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Metabolism Clinical and Experimental 54 (2005) 1407–1409

Metabolism
Clinical and Experimental

www.elsevier.com/locate/metabol

Correspondence

Cheers and jeers for the testing of a tonic promoted for diabetes

To the Editor:

Congratulations to Hsia et al (*Metabolism* 2004;53(9): 1165-73) for subjecting an herbal supplement promoted for the treatment of type 2 diabetes to a rigorous clinical trial, and jeers for misinterpreting the data and drawing erroneous conclusions. When the investigators found that the tonic produced a drop in hemoglobin (Hb) A_{1c} without a parallel fall in glucose, they proclaimed a therapeutic benefit. I interpret the fall in Hb A_{1c} as an artifactual change in a surrogate marker, possibly due to a toxic effect on red blood cells.

Using a randomized, placebo-controlled, double-blind format, Hsia et al studied the effects of a 12-week trial of "Pancreas Tonic" on glycemic control in adults with type 2 diabetes treated with oral agents. Pancreas Tonic, an Ayurvedic herbal supplement, is a commercial product containing crude extracts of 10 agents, each of which has been reported to have glucose-lowering properties. The investigators found a modest but statistically significant decrease in Hb A_{1c} in subjects with initial Hb A_{1c} values between 10% and 12%. No changes in glucose, insulin, or lipid levels, insulin sensitivity, blood pressure, or body weight occurred with Pancreas Tonic administration.

The authors equate the modest decrease in Hb A_{1c} in one group who received Pancreas Tonic with improved glycemic control. They fail to recall that Hb A_{1c} is a surrogate marker of integrated blood glucose levels based upon the degree of glycation of Hb. If total Hb levels or red blood cell life span change, then glycohemoglobin levels will change as well, independent of any change in glucose. In support of a direct effect of Pancreas Tonic on red blood cells, tonic administration was accompanied by a statistically significant decrease in Hb level (13.4 + 1.7 g/dL at randomization, 13.0 ± 1.6 g/dL at study end; $P = .04$). In addition, a number of ingredients in Pancreas Tonic, including *Momordica charantia* [1-3], *Trigonella* [4] *foenumgraecum* [5], *Ficus* [6], and *Azardirachta indica* [7], can have direct effects on erythrocytes and consequently on Hb concentrations and kinetics. Indeed, it is the authors' own observations that invalidate the use of Hb A_{1c} as a meaningful surrogate marker of glycemic control. I agree with the authors "that a significant decrease in Hgb A1C unaccompanied by significant changes in other glycemic parameters is peculiar" and reject the statement that "this is the first study to report a significant effect on intermediate term glycemic control by an Ayurvedic antidiabetic preparation."

The Dietary Supplement Health and Education Act of 1994 (Public Law 103-417) provides a regulatory mechanism for marketing dietary supplements as long as the supplements are safe and the manufacturer has substantiation for any claims of nutritional support. In this regard, an ingredient in Pancreas Tonic, *Aegle marmelos*, appears to be hepatotoxic in animal studies [8] and raises the question of whether Pancreas Tonic is indeed safe. In addition, the Dietary Supplement Health and Education Act of 1994 does not allow any claims related to a disease to be made by a dietary supplement; disease-related claims can only be made by drugs. Pancreas Tonic's claim that it has "antidiabetic properties" or "glucose-lowering benefits for diabetic patients" means this product is a drug [9].

The study on Pancreas Tonic published in *Metabolism* does not demonstrate any effect on glucose control in type 2 diabetes but rather an effect on a surrogate marker of glycemia, Hb A_{1c}, that may well be a result of a direct effect of the ingredients in this botanical mixture on erythrocytes. Using this study as substantiation for a dietary supplement, when the dietary supplement is really a drug, represents poor judgment compounded by flawed logic. The use of Pancreas Tonic, a complex mixture of botanical components with no demonstrable benefit and substantial potential for serious side effects, should be discouraged.

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doi:10.1016/j.metabol.2005.05.001

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Response

To the Editor:

We thank Dr Ehrenkranz for his interest in our paper. However, we reject his hypothesis that the significant drop in hemoglobin A_{1c} (HbA_{1c}) seen in our study [1] was due to red blood cell (RBC) toxicity. Perhaps, the most compelling argument against his hypothesis is the absence of a significant drop in HbA_{1c} in our subjects who entered the study in the lower HbA_{1c} stratum. A direct relationship between the pretreatment HbA_{1c} level and the absolute reduction in HbA_{1c} is well known [2] and is consistent with our explanation that Pancreas Tonic may have only a mild effect on glycemia. Dr Ehrenkranz does not present any plausible or evidence-based explanation as to why RBC toxicity should exclusively affect RBCs that are more heavily glycated.

The literature sources quoted by Dr Ehrenkranz appear to contradict his own arguments. The (−)epicatechin extract of *Pterocarpus marsupium* was shown in the papers that he quotes (mistakenly indicated as references to *Momordica charantia*) to have no effect on hemolysis [3] or even a protective effect on erythrocyte osmotic fragility [4]. Although Suboh et al [5] found that *Trigonella foenum graecum* increased lipid peroxidation, they saw no concurrent effect on erythrocyte deformability that would be expected to result from oxidant stress. Perez et al [6], in studying *Ficus carica* (instead of the *Ficus racemosa* found in Pancreas Tonic), proposed that their extract normalized rather than worsened the pro-oxidant state of diabetes. The animal study of Kar et al [7] with *Aegle marmelose* (mistakenly indicated as a reference to *Azardirachta indica*) demonstrated a reduction in hepatic lipid peroxidation, increased hepatic antioxidant levels, and no mention of any effects on erythrocytes. We do not know the exact mechanism of HbA_{1c} lowering shown in our study, but the hypothesis proposed by Dr Ehrenkranz is clearly not supported by his own literature citations.

Furthermore, hepatotoxicity to an unstated dose of any substance in animals [8] does not necessarily equal hepatotoxicity in humans. We cannot discount the potential for long-term hepatotoxicity of Pancreas Tonic in humans, but within the scope of our 3-month study, no transaminase elevations were seen. As to the Dietary Supplement Health and Education Act regulations, we must point out that our study was intended to establish the metabolic effects of Pancreas Tonic. We have no interest in marketing Pancreas Tonic; whether any disease-related claims are used for marketing purposes is strictly up to the study sponsor who was not involved in establishing the study protocol, conducting the study, writing the manuscript, or even seeing it before submission for publication. In our paper, we stated our reasons why the secondary outcomes were inconclusive. Our findings are consistent with a mild glucose-lowering effect of Pancreas Tonic in poorly controlled patients with type 2 diabetes mellitus (but not in those under better control).

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DOI of original article:10.1016/j.metabol.2005.05.001
doi:10.1016/j.metabol.2005.05.002

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