

Calorie Control Council Response to Choi Editorial “The not-so-sweet side of fructose”

Choi ME. The not-so-sweet side of fructose. *J Am Soc Nephrol* 2009;20:457-9.

Background

This editorial comes from the Department of Medicine, Brigham and Women’s Hospital, Harvard Medical School, Boston. It is written in support of the paper published simultaneously in the *Journal of the American Society of Nephrology* by Cirillo et al in RJ Johnson’s group in Florida entitled, “Ketoheokinase-dependent metabolism of fructose induces proinflammatory mediators in proximal tubular cells.”(1)

Author Justification

Metabolic syndrome has become a global epidemic over the past 20 years, largely attributed to a parallel rise in obesity. Though there are many contributing factors, including the shift to a junk food diet with excessive calorie intake and sedentary lifestyle, an increase in fructose intake is also implicated.

Choi’s not-so-sweet side of fructose

- We have “morphed insidiously into a fructose nation.”(2)
- There has been a marked increase in daily intake of fructose, largely due to widespread use of high fructose corn syrup (HFCS) in beverages (3).
- Links between soda consumption, HFCS and chronic kidney disease (CKD):
 - Metabolic syndrome
 - Insulin-resistant diabetes
 - Kidney disease
 - Albuminuria (4)
 - Kidney stones (5)
 - Gout (6)

Author: Mechanism by which fructose increases risk for CKD

A high-fructose diet induces features of metabolic syndrome in rats (7, 8 [RJ Johnson]): hyperinsulinemia, hypertriglyceridemia, hypertension, weight gain, glomerular hypertension and hyperuricemia. Proposed mechanisms include: insulin resistance, lipotoxicity, oxidative stress, endothelial dysfunction and hemodynamic alterations. And fructose-induced hyperuricemia likely has a pathogenic role (8).

Cirillo/Johnson work and significance

This group previously reported that high-fructose diets accelerate progression of CKD in the rodent remnant kidney model associated with an inflammatory response in the kidney (9 [RJ Johnson]). Cirillo et al (1) report in this paper that fructose induces a proinflammatory response in human proximal tubular epithelial cells through a ketoheokinase-dependent mechanism.

Choi views this work as significant because it:

- Establishes a potential role for direct and detrimental effects of fructose on proximal tubular [kidney] epithelial cells;
- Takes a step toward unraveling the mechanism that may be a causal link between high-fructose intake and metabolic syndrome and the development of renal disease; and
- Extends previous reports of fructose-induced inflammatory state in the kidney that may contribute to the progression of CKD.

Author conclusions and recommendations

1. The potential importance of Cirillo's work to humans remains to be established, though it provides mechanistic insight into the renal consequences of high-fructose intake.
2. Cirillo's work raises concern regarding short- and long-term effects of fructose and its risk to humans. Further human studies are needed to determine whether fructose is causally implicated or there are *yet-unmeasured factors, such as lifestyle and other confounders*.
3. There is urgent need to determine whether policy recommendations regarding sugary soda and high-fructose consumption should be implemented *in the strongest terms*.
4. Tackling this issue will be a major challenge ahead, given the enormous public health implications posed by the worldwide epidemic of metabolic syndrome, especially in children and adolescents who will grow into adulthood, *before it becomes a tsunami of CKD that cannot be prevented*.

Critique

- Choi's metabolic syndrome-based justification is an extension of the well-publicized HFCS/obesity hypothesis of Bray (3) and an endorsement of the RJ Johnson view on fructose. Many of the key citations are to Johnson's work. It is an attempt to build urgency for fructose as a key player in metabolic syndrome and obesity. Note that Choi attempts to elevate the risk of fructose by creating a new and equilateral triumvirate of obesity causes: excessive caloric intake, insufficient caloric expenditure and too much dietary fructose. No perspective is offered to support the promotion of fructose to such prominence.
- The argument that fructose intake has increased in recent decades fails to address the concomitant and equivalent increases in *all* macronutrient categories over the same period (10).
- Though there is abundant literature demonstrating untoward effects of fructose at excessive levels, there is no evidence to support a unique causative role for fructose in either obesity or the metabolic syndrome at common intake levels.
- The rat diet of Cirillo is a serious distortion of the way in which humans consume sweeteners.
 - The primary nutritive sweeteners (sucrose, HFCS, honey, fruit juice concentrates) contain roughly half glucose and half fructose. A diet of fructose as the only simple sugar does not reflect the diet of any human population.
 - Comparing rats fed diets in which carbohydrates are either pure fructose or completely complex has no meaning in the real world, since humans consume mixtures of carbohydrates.
 - It is a huge extrapolation from rat and tissue culture studies at excessive fructose doses to humans at a fraction of the exposure level. That humans are similarly affected has not been established.
 - Feeding rats 60% of calories as fructose exceeds typical human exposure by 6-fold (11). Translating this regimen to humans creates an impossible and preposterous scenario: relying on common nutritive sweeteners (half fructose, half glucose) as the source of fructose, subjects would be forced to consume *all* their calories as sweetener. This is clearly an inappropriate experimental setup from which to make predictions of real world medical outcomes.
- Choi's call for development and implementation of public policy based on Cirillo's experimentation gives it undeserved significance and is ill advised, given the highly contrived nature of study designs and exaggerated levels of dietary fructose.
- Choi is entirely justified in concluding that Cirillo's work provides mechanistic insight into the renal consequences of high-fructose intake—this is its proper and defensible contribution to the literature.

References

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