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LETTER

Serum undercarboxylated osteocalcin was inversely associated with plasma glucose level and fat mass in type 2 diabetes mellitus

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Dear Editor,

We read with interest the article by Kanazawa and co-authors [1] about osteocalcin (OC) and its metabolic associations in a cross-sectional study of a Japanese population affected by type 2 diabetes mellitus. The authors suggest that undercarboxylated OC (ucOC) is associated with fat mass, especially visceral fat, as well as with glucose level in diabetic men, claiming that their study seems to be the first clinical one suggesting that not only OC but also ucOC is associated with lipid/glucose metabolism in type 2 diabetes.

According to the authors, the association showed in their population between OC or ucOC versus glucose level seems not to be because of OC-modulated insulin sensitivity or secretion. Several studies, in fact, have indicated that hyperglycemia can induce a low turnover of bone by evoking osteoblast dysfunction and suppressing serum OC level, as depicted by alterations of bone markers before and after treatment of diabetes [2, 3]. So they hypothesize that, due to the lack of correlation between OC or ucOC versus fasting C peptide as surrogate marker for endogenous insulin secretion in their diabetic patients, it would be high glucose level which suppresses osteoblast function and, consequently, OC expression. Thus, according to contrasting reports in scientific literature, which showed how $Esp^{-/-}$ mice, having an excess of ucOC, display severe hypoglycemia and protection against diet-induced obesity and diabetes [4], the cause and effect between glicemic control and OC is still unresolved.

Adipose tissue (AT) is nowadays considered a true endocrine organ and a source both of AT-specific cytokines (adipokines) and inflammatory cytokines. We have recently reported that human AT expresses both OC and all genes involved in OC carboxylation and, in general, in Gla-protein carboxylation, both producing and releasing OC protein [5]. So the metabolic effects of OC could be partially mediated by an organ striktly implicated in insulin-resistant conditions, due to its endocrine and metabolic functions and its direct cross-talking with the liver through the portal vein.

The authors described also a negative correlation between ucOC and the fat mass [1] and our findings, showing OC production by AT [5], could partially explain it. The balance between ucOCN and cOCN, in fact, could play a role in the pathophysiology of metabolic diseases, as depicted by studies both in $Esp^{-/-}$ hypoglicemic rats and in obese men [4, 5]. AT, being able to release both forms, could be again one of metabolism actors if we consider that, compared with bone, AT is highly represented in the human body and can act both in an endocrine and paracrine way.

On the basis of our results, revealing unexpected actions of AT, we suggest a different approach in order to elucidate the association between diabetes, bone osteoporosis, and cardiovascular diseases, and the role of two different cell types sharing a common precursors, the adipocyte and the osteoblast.

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