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Editorial:
Can high-dose omega-3 fatty acids and high-dose vitamin D3 (cholecalciferol) prevent type 1 diabetes and sustain preservation of beta-cell function after disease onset?

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Modulation of inflammation and immunity could prevent, delay or halt the progression of autoimmunity in Type 1 Diabetes (T1D). Vitamin D and omega-3 long chain polyunsaturated fatty acids (LCPUFA) could attain such modulation[1,2]. Contemporary administration of high dose vitamin D and omega-3 PUFA was recently tested in pilot clinical trials to determine if progression of autoimmunity could be halted following T1D onset[3-5]. The rationale for this combination strategy is that Omega 3 LCPUFA (eicosapentaenoic acid, EPA, and docosahexaenoic acid, DHA) and Vitamin D can have beneficial effects not only on inflammatory markers, but also on immunomodulation-increasing regulatory T cells (Tregs), while decreasing Th17 cells and Th1/Th2 ratios[1,2]. In contrast, arachidonic acid (AA) showed an opposite effect on Tregs, Th17 cells and Th1/Th2 ratios. A very high AA/EPA ratio has been observed in subjects diagnosed with T1D and other autoimmune conditions (F.Cadario and C. Ricordi, personal communication and manuscript in preparation). This may reflect a diet-related pro-inflammatory baseline condition. This condition could predispose to or trigger the subsequent development of autoimmunity. In this direction, anti-inflammatory nutrition could have an important synergistic role, in addition to Vitamin D and Omega 3 LCPUFA supplementation, as already explored by Cadario and collaborators in pilot and ongoing clinical trials. If the initial results will be confirmed, similar strategies to reduce exogenous insulin requirements and promote persistence of residual endogenous insulin production could be of assistance to reduce the risk of complications in T1D[6-9].

The recently reported maintenance of C-peptide production above baseline for over 2 years post diagnosis[5] is very encouraging and warrants randomized controlled trials. Additional mechanistic studies, including assessment of cytokine profiles and inflammatory markers, will be required to determine the effect of the proposed combination therapy for prevention of T1D, as well as for preservation of beta-cell mass and function in patients with recent onset of T1D.

Because of the significant interest raised by these preliminary results, the 1st PreDiRe T1D (Preventing Disease and its Recurrence in Type 1 Diabetes) Symposium was organized to discuss initial results, possible alternatives and complementary combination strategies, to eventually generate consensus on the possibility to extend these interventions to disease prevention strategies (Figure 1).

In summary, the use of combination high-dose omega-3 LCPUFA and high-dose vitamin D_3 (Cholecalciferol) therapy has been well tolerated in pilot trials and may have beneficial effects on the maintenance of beta-cell function before and after T1D onset. Randomized controlled trials are required to validate this hypothesis and initial clinical results. Similar combination therapies aimed at modulating inflammation and promoting immunomodulation may be tested to prevent, reverse, or halt the progression of other autoimmune diseases.

In this issue of CellR4, we share the protocol for the Poseidon Clinical Trial (Pilot Study of OMEGA-3 and Vitamin D in High-Dose in Type I Diabetic Patients, ClinicalTrials.gov Identifier: NCT03406897), recently allowed by the FDA. Its availability in open access could facilitate implementation by interested physicians and centers, and could stimulate the use of a similar design in the context of other autoimmune diseases.

Figure 1.

References

1. 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.
2. Bi X, Li F, Liu S, Jin Y, Zhang X, Yang T, Dai Y, Li X, Zhao AZ. ω-3 polyunsaturated fatty acids ameliorate type 1 diabetes and autoimmunity. J Clin Invest 2017; 127: 1757-1771.
3. 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.
4. Cadario F, Savastio S, Rizzo AM, Carrera D, Bona G, Ricordi C.Can Type 1 diabetes progression be halted? Possible role of high dose vitamin D and omega 3 fatty acids. Eur Rev Med Pharmacol Sci 2017; 21: 1604-1609.
5. Cadario F, Savastio S, Ricotti R, Rizzo AM, Carrera D, Maiuri L, Ricordi C. Administration of vitamin D and high dose of omega 3 to sustain remission of type 1 diabetes. Eur Rev Med Pharmacol Sci 2018; 22: 512-515. DOI: 10.26355/eurrev_201801_14203.
6. Panero F, Novelli G, Zucco C, Fornengo P, Perotto M, Segre O, Grassi G, Cavallo-Perin P, Bruno G. Fasting plasma C-peptide and micro- and macrovascular complications in a large clinic-based cohort of type 1 diabetic patients. Diabetes Care 2009; 32: 301-305.
7. Sima AA, Zhang W, Sugimoto K, Henry D, Li Z, Wahren J, Grunberger G. C-peptide prevents and improves chronic Type I diabetic polyneuropathy in the BB/Wor rat. Diabetologia 2001; 44: 889-897.
8. Johansson BL, Sjoberg S, Wahren J. The influence of human C-peptide on renal function and glucose utilization in type 1 (insulin-dependent) diabetic patients. Diabetologia 1992; 35: 121-128.
9. Johansson BL, Linde B, Wahren J. Effects of C-peptide on blood flow, capillary diffusion capacity and glucose utilization in the exercising forearm of type 1 (insulin-dependent) diabetic patients. Diabetologia 1992; 35: 1151-1158.