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Perspective

Nutrition Interventions as Geroprotectors: Design and Interpretation of Early-Stage Clinical Trial of Strawberries

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In this issue, Hartmann and colleagues present the design of a 10-week, 5-group dose-escalating randomized clinical trial testing whether polyphenol-rich nutritional intervention lowers low-density lipoprotein cholesterol (LDL-C) or inflammation as measured by c-reactive protein (CRP) in healthy middle-aged and older adults[1]. Demonstrating that any dietary or nutritional intervention can deflect biomarkers of cardiometabolic risk would be a major milestone, but this study is framed within the context of geroscience, which hypothesizes that human health can be improved by targeting the biology of aging[2].

Studies of model organisms show that targeting these biological pathways with a variety of therapeutic approaches—including the administration of drugs, biologics, dietary restrictions, and nutraceuticals—can increase health and lifespan. These studies are now being translated to clinical trials in humans, and the breadth of potential geroprotective (preventative) and gerotherapeutic (reparative) approaches is ever-expanding. The testing of geroprotectors and gerotherapeutics in clinical trials is relatively new, and there is uncertainty regarding how to optimally design studies—including early-stage "proof-of-concept" (PoC) trials and those testing nutritional interventions relevant to aging.

Early-stage PoC trials are typically short, relatively inexpensive studies to help design and justify larger clinical trials[3]. Unlike efficacy trials, PoC trials evaluate the feasibility of therapeutic approaches and dosing, present initial estimates of safety, and provide supportive data on clinical outcomes or biomarkers needed for trial planning. These PoC trials may or may not include an untreated control group, commonly feature dose-finding study designs, and may use criteria for success ("go/no-go" decision criteria) that differ from next-stage efficacy trials. There are also subtle differences between disease-centric and geroscience-oriented PoC trials.

For example, a key difference between most traditional disease-targeting studies (which target pathophysiologic mechanisms identified within the disease pathway) and PoC studies testing geroprotectors or gerotherapeutics is that the biological target in geroscience-related studies should be identified from the field of aging and should not directly act on risk factors specific to a disease process (e.g., cholesterol in atherosclerosis studies or HbA1c in diabetes prevention).

In this issue, Hartmann and colleagues report results from an early-stage PoC trial of a nutritional intervention that was identified in the field of geroscience. The report describes a strawberry dose-escalation study. The study assesses circulating biomarkers, patient reports, and functional measures in healthy middle-aged and older adults. The endpoints, criteria for "success," and attributes of nutritional intervention warrant brief discussion.

Endpoint Selection

A key uncertainty in designing geroscience trials at any stage is endpoint selection[4]. Biological age from metabolic, genetic, and cellular dysfunction manifests as chronic conditions prevalent in middle and older age (e.g., cardiovascular and metabolic diseases, mobility or cognitive impairment, osteoporosis, cancers, loss of immune resilience, etc.). As such, a heterogeneity of outcomes or composite endpoints could have utility. Given the short duration of PoC trials, molecular or biomarker outcomes may provide a stronger signal than more heterogeneous clinical outcomes. The endpoints should still have face validity as "aging" and salience. Hartmann and colleagues selected LDL-C and CRP as the co-primary endpoints. This biomarker pair has questionable face validity and may not adequately reflect the multifactorial nature of aging, but it is aligned with cardiometablic risk in the general population. Fortunately, the study is enriched by a number of secondary and exploratory biomarker, functional, and patient-reported assessments, which permits a more comprehensive evaluation of the strawberry-based intervention as a potential geroprotector.

Criteria for "Success"

Relatedly, early-stage trials are most useful when they inform feasibility and de-risk next-stage trials. As such, the efficacy of a trial based on traditional statistical thresholds may not be as informative as evaluating the number of participants who meet or exceed meaningful thresholds for change. Substantial data underscore the robust prediction of adverse cardiovascular outcomes with LDL-C, and the Cholesterol Treatment Trialists' Collaboration found a 22% reduction in combined cardiovascular events for every 1.0 mmol/L (38.7 mg/dL) in LDL-C, and 10% reduction is considered a minimal threshold for change in many trials[5]. Thus, though perhaps lacking in face validity as "aging,"

LDL-C does provide an evidence-based threshold to gauge trial "success" for cardiometabolic risk. In this study, though the highest dosed intervention group improved LDL-C statistically, the −5.72 mg/dL reduction in LDL-C is well below the threshold for a clinically important difference in cardiovascular health events. Moreover, CRP was only improved in the subset of participants with elevated baseline levels, suggesting refinement is needed in both criteria for "success" and inclusion criteria for next-stage trials.

Nutritional Interventions as Geroprotectors

Strawberries are theoretically rich in quercetin and fisetin, which may have senotherapeutic effects[6]. Ideally, the effect of a food-based nutritional intervention should result from a change in specific nutrient status—in this case, specific senotherapeutic flavanols—rather than just a change in diet[7]. Hartmann and colleagues assayed both quercetin and fisetin in both strawberries and study participants. Yet only quercetin (not fisetin) was detected in strawberries, and neither was detectable in serum. Thus, it is difficult to say whether the observed effects were due to these flavonols or some other food-based nutritional factor. Moreover, the amount of quercetin measured in strawberries is orders of magnitude lower than the daily quercetin doses used for senolytic effects (14.23 μg/g versus 1000–1250 mg/g, respectively)[8]. This calls into question whether a sufficiently high dose of quercetin or fisetin was achieved for the "hit-and-run" approach to intermittent senolytic dosing. Further evaluation is warranted.

Conclusions

Given the relative infancy of testing geroprotectors, uncertainties on study designs and interpretations persist. These choices might depend on the biological target, intervention type, and population. As knowledge emerges, investigators must work together to build consensus. Until we have a solid empiric foundation, readers and peer reviewers should be open-minded and pay attention to exploratory endpoints and criteria used for go/no-go decision-making. To minimize missteps and accelerate progress, we must develop and incentivize standardized approaches, share data and results, and avoid overstating findings from PoC trials of geroprotectors.

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