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Letter to the Editor

36-month follow-up of a pure sensory mononeuritis multiplex and IgG1 deficiency improved after treatment with sitagliptin and Vitamin D3

Dear Editor,

Our group has previously published in this Journal a unique case report showing that co-administration of sitagliptin and vitamin D3 led to an increase in IgG1 (immunoglobulin G subclass 1) levels and remarkable clinical benefits in terms of improvement of peripheral neuropathy and recurrent candidiasis in a 51-year-old man with pure sensory mononeuritis multiplex (MNM) associated with IgG1 deficiency[1]. In the present letter, we are pleased to add relevant information on the clinical evolution of our case and broaden the discussion on the potential beneficial effects of combination therapy with sitagliptin plus vitamin D3 (cholecalciferol). Surprisingly, the last protein electrophoresis (performed 36 months after the initiation of the combination therapy) showed normal gamma globulin levels. Moreover, we observed a normalization of IgG1 levels, which were within the lower reference limits (results were confirmed by two consecutive measurements):

- Gamma globulins: 0.79 g/dL, 12.2% (reference range: 0.66-1.5 g/dL; percentage: 11.1-18.8%)
- IgG1 levels: 4500 mg/L (reference range for adults: 4050-10110 mg/L)
- IgG2 levels: 3570 mg/L (reference range for adults: 1690-7860 mg/L)
- IgG3 levels: 170 mg/L (reference range for adults: 110-850 mg/L)
- IgG4 levels: 368 mg/L (reference range for adults: 30-2010 mg/L)

What may have occurred? Mahmoudi et al[2] demonstrated that patients with common variable immunodeficiency exhibit significantly higher serum levels of soluble CD26 (sCD26, which is also referred to as soluble DDP-4) compared to sex-matched controls, suggesting that these patients have a polarized immune response towards the T-helper 1 (Th1)-like pro-inflammatory phenotype. In our case report[1], the use of dipeptidyl peptidase-4 (DDP-4) inhibitor sitagliptin (at an initial dose of 300 mg/day, followed by a maintenance dose of 200 mg/day) may have allowed for a more sustained inhibition of sCD26, thus inducing an anti-inflammatory/regulatory T-cell phenotype and concurrently improving immunoglobulin synthesis by activated B cells and plasma cells. Handa et al[3] have recently reported a case of *pemphigus vulgaris* in a patient with type 2 diabetes treated with sitagliptin. Authors showed that the titer of anti-desmoglein (DSG) 3 antibody immediately decreased after the cessation of sitagliptin treatment[3], suggesting that DPP-4 inhibition may facilitate immunoglobulin production. Moreover, Chambers et al[4] have recently showed that high-dose vitamin D3 supplementation (6,400 IU/day) for 14 weeks in vitamin D-insufficient older adults led to a significant increase in the response to cutaneous varicella zoster virus antigen challenge, accompanied by a decrease in inflammatory monocyte infiltration with a concomitant increase of T-cell recruitment to the site of antigen challenge in the skin. These findings suggest that vitamin D supplementation is able to boost antigen-specific immunity in older adults with a low vitamin D status. In addition, high-dose vitamin D3 supplementation (40,000 IU once/week for 24 weeks) was associated with a significant reduction in neuropathy severity, accompanied by a significant improvement of cutaneous microcirculation and by a significant decrease of inflammatory markers in patients with type 2 diabetes and peripheral neuropathy[5]. Given the unexpected evolution of our case, future prospective studies are warranted to establish the efficacy of combination therapy with DPP-4 inhibitors and vitamin D3 in different clinical settings such as peripheral neuropathies, immunodeficiency diseases and autoimmune disorders (including autoimmune neuropathies).

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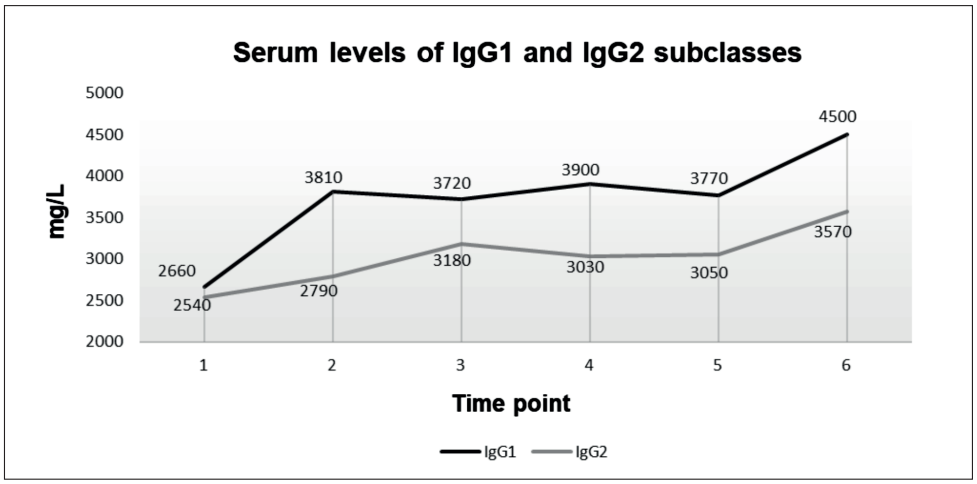

Figure 1. Serum levels of IgG1 (reference range for adults: 4050-10110 mg/L) and IgG2 (reference range for adults: 1690-7860 mg/L) subclasses before (time point 1) and after (time point 2 = 3 months, time point 3 = 6 months, time point 4 = 12 months, time point 5 = 24 months, time point 6 = 36 months) the initiation of combination therapy with sitagliptin plus vitamin D3.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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