LOW-CALORIE DIETING AND DIETERS' CORTISOL LEVELS: DON'T FORGET CORTISONE

In a recent article published in *Psychosomatic Medicine*, Tomiyama et al. (1) reported results of a controlled dietary intervention study in 121 female participants who were randomly assigned to dietary interventions for 3 weeks. Before and after the interventions, participants completed measures of perceived stress and 2 days of diurnal saliva sampling to test for cortisol. The study's major findings were: monitoring calories increased perceived stress and restricting calories increased overall cortisol levels. Extremely reduced caloric intakes, as in anorexia nervosa (2) or during an acute fast or starvation period (3–5), result in elevated circulating cortisol levels. However, less extreme caloric restrictions do not necessarily lead to an increased glucocorticoid activity. Both unaffected circulating cortisol levels (6,7) and even reduced cortisol secretions (5,8) have been observed under moderate or stronger forms of caloric restriction.

Tomiyama et al. (1) stated that, in their study, caloric restriction led to increased total output of cortisol. However, the authors did not measure total adrenal cortisol output (i.e., total adrenal cortisol secretion), which, for example, can be noninvasively determined by analyses of the 24-hour excretion rates of the quantitatively most important urinary glucocorticoid metabolites (C21 steroids) (9–11). The authors quantified saliva cortisol as a marker for cortisol circulating in blood.

Although adrenal cortisol secretion and circulating cortisol are correlated, changes in both parameters can considerably dissociate, depending on the metabolic situation. For example, after 3 weeks on a very low-calorie diet providing only 600 kcal/day, total adrenal cortisol secretion in obese otherwise healthy males has been observed to halve from 15.8 mg/day to 7.0 mg/day, but plasma cortisol concentration did not correspondingly change in that study (5). This seems to be primarily a result of the reversal of the obesity-related up-regulation of cortisol-catabolizing hepatic steroid A-ring reductase (5). In other words, hepatic cortisol degradation, often raised in obesity (via increased 5 α reductase activity), falls after weight reduction, hence allowing maintenance of "normal" circulating cortisol levels at a markedly reduced adrenal cortisol secretion. Accordingly, conditions with functional hypercortisolism (or increased glucocorticoid bioactivity) are not necessarily related to an elevated adrenocortical glucocorticoid output.

Urinary free cortisol excretion in 24-hour urine samples and salivary cortisol concentration, as quantified by Tomiyama et al. (1), are the most frequently used measurements to assess functional glucocorticoid activity. With regard to urinary free cortisol excretion, there is clear evidence that important pitfalls exist (9,11). The highly expressed enzyme 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in the human kidney that inactivates cortisol to cortisone can markedly increase or decrease (confound) renal cortisol excretion by correspondingly decreasing or increasing renal cortisone production (11).

Average urinary excretion rates of free cortisone are twice that of free cortisol (10–12). Because cortisone can be readily activated to cortisol in almost all extrarenal tissues, cortisone is a potentially bioactive glucocorticoid (9,11). Accordingly, a physiologically plausible and specific assessment of functional glucocorticoid activity should consider free cortisone together with free cortisol. In principle, this also applies to the salivary glucocorticoid assessment as performed by Tomiyama and colleagues (1). The 11b-HDS2 activity is highly expressed in the salivary gland (12). In line herewith in saliva (as in the urine), concentrations of cortisone are higher than of cortisol (12,13). Katz and Shannon (13) have shown several decades ago that the sum of parotid fluid cortisol and cortisone is very closely correlated with the free fraction of cortisol in plasma (dialyzable cortisol), substantiating that a large part of the cortisol taken up from circulation is rapidly converted to cortisone in the salivary gland.

In obese but otherwise healthy subjects, the urinary free cortisone/cortisol ratio (a marker of renal 11β-HSD2) is higher than in lean subjects and is negatively associated with insulin sensitivity (14). Because the dieters in the study of Tomiyama et al. (1) must have experienced an increase in insulin sensitivity (due to their weight loss), a fall of the cortisone/cortisol ratio also in the saliva cannot be ruled out. Such a decrease in salivary 11β-HSD2 activity could explain the cortisol rise of the dieters. Therefore, this cortisol rise alone is no proof for an elevation of plasma free (bioavailable) cortisol. To avoid possible misinterpretations and to corroborate the presence of a glucocorticoid-related stress, we strongly recommend quantifying both cortisol and cortisone (i.e., potentially bioactive free glucocorticoids) (10,11,15), whether urine or saliva measurements are performed.

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THE AUTHORS REPLY

The Cortisol-Cortisone Shuttle in Caloric Restriction

In their letter, Drs. Remer and Shi make the following points regarding the study conducted by Tomiyama and colleagues (1). The first is that we should have measured total cortisol output by examining both cortisol and cortisone together to determine whether reducing caloric intake actually increased the adrenal secretion of glucocorticoids in our study. This point is well taken and indeed serves as a good reminder to any and all studies using salivary cortisol output as a measure of bioactive cortisol.

Second, Drs. Remer and Shi suggest that the increase in salivary cortisol observed in the participants who restricted their calories in our study did not necessarily equate to higher levels of functional glucocorticoid activity. In particular, they highlight the role of 11β-HSD2 in oxidizing cortisol into biologically inactive cortisone. Their argument is that if 11β-HSD2 levels (not measured in our study) were high in the unrestricted but fell in the restricted groups, then this may have resulted in a false conclusion that adrenal cortisol secretion was increased in the restricted groups. They cite the relationship between 11β-HSD2, cortisol, and insulin resistance, suggesting that the weight loss incurred by the participants in our study could have increased insulin sensitivity and, thus, a fall in the cortisone to cortisol ratio could have occurred.

Their argument relies on several key studies that they cite in their letter. The first is that 11β-HSD2 activity is highly expressed in the salivary gland (2). The study they cite to support this point, however, shows that 11β-HSD deficient individuals have salivary cortisone levels within the range of normal, non-11β-HSD-deficient participants. This calls into question the relevance of 11β-HSD2 in the salivary glands.

Second, Drs. Remer and Shi invoke the finding from Katz and Shannon (3), in which salivary cortisone and cortisol levels were higher than free cortisol concentrations in plasma. Katz and Shannon, however, did not measure plasma free cortisone. This leaves open the possibility that the two may have been equal, had they directly compared salivary cortisone/cortisol ratios directly against plasma free cortisone/cortisol ratios.

Third, they point to a study (4) demonstrating that 11β-HSD2 activity is elevated in obese participants and is negatively correlated with insulin sensitivity. We point out that the study in question consisted of 72 extremely obese participants, whose mean body mass index was 45.5, whereas the participants in our study had a mean body mass index of 24.8. Furthermore, it is unlikely that the observed weight loss of 1.9 pounds in our participants would significantly change insulin sensitivity. Finally, we know of no study that directly tests their assertion that changes in 11β-HSD2 through weight loss account for changes in salivary cortisol without changing total adrenal cortisol production rate.

Several other points bear mentioning. Remer and Shi focus on 11β-HSD2 to the neglect of 11β-HSD1, an enzyme that amplifies the actions of cortisol by regenerating cortisol from cortisone (5). They make no mention of 11β-HSD1, but a complete understanding of glucocorticoid bioactivity should take into account the equilibrium of both enzyme activities against cortisol.

Furthermore, we note that, in our study, the cortisol awakening response was statistically no different across the groups. It is unlikely that the 11β-HSD2/cortisol ratio would specifically shift, only in the calorie-restricted participants, to be smaller in the morning but larger in the evening—the pattern that would be required if Remer's and Shi's allegations are correct.

In sum, we agree that a more complete examination of activity in the hypothalamic-pituitary-adrenal axis, including activities of the peripheral and hepatic enzymes involved in cortisol metabolism, would provide a fuller understanding of the precise means by which cortisol concentrations are altered. We continue, however, to be confident in the original conclusion of the study by Tomiyama et al.—that caloric restriction increases salivary cortisol in a manner that strongly suggests increased adrenal cortisol secretion.

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