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Commentary

Diabetes risk associated with plasma epoxylipid levels

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An association of plasma epoxylipids, epoxyeicosatrienoic acids (EETs), and their corresponding diols, dihydroxyeicosatrienoic acids (DHETs), with diabetes risk in American Indians was identified by Lemaitre et al. in this edition of *EBioMedicine* [1]. The findings of this prospective study on plasma samples from the Strong Heart Study found a novel association of high total plasma 14,15-DHET levels with lower plasma insulin and lower glucose levels. On the other hand, the study failed to find an association for total plasma EETs and DHETs and diabetes risk among American Indians. These findings add to previous animal and human studies that demonstrate epoxylipids could importantly contribute to diabetes [2,3]; however, the current findings suggest that the contribution for 14,15-DHET requires further investigation.

The importance of arachidonic acid epoxylipids in metabolic diseases including diabetes has been demonstrated in animal disease models and human studies [2,3]. EETs are generated from arachidonic acid by CYP2C enzymes. EETs are subsequently metabolized by soluble epoxide hydrolase (sEH) to DHETs (Fig. 1). Several biological actions including vasodilation, anti-inflammation, and natriuresis have been demonstrated for EETs [3]. In contrast, the DHETs have been found to be less active or inactive [3]. Animal metabolic disease and diabetes studies have found that increasing EET levels pharmacologically or genetically results in improved insulin sensitivity and decreased diabetes associated cardiovascular and kidney damage [2]. Human studies have also found compelling evidence that decreased EET levels and increased degradation by sEH to DHETs contribute to cardiovascular disease risk [3]. Increased insulin sensitivity in humans is associated with a genetic polymorphism in *EPHX2*, the gene responsible for sEH, that results in decreased EET hydrolysis [4]. Likewise, a study conducted in mild hypertensive humans demonstrated that CYP2C-derived EETs increase insulin sensitivity and reduce blood pressure [5]. Plasma EETs were found to strongly associate with insulin sensitivity and HDL-cholesterol levels [5]. The controversial findings of the current study by Lemaitre et al. suggest that the contribution for EETs and DHETs to insulin and glucose homeostasis and diabetes risk requires further exploration of the mechanisms by which they regulate insulin and glucose levels.

Although the cardiovascular and kidney actions and cell signaling mechanisms for EETs and DHETs have been extensively studied, their biological actions on the pancreas, insulin levels, and glucose regulation remain largely unknown. An early study found that 5,6-EET stimulated insulin secretion in islets isolated from rats [6]; however, very little 5,6-EET is generated by CYP2C epoxygenases [3]. As mentioned, several metabolic disease animal studies have found improved insulin sensitivity and lower glucose levels with sEH inhibition and increased EET levels [2,3]. Missing components to these animal studies are the site of action for EETs and the cellular signaling mechanisms. EET actions on pancreatic islet cells, liver glucose regulation, skeletal muscle glucose uptake, sodium glucose transporters (SGLTs), glucagon levels, and insulin actions have not been properly or extensively explored. DHETs have been found to lack or have significantly reduced kidney, immune, and cardiovascular actions [3]. Intriguingly,

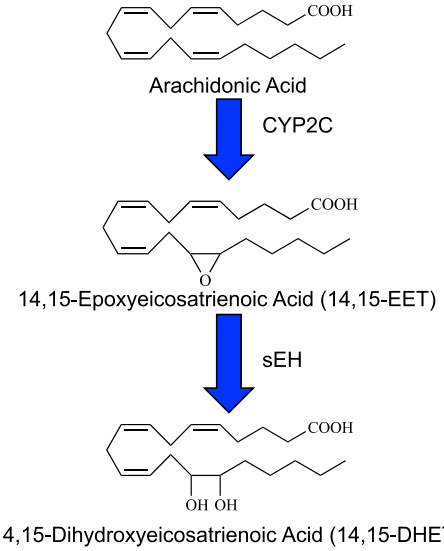

Fig. 1. *Arachidonic acid epoyxlipid metabolism:* Arachidonic acid is converted to epoxyeicosatrienoic acids (EETs) by cytochrome P450 (CYP2C). Dihydroxyeicosatrienoic acids (DHETs) are generated from EETs by soluble epoxide hydrolase (sEH).

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one biological action demonstrated for 14,15-DHET is binding to peroxisome proliferator-activated receptor-alpha (PPARα) to increase expression of PPARα responsive genes [7]. PPARα activation has several positive actions in metabolic diseases and diabetes including reducing insulin resistance [8]. Findings by Lemaitre et al. found a strong association for plasma 14,15-DHET levels in American Indians with lower plasma insulin and glucose levels [1]. Future metabolic disease and diabetes studies need to rigorously examine the actions and cell signaling mechanisms of EETs and DHETs on insulin and glucose regulation.

Lemaitre et al. recognized the limitations of the study which included stability of free EETs and DHETs stored at −80 °C over long periods of time and the inability to conduct temporal analysis. Another consideration is the possible influence of genetic polymorphisms in this American Indian population that could influence plasma EET and DHET levels. Findings in the current study need to be confirmed in different human populations and in better controlled temporal studies. Moreover, other pools of EETs and DHETs in humans need to be considered. Studies on salt-sensitive blood pressure control in humans have found that urine EET and DHET levels represent the generation of EETs and DHETs in the kidney [9]. These urine EET levels were found to be involved in renal salt handling while plasma EET levels did not correlate with aldosterone and salt regulation [9]. Interestingly, a role for kidney sEH to glucose regulation in type 1 diabetes and high fat diet induced insulin resistance in mice has been demonstrated [10]. In this study, sEH deficiency in the renal podocyte cell improved glucose regulation in these diabetic mice [10]. Therefore, the association of both the plasma and urine EET and DHET pools with diabetes risk requires investigation.

In conclusion, Lemaitre et al. in this edition of *EBioMedicine* provide evidence for an intriguing association between plasma 14,15-DHET levels and diabetes risk in American Indians that challenges the current paradigm on the contribution of EETs and DHETs to diabetes. Future research needs to extensively examine the biological and cell signaling actions of EETs and DHETs to regulate insulin and glucose levels.

Declaration of Competing Interest

John D. Imig reports three issued and licensed patents related to diabetes and epoxyeicosatrienoic acids: U.S. Patent 10,927,069, U.S. Patent 9,422,318, U.S. Patent 9,127,027 B2 and one pending patent U.S. Patent Application 20,200,255,433.

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