Letter to the Editor

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Convicting a wrong molecule?

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To the Editor,

Dr. Tilg's brilliant insights on metabolic diseases are well-known. However, we do not agree with his commentary on artificial sweeteners appeared in the *New England Journal of Medicine* [1]. The results presented by numerous bench scientists require a focused re-appraisal, because these scientists are not familiar with confounding or biases [2]. For example, Dr. Tilg quoted the report by Zani et al. that sucralose inhibited T-cell mobilization in mice. Since sugar is the key energy source for immune-activation [3], this study proves that sucralose is not a major source of sugar. The second article Dr. Tilg quoted was by Suez et al. who fed mice a high fat diet and saccharin and observed glucose intolerance. High fat diet is an independent risk factor for glucose intolerance [4]. Thus, we cannot blame saccharin as the true culprit of glucose intolerance when two risk factors coexist. The third article Dr. Tilg cited was Witkowski and colleagues' report [5]. They claimed that erythritol increased platelet activation. However, the process generating platelet-rich-plasma which Witkowski et al. used can activate platelets [6]. Moreover, erythritol can be synthesized endogenously from glucose via the pentose-phosphate-pathway and those who developed obesity have 15-fold higher blood erythritol levels than those without obesity [7]. Thus, glucose may be the key contributor to obesity which activates platelets. When we examined the distribution of CVD risk factors per erythritol levels from Witkowski et al.'s supplementary table (our Table 1), highly positive correlations between cardiovascular risk factors and erythritol levels emerged. Thus, it is likely that major cardiac events in the study of Witkowski et al. [5]. may be due to the underlying cardiovascular risk factors and erythritol may be an epiphenomenon.

Table 1: Distribution of CVD risk factors per erythritol levels in US validation cohorts.

	Erythritol Q1	Erythritol Q2	Erythritol Q3	Erythritol Q4	p-Value
Diabetes mellitus, %	12.4	15.7	23.9	36.6	<0.001
CAD, %	66.7	71.1	77.4	85.0	<0.001
Heart failure, %	16.1	21.2	26.7	37.9	<0.001
History of MI, %	30.9	35.9	41.2	50.1	<0.001
Triglycerides, mg/dL	103	111	119	131	<0.001

Adapted from supplementary table of Witkowski et al. [5].

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