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REVIEW ARTICLE

Behavior of total and free serum testosterone as a predictor for the risk of prostate cancer and its aggressiveness☆

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Abstract

Context: Serum testosterone is mostly bound to the sex hormone-binding globulin and albumin. A small metabolically active part is present in the form of free testosterone (FT). The relationship between serum total testosterone (TT) levels and prostate carcinogenesis is debated. Our hypothesis is that the serum FT concentration is more closely associated with the risk of prostate cancer (PC) and its aggressiveness than TT.

Objective: To analyze the scientific evidence that relates serum TT and/or FT levels with the diagnosis of PC and its aggressiveness.

Acquisition of evidence: A systematic review was conducted in PubMed up to January 2015 using the following mesh terms: prostate cancer, sex hormone, androgen, testosterone and free testosterone.

Synthesis of the evidence: We found 460 publications, 124 of which were reviewed to analyze the evidence. The relationship between serum TT levels and the diagnosis of PC and its aggressiveness is highly heterogeneous. The variability in the design of the studies, the quantification methods and other variables could explain this heterogeneity. In a number of studies that evaluated the estimated or measured FT, the evidence remains equally conflicting.

Conclusions: Based on the current evidence, we cannot recommend the measurement of serum TT and/or TL levels for the diagnosis of PC or for assessing its aggressiveness.

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PALABRAS CLAVE
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Comportamiento de la testosterona total y libre en suero como predictores del riesgo de cáncer de próstata y de su agresividad

Resumen

Contexto: La testosterona en suero está unida mayoritariamente a la hormona transportadora de esteroides sexuales y a la albúmina, existiendo una pequeña parte metabólicamente activa en forma de testosterona libre (TL). La relación entre los niveles séricos de testosterona total (TT) y la carcinogénesis prostática es controvertida. Nuestra hipótesis es que la concentración de TL en suero se relacionaría mejor que la de TT con el riesgo de cáncer de próstata (CP) y su agresividad.

Objetivo: Analizar la evidencia científica que ha relacionado los niveles séricos de TT y/o TL con el diagnóstico de CP y su agresividad.

Adquisición de la evidencia: Se ha realizado una revisión sistemática en PubMed hasta enero de 2015, utilizando los términos MeSH: *prostate cancer*, *sex hormone*, *androgen*, *testosterone*, *free testosterone*.

Síntesis de la evidencia: Se encontraron 460 publicaciones, de las cuales se han revisado 124 para analizar la evidencia. La relación entre niveles séricos de TT y el diagnóstico de CP y su agresividad es muy heterogénea. La variabilidad en el diseño de los estudios, en los métodos de cuantificación y otras variables puede justificar esta heterogeneidad. En algunos estudios en los que se ha evaluado la TL calculada o determinada la evidencia sigue siendo igualmente contradictoria.

Conclusiones: La evidencia actual no permite recomendar la determinación sérica de TT y/o TL en el proceso diagnóstico del CP ni en la evaluación de su agresividad.

Introduction

Prostate cancer (PC) is the most frequently diagnosed solid tumor among men in industrialized countries. In Europe the incidence is estimated at 59.3 cases per 100,000 men and accounts for 15% of male neoplasms.[1]

Normal growth and development of the prostate gland requires the presence of androgens. Since Huggins and Hodges described the hormone dependence of PC in 1941, the elevation of serum testosterone levels has been linked to prostate carcinogenesis.[2] Moreover, some studies conducted on specimens of radical prostatectomy (RP) suggest that low serum total testosterone (TT) is associated with more aggressive tumors.[3] Today, most clinical practice guidelines only recommend determining TT during the follow-up of the androgen suppression.

Free testosterone (free-T) is the active moiety of the androgen group and therefore free-T could relate in a more reliable way than the TT to the risk of detection of PC and its aggressiveness. The aim of this study was to perform a systematic review of the literature to determine the relationship between serum TT and/or free-T levels and the risk of PC and its aggressiveness.

Obtaining the evidence

There has been a systematic review of the literature in PubMed until January 2015. The terms employed by *Medical Subject Headings* were: *prostate cancer, sex hormone, androgen, testosterone, free testosterone*. Articles about humans, adults and published in English or Spanish were selected. 460 publications were found, of which 124 articles that analyze the risk of detection of PC and its aggressiveness with the serum concentrations of TT or free-T have been selected (Fig. 1).

Synthesis of the evidence

Performance of serum testosterone

The binding of androgens to the receptor and the successive reactions promote the activation of promoter regions of androgen-regulated genes regulating its transcription. The normal expression of this binding is required to maintain the balance between proliferation and apoptosis signals, tissue regeneration and the production of specific proteins such as PSA. There are currently drugs developed to inhibit testosterone synthesis in different levels whose ultimate aim would be to block prostate cell growth.[4]

About 95% of circulating testosterone is produced by the Leydig cells in the testis interstitium in response to stimulation of LH secreted in the anterior pituitary. The remaining 5% comes from the adrenal cortex. However, the persistence up to 20% of testosterone and 30% of the dihydrotestosterone (DHT) has been described in castrated patients. Those components are usual in the prostate tissue, as a result of the synthesis of intraglandular steroid hormones.[4]

The parameter that is considered more representative of the intraprostatic androgen activity is serum TT. Nevertheless, most testosterone is bound to plasma proteins, particularly albumin and sex hormone-binding globulin (SHBG). About 44% of the TT is bound with high affinity