Letter to the Editor

Comment on “Bone Regulates Glucose Metabolism as an Endocrine Organ through Osteocalcin”

Hitesh Verma^{1,2,3} and Rajeev Garg^{1,2}

¹IKG Punjab Technical University, Kapurthala 144603, India

²Department of Pharmaceutics, ASBASJSM College of Pharmacy, Bela, Ropar 140111, India

³Overseas R&D Centre, Overseas HealthCare Pvt. Ltd., Phillaur, Punjab 144410, India

Correspondence should be addressed to Hitesh Verma; frd.ohcpl@gmail.com

Received 20 June 2016; Accepted 21 August 2016

Academic Editor: Kristin Eckardt

Copyright © 2016 H. Verma and R. Garg. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

While reading the insightful review of Shao et al. [1] on the effect of osteocalcin (OC) on glucose homeostasis, we came across a few lacunas which we want to fill up so as to generalise the osteocalcin concept. Firstly, Shao et al. reported that the concentration of uncarboxylated osteocalcin (ucOC) is controlled by decarboxylation of carboxylated osteocalcin (cOC), which is not true; it has been reported in the literature that during the bone resorption process initially a small fraction of intact OC is released in the acidic environment created by osteoclasts, which undergoes enzymatic proteolysis and subsequently excretion of OC fragments in urine. In the same research, researchers also prove that incubation of cOC in simulated osteoclastic lacuna medium (pH 4.8, 37°C) for 48 hours did not result in decarboxylation process and it requires heating of cOC at 110°C for 3 hours in HCl (50 mmol/L) to cause its decarboxylation [2]. Clearly, such conditions are not available in a physiological environment; therefore, the concept of decarboxylation from our point of view requires further investigation. Secondly, it is still a questionable fact that impairment in OC (any form) levels causes disturbance in glucose homeostasis because hyperglycemia, both *in vitro* [3] and clinically [4], is reported to cause impaired osteoblastic activity too. Therefore, whether OC imbalance causes impaired glucose homeostasis or vice versa is a matter of research. Thirdly, if as mentioned by Shao et al. ucOC is the only active form of OC, then supplementation of Vitamin K or various antiresorptive therapies (raloxifene, alendronate,

and strontium) should theoretically increase risk of Type 2 Diabetes because they decrease the level of circulating OC (ucOC) but it is not the case [5–9]; rather, they are reported to decrease the risk of Type 2 Diabetes. Therefore, which form of osteocalcin is responsible for benefit in glucose homeostasis is not clear till now. Moreover, the presence of γ -glutamate carboxylase has been reported on osteoblasts [10], absence of which results in impaired glucose homeostasis, clearly indicating the protective role of Vitamin K (cofactor of γ -glutamate carboxylase) in maintaining glucose balance. Lastly, Shao et al. did not list the major difference in OC physiology in mice and humans, while extrapolating the benefits; for example, mice have three genes for OC while humans have only one gene and Vitamin D3 downregulates the OC expression in mice while it causes the opposite in humans [11, 12]. We appreciate the work of Shao et al., for their efforts to compile such a controversial topic, and we are looking forward to further research on this topic.

Competing Interests

Authors declare that there is no conflict of interests.

References

- [1] J. Shao, Z. Wang, T. Yang, H. Ying, Y. Zhang, and S. Liu, “Bone regulates glucose metabolism as an endocrine organ through

- osteocalcin," *International Journal of Endocrinology*, vol. 2015, Article ID 967673, 9 pages, 2015.
- [2] J. W. Poser and P. A. Price, "A method for decarboxylation of gamma-carboxyglutamic acid in proteins. Properties of the decarboxylated gamma-carboxyglutamic acid protein from calf bone," *The Journal of Biological Chemistry*, vol. 254, no. 2, pp. 431–436, 1979.
  - [3] M. Terada, M. Inaba, Y. Yano et al., "Growth-inhibitory effect of a high glucose concentration on osteoblast-like cells," *Bone*, vol. 22, no. 1, pp. 17–23, 1998.
  - [4] I. Levinger, E. Seeman, G. Jerums et al., "Glucose-loading reduces bone remodeling in women and osteoblast function in vitro," *Physiological Reports*, vol. 4, no. 3, p. E12700, 2016.
  - [5] R. Kumar, N. Binkley, and A. Vella, "Effect of phylloquinone supplementation on glucose homeostasis in humans," *American Journal of Clinical Nutrition*, vol. 92, no. 6, pp. 1528–1532, 2010.
  - [6] M. Hirao, J. Hashimoto, W. Ando, T. Ono, and H. Yoshikawa, "Response of serum carboxylated and undercarboxylated osteocalcin to alendronate monotherapy and combined therapy with vitamin K2 in postmenopausal women," *Journal of Bone and Mineral Metabolism*, vol. 26, no. 3, pp. 260–264, 2008.
  - [7] S. Adami, M. Passeri, S. Ortolani et al., "Effects of oral alendronate and intranasal salmon calcitonin on bone mass and biochemical markers of bone turnover in postmenopausal women with osteoporosis," *Bone*, vol. 17, no. 4, pp. 383–390, 1995.
  - [8] N. H. Bjarnason, S. Sarkar, T. Duong, B. Mitlak, P. D. Delmas, and C. Christiansen, "Six and twelve month changes in bone turnover are related to reduction in vertebral fracture risk during 3 years of raloxifene treatment in postmenopausal osteoporosis," *Osteoporosis International*, vol. 12, no. 11, pp. 922–930, 2001.
  - [9] S. C. Verberckmoes, M. E. De Broe, and P. C. D'Haese, "Dose-dependent effects of strontium on osteoblast function and mineralization," *Kidney International*, vol. 64, no. 2, pp. 534–543, 2003.
  - [10] S. Shiba, K. Ikeda, K. Azuma et al., " γ -Glutamyl carboxylase in osteoblasts regulates glucose metabolism in mice," *Biochemical and Biophysical Research Communications*, vol. 453, no. 3, pp. 350–355, 2014.
  - [11] S. L. Booth, A. Centi, S. R. Smith, and C. Gundberg, "The role of osteocalcin in human glucose metabolism: marker or mediator?" *Nature Reviews Endocrinology*, vol. 9, no. 1, pp. 43–55, 2013.
  - [12] A. G. Veldhuis-Vlug, E. Fliers, and P. H. Bisschop, "Bone as a regulator of glucose metabolism," *Netherlands Journal of Medicine*, vol. 71, no. 8, pp. 396–400, 2013.