High serum testosterone concentrations in a diabetic woman with end-stage renal disease

Concentraciones séricas elevadas de testosterona en una mujer con diabetes e insuficiencia renal terminal

A simultaneous pancreas–kidney transplant (SPK) is indicated in patients with type 1 diabetes (T1D) and end-stage renal disease. In patients with type 2 diabetes (T2D) it is not generally indicated, because steroid and immunosuppression treatment exacerbates insulin resistance and weight gain. However, in carefully selected patients with T2D who are not obese, SPK results may be similar to those observed in T1D. Experiences with other types of diabetes are seldom reported although one study showed a favorable outcome in monogenic diabetes due to mutations in the HNF1A gene.

The potential candidates for an SPK should be evaluated for any existing neoplasias which would contraindicate the transplant. In women with hyperandrogenism, tumors are rarely the underlying cause, but ruling them out is considered necessary, especially in cases in which clinical and analytical data, such as notably high levels of androgens, are observed.

We report the case of a patient with diabetes and end-stage renal disease who presented high serum testosterone levels during pre-transplant evaluation.

A 32-year-old woman with a 16-year history of diabetes on insulin treatment presented moderate diabetic retinopathy and end-stage diabetic nephropathy for the previous 3 years. Several members of her family had also been diagnosed with diabetes: her father was diagnosed at the age of 30, received insulin treatment and had renal impairment; her mother, her maternal grandmother and a paternal aunt were on hypoglycemic oral agents.

The patient used pre-mixed insulins (30/70) at breakfast and dinner and aspart insulin at lunch. This regime was modified to a basal-bolus scheme with glargine and aspart insulins. She also took candesartan, atorvastatin, calcitriol, omeprazole, amitriptyline and flunazine.


She was referred for evaluation for an SPK. She reported increased hair growth over the previous two years, but no menstrual disturbances. She had never been pregnant. A physical examination revealed mild hirsutism (Ferriman–Gallwey 8), moderate frontal alopecia, hypotrophic breasts and normal external genitalia. Laboratory analysis revealed an HbA1c value of 6.5%, C-peptide (Cp) 3.79 ng/mL (normal values [N] 1.1–4.4), and negative anti-glutamic acid decarboxylase, anti-tyrosine phosphatase and anti-insulin antibodies. Genetic testing proved mutation p.R200W heterozygosis “non-synonymous-coding” on exon 3 of gene HFN1A.

Hormonal evaluation was as follows: total testosterone (TST) (folicular phase) 6.13 ng/mL (N in women <0.8 ng/mL), 17-OH progesterone 2.4 ng/mL (N 1.0–2.4), FSH 2.5 mU/mL (N 1.7–21.5), LH 7.1 mU/mL (N 1.0–12.6), androstendione 4.7 ng/mL (N 0.8–2.4), DHEA-S 4906 ng/mL (N 609–3400). Serum albumin and serum sex-hormone binding globulin (SHBG) levels were normal (4.4 g/dL and 28 nmol/L, respectively). Serum proteinogram was also normal, except for a mild increase in polyclonal gamma fraction: 1.5 g/dL (N 0.7–1.3).

Serial dilutions for TST were: 50% 2.0 ng/mL and 25% 1.37 ng/mL. These levels were confirmed by three different analyses in our laboratory using immunoassay Elecsys® Testo II (Siemens Healthcare Diagnostics Inc., USA): 6.99, 7.16 and 9.36 ng/mL. The result from another laboratory which used another immunoassay (Immulite 2000®: Siemens Healthcare Diagnostics Inc., USA) was 7.2 ng/mL. Free testosterone levels were evaluated in an external laboratory with radioimmunoeanalysis (RIA Coat-A-Count Free Testosterone, Siemens Healthcare Diagnostics Inc., USA) in two different samples, showing normal results: 1.4 and 3.0 pg/mL (N 0.7–3.6).

Imaging techniques (abdominal ultrasonography, magnetic resonance [MRI] and computerized tomography angiography [CTA]) did not show evidence of alterations in the ovaries or adrenal glands. Transvaginal ultrasonography, however, showed a 13-mm mixed solid and cystic lesion in the central portion of the left ovary, with increased peripheral vascularization, although this lesion was not confirmed on a second evaluation. Tumor markers were normal.

Due to the presence of only mild androgenism and the absence of morphologic alterations, other options were considered. Serum testosterone levels were evaluated before (7.47 ng/mL) and after (7.1 ng/mL) hemodialysis. Ruling out the possibility of existing neoplasias was necessary before proceeding to the SPK, so catheterization of the ovarian venous sinuses was performed, which ruled out an
complement levels may be altered. Therefore, there is some evidence suggesting that genetic diabetes may affect hepatic protein production.

In summary, our patient presented mild hirsutism, regular menses, significant high levels of TST and normal free testosterone, all of which determined a convoluted differential diagnosis. Given the discrepancy between symptoms and laboratory results, the suspicion of analytical assay interference was high, as this has been previously reported, for example, in cases involving heterophilic antibodies, rheumatoid factor, several drugs, conjugated steroids, immunoglobulins, etc. All currently available direct immunoassays may provide falsely elevated levels of testosterone in certain samples. These interferences are mostly detected in women, since higher reference values in men may disguise their identification. The reason for the interference remains unidentified in the majority of cases. A recent study described assay-interference in samples of women with renal impairment and hemodialysis using the same method as the one we used in our laboratory. However, serum androgen levels did not reach the markedly increased ones reported in our case.

When assay interference is suspected, samples may be reanalyzed using other methods. Nevertheless, the best option is to use a reference method. LC–MS/MS has proved to be a highly specific technique for the evaluation of serum testosterone and is useful in cases of low concentrations, such as those found in women and children. In recent years, this method has become increasingly available in clinical laboratories working with steroid hormones, since immunoassays are not usually sensitive enough to detect variations <1 ng/mL.

The evaluation of pretransplant samples from our patient using LC–MS/MS confirmed that testosterone serum concentrations had always been normal and that, therefore, the elevated levels previously found using an immunoassay method were in fact due to analytical interference. This interference disappeared after the SPK, so we believe that it was related to the presence of end-stage renal disease or to hemodialysis. If an appropriate laboratory method had been used from the beginning, invasive and costly diagnostic procedures could have been avoided, and the SPK could have been performed earlier.

References

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