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Acid–base balance may influence risk for insulin resistance syndrome by modulating cortisol output

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Summary Frank metabolic acidosis is known to promote renal excretion of hydrogen ion by induction of glutaminase and other enzymes in the renal tubules. This induction, at least in part, reflects an increase in pituitary output of ACTH and a consequent increased production of cortisol and aldosterone; these latter hormones act on the renal tubules to promote generation of ammonia, which expedites renal acid excretion. Recent evidence suggests that the moderate metabolic acidosis associated with a protein-rich diet low in organic potassium salts – quantifiable by net acid output in daily urine – can likewise evoke a modest increase in cortisol production. Since cortisol promotes development of visceral obesity, and has a direct negative impact on insulin function throughout the body, even a modest sustained up-regulation of cortisol production may have the potential to increase risk for insulin resistance syndrome and type 2 diabetes. This thesis appears to be consistent with previous epidemiological reports correlating high potassium consumption, or a high intake of fruits and vegetables, with reduced risk for diabetes and coronary disease. Future prospective epidemiology should assess whether the estimated acid–base balance of habitual diets – calculated from the ratio of dietary protein and potassium – correlates with risk for insulin resistance syndrome and diabetes.

Acid–base balance as a determinant of cortisol production

Remer and colleagues [1], in a crossover study examining physiological effects of three diets – a "normal protein" omnivore diet, a higher protein omnivore diet, and a relatively low protein lacto-vegetarian diet (50 g protein daily) – found that 24-h urinary excretion of cortisol was about 30% lower ($p < 0.01$) on the latter diet than on the normal protein diet. Conversely, this parameter trended higher on the high-protein as compared to the normal protein diet, though this difference did not achieve statistical significance. The authors characterize 24-h urine cortisol as "the most direct and reliable practical index of cortisol secretion." These findings suggest that dietary protein intakes somehow modulate the HPA axis.

Remer later employed these findings to rationalize another curious finding. Longcope et al. [2], in a cross-sectional study, correlated sex hormone-binding globulin (SHBG) levels with dietary intakes, and found a negative correlation between SHBG and dietary protein; no such correlation was seen with dietary carbohydrate. Inasmuch as insulin is a

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well known negative regulator of hepatic SHBG production, the authors suggested that the ability of protein to potentiate carbohydrate-evoked insulin secretion mediated the apparent impact of dietary protein on SHBG. Yet this explanation seemed inconsistent with the neutral impact of dietary carbohydrate in this regard. Remer, noting that cortisol is another negative modulator of SHBG production, suggested that the increased cortisol production evoked by higher-protein diets might explain the negative association of dietary protein and SHBG [3].

The very recent findings of Maurer and colleagues [4] may help to rationalize the apparent impact of dietary protein on cortisol production. These investigators looked at serum levels of cortisol, and urinary excretion of total cortisol metabolites, when sodium and potassium chloride were replaced by equimolar amounts of sodium and potassium bicarbonate within the context of an otherwise constant diet under metabolic ward conditions; the latter regimen was intended to have an alkalinizing impact on systemic metabolism. 24-h urinary excretion of cortisol, and of the major cortisol metabolites, was found to be significantly lower when the bicarbonates were administered.

Indeed, there is much previous evidence that chronic metabolic acidosis is associated with increased glucocorticoid production. Acidosis upregulates expression of glutaminase in kidney tubules; the evolved ammonia acts as a buffer that aids excretion of excess protons [5–7]. The physiological trigger for this induction of glutaminase appears to be an increased adrenal production of both cortisol and aldosterone – in turn reflective of increased ACTH release [8–10]. Maurer's findings suggest that an analogous (though more subtle) effect may be evoked by normal dietary conditions which provoke mild systemic acidosis – e.g. a high-protein diet relatively poor in potassium-rich fruits and vegetables. The correlation of dietary protein with urinary cortisol output noted by Remer could then be rationalized by the acidifying impact of a high dietary protein intake.

Investigators have long known that certain diets are typically associated with an acidic urine, whereas other diets promote a more alkaline urine; high protein diets usually fall into the former category, whereas plant-based diets rich in potassium fall into the latter [11,12]. The acidifying impact of protein reflects the fact that methionine and cysteine are metabolized to yield free sulfuric acid. Conversely, organic anions present in food that yield bicarbonate when metabolized – for e.g., citrate – have a countervailing alkalinizing impact [13,14]. Since these anions are found in association with cations – most prominently the electrolyte potassium – the dietary potassium content (exclusive of any supplemented potassium chloride) can serve as a good rough index of the diet's alkalinizing potential, and the ratio of dietary protein to dietary potassium can provide a useful estimate of a diet's net impact on acid–base balance [12]. This phenomenon has been studied primarily in regard to bone density, inasmuch as metabolic generation of acid promotes release of phosphate from bone mineral as a buffering strategy, and thus tends to diminish bone density. Conversely, diets which generate bicarbonate buffer tend to have a favorable effect on bone, as demonstrated by the many studies correlating high intakes of potassium-rich fruits and vegetables with improved bone density; [15–17] more acutely, supplementation with alkaline potassium salts has a favorable impact on indices of bone catabolism [18,19]. (The association of protein intake with bone status has been found to more complex, probably reflecting the fact that dietary protein can have some countervailing favorable effects on bone metabolism.) The considerations cited above suggest that the acid–base balance of diets can have metabolic implications that extend beyond bone health.

Cortisol modulation of insulin function

It is clear that prolonged frank hyperglucocorticoidism – as seen in Cushing's syndrome, or during clinical use of high-dose glucocorticoids – tends to promote visceral obesity, compromises insulin sensitivity, and increases risk for insulin resistance syndrome and diabetes. Although glucocorticoids can act directly on skeletal muscle to compromise its insulin responsiveness, induction of global insulin resistance syndrome may reflect an impact of glucocorticoids on adipocytes – most notably visceral, but also subcutaneous abdominal adipocytes. Visceral adipocytes appear to be most responsive to glucocorticoids, both because they express more glucocorticoid receptors than subcutaneous adipocytes do [20,21], and also possibly become the stromal tissue in visceral fat stores has higher activity of the type 1 11β-hydroxysteroid dehydrogenase, which converts (inactive) cortisone to (active) cortisol [22]. Glucocorticoids act on adipocytes to boost their activity of lipoprotein lipase, while simultaneously suppressing the ability to insulin to promote

glucose uptake by adipocytes [23–28]. This implies that, following fatty meals, glucocorticoid-primed visceral adipocytes should efficiently cleave triglycerides in circulating chylomicrons, but do an inefficient job of esterifying and storing the evolved free fatty acids, resulting in a large postprandial surge in serum free fatty acids that may be a key mediator of the range of phenomena associated with insulin resistance syndrome and, ultimately, type 2 diabetes [29–31]. The selective central accumulation of fat characteristic of prolonged corticosteroid excess may reflect site-specific suppression of the in vivo activity of hormone-sensitive lipase; [32] the resulting hypertrophy of central adipocytes can be expected to exacerbate their relative insulin resistance. Conceivably, the greater pathogenicity of certain adipose depots with respect to insulin resistance syndrome reflects their greater sensitivity to glucocorticoids, and their propensity to down-regulate hormone-sensitive lipase (and thus to hypertrophy) in response to glucocorticoids.

Many investigators have suggested that more moderate physiological up-regulations of cortisol production – as are seen in chronic stress, for e.g. – may likewise promote development of insulin resistance syndrome [33–38] In this regard, Seckl and colleagues [35] have suggested that the tendency of low-weight-for-gestational-age babies to be at increased risk for insulin resistance syndrome during adulthood, may possibly reflect chronic up-regulation of the HPA axis stemming from excessive glucocorticoid exposure in utero during the last trimester. High glucocorticoid exposure during this critical time, in addition to suppressing growth of the fetus, is thought to lead to a permanent down-regulation of hypothalamic glucocorticoid receptors that mediate feedback control of ACTH production; as a result, chronic up-regulation of the HPA axis is observed that promotes insulin resistance syndrome in middle age [39]. Another condition associated with increased cortisol production – endogenous depression – has likewise been linked to insulin resistance and glucose intolerance [40]. In monozygotic twins discordant for obesity, visceral but not gynoid obesity is associated with increased psychosocial stress [41]. A polymorphism of the glucocorticoid receptor gene correlates with insulin resistance in obese women [42]. and increased dermal sensitivity to glucocorticoids also correlates with insulin resistance [43]. These findings are thus concordant with the intuitively appealing proposition that modest up-regulation of cortisol production and/or sensitivity increases risk for insulin resistance syndrome.

An "alkaline diet" may decrease risk for insulin resistance syndrome

These considerations suggest the intriguing possibility that – other factors being equal – a diet which promotes an acidic metabolic environment will tend to promote visceral obesity and insulin resistance syndrome via a modest up-regulation of cortisol production – whereas diets promoting a more alkaline metabolic environment may be protective in this regard. Of course, countervailing factors may come into play – notably, a diet quite high in protein, while acidifying, also has a favorable effect on appetite control that can promote leanness and thus act to improve insulin sensitivity [44,45]. But conceivably it would be even more useful in this regard if accompanied by a high intake of potassium- rich fruits and vegetables that buffers the acidifying impact of the protein.

These considerations perhaps explain an intriguing decade-old observation. Prospective analysis of data from the Nurses' Health Study revealed that risk of newly developing type 2 diabetes over 6 years of follow-up was about 40% lower in women whose baseline energy-adjusted potassium intake was in the highest quintile, as compared to those in the lowest quintile [46]. Conceivably, a portion of this effect reflects the fact that potassium- rich diets tend to be higher in whole foods that are somewhat lower in glycemic index and caloric density than the over-refined foods that predominate in many modern diets [47,48]. But the magnitude of the observed effect suggests that additional factors may be at play. Thus, it is postulated that a more alkaline metabolism contributes to the noted protection from diabetes enjoyed by those with high potassium intakes.

Surprisingly, a MedLine review fails to turn up any subsequent prospective epidemiology that has examined the impact of dietary potassium on risk for diabetes or insulin resistance syndrome. There is however one prospective study reporting lower risk for diabetes in women with high intakes of salad vegetables; fruit intake also correlated negatively (though not significantly) with diabetes risk in this study [49]. Conceivably, a favorable impact of potassium-rich diets on risk for insulin resistance syndrome contributes to the reduced cardiovascular risk associated with diets high in fruits and vegetables [50,51].

Conversely, Ludwig and colleagues [52,53], examining data from the CARDIA Study, have observed that higher intakes of protein are associated with increased risk for weight gain and for insulin resistance syndrome. (Note, however, that few

people in such studies would be expected to consume, on a continuing basis, the relatively high intakes of protein associated with improved appetite control.)

In passing, it may be noted that the apparent ability of a potassium-rich diet to regulate cortisol production might play a role in another interesting phenomenon – potassium bicarbonate supplementation has been found to decrease protein catabolism in postmenopausal women [54]. Whether mild metabolic acidosis might have a more direct impact on muscle protein turnover also deserves consideration.

I propose that, using dietary protein/potassium ratio, or some equivalent rough marker for the impact of diet on acid–base status, epidemiologists should examine the impact of acid–base status at baseline to subsequent risk for insulin resistance syndrome and type 2 diabetes. If such studies do indeed point to alkaline diets as being protective in this regard, it will provide an additional rationale for recommending high intakes of fruits and vegetables (and/or supplemental organic potassium salts), particularly for individuals who chose to consume high amounts of dietary protein. (Such a recommendation is advisable in any case, owing to the impact of acid–base status on maintenance of bone density [18,55,56], and of course the many other health benefits conferred by an ample intake of fruits and vegetables.)

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