LETTERS TO THE EDITOR

Frequent Occurrence of Hypogonadotropic Hypogonadism in Type 2 Diabetes

To the editor:

Dhindsa et al. (1) recently described the frequent occurrence of hypogonadotropic hypogonadism in type 2 diabetes mellitus and the progressive fall in total, bioavailable, and free testosterone levels with increase in body mass index. They considered possible mechanisms including increased plasma levels of proinflammatory cytokines. Another practically important mechanism of hypogonadism in individuals with type 2 diabetes is obstructive sleep apnea (OSA). In one study (2), the prevalence of severe OSA in diabetic hypertensive men was 36%, significantly higher than the prevalence of 14.5% in normoglycemic hypertensive subjects. OSA is also associated with other insulin-resistant states, occurring 30 times more commonly in women with polycystic ovary syndrome than in matched controls (3). OSA is associated with hypogonadotropic hypogonadism, with improvements in testosterone levels after intervention with continuous positive airway pressure (CPAP) and surgery (4–6). CPAP treatment also improves insulin sensitivity (7). Dhindsa et al. also raise the question of testosterone replacement in hypogonadal men with type 2 diabetes, citing the need for prospective randomized trials to answer this question. Before entering such trials, it would be important that OSA be excluded as a cause of hypogonadism, not only because CPAP treatment may resolve their hypogonadism and symptoms, but also because exogenous testosterone may precipitate or aggravate OSA in susceptible individuals (8, 9). Hemochromatosis would also need to be excluded, given that it may be complicated by hypogonadotropic hypogonadism and type 2 diabetes mellitus.

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References
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Authors’ Response: Frequent Occurrence of Hypogonadotropic Hypogonadism in Type 2 Diabetes

To the editor:

We thank Dr. Morton (1) for his comments on our recent article in JCEM (2). Whereas obstructive sleep apnea (OSA) is associated with both type 2 diabetes and hypogonadotropic hypogonadism, OSA is also associated with increased concentration of inflammatory cytokines, such as C-reactive protein and IL-6, compared with body mass index-matched controls (3). Treatment with continuous positive airway pressure decreases the level of cytokines in these patients (3). It is therefore possible that the hypogonadotropic hypogonadism of OSA is mediated by cytokines.

Comorbidities associated with type 2 diabetes can contribute to the state of hypogonadism, and we agree that patients should be carefully evaluated for reversible or treatable causes of hypogonadism before considering testosterone replacement. However, it is worth mentioning here that neuron-specific insulin receptor knockout mice exhibit hypogonadotropic hypogonadism (4). Thus, it is possible that the state of insulin resistance is independently associated with hypogonadotropic hypogonadism, which may be the result of a hypothalamic defect in GnRH secretion.

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