

PTH excess may promote weight gain by impeding catecholamine-induced lipolysis-implications for the impact of calcium, vitamin D, and alcohol on body weight

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Summary Increased free intracellular calcium ($[Ca^{2+}]_i$) in adipocytes blunts the lipolytic response to catecholamines by activating phosphodiesterase 3B – the same enzyme that mediates the antilipolytic effect of insulin – while also compromising the efficiency of insulin-stimulated glucose uptake. Physiological increases in parathyroid hormone (PTH) have been shown to increase $[Ca^{2+}]_i$ in adipocytes. These considerations may rationalize recent evidence that high dietary intakes of calcium and/or dairy products may reduce risk for obesity, diabetes, and insulin-resistance syndrome, and they predict that other dietary measures which down-regulate PTH – such as good vitamin D status, and moderation in phosphate and salt intakes – may likewise be beneficial in these respects. Consistent with this position are reports that body weight is elevated in elderly subjects with both primary and secondary hyperparathyroidism; furthermore, insulin resistance is a well-known complication of both forms of hyperparathyroidism. The fact that regular alcohol consumption is associated with decreased PTH secretion may help to explain why moderate drinkers are less prone to insulin resistance, diabetes, and – in women – obesity. Down-regulation of PTH cannot be expected to promote dramatic weight loss, but in the long-term it may lessen risk for significant weight gain and diabetes, and conceivably may potentiate the fat loss achievable with caloric restriction and/or exercise.

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PTH INCREASES $[Ca^{2+}]_i$ IN ADIPOCYTES – IMPLICATIONS FOR WEIGHT AND INSULIN FUNCTION

Although the chief target organs for parathyroid hormone (PTH) are kidney and bone, many other tissues express receptors for PTH (and PTH-related protein). This receptor is a seven-pass receptor that activates

heterotrimeric G proteins; these G proteins, in turn, can activate either adenylate cyclase or phospholipase C- β . The effects of PTH vary from tissue to tissue depending on their characteristic pattern of G protein expression. In both adipocytes and skeletal muscle, PTH stimulates phospholipase C- β , inducing an increase in free intracellular calcium ($[Ca^{2+}]_i$) (1–5).

The consequences of a chronic increase of $[Ca^{2+}]_i$ in adipocytes were first analyzed by Draznin and colleagues. These researchers found that such an increase compromised the efficiency of insulin-stimulated glucose uptake; they traced the problem to a failure of insulin to induce dephosphorylation of GLUT4 (6–8). In its phosphorylated form, GLUT-4, even though it translocates to membranes appropriately in response to an

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insulin signal, is a relatively poor glucose transporter; thus, one of the effects of insulin is to activate a class 1 phosphoserine phosphatase that dephosphorylates GLUT4. Elevated $[Ca^{2+}]_i$ blunts the insulin-mediated activation of this phosphatase by increasing the activity of its physiological inhibitor, inhibitor 1. As a consequence, elevated $[Ca^{2+}]_i$ dose-dependently suppresses insulin-stimulated glucose uptake in adipocytes, an effect which compromises the efficiency of free fatty acid storage following a fatty meal. Draznin showed that a PTH-triggered increase in $[Ca^{2+}]_i$ of skeletal muscle likewise activates inhibitor 1, and thus has at least the potential to prevent GLUT4 dephosphorylation in skeletal muscle as well. In any case, inefficient postprandial fatty acid storage in adipocytes would be expected to have an adverse impact on muscle insulin sensitivity, and induce other aspects of the insulin-resistance syndrome. This perspective rationalizes the fact that both primary hyperparathyroidism, as well as the secondary hyperparathyroidism observed in chronic renal failure, are associated with insulin resistance that is at least partially reversible following parathyroidectomy or calcitriol treatment (9–14).

Nonetheless, there is no evidence that PTH interferes with insulin's ability to suppress lipolysis. Indeed, an increase in $[Ca^{2+}]_i$ can blunt the ability of catecholamines to *activate* lipolysis, apparently owing to increased activity of a Ca^{2+} -stimulated cAMP phosphodiesterase – the same phosphodiesterase-3B that insulin activates to suppress lipolysis (15). (The effects of insulin and of free calcium on the activity of this enzyme appear to be additive (15).) These considerations suggest that PTH excess might compromise the ability of exercise or caloric restriction to mobilize stored fat and thereby promote fat loss. Admittedly, the impact of PTH on baseline lipolysis may be equivocal, since PTH can stimulate cAMP production in some adipocytes (16,17). However, the increase in $[Ca^{2+}]_i$ provoked by PTH would be expected to suppress the physiologically appropriate *increase* in lipolysis that occurs in circumstances (such as exercise) conducive to fat oxidation; thus, the net effect of PTH excess on regulation of lipolysis would most likely promote an increase in fat mass. Furthermore, the up-regulation of insulin secretion associated with PTH-induced insulin resistance would be expected to potentiate this effect.

Moreover, there is also recent evidence that increased $[Ca^{2+}]_i$ in adipocytes promotes expression of fatty acid synthase, and thereby enhances *de novo* lipogenesis (5,18,19). While this effect could contribute to weight gain associated with PTH excess, it presumably would be much more significant in rodents than in humans; under ordinary circumstances, the rate of *de novo* lipogenesis in humans represents only a small fraction of the

rate of dietary fat ingestion (20,21). Nonetheless, a very gradual long-term effect of up-regulated adipocyte lipogenesis on body fat stores in humans cannot be ruled out. For example, other factors being equal, synthesizing and storing one extra gram of fat per day, over the course of a decade, would increase body fat stores by 3.65 kg.

Zemel and colleagues have demonstrated that increased $[Ca^{2+}]_i$ mediates the excess adiposity of transgenic mice overexpressing the agouti protein – a protein which boosts intracellular calcium in adipocytes and other tissues by increasing the open probability of plasma membrane calcium channels. These researchers found that either a high-calcium diet or treatment with calcium channel blockers could suppress weight gain in these mice (5,18,22,23).

PERTINENT CLINICAL FINDINGS

Does a chronic increase of $[Ca^{2+}]_i$ in adipocytes promote increased body fat in humans? The answer to this is not immediately apparent, inasmuch as reduced efficiency of postprandial glucose uptake might have a counter-vailing effect, slowing the storage of fat following meals and decreasing the re-esterification of fatty acids released by lipolysis. One straightforward way to resolve this issue is to examine people with longstanding hyperparathyroidism. Grey has reported that postmenopausal women with mild untreated primary hyperparathyroidism are markedly heavier than age-matched controls – they averaged 75.5 kg, as compared to 66.3 kg in controls (24,25). This differential in body weight was attributable to increased fat mass in the hyperparathyroid subjects; moreover, the android-to-gynoid ratio of body fat was greater in these patients, suggesting that PTH excess has its most substantial impact on the android depot. More recently, an Australian group has attempted to correlate PTH status with body weight in elderly nursing home residents (median age 84 years) (26). Owing to increased risk for poor vitamin D status, secondary hyperparathyroidism is not uncommon in such subjects. The average body weight of women with elevated PTH – 62.5 kg – was significantly greater than the 54 kg average body weight of women whose PTH was in the reference range. Similarly, men with secondary hyperparathyroidism were on average 7 kg heavier than those whose PTH was not elevated; this difference did not achieve statistical significance, however, as comparatively few men participated in the study. In the group as a whole, body weight correlated with PTH ($r = 0.32$). This study did not analyze body composition. Of related interest are studies demonstrating that treatment of hyperparathyroid, hypertensive, or glucose intolerant subjects with α -calcidol (1α -OH-vitamin D3) –

which, like dietary calcium, suppresses PTH secretion - provokes modest but significant weight loss (27-29).

Other studies are consistent with the possibility that normal ambient variations in PTH status influence risk for obesity in humans. In several cross-sectional epidemiological surveys, subjects with relatively high dietary intakes of calcium, who of course would be expected to have relatively low PTH levels, have been found to have lower body weight than subjects with lower calcium intakes (5,30,31). Similarly, in several longitudinal studies, calcium and/or dairy intake at baseline have been shown to be predictive of subsequent weight gain - those with high calcium or dairy intakes were less likely to gain weight (31-33). Very recently, Zemel has presented clinical evidence that, as an adjunct to a reduced-calorie diet, concurrent calcium supplementation or use of dairy products potentiates the loss of body fat (34).

Inasmuch as many long-term clinical studies of calcium supplementation have been conducted, it would be of interest to re-analyze the data from these studies to determine calcium's impact on body weight; Davies and colleagues have conducted one such analysis, and found that, relative to the placebo-treated group, the subjects receiving calcium lost significantly more weight - albeit the differential was less than a pound per year (30).

There is also limited but intriguing evidence that good calcium nutrition may be favorable to insulin sensitivity. Thus, an analysis of the prospective Nurses' Health Study suggests that increased intakes of calcium are associated with a significant reduction in risk for type 2 diabetes (35). More recently, Pereira and colleagues have analyzed data from the prospective CARDIA Study, and found that, in subjects modestly overweight at baseline, dairy intake at baseline was predictive of risk for developing two or more components of the insulin-resistance syndrome (dysglycemia, dyslipidemia, hypertension, and obesity). Over the subsequent ten years; this effect was robust - for each additional daily serving of a dairy product, risk for insulin-resistance syndrome fell by 21% (31). Moreover, these authors cite other prospective studies in which increased dairy and/or calcium consumption was associated with reduced risk for hypertension, coronary disease and stroke (36-40) - conceivably, superior insulin sensitivity may have contributed to this protection. And calcium supplementation has been reported to improve the insulin sensitivity of hypertensives (in whom mild secondary hyperparathyroidism is common owing to renal calcium leak) (41,42). A reasonable interpretation of these findings is that down-regulation of PTH secretion has a favorable impact on adipocyte insulin sensitivity - and thus helps to prevent the postprandial free fatty acid overexposure that appears to be at the root of insulin-resistance syndrome (43).

Recently, Chiu and colleagues have reported that, in normotensive, glucose-tolerant healthy subjects, insulin sensitivity measured by hyperglycemic clamp correlates inversely with plasma PTH; this correlation lost little of its strength after adjustments for other correlates of insulin sensitivity, including age and waist-to-hip ratio (44). In their multiple regression analysis, PTH could account for about 10% of the variation in insulin sensitivity. These findings are evidently consistent with the thesis that normal ambient variations of PTH production in healthy subjects can influence insulin sensitivity.

In some of the epidemiological surveys cited above, dairy calcium or dairy intake, but not non-dairy food calcium, emerge as protective (31,39). Moreover, Zemel's initial clinical findings suggest that low-fat dairy products may be more effective for accelerating weight loss in dieters than are supplements providing a comparable intake of calcium (34). Perhaps these findings reflect the fact that dairy products are not only the chief dietary source of calcium, but also of vitamin D - which, like calcium, down-regulates PTH secretion. In a cross-sectional survey examining elderly women, serum PTH correlated inversely with milk calcium intake, but not with intake of other food calcium; the authors concluded that superior vitamin D status associated with increased milk intake was the likely explanation for this finding (45). The health protection often associated with dairy intake is particularly striking in the context of the fact that dairy products are often rich in saturated fat - the adverse impact of which on LDL cholesterol and on insulin sensitivity (46,47) is well known. Evidently, the countervailing protection mediated by dairy calcium and vitamin D (or other dairy components) must be substantial to overcome the health risk posed by increased saturated fat intake.

Despite the fact that PTH excess can compromise insulin sensitivity, PTH secretion is often subnormal in diabetics, likely owing to the impact of chronic hyperglycemia on the parathyroid gland (13). This suggests that measures which down-regulate PTH should be more effective for preventing diabetes than for treating it.

ALTERNATIVE STRATEGIES FOR DOWN-REGULATING PTH

If suppression of PTH secretion does indeed mediate the apparent impact of dietary calcium on fat mass, it should follow that, other factors being equal, other measures that down-regulate PTH production - such as optimal uv exposure (48,49), supplementation with ample doses of vitamin D (50), or diets moderately low in bioavailable phosphorus (51-53) or salt (42) - should likewise promote leanness. In this regard, the fact that body weight

typically increases slightly during winter months (54), while likely attributable in part to a reduction in exercise or to dietary changes, may also reflect a decline in vitamin D status associated with mild secondary hyperparathyroidism. (However, the failure of insulin secretion associated with *severe* vitamin D deficiency (55) would seem unlikely to promote weight gain.) Furthermore, these measures could also be predicted to have a favorable influence on insulin sensitivity.

IS CALCITRIOL THE MEDIATOR?

Zemel proposes that calcium's down-regulation of *calcitriol* synthesis is primarily responsible for its beneficial impact on body weight (5,19). This view is based on *in vitro* studies in which treatment of adipocytes with supraphysiological (nanomolar) levels of free calcitriol produces a rapid influx of calcium; this effect is observed almost immediately, and is not mediated by interaction with the nuclear vitamin D receptor (19). However, until this phenomenon is demonstrated with physiological concentrations of *free* calcitriol – i.e., the calcitriol not bound to vitamin D-binding protein – which are in the high femtomolar range (56), its relevance *in vivo* is questionable. Thus, at this time there is better reason to suspect that down-regulation of PTH production mediates any beneficial impact of dietary calcium on fat mass. In this regard, it is relevant to recall that treatment with α -calcidol has been associated with weight loss, not gain (27–29). Furthermore, administration of calcitriol under various circumstances has been reported to either improve insulin sensitivity (14,57,58), or to have a null effect in this regard; (59); since intracellular calcium excess promotes insulin resistance (8), these findings are hard to reconcile with the notion that calcitriol functions physiologically to promote calcium influx in adipocytes.

Resolving this issue is of more than just theoretical interest. If increased calcitriol mediates the impact of poor calcium nutrition or of hyperparathyroidism on obesity risk, supplemental vitamin D – which has little impact on calcitriol – or a diet moderately low in bioavailable phosphate – which tends to up-regulate calcitriol – would not be expected to have a favorable impact on obesity risk or insulin sensitivity. On the other hand, these measures *would* be expected to be beneficial in this regard if the direct effect of PTH on adipocytes and other tissues is primarily responsible for raising $[Ca^{2+}]_i$.

There are several reports that serum 25-hydroxyvitamin D (25-OH-D) levels tend to be decreased in obese subjects (60–62). If our thesis is correct, this association may arise in part because chronic poor vitamin D status promotes weight gain. On the other hand, low 25-OH-D could reflect the fact that overweight people are less likely to engage in outdoors activities. Holick and col-

leagues have presented evidence that a fixed dose of whole-body irradiation or of oral vitamin D raises serum vitamin D levels less dramatically in obese than in normal weight subjects, presumably because much of the new vitamin D is sequestered in the ample fat stores of obese subjects (63). (Vieth notes that he did not confirm this effect in a chronic oral dosing study – personal communication.) However, the flip side of this argument is that, in overweight people, the adipose stores of vitamin D could be expected to buffer the wintertime decline in serum 25-OH-D – and, indeed, there is a report that 25-OH-D levels show less seasonal variation in overweight than in normal weight subjects (64). While it is difficult to see what should be concluded from all this, the fact that 25-OH-D tends to be low in obesity is seemingly more consistent with our thesis than the opposite result would be.

With respect to insulin sensitivity, several cross-sectional studies have observed that it correlates directly with serum 25-OH-D – even after statistical correction for BMI and physical activity (65–67). Boucher has marshalled evidence supporting the thesis that poor vitamin D status plays a role in the high risk for insulin-resistance syndrome and diabetes experienced by South Asians residing in Britain (68). Hypertension, which is associated with both the insulin-resistance syndrome and hyperparathyroidism, may likewise be influenced by vitamin D status; a double-blind clinical trial has demonstrated that increased uv-B exposure can achieve a clinically worthwhile reduction in elevated blood pressure (49). Furthermore, Rostand suggests that latitudinal, seasonal, and racial gradients in blood pressure may reflect variations in effective uv exposure (69,70). Age-adjusted coronary mortality likewise shows a north-south gradient – with highest risk in the north – in Europe, China, and within Great Britain, Sweden, and France (71–76). In an analysis incorporating 68 sites in Eurasia, Peter et al. described 'a north-south trend for total mortality rate, for death from cardiovascular and ischemic heart diseases, for diastolic and systolic blood pressure and for body mass index...' (77) – an observation strikingly consistent with the view that uv exposure can influence risk for insulin resistance and obesity. It is notable that total serum cholesterol – which is not characteristically elevated in the insulin-resistance syndrome – showed no such latitudinal gradient.

Thus, there is at least suggestive evidence that good vitamin D status may have a favorable impact on insulin sensitivity, blood pressure, and BMI; down-regulation of PTH secretion is a likely explanation for this phenomenon. Evidently, clinical studies evaluating ample supplemental intakes of vitamin D – sufficient to replicate the benefit of healthful uv exposure (50,78) – are needed to validate these conclusions.

ALCOHOL DOWN-REGULATES PTH – A KEY TO ITS HEALTH BENEFITS?

Moderate alcohol consumption, like higher calcium intakes, is associated – at least in women – with lower BMI in cross-sectional studies, and with reduced risk for weight gain in prospective studies; in men, drinkers tend to be no heavier than non-drinkers despite decidedly higher calorie intakes (the so-called ‘alcohol paradox’) (79–84). This analogy may not be sheerly coincidental. PTH levels tend to be lower in drinkers than in non-drinkers, and acute administration of ethanol appears to decrease the responsiveness of the parathyroid glands to a reduction in serum calcium (85–91). Thus, down-regulation of PTH secretion associated with moderate alcohol consumption might help to explain the lower body weight of women drinkers – as well as the superior insulin sensitivity (92–94), reduced risk for diabetes (95,96), and increased bone density (90) associated with moderate drinking in both sexes.

It seems probable that supplemental calcium, moderate alcohol consumption, or other measures that decrease PTH secretion, will rarely if ever induce substantial weight loss; if they did, this effect would have been documented long ago. Rather, it seems more likely that such measures will, over the long-term, help to reduce risk for excessive weight *gain* – and possibly potentiate, to a modest but clinically worthwhile degree, the fat loss achievable with exercise or caloric restriction. This latter possibility is readily susceptible to clinical evaluation; Zemel’s initial findings in this regard are promising, but require further verification.

Ideally, if insulin sensitivity is to be maintained and leanness preserved, adipocytes should store chylomicron lipid efficiently following meals, and should release fatty acids efficiently in response to a catecholamine signal when fat is required as a metabolic fuel during the postabsorptive period. PTH excess, by promoting an undue increase in adipocyte $[Ca^{2+}]_i$, can impair the efficiency of both of these phases of adipocyte function. Thus, dietary measures which down-regulate PTH secretion – high intakes of calcium and vitamin D, relatively low intakes of salt and phosphorus, and moderate regular alcohol consumption – may have subtle favorable effects on insulin sensitivity and adiposity that, integrated over decades, may have a quite useful impact on vascular health and weight control.

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