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## Is Plasma Pentadecanoic Acid a Reasonable Biomarker of Dairy Consumption?

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## Is Plasma Pentadecanoic Acid a Reasonable Biomarker of Dairy Consumption?

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Despite advances in biomedical research and clinical medicine, the burden of cardiovascular disease (CVD) remains extremely high.<sup>1</sup> This underscores the importance of primary prevention and the search for novel therapeutic strategies. Modifiable lifestyle factors, including dietary habits, play a critical role in the primary and secondary prevention of CVD.<sup>2–4</sup> Among food groups, dairy products have been studied for many years partly due to concerns that saturated fat contained in dairy foods may raise low-density lipoprotein cholesterol, a major risk factor for CVD. However, reported effects of saturated fats and dairy products including milk, butter, cheese, yoghurt, etc, on CVD risk have been inconsistent.<sup>5–11</sup>

Such inconsistency could be partly attributable to the type of fatty acids in dairy products, the amount of fat per fixed quantity in dairy products (ie, fat-free milk versus reduced-fat/whole milk), and difficulties in accurate assessment of dairy consumption in population science. Of note is that in large epidemiologic studies and randomized trials, dietary assessment is mostly completed via food frequency questionnaires, food diary for a short-term period, or 24-hour dietary recall to minimize costs. More importantly, several food groups lack reliable and valid biomarkers that can be used to assess their intake. These limitations could introduce bias in studies assessing the relation or effects of dairy products with CVD (due to exposure misclassification, erroneous or missing values).

In this issue of *JAHA*, Otto et al<sup>12</sup> address one of the above gaps by examining whether plasma phospholipid fatty acids

such as pentadecanoic acid (15:0), myristic acid (14:0), and *trans*-palmitoleic acid (*t*16:1n7) could serve as biomarkers for dairy intake and the association of those fatty acids with CVD risk in about 2800 US adult men and women from the Multi-Ethnic Study of Atherosclerosis (MESA). The authors found that plasma phospholipid pentadecanoic acid was positively correlated with self-reported total dairy intake (Spearman correlation coefficient of 0.22), regular cheese ( $r=0.20$ ), whole-fat dairy ( $r=0.16$ ), low-fat dairy ( $r=0.17$ ), and butter ( $r=0.13$ ). Each standard deviation of pentadecanoic acid was associated with 19% lower risk of CVD (95% CI: 2% to 32%) and 26% lower risk of coronary heart disease (95% CI: 8% to 40%) in multivariable adjusted models. Plasma phospholipid myristic acid was weakly correlated with self-reported total dairy ( $r=0.14$ ), whereas *trans*-palmitoleic acid was not correlated with self-reported total dairy ( $r=0.07$ ). Lastly, in multivariable analyses, there was no meaningful association of either plasma phospholipid myristic acid or *trans*-palmitoleic acid with CVD risk. These data suggest that plasma phospholipid pentadecanoic acid could be a reasonable biomarker of dairy intake. In addition, current data raise the following question: What implications do current findings underscore for the scientific community and translational medicine?

It is important to acknowledge some weaknesses inherent to the current study. Although plasma levels of 15:0 were measured using a reproducible and valid method, self-reported dairy intake used to estimate Spearman correlation coefficients is far from optimal due to potential recall bias. A long-term intervention with known quantity and quality of dairy product(s) would be ideal to estimate the true correlation between plasma 15:0 and consumed dairy product(s). Concentration of plasma 15:0 is relatively low (median below 1% of total fatty acids), suggesting that small measurement errors could have a larger impact on reported values. A large coefficient of variation (14.5%) for pentadecanoic acid is consistent with the above conjecture. In addition, a wide range of Spearman correlation of plasma 15:0 with various dairy products (ranging from 0.05 for 2% milk to 0.20 for regular cheese) suggests that content of 15:0 may vary across individual dairy products. Alternatively, reporting error may vary by types of dairy products. Given a diversity of individual dietary patterns, it is important to recognize that

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plasma phospholipid 15:0 would then vary according to the type of dairy foods consumed. Lastly, despite an observed association of plasma 15:0 with CVD risk, it is important to emphasize that 15:0 cannot be singled out as a causal nutrient responsible for the overall effect of dairy products. Dairy products are a good source of other nutrients known to exert CVD benefits including vitamin D and calcium.<sup>13,14</sup> Furthermore, people consume dairy products as part of overall dietary patterns, underscoring the importance of nutrient/nutrient, nutrient/drug, or nutrient/other lifestyle interactions on CVD risk. The contribution of such interaction cannot be estimated from current results.

Nonetheless, current findings are consistent with previous data supporting the role of plasma 15:0 as a biomarker of dairy intake.<sup>5,15–17</sup> In older men aged >70 years, phospholipid 15:0 was positively correlated with total dairy assessed by 7-day records ( $r=0.34$ ).<sup>17</sup> A similar correlation was observed in the Nurses' Health Study ( $r=0.29$ ).<sup>5</sup> Inverse relation of plasma 15:0 with CVD is consistent with the notion that dairy products may confer cardiovascular benefits.<sup>9,11,18,19</sup> However, it remains important for consumers to consider their overall dietary patterns, which should favor a healthy diet that is rich in fruits, vegetables, and whole grains, but low in sodium, red meats, sugar sweetened beverages, trans fat, etc.<sup>20</sup>

Future endeavors are necessary to confirm the utility of plasma 15:0 as a biomarker of dairy intake using better designs to assess dairy intake. Ideal biomarkers should be quantifiable with a reasonable coefficient of variation and their blood levels should not be influenced by endogenous biosynthesis. Lastly, ideal biomarkers should be cost-effective to allow for usage in large epidemiologic studies or trials and their blood levels should increase upon external supplementation.

In summary, there is a growing body of evidence in support of potential biomarkers for dairy intake, especially pentadecanoic acid. However, additional work from randomized trials where subjects are fed specific amounts and types of dairy products is needed before making general recommendations for the use of pentadecanoic acid as valid biomarker of dairy intake.

## Disclosures

None.

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