RESPONSE TO COMMENT ON LONTCHI-YIMAGOU ET AL.

An Atypical Form of Diabetes Among Individuals With Low BMI. Diabetes Care 2022;45:1428–1437

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We thank Unnikrishnan et al. (1) for their thoughtful comments on our article (2). We agree with the need for further research into the globally prevalent condition we termed "low-BMI diabetes" (LD) and that the previous nomenclature "malnutrition-related diabetes" requires more evidence. We propose, nonetheless, on the basis of extensive phenotyping, that LD represents a distinct form of diabetes with implications for prevention and treatment (2).

Lean individuals with diabetes have been reported in many low- and middle-income countries (LMICs) (2). Our goal in performing these studies at Christian Medical College, Vellore, India, was not to address "Indian" presentations of diabetes (which have been extensively studied by authors of the comment letter) but to use state-of-the art techniques generally unavailable in LMICs: stepped insulin pancreatic clamps, C-peptide deconvolution, and sophisticated anthropometric measures. Glucose toxicity was corrected, and patients with pancreatic calculi, type 1 diabetes, and monogenic diabetes were excluded (2).

Most type 2 diabetes (T2D) patients have some degree of impaired β-cell function, the magnitude of which differs between patients and over time. Our intensive measures of insulin secretion revealed more severe defects in LD patients than in T2D patients. Might some patients with severe insulin-deficient diabetes, as described by Anjana et al., also be considered LD patients, given their apparently wide range of BMI (3)? It would be intriguing to use C-peptide deconvolution techniques to study individuals with severe insulin-deficient diabetes along that BMI spectrum (while correcting confounding glucose toxicity) to determine whether there is a gradient of insulin secretory defects.

LD is anthropometrically distinct from the classic description of the so-called thin-fat Indian developed extensively by Yajnik (4), because our LD subjects have a BMI well below the South Asian inflection point of ~22 kg/m^2 and lack visceral adiposity. It should be emphasized that the LD phenotype revealed in our article, characterized by low BMI with low body fat content, was unconfounded by later life overnutrition and deserves consideration as a distinct phenotype.

Notably, only time course studies can prospectively determine the pathophysiologic relationship between nutrition and diabetes. Such determinations are challenging, since malnutrition often occurs in the setting of other stressors. While much research has established the effect of fetal malnutrition on risk of T2D (4,5), some research in animals and humans suggests that continued undernutrition in childhood and adulthood contributes to the distinct LD phenotype (6).

Importantly, we believe that recognizing LD as a distinct entity is essential from a therapeutic perspective. Weight loss would be inappropriate, and metformin would fail to address the reduced insulin secretion. Moreover, agents that precipitate hypoglycemia are dangerous in the face of food insecurity, and insulin use is problematic in many LMICs.

Further research to understand the pathophysiology of LD would be important but challenging. Many genes that limit β-cell development in undernutrition can also hasten β-cell exhaustion in obesity, raising the question of whether biomarkers or putative genes could distinguish this condition. Meanwhile, developing appropriate treatment strategies is critical given the high estimated global prevalence of LD and the pending food crisis.

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References

1. Unnikrishnan R, Anjana RM, Mukhopadhyay S, et al. Comment on Lontchi-Yimagou et al. An atypical form of diabetes among individuals with low BMI. Diabetes Care 2022;45:1428–1437 (Letter). Diabetes Care 2022;45:e157–e158. DOI: 10.2337/dc22-1257

2. Lontchi-Yimagou E, Dasgupta R, Anoop S, et al. An atypical form of diabetes among individuals with low BMI. Diabetes Care 2022;45: 1428–1437

3. Anjana RM, Baskar V, Nair ATN, et al. Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis: the INSPIRED study. BMJ Open Diabetes Res Care 2020;8:e001506

4. Yajnik CS, Yudkin JS. The Y-Y paradox. Lancet 2004;363:163

5. Vaag AA, Grunnet LG, Arora GP, Brøns C. The thrifty phenotype hypothesis revisited. Diabetologia 2012;55:2085–2088

6. Ferdous F, Filteau S, Schwartz NB, Gumede-Moyo S, Cox SE. Association of postnatal severe acute malnutrition with pancreatic exocrine and endocrine function in children and adults: a systematic review. Br J Nutr 2022;128:1–34