Editorial: Autoimmunity, Obesity, and Ghrelin

There is increasing evidence that autoimmunity is intimately related to obesity [1] and the orexigenic hormone, ghrelin may play an important role in the pathogenesis and maintenance of obesity through its central effects on the endocannabinoid system [2].

The incidences of obesity and autoimmunity have been rising worldwide in parallel for several decades [1] and a number of the adipokines secreted by adipose tissue and macrophages embedded within adipose tissue seem to play a role in the pathogenesis of an increasing number of autoimmune disorders including: rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, inflammatory bowel disease, psoriasis, type 1 diabetes mellitus, and autoimmune thyroid disease. These adipokines include:leptin, resistin, and visfatin. Levels of a number of inflammatory cytokines, including interleukins 1 and 6 and tumor necrosis factor-α are highly correlated with obesity and have been implicated in the pathogenesis of a number of autoimmune disorders. Many current biologic therapies for autoimmune disorders as diverse as Graves' opthalmopathy, psoriasis, rheumatoid arthritis, and Crohn's disease are based on inhibition of tumor necrosis factor-α.

Vitamin D deficiency/insufficiency has been implicated in the pathogenesis of many autoimmune disorders [3], an association that was suspected from the time the effect of sunlight on Vitamin D synthesis was first understood and it was recognized that the incidence of multiple sclerosis (MS) was proportional to the distance from the equator in which people spend their early years. In animal models Vitamin D supplementation has been therapeutically effective in allergic encephalomyelitis, inflammatory bowel disease, Type 1 diabetes mellitus, systemic lupus, collagen-induced arthritis, and Hashimoto's thyroiditis [3]. In patients with undifferentiated connective tissue disease (UCTD) mean serum 25-OH-Vitamin D levels were significantly lower than in matched controls and 21.7% of the patients with both Vitamin D deficiency and UTCD developed a defined autoimmune connective tissue disease including: mixed connective tissue disease, systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), and Sjögren's syndrome. The serum Vitamin D levels in the latter patients were significantly lower than in those who remained with UTCD [3].

Vitamin D deficiency was reported in 27% of Crohn's disease patients and 15% of ulcerative colitis patients. In IL-10 knockout rats Vitamin D deficiency accelerated the deterioration of inflammatory bowel disease (IBD) with earlier onset of diarrhea and inanition and a higher mortality rate. Supplementation with calcitriol prevented symptom development and disease progression [3].

The risk of developing MS was reported to be reduced by 40% in white patients with high vitamin D intake, but this benefit was not observed in Black or Latino patients. In experimental MS vitamin D administration reduced disease progression and prevented autoimmune allergic encephalitis [3].

In NOD mice Vitamin D deficiency accelerated the development of Type 1 diabetes mellitus (T1DM). In the same model, supplementation with calcitriol before the development of a pancreatic mononuclear infiltrate reduced insulinitis and prevented diabetes [3].

In an open label study of 19 patients with RA treated with alfacalcidiol in addition to standard disease modifying therapy for 3 months 89% of patients experienced reduced disease severity with 45% experiencing complete remission and the remainder of the responders achieving partial remission [3]. An inverse relationship has been reported between RA disease activity and the concentrations of Vitamin D metabolites. In the pre-treatment state an inverse relationship was observed between serum 25-(OH)-vitamin D and the number of painful joints, DAS28, and HAQ. Each increase of 10 ng/dl in serum 25-(OH)-vitamin D was associated with a 0.3 point reduction in DAS28 and a 25% reduction in CRP [3].

In SLE patients it was shown that lower serum 25-(OH)-vitamin d levels were associated with higher SLEDAI (disease activity) in a Brazilian cross-sectional study [3].

Patients with alopecia areata or alopecia universalis have reduced expression of the Vitamin D receptor (VDR) due to decreased expression of Wnt/β-catenin which render them insensitive to even otherwise adequate circulating levels of Vitamin D [4]. Vitamin D levels are significantly lower in the alopecia areata and universalis patients than in matched controls despite the fact that more skin surface area is potentially available for sun exposure in the former [5].

Cutaneous psoriasis and vitiligo are successfully treated with topical Vitamin D analogues [6,7].

Vitamin D deficiency/insufficiency is more common in obesity [8] because Vitamin D is stored in adipose tissue, thereby lowering serum levels. In addition, overweight and obese individuals are less likely to exercise outdoors or to expose much of their skin to sunlight.

Both obesity and Vitamin D deficiency/insufficiency contribute to insulin resistance [9], which is a low grade, chronic inflammatory state, characterized by increased circulating and paracrine concentrations of many of the same adipokines and cytokines involved in the pathogenesis of autoimmune disorders.

While ghrelin, by stimulating appetite and leading to weight gain, indirectly contributes to an inflammatory state, the direct effect of ghrelin is anti-inflammatory [10].

The article in this issue, The Effect of Exercise on Plasma Ghrelin in Obesity, sheds important light on the frequent observation that maintenance of weight loss is more easily accomplished when exercise is combined with nutritional intervention than with nutritional intervention alone. Rather than simply being 1+1=2, less caloric intake + more caloric expenditure=more weight loss, the combined effect of exercise + diet is more like !+!=3, since ghrelin is reduced by this combined approach, presumably resulting in decreased appetite and further weight loss.

Lastly, a direct effect of obesity, increased weight bearing, results in more joint destruction in weight bearing joints, whether the cause of joint damage is osteoarthritis, gout (also obesity-related) pseudogout, autoimmune, or infectious.

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