Using a novel culture system, researchers have found that endothelial stem cells exposed to flavored e-cigarette liquids demonstrate diminished cell viability and function.

When exposed to several different e-liquids, stem-cell-derived endothelial cells showed increased reactive oxygen species (ROS) levels, inflammatory signaling, and low-density-lipoprotein uptake, along with impaired tube formation and migration.

“Often patients will say, ‘Hey doc, I’m trying to quit smoking, can I switch to e-cigarettes because they’re safer for me?’” said Joseph C. Wu, MD, PhD, Stanford School of Medicine, California, in an interview.

“But the reality is that, besides the nicotine, which we know has adverse cardiovascular effects, e-cigarettes — even when the liquids don't include nicotine — have other flavoring components that can cause vascular dysfunction, particularly inflammation, apoptosis, cell death, and activation of oxidative stress. So I think the best advice one can give as a physician to a patient is to quit smoking, rather than switching to e-cigarettes instead.”

The findings of Wu's team, led by first author Won Lee Hee, PhD, a former Stanford fellow who is now at University of Arizona, Phoenix, were published in the June 4 issue of the Journal of the American College of Cardiology.

Wu acknowledged that although some patients are able to stop cigarette smoking by switching to e-cigarettes, many more fail to do so, and the uptake of e-cigarettes among teenagers is alarming.

“We see many more teenagers now smoking e-cigarettes because they assume that it's safer than regular cigarettes, which is true from the carcinogenic standpoint, but there is still harm, for example to cardiovascular health. I think that for society as a whole, it may induce much more long-term damage than we realize if we have a whole generation of teenagers who become addicted to e-cigarettes,” said Wu.

To test the impact of e-liquids — the "juice" used inside of an e-cigarette — on endothelial integrity, the researchers used induced pluripotent stem-cell-derived endothelial cells (iPSC-ECs) from three healthy volunteers and a subject population that included five healthy nonsmokers, five active smokers, two dual users of e-cigarettes and cigarettes, and two users of e-cigarettes only.

High-throughput screening was used to study the effects of e-liquids on endothelial cell viability by treating the iPSC-ECs with a dilution of six different e-liquids with varying nicotine concentrations, including some that had no nicotine at all.

All of the six flavored e-liquids tested had adverse effects on endothelial cell function, but a cinnamon-flavored liquid appeared to have the worst impact, followed by a menthol-flavored product.

The other flavors tested — a fruit-flavored liquid, a sweet tobacco with undertones of caramel and vanilla-flavored liquid, a tobacco-flavored product, and a sweet butterscotch liquid — all had moderate toxic effects on the endothelial cells.

Although most of the chemicals used in e-liquids are generally recognized as safe for ingestion as food additives, they have not been adequately tested as inhalants.

The researchers also performed tests where they incubated iPSC-ECs with serum derived from nonsmokers, e-cigarette users, and cigarette smokers to mimic cellular exposure in vivo.

After exposure of the iPSC-ECs to serum, increased ROS linked to endothelial dysfunction was noted in the serum of both e-smokers and smokers (compared with serum from nonsmokers), as was an increase in cytokine expression.
The impact on endothelial function was similar for smokers and e-smokers.

"In these tests, we validated our findings and show definitive proof that, after exposure of these iPSC-ECs to the serum of e-cigarette users, multiple inflammatory pathways were activated," said Wu.

This new study adds fuel to the controversy surrounding e-cigarettes, which despite concerns that they have adverse effects on health, have surged in popularity. Most worrying is evidence showing dramatic uptake among youth who are not conventional cigarette smokers.

Among adults, it appears that e-cigarettes are more often used by current smokers or as a means of smoking cessation than by nonsmokers.

A Sophisticated Model, but Still a Model

Wu, who is the director of the Stanford Cardiovascular Institute and runs the lab in which the "clinical trial in a dish" concept was developed, explained that to do a study that would show the effect of e-cigarettes on human blood vessels, "we'd have to strip an artery, probably from the leg or forearm, which would not be something most individuals would be willing to submit to."

"But with this technique, we can noninvasively take some blood cells from patients, convert blood cells into iPSCs, and then generate large quantities of these vascular endothelial cells for us to study the whole process expeditiously," he explained.

In an editorial comment, Jane E. Freedman, MD, and Chinmay M. Trivedi, MD, PhD, both from University of Massachusetts Medical School in Worcester, said that the use of iPSC-ECs is "notable" in that these cells are derived from reprogramming adult somatic cells into pluripotency and have "unlimited proliferation capacity."

They add, however, that this use of an in vitro culture system is "a clear limitation" of the study, although the findings are in keeping with a growing body of data suggesting potential harm from e-cigarette use.

For Peter Hajek, PhD, a leading expert on treatments for smoking cessation, this use of an in vitro model is an important limitation.

"I am not sure what can be learned from exposing cells to e-liquid (vapers do not pour e-liquid on their endothelial cells), especially when there was no comparison with effects of smoking," he told theheart.org | Medscape Cardiology.

"Studies that leave out smoking control are unlikely to provide much useful information," he added.

Hajek is director of the tobacco dependence research unit, Wolfson Institute of Preventive Medicine, Queen Mary University of London. His group published a randomized trial in the New England Journal of Medicine a few months ago showing that e-cigarettes are almost twice as effective as nicotine replacement products for smoking cessation at 1 year.

This work was supported by the American Heart Association (AHA) Scientist Development Grant, a Pilot Award from the Stanford Diabetes Research Center from a grant sponsored by the National Institutes of Health (NIH), and other grants to various coauthors from NIH, the University of California Tobacco Related Disease Research Program, and the US Food and Drug Administration Center for Tobacco Products. Wu reported he is a cofounder of Khloris Biosciences, "but has no competing interests, as the work presented here is completely independent." Freedman and Trivedi reported no conflict of interest.


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Cite this: Exposure to e-Cig Liquids Linked to Cell Damage In Vitro - Medscape - May 28, 2019.