

July 2018

CHORI-bar, a nutrient-rich, fruit-based, high fiber, low calorie, good tasting supplement bar to tackle diseases associated with obesity and aging

Background. The increasing prevalence of obesity is taking a huge toll on public health, adding significantly to global health care costs. Since poor diets are well known to be a major cause of obesity, an obvious approach is to improve dietary habits. Conventional approaches that encourage weight loss by reducing caloric intake and modifying lifestyle can be successful, but wholesale changes in diet and behavior are difficult for many to initiate and sustain.

Over the past 10 years, a team of Children's Hospital of Oakland Research Institute ("CHORI") nutrition scientists and clinicians assisted by local United States Department of Agriculture collaborators developed a nutrient-rich, fruit-based supplement bar (referred to here informally as the "CHORI-bar") as a non-traditional means to positively impact the obesity epidemic by improving the metabolic dysregulation that frequently accompanies obesity and is the primary cause of increased risk of many diseases such as diabetes and cardiovascular disease.

The motivating idea behind development of the CHORI-bar was that dietary-induced metabolic dysregulation is due as much to what poor diets are lacking (e.g., vitamins, minerals, and fiber) as to what they contain (e.g., trans fats, sugar). Thus, ingredient selection for the CHORI-bar emphasized food components whose deficiencies were linked to increased disease risk and which were known to be deficient or missing in typical Western diets. There is considerable evidence in the literature as well as from Dr. Bruce Ames' and Dr.

Joyce McCann's work on micronutrients that support this idea¹⁻⁴. Development of the CHORI-bar was also guided by Dr. Mark Shigenaga's ideas on the importance for disease prevention of maintaining a healthy gut, known to be impaired in the obese.

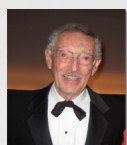
CHORI-bar fills gaps in poor diets

From a disease risk perspective, the problem with poor diets is as much due to what they do **not** contain, as to what they do contain

Supported by research of Drs. Ames, Shigenaga, and a large body of evidence in the published literature

Health improvements occur in both the lean and overweight/obese without the need to change dietary or other lifestyle habits.

HDL-c↑, small LDL↓, Triglycerides↓, Blood pressure↓, Heart rate↓
Insulin resistance↓, Weight↓, Waist circumference↓

The CHORI-bar Development Team

Bruce Ames



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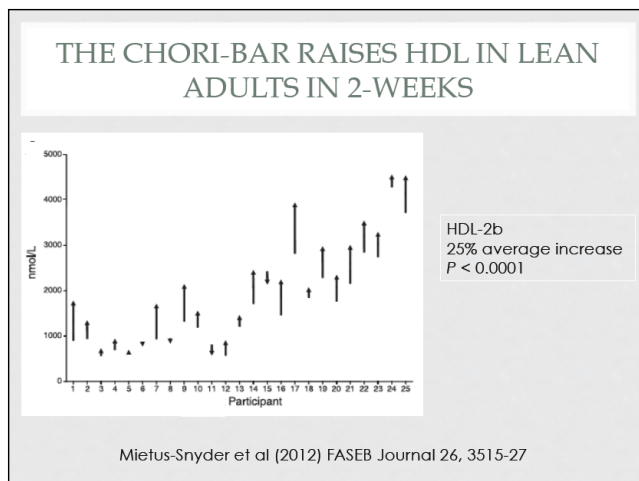
Ash Lal

A high fiber, low-calorie (110-130 kcal), good tasting bar formulation has been developed and produced in pilot scale quantities. Throughout development of the CHORI-bar, formulation modifications to improve palatability and efficacy were guided by a series of over 15 small clinical trials^{5,6}. A straightforward experimental design was used for these trials. Participants acted as their own controls, and were not required to modify their existing diets during the course of the trial, consistent with our hypothesis that adding back deficient dietary components would be sufficient to result in positive change.

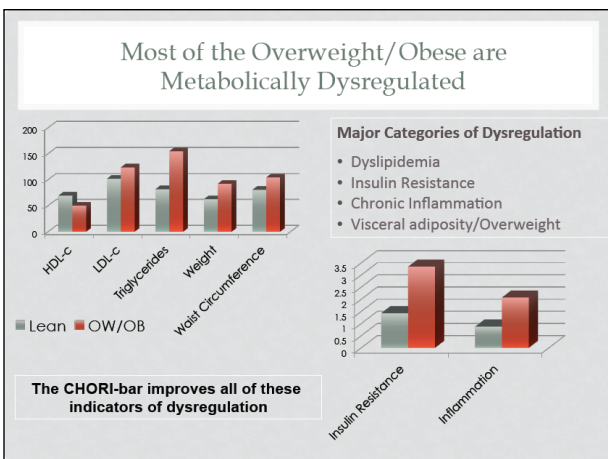
Clinical Trials

Metabolic Dysregulation. Early clinical trials guiding development of the CHORI-bar were of short duration (2-weeks). They included predominantly lean or only slightly overweight adults.

Our published report⁵ showed that twice-daily consumption of the CHORI-bar for 2-weeks resulted in a striking increase in HDL-c, particularly the large HDL particle, HDL-L (*aka* HDL-2b), associated with lower cardiovascular risk.



Change in plasma concentration of HDL2b in each participant is plotted separately as an arrow. The base of the arrow is before eating 2 CHORI-bars each day for 2-weeks, and the arrowhead is the plasma concentration of HDL2b at the end of the 2-weeks.

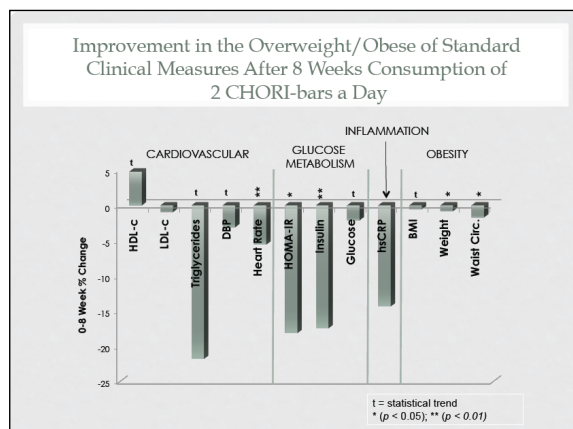


other metabolic dysregulation.

Subsequent trials of longer duration (2-months) focused on overweight/obese (OW/OB) adults.⁶ The metabolism of many OW/OB is abnormal in ways that put them at high risk of short lifespan and a wide range of diseases. The figure shows the differences among participants in our studies. In the OW/OB compared to the lean, HDL is lower, LDL is higher, triglycerides are higher, and the OW/OB are insulin resistant, which impairs the ability of the body to carry out many essential tasks. Importantly, although the OW/OB do not have a fever, most have a low-level of internal inflammation called “chronic inflammation” that has broad-spectrum adverse effects, and may actually be a major cause of much of their

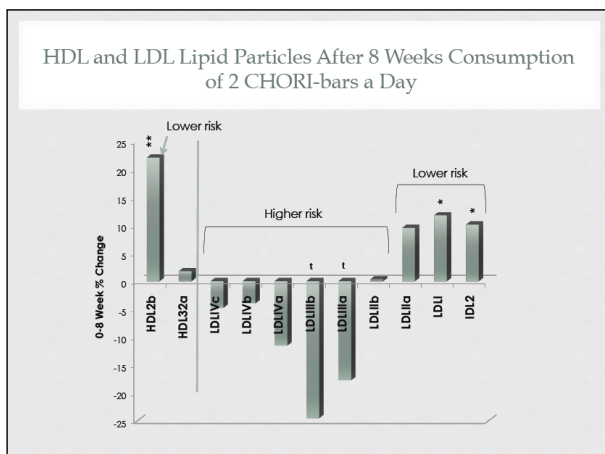
Results were striking, as shown in the 2 figures.

Statistically significant improvements were observed in indicators of cardiovascular health [HDL-c (primarily the less atherogenic particle HDL 2b), the LDL particle profile, triglycerides, heart rate, diastolic blood pressure], glucose metabolism (insulin resistance, insulin, glucose), inflammation (high sensitivity C-reactive protein: hsCRP) and obesity (weight, waist circumference). Improvements occurred primarily in the OW/OB with less chronic inflammation, as measured by high sensitivity C-reactive protein (hsCRP<1.5).



The average change in the overweight/obese after 8-weeks consumption of 2 CHORI-bars each day is plotted as a percent of the overall average of each measure before eating the CHORI-bar. DBP = diastolic blood pressure; HOMA-IR is a measure of insulin resistance that incorporates changes in glucose and insulin. hsCRP = high sensitivity c-reactive protein, the standard clinical measure of chronic inflammation

As shown in the above figure, there do not appear to be any changes in LDL cholesterol (LDL-c). But, LDL-c is actually comprised of a collection of particles of different sizes. In general, people who have mostly smaller, denser particles are at greater risk for cardiovascular disease. CHORI-bar consumption actually shifted the LDL particle profile toward one with less cardiovascular risk. The “higher risk” particles all decreased, and the “lower risk” particles increased. Thus, while there was not a significant overall decrease in total LDL cholesterol, there was a striking shift toward a lower risk LDL profile. The 2 HDL particles shown on the left side of the figure are a large “low risk” particle (HDL2b) and smaller “higher risk” particles (HDL3 2a).



Almost all of the increase in HDL cholesterol is due to increase in the lower risk particle HDL2b, as was also observed in our study of lean adults.⁵

We think the broadscale improvements in virtually all aspects of the dysregulation of obesity by CHORI-bar consumption may be due to the restoration of impaired critical underlying functions, such as poor energy production by mitochondria and an unhealthy gut wall. Restoration of these critical functions by supply of

dietary components deficient in Western diets with the CHORI-bar would be expected to have multiple favorable consequences similar to those observed.

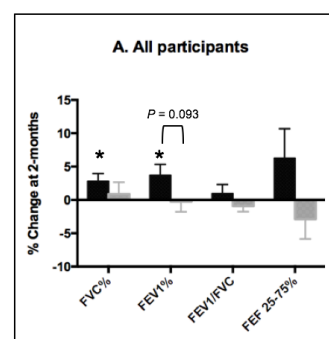
Obesity-Associated Conditions. Obesity per se does not increase disease risk; the culprit is the metabolic dysregulation that accompanies obesity in about 70% of the obese and about 30% of the lean. A primary motivating factor guiding our research is the conviction that the key to reducing disease risk in all people is restoring healthy metabolism. Thus, we believe that the primary focus of the medical community on weight loss as the solution for obesity-associated conditions is misdirected, and we think that it is plausible that restoring healthy metabolism will improve these conditions and make it easier to achieve and maintain a healthy weight⁶. We have begun to use the CHORI-bar, which we know improves metabolism, as a tool to explore the viability of this hypothesis. We have obtained evidence that 8-weeks consumption of 2 CHORI-bars a day improves lung function without weight loss in obese teenagers with poorly controlled asthma⁷



A family-based 8-week pilot clinical trial was conducted in obese adolescent in collaboration with our Children's Hospital pulmonary department.⁷ Asthma in the obese is poorly understood. It is often severe, difficult to treat, and characterized by less eosinophilic inflammation than asthma in the non-obese. The characteristic of obese asthma that led us to test whether the CHORI-bar might be of help is that it occurs in people who have the kind of metabolic dysregulation that the CHORI-bar improves. In a clinical trial conducted in the summers of 2012 and 2013, overweight/obese teen-age asthmatics and their parent/guardian attended weekly classes for 8 weeks and the teens ate 2 CHORI-bars daily. A comparable group of obese asthmatics attended parallel classes but were not given the CHORI-bar to eat. At each class, participants received the same nutrition and exercise instruction. At the end of 8 weeks, effects of CHORI-bar consumption on lung function and metabolism were compared.

The figure shows results in the CHORI-bar group (black columns) compared to the control group (grey columns). Different measures of lung function are shown: Forced Expiratory Volume, the amount of air that can be forcefully breathed out of the lungs in 1 second ("FEV1"), Forced Vital Capacity, the total amount of air that can be forcefully breathed out ("FVC"), and Forced Expiratory Flow, the speed that air is breathed out during the middle half of FVC ("FEF 25-75%"). As shown, lung function improved only in the group that ate CHORI-bar. An important additional result of this study is that lung function improved only in participants who had a relatively low level of internal chronic inflammation. Figure A includes all participants, and Figures B and C show results in the low inflamed and higher inflamed participants respectively.

Optimization for Maximal Benefit. Because the composition of CHORI-bar is controlled and defined, it can be used in a cost-effective way to understand how diet and dietary components interact with metabolic pathways in disease and health. As a research tool, the CHORI-bar presents significant opportunities to better understand mechanisms whereby nutrients delivered at physiological doses in a food-based matrix positively impact metabolism linked to future disease risk. This is virtually impossible to do, and enormously expensive, with an entire diet that must be individually controlled and managed in every participant. Because of the CHORI-bar's potency, it is effective without requiring participants to modify their existing diets. Thus, clinical trials of "deconstructed" CHORI-bars offer a new approach for understanding relationships between diet and disease, which will provide the information needed to optimize diets that prevent disease. A series of clinical trials was conducted to determine which CHORI-bar ingredients are required to simultaneously raise HDL-c and lower LDL-c. Results indicated that at least three different types of CHORI-bar components were



Deleted:

required (unpublished results). Additional “deconstruction” trials can help to design the optimum diet for improving other aspects of metabolism linked to disease risk.

Conclusion. The power of nutrient-rich, properly formulated food-based supplements to restore healthy metabolism and thereby prevent or ameliorate disease has not yet been adequately appreciated by the medical and scientific communities. This is in part because the field of nutritional supplements and natural products is tainted by uncritical and biased science. It is also because complex food-based supplements are not usually suitable for traditional placebo-controlled, double-blind clinical trials, considered the “gold standard” for testing drug efficacy.

These problems should not deter serious investigators because the promise of appropriately formulated nutritional supplements to prevent and ameliorate disease is enormous and could be paradigm-shifting. Why use an expensive drug with undesirable or unknown side effects to improve cholesterol when the same effect may be possible with a natural food-based supplement that has no negative side effects? The full potential of food-based supplements to do the work of some drugs without their negative side effects is just beginning to be seriously investigated, but it will require critical un-biased scientific investigation and creative experimental designs.

Current Status. After more than 12 years of research, we now have available a precisely formulated, nutrient-rich, fruit-based supplement bar that significantly improves key features of the metabolic dysregulation of obesity and its related co-morbidities. A U.S. patent application claiming CHORI-bar formulations, composition-of-matter and uses has been filed⁸. CHORI-bar’s dietary approach, naturally efficacious without undesirable side effects, has the potential to provide a healthy alternative to drugs for treatment of obesity-related conditions. In January 2018, Keen Growth Capital, an impact investment fund that focuses on new food and beverage brands and technologies that improve health and wellness, acquired the patent rights to the CHORI-bar and have created a company (Advanced Micronutrition) that is developing a product for market that will preserve the CHORI-bar formula.

THE CHORI-BAR IS UNIQUELY POSITIONED
TO HAVE A POSITIVE IMPACT ON HEALTH

- To help people transition to healthier dietary habits – people feel better when they eat the bar.
- To improve metabolic conditions known to lead to obesity-associated diseases (e.g., type 2 diabetes, hypertension, cardiovascular disease), and thus to reduce future risk of these diseases.
- To promote weight loss – weight loss requires metabolic flexibility which, based on its metabolic effects, should be enabled by the CHORI-bar.

¹ Ames, B. N. Low micronutrient intake may accelerate the degenerative diseases of aging through allocation of scarce micronutrients by triage. PNAS 103, 17589-17594 (2006)

² Ames, B. N. Prevention of mutation, cancer, and other age-associated diseases by optimizing micronutrient intake. J Nucleic Acids pli:725071. doi:10.4061/2010/72507 (2010)

³ McCann, J. C., and Ames, B. N. Vitamin K, an example of triage theory: is micronutrient inadequacy linked to diseases of aging? Am J Clin Nutr 90, 889-907 (2009)

⁴ McCann, J. C., and Ames, B. N. adaptive dysfunction of selenoproteins from the perspective of the triage theory: why modest selenium deficiency may increase risk of diseases of aging. FASEB J 25, 1793-1814 (2011)

⁵ Mietus-Snyder, M. L., Shigenaga, M. K., Suh, J. H., Shenvi, S. V., Lal, A., McHugh, T., Olson, D., Lilienstein, J., Krauss, R. M., Gildengoren, G., McCann, J. C., and Ames, B. N. A nutrient-dense, high-fiber, fruit-based supplement bar increases HDL cholesterol, particularly large HDL, lowers homocysteine, and raises glutathione in a 2-wk trial.

FASEB J 26, 3515-3527 (2012)

⁶McCann, J. C., Shigenaga, M. K., Mietus-Snyder, M. L., Lal, A., Suh, J. H., Krauss, R. M., Gildengorin, G. L., Goldrich, A. M., Block, D. S., Shenvi, S. V., McHugh, T. H., Olson, D. A., and Ames, B. N. (2015) A multi-component nutrient bar promotes weight loss and improves dyslipidemia and insulin resistance in the overweight/obese: Chronic inflammation blunts these improvements. *FASEB J* 29, 3287-3301 (2015).

⁷Bseikri, M., McCann, J.C., Lal, A., Fong, E., Graves, K., Goldrich, A., Block, D., Gildengoren, G.L., Mietus-Snyder, M., Shigenaga, M., Suh, J., Hardy, K., Ames, B.N. A novel nutritional intervention improves lung function in overweight/obese adolescents with poorly controlled asthma: The Supplemental Nutrition in Asthma Control (SNAC) Pilot Study. *FASEB J in press* (2018).

⁸CHRCO/CHORI (2009). Pending United States patent application no. 13/877,103, owned by Children's Hospital & Research Center Oakland, California.