KNOWLEDGE BY THE GLASS

THE SCIENCE AND CLINICAL RESULTS BEHIND GOOD IDEA®
THE SWEDISH "SUGAR BUSTER"

SUMMARY

Good Idea® is a dietary supplement developed to help the metabolism handle the blood sugar spike normally following a meal rich in fast carbohydrates and/or sugar.

Research by scientists at Lund University, established the connection between the intake of dairy and a relatively high insulin response. They found that the intake of whey before and with a meal rich in fast carbohydrates could substantially lower the blood sugar spike following a meal.

The effect was observed also with other food proteins. The presence of five specific essential amino acids appeared to be significant. Repeated meal studies confirmed that the effect on insulin and glucose response from whey could be mimicked by serving a drink containing a proportion of the five essential amino acids before and with the meal.

As an additional development of the concept, a small quantity of chromium (CrPic) was added. Chromium is well known by scientists to have an important role in blood glucose regulation. Taken together, it was hypothesized that a combination of amino acids and chromium would have a synergistic effect that would further improve the effect on blood sugar rise.

A collaboration between the Food for Health Science Centre at Lund University, and Aventure AB – a research based company specialized in bringing healthy food concepts to the market – was formed with the objective to apply the findings to benefit consumers in the most convenient way. A line of lightly flavored, sparkling waters was developed. The efficacy of the concept has since been evaluated in a series of double-blind, placebo controlled meal studies. The results consistently reflect a typical reduction of 25-30% in blood sugar rise following a meal rich in carbohydrates, compared to placebo.

The Good Idea® line of sparkling waters was launched in the US as a dietary supplement carrying an FDA compliant structure-function claim *"May help those with normal blood sugar levels handle the sugar spike following a meal".*

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SCIENTIFIC BACKGROUND TO THE INVENTION

In 1986, a study in patients with type 2 diabetes mellitus (T2DM) showed that the insulin response to milk was unexpectedly high (Gannon, Nuttall et al. 1986). This inconsistency between glucose and insulin responses to milk products was later established also in healthy humans by Östman et al. (2001). A couple of years later, Nilsson et al. (2004) compared gluten, cod, milk, whey and casein protein on glucose and insulin responses to lactose-equivalent meals in healthy subjects. About the same time, also von Post-Skagegård et al. (2006) reported that cod-, milk- and soy protein differed in their metabolic effect. In both of the latter studies it was concluded that the protein sources differed in their insulin stimulating properties and thereby their potential to lower postprandial glycemia. Both the milk and whey meals lowered glycemia about 60% compared with white wheat bread (WWB) but the insulin response after whey (+90%) was almost three times as high as that of milk (+24%) (Nilsson, Stenberg et al. 2004). When looking for the insulinogenic components of whey, a set of amino acids that showed large postprandial increases in plasma after the whey meal was identified. The BCAA (Leu, Ile, Val) along with Lys and Thr (5AA) were identified as the most interesting candidates for further evaluation. In the follow-up study, Nilsson et al. (2007) investigated the potential of serving either whey or mixes of the identified insulinogenic 5AA in glucose equivalent drinks to healthy subjects. Interestingly, the glucose drink containing 5AA mimicked well the glycemic and insulinemic responses seen after whey ingestion.

In more recent work, linear dose-response relations were found in healthy subjects between whey dose and acute glycemia (inverse relation), insulinemia (positive) and plasma AA (positive), respectively (Gunnerud, Ostman et al. 2013). The improvement in glycemic regulation was substantial with whey doses of 9g and 18g, respectively, and nearly significant in the case of a 4.5g dose. In yet another study by the same authors, whey proteins with different solubility (whey isolate and hydrolyzed whey, respectively) were served in the intermediate dose (9g) to healthy humans in form of glucose containing drinks (Gunnerud, Östman and Björck, ***unpublished observation***). In addition, the efficacy of exchanging half of the proteins for the 5AA (Val, Leu, Ile, Lys and Thr) was evaluated. The test drinks consisted of isolated whey, isolated whey + 5AA, hydrolyzed whey or hydrolyzed whey + 5AA. The protein/5AA-mixes were added to cold coffee and had the appearance of a café latte. It turned out that introducing 5AA at the expense of whey protein or whey hydrolysate significantly reduced the glycemic response to the café latte drink compared with the reference. No significant differences were found between the insulin responses of the protein/5AA-drinks suggesting that the glucose lowering potential was improved in a drink added with protein and 5AA, compared with only protein.

A new study was designed taking into consideration the above findings and that timing of the protein/5AA-intake in relation to the meal, may influence its insulinogenic properties (Gunnerud, Heinzle et al. 2012). The test subjects were instructed to drink 9g of the protein/5AA as a bolus load (100 ml) before a standardized sandwich meal, as well as to finish the entire breakfast within 12 min. In comparison to the reference meal, all the protein/5AA meals displayed lower glycemic responses, expressed as iAUC 0-120 min ($p<0.05$). Moreover, the incremental glucose peaks (Δ mmol/L) were lower after all test meals compared to the reference. No differences were, however, found between the test meals in either insulinemic indices (II) or incremental insulin peaks (Δ mmol/L). Interestingly, the early insulin response (iAUC 0-15 min) was positively correlated with plasma levels of AA, GIP (gastric inhibitory polypeptide) and GLP-1 (glucagon-like peptide 1), respectively, and inversely correlated with

the glucose peak. Taken together, these results support a hypothesis that having a preload drink of protein/5AA just before beginning a high-glycemic meal could substantially reduce postprandial glycemia without increasing overall insulinemia.

In a recent pilot study from Shukla et al. (2015), it was shown that the order of food intake has a dramatic effect on glucose regulation in overweight subjects with T2DM. By serving the protein and vegetable components of a meal, 15 min ahead of the carbohydrates, the iAUC for glucose (0-120 min) was reduced by 73% compared with serving the carbohydrates first. Also the insulin response was significantly lowered when protein and vegetables were consumed first. Furthermore, Tricò et al. recently concluded that by serving a preload containing fat and protein (50 g parmesan cheese and a boiled egg) before an OGTT, the glucose increase in plasma was reduced by more than 30% in healthy subjects (-32%) as well as those with IGT (impaired glucose tolerance, -37 %) or T2DM (-49%) (Trico, Baldi et al. 2015).

From the results above it may be hypothesized that intake of a mix of free AA to the meal instead of a combination of protein and AA may be as efficient in conjunction to a meal, leading to a similar early intestinal uptake of AA, that seems to be connected to a positive effect on insulin economy and a concomitant improvement in postprandial glycemia.

Although no precise mechanism of the effect has been found, the trace element Cr has long been known to be related to blood glucose regulation, and is considered as an essential micronutrient in textbooks on human nutrition (Thurnham, 2005). In a review on Cr and insulin resistance (Hua, Clark et al. 2012) it was concluded that clinical studies on Cr in diabetic and healthy subjects in fact have shown mixed results. Such differences may partly originate from variations in study design and/or study quality, but may also be dependent on the specific conditions of the subjects included the study (i.e. degree of insulin resistance), including their genetic “make up” or, in other words, “subject phenotype”. In animal experiments, the results seem to be conclusive with respect to the positive effects of Cr on alleviating diabetic symptoms (Hua, Clark et al. 2012). Furthermore, experimental data strongly support the various roles of Cr (III) at several points in the insulin signaling cascade including the binding of insulin to the insulin receptor at the cell membrane and eventually regulating cellular uptake of glucose. The authors conclude that the beneficial effects of Cr, together with its wide safety profile, may justify its use as an adjunct therapy in the management of insulin resistance and T2D (Hua, Clark et al. 2012).

In Europe, the EFSA Panel on Dietetic Products, Nutrition and Allergies have provided a scientific opinion on the substantiation of health claims related to chromium (EFSA Panel on Dietetic Products 2010). It is noteworthy that, in the conclusion of the opinion, EFSA state that ”a cause and effect relationship has been established between the dietary intake of Cr and the maintenance of normal blood glucose concentration”. In USA the FDA has approved a considerably weaker claim around the relationship between chromium picolinate on insulin resistance, based on one single study.

Taken together, it was hypothesized that a combination of amino acids and Cr would have synergistic effects on insulin release and insulin sensitivity that would improve postprandial glycemia.

Development and scientific evaluation of the invention

With the ambition to apply the above findings to the benefit of consumers caring about their post-prandial glucose response, a 'sparkling water' concept was developed. The efficacy of the concept has since then been evaluated in a series of meal studies with healthy and either normal weight or overweight subjects representing potential target groups of consumers. The sparkling water bore the rationale of having the active components (5AA and Cr) pre-solubilized and ready for direct intestinal uptake that, in a 'natural' way, enables the supply of AA in a timely manner to a meal.

In a first meal study (Östman et al, 2017) the effect of five combined AA (total 6.9 g) with (5AA+CrPic; US patent pending no 14/128739) or without (5AA; EP 1983849 B1) the addition of Cr(III)picolinate (CrPic, 500 µg eq. to 60 µg Cr) was evaluated in 300 ml lightly carbonated water served with a of white bread meal containing 50 g carbohydrates and 9 g wheat protein. A randomized cross-over study was performed to show the effect of the respective components when taken separately, as well as in combination. Nineteen healthy, overweigh persons aged 40-60 years and with BMI between 25-30 kg/m^2 were included. The test subjects were asked to avoid foods rich in indigestible carbohydrates and alcohol on the day before each experiment and also to refrain from strenuous physical exercise. On the day of each experiment the subjects came fasting to the research facility at Lund University. All test subjects were allowed to read or do computer work during the experiment, but they had to remain seated and not fall asleep. The results showed that the carbonated water containing 5AA, served either alone or in combination with CrPic, was able to significantly reduce the glucose response. No glucose reducing potential was found when CrPic was served without 5AA. When looking at the insulin responses to the drinks containing 5AA, the early insulin responses (0-30 min) were significantly increased after intake of the 5AA and the 5AA+CrPic mix, respectively, compared with the reference and the CrPic meals. Interestingly, the insulin economy was clearly improved when 5AA was combined with CrPic. This conclusion is based on the fact that the overall insulin demand was halved when 5AA and CrPic were combined, compared with only 5AA.

In a second study on a similar group of 16 subjects (BMI 23-32, age 37-66), a dose-response relation was investigated (Östman, Svensson, Öste and Björck, ***manuscript to be submitted***). Instead of a carbohydrate rich sandwich meal, the 5AA+CrPic sparkling water was now evaluated at a lunch/dinner type of warm meal consisting of instant potato mash, oven baked cod, melted butter, cucumber and lingonberry sauce. The meal had the same amount of carbohydrates as the first study (50 g) but higher overall protein content (27 g). Still the meal was served in the morning after an overnight fast and after giving the same instructions to the test subjects as in the previous study. The study was performed with three levels of the 5AA+CrPic mix, in order to establish a dose response relationship. The highest level (6.9 g 5AA) was identical with the level used in the first study and the two other levels included were 3.5 g 5AA+250 ug CrPic (medium) as well as 1.75 g 5AA+125 ug CrPic (low). Another adjustment was made compared with Östman et al, 2017 in that the subjects were instructed to take a couple of sips of the drink at 3 min before starting the meal and then consume the rest during the meal. All three doses of 5AA+CrPic resulted in significantly lower blood glucose responses compared to the reference, measured by iAUC 0-120 and 0-180 minutes. By reducing the dose of the 5AA+CrPic, less insulin was required to obtain essentially the same improvement in postprandial glycemia as seen with the highest dose. Plasma

levels of GLP-1 tended to increase for all DG-containing meals (+39% (high), +55% (med), +65% (low)) but did not reach significance.

In a third study, the lowest dose of 5AA+CrPic (1.75 g 5AA+125 ug CrPic) was repeated in a similar group of 20 subjects (BMI 20-31, age 22-59) but this time served with a sandwich meal. Glucose iAUC (0-180 min) was reduced by 41% without an increase in insulin response, compared to the reference meal.

More studies are in pipeline and will be reported once they are completed.

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