Polycythemia From Testosterone Therapy: To Treat or Not?

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Question

What is the clinical significance of the increase in hemoglobin and hematocrit that develops secondary to testosterone replacement?

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Testosterone replacement therapy is the mainstay of treatment for male hypogonadism. Hypogonadism is sometimes referred to in the lay media as low testosterone, though there are certain medical distinctions. Hypogonadism is marked by a decrease in testicular sperm production and/or a decrease in endogenous testosterone production. This may result from diseases of the testes, such as primary hypogonadism, or from secondary causes, such as diseases of the pituitary or hypothalamus.[1]

Clinicians often encounter patients with hypogonadism in association with declining endogenous testosterone production that occurs as men age. This is sometimes referred to as andropause. Signs and symptoms of low testosterone include decreased libido, impotence, decreased body hair, decreased muscle mass, fatigue, and decreased bone mineral density.

Testosterone and other androgens have an erythropoietic stimulating effect that can cause polycythemia, which manifests as an increase in hemoglobin, hematocrit, or red blood cell count. The incidence of polycythemia secondary to testosterone use ranges from 2.5% to 40% depending on the testosterone dose and formulation and is less common with transdermal vs injectable formulations.[2,3,4] Definitions in men vary, but polycythemia generally occurs when hemoglobin is above 18.5 g/dL or hematocrit is above 52%.

Polycythemia is sometimes called erythrocytosis, but the terms are not synonymous because polycythemia refers to any increase in red blood cells, whereas erythrocytosis only refers to a documented increase of red cell mass. The increase in hemoglobin and hematocrit secondary to testosterone use is usually accompanied by an increase in the red blood cell count, which can lead to an increase in blood viscosity. This increase in blood viscosity can reduce cerebral blood flow which could theoretically be a risk factor for thrombosis and stroke.[3]

Polycythemia is also associated with hypertension due to increased blood viscosity and thrombosis. Severe, chronic polycythemia secondary to increased blood viscosity can raise pulmonary arterial pressure and cause increased pulmonary resistance with potential hypoxia, resulting in cor pulmonale. Thus, increased hemoglobin and hematocrit secondary to testosterone replacement can be significant[4] and in a recent meta-analysis[5] has been cited as the most common side effect of androgen therapy

The patient with polycythemia on physical exam may present with a ruddy (reddish) complexion, easy bruising, fatigue, and epistaxis. Hematocrit and hemoglobin should be measured before starting testosterone replacement to determine the patient's baseline. Clearly, if hematocrit is elevated before starting testosterone, the cause should be determined prior to starting androgen therapy. Practice guidelines from the American Association of Clinical Endocrinologists recommend checking hematocrit every 6 months for the first 18 months after starting testosterone, and then check it yearly thereafter if levels remain normal and stable.[1] Testosterone dosages should be decreased or possibly discontinued if the hematocrit increases to over 50%.[1]

Patients with primary polycythemia sometimes receive therapeutic phlebotomy; however, there are no data to support widespread adoption of this practice in testosterone-induced polycythemia. Although this approach seems plausible and may prove beneficial, there are no guidelines for when and how often to perform phlebotomy in this population.

In conclusion, testosterone replacement therapy sometimes increases hemoglobin and hematocrit with or without an increase the red cell mass. Thus, it is prudent to monitor for polycythemia in patients receiving chronic testosterone replacement therapy. Testosterone dosages should be decreased or possibly discontinued if the hematocrit increases to above 50%. Likewise, clinicians should monitor for the onset of signs and symptoms of polycythemia in these patients, such as ruddy skin, easy bruising, and epistaxis.