

Bioavailable Testosterone in Salivary Glands

The determination of testosterone in the clinical evaluation of hyper- and hypoandrogenic states has historically involved the measurement of total and free testosterone in the circulation. The free testosterone has been determined as the absolute free concentration, which normally represents only 2-3% of the total testosterone. Testosterone circulates bound primarily to sex-hormone-binding globulin (SHBG) and albumin, with only a very small and insignificant fraction bound to cortisol-binding globulin (CBG). Under normal circumstances, ~44% of the testosterone in the male is SHBG-bound, while 54% is bound to albumin. In females, the figures are 78% SHBG-bound and 20% albumin-bound. In recent years the concept of bioavailable testosterone has emerged, in which the testosterone fraction bound to albumin is considered to be as readily available to the tissues as is absolute free testosterone; the non-SHBG-bound fraction, which includes both the free and albumin-bound fraction, appears to represent the biologically active form of the hormone. A few laboratories have also used the term "free and weakly bound" to indicate the non-SHBG-bound fraction. Most laboratories now report the bioavailable testosterone (non-SHBG-bound fraction) as the free fraction along with the total testosterone concentration.

Recent evidence suggests that steroid measurements in saliva may be a useful, noninvasive approach to the assessment of free hormone concentrations. The salivary concentrate represents a filtered fraction of the hormone and is independent of flow rate. The study by Swinkels et al. (1) in this issue addresses the bioavailable testosterone concept in saliva and examines the issue of non-SHBG-bound testosterone vs absolute free testosterone in this context.

Swinkels et al. have measured total, free, and salivary fluid testosterone concentrations after inducing an approximately 15-fold increase in plasma cortisol with administration of combined dexamethasone/synthetic corticotropin. They observe that the concentration of total testosterone increases, the concentration of free testosterone increases even further, and the concentration of non-SHBG-bound testosterone is either unchanged or, in the case of hirsute individuals, actually decreased. Salivary testosterone concentrations are observed to increase in parallel with changes in either total or free testosterone, but do not parallel the changes in non-SHBG-bound testosterone concentration. On the basis of these findings, the authors conclude that the clinical status of androgenicity is best reflected in measurements of either salivary testosterone or free testosterone, rather than measurements of non-SHBG-

bound testosterone.

The interesting data reported by the authors can also be interpreted in the context of a model proposing that the non-SHBG-bound testosterone is the better index of clinical androgenicity than is the measurement of either total or free testosterone. The authors demonstrate that increased cortisol in plasma increases the distribution of testosterone to SHBG, presumably because of impairment of albumin binding of testosterone. This decrease in the distribution of testosterone to albumin offsets the increase in total testosterone; accordingly, the concentration of non-SHBG-bound testosterone is unchanged in the follicular-phase individuals and is actually decreased in individuals with hirsutism. On this basis, one would predict that the concentration of bioavailable testosterone in the salivary gland is either normal or decreased in the study subjects. However, the concentration of testosterone in salivary fluid reflects the concentration of *in vivo* bioavailable testosterone in salivary glands *only when there is no change in the rate of metabolism of testosterone by salivary gland epithelium* (2). If cortisol decreases the metabolism of testosterone in salivary gland tissue, then the salivary fluid testosterone concentration will increase relative to the bioavailable testosterone concentration in plasma, which is, in fact, what the authors observe. Thus, the authors' data suggest that acute increases in plasma cortisol may diminish the rate of metabolism of circulating testosterone by salivary gland tissues. Indeed, an acute increase in cortisol concentration may cause a generalized impairment of testosterone metabolism by tissues, which probably explains the increase in total circulating testosterone in the study subjects after an acute increase in plasma cortisol.

Salivary glands rapidly metabolize testosterone nearly as avidly as the prostate gland does (2). The rapid cellular metabolism of circulating testosterone causes the size of the pool of cellular exchangeable testosterone to constrict in relationship to the bioavailable pool of circulating testosterone (2). This explains why the concentration of testosterone in salivary fluid is only 2-4% of the total serum testosterone, whereas the concentration of plasma bioavailable testosterone in salivary glands is 15-20% of the total serum testosterone (2). Any condition that causes enzymatic degradation of circulating testosterone in salivary tissues to increase relative to the plasma bioavailable hormone will cause salivary fluid testosterone concentrations to decrease. Conversely, any condition, e.g., cortisol treatment, that causes a decrease in the enzymatic metabolism of testosterone within salivary gland cells will cause the

concentration of salivary fluid testosterone to increase relative to the concentration of bioavailable hormone in plasma.

The concentration of cellular exchangeable testosterone in salivary gland tissue, which is probably in rapid equilibrium with the testosterone pool in salivary fluid, is a complex but predictable function of the relative rates of testosterone metabolism within salivary gland tissues vs the rates of testosterone delivery to salivary gland cells from the circulation. The latter is regulated by three principal factors: (a) microvascular endothelial permeability to testosterone, (b) salivary gland plasma transit time, and (c) the in vivo intravascular kinetics of testosterone binding to albumin and to SHBG. These physiological processes may be ignored in the measurement of free testosterone in vitro, but not in the extrapolation of salivary testosterone measurements to the clinical status of androgenicity in patients.

In summary, the measurement of testosterone concentrations in salivary fluid tells us much about the relative balance between testosterone transport vs testosterone metabolism in salivary gland tissue. However,

in comparison with the non-SHBG-bound testosterone concentration, the salivary fluid testosterone tells us relatively little about the clinical androgenicity status in patients.

References

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2. Pardridge WM. Selective delivery of sex steroid hormones to tissues by albumin and by sex hormone binding globulin. *Oxford Rev Reprod Biol* 1988;10:137-92.

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