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Administration of vitamin D and high dose of omega 3 to sustain remission of type 1 diabetes

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Abstract. – OBJECTIVE: Two cases of Type 1 Diabetes (T1D) in pediatric subjects treated with supplementation with high dose vitamin D and omega 3 are reported. A similar pattern of remission of the disease was observed, resulting in restoration and subsequent persistence of optimal metabolic control, one and two years after T1D onset. Minimal basal insulin administration (0.1 IU/kg/die) in a single evening injection was required. The immunomodulatory and anti-inflammatory properties of the supplements were likely contributing to the observed effect. Similarities in genotyping and autoantibody patterns in these two cases could be of assistance to identify which subjects with T1D could benefit from this supplemental therapy. High dose vitamin D and omega 3 could be of assistance in childhood T1D therapy, to prolong preservation of endogenous insulin secretion in the absence of side effects. We do not know how long the state of remission can last, but these initial results are promising and represented a significant benefit for the two pediatric subjects treated. Larger controlled studies will determine the long-term effect of this proposed supplementation and its possible cost-benefits, including reduction of hypoglycemic episodes and complications.

Key Words:
Type 1 diabetes, Remission, Vitamin D, Omega 3.

Case Report

Recently, we described an anecdotic case of a child with type 1 diabetes (T1D) who just after the start of insulin therapy and normalization of blood glucose achieved a recovery of endogenous insulin secretion (REIS). Through supplements of vitamin D and omega 3, the child showed persistent metabolic control and regular physical growth over time with minimal long acting insulin (0.1 IU/kg/day) administered once a day at bedtime[1]. Now we report an update of this child two years after the onset of the disease, and present another T1D case with a similar clinical course and 1 year follow-up. To date, for both, the unusual trend continues with unquestionable benefit.

Both children were male of school age, with normal weight and otherwise healthy. After a short clinical history of classic symptoms of overt disease, they arrived to the hospital. The clinical and laboratory findings are summarized in Table I.

The blood glucose normalization was easy and rapid after the start of insulin therapy. Vitamin D was dosed as serum 25(OH)D_3 and a complete lipidogram was performed on a blood spot. The concentration of 25(OH)D_3 serum was defined, according to Endocrine Society graduation, as vitamin D insufficiency < 30, normal 30-50 ng/ml[2]. The lipid status of omega 6 and omega 3 was considered as Arachidonic Acid (AA) and EicosaPentaenoic Acid (EPA) ratio. Both children were vitamin D insufficient and far off the target AA/EPA < 3. Supplements of vitamin D (1000 IU/day) started just at the discharge and omega 3 (EPA + DHA 50-60 mg/kg/day, EnerZona® Omega 3) within three months after. The amount of omega 3 (EPA + DHA) in food was quantified, with the support of the Food Composition Data-

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Table I. Characteristics of patients at T1D onset.

	Case 1 (onset 11/21/2015)	Case 2 (onset 12/18/2016)
Age (yrs)	7	7
Gender	M	M
Weight kg (centile)	25.5 (25)	20 (10)
High cm (centile)	130 (75)	120.4 (10)
Tanner pubertal grade	PH 1, G 1	PH 1, G1
EGA: pH, [$HCO3^-$]	7.46 [17.4]	7.37 [22.0]
Urine test	Ketone +, Glucose +++	Ketone +, Glucose ++++
HbA1c % (mmol/mol)	9.6% (81)	11.1% (98)
Blood glucose mg/dl	227	219
Clinic symptoms of T1D	+++	+++
C-peptide ng/ml	0.5	0.3
Islet auto antibodies:		
GAD IU/ml (n.v. < 1.0)	68	2.9
IAA IU/ml (n.v. < 0.4)	0.10	0.1
IA-2 IU/ml (n.v. < 0.9)	1.2	< 0.7
ZnT8 UA/ml (n.v. < 15)	162	
HLA	DR3-DQ2	DR3, DR4, DQ2
$25(OH)D_3$ ng/ml	25.9	24.7
AA/EPA	33.67	20.45

Note: To convert vitamin D ng/ml to mmol/ml, divide 2.5.

base for Epidemiological Studies (BDA version 1-2015), by a dietician in 1000 mg (case 1) and 150 mg (case 2) daily. The target of $25(OH)D_3$ and AA/EPA were 40 ng/ml and 1.5-3, respectively. Main results are reported in Table II.

After discharge, the clinical course of the disease for both children was initially characterized by repeated hypoglycemia, especially after meals, so insulin doses of lys-pro were progressively reduced; then, in case 2 an insulin dilution was included to use doses 0.25 IU dosage adjustments by pen at meals. For both, the tendency to hypoglycemia improved after the definitive suspension of lys-pro. Sometimes, when the carbohydrates load of meals was high, as with a pizza, the blood glucose increased, but spontaneously reduced without insulin in the following hours. A tendency of blood glucose to rise in the night was observed especially in the early hours after midnight, so in both cases a small amount of basal insulin at bedtime was maintained. The dose of insulin glargine or degludec has also been progressively reduced in relation to blood glucose at awakening. The insulin demand, therefore, has been dramatically reduced after the onset, to avoid hypoglycemia, and then maintained with small doses of basal insulin until today.

No serious hypoglycemic episodes were reported, and glucose level corrections were done only exceptionally after a few meals. The near normal blood glucose has consistently been maintained during sports without any particular dietary supplement. Invariably, the episodes surrounding illness, as catarrhal or gastroenteric or

Table II. First and last results after supplements.

	Case 1		Case 2	
	First result	Last result	First result	Last result
Vitamin D ng/ml	38.3	43.8	24.7	46
AA/EPA	1.76	2.97		2.5
Insulin IU/kg/d	0.07	0.09	0.1	0.11
C-peptide ng/ml	0.5	0.6	1.07	2.24
HbA1c % (mmol/mL)	5.8% (40)	5.9% (41)	6.8% (51)	5.7% (39)
Mean blood glucose	97 mg/dl	86 mg/dl	116 mg/dl	103 mg/dl
SD	20 mg/dl	21 mg/dl	48 mg/dl	32 mg/dl

febrile events, led to increased blood glucose levels, spontaneously reduced in the following days, with small adjustments of insulin at bedtime. Case 1 underwent a tonsillectomy with moderate increase of blood glucose, and spontaneous recovery of normal blood glucose within 2 hours post-surgery. The metabolic adequacy of therapy was evaluated from finger-sticks blood glucose tests (Conturnext USB® Ascensia Diabetes Care, Parsippany, NJ, USA) or by flash glucose monitoring (FreeStyle Libre® Abbott, Abbott Park, IL, USA) to replace glucose measurements.

Clinical observations were focused to detect side effects and observe the growth of children. In both no height-weight slowdown was found within the period of one-two years and the prepuberal stages remained unchanged.

The family pediatrician was advised to provide a reduction in omega 3 dosage in preparation for any surgical intervention, or in the event of physical major trauma for a possible involvement of omega-3 in the coagulation. However, there was no particular bleeding problem inter or post-operative when Case 1 underwent the tonsillectomy. No particular bleeding was observed during dental surgery. No epistaxis was reported. No particular coagulation abnormalities, such as ecchymosis, were observed related to sport.

A call alert was set up for possible events, which led to consultations only within sick days with fever, to handle the rise of blood glucose, as previously reported. Throughout the observation period, no adverse effects of supplementations were noted. Even coagulation adequacy was confirmed by tests, and triglycerides levels resulted in normal range.

The metabolic adequacy of therapy was evaluated in case 1 and case 2, respectively at two and one years after the onset of T1D, with a C-peptide 2 h after mixed-meal tolerance test (MMTT), and insulin dose-adjusted HbA1c [%] index (IDAA1C). C-peptide resulted 0.71, and 0.8 ng/ml, and IDAA1C, 6.5 and 6.1 respectively, both results showed the persistence of REIS[3]. The outcomes are summarized in Table III.

Conclusions

There are some clear analogies in the course of the disease and between the two children: sex, school age, HLA DR3-DQ2 genetic predisposition, and similar anti-beta cell antibody pattern with GADA. These last two features seem to identify a cluster of subjects with T1D, yet elsewhere described[4]. Both children showed a quite total and persistent remission from the onset of T1D. Notably the supplements were administered close to the start of insulin therapy, with vitamin D just after, and with omega 3 within the 3rd month.

Table III. Outcomes and clinical course.

		Start point	One year after	Two years after
Weight	C1	Kg 25.2	Kg 27.5	Kg 28.1
	C2	Kg 21	Kg 22.3	
BMI	C1	15.0	15.1	15.2
	C2	15.5	15.4	
Triglycerides	C1		35 mg/dl	41 mg/dl
	C2	73 mg/dl	74 mg/dl	
T. Quick	C1		PT 1.06'', aPTT 32.9''	PT 1.02'', aPTT 30.7''
	C2		PT 1.07'', aPTT 35.3''	
Side effects	C1		None	None
	C2		None	
HbA1c % (mmol/mol)	C1		6.2 (44)	5.9 (41)
	C2		5.7 (39)	
IDAA1C*	C1		6.4	6.5
	C2		6.0	
MMTT (2h)	C1			
	C-peptide			0.71 ng/ml
	Blood glucose			143 mg/dl
	C2			
	C-peptide		0.8 ng/ml	
	Blood glucose		112 mg/dl	

Case 1 (C1) and Case 2 (C2); *Insulin dose-adjusted HbA1c [%]; to calculate IDAA1C: insulin dose (units/kg/24h) × 4 + HbA1c [%]; definition of partial remission if ≤ 9.

There are extensive references about vitamin D and omega 3 in the pathogenesis of autoimmune diabetes, excellently highlighted in two recent works[5,6]. Surprisingly, there is no specific literature about the contemporary administration of vitamin D and omega 3 during the remission or "honeymoon" of T1D in childhood. In our knowledge, references of clinical studies with this double supplementation focused on preservation of REIS are lacking.

Since it is unlikely to find two similar cases of persistent remission of T1D in a limited series of subjects as ours, quantifiable in 20 annual debuts, the immunomodulatory and anti-inflammatory effects of the supplements are likely determinants. Therefore, it is desirable to set up investigations on a greater number of new onset subjects with T1D.

The undoubted advantage of a good T1D metabolic balance with a single injection per day, and with a minimum insulin dose, are obvious reasons to support remission through vitamin D and omega 3 just after the onset of T1D. Moreover, a reduced insulin dose correlates with fewer hypoglycemic events, and the persistence of a minimal C-peptide reduces complications[7-11].

The limit of this study is the short time of observation, and we do not know if T1D remission may persist over time, but we will proceed with this double supplementation since no adverse effects have been observed. Vitamin D and omega 3 supplementation may represent a cost-effective strategy in T1D, and larger controlled studies are warranted to determine the effect of the proposed intervention to slow down or halt the progression of autoimmunity.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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