The World-India Diabetes Foundation (W-IDF), Mayo Clinic, Rochester, Minnesota, USA offers an award to honour outstanding achievement or research results in the field of diabetes by a researcher based in India. The principal selection criteria are the originality and significance of the research or research idea. The awardee receives a plaque and a cash award at the Annual International Diabetes Symposium.

Prof. Satinath Mukhopadhyay was the recipient of the first Mayo Clinic World-IDF outstanding investigator award for the year 2020 for his significant contribution on the pathophysiology of diabetes.

Award lecture: Does Vitamin-D deficiency contribute to the pathophysiology of diabetes?

Vitamin-D has existed on this planet for >500 million years, long before organisms started to develop skeletal architecture or trotting on the land. Exposure of Phytoplanktons to simulated sunlight has shown that the phytoplanktons harness energy from the Sun for survival. In saline medium, early life forms could absorb calcium straight into primitive vertebral skeletons or consume Vitamin-D rich Phytoplankton/Zooplanktons. When life forms began to roam on the Earth some 350 million years ago, calcium absorption was problematic, with relatively scarce sources on the land, with consequent necessity for a built mechanism to synthesize Vitamin-D hormone within the organism itself.

In addition to the asteroid theory, the following theory has also been very popular- With the advent of an epidemic of vitamin-D deficiency, dinosaurs developed profound Musculo-skeletal weakness and had trouble laying eggs, as the poorly calcified brittle shells interfered with successful delivery of live baby dinosaurs. Cloud & Debris from Asteroid falls screened out the UVB radiation critical for the cutaneous synthesis of vitamin-D with consequent deleterious effects in huge vertebral skeletons. These events may have a role in the extinction of dinosaurs from the surface of our planet.

Fishes are not able to synthesize Vitamin-D and are fully dependent on dietary sources to satisfy their needs for it. They store vitamin-D in liver and muscle. Responses through vitamin-D receptor (VDR) action have been shown in gill, intestine, kidneys and bones.
Metabolism of Vitamin-D through VDR has been demonstrated in Teleostean fishes, amphibians, reptiles and all avian species. Most mammals still depend on sunlight for their vitamin D requirement.

Birds are not able to make any vitamin D in the skin covered with feathers. The 7-dehydrocholesterol concentrations are 10-fold higher in the non-feathered skin areas including the legs.

For reasons that are not well understood, cats have no 7-dehyrocholesterol in their skin and therefore cannot make vitamin any D3 in their skin and have to depend solely on their diets to meet their daily vitamin D3 needs.

Skin pigmentation *evolved* to protect animals and humans from excessive exposure to sunlight, which increased the risk of non-melanoma skin cancers. However, as primitive humans migrated to the north and the south of the equator, it is likely that their skin pigment *devolved* for them to produce enough vitamin D3 to maintain calcium homeostasis and a healthy skeleton throughout life. Exposure to sunlight and the photosynthesis of vitamin D3 in the skin has been critically important for the evolution of land vertebrates. During exposure to sunlight, the solar UVB photons with energies between 290 and 315 nm are absorbed by 7-dehydrocholesterol in the epidermis and are converted to pre-vitamin D3, which then undergoes a rapid transformation within the cellular plasma membrane to vitamin- D3.

Excessive exposure to sunlight usually do not result in vitamin D intoxication because both pre-vitamin-D3 and vitamin-D3 are photolyzed to several non-calcemic photo products. During the winter at latitudes above ~ 35 degrees, there is minimal, if any, pre-vitamin-D3 production in the skin. Altitude also has a significant effect on vitamin-D3 production. At 27degrees North in November, very little (~ 0.5%) pre-vitamin D3 synthesis was detected in Agra (169 metres) and Kathmandu (1400 meters). There were ~ 2- and 4-fold increases in pre-vitamin-D3 production at ~ 3400 meters and at Everest base camp (5300 meters), respectively. Increased skin pigmentation, application of sunscreens, aging and clothing have dramatic effects on pre-vitamin-D3 production in the skin. It is estimated that exposure in a bathing suit to 1 minimal erythemal dose (MED) is equivalent to ingesting between 10,000 and 25,000 IU of vitamin-D2. The importance of sunlight for providing most humans with their vitamin D requirement is well documented by the seasonal variation in circulating levels of 25-hydroxyvitamin-D [25(OH)D]. Vitamin-D deficiency (VDD), defined as serum 25(OH)D levels < 20 ng/ml, is common in both children and adults worldwide. Exposure to lamps that produce UVB radiation is an excellent source for producing vitamin-D3 in the skin and is especially efficacious in patients with fat malabsorption syndromes. The major cause of VDD globally is an underappreciation of sunlight's role in providing humans with their vitamin-D3 requirement. Very few foods naturally contain vitamin D, and those that do have a very variable vitamin D content. Recently, it was observed that wild caught salmon had between 75% and 90% more vitamin-D3 compared with farmed salmon. The associations regarding increased risk of common deadly cancers, autoimmune diseases, infectious diseases, and cardiovascular disease with living at higher latitudes and being prone to vitamin D deficiency should alert all health care professionals about the importance of vitamin D for overall health and well-being.

[J Bone Miner Res 2007;22: S2; V28–V33. doi: 10.1359/JBMR.07S211]

Vitamin-D is essential for bone mineral acquisition in children and maintenance of bone health in adults. A serum 25OHD level above 20 ng/ml is enough for the skeletal effects (IOM, USA). A serum level above 30 ng/ml is probably needed for the extra-skeletal effects (The Endocrine Society, USA).

A common misconception is that the recommended daily allowance (RDA) for vitamin-D functions as a “cut point” and that nearly the entire population must have a serum 25(OH)D level above 20 ng/ml to achieve good bone health. The reality is that the majority (about 97.5%) of the population has a requirement of 20 ng/ml or less. Moreover, by definition of an average requirement, approximately half the population has a requirement of 16 ng/ml, the estimated average requirement (EAR) or less.
These concepts are depicted in the population reference-value distribution shown in Panel A, which highlights the relationship between the EAR and the RDA. [NEJM 375;19, November 10, 2016. Vitamin-D deficiency- is there really a pandemic? JoAnn E. Manson, M.D., Patsy M Brannon, M.D., et. al.]

EAR**:** a nutrient intake value that is estimated to meet the requirement of **half the healthy individuals** in a group- it reflects the most likely requirements in the population.
RDA**:** the average daily dietary intake level that is sufficient to meet the nutrient requirement of **nearly all** (97 to 98 percent) healthy individuals in a group.
Adequate Intake (AI)**:** a value based on observed or experimentally determined approximations of nutrient intake by a group (or groups) of healthy people—used when an RDA cannot be determined.
Tolerable Upper Intake Level (UL): the highest level of daily nutrient intake that is likely to pose no risk of adverse health effects to almost all individuals in the general population. As intake increases above the UL, the risk of adverse effects increases.

Upward Shift in Distribution Required to Attain the RDA-Linked Serum 25(OH)D Concentration in 97.5% of the Population

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Does vitamin-D supplementation prevent type 2 diabetes (T2D)? – the D2d study, NEJM, 2019.

The mean serum 25OHD level at baseline was 28.0 ng/ml. Participants with a serum 25OHD level < 12 ng/ml showed greater benefits of vitamin D supplementation (HR, 0.38; 95% CI, 0.18 to 0.80), a finding consistent with those of previous meta-analyses.
The trial was not restricted only to participants with vitamin-D insufficiency, given ethical considerations, and healthy people with pre-diabetes were also included.
Although the mean baseline vitamin D levels are well balanced between the trial groups and above insufficiency limits, more than 20% of the participants in the placebo group had a vitamin-D level of less than 20 ng/ml. Furthermore, 43 participants (3.6% of the group) had a vitamin-D level of less than 12 ng/ml, currently considered as vitamin-D deficiency. So, the conclusion that vitamin-d does not prevent the onset of T2D in people with pre-diabetes seems to be valid only for those people who do not have baseline vitamin-D deficiency. An impressive relative risk reduction of 82% was seen in the same study in the subgroup with baseline vitamin-D deficiency. The conclusion of the work should be that vitamin D does not prevent diabetes in participants who do not have vitamin D deficiency.
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We recruited around 2000 individuals with pre-diabetes. 73.25% had vitamin-D deficiency (VDD). 14.65% had severe VDD. Severe VDD was about twice more common in pre-diabetes. Individuals with severe VDD had the highest insulin resistance. Significant -ve correlation between 25-OHD & insulin resistance, as measured by HOMA-IR (BMI & hs-cRP adjusted). We concluded that VDD may have some role in the development of T2D and it could represent an independent risk factor for the progression of pre-diabetes to T2D. [Dutta D, **Mukhopadhyay S**., et. al. Indian Journal of Medical Research, 2013]

We then went on to initiate the first intervention study to see the effect of vitamin-D supplementation on the risk of progression of pre-diabetes to T2D and also to see if vitamin-D treatment could reverse pre-diabetes to normal glucose tolerance.

Study Aims & Objectives:

1. To evaluate the role of vitamin-D treatment on progression of prediabetes to type 2 diabetes and/or reversal to normoglycemia (**primary end point**)
2. To study the effect of vitamin-D treatment on insulin resistance, systemic inflammation and lipid profile (**secondary end point**)

Results:

125/170 (73.52%) had vitamin-D deficiency. Following one year follow-up datasets were available for analysis: Group A; n=55; Group B; n: =49; Group C; n= 32
Mean follow-up (months): Gr. A: 28.2±8.83, Gr. B:29.15± 7.69, Gr. C: 27.51±7.8
Compliance: vit-D sachets: 97%; calcium tabs: 91%.
Vitamin-D supplementation in vitamin-D insufficient/ deficient individuals was associated with significantly lower progression to type 2 diabetes (6/55 vs 13/49; p=0.04) and higher rate of reversal to normal glucose tolerance (23/55 vs 10/49; p=0.02), associated with decreased insulin resistance and systemic inflammation, characterized by significant reductions in the serum levels of TNF- alpha and IL-6 in the group receiving vitamin-D. Baseline serum vitamin-D levels and two hours post glucose plasma glucose levels were independent predictors of the likelihood of progression to type 2 diabetes. Our study had the following limitations: 1. Single center study 2. Small sample size. 3. Short period of follow-up. 4. Open labeled design 5. Single ethnic group. [Dutta D, **Mukhopadhyay S**, et. al. Diabetes Research and Clinical practice, 2014]

Anoop Mishra and his group recently published their results on the effect of vitamin-D supplementation on glycemic profile and body composition in overweight/obese, prediabetic and vitamin D deficient Asian Indian women. It was an open label randomized controlled trial of 78 weeks duration involving 121 females aged 20–60 years. Significant decreases in fasting plasma glucose, 2-hour post glucose plasma glucose and HbA1c were observed in the cohort receiving vitamin-D compared to the placebo group. As expected, a significant increase in serum 25(OH) D levels was also documented in the intervention group as compared to the placebo group. [Anoop Mishra et. al. Scientific reports, 2020.]

Conclusions:

- Vitamin D deficiency increases the risk of insulin resistance & type 2 Diabetes
- Vitamin D supplementation in vitamin- D deficient people with prediabetes increased the rate of reversal to normal glucose tolerance.
- *D2d study*, where participants had prediabetes at baseline but no vitamin-D deficiency, Vitamin-D did not protect against type 2 diabetes (HR 0.88)
- In the *post hoc* analysis, 103 participants with Vitamin-D deficiency at baseline had an impressive 62% risk reduction for type 2 diabetes (HR 0.38)
- Future studies should determine whether vit D is effective in preventing type 2 diabetes in in persons with baseline vitamin D deficiency.
- Routine screening of healthy population is not recommended
- For high risk patients, vitamin D supplementation at levels above the recommended daily allowance (RDA) may be necessary.
- Healthy population should meet their estimated average requirement (EAR) through lifestyle measures.
- Over-screening and overprescribing of supplemental vitamin D should be avoided.

WORLD-INDIA DIABETES FOUNDATION (WIDF)

2020 WIDF OUTSTANDING ACHIEVEMENT

PROFESSOR SATINATH MUKHOPADHYAY, MD, DM

INSTITUTE OF POST GRADUATE MEDICAL EDUCATION & RESEARCH

To honor your contributions to the advancement of our understanding of pathophysiology of diabetes

Award given in honor of Mr. Raman Kapur
19th International Symposium on Diabetes, January 18-19, 2020 — Mumbai, India

World-India Diabetes Foundation (USA)