European Review for Medical and Pharmacological Sciences 2017; 21: 1604-1609

Can Type 1 diabetes progression be halted? Possible role of high dose vitamin D and omega 3 fatty acids

F. CADARIO[1,2], S. SAVASTIO[1], A.M. RIZZO[3], D. CARRERA[4], G. BONA[1,2], AND C. RICORDI[5]

[1]Division of Pediatrics, Department of Health Sciences, University of Piemonte Orientale, Novara, Italy
[2]IRCAD (Interdisciplinary Research Center of Autoimmune Diseases), Novara, Italy
[3]Department of Pharmacological and Biomolecular Sciences (DiSFEB), Laboratory of Membrane Biochemistry and Applied Nutrition, Università degli Studi di Milano, Milan, Italy
[4]Department Dietetics and Clinical Nutrition, University Hospital Maggiore, Novara, Italy
[5]Diabetes Research Institute and Cell Transplant Program, University of Miami Miller School of Medicine, Miami, FL, USA

Abstract. – In Type 1 Diabetes (T1D) in children, close to the onset the requirements of insulin are often reduced. This represents a transient recovery of endogenous insulin secretion named "honeymoon" because transient and followed by a progressive decline in C-peptide secretion. This case report describes the effect of administration of high dose vitamin D and Ω-3 fatty acids on T1D progression in a 8-year-old child. At today after one year and a half from the onset of T1D, the subject shows a near-normal blood glucose with the administration of 1.5-2 UI of insulin once a day. Thus this report may be of assistance to design additional studies to determine and validate the effect of administration of vitamin D and Ω-3 fatty acids on the progression of T1D

Key Words
Type 1 Diabetes, Omega 3 fatty acids, Vitamin D.

Introduction

Following the onset of Type 1 Diabetes (T1D) in children, the initial requirements for exogenous insulin therapy to reverse keto-acidosis and stabilize blood glucose levels, are generally substantially reduced. This partial remission is named the "honeymoon" phase and represents a transient recovery of endogenous insulin secretion (REIS). The "honeymoon" phase usually occurs shortly after T1D diagnosis, but is transient in nature and could last weeks to several months and even over one year, during which a progressive decline in C-peptide secretion is usually observed. The decline in endogenous insulin production is generally more severe in younger children compared to adolescents and young adult subjects. Additional factors contribute to determine the endogen insulin decrease and the autoimmune process progressively decreasing and virtually eliminating any significant residual insulin secreting β cells mass in subsequent years. A goal of diabetes care is to maintain metabolic control, stabilizing blood glucose levels and minimizing glycemic variability, to decrease the risk of hypoglycemia and development of complications of the disease in the following decades. In this direction preservation of even residual β-cell mass would be highly desirable[1,2]. The autoimmune mediated apoptosis of β-cells represents the underlying process both of T1D onset and relapse of insulin needs, whose correspondent histology is an infiltration of neutrophils, T-lymphocytes and peripheral blood mononuclear cells into the pancreatic islets named "insulitis". Several cytokines are involved as mediators of inflammation[3,4], Vitamin D and Ω-3 and Ω-6 fatty acids are hypothesized to play a role in those complex events as immune modulators and as agonists or antagonist of inflammation[5-7].

The usual definition honeymoon is when close to the onset the need of insulin is less than 0.5 IU/ kg/day, to assume the metabolic control is achieved with significantly REIS.

Corresponding Authors: Francesco Cadario, MD; e-mail: francesco.cadario@gmail.com
Camillo Ricordi, MD; e-mail: CRicordi@med.miami.edu

This case report describes the effect of administration of high dose vitamin D and Ω-3 fatty acids on T1D progression in a 8-year-old child. At today after one year and a half from the onset of T1D, the subject shows a near-normal blood glucose with the administration of 1.5-2 UI of insulin once a day. Thus this report may be of assistance to design additional studies to determine and validate the effect of administration of vitamin D and Ω-3 fatty acids on the progression of T1D.

Case Report

The subject is the first-born child in a family without a history of T1D, only the paternal grandmother referred Type 2 Diabetes and a sister one year and a half younger is gluten intolerant. At the age of 7 years and 4 months, he had the classic symptoms of diabetes (thirst, hunger, weight loss and copious urination during day and night), which after ten days led him to the hospital on November 21, 2015, after his mother detected glucose in urine through a stick test. At the arrival he was healthy, the blood glucose was 227 mg/dl, and EGA was normal (pH 7.4, pO^2 146 mmHg, [HCO_3] 17.4 mmol/L). The weigh was kg 24, and high 127 (respectively 50° and 75° Italian childhood percentiles).

During hospitalization the balance has been easy achieved with MDI, with Lys-pro and insulin glargine, progressively reduced from 0.7 to 0.37 IU/Kg/die at the discharge five days later. There were found genetic phenotype DQ2-DR3 (corresponding to DQA1* 05:01, DQB1* 02:01, DRB1* 03), and specific autoimmunity pattern of T1Da [GAD 22.4 IU/ml (n.v. <1.0), IA-2 0.90 IU/ml (n.v. <0.70), IAA 0.30 IU/ml (n.v. 0.00-0.40) and ZnT8 162 UA/ml (n.v. <15)], none for CD [Transglut-A 2.9 CU (n.v. 0-20), Antigliadin-dm Ab IgA 2.5 CU (n.v. 0-20), IgG 3.2 CU (n.v. 0-20)] and partial against thyroid [Ab TPO 71 IU/ml (n.v. 0-60), Ab TRG < 30 IU/ml (n.v. 0-60)] with normal TSH [2.932 μIU/ml (n.v. 0.45-3.50)] and fT4 [1.55 ng/dl (n.v. 0.89-1.76)]. Blood count (Neutrophil leukocytes 6816 mm^3), electrolytes, transaminases, amylase and lipase were normal. Serum creatinine was normal (0.43 mg/dl). Notably at onset HbA1c was 9.6% (120 mmol/l). C-peptide was 0.5 ng/ml (n.v. 0.8-4.2), with a C-peptide/Glucose ratio of 0.42 (Glucose level of 120 mg/dl at the time of C-Peptide sample). Vitamin D [25(OH) D_3] was 25.9 ng/ml.

After discharge the metabolic control of the child was optimal, but a month later overcoming hypoglycemia entailed a rapid decrease of insulin needs (from 0.37 to 0.08 IU/kg/day). Especially the need for insulin for meals decreased and Lys-Pro was removed, while a relatively higher awakening blood glucose advised to keep a dose of glargine 1.5 IU/die at bedtime. Insulin glargine average dose was 1.5 IU/die (dosages 1, 1.5, 2 IU/day, according to the previous blood glucose on awakening, <110, 111-119, >120 mg/dl). The glycosylated hemoglobin rapidly fell near normal. The reduced glycemic variability confirmed the REIS and metabolic stability. The child always presented regular weight gain and normal BMI. Data are summarized in Table I, mean blood glucose and DS are shown in Figure 1.

The overall picture of blood sugar levels is deductible by the discharge of the meter (Conturnext USB® Ascensia Diabetes Care) and is summarized in Figure 1. DS are detailed before three meals.

Table I A. Auxological and metabolic parameters.

Time (born 5/07/2008)	Age (ys)	BMI (kg/m²)	HbA1c% (mmol/mol)	Blood glucose (mg/dL)	Insulin needs (IU/kg/d)	C-peptide (ng/ml)	C-peptide/ Glucose ratio*
T. 0 (onset 11/22/15)	7ys 4m	15 (25.5/1.3²)	9.6 (82.0)	120	0.39	0.5	0.41
T. 1 (04/06/16)	7 ys 9m	14.4 (25/1.32²)	6.0 (42.0)		0.08		
T. 2 (09/14/16)	8ys 2m	14.4 (26//1.35²)	5.7 (39.0)	84	0.04	0.5	0.59
T. 3 (02/12/17)	8ys 7m	14.9 (27.5/1.36²)	6.2 (45.0)		0.05		
T. 4 (03/13/17)	8ys 8m		5.8 (40.0)	98 (fasting) 102 (post meal)	0.05	0.6 (fasting) 1.6 (post meal)	0.61 (fasting) 1.56 (post meal)

*C-peptide (ng/mL)/glucose (mg/dL) x100. Assessed in fasting or in postprandial state (2 h)

Table I B. Blood glucose mean values from the meter.

Year/ month, n. test	Average blood glucose wake up (DS) mg/dl	Average blood glucose lunch (DS) mg/dl	Average blood glucose dinner (DS) mg/dl
2015/ 11-12, test 234	166 (52)	123 (40)	123 (48)
2016/ 01-12, test 1538	104 (27)	95 (22)	116 (30)
2017/ 01-03, test 228	119 (10)	88 (18)	121 (38)

When was programmed tonsillectomy further investigations were C-peptide/Glucose ratio (0.61 before breakfast, increased to 1.56 after that), lipid profile (showing low triglycerides. Total cholesterol 163, HDL 74, LDL 82 mg/dl, and triglycerides 35 mg/dl) and coagulation (normal, PT-INR 1.06, PT 12.2", PT ratio 1.07). Additional subcutaneous glucose monitoring was arranged for the short period close to tonsillectomy (see additional FGM with FreeStyle Libre® Abbott).

At discharge, it was indicated vitamin D therapy at a dose of 1000 IU/day until today, and subsequently undertaken the administration of highly purified Ω-3 fatty acids at a dose of 55-60 mg/kg/day, divided into three doses a day (T.1). Average daily supplementation was DHA 500 mg EPA 1000 mg. The intake of Ω-3 EPA and DHA had been finalized to point AA/EPA ratio <3, referred as optimal[8,9], and vitamin D supplementation as cholecalciferol, to obtain a concentration of 25(OH)D3 in the range 30-50 ng/dl.

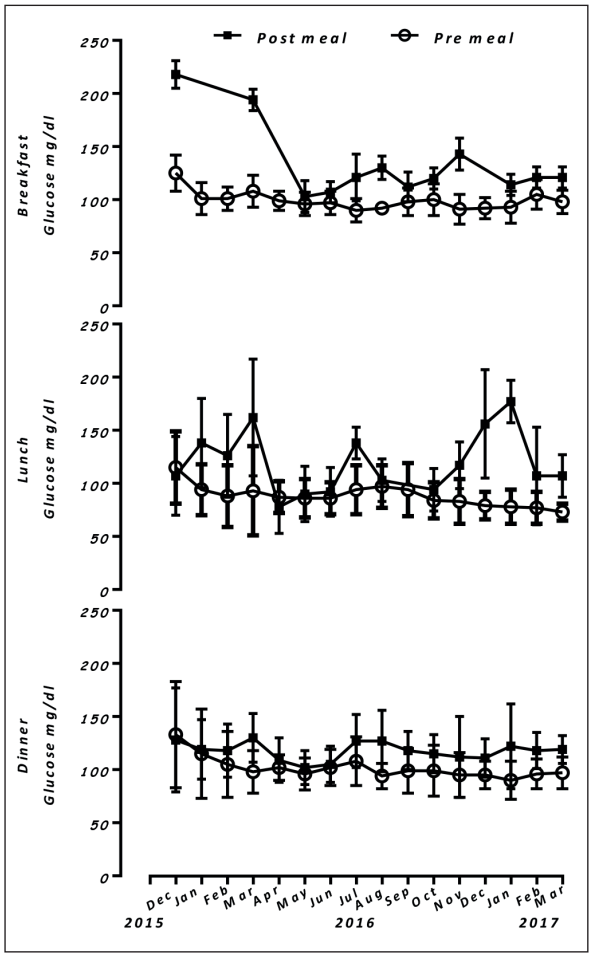

Figure 1. Mean blood glucose levels (mean±SD) pre and post breakfast, lunch and dinner during the months.

Whole blood fatty acid composition was determined three times: at baseline (T.1), after five (T.2) and ten months (T.3) to monitor Ω-3 and Ω-6 percentages of fatty acids in the venous blood (Table III). At T.3 a dietetic assessment of the food intake was performed on the basis of a food diary from 5 different days. A further interview with a dietitian was done with parents to evaluate the macro and micronutrients intake of food as precise as possible. The amounts of the various nutrients have been developed with the support of the Food Composition Database for Epidemiological Studies (BDA version 1-2015). Were evaluated protein (g/day), energy (Kcal/day), cholesterol (mg/day), simple carbohydrates (g/day), dietary fiber (g/day) calcium (mg/day), sodium (g/day), potassium (g/day), vitamin D (g/day), vitamin K (mg/day), polyunsaturated fatty acids (g/day), arachidonic acid (AA g/day), EPA (g/day) and DHA (g/day). Intake of AA, EPA and DHA are summarized in Table II. The diet analysis is reported in Table IV.

Discussion

Throughout the period considered, the level of child's growth was normal, with a weight gain of 2 kg in 1 year and a half, and wasn't reported particular problems, with excellent acceptance of the supplementation. The intake of Ω-3 capsules was performed in three times a day without any swallowing difficulty. Even the diet through a particular skill of the mother in the selection and preparation of the food was well-accepted. The gluten intolerance of the sister resulted in a virtually gluten free diet for him as well. In the diaries, only 3% of glucose values

Table II. Supportive and nutritional therapies.

	AA intake mg/d in diet	EPA+DHA intake mg/d in diet	Supplementation EPA+DHA mg mg/kg/d	Vit. D 25(OH)D3 ng/ml	EPA % fatty acids	DHA % fatty acids	AA/EPA
T. 0 (onset 11/21/15)				25.9 Start point 1000UI VitD			
T. 1 (04/06/16)			0 59		0.396	2.792	33.674
T. 2 (09/14/16)			1500 60	38.3	3.128	1.839	2.270
T. 3 (02/12/17)	392	349 + 661	1500 54.5	41.8	3.541	3.940	2.971

were over and 8% under the recommended blood glucose target (respectively >180 and <70 mg/dl), and in the last three months 1% over, and 12% under target (see Figure 2). A few hypoglycemic episodes were reported during the first month of insulin treatment; then, the therapy was corrected reducing insulin doses. None hypoglycemia was severe requiring assistance or glucagon. Occasional single elevated blood sugar levels are reported, especially during intercurrent inflammations of the upper airways.

Table III. Blood fatty acid composition.

% Fatty acid	PRE	+5 Months	+1 Year
C16:0	25.386	21.900	18.694
C16:1	0.530	2.106	0.899
C18:0	9.607	14.988	10.915
C18:1	19.721	24.080	27.205
C18:2	25.773	21.350	20.188
α C18:3	0.118	0.635	0.691
γ C18:3	0.960	1.572	0.688
C20:3	0.753	0.766	1.066
C20:4 (AA)	**13.325**	**7.101**	**10.521**
C20:5 (EPA)	**0.396**	**3.128**	**3.541**
C22:5 (DPA)	0.639	0.536	1.651
C22:6 (DHA)	2.792	1.839	3.940
SFA	34.993	36.888	29.608
MUFA	20.251	26.186	28.104
PUFA	44.756	36.926	42.287
OMEGA-6	40.811	29.851	32.464
OMEGA-3	3.945	7.075	9.824
OMEGA-6/OMEGA-3	10.346	4.219	3.305
AA/EPA	**33.674**	**2.270**	**2.971**

Whole blood fatty acid composition was determined on a droop of venous blood collected by the family at home by fingerstick and deposited on absorbent paper treated with BHT. This method allows easy sample shipment to the analytical laboratory, without deterioration of Polyunsaturated fatty acids (Rizzo et al. Lipids in Health and Disease 2010; 9: 7).

Surprisingly without administrations of insulin, the blood glucose spontaneously returned to the normal range within 2-3 hours. Even during a tonsillectomy, there was one episode of hyperglycemia and later in the post-surgical observation hypoglycemia with spontaneous resolutions and without insulin nor intravenous glucose administration, only two packets of sugar were dispensed when blood glucose decreased below 50 mg/dl. The rapid recovery of normal blood glucose concentrations after occasional hyperglycemia suggests a substantial persistence of β-cell mass. Also, the absence of hypoglycemia when insulin dosage was stabilized with 1-2 IU glargine at evening, strongly argues for endogenous insulin production. The higher average blood glucose and increased variability in the wake reflect the physiologic circadian rhythm of insulin sensibility with downregulation in the early morning. Moreover, the persistence of C-peptide levels ≥ 0.5 ng/ml is the direct evidence of REIS over time, and comparing with fasting blood glucose measured simultaneously

Table IV. Nutrients daily intake.

Nutrients	Daily intake
Protein (g)	89
Energy (kcal)	2005
Soluble carbohydrates (g)	54.7
Dietary fiber (g)	19.3
Calcium (mg)	709.8
Sodium (mg)	1216
Potassium (mg)	2413
Vitamin D (μg)	8.94
Vitamin K (μg)	0.81
AG polyunsaturated (g)	22.83
Arachidonic acid (g)	0.392
EPA (g)	0.349
DHA (g)	0.661

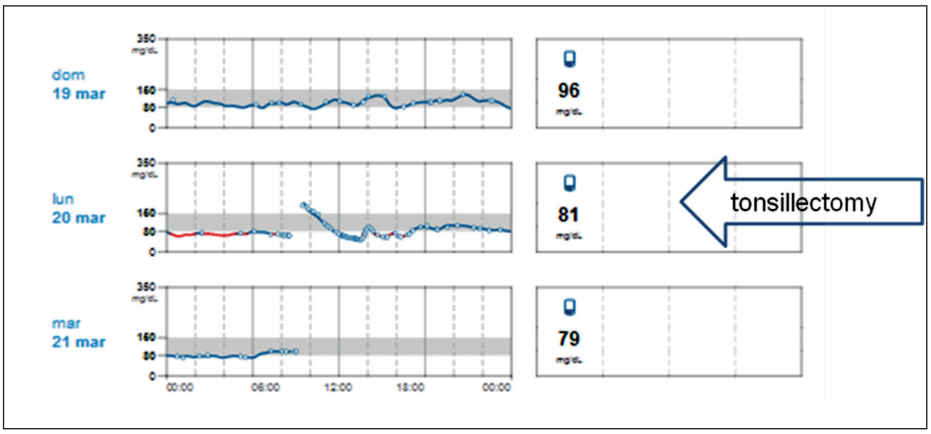

Figure 2. Interstitial glucose levels before and after tonsillectomy (March-20-2017).

it states an adequate steady basal insulin secretion (C-peptide/Glucose ratio slightly raised from 0.5 to 0.6 ng/ml, from T.0 to T4). Finally, at T.4 the measurement of C-peptide stimulated by a meal provides an adequate β-cell mass to control blood sugar levels in post-prandium[11]. Undoubtedly the carefully adopted high fiber diet that minimized high glycemic index foods could have contributed to the limited elevation of blood glucose levels after meals. The gluten-free diet does not usually reduce insulin requirements, but we don't exclude it may play a role in the modulation of inflammation and autoimmunity. Even during surgical stress both the capillary blood glucose and the interstitial glucose recorded confirmed a substantial autonomous capacity of the subject's blood glucose control (Figure 2).

Nevertheless, the exceptional clinical course observed in this child, "honeymoon" phase strongly suggests a possible role of vitamin D and Ω-3 supplemental administration. The administration of Ω-3 fatty acids has been reported to suppress synthesis of interleukin-1β (IL-1 β) and tumor necrosis factor, and vitamin D has been associated with immunomodulation and enhancement of regulatory T-cells function.

The rapid decline of β-cell function after the diagnosis of T1D is a paradigm that could be revisited today, since recent evidence shows that it is possible to delay progression of the disease. In fact, recent findings from TrialNet describe a detectable C-peptide in 93% of patients 2 years after diagnosis, and ongoing trials are testing immunosuppressive drugs that could have an effect on the progression of autoimmunity[12,13]. Nevertheless, maintenance or improvement of fasting C-Peptide 15 months after T1D onset has never been reported in young children below age 9. Unfortunately, the robust data on C-peptide secretion obtained in adults cannot be transferred to younger children, which have a different insulin secretion and many rapid patterns of C-Peptide disappearance following T1D onset. Furthermore, the immunosuppressive drugs used in adult intervention trials aren't always advisable for children because of their toxicity and side effects. Thus, the identification of potentially effective "safe therapies" is of particular interest, as it would allow for the broader inclusion of children in adequate prevention trials. These findings support the positive results of previous publications on the effect of high dose Ω-3 and Vitamin D on modulation of inflammation and immunity in autoimmune disease conditions, including T1D[13,14]. Recently a synergy between vitamin D and Ω-3 has been found also in a randomized study of pregnant women with gestational diabetes lowering the blood glucose and improving the insulin sensitivity[15].

Conclusions

This case report supports the concept that co-administration of high dose vitamin D and Ω-3 fatty acids could represent a safe and cost-effective strategy that may be of assistance to halt the progression of Type 1 Diabetes. These findings should be confirmed by randomized prospective trials and could be of assistance to define novel strategies for immune interventions in other autoimmune disease conditions.

Declaration of interest

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

References

1) Steffes MW, Sibley S, Jackson M, Thomas W. Beta-cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care 2003; 26: 832-836.
2) The Diabetes Control and Complications Trial Research Group. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. Ann Intern Med 1998; 128: 517-523.
3) Moran A, Bundy B, Becker DJ, DiMeg lio LA , Gitelman SE, Goland R, Greenbaum CJ, Herold KC , Marks JB, Raskin P, Sanda S, Schatz D, Wherrett DK, Wilson DM, Krischer JP, Skyler JS; Type 1 Diabetes TrialNet-Canakinumab Study Group, Pickersgill L, de Koning E, Zieg ler AG, Böehm B, Bade nhoop K, Schloot N, Bak JF, Pozzilli P, Mauricio D, Donath MY, Castaño L, Wägner A, Lervang HH, Perrild H, Mandrup-Poulsen T; AIDA Study Group. Interleukin-1 antagonism in type 1 diabetes of recent onset: two multicentre, randomised, double-blind, placebo-controlled trials. Lancet 2013; 38: 1905-1915.
4) Chase HP, Cooper S, Osberg I, Stene LC, Barriga K, Norris J, Eisenbarth GS, Rewers M. Elevated C-reactive protein levels in the development of type 1 diabetes. Diabetes 2004; 53: 2569-2573.
5) Chase HP, Boulware D, Rodriguez H, Donaldson D, Chritton S, Rafkin-Mervis L, Krischer J, Skyler JS, Clare-Salzler M; Type 1 Diabetes TrialNet Nutritional Intervention to Prevent (NIP) Type 1 Diabetes Study Group. Effect of docosahexaenoic acid supplementation on inflammatory cytokine levels in infants at high genetic risk for type 1 diabetes. Pediatr Diabetes 2015; 16: 271-279.
6) Norris JM, Yin X, Lamb MM, Barriga K, Seifert J, Hoffman M, Orton HD, Barón AE, Clare-Salzler M, Chase HP, Szabo NJ, Erlich H, Eisenbarth GS, Rewers M. Omega-3 polyunsaturated fatty acid intake and islet autoimmunity in children at increased risk for type 1 diabetes. JAMA 2007; 298: 1420-1428.
7) Treiber G, Prietl B, Fröhlich-Reiterer E, Lechner E, Ribitsch A, Fritsch M, Rami-Merhar B, Steigleder-Schweiger C, Graninger W, Borkenstein M, Pieber TR. Cholecalciferol supplementation improves suppressive capacity of regulatory T-cells in young patients with new-onset type 1 diabetes mellitus--A randomized clinical trial. Clin Immunol 2015; 161: 217-224.
8) Sears B. Delaying adverse health consequences of aging: the role of omega 3 fatty acids on inflammation and resoleomics. CellR4 2016; 4: e2111.
9) Sears B. Commentary – High-dose omega-3 fatty acids and vitamin D for preservation of residual beta cell mass in type 1 diabetes. CellR4 2016; 4: e2107.
10) Saisho Y. Postprandial C-peptide to glucose ratio as a marker of β cell function: implication for the management of type 2 diabetes. Int J Mol Sci 2016; 17: 744.
11) Greenbaum CJ, Beam CA, Bouware D, GitelmanSE, Gottlieb PA, Herold KC, Lachin JM, McGee P, Palmer JP, Pescovitz MD, Krause-Steirnrauf H, Skyler JS, Sosenko JM, on behalf of Type 1 Diabetes TrialNet Study Group. Fall in C-peptide during first 2 years from diagnosis evidence of at least two distinct phases From Composite Type 1 Diabetes TrialNet Data. Diabetes 2012; 61: 2066-2073.
12) Skyler JS, Pugliese A. Immunotherapy trials for type 1 diabetes: the contribution of George Eisenbarth. Diabetes Technol Ther 2013; 15 Suppl 2: S2-13-S2-20.
13) Caprio M, Infante M, Calanchini M, Mammi C, Fabbri A. Vitamin D: not just the bone. Evidence for beneficial pleiotropic extraskeletal effects. Eat Weight Disord 2017; 22: 27-41.
14) Baidal DA, Ricordi C, Garcia-Contreras M, Sonnino A, Fabbri A. Combination high-dose omega-3 fatty acids and high-dose cholecalciferol in new onset type 1 diabetes: a potential role in preservation of beta-cell mass. Eur Rev Med Pharmacol Sci 2016; 20: 3313-3318.
15) Jamilian M, Samimi M, Ebrahimi FA, Hashemi T, Taghizadeh M, PhD, Razavi M, Sanami M, Asemi Z. The effects of vitamin D and omega-3 fatty acid co-supplementation on glycemic control and lipid concentrations in patients with gestational diabetes. J Clin Lipidol 2017; in press; http://dx.doi.org/10.2016/j.jact.2017.01.011.