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LETTER TO THE EDITOR

Reported particles are not blood clots, so anticoagulant drugs are not a plausible treatment

We thank Kell et al. [1] for their response to our forum article [2] critiquing the theory that amyloid fibrin(ogen) particles cause the post–COVID-19 condition. We agree that any scientific endeavor depends on dialectic. This has to build on the intelligent interpretation of existing reliable research. Our careful work systematically appraising the available evidence concludes that, while the theory may stand, data supporting this theory are currently absent.

Terminology is important in medicine. We reiterate that the term "microclots" is inaccurate as the amyloid fibrin(ogen) particles described are not clots. Three hundred fifty years ago, Malpighi identified red blood cells in clots, and, in current medical science, clots are a network of polymerized fibrin, aggregated platelets, red blood cells, and even leukocytes [3,4]. The particles Kell et al. [1] describe do not fit this definition; therefore, the term "microclots" is misleading.

Kell et al. [1] will know that the publicity surrounding this theory has led to patients seeking various treatments in the public and private for-profit sectors, including apheresis and triple therapy with anticoagulant medications ("anti-clot medications"). Our concern is that these treatments have established adverse effects and no proven benefit. We would also argue that an unfounded biomedical explanation of a recognized postviral condition can create fear in the public, which itself leads to hypervigilance, amplification of symptoms, and nocebo effects.

In their response, Kell et al. [1] return to their research papers to question our forum article [2]. We would refer Kell et al. [1] to our formal appraisal and bias assessment of these research papers, summarized in the Table [5-10], one of which appears to remain unpublished [8]. This Table reports the data presented, highlighting the lack of individual sample data and limited efforts to quantify amyloid fibrin(ogen) particles. We assessed risk of bias using signaling questions across domains using a method that has now been published [11]. This appraisal identified substantial concerns related to the collection and handling of samples, the experimental methods used, and the reporting of the results across all 5 papers [10]. So, the findings of the Cochrane review of laboratory studies still stand: these research papers fail to quantify the presence of amyloid fibrin(ogen) particles or present data beyond selected images [10].

In high-quality experimental studies, the scientific community expects the theory to be tested in large numbers of persons, comparing the state of healthy controls (persons without the condition) and persons with the condition. Valid comparison of values between the groups to determine any difference should use modern statistical analysis techniques. To date, this has not been demonstrated for amyloid fibrin(ogen particles). Further, we are concerned that a new assay should have published details concerning verification, such as the coefficient of variation of inter- and intraassay variability. These details are lacking.

Put simply, what is absent is basic data regarding statistical differences in the proportion and size of these particles between patients with post–COVID-19 condition, healthy controls, and other comparison groups. That is, the question of whether there is any statistical difference in the presence of these particles in healthy persons compared with persons with post–COVID-19 is unknown. The answers to these questions are of high clinical importance in the interpretation of this data, without which we conclude that there is no reliable evidence to support a relationship between amyloid fibrin(ogen) particles and post–COVID-19 conditions.

Indeed, in these studies, the presence of amyloid fibrin(ogen) particles has been documented in healthy persons, persons with states of chronic inflammation, and persons with post–COVID-19 conditions. Without the aforementioned basic data, at the very least, it is unclear how or why amyloid fibrin(ogen) particles could be causing symptoms in persons with post–COVID-19 conditions and not cause symptoms in healthy people.

The diagram shared by Kell et al. [1] in their response is referred to as an overview of their understanding of the key pathologies involved in post–COVID-19 and their interactions with each other. We wish to restate that Hunt et al. [2] have only assessed the evidence for amyloid fibrin(ogen) particles in the blood as one of the pathologies, and as we have outlined, this causative pathology remains unproven. The diagram itself is of little clinical utility and provides no rationale for the use of anticoagulants or apheresis.

As these particles are not blood clots, anticoagulant drugs are not a plausible treatment; it therefore challenges basic ethical principles to expose children and adults to triple therapy with anticoagulant drugs.

TABLE Summary of experimental methods and results in studies appraised in the Cochrane review (from Fox et al. 10).

Study	Experimental methods	Quantification of results	Availability of results
Pretorius et al. 2022 [5]	Fluorescence microscopy; not clearly described	No methods reported for experimental repeats. Criteria used to quantify amyloid fibrin(ogen) particles reported. No data on assay reproducibility.	A combined severity score for amyloid fibrin(ogen) and platelet pathology was reported. Four microscopy images presented. No individual results.
Pretorius et al. 2021 [6]	Fluorescence microscopy; not clearly described	No methods reported for duplication of experiments or quantification of amyloid fibrin(ogen) particles. No data on assay reproducibility reported.	14 microscopy images presented. Individual sample results not reported.
Kruger et al. 2022 [7]	Fluorescence microscopy; not clearly described	No methods reported for duplication of experiments or quantification of amyloid fibrin(ogen) particles. No data on assay reproducibility reported.	3 microscopy images reported. Individual sample results not reported.
Laubscher et al. 2023 [8]	Fluorescence microscopy; not clearly described	No methods reported for duplication of experiments or quantification of amyloid fibrin(ogen) particles. No data on assay reproducibility reported.	7 microscopy images reported. Individual sample results not reported.
Turner et al. 2023 [9]	Flow cytometry	Quantified by objects/mL, mean area, and amyloid fibrin(ogen) particles in area range.	Median values presented for the sample set.

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AUTHOR CONTRIBUTIONS

T.F. and R.K. drafted the response. All authors then contributed to revisions. The final document was agreed upon by all authors.

RELATIONSHIP DISCLOSURE

There are no competing interests to disclose.

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