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Why Use Saliva?

Saliva testing is an easy and noninvasive way of assessing your patient's hormone status and balancing needs and is proving to be the most reliable medium for measuring hormone levels.

Appreciating the reliability of saliva testing is based on understanding the difference between steroid hormones in saliva and serum. This difference is based on whether or not the hormones are bound to proteins in the medium used for testing. The majority of hormones exist in one of two forms: free (5%) or protein bound (95%). It is only the free hormones that are biologically active, or bio-available, and available for delivery to receptors in the body. Those which are protein bound do not fit those receptors and are considered non-bioavailable. When blood is filtered through the salivary glands, the bound hormone components are too large to pass through the cell membranes. Only the unbound hormones pass through and into the saliva. What is measured in the saliva is the bioavailable hormone, the clinically relevant portion which will be delivered to the receptors in the tissues of the body.

Salivary hormone levels are expected to be much lower than serum levels, as only the unbound hormones are being measured. When health care providers measure serum hormone levels and prescribe hormone replacement therapy based on those results, patients are often overdosed. If the patients are then tested using saliva, the results are extraordinarily high, and confusion results from a lack of correlation between the two methods.

This discrepancy becomes especially important when monitoring topical, or transdermal, hormone therapy. Studies show that this method of delivery results in increased tissue hormone levels (thus measurable in saliva), but no parallel increase in serum levels. Therefore, serum testing cannot be used to monitor topical hormone therapy.

Saliva Measures the "Unbound" Biologically Active or Free Hormone Levels in the Body:

When blood is filtered through the salivary glands, the bound hormone components are too large to pass through the cell membranes of the salivary glands. Only the unbound hormones pass through and into the saliva. What is measured in the saliva is considered the "free", or bioavailable hormone, that which will be delivered to the receptors in the tissues of the body.

Serum Measures the "Protein Bound" Biologically Inactive Hormone Levels in the Body:

In order for steroid hormones to be detected in serum, they must be bound to circulating proteins. In this bound state, they are unable to fit into receptors in the body, and therefore will not be delivered to tissues. They are considered inactive, or non-bioavailable.

Only Saliva Testing Measures Topically Dosed Hormones:

The discrepancy between free and protein bound hormones becomes especially important when monitoring topical, or transdermal, hormone therapy. Studies show that this method of delivery results in increased tissue hormone levels (thus measurable in saliva), but no parallel increase in serum levels. Therefore, serum testing cannot be used to monitor topical hormone therapy.

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Saliva versus Serum References

Salivary References

The following references are articles found by searching the peer reviewed literature that address the benefits of saliva over serum.

Percutaneous administration of progesterone: blood levels and endometrial protection.
Stanczyk FZ, et al. Menopause (2005), 12(2): 232-237.

A very good review of the issues related to the effectiveness of topical administration of progesterone on the endometrium and the disparity between saliva and serum levels. The RBC carrier theory is validated.

Salivary, but not serum or urinary levels of progesterone are elevated after topical application of progesterone cream to pre- and postmenopausal women.
O'Leary P, et al. Clin Endo (2005) 53: 615-620.

Researchers applied 64mg of progesterone topically to 6 each pre- and postmenopausal women. The continuous 3hr serum and 24hr urine (including pregnanediol-3-glucuronide metabolite) samples showed no significant level changes; whereas, remarkable elevations were noted in the saliva. Authors question clinical organ response without a measurable serum level, though organ delivery was obvious. They also suggest that the lymphatic system delivers the hormones rather than RBCs.

A study to evaluate serum and urinary hormone levels following short and long term administration of two regimens of progesterone cream in postmenopausal women.
Carey BJ, et al. British J Obstetrics and Gynecology (2000) 107:722-726.

Authors evaluated serum and urine levels in 24 pre and postmenopausal women following the topical application of 40mg of progesterone either bid divided dosage or qd. Conclusion: "Transdermal progesterone (40mg) per day for 42 days causes a small increase in serum progesterone concentration, although there is wide variation. Whether such levels are of clinical benefit remain to be seen." There was no change in the metabolite.

Topical progesterone cream has an antiproliferative effect on estrogen-stimulated endometrium.
Leonetti HB, et al. Fertility and Sterility (2003) 79:221-2.

Authors monitored endometrial biopsies proliferative activity in 32 postmenopausal women following 0.625 CEE and given either bid daily 0, 1.5% or 4% progesterone topically. Endometrial biopsy evaluation after 2 weeks of progesterone clearly showed an antiproliferative effect of topical progesterone. The antiproliferative effect was essentially the same for the 1.5% and 4% dosages. Regarding serum testing, the authors comment: "The plasma concentrations of progesterone were low and varied greatly among individuals. However, elevated serum levels are irrelevant, provided one obtains the desired clinical outcome."

Micronized transdermal progesterone and endometrial response.
Wren BG, et al. Lancet (1999) 354: 1447-8.

Authors randomized 27 estradiol exposed (Climara 100 weekly) postmenopausal women into 16mg, 32mg or 64mg groups. Serum levels and endometrial biopsies were monitored. Summary: The use of transdermal progesterone for 14 days over three cycles, even at concentrations as high as 64 mg daily, did not increase circulation blood progesterone concentrations sufficiently to induce any evidence of secretory effect in the endometrium.

Hormones in Saliva.
Vining RF and McGinley RA. Critical Reviews in Clinical Laboratory Sciences. (1986) 23(2):95-146.

An excellent review article looking at the constituents of saliva. Conclusion: "Saliva flow rate does affect saliva pH and the concentration of many salivary ions. This has led many clinicians to assume that it would also affect all salivary steroid levels. This is not the case—a number of clinically important steroids, such as cortisol, testosterone, estriol and progesterone, have salivary concentrations which are not appreciably affected by saliva flow rate. However, the conjugated steroids (e.g., DHEAS) and some unconjugated (e.g., cortisone) may exhibit marked flow rate dependence."

Salivary cortisol: a better measure of adrenal cortical function than serum.
Vining RF, et al. Ann Clin Biochem (1983) 20:329-35.

Prospective study: three groups (ages 24-32) consisting of 7 healthy men and women and 10 third trimester pregnant women). Advantages of saliva: reflects bio-available cortisol and unaffected by CBG level, which rises with BCP and during pregnancy. Stress free and easy to collect. Lends itself to multiple samples. IV cortisol injection shows salivary rise within 5 mins. Routine serum samples at 0900 and 1700 do not accurately reflect adrenal dysfunction.

Influences of percutaneous administration of estradiol and progesterone on human breast epithelial cell cycle in vivo.
Chang KJ, et al. Fertil Steril (1995) 63(4):785-91.

Randomized placebo controlled study of 40 Premenopausal women scheduled for excisional biopsy of benign lesions. Study groups were given either Pg 25mg or E2 1.5mg or both topically qd to the surgical breast (10-13 days before surgery. Findings: Both E2 and progesterone readily penetrated the skin, increasing the progesterone level x100. Progesterone induced a major reduction in the acinar cell proliferation rate whether used alone or in combination with E2. The serum levels did not reflect the topical hormone supplementation.

Salivary cortisol determined by enzyme immunoassay is preferable to serum total cortisol for assessment of dynamic hypothalamic-pituitary-adrenal axis activity.
Gozansky WS, et al. Clin Endocrin (2005) 63:336-341.

Author compared salivary and serum cortisol levels between 12 individuals under various conditions: exercise stress, dexamethasone suppression or CRH stimulation. EIA was the salivary test method compared to serum RIA. Conclusion: "Therefore, assessment of salivary cortisol should be considered over serum total cortisol because more physiologically relevant data are obtained, particularly when the cortisol response to an HPA axis stimulus exceeds

Direct assay for progesterone in saliva: comparison with a direct serum assay.
Webley GE, Edwards R. Ann Clin Biochem (1985) 22:579-585.

Study compares direct serum and saliva assays for sensitivity, precision and recovery. Twenty women in various stages of their menstrual cycle were compared using serum and saliva. Conclusion: Saliva showed a significant correlation ($r=0.71$, $P<0.001$) compared to serum with the added advantages of convenience and reduced stress (no needles).

Human Erythrocyte Membrane Uptake of Progesterone and Chemical Alterations.
Devenuto F, et al. Biochem. Biophys. Acta (1969) 193:36-47.

Study of RBC membrane uptake to progesterone, corticosterone and cortisol in fresh and 42 day stored (blood bank) blood. Findings: progesterone showed a much greater affinity for RBC constituents (6 to 8 times greater) than the glucocorticoid hormones. Furthermore, there is a likely direct relationship with the amount of bound progesterone and the viability of RBCs in storage, e.g., female blood may be more stable in storage. Also, indirectly this data supports the RBC as a carrier medium for topically applied progesterone.