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Letters to the Editor

RESPONSE TO "SERUM INSULIN-LIKE GROWTH FACTOR-1 (IGF-1) IN CENTENARIANS: IMPLICATIONS OF IGF-1 AS A TURNOVER PROTEIN"

To the Editor:

Arai and colleagues (1) report serum IGF-1 to be very low in centenarians, a datum in contrast with a previous study (2) showing that healthy centenarians had serum IGF-1/IGF-BP3 molar ratios greater than aged subjects. Indeed, such a discrepancy between Arai and colleagues' and our data is justified by the authors with the smaller sample size of centenarians in our study and by the selection criteria. Indeed, we believe that only the selection criteria should be taken into account. In fact, the main difference between the two studies was that our centenarians were healthy, as assessed by routine clinical and laboratory analyses, unaffected by hypertension or diabetes, had a slight (age-compatible) cognitive impairment but did not have dementia, and were never affected by hip fracture. Such a hypothesis is also supported by the evidence reported in Arai and colleagues' Table 3 that dementia was less frequent in centenarians with high IGF-1. Indeed, even at young age, if one compares healthy to ill patients, this latter group of patients will have serum IGF-1 levels lower than healthy subjects. Furthermore, we also believe that Arai and collegues' report has two other main problems. First, no controls were provided and thus no proof that, with that same method and assay, serum IGF-1 of younger subjects had values higher than ones found in centenarians was provided. Last, it is widely accepted that IGF-1 is mainly bound to binding proteins (especially IGF-BP3). Once one does not take into account such a problem, you can determine the total form of the hormone that might encompass even the binding proteins that are not metabolically active. Indeed, looking carefully at our study (2), one can discover that the total serum IGF-1 was lower in centenarians than in aged subjects but after considering the binding protein (and thus the molar ratio between total IGF-1 and IGF-BP3, which is the expression of the free amount of IGF-1) such a ratio showed differences in favor of centenarians who had less circulating IGF-BP3. An easier way to get such information is to determine the serum-free IGF-1. In light of such considerations, and due to the fact that IGF-1 is a very important hormone for longevity, we would like to prompt Arai and colleagues (1) to reproduce their data sampling only in healthy centenarians and using the free part of the hormone to be assayed.

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2. Paolisso G, Ammendola S, Del Buono A, et al. Serum levels of insulin-like growth factor-I (IGF-1) and IGF-binding protein-3 in healthy centenarians: relationship with plasma leptin and lipid concentration, insulin action and cognitive function. *J Clin Endocrinol Metab.* 1997;8: 2204–2209.

Drs. Arai and Hirose reply:

Drs. Paolisso and Barbieri (1) have raised important considerations regarding the study of IGF-1 in centenarians that we reported (2). We agree about the importance of comparisons of centenarian data with proper controls. Concerning this issue, we have a great interest in metabolic remodeling of IGF-1 and other hormones in the oldest old population. Much evidence has accumulated showing the regulatory roles of IGF-1 on body composition and immune function changes as a part of normal aging. When and how would dissociations of IGF-1 levels and body composition occur? To answer this issue, longitudinal as well as cross-sectional studies involving elderly persons in the sixth to ninth decades are ongoing by our team. Drs. Paolisso and Barbieri mentioned the indication of simultaneous determination of IGF-1 and IGF-BP3, which is a major binding protein of IGF-1 in serum. As we had already commented in the article, we certainly agree with this point. Preliminary data from our ongoing study show that the IGF-1/IGF-BP3 molar ratio in 55 centenarians (35 women, 20 men) is 1.58 $\pm$ 0.48. More detailed analysis of the associations between various phenotypic markers and IGF-1, IGF-BP3, the molar ratio, and also data sampling is in progress.

It is well documented that centenarians have heterogeneous traits. Remodeling in the coagulation-fibrinolysis system, immune function, and lipid metabolism has occurred even in healthy centenarians. Without doubt it is important to investigate truly healthy centenarians as a model of human longevity. However, we believe that comprehensive descriptive studies targeting a large cohort of centenarians is also valuable for gerontological research because most centenarians are likely to suffer from comorbidity and frailty, and, therefore, underlying mechanisms remain to be elucidated.

To this end, we appreciate that Drs. Paolisso and Barbieri made an important point about the need for further research in the field of IGF-1 and longevity.

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