Comment on:
Efficacy and safety of enteral recombinant human insulin for reduction of time-to-full enteral feeding in preterm infants: a randomized, double-blind, placebo-controlled trial
(*IMAJ* September 2021)

Robert J. Shulman MD

Department of Pediatrics, USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas

TO THE EDITOR:

I read with great interest the recent article by Shedadeh and colleagues [1] regarding the use of recombinant human insulin to reduce the time required for preterm infants to reach full enteral feeding. There is substantial preclinical work supporting the potential ability of enterally administered insulin to enhance newborn gut growth and/or function (for examples, see references [2,3].

The results of the study by Shedadeh et al. support findings of a previous study of preterm infants given enteral human insulin. The insulin-treated infants (n=8) demonstrated increased lactase activity and faster attainment of full enteral feedings compared to a historical control group (n=80) matched for gestational age, birth weight, age feedings were started, proportion of feedings that were human milk, and feeding method (intermittent bolus) [4].

Shedadeh et al. are to be commended for conducting the first randomized, blinded trial. However, some additional details potentially would make their findings more compelling. For example, how many centers were involved, how many infants were studied at each center, and in the analysis was the center where the study was conducted used as a covariate? Was there a standardized feeding protocol among centers that included why feedings might be withheld? If so, what was the degree of adherence to the protocol? What was the method used to generate the random allocation sequence and who generated and administered the randomization?

Finally, it is not clear what is meant by "the current sponsor…recently released the data for publication." Does this mean that the investigators did not carry out the analyses or have access to the raw data? Was the data independently verified (by someone outside the study)?

Again, I congratulate the investigators for taking a first step to investigating what may be a future, important treatment for the vexing problem of feeding intolerance in preterm infants.

Correspondence

Dr. R.J. Shulman
Dept. of Pediatrics, USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine and Texas Children's Hospital, Houston 77030, Texas
Phone: (1-713) 798-7145
Fax: (1-713) 798-7187
email: rshulman@bcm.edu

References

1. Shehadeh N, Simmonds A, Zangen S, Riskin A, Shamir R. Efficacy and safety of enteral recombinant human insulin for reduction of time-to-full enteral feeding in preterm infants: a randomized, double-blind, placebo-controlled trial. *IMAJ* 2021; 23: 563-8.
2. Shulman RJ. Oral insulin increases small intestinal mass and disaccharidase activity in the newborn miniature pig. *Pediatr Res* 1990; 28: 171-5.
3. Harada E, Syuto B. Precocious cessation of intestinal macromolecular transmission and sucrase development induced by insulin in adrenalectomized suckling rat. *Comp Biochem Physiol A Comp Physiol* 1991; 99: 327-31.
4. Shulman RJ. Effect of enteral administration of insulin on intestinal development and feeding tolerance in preterm infants: a pilot study. *Arch Dis Child Fetal Neonatal Ed* 2002; 86: F131-3.

Capsule

Distinct systemic and mucosal immune responses during acute SARS-CoV-2 infection

Coordinated local mucosal and systemic immune responses following severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection either protect against coronavirus disease 2019 (COVID-19) pathologies or fail, leading to severe clinical outcomes. To understand this process, **Smith** and colleagues performed an integrated analysis of SARS-CoV-2 spike-specific antibodies, cytokines, viral load and bacterial communities in paired nasopharyngeal swabs and plasma samples from a cohort of clinically distinct patients with COVID-19 during acute infection. Plasma viral load was associated with systemic inflammatory cytokines that were elevated in severe COVID-19, and also with spike-specific neutralizing antibodies. By contrast, nasopharyngeal viral load correlated with SARS-CoV-2 humoral responses but inversely with interferon responses, the latter associating with protective microbial communities. Potential pathogenic microorganisms, often implicated in secondary respiratory infections, were associated with mucosal inflammation and elevated in severe COVID-19. These results demonstrate distinct tissue compartmentalization of SARS-CoV-2 immune responses and highlight a role for the nasopharyngeal microbiome in regulating local and systemic immunity that determines COVID-19 clinical outcomes.

Nature Immunol 2021; 22: 1428
Eitan Israeli