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COMMENTARY

# UP-REGULATION OF VITAMIN D SYSTEM IN ADIPOCYTES BY MACROPHAGE-DERIVED FACTORS: IMPLICATIONS FOR (PATHO) PHYSIOLOGY OF ADIPOSE TISSUE

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Vitamin $D_3$ (cholecalciferol) plays an important role in calcium, phosphate, and bone metabolism. Vitamin $D_3$, either synthesized endogenously or derived from alimentary sources, is first activated through sequential hydroxylations by vitamin $D_3$ 25-hydroxylase in the liver and 25-hydroxyvitamin $D_3$ 1α-hydroxylase (CYP27B1) in the kidney to 25-OH-$D_3$ and 1,25$(OH)_2D_3$ (calcitriol), respectively. Calcitriol – the active vitamin D derivative – regulates calcium metabolism by acting on nuclear and extranuclear vitamin D receptors (VDR). Apart from mineral metabolism, vitamin D is involved in many other processes such as cell proliferation, inflammatory and immune reactions, glucose and lipid metabolism, etc. Indeed, VDR are expressed in virtually all tissues and vitamin D deficiency is suggested to contribute to the pathogenesis of various diseases including certain types of cancer, inflammatory bowel disease, multiple sclerosis, peridontal diseases, diabetes, hypertension, atherosclerosis and neurodegenerative diseases (see below). In addition, vitamin D supplementation is beneficial in humans with at least some of these disorders and in animal experimental models of them (1-3).

Several lines of evidence suggest the link between vitamin D and adipose tissue. First, both CYP27B1 and VDR are expressed in the adipose tissue. Second, calcitriol has been demonstrated to regulate various aspects of adipose tissue function such as preadipocyte proliferation/differentiation, fat storage, adipokine secretion, cortisol/cortisone interconversion and local inflammatory reaction, although the results of these studies are sometimes controversial. Third, decrease in serum 25-OH-$D_3$ (the best marker of vitamin D supply) was observed in obese individuals. This vitamin D insufficiency was attributed to various factors such as reduced exposure to sunlight due to sedentary lifestyle, sequestration of lipohilic vitamin in fat tissue, insulin resistance or hyperleptinemia (4, 5).

Infiltration of adipose tissue with activated macrophages is a hallmark of obesity, and macrophage-derived factors are responsible for many abnormalities of adipocyte function observed in obese individuals. In this issue of *Adipobiology*, Paul Trayhurn with his colleagues present very interesting findings about the influence of macrophages on vitamin D system in adipocytes (6). By using a microarray approach, they demonstrated that macrophage conditioned medium increases the expression of CYP27B1 and VDR mRNA in adipocytes. These results suggest that macrophage-derived factors may stimulate local vitamin D signaling in the adipose tissue. Several question arise while analyzing these data. First, it is unclear if changes of mRNA expression are mirrored at the protein level. Second, it is interesting if the same is observed in macrophage-infiltrated adipose tissue in obese animals and humans in vivo. In contrast to in vitro conditions, in vivo adipocytes are exposed to many other factors in addition to macrophage-derived, such as hypoxia, hy-

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perinsulinemia/insulin resistance, altered profile of adipokines, abnormal plasma lipid and/or glucose level; at least some of them may influence vitamin D system. Even if CYP27B1 and VDR are up-regulated in vivo, it will not necessarily result in enhanced vitamin D signaling. As stated before, circulating 25-OH-$D_3$ is often reduced in obesity. In general, it is assumed that extrarenal 1α-hydroxylase is less regulated than renal enzyme, and the amount of locally produced calcitriol is more dependent on systemic concentration of its immediate precursor 25-OH-$D_3$ (although up-regulation of CYP27B1 by proinflammatory cytokines in macrophages is a well-known phenomenon). Thus, local 1,25$(OH)_2D_3$ in adipose tissue may be unchanged or even reduced despite greater local CYP27B1 expression. Thus, it would be interesting to measure local calcitriol concentration in adipose tissue of obese subjects. As suggested (6), up-regulation of vitamin D signaling may be a compensatory response aimed to reduce local inflammation. Recently, we have demonstrated that small doses of 1,25$(OH)_2D_3$ which have no effect on calcium metabolism increase insulin sensitivity in healthy rats (7). Not only fasting serum insulin was reduced (suggestive of increased insulin sensitivity of the liver) and glucose disposal rate in hyperinsulinemic euglycemic clamp was increased (indicative of skeletal muscle insulin sensitization), but also decrease in plasma nonesterified fatty acids and glycerol were noted, which is the evidence of improved ability of insulin to suppress adipose tissue lipolysis. In addition, vitamin D supplementation increased insulin sensitivity in some interventional human studies (8). Thus, up-regulation of vitamin $D_3$ in adipocytes may also counteract insulin resistance induced by macrophage activation. However, on the other hand, the recent study has demonstrated that targeted overexpression of VDR in adipocytes results in reduced lipolysis, decrease in energy expenditure and obesity (9). Thus, it cannot be definitely concluded if up-regulation of vitamin D signaling in adipocytes is beneficial or detrimental. In any case, local vitamin D system in adipose tissue needs to be examined in more detail since it may significantly contribute to adipose dysfunction associated with obesity and is also a potential target for therapy. Another intriguing target might be the association between vitamin $D_3$ and nerve growth factor (NGF) (10,11) including the possible role of vitamin $D_3$ in adipose-derived NGF (12)

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