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REVIEW ARTICLE

A systematic review of methods for quantifying serum testosterone in patients with prostate cancer who underwent castration☆

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Abstract

Background: The clinical practice guidelines recommend measuring serum testosterone in patients with prostate cancer (PC) who undergo castration. The serum testosterone concentration should be <50 ng/dL, a level established by using a radioimmunoassay method. The use of chemiluminescent immunoassays (IA) has become widespread, although their metrological characteristics do not seem appropriate for quantifying low testosterone concentrations. The objective of this review is to analyze the methods for quantifying testosterone and to establish whether there is scientific evidence that justifies measuring it in patients with PC who undergo castration, through liquid chromatography attached to a mass spectrometry in tandem (LC–MSMS).

Material and methods: We performed a search in PubMed with the following MeSH terms: measurement, testosterone, androgen suppression and prostate cancer. We selected 12 studies that compared the metrological characteristics of various methods for quantifying serum testosterone compared with MS detection methods.

Results: IAs are standard tools for measuring testosterone levels; however, there is evidence that IAs lack accuracy and precision for quantifying low concentrations. Most chemiluminescent IAs overestimate their concentration, especially below 100 ng/dL. The procedures that use LC–MSMS have an adequate lower quantification limit and proper accuracy and precision. We found no specific evidence in patients with PC who underwent castration.

Conclusions: LC–MSMS is the appropriate method for quantifying low serum testosterone concentrations. We need to define the level of castration with this method and the optimal level related to better progression of the disease.

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PALABRAS CLAVE
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Métodos para cuantificar la testosterona sérica en pacientes con cáncer de próstata sometidos a castración: una revisión sistemática

Resumen

Introducción: Las guías de práctica clínica recomiendan determinar la testosterona sérica en pacientes con cáncer de próstata (CP) sometidos a castración. Su concentración debe ser inferior a 50 ng/dL, nivel establecido utilizando un método de radioinmunoanálisis. Actualmente el uso de inmunoanálisis (IA) quimioluminiscentes se ha generalizado, aunque sus características metrológicas no parecen adecuadas para cuantificar concentraciones bajas de testosterona. El objetivo de esta revisión es analizar los métodos de cuantificación de testosterona y establecer si existe evidencia científica que justifique determinarla, en pacientes con CP sometidos a castración, mediante cromatografía líquida acoplada a espectrometría de masas en tándem (LC-MSMS).

Material y métodos: Se ha realizado una revisión en PubMed con los términos MeSH: *measurement, testosterone, androgen suppression* y *prostate cancer*. Se seleccionaron 12 estudios que comparaban las características metrológicas de diversos métodos para cuantificar testosterona sérica respecto a métodos de detección con MS.

Resultados: Los IA son una herramienta común para la medición de la concentración de testosterona; sin embargo, existe evidencia de que carecen de exactitud y precisión para cuantificar concentraciones bajas. La mayoría de los IA quimioluminiscentes sobrestiman su concentración, especialmente por debajo de 100 ng/dL. Los procedimientos que utilizan LC-MSMS poseen un límite inferior de cuantificación adecuado y una correcta exactitud y precisión. No hemos encontrado evidencia específica en pacientes con CP sometidos a castración.

Conclusiones: La LC-MSMS es el método adecuado para cuantificar concentraciones bajas de testosterona sérica. Es necesario definir el nivel de castración con este método y el nivel óptimo que se relaciona con la mejor evolución de la enfermedad.

Introduction

Prostate cancer (PCa) is the malignant tumor most frequently diagnosed among men in industrialized countries.[1] Their hormonodependence was demonstrated in 1941 by Huggins and Hodges.[2] Since then, androgen deprivation by castration is the standard treatment when the disease is advanced and medical castration by analogues or antagonists of luteinizing hormone-releasing hormone is the most frequently used.[3]

Castration involves a rapid and intense reduction of serum testosterone levels, with persistence only of its adrenal source which, in normal conditions, represents between 2 and 4% of its overall concentration.[4] This reduced concentration of testosterone, called castration, was established at 50 ng/dL by the Food and Drug Administration in the early eighties, based on measurements made in patients with PCa who underwent orchiectomy, and corresponded to the minimum quantifiable level (LOQ) of the radioimmunoassays (RIAs) used at that time.[5] Since then, this level has been used by regulatory agencies to evaluate the efficacy of any product whose objective was castration and, in addition, clinical practice guidelines consider it to diagnose castration resistance and evaluate the efficacy of the treatment.[3]

In the year 2000, Oefelein et al. redefined the castration level of testosterone at 20 ng/dL, using the new chemiluminescent assays (CLIA) whose LOQ was lower.[6] In 2007, Morote et al., also using a CLIA, placed the level of castration testosterone with a clinical impact at 32 ng/dL.[7]

Based on some studies conducted in the early 2000s, which revealed the inaccuracy of the RIA or CLIA methods to quantify testosterone, especially at low concentrations,[8,9] in 2007 the Endocrine Society together with the Center for Disease Control and Prevention were positioned recommending the measurement procedures that use mass spectrometry (MS) as a detection method, after separation by liquid or gas chromatography (LC/GC), especially in children and women.[10] Despite this recommendation, the testosterone determinations are currently performed mostly with CLIA incorporated in automated platforms because they are fast and cheap methods; however, their accuracy and reproducibility seem inadequate, especially to quantify low levels.[11]

The aim of this review was to analyze the methods of quantifying serum testosterone and establish the scientific evidence that justifies their determination, in PCa patients undergoing castration, using LC–MSMS.

Acquisition of scientific evidence

We have carried out a systematic review of the literature following the indications of the guideline Preferred Reporting Items for Systematic Review and Meta-analyses (PRISMA).[12] The selection criteria for the identification of useful publications for this review were: (1) that they were studies that measured the concentration of testosterone in serum, (2) that they analyzed the measurement of testosterone by different procedures, and (3) that they compared the metrological characteristics of these procedures. A systematic search was made in the PubMed database, between 1980 and 2016, including the search terms of the Medical Subject Headings: measurement, testosterone, androgen suppression, and prostate cancer. In addition, the manual search of those articles referenced in potentially eligible reviews was carried out.