Nutraceutical resources for diabetes prevention — an update

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Summary There is considerable need for safe agents that can reduce risk for diabetes in at-risk subjects. Although certain drugs — including metformin, acarbose, and orlistat — have shown diabetes-preventive activity in large randomized studies, nutraceuticals have potential in this regard as well. Natural agents which slow carbohydrate absorption may mimic the protective effect of acarbose; these include: soluble fiber — most notably glucomannan; chlorogenic acid — likely responsible for reduction in diabetes risk associated with heavy coffee intake; and legume-derived α-amylase inhibitors. There does not appear to be a natural lipase inhibitor functionally equivalent to orlistat, although there are poorly documented claims for Cassia nomame extracts. Metformin's efficacy reflects activation of AMP-activated kinase; there is preliminary evidence that certain compounds in barley malt have similar activity, without the side effects associated with metformin. In supraphysiological concentrations, biotin directly activates soluble guanylate cyclase; this implies that, at some sufficient intake, biotin should exert effects on β cells, the liver, and skeletal muscle that favor good glucose tolerance and maintenance of effective β cell function. Good magnesium status is associated with reduced diabetes risk and superior insulin sensitivity in recent epidemiology; ample intakes of chromium picolinate appear to promote insulin sensitivity in many individuals and improve glycemic control in some diabetics; calcium/vitamin D may help preserve insulin sensitivity by preventing secondary hyperparathyroidism. Although conjugated linoleic acid — like thiazolidinediones, a PPAR-γ agonist — has not aided insulin sensitivity in clinical trials, the natural rexinoid phytanic acid exerts thiazolidinedione-like effect in animals and cell cultures, and merits clinical examination. Other natural agents with the potential to treat and possibly prevent diabetes include extracts of bitter melon and of cinnamon. Nutraceuticals featuring meaningful doses of combinations of these agents would likely have substantial diabetes-preventive efficacy, and presumably could be marketed legally as aids to good glucose tolerance and insulin sensitivity.

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The need for diabetes-preventive nutraceuticals

Although very-low-fat and lower-glycemic-index diets, regular exercise, and weight control have evident potential for prevention of type 2 diabetes, it can be anticipated that a high proportion of at-risk subjects will continue to eat whatever they want, shun exercise, and stay fat. In light of the tremendous cost of diabetes, both in terms of monetary resources and of human suffering, it would be highly desirable to have practical nutraceuticals and pharmaceuticals which such individuals could use to reduce their risk for diabetes. The range of...
nutraceutical compounds which might have efficacy in this regard continues to expand, and there is considerable scope for the development of products which combine effective doses of several of these compounds. Some of these possibilities have been discussed in an earlier communication [1].

**Slowing carbohydrate absorption**

The STOP-NIDDM has demonstrated that, in subjects with glucose intolerance at baseline, acarbose reduces the subsequent incidence of diabetes over a 4-year follow-up by about 25% [2,3]. Conversely, high-glycemic-load diets have been linked to increased risk for diabetes in recent prospective epidemiology [4-6]. These findings strongly suggest that nutraceuticals which can slow the absorption of ingested carbohydrate may be effective for diabetes prevention. These may include the following.

**Soluble fiber**

Perhaps the most impressive of these is glucomannan, which produces a solution of higher viscosity than any other known natural fiber [7,8]. Purified high-molecular-weight preparations of glucomannan are optimal in this respect, and have the advantage that they are flavorless, odorless, and suspend quickly in fluid without clumping. Viscosity develops only gradually, so that it is easy to drink a glucomannan solution for several minutes after mixing it. It seems likely that glucomannan and other fibers are more effective for depressing the glycemic index of meals if administered blended into fluid or dispersed in food, rather than taken in pill form. A special preparation of guar gum with latentiated development of viscosity has recently been shown to suppress the glycemic index of meals when concurrently administered in fluid [9].

**Chlorogenic acid**

The recent discovery that heavy consumption of coffee markedly lowers risk for diabetes [10-13], has not yet been adequately explained, but it is suspected that chlorogenic acid (CGA), the chief polyphenolic compound in coffee, mediates this benefit. There is suggestive evidence that CGA may slow carbohydrate absorption by inhibiting intestinal glucose transport [14-16]; if so, CGA may have utility similar to acarbose. CGA inhibits the activity of glucose-6-phosphate translocase [17], now believed to play a role in glucose absorption [18,19]. An extracts of green coffee beans enriched in CGA (55%) is now commercially available and, like glucomannan, is rapidly soluble and nearly flavorless.

**α-Amylase inhibitors**

One reason why beans have a favorable glycemic index is that they contain α-amylase inhibitors [20-22]. One of these, phaseolamin, is now available commercially in a concentrated extract. Clinical studies with this preparation, as yet unpublished but cited on the internet, allegedly demonstrate that co-administration of this agent can markedly lower the glycemic index of a starchy meal. If these findings are accurate and confirmable, phaseolamin may offer an additional resource for slowing carbohydrate absorption. Although attempts to commercialize legume-derived "starch blockers" in the 1980s did not yield a useful product [23-26], it is claimed that the current product is more concentrated and thus more effective. Hopefully, credible clinical data evaluating this extract will soon be available in the refereed medical literature. Contrary to misleading representations in the lay press, there is no evidence (or reason to believe) that phaseolamin supplements will literally render dietary starch calories metabolically unavailable; any starch undigested in the intestine will likely be converted to absorbable short-chain fatty acids by bacterial action in the colon — as is the case with "resistant" starch [27,28]. Nonetheless, from the standpoint of diabetes prevention or control, a slowing of starch digestion could be quite worthwhile.

With respect to α-glucosidase inhibition — the mechanism of action of drugs such as acarbose and miglitol [3] — there do not appear to be nutraceutical compounds currently available which have comparable activity.

Although it may be feasible to combine several of these agents in a single product, the extent to which absorption of dietary carbohydrate can be slowed without inducing undesirable gastrointestinal side-effects is limited. Thus, doses must be chosen carefully to assure both efficacy and tolerability.

**Inhibiting fat absorption**

Since very-low-fat diets are known to improve compromised insulin sensitivity while promoting leanness, it is reasonable to expect that agents which inhibit dietary fat absorption — like the drug orlistat — can decrease diabetes risk. Indeed, a recent 4-year controlled clinical trial has demonstrated that orlistat, as an adjuvant to appropriate
lifestyle measures, does indeed lower risk for diabetes [29]. Unfortunately, there do not appear to be any nutraceutical compounds available at present which have clinically documented activity comparable to that of orlistat (reduction of fat absorption by about one-third). Despite hyperbolic promotional claims for chitosan, there is no evidence that this agent can produce sufficient fat malabsorption to achieve meaningful weight loss or notably improve insulin sensitivity – albeit it may have a modestly favorable effect on serum lipids by promoting bile acid secretion [30,31]. However, it would not be surprising if some effective natural lipase inhibitors eventually emerge as nutraceutical alternatives to orlistat. Documents currently posted on the internet claim that an extract of the fruit of *Cassia nomame* has lipase inhibitory activity comparable to that of orlistat, but no information on this compound is traceable on MedLine.

**AMPK activation**

Another drug which shows clear utility for diabetes prevention is metformin. The efficacy of this drug has recently been traced to its ability to activate AMP-activated kinase (AMPK) [32–35]. The favorable effects of metformin on insulin sensitivity and on hepatic glucose output — which are responsible for its efficacy in diabetes - can be rationalized in terms of the known effects of this enzyme. Pharmaceutical and nutraceutical companies are currently working feverishly to identify agents which can activate AMPK with greater potency and fewer side effects than metformin. There is recent evidence that a class of compounds found in barley malt and brewers’ yeast can indeed activate AMPK, with minimal if any side effects in effective doses (D. Miljkovic, personal communication). Barley malt extracts enriched in these compounds are now commercially available, and the first clinical trial with these extracts in type 2 diabetics is currently underway. If subsequent clinical work documents the therapeutic efficacy of such extracts, they will likely be of use in diabetes prevention as well, while also promoting weight control and vascular health. As a treatment for diabetes, metformin is notable for its substantial favorable impact on risk for heart attack and stroke [36,37].

**Versatile effects of biotin**

In supraphysiological concentrations (0.1–1 μM), biotin directly activates soluble guanylate cyclase [38,39]. cGMP exerts a number of effects which can counteract the organ dysfunctions which conspire to induce type 2 diabetes. Thus, cGMP has trophic effects on beta cells, potentiating glucose-stimulated insulin release, promoting a proper state of β cell differentiation by boosting expression of the key transcription factor PDX-1, and preventing β cell apoptosis [40–43] — effects which have been demonstrated with biotin as well [44]. In skeletal muscle, cGMP may be a mediator of the favorable impact of exercise on insulin sensitivity and glucose effectiveness [45–47]. In liver, cGMP has the potential to suppress excessive hepatic glucose output by enhancing expression of glucokinase and decreasing that of phosphoenolpyruvate carboxykinase [39,48,49]. It thus is not surprising that clinical as well as animal studies have suggested that high intakes of biotin (9–16 mg daily in clinical trials) can aid glycemic control in diabetics [50–54]. However, this evidence is a bit thin and requires further confirmation. The optimal dose schedule for biotin that achieves meaningful systemic activation of guanylate cyclase, without inducing unacceptable side effects or risks, remains to be determined. No clear side effects have emerged when daily doses in excess of 100 mg were used to treat children with genetic biotin-dependency disorders, and most nutrition experts characterize biotin as “non-toxic” [55], so there may be considerable scope for pressing the dose of this agent to achieve optimal benefit. A modest systemic increase in cGMP production might also be expected to have a favorable impact on vascular health [56].

**Protective minerals**

**Organic chromium**

In the form of chromium tripicolinate, moderately supranutritional doses (around 1 mg daily) of trivalent chromium appear to have an insulin sensitizing impact in many subjects that aids glycemic control in some diabetics [57–59]. The biochemical basis of this effect remains obscure. In some diabetics, a chromium-induced increased in hepatic insulin clearance may offset the improvement in insulin sensitivity, such that glycemic control does not improve appreciably group [60]. Although there is currently no evidence that such supplementation can aid prevention of diabetes, it is reasonable to expect that, absent countervailing adverse effects, a safe agent which boosts the insulin responsiveness of adipocytes and muscle will ameliorate the
glucolipotoxicity which precipitates β cell failure, and thus prevent or postpone onset of diabetes. A small study demonstrating increase of both average and maximal lifespan in rats fed chromium tripicolinate [61], suggests that this agent may be of particular benefit to overall health. The particular utility of the tripicolinate complex may reflect its ability to "smuggle" chromium into the intracellular space. It seems likely that certain other chelated organic forms of trivalent chromium may prove to have useful insulin-sensitizing efficacy as well.

### Magnesium

Prospective epidemiology links magnesium-rich diets to decreased risk for diabetes, and a recent cross-sectional study demonstrates an inverse correlation between habitual magnesium intake and fasting insulin levels [62–67]. This latter findings suggests that improved insulin sensitivity underlies the apparent favorable effect of magnesium on diabetes risk. This view is supported by limited clinical data [68,69], as well as by rodent studies demonstrating that magnesium helps to preserve adipocyte insulin sensitivity [70–72]. In obese diabetes-prone rodents, high magnesium intakes have proven to be more effective for preventing diabetes than treating it; this accords well with the fact that supplemental magnesium has at best a modest impact on glycemic control in diabetics [73], but seems to have a very robust impact on diabetes risk in prospective epidemiology. (In the most recent such study, risk for diabetes in the upper quintile of magnesium intake, as compared to that in the bottom quintile, was about a third lower after adjustment for a number of potentially confounding variables; the follow-up period was 12–18 years.) Although it is not yet clear how good magnesium status helps to preserve insulin sensitivity, it has been suggested that magnesium may counteract the adverse impact of increased intracellular free calcium on insulin sensitivity [74].

### Calcium/vitamin D

One of the first large prospective studies to examine the role of habitual diet on diabetes risk identified high calcium intake as protective; women in the top quintile of calcium intake, as contrasted to those in the bottom quintile, were 30% less likely to develop diabetes over a 6 year follow-up, after correction for various potential confounders [62]. Surprisingly, it appears that no subsequent studies have followed this lead. No prospective studies have examined the implications of habitual vitamin D intake (or sunlight exposure) for diabetes risk. Yet there are theoretical grounds for suspecting that, by suppressing secretion of parathyroid hormone (PTH), good calcium/vitamin D status may help to preserve insulin sensitivity and thus help prevent diabetes.

Mild secondary hyperparathyroidism is quite common in those who have limited exposure to ultraviolet light – particularly in dark-skinned or the elderly, whose capacity to manufacture vitamin D is somewhat diminished. Parathyroid hormone can compromise the insulin sensitivity of adipocytes (and possibly other tissues) by increasing intracellular free calcium [75–77]. Thus, hyperparathyroidism, whether primary or secondary, is associated clinically with reduced insulin sensitivity [78–83], and, in a group of healthy volunteers, fasting serum insulin was found to correlate directly with serum PTH [84]. An inverse correlation between fasting insulin and the chief circulating vitamin D metabolite, 25-hydroxyvitamin D, has also been reported [85], and Boucher has suggested that poor vitamin D status may contribute to the high risk of diabetes in South Asians who have migrated to Britain [86]. The possibility that ample intakes of calcium and vitamin D may reduce diabetes risk, particularly in elderly or dark-skinned people in northern latitudes, merits further examination by epidemiologists.

### PPAR-γ agonists and rexinoids

Thiazolidinedione drugs, increasingly used in the management of type 2 diabetes, have insulin-sensitizing activity, and are thought likely to reduce diabetes risk [87], although the long-term studies required to confirm this have not yet been completed. The efficacy of these drugs hinges on their ability to activate peroxisome proliferator-activated receptor-gamma (PPAR-γ) in adipocytes. It is thus of interest to explore natural compounds which might possess such activity.

Conjugated linoleic acid (CLA) appears to be a PPAR-γ agonist [88–90], and has shown insulin-sensitizing activity in diabetes-prone rats [90–93]. A previous suggestion that CLA might promote insulin sensitivity in humans, and thus reduce diabetes risk [1], has unfortunately not panned out. In fact, one of the isomers of CLA (t10,c12) has been found to have a negative impact on human insulin sensitivity [94,95]. Why the results in humans have been at odds with those in rats remains unclear.

Phytanic acid, a chlorophyll metabolite found in ruminant animal products, has effects on adipocyte...
diation similar to those of PPAR-γ agonists, likely because it acts as a “rexinoid”, activating the RXR receptor that forms a heterodimer with PPAR-γ [96–98]. Synthetic rexinoids have shown insulin-sensitizing antidiabetic activity in rodents comparable to that of thiazolidinediones [98–101]. Phytanic acid also increases expression of glucokinase in rat hepatocytes, an effect which if clinically relevant could be beneficial to diabetics. Thus, phytanic acid — or its precursor phytol, a hydrolysis product of chlorophyll readily converted to phytanic acid in vivo — might have potential in the treatment and prevention of diabetes [96,102,103]. Unfortunately, bulk commercial sources of these compounds do not appear to be available presently for nutraceutical use, but further efforts to explore their clinical potential can be anticipated.

Miscellaneous agents

Various foods and herbal extracts are reputed to aid diabetic glycemic control in traditional folk wisdom [104–106]. Bitter melon (Momordica charantia) appears to have some genuine utility in this regard, both clinically and in diabetic rodents, and aqueous extracts of bitter melon are currently commercially available [107–117]. The mechanism of action of bitter melon extract remains obscure; it has been noted that these extracts contain peptides with direct insulin-like activity, but it is unlikely that these proteins are absorbed intact. The systemic effects of bitter melon seem somewhat similar to those of metformin, but the impact of this agent on AMPK has not been evaluated [118].

Cinnamon has recently been shown to contain hydroxychalcone compounds which inhibit a tyrosine phosphatase that targets the insulin receptor [119]; thus, these compounds have the potential to potentiate insulin signaling. Indeed, a recent clinical study reports that, in doses of 1–6 g daily, whole cinnamon decreases the fasting glucose of diabetics by about 20% and also improves serum lipid profile [120]. Aqueous extracts of cinnamon enriched in the active principles are being developed for use in nutritional supplements. Whether systemic potentiation of insulin receptor activity is appropriate as a strategy for preventing diabetes remains to be seen, as certain actions of insulin may not be beneficial for health; for example, insulin may have cancer-promotional activity [121–123]. (The health benefits of certain “insulin sensitizers” with tissue-specific activity — such as exercise — may actually reflect a decrease of net insulin activity in some tissues, consequent to down-regulation of insulin secretion.) In any case, further research with cinnamon should be followed with great interest.

Practical considerations

As suggested above, it should be feasible to combine effective doses of various of the agents discussed above to produce nutraceuticals that have genuine and potent efficacy for diabetes prevention. Unfortunately, it will not be feasible to advertise such agents as diabetes preventives — at least for the foreseeable future — since the clinical studies required to prove such a claim would be massive and lengthy, well beyond the means of most nutraceutical companies. Nonetheless, these products will probably have demonstrable effects on measurable clinical parameters in subjects who are insulin resistant or diabetic — in other words, they should improve glucose tolerance, glycemic control, insulin sensitivity, and lipid profiles — and so they could reasonably be promoted as aids to good glucose tolerance and insulin sensitivity. Indeed, people who have impaired glucose tolerance are those most in need of resources for diabetes prevention. Thus, it may be feasible to market products of this type in an honest way that targets them to people most likely to derive benefit. Most of the agents discussed above are also likely to have a favorable impact on vascular risk, even in non-diabetics; this is an important consideration, inasmuch as non-diabetic insulin resistance is associated with a substantial increase in vascular risk.

References


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