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File: ▪ Cocoa (*Theobroma cacao*)
▪ Cognitive Function
▪ Blood Pressure
▪ Insulin Resistance

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RE: Cocoa Flavanol Consumption Demonstrates Cognitive Improvements in First Long-term Study in Older Adults with Mild Cognitive Impairment

Desideri G, Kwik-Uribe C, Grassi D, et al. Benefits in cognitive function, blood pressure and insulin resistance through cocoa flavanol consumption in elderly subjects with mild cognitive impairment: The Cocoa, Cognition, and Aging (CoCoA) study. *Hypertension.* 2012;60(3):794-801.

Cocoa (*Theobroma cacao*) has been associated with cognitive benefits. Mild cognitive impairment (MCI) can lead to dementia, but at this earlier stage can be impacted positively by dietary intervention. Flavanols, such as those found in cocoa, have been shown to reverse age-related cognitive decline by increasing the number and strength of connections between neurons, reducing neuronal loss attributed to neurodegenerative processes, and interacting with the cellular and molecular architecture of the brain responsible for memory. In addition, there is strong evidence of a link between cognitive health and cardiovascular health and insulin function, both of which can also be favorably impacted by flavanols. This double-blind, randomized, parallel-arm study is the first to examine the effects of a beverage containing cocoa flavanols on the cognitive performance of patients with MCI. Effects on blood pressure, glucose metabolism, and oxidative stress were also studied because of their probable effect on cognitive function.

Patients (n=90; aged 65-82 years) who had been referred for MCI and were diagnosed according to the revised Petersen criteria were recruited from the University of L'Aquila Geriatric Division (L'Aquila, Italy). After a 1-week run-in period, patients were randomly assigned to receive a dairy-based cocoa drink containing cocoa flavanols (Cocoapro® processed powder; Mars, Inc.; McLean, Virginia) at either a high-flavanol (HF; ~990 mg of flavanols per serving), intermediate-flavanol (IF; ~520 mg of flavanols per serving), or low-flavanol level (LF; ~45 mg of flavanols per serving) for 8 weeks. The 3 drinks were matched for taste, appearance, and caloric, macronutrient, caffeine, and theobromine content. The LF drink was made with a highly processed, alkalized cocoa powder.

The primary outcome measure was a change in cognitive function after 8 weeks of treatment. Secondary outcome measures were changes in blood pressure, metabolic parameters, and plasma markers of lipid peroxidation. Cognitive function was assessed at baseline and 8 weeks using a combination of 4 well-validated standardized tests – the Mini-Mental State Examination (MMSE), Trail Making Test (TMT)-A, TMT-B, and a verbal fluency test.

The study population did not consist of any individuals who were obese, smokers, or taking statins. There was no difference in anthropometric parameters or dietary flavanol intake between the 3 groups. Two patients withdrew from the IF group for personal reasons, and 1 patient withdrew from the LF group due to gastrointestinal discomfort; however, they were followed up for the duration of the study and were included in the intention-to-treat analysis. Compliance was greater than 99% for all groups at both 4 and 8 weeks, and patients complied with the restriction on consuming other flavanol-rich foods and beverages during the study period.

Baseline cognitive performance was similar between groups, showing that randomization was adequate. The MMSE did not change for any of the treatment groups compared to their baselines (P<0.13).

The time to complete the TMT-A declined significantly for both the HF (-14.3 ± 4.2 seconds; P<0.0001) and IF (-8.8 ± 3.4 seconds; P<0.0001) groups, but not for the LF group (+1.1 ± 13.0 seconds; P<0.65). Similar results were seen for the TMT-B, with significant reductions among the HF (-29.2 ± 8.0 seconds; P<0.0001) and IF groups (-22.8 ± 5.1 seconds; P<0.0001), but not in the LF intervention (+3.8 ± 16.3 seconds; P<0.21). For the TMT-A and TMT-B, both the HF and IF groups were significantly better than the LF group (P<0.05).

Verbal fluency test scores also significantly improved in both the HF (+8.0 ± 5.3 words per 60 seconds) and IF (+5.1 ± 3.1 words per 60 seconds) (P<0.0001 for both) groups, but not in the LF group (+1.2 ± 2.7 words per 60 seconds). The HF group scores were statistically significantly higher than the LF group scores (P<0.05).

Given these changes, the composite cognitive *z* score significantly changed during the study period (P<0.0001), with significant improvement in both the HF (+0.693 ± 0.223; P<0.0001) and IF (+0.404 ± 0.141; P<0.0001) groups, but no change in the LF group (-0.072 ± 0.383; P<0.31). The composite cognitive *z* score was significantly better in the HF group compared to that of the LF group (P<0.05).

There were no differences in blood pressure or other metabolic parameters between the groups at baseline. Blood pressure decreased significantly in both the HF (systolic: -10.0 ± 3.1 mmHg, P<0.0001; diastolic: -4.8 ± 1.8 mmHg, P<0.0001) and IF (systolic: -8.2 ± 3.5 mmHg, P<0.0001; diastolic: -3.4 ± 2.0 mmHg, P<0.0001) groups, but not in the LF group (systolic: -1.4 ± 5.4 mmHg, P=0.16; diastolic: -0.9 ± 3.4 mmHg, P=0.14). The HF and IF scores for both systolic and diastolic blood pressure were statistically significantly higher than the LF scores (P<0.05).

Plasma glucose levels decreased significantly in the HF (-0.6 ± 0.3 mmol/L; P<0.0001) and IF (-0.5 ± 0.1 mmol/L; P<0.0001) groups, but not in the LF group (-0.1 ± 0.5 mmol/L; P=0.19). The glucose levels for the HF and IF groups were statistically significantly higher than the LF levels (P<0.05). The homeostatic model assessment of insulin resistance (HOMA-IR) also improved significantly in the HF (-1.6 ± 1.0; P<0.0001) and IF (-0.9 ± 0.2; P<0.0001) groups, but not in the LF group (-0.1 ± 0.5; P=0.29). There was a significant correlation between changes of plasma glucose and HOMA-IR during treatment compared to baseline levels (r=-0.325, P=0.0018 and r=-0.421 and P<0.0001, respectively). No significant differences were found in plasma insulin levels for any group.

No significant differences were found in total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, or triglycerides for any group. Plasma total 8-iso-prostaglandin $F_{2\alpha}$ (8-iso-$PGF_{2\alpha}$) levels significantly decreased in the HF (-99.8 ± 60.3 pg/L; P<0.0001) and IF (-65.2 ± 87.2 pg/L; P=0.0003) groups, but not in the LF group (-3.6 ± 51.4 pg/L; P=0.71). The HF and IF scores for plasma total 8-iso-$PGF_{2\alpha}$ levels were statistically significantly higher than the LF scores (P<0.05).

Changes of HOMA-IR were found to be the main determinants of changes in cognitive function, explaining ~40% of the composite cognitive *z* score variability through the study period (r^2=0.4013, β=-0.2910; P<0.0001). Changes in systolic blood pressure levels and plasma isoprostane concentrations explained ~2% and ~7% of the cognitive improvement throughout the study period, respectively.

This paper describes the first, well-controlled dietary intervention study of this size and duration using multiple doses of cocoa flavanols to show cognitive benefits in older adults with MCI, in particular for processing speed, executive function, language, and working memory. The lack of effect on the MMSE may reflect its low sensitivity to detect small changes at the upper levels of function.

Though the use of 2 different doses did show a dose-dependence, the study did not determine effective dose levels. It also did not elucidate the mechanisms by which cognitive improvements occurred; however, results do suggest a possible influential role of insulin resistance in modulating cognitive function. Cardiovascular parameters (blood pressure), oxidative stress (isoprostane), and increased blood perfusion in the brain may also contribute to the improvements seen.

While the results of the intervention were quite remarkable, their clinical significance must be considered carefully, given the testing of only some aspects of complex cognitive functions, the short 2-month duration, the use of a healthy population, and the inability to distinguish whether cognitive improvements were due to cocoa flavanols, or rather, their effects on the cardiovascular system which in turn affected cognition.

Nonetheless, the authors conclude by saying, "The results of the current study provide encouraging evidence that the regular inclusion of flavanol-containing foods may be an effective dietary approach for improving some aspects of cognitive dysfunction in adults with MCI."

—Risa Schulman, PhD

The American Botanical Council has chosen not to reprint the original article.