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Vitamin D regulates macrophage cholesterol metabolism in diabetes☆

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ABSTRACT

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). In type 2 diabetics, the prevalence of vitamin D deficiency is 20% higher than in non-diabetics, and low vitamin D levels nearly double the relative risk of developing CVD compared to diabetic patients with normal vitamin D levels. However, the mechanism(s) by which vitamin D deficiency leads to an increased susceptibility to atherosclerosis in these patients is unknown. We studied the effects of vitamin D replacement on macrophage cholesterol metabolism and foam cell formation in obese, hypertensive diabetics and non-diabetic controls. We found that 1,25-dihydroxy vitamin D_3 [$1,25(OH)_2D_3$] suppressed foam cell formation by reducing acetylated low density lipoprotein (AcLDL) and oxidized low density lipoprotein (oxLDL) cholesterol uptake in diabetics only. $1,25(OH)_2D_3$ downregulation of c-Jun N-terminal kinase activation reduced PPARγ and CD36 expression, and prevented oxLDL-derived cholesterol uptake. In addition, $1,25(OH)_2D_3$ suppression of macrophage endoplasmic reticulum stress improved insulin signaling, downregulated SR-A1 expression, and prevented oxLDL- and AcLDL-derived cholesterol uptake. The results of this research reveal novel insights into the mechanisms linking vitamin D signaling to foam cell formation in diabetics and suggest a potential new therapeutic target to reduce cardiovascular risk in this population.

1. Diabetes and cardiovascular disease

More than 24 million people in the United States and 100 million people worldwide carry a diagnosis of type 2 diabetes mellitus (T2DM), a disease frequently associated with elevated blood pressure and characterized by an increased risk of cardiovascular disease (CVD) [1]. The combination of these metabolic abnormalities is the most common cause of morbidity and mortality in Western populations [2]. Hyperglycemia accounts for some of the increased risk of CVD in this population. However, the effects of intensive glucose lowering on macrovascular complications are unpredictable and may result in increased mortality [3]. Therefore, the identification of glucose-independent mechanisms that link cardiovascular disease and diabetes is critical to establish novel targets for therapy to decrease this global epidemic.

2. Epidemiology of vitamin D and vascular disease

Vitamin D deficiency is a largely unacknowledged epidemic associated with CVD. Data linking vitamin D, insulin resistance, and atherosclerosis comes from large epidemiological and clinical studies. Data from NHANES III showed that 25 hydroxy vitamin D [25(OH)D] levels were inversely associated with diabetes, hypertension, high triglycerides, and obesity [4]. Additionally, vitamin D deficiency was independently associated with self-reported CVD and increased all-cause mortality [5–8]. In patients with T2DM, the prevalence of 25(OH)D deficiency was nearly 20% higher than for non-diabetics, and low vitamin D levels nearly doubled the relative risk of developing cardiovascular disease compared with diabetic patients with normal vitamin D levels [9]. Similarly, in diabetic patients with mild renal failure, low vitamin D levels increased the relative risk of CVD when compared to their vitamin D-sufficient counterparts [10]. Prospective cohort studies further support the association between vitamin D deficiency and CVD in non-diabetics. In hypertensive patients from the Framingham offspring study, CVD was increased by 60% over 5.4 years of follow-up in those who were vitamin D deficient [25(OH)D level < 15 ng/ml] [11]. Men in the Health Professionals Follow-up Study with vitamin D deficiency [25(OH)D < 15 ng/ml] and without previous CVD exhibited a 2-fold increased rate of myocardial infarction over 10 years of follow-up [12]. Finally, an interventional study evaluating flow mediated dilatation (FMD) as an assessment of endothelial dysfunction, which is one of the first steps in the development of atherosclerosis, has shown that a single dose of 100,000 units of vitamin D_2 significantly decreased FMD in diabetics by 2.3% 8 weeks later after adjusting for changes in blood pressure [13]. Therefore,

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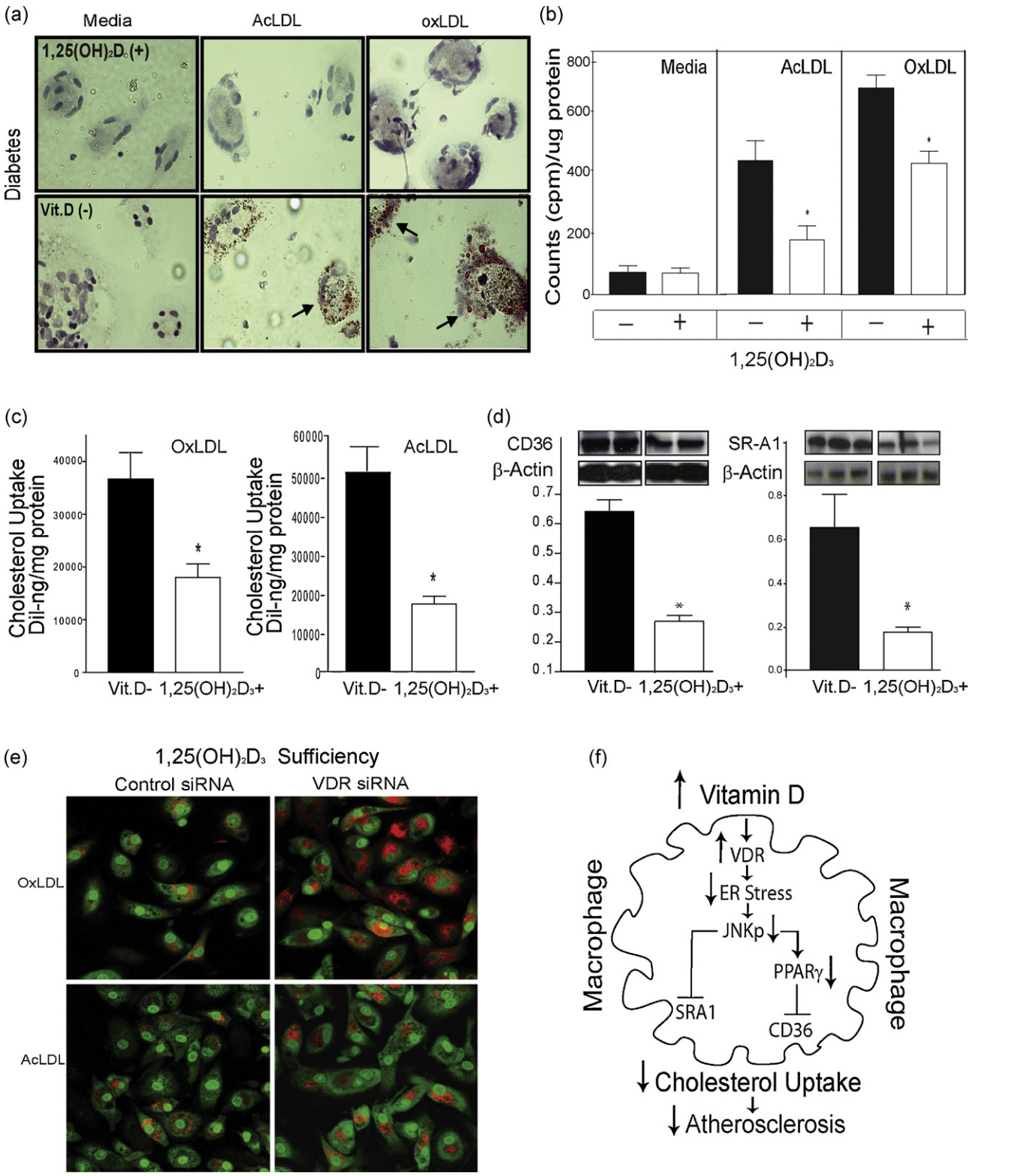

Fig. 1. Vitamin D and macrophage cholesterol metabolism. The same patient's macrophages from vitamin D-deficient diabetics were cultured in vitamin D-deficient or 1,25-dihydroxyvitamin D_3 ($1,25(OH)_2D_3$) supplemented media and exposed to oxLDL or AcLDL. (a) Macrophages stained with Oil-red-O. *Top panel*, $1,25(OH)_2D_3$-treated cells, *bottom panel*, vitamin D-deficient cells. *Arrowheads* indicate foam cells. (b) Cholesteryl ester formation in macrophages from diabetics cultured in vitamin D-deficient (*black bars*) or $1,25(OH)_2D_3$-supplemented (*white bars*) media (*$p < 0.01$ vs. vitamin D-deficient). (c) Quantification of cholesterol uptake in macrophages from diabetics cultured in vitamin D-deficient (*black bars*) and $1,25(OH)_2D_3$-supplemented (*white bars*) media. Mean fluorescence absorbance after Dil-oxLDL (*left panel*) or after Dil-AcLDL (*right panel*) stimulation (*$p < 0.01$ vs. vitamin D-deficient). (d) In macrophages from diabetics cultured in vitamin D-deficient (*black bars*) or $1,25(OH)_2D_3$-supplemented media (*white bars*), densitometric analysis of CD36 protein expression normalized to β-actin (*$p < 0.002$ vs. vitamin D-deficient) and SR-A1 protein expression normalized to β-actin (*$p < 0.001$ vs. vitamin D-deficient). (e) Cholesterol uptake assessed by confocal microscopy in macrophages cultured in $1,25(OH)_2D_3$-supplemented media after infection with either VDR-siRNA (*right panels*) or control-siRNA (*left panels*) lentivirus. *Red* represents labeled cholesterol uptake after Dil-oxLDL (*top panel*) or Dil-AcLDL (*bottom panel*) stimulation; *green fluorescence* represents nuclear counterstains. (f) Mechanistic pathways involved in $1,25(OH)_2D_3$ suppression of foam cell formation.

understanding the mechanism of the accelerated atherosclerosis induced by vitamin D deficiency may be crucial for treating the epidemic of CVD in diabetics.

3. Vitamin D, inflammation, and foam cell formation

Increased accumulation of lipid-laden macrophages (foam cells) in the vascular wall constitutes fatty streaks, the pathologic hallmark of the early atherosclerotic lesion. Active macrophages in the subendothelial space express scavenger cell surface receptors CD36 and SR-A1 that facilitate cholesterol uptake of oxidized LDL (oxLDL) and acetylated LDL (AcLDL) cholesterol, respectively [14–18]. In response to this lipid load, a compensatory cholesterol efflux is activated preventing accumulation of cholesteryl ester deposition [19–21]. Increased proinflammatory cytokines contribute to the atherosclerotic process by inducing immune cell recruitment in the vascular wall and promoting an imbalance between cholesterol uptake and cholesterol efflux that results in retention of foam cells in the vascular wall [22]. Active vitamin D [$1,25(OH)_2D_3$] promotes monocyte/macrophage growth and differentiation and diminishes the expression of proinflammatory cytokines including tumor necrosis factor α (TNFα) and interleukins (IL)-1, IL-6, and IL-8 in immune mononuclear cells from type 2 diabetics, suggesting that $1,25(OH)_2D_3$ signaling may regulate monocyte vascular infiltration and macrophage cholesterol retention in the vessel wall in these patients [23,24].

Initial studies exploring the influence of $1,25(OH)_2D_3$ on macrophage cholesterol metabolism are contradictory. In human promyelocytic leukemic (HL-60) and monocytic (THP-1) cell lines, $1,25(OH)_2D_3$ decreased SR-A1 expression and AcLDL binding [25,26]. In contrast, in normal subjects, $1,25(OH)_2D_3$ increased cholesteryl ester formation stimulated by AcLDL but only under conditions of lipid deprivation [27]. To determine whether $1,25(OH)_2D_3$ contributes to the increase in macrophage-mediated cholesterol deposition seen in patients with diabetes, we isolated monocytes from 76 obese, diabetic, hypertensive patients with vitamin D deficiency [25(OH)D < 32 ng/dl] and three non-diabetic control groups and transformed them into macrophages with M-CSF. The same patient's macrophages from all groups were cultured in vitamin D-deficient or $1,25(OH)_2D_3$-supplemented media and exposed to AcLDL or oxLDL cholesterol as previously described [28].

$1,25(OH)_2D_3$ suppressed foam cell formation in diabetics by reducing cholesteryl ester formation (Fig. 1a and b), but this effect was not seen in non-diabetic controls. Similarly, macrophages isolated from vitamin D-sufficient hypercholesterolemic $LDLR^{-/-}$ mice on a high-fat diet exhibited less Oil-red-O droplets and lower total cholesterol and triglycerides immediately after peritoneal isolation when compared to macrophages isolated from vitamin D-deficient control mice. These findings indicate that vitamin D status may be sufficient to inhibit foam cell formation. To determine the mechanism by which foam cell formation is suppressed by $1,25(OH)_2D_3$ in patients with diabetes, we assessed cholesterol uptake using fluorescent-labeled oxLDL or AcLDL and efflux using ^{3}H-cholesterol as previously described, [29] demonstrating that $1,25(OH)_2D_3$ suppressed foam cell formation by reducing AcLDL and oxLDL cholesterol uptake when compared to vitamin D-deficient macrophages (Fig. 1c). Cholesterol efflux was unaffected by $1,25(OH)_2D_3$. Then, we evaluated the mRNA, protein, and membrane expression of scavenger receptors CD-36 and SR-A1, essential receptors for modified LDL uptake, by QT-PCR, western blot, and flow cytometry, respectively. Both receptors were downregulated in diabetic-derived, modified LDL-stimulated macrophages supplemented with $1,25(OH)_2D_3$ compared to vitamin D-deficient controls (Fig. 1d shows Western blot results). These findings demonstrate decreased foam cell formation in diabetics by $1,25(OH)_2D_3$ supplementation that is produced by suppression of cholesterol uptake dependent upon decreased expression of scavenger receptors CD-36 and SR-A1 [28].

4. Vitamin D signaling pathways suppress macrophage cholesterol uptake

In the atherosclerotic plaque, macrophage cholesterol uptake triggers endoplasmic reticulum (ER) stress and c-Jun N-terminal kinase phosphorylation (JNKp). ER stress induces SR-A1 and CD36 expression [30–35]. To further determine the pathways leading to decreased CD-36 and SR-A1 expression induced by $1,25(OH)_2D_3$ supplementation in diabetics, we looked at markers of ER stress and JNKp. We found that $1,25(OH)_2D_3$-supplemented macrophages from diabetics had reduced CHOP (GADD153) and GADD34 protein expression and suppressed JNKp compared to vitamin D-deficient controls. Incubation with JNKp inhibitor decreased cholesterol uptake stimulated by oxLDL and AcLDL when compared to vitamin D-deficient macrophages not exposed to the JNK inhibitor. PPARγ can be activated by oxLDL, controls macrophage CD36 expression [36], and is expressed in foam cells of human atherosclerotic lesions [37]. Incubation of vitamin D-deficient or $1,25(OH)_2D_3$-supplemented macrophages with JNKp inhibitor almost abolished oxLDL-stimulated PPARγ and CD36 protein expression compared to macrophages without JNK inhibitor, suggesting that $1,25(OH)_2D_3$-mediated downregulation of JNKp suppresses PPARγ expression, leading to suppression of CD36 protein expression. Defective macrophage insulin signaling is known to induce ER stress [38]. In diabetics, we found that by improving AKT phosphorylation, a marker of insulin sensitivity, and reducing ER stress markers and JNKp, $1,25(OH)_2D_3$ reduced CD-36 and SR-A1 dependent cholesterol uptake [28].

Finally, by infecting diabetic-derived, $1,25(OH)_2D_3$-supplemented macrophages with vitamin D receptor silencing RNA (VDR-siRNA) by lentivirus as previously described [28,39] we confirmed that the effects of $1,25(OH)_2D_3$ on cholesterol uptake were VDR-dependent. Reduction of macrophage VDR expression blunted the $1,25(OH)_2D_3$ suppression of both oxLDL- and AcLDL-induced cholesterol uptake (Fig. 1e). Furthermore, downregulation of ER stress proteins (CHOP and GADD34), JNKp, and scavenger receptor CD-36 and SR-A1 protein expression by $1,25(OH)_2D_3$ were also significantly blunted in the VDR-siRNA-infected cells. These data confirm the importance of the activation of VDR signaling in the regulation of the expression of both scavenger receptors and cell signaling pathways involved in macrophage foam cell formation (Fig. 1f) [28].

5. Conclusion

A growing body of evidence from animal and human studies illustrates that vitamin D influences multiple known mechanisms responsible for the increased vascular inflammation seen in diabetic patients: it improves peripheral insulin action, suppresses the renin–angiotensin system, decreases systemic inflammatory mediators of vascular disease and imbues immune cells with anti-inflammatory properties [40–45]. This study reveals a novel mechanistic link between vitamin D deficiency in diabetic-derived macrophages and foam cell formation, a critical step in the development of atherosclerosis. Interventional studies are needed to assess the effects of vitamin D status on CVD in diabetic subjects.

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