assays for serum and plasma. The nonsignificant differences between cutoffs for serum and plasma and between assays are encouraging regarding the ease of interpretation by clinicians and laboratories. Also encouraging were improvements in the analytical sensitivity of these newer-generation assays. Interestingly, only 3 samples were identified as above the 99th percentile by all 3 assays. The mechanisms responsible for this lack of agreement are not known, but antibody differences and the cTnI epitopes recognized on the different circulating cTnI forms are the most likely causes (4). The discrepancies between assays in regard to individual samples identified as above the 99th percentile raise questions as to whether healthy individuals can be better characterized for use in defining reference limits. A prototype cTnI assay has shown sensitivity to 0.001 μg/L with gaussian-distributed results (3). As assays become more sensitive, increasing numbers of MIs will be detected, but an increased prevalence of myocardial injury not related to ischemic pathologies will also be seen (5). The latter may complicate schemes for selecting healthy individuals when defining reference limits. The 99th percentile reference cutoffs derived here in 2 large apparently healthy populations for 3 2nd-generation cTnI assays should prove useful in clinical practice.

Grant/funding support: We thank Sheryl Sullivan, Jody Parsells, Michele Steinmann, and Theresa Tubbs (all from Ortho-Clinical Diagnostics) for their assistance and for the partial financial support provided by OCD for this study. Financial disclosures: F.S.A. has both consulted for and received research grant support from Abbott, Beckman, and Ortho-Clinical Diagnostics.

References


3. Apple FS, Jesse RL, Newby LK, Wu AHB, Chris


Fred S. Apple* MaryAnn M. Murakami
Hennepin County Medical Center Minneapolis, MN

*Address correspondence to this author at: Hennepin County Medical Center, Clinical Laboratories P4, 701 Park Ave., Minneapolis, MN 55415. Fax 612-904-4229; e-mail apple004@umn.edu.

DOI: 10.1373/clinchem.2007.087718

Increased Human Chorionic Gonadotropin Due to Hypogonadism after Treatment of a Testicular Seminoma

To the Editor:
Alfa-fetoprotein (AFP) and serum human chorionic gonadotropin (hCG) are reliable markers of testicular cancer, and treatment of a relapse is often initiated on the basis of marker increase alone. Slightly increased hCG concentrations have occasionally been misinterpreted to indicate a relapse, leading to inappropriate chemotherapy (1). We describe a seminoma patient in whom a relapse was suspected 10 years after therapy because the patient had increased hCG concentrations found to be caused by hypogonadism-induced pituitary hCG secretion.

A 27-year-old man underwent left radical orchitectomy and adjuvant radiotherapy for stage I testicular seminoma in the early 1990s at Helsinki University Central Hospital. The patient had a preoperative serum hCG of 0.5 IU/L (upper reference limit 0.7 IU/L) and AFP <1 IU/L (upper reference limit 9 IU/L). Atrophy of the nonmalignant testicle was suspected on the basis of preoperative ultrasound findings, but the serum testosterone concentration, 10.2 nmol/L, was within the reference interval (10–38 nmol/L), whereas follicle-stimulating hormone (FSH) concentration was increased, at 28 IU/L (reference interval 1–7 IU/L), suggesting partially compensated hypogonadism. One year later, examinations revealed a subnormal serum testosterone concentration and azoospermia. At this point the patient’s hCG had increased to 3.7 IU/L, FSH to 50 IU/L, and luteinizing hormone (LH) to 20 IU/L (reference interval 1–9 IU/L). Testosterone replacement therapy was administered, but the patient discontinued its use within a few weeks. During the next 2.5 years, when he did not receive replacement therapy, the serum concentration of hCG remained slightly increased. Intramuscular testosterone replacement therapy was reinstated 3.5 years after surgery, and serum concentrations of hCG, FSH, and LH normalized. Approximately 9 years after surgery, the patient stopped the testosterone medication because of acne. His hCG gradually increased to 4.5 IU/L, and this finding led to suspicion of a tumor relapse. Serum testosterone was 2.9 nmol/L, FSH 62 IU/L, and LH 31 IU/L, indicating hypogonadism. Testosterone therapy was reinstalled and hCG, FSH, and LH concentrations decreased rapidly (Fig. 1). Follow-up consisting of radiographic imaging, serum tumor marker determinations, and clinical examinations was discontinued a few months later, almost 11 years after primary therapy. Apart from the increasing serum hCG concentration, there were no other signs of relapse during follow-up.

The pituitary is a source of hCG, and low serum concentrations can be detected with sensitive assays in most healthy men and women (2, 3).
hCG concentrations increase with age, and with our assay values up to 10 IU/L can be observed in postmenopausal women (2). This increase is caused by increased pituitary gonadotropin secretion and is suppressed by hormone replacement therapy (3). hCG concentrations also increase in elderly men, but values exceeding 2 IU/L are rare (2). Testicular cancer and its treatment, particularly cytotoxic chemotherapy, may cause gonadal suppression leading to hypogonadism, which is mostly transient (4) and may lead to increased serum concentrations of LH and FSH, which normalize with testosterone replacement therapy (1). Increased hCG immunoreactivity after treatment of testicular cancer has been described previously but was ascribed to cross-reaction of LH in the hCG assay rather than to hCG itself (1). Cross-reaction is not a problem with assays using highly specific monoclonal antibodies. We determined hCG in serum with a highly sensitive time-resolved immunofluorometric assay (PerkinElmer Wallac) (analytical and functional sensitivities 0.27 IU/L and 0.5 IU/L, respectively) with negligible cross-reactivity with LH (2). Thus we determined that the increased serum hCG was caused by pituitary hCG secretion in response to hypogonadism.

With our hCG-assay the upper reference limit in healthy males younger than 50 years is 0.7 IU/L and in men older than 50 years it is 2.1 IU/L (2). In our patient, the hCG concentration exceeded this limit, although it did not exceed 5 IU/L, which is a commonly used decision limit. Concentrations up to 32 IU/L have been observed in postmenopausal, hypogonadal women (5) but not in men, possibly because of a physiological difference between men and women or differences in calibration and broader assay specificity, i.e., detection of hCG and the free beta subunit of hCG together. With other assays, hCG >5 IU/L will most likely be observed in male patients with severe hypogonadism.

The case we describe shows that a moderate increase of serum hCG in men treated for testicular cancer are not always caused by cancer relapses.

Grant/funding support: Finska Läkaresällskapet.
Financial disclosures: None declared.

References

Anna Lempiainen1 Kristina Hotakainen1 Carl Blomqvist2 Henrik Alfthan1 Ulf-Håkan Stenman*
1 Departments of Clinical Chemistry and Oncology Helsinki University Central Hospital Helsinki University Helsinki, Finland
2 Address correspondence to this author at: Ulf-Håkan Stenman, Helsinki University Central Hospital, Biomedicum Helsinki, Rm. A423a, Haartmaninkatu 8, P.O. Box 700, FIN-00029 Helsinki, Finland. Fax 358-9-47171737; e-mail ulf-hakan.stenman@hus.fi.

DOI: 10.1373/clinchem.2007.088518