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Original Article

1, 25 Dihydroxyvitamin D3 Protects the Heart Against Pressure Overload-induced Hypertrophy without Affecting SIRT1 mRNA Level

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Background and Aims: There has been scant information concerning antihypertrophic effects of vitamin D specifically on its cellular and molecular mechanisms. Sirtuin 1 (SIRT1) is regarded as a key deacetylase enzyme in cardiomyocytes which applies potential cardioprotective effects by functional regulation of different proteins. This study aimed to evaluate the effects of 1, 25-dihydroxyvitamin D on the hypertrophic markers and cardiac level of SIRT1 mRNA in rats following the aortic banding.

Material and Methods: In this study, male Wistar rats (170-220g) were used, which were divided into 4 groups: rats subjected to hypertrophy without treatment (H), rats pretreated with 1,25 dihydroxyvitamin D3 (H+VD), rats received propyleneglycol as a vitamin solvent (H+P), and intact animals which were elected as the control group. Arterial blood pressure was directly measured by the carotid cannulation. Transcription level of target genes was measured by real time polymerase chain reaction technique.

Results: In H+VD group, systolic blood pressure as well as heart weight-to-body weight ratio decreased significantly compared to the group H ($P<0.01$). Moreover, regarding hypertrophy marker genes in H+VD group, both atrial natriuretic peptide mRNA (H+VD:64.8±14% vs. H:127±26%; $P<0.05$) and brain natriuretic peptide mRNA (H+VD:25.6±6% vs. H:84.2±12%; $P<0.01$) levels decreased significantly. SIRT1 mRNA level was increased by 56.8±14% in group H and by 42.6±12% in group H+VD which were significant in comparison to the control group ($P<0.01$ and $P<0.05$, respectively). No significant difference was noted between H+VD and H groups.

Conclusions: The results of the present study revealed that administration of 1, 25-dihydroxyvitamin D decreases myocardial hypertrophy markers in rats following the abdominal aortic banding. The pressure overload-induced hypertrophy accompanies with SIRT1 mRNA upregulation, though antihypertrophic effects of vitamin didnot participate in SIRT1 transcription level.

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Introduction

Cardiac hypertrophy is a normal response of heart to internal and external stimuli which occurs as an adaptive response for maintaining normal heart function under biochemical stress. For instance, heart will be under high pressure overload within chronic hypertension, which is considered as one of the most common risk factors of cardiac hypertrophy. Since cardiac myocytes are not able to divide, as compensation, hypertrophy will be the first way of suppressing stress against ventricular wall. Continuing this process reduces the heart capability to resist against hypertrophic stimuli and thus, hypertrophy will remain in a maladaptive form and will eventually lead to the cardiac failure. Hypertrophy progression toward maladaptive form changes the profile of a wide range of genes expression, which is generally expressed during embryonic heart evolution. The changes initially increase the heart ability, though it will lead hypertrophy to heart failure [1, 2].

Sirtuins (SIRTs) are a group of cell deacetylases in heart that control lots of cardiomyocyte functions such as metabolism, division, differentiation, apoptosis and oxidative stress by deacetylation of histone and non-histone proteins [3, 4]. Among the seven groups of known SIRTs in mammals, SIRT1, expressed in cardiomyocytes, protects the heart from oxidative stress-induced damage caused by ischemic reperfusion, hypertrophy and heart failure by deacetylation and thereby it can regulate multiple transcription factors [5, 6]. Although nowadays a great number of pharmacological agents such as angiotensin-converting enzyme inhibitors, beta blockers and angiotensin II receptor blockers like losartan are utilized in treatment of cardiac hypertrophy and early stages of heart failure, death rate due to cardiac failure is increasing. As a result, an alternative therapy for reversing heart from hypertrophy and preventing heart failure is necessitated. Recent clinical and experimental studies have revealed the relationship between vitamin D deficiency and risk factors of heart disease [7-11]. It has been shown that the mice lacking vitamin D receptor or the enzyme, synthesizes this vitamin D involve structural and functional abnormalities of heart which are demonstrated as hypertrophy and myocardial failure [12, 13]. Therefore, lack of this vitamin is recognized as an independent risk factor of death due to the cardiovascular diseases.

Considering the importance of precise knowledge on cardioprotective effects of vitamin D, the present study intended to investigate the effect of 1, 25-dihydroxy vitamin D on myocardial hypertrophy caused by abdominal aorta stenosis. Moreover, level of SIRT1 gene expression was examined, as well.

Materials and Methods

Animal model and experimental design

Rats were anesthetized by intraperitoneal injection of Ketamine (70 mg/kg) and xylazine (10 mg/kg). After opening a space between the last rib and left femur, abdominal aorta was

exposed. A 21-gauge needle was placed along the side of the aorta in suprarenal region. Then a suture was tied around the artery and the needle was removed. After surgery tetracycline spray was used as the antibiotic in the incision region. It should be noted that in all cases 21-gauge needle was used and surgery was performed by an expert technician. The animals (N=7 in each group) were divided into the following groups; I) Control group: myocardial tissue was collected from intact animals, II) Sham (H+P) group: animals received propylene glycol as the vitamin solvent, III) Hypertrophy (H) group: Since previous studies as well as the pilot study have demonstrated that after 2 weeks of aortic banding, the blood pressure increased significantly and heart involved hypertrophy determined by a significant increase in heart weight-to-body weight ratio; this group of animals underwent hypertrophy induction. IV) Vitamin D+ hypertrophy (H+VD) group: In order to study the effect of vitamin on hypertrophy markers and SIRT1 mRNA level, 1, 25-dihydroxyvitamin D was injected intraperitoneally (0.1 µg/kg/d, ip) for 14 days in this group of animals, and then the animals underwent surgery to induce hypertrophy model. After surgery, the treatment with vitamin D was continued for 2 weeks. It is notable that our previous experiments approved ineffectiveness of the mentioned dose on basic blood pressure of rats. V) Vitamin D (VD) group: In this group of animals, 1, 25-dihydroxyvitamin D was administrated for 28 days and the samples were collected without induction of hypertrophy.

In all above groups (except the control group), the animals were anesthetized again 2 weeks after banding of aorta and arterial blood pressure was measured directly through carotid artery cannulation. Then the heart was removed and weighed immediately to report the ratio of heart weight-to-body weight as a hypertrophy marker. Eventually, the left ventricular tissue was collected and transferred to liquid nitrogen for molecular studies.

Evaluation of mRNA changes by real time-polymerase chain reaction (RT-PCR) technique

Atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) mRNA levels were studied as the genetic markers of myocardial hypertrophy. Moreover, since one of our goals was to study the changes of SIRT1 transcription level in myocardial hypertrophy in response to vitamin D, the SIRT1 mRNA level was also measured. For this purpose, RNA was extracted using RNX plus (Cinnagen, Iran) according to the manufacturer's protocol. After reading the absorption of mRNA in the NanoDrop Spectrophotometer, a volume of 1000 ng of RNA was used for cDNA synthesis. Reverse transcription reaction was done using revert Aid™M-MuLV reverse transcriptase enzyme (Fermentas). After optimizing PCR reaction, cDNA of experimented groups were tested by RT-PCR reaction using master mix containing SYBR green and specific primers. Primer sequence used in this experiment was listed in table. ΔΔCt method was applied to compare the relative gene expression. It is worth mentioning that the Ethics Committee

of Shahid Sadoughi University of Medical Sciences approved this study.

Table 1. Primer sequences used for quantitative real-time polymerase chain reaction

Gene	Forward primer	Reverse primer
ANP	GAGGAGAAGATGCCGGTAG	CTAGAGAGGGAGCTAAGTG
BNP	TGATTCTGCTCCTGCTTTTC	GTGGATTGTTCTGGAGACTG
SIRT1	TGTTTCCTGTGGGATACCTGA	TGAAGAATGGTCTTGGGTCTTT
Beta-actin	GAACCCTAAGGCCAACCGTGAA	ATAGCAGCCACAAAAAGGGAAA

Results

As it is reported in Table 2, in group H in which animals were exposed to abdominal aortic banding, a significant increase was observed in systolic blood pressure as well as heart weight-to-body weight ratio (HW/BW). In H+VD group, the mean of arterial blood pressure and HW/BW were significantly decreased in comparison to group H (P<0.01).

Table 2. Systolic blood pressure and heart weight-to-body weight ratio in rats subjected to abdominal aortic banding to induce hypertrophy (H) and rats treated with 1, 25-dihydroxyvitamin D (VD) or propylene glycol as a vitamin solvent (P)

Groups	Systolic BP (mm Hg)	HW/BW (mg/kg)
Control	106.2±12.7	2.59±0.18
H	161.4±9.7***	4.05±0.3***
H+VD	139±7.3$^{\$\$}$	3.1±0.18$^{\$\$}$
H+P	158±9.9**	3.97±0.3*
VD	119±8.6	2.63±0.3

Data are presented as mean±SEM. *P<0.05, **P<0.01, ***P<0.001 vs. control and $^{\$\$}$P<0.01 vs. H group.

ANP and BNP mRNA level changes is one of the important genetically markers of left ventricular hypertrophy. In the present study, as it is demonstrated in Fig. 1, ANP mRNA level increased in group H by 127±26% which is significant in comparison to control group (P<0.001). In H+VD group, this transcription level reached 64.8±14% reporting a significant decrease compared to group H (P<0.05). Regarding BNP mRNA changes, in group H, BNP mRNA level increased by 84.2±12% which shows a significant increase in comparison to control group (P<0.001). In (H+VD)group, BNP mRNA level increased only 25.6±6% which was not significant compared with the control group , though a significant decrease was revealed in comparison to group H (P<0.01). In H+VD group, no significant change was observed in ANP and BNP mRNA levels.

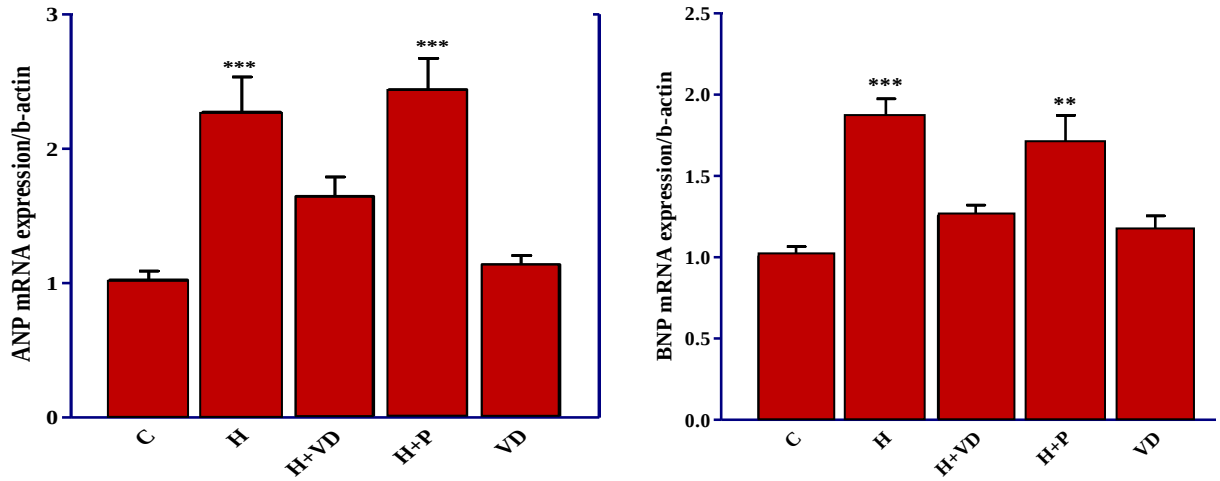

Fig. 1. Transcription level of ANP and BNP genes in intact rats as the control (C) and hypertrophied rat heart which were subjected to abdominal aortic banding (H) with or without 1,25 dihydroxyvitamin D (VD). Propylene glycol (P) was used as the vitamin solvent. Data are reported as mean±SEM. **P<0.01,and ***P<0.001 vs. control group.

One of our study aims was to investigate SIRT1 mRNA level changes in the experimental groups. As shown in Fig. 2, SIRT1 mRNA level increased in group H by 56.8±14% which is significant in comparison to control group (P<0.01). In H+VD group, this measure increased by 42.6±12% in comparison to control group which is statistically significant (P<0.05), whereas no significant difference was observed between H and H+VD groups.

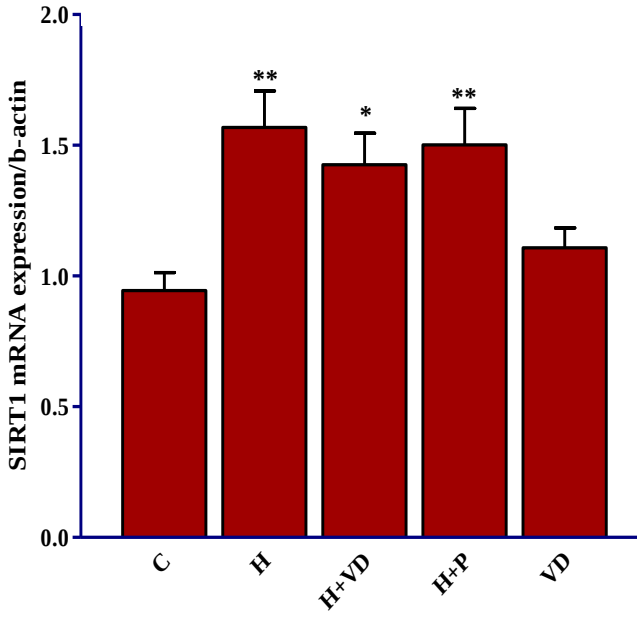

Fig. 2. SIRT3 mRNA level in rats subjected to abdominal aortic banding to induce hypertrophy (H) and rats treated with 1, 25-dihydroxyvitamin D (VD) or propylene glycol as a vitamin solvent (P). Intact animals served as the controls. Data are expressed as mean±SEM. *P<0.05, **P<0.01.

Discussion

Results of the current study indicated that short-term administration of non-hypotensive dose of 1, 25-dihydroxyvitamin D prevents increase of blood pressure in rats subjected to cardiac hypertrophy and reduces hypertrophy markers such as HW/BW as well as ANP and BNP mRNA levels which can directly be related to vitamin D, and blood pressure reduction. In recent years, developing studies are carried out in regard with cardio protective effects of vitamin D which is mainly produced in skin by photochemical conversion of 7-Dehydrocholesterol to vitamin D3 (cholecalciferol) and by successive hydroxylation in liver and kidney is converted to its active form, 1, 25 dihydroxyvitamin D3 or calcitriol and eventually by binding to its nuclear receptor applies its broad physiological effects in cells [14, 15]. In other words, nowadays vitamin D is considered as a prehormone instead of a vitamin which possesses membrane and nuclear receptors in most cells such as cardiomyocytes, endothelial cells and vascular smooth muscle cells. As a matter of fact, vitamin D plays a role beyond calcium homoestasis regulation [16-18]. Existence of nuclear receptors of vitamin D, acting actually as a transcription factor in cardiomyocytes, can affect function of these cells by inserting some effects on transcription of hundreds of genes. Pathophysiological studies have demonstrated a relation between low level of vitamin D and left ventricular hypertrophy [9, 19]. Investigations have shown that rats lacking vitamin D receptor or enzyme synthesizes this vitamin involve structural and functional abnormalities in heart which are demonstrated in form of hypertrophy or cardiac failure and treatment with vitamin D and its analogues prevents mentioned disorders [13, 20].

The results of the present study concerning anti hypertrophic effects of the vitamin is consistent with the findings of some previous studies. Simpson et al. claimed that in rats lacking vitamin receptors (VDRKO), HW/BW ration and hypertrophy severity were reported more in comparison to normal rats [13]. In the current study, 0.1 µgr/kg/day dose of vitamin D was injected up to 2 weeks after surgery (hypertrophy induction). It is notable that a previous study conducted by the authors of the present study has approved the ineffectiveness of mentioned dose on the basic blood pressure of rats. Moreover, Wong et al. have shown that consumption of vitamin D at 10 ngr/100gr BW dose in intact animals did not affect blood pressure which is also confirmed in our present study. However, the vitamin was administrated for 6 weeks in Wong et al.'s study that shows longer time duration of treatment compared to the present study [21]. In another study carried out on elderly women, Pfeifer et al. concluded that taking vitamin D supplement and calcium produce a more efficient effect on systolic pressure than taking calcium supplement alone [22]. However, another study stated that in trial level, no effect of vitamin D was observed on systolic and diastolic blood pressure [23].

Today, investigating signals responsible for the effect of this vitamin is considered as a new approach in cardiac disease treatment field. One of the most important suggested mechanisms responsible for protective effects of vitamin D is renin–angiotensin system suppression. Furthermore, the inverse relation between serum level of this vitamin and serum renin activity is proved so that vitamin D is introduced as a negative regulator of renin–angiotensin system. Therefore, taking the key role of angiotensin into account in cardiac disease pathogenesis such as myocardial hypertrophy, a part of effects of vitamin maybe applied through renin–angiotensin system suppression [24-26].

The findings of the present study also revealed invariability of SIRT1 mRNA level in myocardial tissue of rats treated with the vitamin. SIRT1 with molecular weight of 747 amino acids is considered as the biggest member of Sirtuins family and in fact is regarded as a nucleocytoplasmic protein. It mainly exists within cardiomyocytes cytoplasm in adults and migrates to the nucleus in order to regulate gene expression [27, 28]. SIRT1 by deacetylation of histone proteins (H1, H3 ,H4) as well as non-histone proteins like transcription factors (PGC1α-Bcl6-FOXO-P53-Rab-P73-NFκB), DNA repairing proteins, and multiple signaling factors affect transcription and function of great many intracellular proteins and shows anti inflammatory, reduction of platelet aggregation, increase free radical uptake and anti-apoptotic function in cardiovascular system [29- 31]. Low-to-moderate expression of SIRT1 can resist heart against hypertrophy, apoptosis and functional disorders of heart caused by aging. One of the SIRT1 target molecules is FOXO transcription factor. SIRT1 by FOXO deacetylation increases its migration to nucleus and reinforces anti-oxidant factor expression to enhance the heart resistance against oxidative damages [32]. Few studies have been carried out on the possible relation between vitamin D and SIRTs. In some reports, synergistic effect of vitamin D and resveratrol (SIRT1 activator) have been examined. Guo et al. reported that combination of resveratrol and 1, 25-dihydroxyvitamin D together will create a synergistic response in order to boost the immune response in monocytes [33]. In a previous study conducted by the authors of the present study, the synergistic effect of 1, 25-dihydroxyvitamin D and resveratrol has been demonstrated on myocardial ischemia reperfusion injury. That was identified by reduction of the size of infarct area and decreasing the incidence of reperfusion-induced arrhythmia. This cardioprotective effect was accompanied by the survival factors upregulation of heart. Recently, Polidoro et al. proposed that treating endothelial cells with vitamin D through activation of SIRT1 can decrease oxidative stress and apoptosis in the mentioned cells [34]. In another study, activation of SIRT1-foxo3a pathway is considered as one of the manifestations of protective effects of the vitamin against chemotherapy [35]. In the present study, SIRT1 mRNA level increased in hypertrophied left ventricle. Considering that activation of SIRT1 in heart activates survival

pathways and that in this experiment, the heart is not yet entered in mal adaptive phase of hypertrophy, it can be proposed that increase of SIRT1 mRNA level occurs in heart as a compensatory protective response.

The current study results also revealed that vitamin D did not change SIRT1 transcription level in hypertrophied left ventricles, therefore; one possible explanation is that SIRT1 is not involved in antihypertrophic effects of vitamin D. However, it should be noted that SIRT1 is an enzyme, which only its transcription level was taken into consideration in the current study. Since the vitamin possibly changed the enzymatic activity, evaluation of SIRT1 activity would provide valuable data in this regard. Evaluating the probable roles of other SIRTs such as SIRT3 can lead us towards understanding the molecular mechanisms of antihypertrophic effects of vitamin D.

Conclusion

The current study findings revealed that short-term administration of non-hypotensive dose of vitamin D protects the heart against pressure overload–induced hypertrophy in rats, which this effect was characterized by decreasing hypertrophy markers such as HW/BW and natriuretic transcription levels. In the present study, SIRT1 mRNA level did not change that may be due to short-term prescription of the vitamin. Future studies on increased prescription period of the vitamin, measuring SIRT1 protein level, as well as its activity can provide valuable findings in regard with the possible association between vitamin D and sirtuins.

Conflict of interest

The authors confirm that this article content has no conflict of interest**.**

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