Talsma EF, Brouwer ID, Verhoef H, Mbera GNK, Mwangi AM, Demir AY, Maziya-Dixon B, Boy E, Zimmermann MB, Melse-Boonstra A. **Biofortified yellow cassava and vitamin A status of Kenyan children: a randomized controlled trial. American Journal of Clinical Nutrition.** January 2016. Vol 103 No 1. Pages 258-267.

Introduction

The estimated prevalence of vitamin A deficiency (VAD) was 29% among all low and middle-income countries and 48% for Sub-Saharan Africa in 2013 (1). This burden is predicted to contribute to 105,700 excess deaths globally, with 62,500 of those occurring in sub-Saharan Africa. Increasing vitamin A intake through biofortification of staple foods, such as cassava or maize, with provitamin A carotenoids has several potential advantages, including 1) expected low cost of the intervention after breeding and testing are complete, 2) the potential to reach rural populations that may not have consistent access to health service delivery platforms, and 3) because conversion of β-carotene to retinol is regulated, β-carotene does not contribute to excessive vitamin A. Yellow cassava varieties with high provitamin A content have been identified and selectively bred with African varieties, which are typically white, with no vitamin A.

This issue of NNA describes the results of a study published in the *American Journal of Clinical Nutrition* (2). The objective of the study was to test the effect of consumption of yellow cassava on the vitamin A status of children with mild to moderate vitamin A deficiency in Kenya. The investigators also explored whether zinc status and β-carotene monooxygenase (BCMO1; the enzyme responsible for converting β-carotene to retinol) genotype would modify the effect of the intervention.

Methods

The study was conducted as a randomized, controlled trial among children 5-13 years of age in rural Kenya. After screening 1177 children, the 360 children with the lowest plasma retinol-binding protein concentrations (and who did not have malaria, severe anemia, or history of morbidity in the past 14 days) were identified. The selected children participated in a "run-in" period which included deworming followed by consumption of white cassava and placebo capsules for 2 weeks. The purpose of this "run-in" period was to identify children who may be likely to drop out during the study.

Hemoglobin (Hb) concentration and C-reactive protein concentration (CRP) were measured at the end of the run-in period (baseline for the trial) and children with Hb < 70 g/L or CRP > 8 mg/L were excluded. Subsequently, the 342 remaining eligible children were randomly assigned to one of three groups: control (white cassava and placebo supplement), yellow cassava group (provitamin A-rich cassava and placebo supplement), and β-carotene supplement group (white cassava and β-carotene supplement). The cassava was planted so that it could be harvested daily during the study. Cassava was boiled, mashed with oil, and served as a snack, 6 days per week, for 18.5 weeks. The amount of cassava eaten was recorded daily. The investigators and participants were blinded with respect to the contents of the supplement capsule (placebo or β-carotene), but not to the type of cassava (white or yellow). The yellow cassava contained 4.7-6.9 μg/g total β-carotene (fresh weight) and was served in 375 g cooked portions, and the supplement capsules contained 1053 μg

β-carotene or only starch filler.

Serum concentrations of retinol, carotenoids, zinc, prealbumin (transthyretin), and markers of iron status (ferritin and soluble transferrin receptor) and inflammation (CRP and α_1-acid glycoprotein, AGP) were measured at baseline and after the intervention period. Retinol-binding protein was also measured at the end of the intervention, and BCMO1 variants were assessed by genotyping. Dietary intake was assessed during the intervention by 24 hour dietary recalls in all subjects, and duplicates in a ~1/3 subset.

Results and Conclusions:

At baseline, 21-26% of children had inflammation (elevated CRP and/or AGP). Among children without inflammation, serum retinol concentrations were in the range of 0.82 to 0.84 μmol/L, with 22-24% < 0.70 μmol/L; vitamin A status did not differ by group. Less than 5% of children had plasma zinc concentration <9.9 μmol/L, 6-7% were anemic (Hb <115 g/L for children 5-11 y and < 120 g/L for children > 12 y) and 31-42% had ferritin concentration < 15 μg/L (among those without inflammation).

Compliance with the cassava consumption was 100%. Estimated daily vitamin A intakes including the yellow cassava intervention were 22 μg retinol activity equivalents (RAE)/d (control group), 220 μg RAE/d (yellow cassava group; 1463 μg β-carotene/day from cassava), and 175 μg RAE/d (β-carotene supplement group; 1053 μg β-carotene/day from supplement).

Adjusting for baseline values and endline CRP and AGP concentrations, serum retinol concentrations in both the yellow cassava and β-carotene supplement groups increased by 0.04 μmol/L (95% CI: 0.00-0.07 μmol/L) compared to the control group. However, the prevalence of vitamin A deficiency did not differ significantly. Serum β-carotene concentrations increased significantly by 524% and 166%, in the yellow cassava and β-carotene supplement groups, respectively.

There was no change in RBP, prealbumin, or Hb concentrations. The intervention effect on serum retinol was not modified by baseline vitamin A or zinc status, or BCMO1 genotype.

Policy Implications:

This study suggests that, in populations with marginal vitamin A status, provitamin A-rich yellow cassava is efficacious in increasing serum retinol concentrations. However, the effect was modest and did not appear to be stronger in those with lower baseline vitamin A status, as would be expected. The large increases in serum β-carotene indicate that β-carotene was absorbed but not converted to retinol. It is possible that poor bioconversion was related to genetic factors, or other micronutrient deficiencies, but low sample size of individuals with low serum zinc or certain BCMO1 variants may have limited the ability to detect effect modification by these characteristics. The lack of effect on RBP may be explained by lack of baseline values to assess change within individuals.

NNA Editor's Comments *

The strengths of this study include the randomized controlled design, individual screening for low vitamin A status, and the low attrition and high compliance. Although the population appeared to have marginal vitamin A status, the effect might have been greater in a more deficient population.

Inflammation (primarily due to infection) causes transient decreases in serum retinol concentrations. The authors controlled for inflammation at the endline blood draw, but not inflammation at baseline, which could potentially alter the results. Because iron is necessary for the activity of the enzyme that converts β-carotene to retinol (3), further work could explore whether the high prevalence of iron deficiency may have limited the efficacy of conversion to retinol.

Biofortified crops, such as yellow cassava, have the potential to safely increase vitamin A status in vulnerable populations, although more research is needed on the efficacy, acceptability, and cost of these programs. Where the effect of these foods on micronutrient status is expected to be modest, complementary programs may be needed to fully address the burden of VAD and other micronutrient deficiencies.

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