



Exenatide and biotin in conjunction with a protein-sparing fast for normalization of beta cell function in type 2 diabetics

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Summary The dysdifferentiation of beta cells in type 2 diabetes appears to be caused and maintained by a vicious cycle of glucolipotoxicity: chronic elevations of glucose and free fatty acids induce beta cell dysdifferentiation as well as apoptosis; the resulting failure of glucose-stimulated insulin secretion tends to maintain the elevations of glucose and free fatty acids. Since extended fasts restore normoglycemia in diabetics, the resulting relief from glucotoxicity has been associated with a marked improvement in beta cell function that can be conserved after the fast if the factors precipitating diabetes – obesity, fatty and high-glycemic-index diets, sedentary lifestyle – have been adequately addressed. The new drug exenatide, an analog of the incretin hormone glucagon-like peptide-1, may be a worthwhile adjuvant to such fasting therapy, since it tends to counteract the glucolipotoxicity-induced down-regulation of the crucially important beta cell transcription factor IDX-1. Exenatide also exerts trophic effects on beta cell mass that in the longer term might help to restore diminished beta cell mass. Supraphysiological concentrations of biotin, possibly because they activate the soluble guanylate cyclase, also promote induction of IDX-1 and counteract the adverse impact of glucolipotoxicity in this regard; thus, high-dose biotin, which is well tolerated, may represent an additional adjuvant for therapeutic fasting intended to normalize beta cell function in type 2 diabetics.

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Fasting as a strategy for normalizing diabetic beta cell function

The relative failure of glucose-stimulated insulin secretion in type 2 diabetics – especially the loss of the first-phase response – appears to reflect a dysdifferentiation of beta cells that is induced and maintained by chronic glucolipotoxicity [1–4]. The resulting failure of beta cells to respond

properly to elevations in serum glucose tends to perpetuate the chronic elevation of glucose and free fatty acids, thus leading to a vicious cycle that maintains beta cell failure. Rodent studies suggest that down-regulation of the homeobox transcription factor IDX-1 (islet/duodenum homeobox-1, a.k.a. PDX-1, pancreatic duodenal homeobox gene-1) may largely mediate the adverse impact of glucolipotoxicity on beta cells [5–7]. IDX-1 induces expression of glucokinase, GLUT2, and other key proteins required for effective beta cell function, and may be considered the single most

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important factor in promoting and maintaining proper differentiation of beta cells [8–11].

Allen in 1915 [12], and more recently Fuhrman [13], have reported that, by temporarily maintaining plasma glucose in the normal range, a prolonged fast tends to alleviate glucotoxicity, thereby enabling beta cell function to normalize temporarily. (Fasting should also alleviate lipotoxicity, as this only manifests in the context of hyperglycemia) [14,15]. If substantial appropriate weight loss has preceded this fast, and if a very-low-fat, whole-food diet is fed following the fast, this normalization of beta cell function can be preserved for months thereafter, effectively eliminating the diabetic phenotype. In this way, the vicious cycle of glucotoxicity can be broken. Indeed, other clinicians have noted that the improvement in beta cell function in diabetics following weight loss with very-low-calorie diets seems to be disproportionately large relative to the degree of weight loss achieved [16–22] – albeit such improvements have rarely been conserved in the long run, possibly because patients are still too overweight or the follow-up diet is too high in fats and glycemic index. Even though Fasting can also be expected to alleviate lipotoxicity, as this only develops in the context of hyperglycemia.

A role for exenatide in beta cell redifferentiation therapy

The novel drug exenatide, an analog of glucagon-like peptide-1 (GLP-1) found in the saliva of gila monsters, is now approved as an insulinotropic therapy for type 2 diabetics [23,24]. By acting as an agonist for GLP-1 receptors on beta cells – which increase cAMP production in these cells – exenatide acts to potentiate insulin secretion in response to a rise in plasma glucose, just like natural incretin hormones do [25]. However, unlike sulphonylureas, GLP-1 and exenatide cannot promote beta cell depolarization and calcium influx when glucose concentrations are low – for which reason exenatide monotherapy is not prone to induce hypoglycemia. When administered parenterally, exenatide has a much longer half-life than does GLP-1, since it is resistant to the circulating protease that rapidly degrades circulating GLP-1. Thus, exenatide is therapeutically useful when injected twice daily prior to major meals.

In addition to exerting an acute impact on beta cell responsiveness, exenatide may have a more durable impact on beta cell function, inasmuch as it has been shown to boost beta cell expression of

IDX-1, as well as to increase nuclear translocation of this factor [26–30]. Thus, this drug may counteract a crucial adverse impact of glucolipotoxicity on beta cell differentiation. The stimulatory impact of exenatide on IDX-1 transcription appears to be mediated by cAMP, and reflects, at least in part, increased expression and nuclear binding of the HNF-3 β transcription factor [27].

Moreover, like incretin hormones, exenatide can exert a trophic effect on beta cells – favoring proliferation, suppressing apoptosis – that potentially can increase beta cell mass [23,31–33]. A reduction in beta cell mass is often a factor in the pancreatic dysfunction of type 2 diabetics [34–36], presumably owing to the fact that glucolipotoxicity promotes apoptosis in beta cells [34,37–39] – an effect specifically antagonized by GLP-1 [40]. The trophic effect of GLP-1 reflects the fact that cAMP, acting via the CREB transcription factor, increases beta cell expression of IRS-2; this in turn boosts the ability of the pro-proliferative/anti-apoptotic P13K/Akt pathway in beta cells to respond to ambient IGF-I [41].

These considerations suggest the possibility that exenatide could be administered *in conjunction* with a protein-sparing fast to amplify the favorable impact of sustained normoglycemia on beta cell differentiation and function. As noted above, this would entail no risk for hypoglycemia, since exenatide only potentiates the insulin response to elevated glucose [23,24]. This strategy could be viewed as a type of “beta cell redifferentiation therapy” [4]. It should be acknowledged, however, that it would be unrealistic to expect a diminished beta cell mass to be reconstituted during a fast of moderate duration – particularly since systemic IGF-I activity is decreased by fasting. Thus, long-term use of exenatide, coupled with measures designed to minimize glucolipotoxicity, may be required to correct deficits in beta cell mass.

High-dose biotin may complement these benefits

The vitamin biotin, which in modestly supraphysiological concentrations (0.1–1 μ M) can directly activate soluble guanylate cyclase [42–44] – albeit less dramatically than nitric oxide can – has replicated many of the favorable effects of GLP-1 on beta cell function and differentiation in cell culture and rodent studies. Thus, biotin potentiates the insulin secretory response to elevated glucose (without directly provoking insulin secretion), and also boosts expression of IDX-1 and of glucokinase

[45–49]; moreover, at 1 μM , biotin reverses the suppressive effect of hyperglycemia or elevated free fatty acids on expression of IDX-1 [49]. These effects are likely mediated by arise in cGMP. Indeed, the calcium influx associated with beta cell stimulation activates the endothelial isoform of nitric oxide synthase to boost nitric oxide production; the subsequent rise in cGMP potentiates the insulin secretory response [50–52]; biotin has the potential to exploit this physiological mechanism through direct activation of guanylate cyclase. It also seems likely that cGMP mediates the impact of biotin on IDX-1 induction, although this has not yet been demonstrated. In addition, there is reason to believe that biotin can also exert trophic effects on beta cells, since carbon monoxide, another endogenous activator of the soluble guanylate cyclase, exerts a cGMP-dependent anti-apoptotic effect on beta cells [53]. In this regard, it may be noted that protein kinase G, like protein kinase A, can activate CREB, and thus presumably could boost beta cell expression of IRS-2 [54].

cGMP also has the potential to up-regulate the cAMP concentration in beta cells, inasmuch as the chief isoform of phosphodiesterase expressed by these cells, PDE3B, is inhibited by physiological concentrations of cGMP [55]. Thus, high-dose biotin could be expected to at least modestly amplify beta cell response to exenatide.

Some, though not all [56], reports conclude that high-dose biotin can improve glycemic control in human type 2 diabetes as well as in rodent models of this disorder [57–59]; although the liver may be the chief target for biotin's activity in this regard [43,60,61] (it boosts the impact of insulin on expression of key enzymes regulating gluconeogenesis), a favorable impact on beta cell function is reasonable to expect at sufficiently high intakes. Daily intakes of biotin as high as 100 mg are well tolerated (by children!) [62], so it would be quite reasonable to explore the impact of high-dose biotin in beta cell redifferentiation therapy. (Good tolerance to biotin presumably reflects the fact that biotin can activate guanylate cyclase by no more than 2–3-fold [42], whereas optimal concentrations of nitric oxide can increase the V_{max} of this enzyme by over to 100-fold [63]). Thus, it is proposed that both exenatide and high-dose biotin could be used as adjuvants to protein-sparing fasting as a strategy for normalizing beta cell function in diabetics. Pharmacokinetic studies are needed to determine what dosage regimen of biotin would be sufficient to maintain a plasma concentration of 1 μM – the concentration at which biotin's activation of guanylate cyclase is maximized.

A prudent lifestyle required to preserve normalized beta cell function

In diabetic patients who manage to achieve substantial weight loss, and who become dedicated to regular exercise and prudent eating, diabetes is sometimes reversible without ancillary measures [64]. However, in selected patients in whom such efforts nonetheless fail to normalize beta cell function, a protein-sparing fast of moderate duration (for example, a week to 10 days), coupled with concurrent exenatide and biotin therapy, may have the potential to restore normal beta cell differentiation and function. Such normalization can only be expected to persist, however, if subsequent inappropriate elevations of plasma glucose and free fatty acids are prevented by appropriate diet, exercise, and – if necessary – pharmacotherapy.

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