

Preserving Endogenous Insulin in Children with Type 1 and 2 Diabetes

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Monument Health

Pediatric Endocrinology



No disclosures



MONUMENT HEALTH

Goal

At the end of this discussion more awareness of

- Type 1 and type 2 diabetes incidences increasing
 - Lifestyle increasing endogenous insulin action
 - Using vit D as another tool to increase endogenous insulin action
- Vit D deficiency is increasing globally over all age ranges
 - 80% should come from conversion sun to skin
 - Vit D effect on autoimmunity
 - Vit D as a nutrient not a medication hard to quantify effect
- TrialNet information as an option to screen for **at risk** individual for T1D risk

No diabetes prevention program for kids

- Track baseline and progress
- Vit D study caught my attention this fall

Healthy Lifestyle Changes

1. Increase activity – Work up to 60 minutes per day on 7 days of the week. Find an activity you will enjoy.
2. Decrease the amount of food you are eating – per meal and snack by 20% (1/5) until the portion size you are eating is the size of your 2 fists (the size of your stomach) for each meal and 1 fist for each snack. Consider healthy plate, 50% low carbohydrate vegetables, 25% protein, and 25% whole-grain carbohydrates.
 - *Reduce processed carbohydrates such as cereals, and pre-packaged foods.*

Healthy Lifestyle Changes (cont)

3. Weigh weekly - People who monitor progress find out what works best for their bodies.
4. Cut out sugary drinks and drink more water— Anything that has more than 5 calories per 8 oz. serving has too much sugar.
 - *Limit added sugars in food and beverages to no more than 25 grams daily.*

Healthy Lifestyle Changes (cont)

5. Get in at least 2-3 servings of calcium containing foods daily (full fat dairy is okay).
6. Take a multivitamin daily and **2000 IU vitamin D daily.**
usually, OTC vit D3 if high dose maybe cholecalciferol D3 or ergocalciferol vit D2
7. Limit screen time – One hour per day, this will help you be more active. Try standing during screen time.

Healthy Lifestyle Changes (cont)

8. Behavior and Mindset

- ✓ Get a full nights sleep (7-8 hours)
- ✓ Eating mindfully and address emotional and social eating
- ✓ Focus on small changes
- ✓ Prepare for how to handle setbacks

- Current waist measurement:
- For next visit
 - Potentially start metformin

Metformin at Times for All Diabetes

- Best for those with signs of insulin resistance
 - ✓ Abnormal OGTT (if not already diabetic)
 - ✓ Acanthosis nigricans
 - ✓ Hidradenitis supertiva
 - ✓ BMI over 85%tile or increasing quickly
 - ✓ Abnormal appetite
 - Eats too, much too fast too often , wakes up at night hungry
- Insulin sensitizer
- Decrease hepatic glucose production
- Slow down carb absorption
- Increase the incretins (incretins for a future talk)

Ergocalciferol in New-onset Type 1 Diabetes a Randomized Control Trial

- Would ergocalciferol supplementation increase residual B cell function and increase the duration of partial clinical remission in type 1 diabetes?
- 12 month randomized double blinded placebo-controlled trial
 - ✓ 50,000 IU ergocal per week for 2 months then every 2 weeks for 10 months
 - ✓ Vs placebo
 - ✓ 36 individuals aged 10-21 years with T1D duration less than 3 months and stimulated C peptide. > or = to 0.2 nmol/L (≥ 0.6 ng/ml)

Subjects Are Statistically Similar

Table 3. Baseline anthropometric and biochemical characteristics of participants

Parameters	Placebo (n = 18)		Ergocalciferol (n = 18)		P
	Mean	SD	Mean	SD	
Age, y	14.28	2.86	13.25	2.76	.28
Height, cm	158.65	11.30	156.12	12.77	.53
Height z score	0.48	1.18	0.50	0.73	.93
Weight, kg	56.16	14.66	53.33	15.19	.58
Weight z score	0.67	0.68	0.86	0.81	.45
Body mass index	22.01	4.15	22.03	5.41	.99
Body mass index z score	0.74	0.68	0.89	0.94	.59
Waist circumference, cm	76.22	11.56	76.16	14.83	.99
Systolic blood pressure, mm Hg	104.94	9.06	106.44	10.60	.65
Diastolic blood pressure, mm Hg	64.67	6.80	64.72	9.14	.98
Fasting plasma glucose, mg/dL	111.13	35.78	125.83	25.00	.18
HbA _{1c} , %	7.47	1.69	7.62	1.35	.77
TDD insulin, units/d	27.17	14.41	37.00	29.61	.23
TDD insulin, units/kg/d	0.48	0.23	0.51	0.23	.72
TDD long-acting insulin only, units	14.14	7.30	18.50	14.81	.28
	n	%	n	%	
Male sex	14	77.9	10	55.6	.16
White ethnicity	15	88.2	12	85.7	≥ .999
Pubertal stage, Tanner II-V	10	71.4	12	85.7	.65

P values for continuous variables were obtained by 2 sample *t* test, or Satterthwaite test in case variances were not equal, and for dichotomized variables, either chi-square or Fisher exact test, whichever was appropriate.

Table 5. Longitudinal changes in therapeutic and biochemical parameters during the trial

Parameter	Placebo (n = 18)		Ergocalciferol (n = 18)		Placebo (n = 18)		Ergocalciferol (n = 18)		<i>P</i>			
	Mean	SD	Mean	SD	LSE Mean	SE	LSE mean	SE	Difference in overall mean	Overall trend	Difference in trend	Difference at specific time (adjusted for multiple comparisons)
TDDI, units/kg/d												
Baseline	0.48	0.23	0.51	0.23	0.48	0.05	0.55	0.06	.046	.001	.097	.41
Mo 3	0.46	0.18	0.62	0.36	0.43	0.05	0.62	0.08				.049
Mo 6	0.49	0.27	0.62	0.30	0.48	0.06	0.67	0.08				.06
Mo 9	0.62	0.28	0.69	0.26	0.63	0.07	0.73	0.07				.31
Mo 12	0.67	0.30	0.65	0.24	0.67	0.07	0.72	0.07				.65
FBG, mg/dL												
Baseline	111	36	126	25	115	9	126	6	.13	.03	.10	.31
Mo 3	131	53	157	61	130	12	157	15				.17
Mo 6	146	72	146	54	146	17	147	14				.97
Mo 9	140	61	141	43	137	16	143	12				.75
Mo 12	158	61	145	49	158	15	145	14				.52
Fasting C-peptide, ng/mL												
Baseline	0.68	0.40	0.80	0.82	0.71	0.10	0.80	0.19	.54	.01	.72	.67
Mo 3	0.65	0.38	0.59	0.40	0.69	0.09	0.71	0.12				.90
Mo 6	0.71	0.55	0.46	0.29	0.71	0.13	0.51	0.08				.19
Mo 9	0.44	0.24	0.42	0.24	0.49	0.07	0.46	0.06				.80
Mo 12	0.50	0.47	0.35	0.21	0.50	0.11	0.37	0.06				.29
Stimulated C-peptide, ng/mL												
Baseline	2.22	1.31	1.78	1.18	2.27	0.31	1.78	0.28	.08	< .001	.31	.24
Mo 3	1.74	0.94	1.28	0.78	1.76	0.21	1.56	0.25				.55
Mo 6	1.51	1.08	1.17	0.92	1.53	0.25	1.40	0.26				.73
Mo 9	1.35	1.34	1.05	0.84	1.36	0.31	1.25	0.24				.79
Mo 12	1.14	1.27	0.82	0.77	1.15	0.29	1.05	0.22				.80
HbA _{1c} , %												
Baseline	7.47	1.69	7.62	1.35	7.47	0.39	7.62	0.32	.09	< .001	.04	.76
Mo 3	6.67	1.23	7.20	1.54	6.67	0.28	7.25	0.37				.21
Mo 6	7.12	1.51	7.26	1.18	7.15	0.34	7.28	0.27				.77
Mo 9	7.59	1.37	7.50	1.42	7.61	0.32	7.48	0.35				.77
Mo 12	8.01	1.70	7.64	2.14	8.03	0.41	7.65	0.57				.59
IDAA _{1c}												
Baseline	9.4	2.4	9.7	1.8	9.4	0.6	9.9	0.4	.03	< .001	.02	.51
Mo 3	8.5	1.8	9.7	2.3	8.4	0.4	9.7	0.6				.05
Mo 6	9.0	2.4	9.8	1.9	9.0	0.5	10.0	0.5				.17
Mo 9	10.1	2.2	10.2	2.1	10.1	0.5	10.4	0.5				.62
Mo 12	10.7	2.5	10.3	2.3	10.7	0.6	10.6	0.6				.89

P values were obtained from repeated-measures trend analysis using generalized linear model with dependent variable equal to clinical parameter, and independent variables equal to group, time, and their interactions. Generalized estimating equation was used for repeated measures.

Abbreviations: FBG, fasting blood glucose; HbA_{1c}, glycated hemoglobin A_{1c}; IDAA_{1c}, insulin dose-adjusted A_{1c}; LSE, least square estimate; TDDI, total daily dose

Vitamin D Supplementation After 1 Year

- Did not statistically improve stimulated C peptide
- Did improve partial remission time
- Did improve insulin dose adjusted A1c
 - Some have a target A1c on less insulin ... why?

Tumor Necrosis Factor Alpha

- Marker of inflammation
- Did statistically lower in the vit D treatment group
- More studies needed

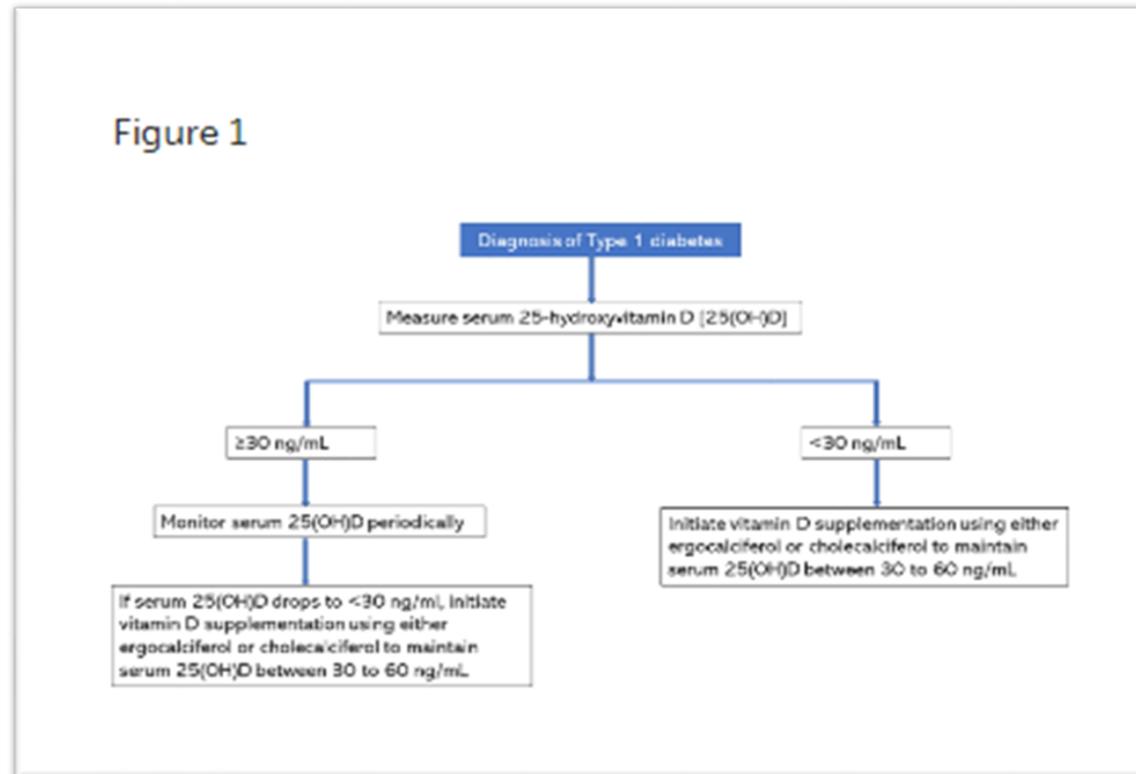
TABLE 1 Summary of Temporal Trends in Hemoglobin A1c and the Insulin Dose Adjusted Hemoglobin A1c during the trial

Table 1

Parameter	Vitamin D (ergocalciferol)	Placebo	P value
Hemoglobin A1c (%)	0.14	0.46	0.044
Insulin-dose adjusted hemoglobin A1c (%)	0.30	0.77	0.015

Figure 1 Protocol for vitamin D supplementation in patients with new-onset type 1 diabetes

Figure 1



Vitamin D 25

- **80% from the sun through the skin historically**
 - We are in the sun less
 - ✓ Lifestyle
 - ✓ Cancer avoidance
- **Ability to absorb through the gut**
 - 70% genetic
 - Sometimes normal level
- **Found in egg, liver, mushroom or fortified foods or cod liver oil**
- **Will look at level earlier and treat**

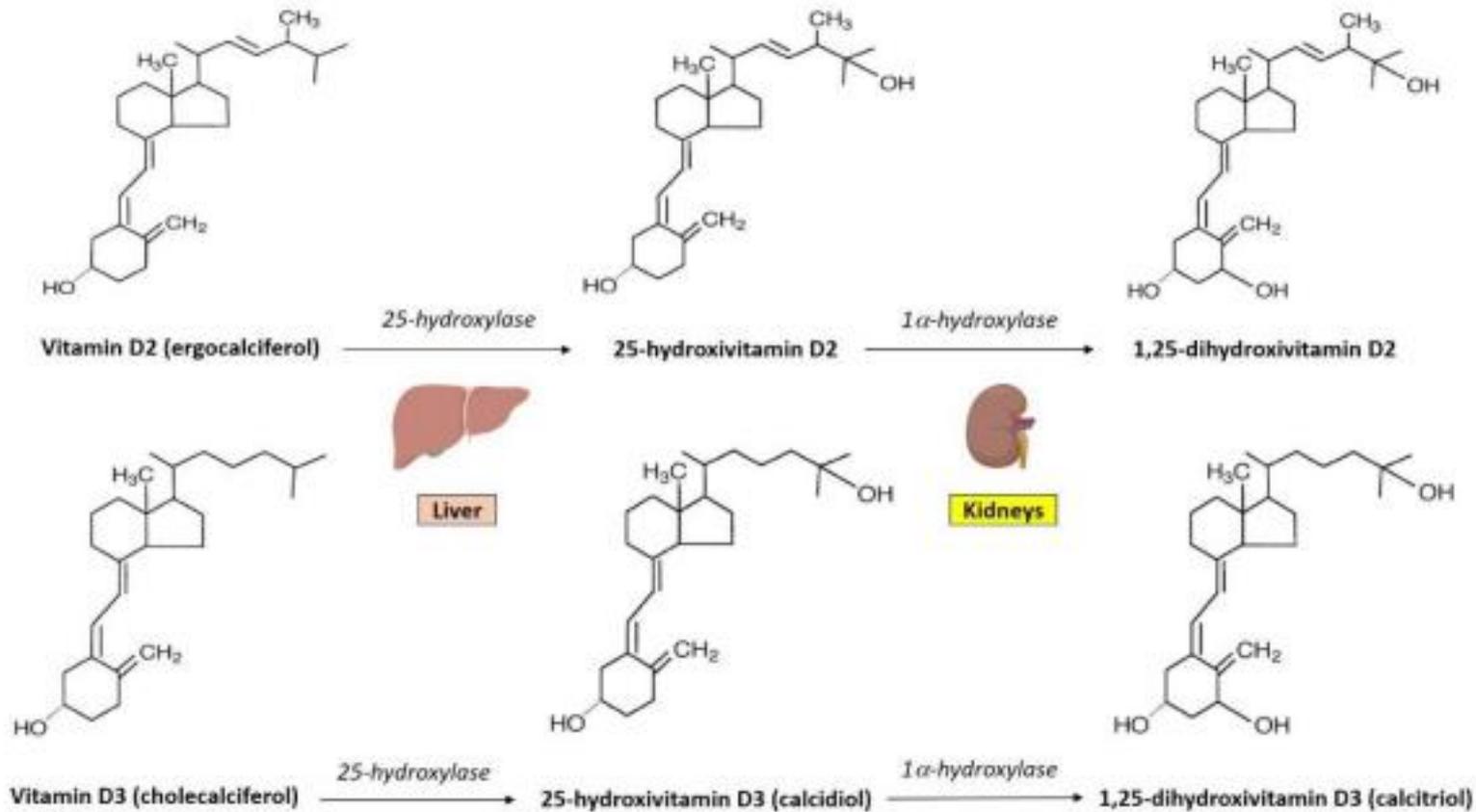


Figure 1. Chemical structure of the main forms of vitamin D and synthesis of biologically-active metabolites (1,25-dihydroxivitamin D2 and 1,25-dihydroxivitamin D3).

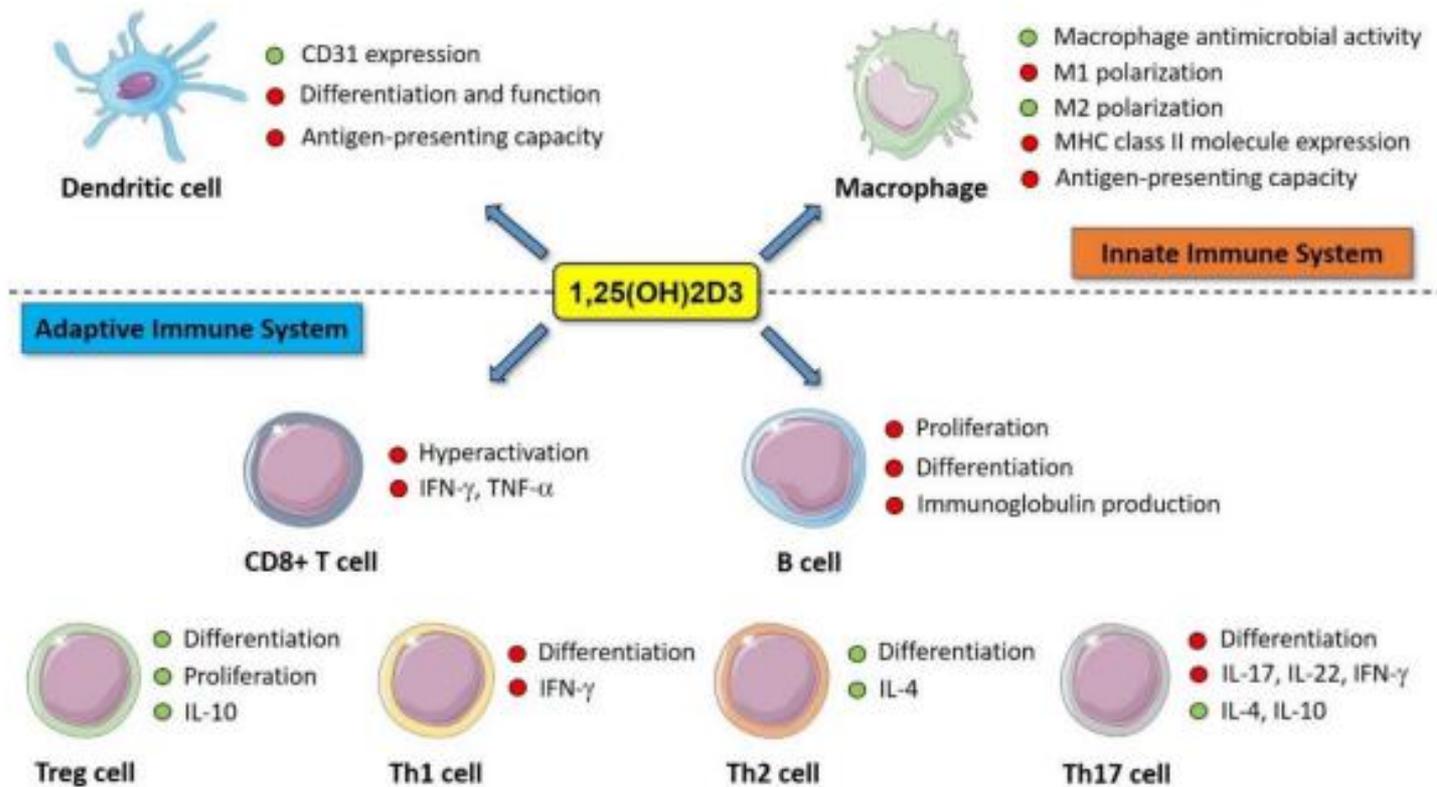


Figure 2. An overview of the anti-inflammatory and immunomodulatory effects exerted by the active metabolite of vitamin D 1,25(OH)₂D₃ (referred to as calcitriol) on innate and adaptive immune system. Red dots represent downregulation, whereas green dots represent upregulation. Abbreviations: IFN- γ , interferon gamma; IL-4, interleukin 4; IL-10, interleukin 10; IL-17, interleukin 17; IL-22, interleukin 22; M1, classically-activated macrophages; M2, alternatively-activated macrophages; MHC, major histocompatibility complex; TNF- α , tumor necrosis factor-alpha.

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- Vit D deficiency is increasing globally over all age ranges
 - Vit D effect on autoimmunity
 - Vit D as a nutrient not a medication hard to quantify effect
- TrialNet information as an option to screen for at risk individual for T1D
- **Note:**
 - ✓ Teplizumab an antiCd-3 antibody will be reviewed by the FDA Nov 17th (Thursday)
 - ✓ Potential as the first medical treatment to prevent type 1 in those **at risk**
 - ✓ Must cost 48,900 or less to be cost effective

TrialNet

- Study Details: Pathway to Prevention screening is the first step for all TrialNet prevention studies.
- Screening is offered at no cost to eligible individuals to evaluate their personal risk of developing the disease.
- This unique screening can identify the early stages of type 1 diabetes (T1D) years before any symptoms appear. It also helps researchers learn more about how T1D develops and plan new studies exploring ways to prevent it.

TrialNet

- Relatives of people with T1D are 15 times more likely to develop the disease than the general population.
- Increased risk of developing T1D is linked to the presence of five diabetes-related autoantibodies, regardless if you have a relative or not.
- The JDRF, ADA and Endocrine Society now classify having two or more of these autoantibodies as early stage T1D.

TrialNet

Who Can Participate: You qualify for free risk screening if you:

- Are between the ages of 2.5 and 45 years and have a parent, brother/sister, or child with T1D
- Are between the ages of 2.5 and 20 years and have an aunt/uncle, cousin, grandparent, niece/nephew, or half-brother/sister with T1D
- OR Are between the ages of 2.5 and 45 years and have tested positive for at least one T1D related autoantibody outside of TrialNet
- Visit the website to contact or call: www.trialnet.org/our-research/risk-screening 1 Diabetes TrialNet Phone: 1-800-425-8361 Monday- Friday 8-5 ET N-FRI 8am-5pm ET

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References

- Ergocalciferol in New-onset Type 1 Diabetes: a randomized controlled trial Nwosu et al Journal of the Endocrine society 2022 vol 6 , 1-13
- Guidance for high dose vit D supplementation for prolonging the honeymoon phase in children and adolescent with new-onset type 1 diabetes. Mini review Frontiers in Endocrinology 18Aug2022
- Why do so many trial of vit D supplementation fail? B.J.Boucher Endocrine connections R195-R206
- An Anti-CD3 Antibody, Teplizumab, in Relatives at Risk for Type 1 Diabetes Harold MD etal NEJM 2019 August 15;381(7): 603-613

References

- Influence of Vitamin D on Islet Autoimmunity and Beta-cell Function in Type 1 diabetes Marco Infante et al Nutrients Open access article distributed under the terms and condition of the Creative Commons Attribution 2019, Sept 11.
- Metabolical By Robert Lustig MD

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- *Families that I see... that patiently listen to my ideas for their children's health. The kids themselves living their best lives.*

Questions?