The effects of vitamin-D deficiency, either alone or in concert, serves to worsen insulin resistance. Although, there is some evidence correlating vitamin-D status and insulin resistance, the underlying mechanisms need to be explored. Individuals with impaired fasting glycemia (IFG) and/or impaired glucose tolerance (IGT) are referred to as having prediabetes. The annual risk of progression to overt diabetes from IGT ranged from 2.5 % in the Diabetes Prevention Trial (DPT) (Knowler WC et al., 2002)[1], 11.5 % in the Chinese diabetes prevention study (CDPS) (Yang W et al., 2001)[2] to 18 % in the Indian Diabetes Prevention Programme- 1(IDPP- 1) (Ramachandran A et al., 2006)[3]. Prediabetes is frequently seen in subjects who are obese or have

metabolic syndrome. On the other hand, obesity as well is associated with low levels of vitamin-D due to the fact that adipose tissue can store 25- hydroxy Vitamin- D [25(OH)D], thereby making it biologically unavailable (Palomer X et al., 2008)[4]. A low level of serum 25(OH)D, calcitriol [1,25(OH)2D] and high parathormone (PTH) can increase the amount of intracellular calcium in the adipocytes. This can trigger lipogenesis predisposing the patient to further gain in weight and thereby increasing the risk of diabetes (Takiishi T et al., 2010)[5]. Defects in pancreatic β- cell function, insulin sensitivity and systemic inflammation all contribute to the development of type 2 diabetes. The present study has been designed with the aim to study the correlation between serum vitamin-D and insulin resistance in subjects with prediabetes.

MATERIALS AND METHODS

This cross-sectional study was conducted among 75 subjects attending the General Medicine outdoor or the Endocrinology outdoor of Sir Sunder Lal Hospital, Varanasi from October, 2017 to December 2018. Cases were scrutinized on the basis of inclusion and exclusion criteria. Ethical approval was obtained from the Institute Ethical Committee. A detailed history, clinical examination and all required investigations were done for all subjects under study. Fifteen subjects were lost to follow up, so the study was finally conducted on 60 subjects.

Inclusion criteria:

1. Patient with impaired glucose tolerance test - defined as impaired fasting glycemia (IFG i.e. fasting blood sugar of 100-125 mg/dl) and impaired glucose tolerance (IGT i.e. 2-hour post prandial blood sugar of 141-199 mg/dl).
2. HbA1c of 5.7 - 6.4 along with documented IFG or IGT by blood sugar levels.

Exclusion criteria:

1. Based on history, clinical examination and investigations (wherever required) - presence of hepatic disease, renal disease, ischemic heart disease, malignancy, hyperparathyroidism, bone diseases, uncontrolled hypothyroidism or subjects with pregnancy.
2. Any history of use of drugs such as insulin, OHA, anticonvulsants, calcium, vitamin-D, lipid lowering agents.
3. $HbA_1c > 6.5\%$.

Methods and procedure:

1) Random subjects and family members of patients with diabetes from Medicine OPD and Endocrine OPD were taken
2) The study protocol was explained to the individuals and only those who underwent informed written consent were included in the study
3) Written informed consent was obtained from each individual;
4) Data was collected including age, gender, and medical history.
5) Individual were assessed for the drug intake and presence of exclusion criteria points
6) Anthropometric measurements included weight on Tanita scale, height on wall-mounted stadiometer, BMI was subsequently calculated
7) At the initial instance sample was drawn and blood sugar levels (fasting and post-prandial) along with HbA1C levels were determined
8) In those who came out to be having IFG or IGT or HbA1C in the range of 5.6 to 6.4 the following investigations were also performed: CBC, RFT, LFT, Fasting Lipid Profile, Fasting Plasma Insulin, Serum 25 OH Vitamin-D, ECG, calcium, phosphate and alkaline phosphatase. Based on the vitamin-D status, individuals were divided into following groups:

Vitamin-D deficiency (classification)

IOM (Institute of Medicine)

<12 ng/ml - 0
12-19 ng/ml - 1
20-50 ng/ml - 2
>50 ng/ml - 3

ES (Endocrine Society)

< 20 ng/ml - 0
20-29 ng/ml - 1
>30 ng/ml - 2

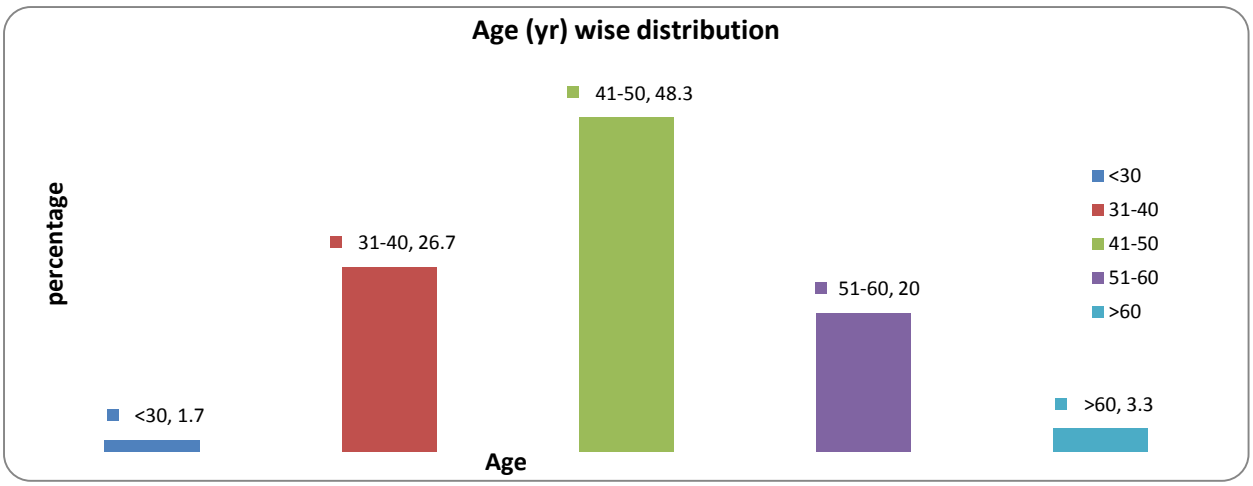
- Insulin resistance in basal state was calculated using HOMA2-IR (homeostatic model assessment for insulin resistance) and beta cell function as estimated using HOMA2-β. Linear formula was not available and calculation of HOMA2 was done by using this online calculator – 'http://www.dtu.ox.ac.uk'.
- QUICKI quantitative insulin sensitivity check index) is also a validated method for estimation of insulin resistance in obese and non-obese diabetic and on diabetic subjects. QUICKI score=1/ {log (Fasting Insulin) + log (Fasting Sugar)}]. QUICKI index correlates well with euglycemic-hyperinsulinemic clamp studies (r= 0.78) and values range between 0.45 for healthy individuals and 0.30 in diabetics.

Statistical analysis

- For statistical analysis, data were entered into a Microsoft excel spreadsheet and then analysed by SPSS (version 23.0; SPSS Inc., Chicago, IL, USA).
- Data had been summarized to count and percentages for categorical variables and mean and standard deviation for numerical variables.
- For categorical data, Chi-square test and Fischer exact test was used and for continuous data Student's t test and Mann Whitney U test were used.
- For paired samples, Paired Student's test and Wilcoxson test was used. Pearson correlation coefficient was used to correlate two continuous variables.
- p-value ≤ 0.05 was considered for statistically significant.

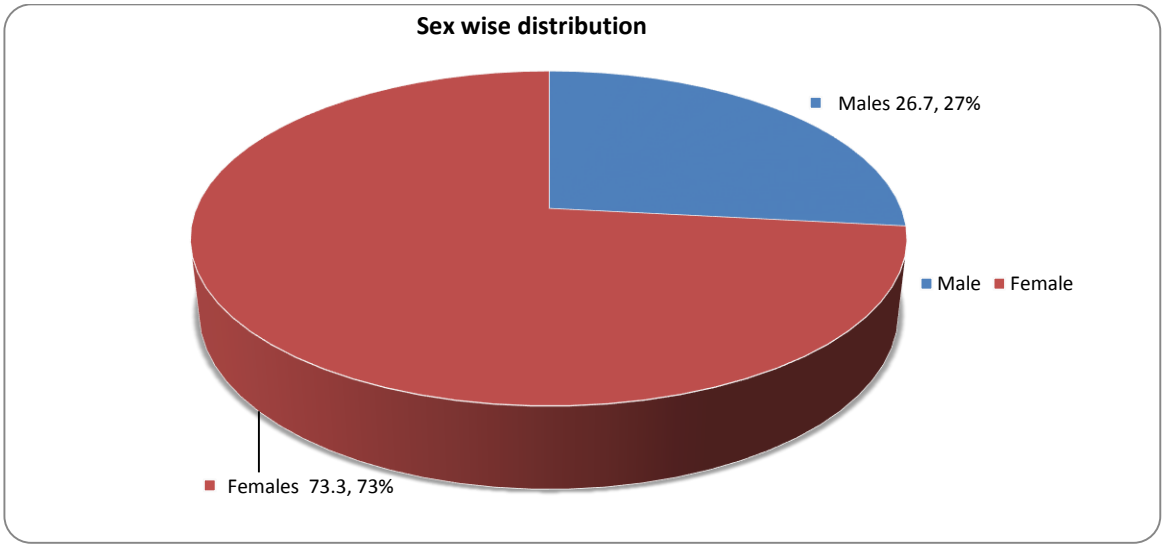
OBSERVATIONS & RESULTS:

Figure 1: Age wise distribution



In our study 1.7 % patients were of less than 30 yrs. of age, 26.7 % were between 31-40 yrs. of age, 48.3% were between 41-50 yrs. of age, 20 % were 51-60 yrs. of age, 3.3% were more than 60 yrs. of age, so we can see that majority of the population were between 41- 50 yrs. of age

Figure 2: Sex wise distribution



In our study female patient (73.3%) outnumbered male patients (26.7%)

Figure 3: Family history of T2DM

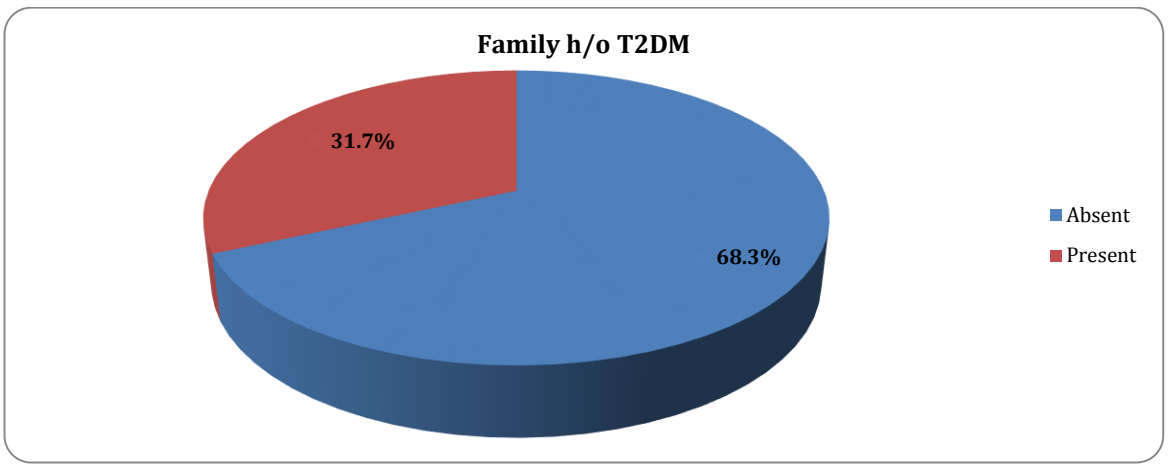
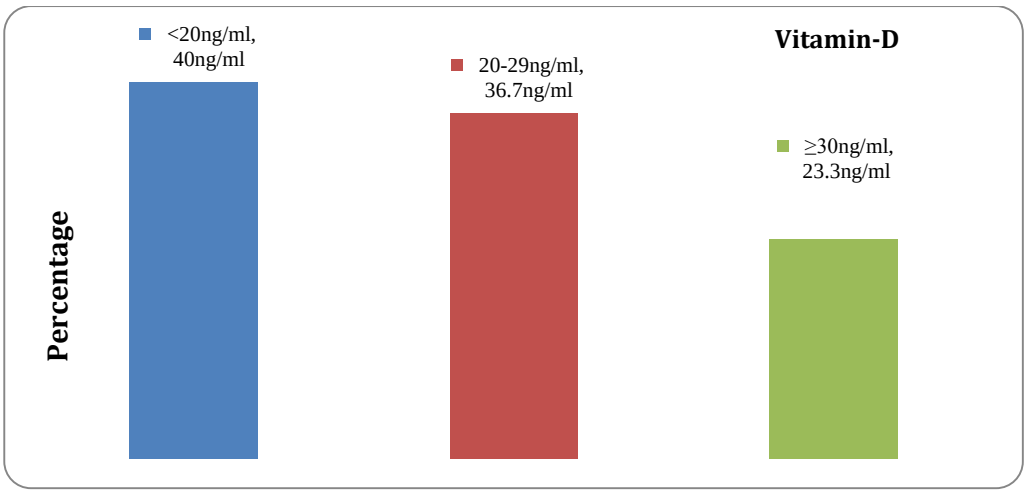
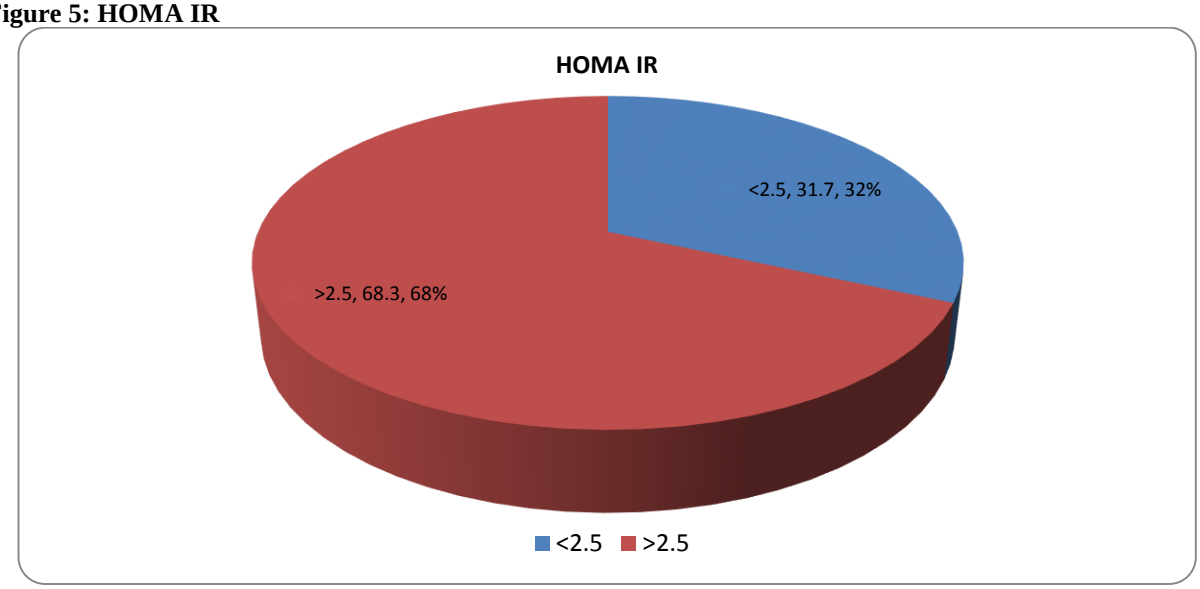


Figure 4: Vitamin-D distribution (US endocrine society)



Above figure shows that as per US Endocrine Society classification of Vitamin-D deficiency, majority of the subjects were in the Vitamin-D deficient category.

Figure 5: HOMA IR



Above figure shows that majority of the prediabetic subjects had insulin resistance (68.3%) while only 31.7 % didn't have insulin resistance

Table 1: Mean parameters of the subjects

	N	Minimum	Maximum	Mean ±SD
Age	60	28	62	45.48±7.734
Height	60	1.5	1.7	1.612±0.0549
Weight	60	49.2	89.6	63.349±10.3672
BMI	60	19.5	32.5	24.313±3.2766
Pulse	60	60	100	78.67±11.419
FBS	60	86	124	107.90±11.268
PPBS_2hrs	60	124	196	162.78±17.560
HbA1C	60	4.6	6.4	5.653±0.4560
Fasting Insulin	60	1.38	50.06	14.9460±10.24235
Serum 25OH Vit-D	60	10.00	77.50	26.3580±16.41587
HOMA IR	60	0.3	14.1	3.998±2.7739
QUICKI	60	0.2	0.6	0.356±0.0539
SGOT	60	15	78	38.10±14.973
SGPT	60	16	80	45.52±14.253
TP	60	5.6	8.5	7.015±0.7846

ALB	60	3.0	5.8	4.492±0.6135
ALP	60	40	199	120.98±50.707
Urea	60	18	36	25.28±5.109
Ca	60	7	10	8.54±0.612
Po4	60	4.2	6.9	5.545±0.7427
TC	60	157	319	247.47±49.211
TG	60	68	298	146.70±50.324
HDL	60	20	65	41.78±12.406
LDL	60	63	175	116.75±32.842
VLDL	60	10	51	30.63±10.947
T3	60	.4	1.9	1.093±0.4278
T4	60	4.8	10.6	7.773±1.5601
TSH	60	1.2	7.8	3.698±1.6393

From the above table following observations were made:

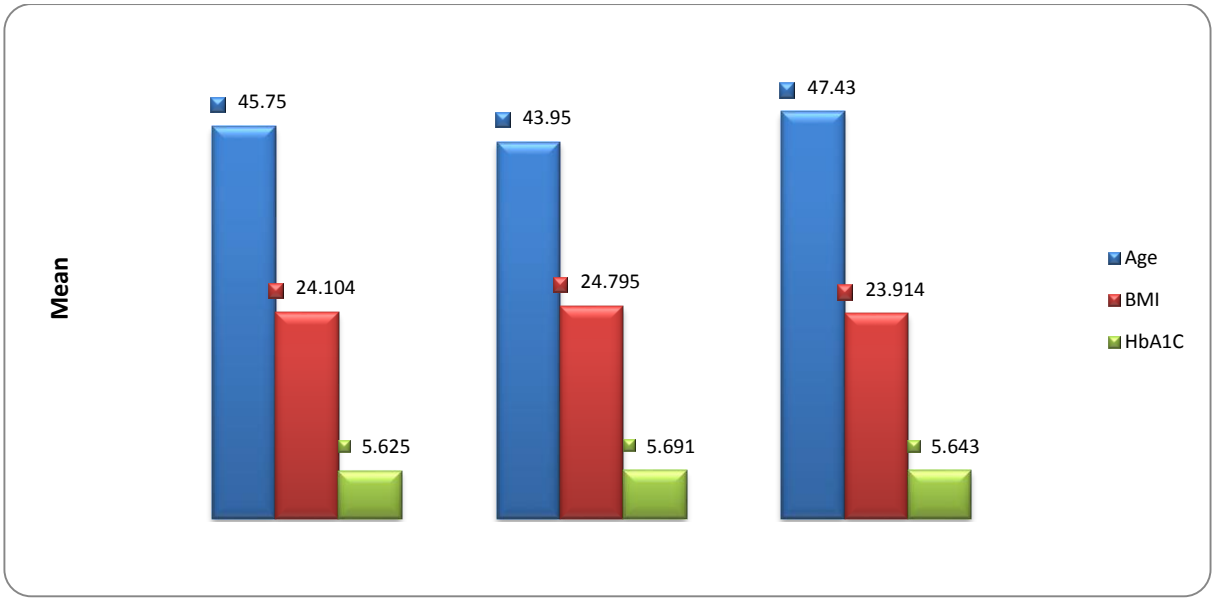
- Mean age was around 45 yrs.
- Mean BMI of the population was 24.3 Kg/m^2 (overweight as per Asian BMI classification)
- Mean HbA1c was 5.65% (prediabetic state)
- Mean fasting insulin levels were 14.960 μU/ml
- Mean HOMA-IR was around 4, i.e. in insulin resistance category (HOMA-IR >2.5)
- Mean serum Vitamin-D levels was 26.35 ng/ml i.e., in Vitamin-D insufficient group as per the Us endocrine society classification

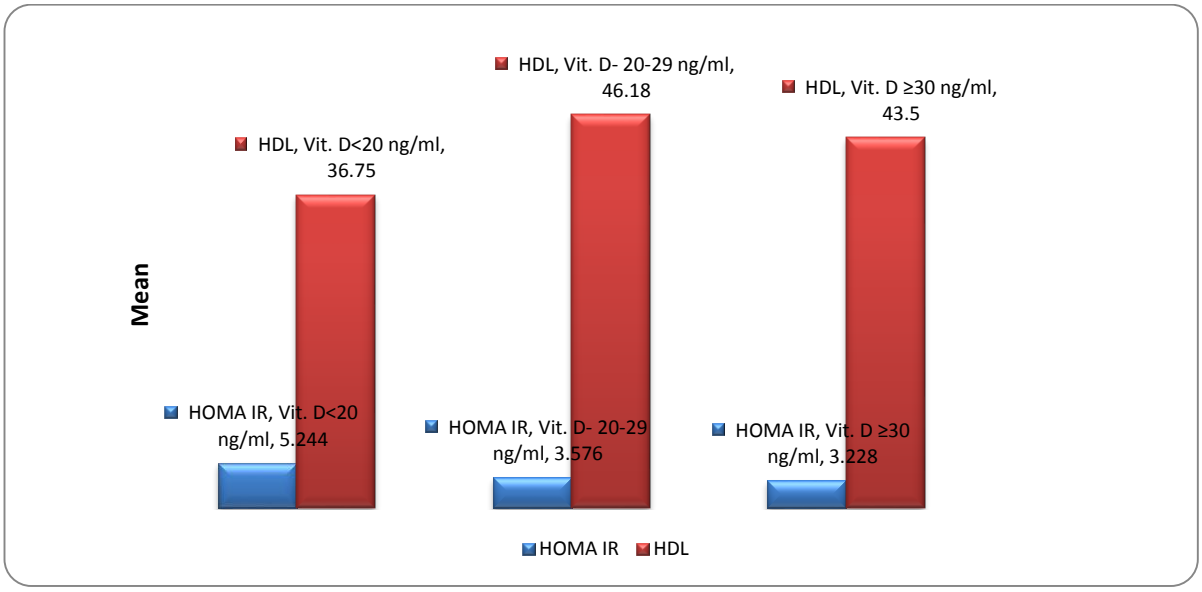
  SGPT levels (45.52 U/L) were higher than the SGOT levels (38.10 U/L)

  Renal parameters were within the normal limit
- Mean HDL was 41.78 mg/dl (lower side of normal range), LDL was 116.75 mg/dl (within normal limits), Total Cholesterol was 247.47 mg/dl (upper side of normal range), Triglycerides were 146.70 mg/dl (within normal limits), VLDL was 30.63 mg/dl (within normal limits)
- Mean TSH was 3.69 μIU/ml (normal)

Table 2: Bonferroni

	Vitamin-D <20ng/ml Mean ± SD n=24	Vitamin-D 20-29ng/ml Mean ± SD n=22	Vitamin-D ≥30ng/ml Mean ± SD n=14	p-value
Age	45.75±8.487	43.95±6.245	47.43±8.537	0.419
BMI	24.104±3.8612	24.795±2.2529	23.914±3.6748	0.684
FBS	110.83±12.907	105.50±10.640	106.64±8.445	0.250
PPBS 2hrs	163.58±19.797	160.55±16.925	164.93±15.122	0.741
HbA1C	5.625±0.5084	5.691±0.4034	5.643±0.4686	0.886
Fasting Insulin	17.5100±14.21218	13.9650±6.3291	12.0921±5.61298	0.251
HOMA IR	5.244±2.854	3.576±1.5266	3.228±1.6235	0.009
QUICKI	0.349±0.0560	0.358±0.0602	0.365±0.0397	0.652
SGOT	40.13±16.711	35.82±13.772	38.21±14.165	0.629
SGPT	46.46±15.767	44.14±13.014	46.07±14.258	0.851
TP	6.404±0.6950	6.823±0.7758	6.650±0.6937	0.148
ALB	4.529±0.6376	4.495±0.6410	4.421±0.5632	0.876
ALP	113.29±48.938	127.36±49.75	124.14±56.959	0.628
Urea	24.92±5.340	25.14±5.111	26.14±4.975	0.770
Ca	8.59±0.601	8.33±0.570	8.77±0.634	0.095
Po4	5.658±0.6965	5.423±0.7546	5.543±0.8225	0.569
TC	244.33±48.710	260.59±41.516	232.21±58.724	0.225
TG	161.21±61.690	140.95±38.406	130.86±40.782	0.160
HDL	36.75±11.532	46.18±10.271	43.50±14.495	0.028
LDL	115.17±40.664	118.50±28.151	116.71±26.072	0.944
VLDL	30.13±12.316	31.41±11.413	30.29±7.966	0.918
T3	0.992±0.3538	1.155±0.4361	1.171±0.5195	0.326
T4	7.883±1.6499	7.823±1.5153	7.507±1.5549	0.766
TSH	4.087±1.9683	3.609±1.5187	3.171±1.0118	0.242

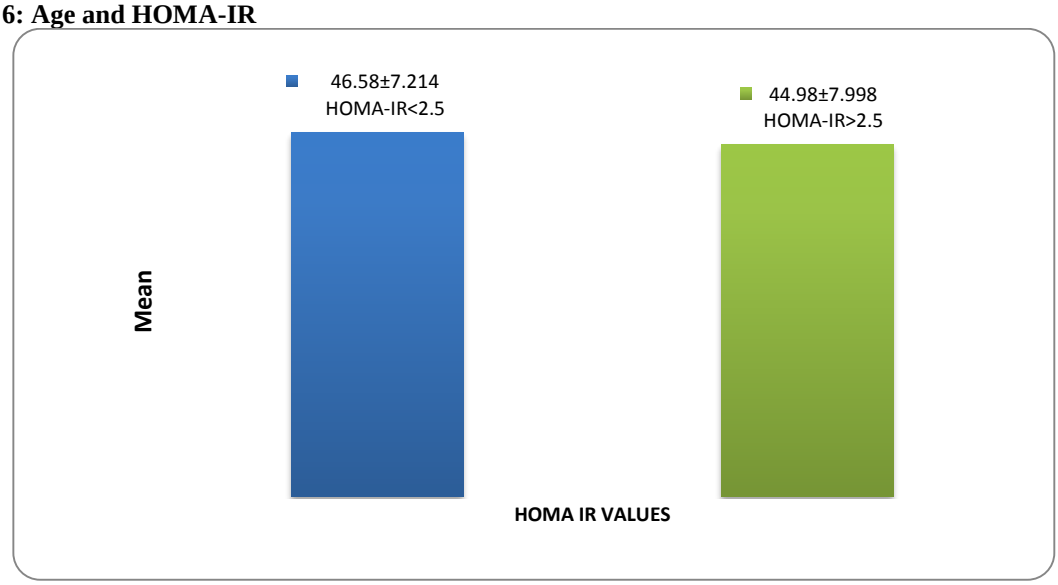




Following observations were drawn from the above table

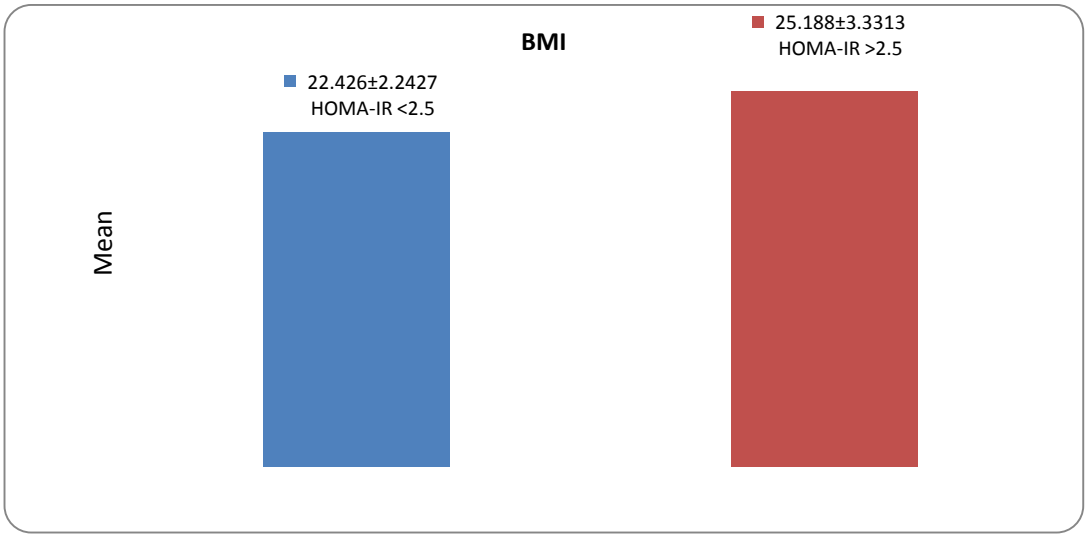
- there was no significant difference in the mean age group of subjects with vitamin-D deficiency, insufficiency, sufficiency (p=0.419)
- there was no significant difference in the mean BMI of the subjects with vitamin-D deficiency, insufficiency, sufficiency (p=0.684)
- there was no significant difference in the mean HbA1C levels of subjects with vitamin-D deficiency, insufficiency, sufficiency (p=0.886)
- there was a statistically significant difference in the HOMA-IR of the subjects with vitamin-D deficiency, insufficiency, sufficiency (p=0.009) although the Fasting serum insulin and fasting plasma glucose values were not significant i.e., there was statistically significant relation between the HOMA-IR values and subjects with vitamin-D levels < 20 ng/ml
- there was a statistically significant difference in the HDL values of the subjects with vitamin-D deficiency, insufficiency, sufficiency (p=0.028) while the Triglycerides, Total Cholesterol, LDL, VLDL were not significant
- there was no significant difference in the mean TSH levels of subjects with vitamin-D deficiency, insufficiency, sufficiency (p=0.242) comparing the p values of the different groups of vitamin-D (group 1, group 2, group 3), it was found that Age, BMI, HbA1C, FBS, PPBS, F. Plasma Insulin didn't have any significant difference when compared with each of the groups
- HOMA-IR was significant when in group 1 (p=0.018) and group II (p=0.024) but was insignificant in group III.
- HDL was significant in group I but non-significant in group II and group III. other lipid parameters showed no significant difference in the 3 groups
- TSH values were non-significant in the 3 groups

Figure 6: Age and HOMA-IR



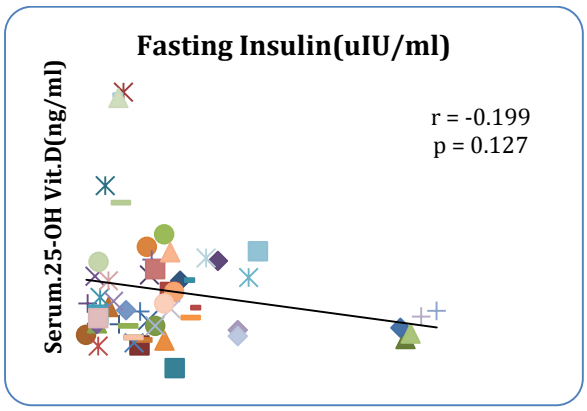
From the above figure it can be inferred that there was no significant age difference among the subjects with or without insulin resistance (p=0.460)

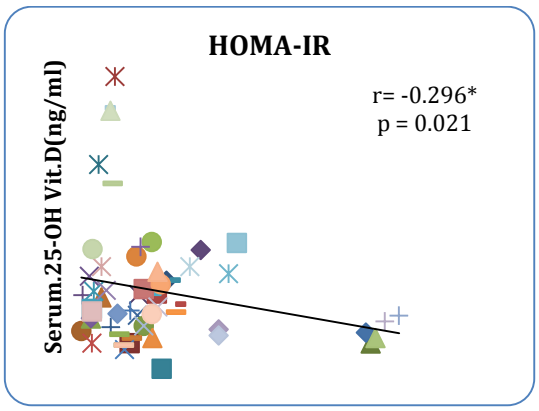
Figure 7: BMI and HOMA-IR

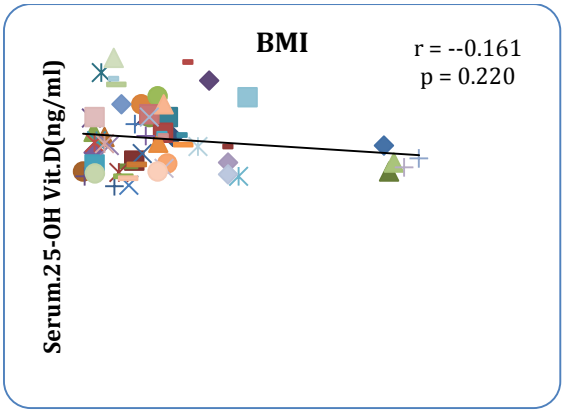


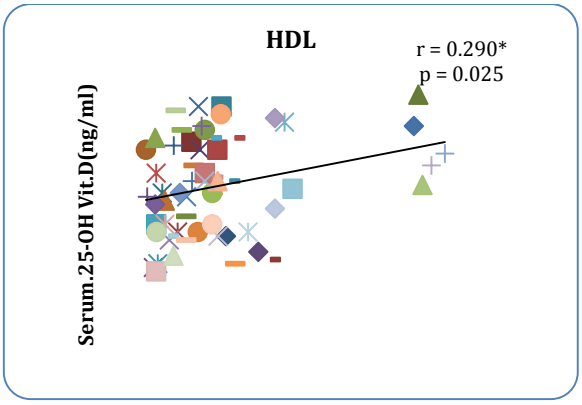
The above figure shows that there was a significant difference (p=0.002) between the BMI of the insulin resistance group (mean =25.188) as compared to that of the non-insulin resistance group (mean =22.46)

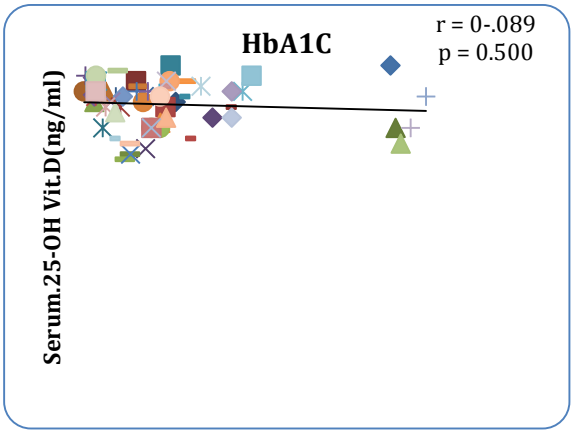
Correlations between vitamin-D and other study variables:

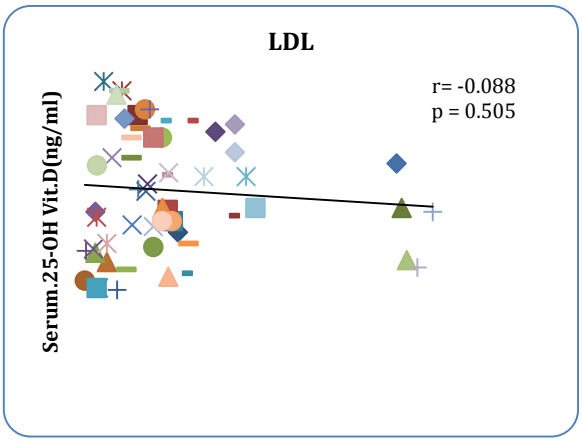


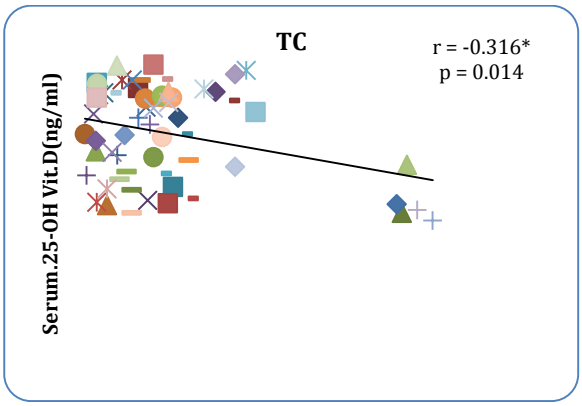


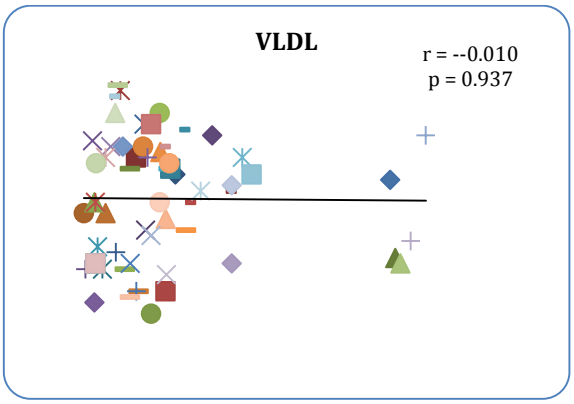


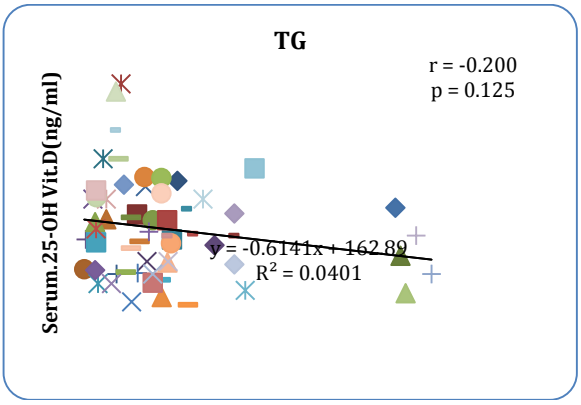












From the above correlation charts following observations were made:

- There was a negative correlation between fasting plasma insulin and serum Vitamin-D levels that was not significant
- HOMA-IR, total cholesterol had a negative correlation with Serum Vitamin-D values and it was statistically significant
- HbA1C, BMI, LDL-C, FBS, VLDL, TRIGLYERIDES, had a negative correlation with serum vitamin-D and that was not significant statistically
- HDL-C had a positive correlation with serum vitamin-D and it was statistically significant

	HOMA IR <2.5 Mean ± SD n=19	HOMA IR>2.5 Mean ± SD n=41	p-value
FBS	103.21±11.370	110.07±10.669	**.027**
PPBS_2hrs	158.00±10.017	165.00±19.843	.153
HbA1C	5.474±0.5704	5.737±0.3713	**.037**
Fasting Insulin	6.9084±1.79720	18.6707±10.41037	**<0.001**
Serum 25OH Vitamin-D	30.7889±19.84628	24.3046±14.37334	0.156
QUICKI	0.414±0.0392	0.329±0.0348	**<0.001**
SGOT	31.68±14.621	41.07±14.348	**0.023**
SGPT	39.05±13.890	48.51±13.556	**0.015**
TP	7.189±0.7880	6.934±0.7793	0.244
ALB	4.716±0.5833	4.388±0.6059	0.053
ALP	123.16±63.176	119.98±44.645	0.823
Urea	24.63±5.356	25.59±5.030	0.506
Ca	8.52±0.554	8.54±0.644	0.897
Po4	5.753±0.7698	5.449±0.7191	0.142
TC	233.89±51.424	253.76±47.476	0.147
TG	124.00±31.220	157.22±54.210	**0.016**
HDL	46.84±11.529	39.44±12.223	**0.030**
LDL	110.00±29.715	119.88±34.087	0.282
VLDL	25.42±9.191	33.05±10.947	**0.011**
T3	1.011±0.4108	1.132±0.4350	0.311
T4	7.784±1.5163	7.768±1.5985	0.971
TSH	3.732±1.5674	3.683±1.6904	0.916

DISCUSSION

The mean age group of the participants in this study was 45.48 ± 7.734 yrs., of which majority of subjects were in 41-50 yrs. age group (48.3%) and majority population was female 73.3%. This is in coherence with the study conducted by Deep Dutta et al (Serum Vitamin-D predicts insulin resistance in individuals with prediabetes Indian J Med Res 138, December 2013, pages 853-860), which had the mean age of 46.6 ± 10.9 yrs. (n=157, prediabetic subjects). A similar study by Anagha Vinay Sahasrabuddhe, Shailesh U Pitale et al (Study of vitamin-D levels and its correlation with insulin resistance, National Journal of Physiology, Pharmacy and Pharmacology, 2017) showed mean age of the subjects to be 38.68 ± 10.86 yrs. Another study by Ayhan R et al (International Journal of Community Medicine and Public Health. Int J Community Med Public Health, 2018 Sep;5(9):3776-3781) had mean age of prediabetics 39.9 ± 8.8 yrs.

Study	**N (prediabetics)**	**Mean age (in years)**
Deep Dutta et al	157	46.6 ± 10.9
Anagha Vinay Sahasrabuddhe, et al	168	38.68 ± 10.86
Ayhan R et al	122	39.9 ± 8.8 yrs
Our study	60	45.48±7.734

Majority of the subjects did not have a family history of diabetes mellitus (68.3 % vs 31.7 %). Vitamin-D levels were deficient in most of the subjects (40%), insufficient in (36.7%), sufficient in (23.3%), this was similar to the study by Deep Dutta et al. where vitamin-D deficient (11-20 ng/ml) and severe deficient (≤10 ng/ml) subjects were more (43.9%, n=69), compared to vitamin-D insufficient (21-30 ng/ml) subjects (29.29%, n=46) and least in vitamin-D sufficient (≥ 31ng/ml) subjects (26.75%, n=42). Similarly, Anagha Vinay Sahasrabuddhe, et al. had found that 65.47% cases had vitamin-D deficiency, 27.97% cases had vitamin-D insufficiency and 6.54 % cases had vitamin-D sufficiency, similar observation was made by Ayhan R et al also. Insulin resistance (calculated by HOMA IR) was found in 68.3% of the prediabetic subjects as compared to 31.7%. Subjects with vitamin-D deficiency, sufficiency and insufficiency had a similar age group and this was not significant statistically (p=0.419). This was similar to observation by Deep Dutta et al. where vitamin-D values in different age groups was insignificant (p value=0.180). BMI of the subjects among different vitamin-D groups showed no significant difference (p=0.684) similar to the study by Dutta et al. where BMI was highest in severe vitamin-D deficiency subjects and least in vitamin-D sufficiency subjects, though it was statistically insignificant (p=0.083). HbA1C values among the different vitamin-D groups showed no significant difference (p =0.886), although there was a negative correlation between Vitamin-D and HbA1C values (r=-0.161). It was similar to study by Dutta et al, where HbA1C values among the different vitamin-D groups was not significant (p=0.064) but a negative correlation was obtained (r=-0.07). HDL-C values also have a positive correlation

and statistically significant association with vitamin-D (r=0.290, p=0.028) that was in contrast to the study of Dutta et al. that showed no significant association between Vitamin-D and HDL-C levels (p=0.893). In our study, among individuals with prediabetes, those having vitamin-D deficiency (<20 ng/ml), had the worst insulin resistance (HOMA-IR, QUICKI and 1/fasting insulin) as compared to those with vitamin-D insufficiency (20-29ng/ml) and Vitamin-D deficiency (> 30 ng/ml), with an inverse correlation between vitamin-D status and insulin resistance that was statistically significant (p=0.018 for vitamin-D deficient vs insufficient group and p=0.024 for vitamin-D deficient vs vitamin-D sufficient group; overall p=0.009). Similar conclusion was drawn by Dutta et al. where they had found significant correlation between vitamin-D and HOMA IR (p=0.021). In our country, Vitamin-D deficiency and insufficiency may thus have some role in triggering or worsening of insulin resistance in individuals with prediabetes. Forouhi et al demonstrated that there is a negative correlation between insulin resistance and 25[OH]D level (Forouhi NG et al., 2008)[6]. In prediabetic patients, pancreatic early phase insulin secretion is impaired, together with increased serum insulin levels. This situation accelerates the development of insulin resistance and overt diabetes in prediabetic patients. Longitudinal studies as done by Talaei et al.[7] and Inzucchi et al.[8] has shown that fasting blood sugar values in diabetic patients reduced after vitamin-D supplementation with significant reduction in HOMA-IR. Von Hurst showed that vitamin-D supplementation significantly improved insulin sensitivity and insulin resistance, though others have reported no improvement in insulin resistance after vitamin-D supplementation. Data on interventional studies involving supplementation of Vitamin-D in prediabetes are not reliable due to the small sample size of subjects participating in these studies and due the use of variable formulations and dosages of Vitamin-D or calcitriol. However in a recent study of D2d (randomized, double-blind, placebo-controlled) clinical trial that evaluated the safety and efficacy of oral administration of vitamin-D3 (cholecalciferol; 4000 IU per day) for diabetes prevention in adults at high risk for type 2 diabetes, a total of 2423 participants underwent randomization (1211 to the vitamin-D group and 1212 to the placebo group) and month 24, the mean serum 25- hydroxyl vitamin-D level in the vitamin-D group was 54.3 ng/ml from 27.7 ng/ml at baseline), as compared with 28.8 ng/ml in the placebo group (from 28.2 ng/ml at baseline). After a median follow-up of 30 months, the primary outcome i.e. new onset diabetes mellitus was detectable in 293 subjects in the vitamin-D group and 323 subjects in the placebo group (9.39 and 10.66 events per 100 person-years, respectively). Hazard ratio for vitamin-D group as compared with placebo was 0.88 (95% CI, 0.75 to 1.04; P = 0.12). The difference between the incidence of adverse events was not significant between the two groups. So it was concluded that among persons who are at high risk for type 2 diabetes and not selected for vitamin-D insufficiency, supplementation of vitamin-D3 at a dose of 4000 IU per day did not result in a significant reduction in the risk of diabetes than placebo. In the Tromsø Vitamin-D and T2DM Trial (Norway), in which 511 white adult subjects with prediabetes were randomly assigned to receive 20,000 IU per week (approx. 2900 IU/day) of vitamin-D3 versus placebo, the risk of diabetes was numerically lower in the vitamin-D group as compared to the placebo group, but the difference was statistically insignificant (hazard ratio, 0.90; 95% CI, 0.69 to 1.18). In the Diabetes Prevention with Active Vitamin-D study done in Japan, 1256 adults with prediabetes were randomly assigned to receive an active form of vitamin-D analogue (eldecalcitol) versus placebo, the risk of diabetes was also lower in the vitamin-D group than in the placebo group, but the difference was again statistically insignificant (hazard ratio, 0.87; 95% CI, 0.68 to 1.09). This contrasts with the findings with our study which may be attributed to the geographical, race, ethnicity variability between the population chosen for study as well as the study subjects that were less in our study. Majority of the studies that evaluated the outcomes over a short period of 2-12 weeks did not show any significant improvement in glycaemic and insulin resistance outcomes. The strength of our study is that it estimated vitamin-D levels and fasting serum insulin instead of taking an indirect parameter and insulin resistance was determined by HOMA-IR instead of BMI or insulin-glucose ratio. Limiting factors of the study are its cross sectional nature and fewer subjects in the study.

Summary and Conclusion

To summarize, Vitamin-D deficiency/insufficiency is common among individuals with prediabetes in our country, a reflection of the Vitamin-D deficiency state in the general population. However, this Vitamin-D deficiency/insufficiency was associated with worsened insulin resistance in individuals with prediabetes. Many previous observational studies support an association between a low blood 25-hydroxyvitamin-D level and the risk of type 2 diabetes. The D2d randomised clinical trial had showed that among persons at high risk for type 2 diabetes not selected for vitamin-D insufficiency, vitamin-D3 supplementation at a dose of 4000 IU per day was not found to be effective in significantly lowering the risk of diabetes than placebo.

Conflicts of interest: None to declare

Declarations to make: The study has been presented in free papers - platform presentation in Endocrinology of Annual Conference of the Association of Physicians of India, 2020 at Agra and the abstract of the presentation has been published in

the January 2020 Issue, Volume 68 of Journal of the Association of Physicians of India.

REFERENCES

1. Knowler WC, Barrett- Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002; 346: 393- 403.
2. Yang W, Lin L, Qi J. The preventive effect of acarbose and metformin on the IGT population from becoming diabetes mellitus: a 3- year multi- centric prospective study. Chin J Endocrinol Metab 2001; 17 : 131- 6.
3. Ramachandran A, Snehalatha C, Mary S, Mukesh B, Bhaskar AD, Vijay V; Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Programmeshowsthatlifestylemodificationandmetformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP- 1). Diabetologia 2006; 49 : 289- 97.
4. Palomer X, Gonzalez- Clemente JM, Blanco- Vaca F, Mauricio D. Role of vitamin-D in the pathogenesis of type 2 diabetes mellitus. Diabetes Obes Metab 2008; 10: 185- 97.
5. Takiishi T, Gyse mans C, Bouillon R, Mathieu C. Vitamin- D and diabetes. Endocrinol Metab Clin North Am 2010; 39 : 419- 46.
6. Forouhi NG, Luan JE, Cooper A, Boucher BJ, Wareham NJ. Baseline serum 25- hydroxy vitamin-D in the future glycemic status and insulin resistance medical research council ely prospective study 1990- 2000. Diabetes. 2008;57(10):2619- 25.
7. Talaei A, Mohamadi M, Adgi Z. The effect of vitamin-D on insulin resistance in patients with Type 2 diabetes. Diabetol Metab Syndr. 2013;5:8.
8. Inzucchi SE, Maggs DG, Spollett GR. Efficacy and metabolic effect of metformin and troglitazone in Type 2 diabetes mellitus. N Engl J Med. 1998; 29(3):142- 5.