

# Weight Loss Strategies for Type 2 Diabetic Patients: Can Dietary Interventions That Reduce Circulating Persistent Organic Pollutants Improve Cardiovascular Outcomes?

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As noted by Lee et al. in this issue, persistent organic pollutants (POPs) released from adipose during weight loss in type 2 diabetic (T2DM) patients may attenuate cardiovascular (CV) benefits<sup>[1]</sup> that should accompany >5% weight reduction and concomitant fall in CV disease risk factors.<sup>[2]</sup> POP contributions to CV complications is a valuable and timely topic to explore, given the slow rate of POP elimination from the food chain and epidemiological evidence that low dose POPs are additional risk factors for metabolic<sup>[3]</sup> and CV diseases.<sup>[4]</sup>

POPs are toxic, lipophilic, semi-volatile chemicals containing highly stable halogen-carbon bonds not found in nature. They are ubiquitous in the environment, bioaccumulative, and hard to eliminate. They “biomagnify” and act as endocrine disruptors, altering thyroid and steroid hormone transport and signaling, and activate transcription factors central to energy balance regulation. They impair immune and reproductive function and development, and induce inflammation and mitochondrial dysfunction. Humans rarely accumulate high enough levels to experience the worst effects; however, POPs are increasingly recognized as risk factors in metabolic disease.<sup>[3]</sup> Although POPs are often presumed benign once sequestered inside adipocyte lipid droplets, POPs can change adipose phenotype and thus alter fat tissue function, potentially contributing to weight (re)gain through stimulation of adipogenesis and chronic inflammation. POPs can induce insulin resistance and impair pancreatic function, which may exacerbate T2DM. During weight loss, POPs are selectively mobilized from adipose, such that more polar POPs are released into the blood. Hydroxylation then makes POPs easier to excrete, but can increase toxicity and mobility,

thus increasing exposure and potential damage to non-fatty tissues. T2DM patients may be most vulnerable to POP effects through uncontrolled lipolysis, which facilitates greater POP mobilization. Causal impacts of POPs on obesity and T2DM are hard to quantify and test because their levels change dynamically with fat mass,<sup>[3]</sup> and hence intervention studies are vital in order to investigate their role in exacerbating metabolic and CV disease.

Caloric restriction and low-fat diets for T2DM patients target improved glycemic control and sustained and modest weight loss. While increased consumption of seafood can help in weight management, contaminants therein may offset other benefits.<sup>[5]</sup> A moderate, rather than low-fat, and largely plant-based diet with intermittent fasting or caloric restriction is envisaged by Lee et al.<sup>[1]</sup> to facilitate biliary POP excretion, provide protective phytochemicals that induce or enhance cellular defense mechanisms, and reduce POP intake through avoidance of animal-derived fats. Such POP-targeted interventions may have additional benefits, such as reducing pancreatic damage and insulin resistance.

Several practical challenges exist. First, the tasks of assessing which POPs, congeners, and mixtures are most problematic—and which to measure to identify effects and ensure studies are comparable—is complicated by the range of compounds involved, the correlation in their levels, variation in biological effects, and “cocktail” effects of POP mixtures with additional chemicals.<sup>[3]</sup> Second, short-term dietary interventions may not rapidly change legacy chemicals with decadal half-lives in adipose. Slow POP clearance may require protracted measurement time courses and long-term diet adherence. Third, if POP-mediated CV damage has already occurred, intervention benefits may be hard to identify.

Challenges notwithstanding, important clinical insights could arise from quantifying the role of POPs in preventing CV benefits of weight loss, including determining whether POPs can be reduced effectively using dietary interventions, teasing out POP-mediated health effects, and identifying T2DM patients who would benefit most from POP reduction to provide tailored weight management.

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## Conflict of Interest

The author declares no conflict of interest.

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