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Review

# Amplification of lipotoxic cardiomyopathy in the VDR gene knockout mouse

Denis J. Glenn*, Michelle C. Cardema, David G. Gardner

*Diabetes Center, 1109 HSW, University of California San Francisco, San Francisco, CA 94143-0540, United States*

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ABSTRACT

Previous studies demonstrated that the liganded vitamin D receptor (VDR) plays an important role in controlling cardiovascular homeostasis. Both the whole animal VDR gene knockout ($VDR^{-/-}$) and the myocyte-specific VDR gene deletion result in changes in cardiac structure and function. Clinical states associated with cardiac steatosis (obesity and diabetes mellitus) are also associated with low circulating 25 OH vitamin D levels. We, therefore, examined the effects of VDR deficiency ($VDR^{-/-}$ mouse) in a murine model of cardiac steatosis that expresses the terminal enzyme involved in triglyceride synthesis, diacylglycerol acyltransferase 1 (DGAT1), selectively in the cardiac myocyte. These mice display early cardiac dysfunction and late cardiomyopathy and heart failure. In the present study, we demonstrate that mice harboring both genetic modifications (i.e., MHC-DGAT1 Tg and $VDR^{-/-}$) exhibit an increase in myocyte size, heart weight/body weight ratio and natriuretic peptide gene expression, all markers of cardiac hypertrophy, that exceed that seen in either $VDR^{-/-}$ or the MHC-DGAT1 Tg mice alone. This was accompanied by a dramatic increase in interstitial fibrosis and increased expression of collagen 1a1 and collagen 3a1, as well as the osteopontin and matrix metalloproteinase 2, genes. At a functional level, this resulted in a 37% reduction in ejection fraction and 55% reduction in fractional shortening in the DGAT1; $VDR^{-/-}$ mice relative to the controls. Collectively, these data demonstrate that deficiency in the vitamin D signaling system enhances the pathological phenotype in this experimental cardiomyopathy and suggest an important role for vitamin D in modulating disease severity in common cardiovascular disorders.



**Contents**



## 1. Introduction

The liganded vitamin D receptor (VDR) has been implicated as playing an important role in the maintenance of cardiovascular homeostasis [1]. Both the VDR null mouse ($VDR^{-/-}$) [2], as well as

* Corresponding author. Fax: +1 415 564 5813.
*E-mail address:* dglenn@diabetes.ucsf.edu (D.J. Glenn).

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the cardiac myocyte-specific VDR gene-deleted mouse [3], show evidence of cardiac hypertrophy and myocyte enlargement.

Clinical states associated with cardiac steatosis (morbid obesity and diabetes mellitus) can lead to metabolic cardiomyopathy. This is often associated with low circulating 25 OH vitamin D levels [4]. This led us to ask whether the absence of VDR might allow for amplification of this metabolic cardiomyopathic phenotype. We examined the effects of VDR deficiency (VDR$^{-/-}$ mouse) in a

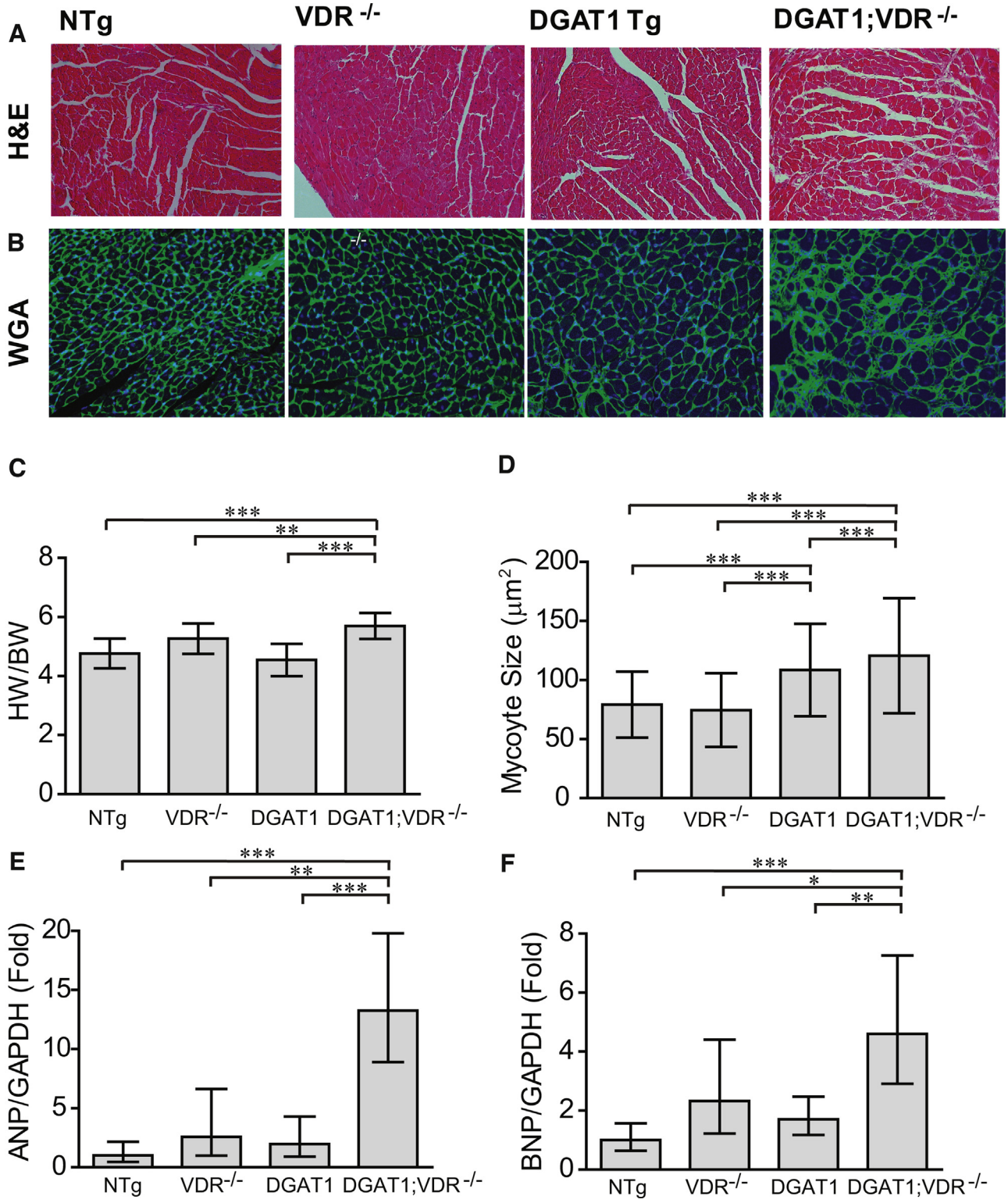


**Fig. 1.** Cardiac hypertrophy and activation of the natriuretic peptide gene program in the DGAT1:VDR$^{-/-}$ mouse. Representative (A) hematoxylin and eosin stained left ventricular micrographs and (B) FITC-wheat-germ agglutinin (WGA) stained left ventricular stained sections in the NTg, VDR$^{-/-}$, DGAT1 Tg and DGAT1:VDR$^{-/-}$ mice. Original magnification 200×. (C) Heart weight normalized to body weight (HW/BW). (D) Mean myocyte diameter calculated from the FITC–WGA stained ventricular micrographs, $N = 6$ each group. (E and F) Atrial and B-type natriuretic peptide (ANP and BNP) gene expression assessed by quantitative-PCR and normalized to GAPDH, $N = 6$–9 each group. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$.