Original Article

Vitamin D deficiency is associated with low levels of tyrosine kinase-2 in ischemic heart diseases

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Abstract

Introduction: Vit-D, a fat-soluble vitamin, has a biovital role in the various physiological processes in a living system. its action is mediated through vitamin D receptors (VDR). Worldwide, cardiovascular diseases (CVD) including ischemic heart diseases (IHD), constitute the leading cause of mortality and associated with low vitamin D levels. However, the mechanisms by which low Vit-D levels enhance IHD pathogenesis are not fully understood. This study highlighted in vivo evidence that illustrates the strong links between vitamin D deficiency, and Tyrosine Kinase 2 in patients with IHD.

Methods: The study was performed between January 2021 to May 2021. 60 subjects were enrolled in this study with IHD (angina =30, MI= 30) with mean age (59 ± 1.5; 38 males, 22 female), and 60 subjects appeared to be normal healthy persons as the control group with mean age (52 ± 1.2; 51 males, 9 female). Serum Vit-D, VDR, and Tyrosine kinase-2 activity (TK2) were measured by ELISA.

Results: The results clearly showed low Vit-D and VDR levels in patient groups with IHD compared to control ($P<0.01$); a great effect was shown in the MI group. The finding also declared that serum activity of TK2 was significantly decreased in patients with IHD compared to control groups ($p <0.01$).

Conclusions: these findings may go some way towards explaining that numerous mechanistic links between vitamin D deficiency, and TK2 are involved in the pathogenesis of CVD.

Keywords: tyrosine kinase-2, Vitamin-D deficiency, Vitamin-D receptor, ischemic heart diseases

Introduction

Worldwide, cardiovascular diseases (CVD) constitute the leading cause of mortality, accounting for about 17.8 million deaths in 2017[1][2]. CVDs are disorders that affect the blood arteries that feed the heart (coronary heart disease), the brain (cerebrovascular disease), and the extremities (peripheral artery disease), As well as conditions that directly impact the heart (rheumatic heart disease, congenital heart disease), and conditions that cause blood clots in the vessels (thrombosis, embolism)[3].

The most significant contribution to CVDs and death is Ischemic Heart Disease (IHD)[4]. IHD is often referred to as Coronary Artery Disease (CAD), atherosclerotic cardiovascular disease, Coronary Heart Disease (CHD), is a disorder in which a section of the myocardium receives insufficient blood and oxygen; it usually happens when myocardial oxygen supply and demand are out of balance[3].

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The highest prevalence rates of IHD are seen in Eastern Europe, North Africa, and the Middle East[2]. According to WHO data published in 2018, IHD deaths in Iraq reach 32,463 or 18,92% of total deaths[6].

Vitamin D is a lipid-soluble category of secosteroid substances, of which 5 forms have been recognized: vitamin D1-D5. The most essential for human physiology are vitamin D2 (ergocalciferol), produced by plants and fungi, and vitamin D3 (cholecalciferol), which is mostly synthesized in the skin from 7-DHC precursor (7-dehydrocholesterol), but it may also be obtained via animals origin or food [7]. Only 10 to 20% of vitamin D in humans is obtained through food, the remaining 80% being generated endogenously [7]. Vitamin D's biological role is intimately linked to VDR; VDR is activated by interacting with 1,25(OH)2D, and two basic mechanisms of VDR activity have been identified. The first mechanism involves nuclear VDR activation and then VDREs (vitamin D–responsive elements) regulate the transcription of many vitamin D-dependent genes. The second is through the membrane VDR, which is necessary for the cell's high reactivity to an external influence[8].

The physiological function of Vit-D goes well beyond Ca metabolism and bone state regulation. Recent research has linked low serum vitamin D levels with a variety of disorders, like as cancer, autoimmune diseases, inflammation, anxiety, and diseases of cardiovascular system like high blood pressure, ischemic heart disease, and heart failure[9].

Vitamin D deficiency has been related to an increased risk of IHD, however, the pathophysiological mechanisms underlying this link are still unclear. The expression of VDR and 1α-hydroxylase enzyme in myocardial cells as well as cells of the blood vessels is the key evidence for such a link, and epidemiological studies have shown that both IHD and vitamin D inadequacy rises during the winter months and in areas farthest from the Equator[10]–[12]

Vitamin D deficiency seems to be highly detrimental to the cell of vessels and the heart since it has been shown to promote endothelial dysfunction and vascular defects through a variety of pathways[13]. Inhibition of renin production may explain direct action of vitamin D on the vascular system[13]. The importance of renin in blood pressure regulation has long been recognized, and various anti-hypertensive medications target this system. This system is important in the fluid volume balance, regulation of electrolyte plasma levels, and vascular resistance[13].

Vitamin D deficiency may contribute to IHD not only through inhibition of renin production but also through endothelial dysfunction and atherosclerosis, as endothelial dysfunction has been identified as a critical element in the beginning and development of atherosclerosis, vitamin D could have an effect in reversing atherosclerosis's consequences [14]. Vitamin D also acts as an antioxidant, protecting endothelium cells from oxidative stress by regulating the expression of genes involved in apoptosis [14]. It is probable that the formation of reactive oxygen species (ROS) and promotion of inflammation contribute to the pathophysiology of IHD[15]. Vitamin D antiatherogenic effects extend beyond the endothelium to the VSMCs, according to recent research[16].

Additionally, vitamin D may also alter the pathogenesis of atherosclerosis by modulating the inflammatory response by lowering TNF, IL-1,6,8 production[16]. Vitamin D has been demonstrated to lower cholesterol buildup in macrophages and LDL absorption in foam cells, which is a characteristic of atherosclerotic plaque development[17]. Recent research demonstrated that 1,25(OH)2 D promotes an antiatherogenic immune pattern by shifting the immune cells from a Th1 to a Th2 pattern. [18].

Tyrosine kinases (TKs) are a group of enzymes that, when activated, phosphorylate critical substrates inside the cell. Tyrosine kinases are classified into two types: membrane-bound receptors, receptor tyrosine kinases (RTKs), and intracellular signal transducers, non-receptor tyrosine kinases (NRTKs)[19]. Tyrosine kinase 2 (TYK2) has been one of four members of NRTKs, which also includes JAK1, JAK2, and JAK3. JAK1, JAK2, and TYK2 are distributed throughout the body, but JAK3 is only found in hematopoietic cells[20]–[22].

The JAK/STAT (Janus tyrosine kinase/signal transducers and activators of transcription) signaling pathway is important in inflammation[23]. JAKs are activated by cytokines connecting to their receptors, activated JAKs subsequently phosphorylate receptor tails, providing binding sites for (STAT). When receptor-localized STATs are phosphorylated, they dissociate from the receptor and translocate into the nucleus, where they induce gene expression in response to cytokine activation[24]. Tk2 is linked to many different heterodimeric cytokine receptor complexes, such as the IFN-1 receptor, IL-12 receptor, IL-10 receptor, and IL-23 receptor[25].

A study by S. Cooper et al. (2019) [26] found in mice and cultured rat cardiomyocytes, a tyrosine kinase inhibitor (Sunitinib) causes mitochondrial damage and apoptosis. On the other hand, Proline-rich TK2 detects hyperlipidemia and activates the ROS/TNF-pathway, which is important for the initiation of proinflammatory responses in the early phases of atherosclerosis[27]. Mei-Hua Bao et al., (2020)[28] found that the stimulation of the Tk2 and STAT1 pathways may play a role in the inflammation reaction of atherosclerosis. In this study, we examined whether the involvement of low Vit –D and TK2 a consequence of IHD pathology

Materials And Methods

Subjects

Sixty IHD patients with mean age (59 ± 1.5; 38 males, 22 female), clinical evidence of IHD was detected depending on the cardiologist's diagnosis. In this research, subjects were selected between January 2021 to May 2021at at the Al-Diwanyah Teaching Hospital & Al-Najaf center for cardiac surgery and transcatheter therapy. Sixty healthy, normal-appearing participants with a mean age (52 ± 1.2; 51 males, 9 female) who visiting the hospital for a routine check-up without any history of CVD, diabetes, with no other

endocrine problem or metabolic renal diseases, acute illness or infection. Systolic blood pressure (SBP), and diastolic blood pressure (DBP) was checked. The BMI is computed as kg/m2. General data: age, gender, history of CVD, smoking, hypertension, FBS, total cholesterol triglycerides and high density lipoprotein were recorded. A group of patients had to be excluded from the current study: End-stage renal disease, subjects with vitamin D or Tyrosine Kinase inhibitor treatment, subject with liver diseases, pulmonary hypertension, pregnant subject, subject has a history of malignancy, subject has a chronic systemic autoimmune disease, and subject with COVID-19.

Methods

From each research group taken a blood sample (5 mL), clotted and serum was obtained and stored at (-80 C) for Vit D, VDR, TK2 analysis. Vitamin D, VDR, TyK-2 levels were determined using the ELISA method following the manufacturer's recommendations (Bioassay, China).

Statistical analysis

The means and standard error of the mean (SEM) are used

to describe data (SEM). The significant difference between control and experimental subjects were determined by Student's t-test. In order to explore significant differences between control and different patient groups, one-way ANOVA or a non-parametric ranking (Kruskal-Wallis) were carried out as appropriate. After ANOVA, post hoc analysis using Tukey's test was carried out. A P value of <0.05 is considered significant throughout

Results

120 subjects were included, 60 patients with IHD, 30 patients with angina (Female= 6, Male = 24) with mean age (58.4±3.13), and 30 patients with myocardial infarction MI, (Female=7, Male =23), with mean age (57.25±3.90). The research included 60 healthy participants (Female=9, Male=51), whose average age was (52.0±2.1) years. The following table summarizes all clinical and hemodynamic variables (Table 1). The clinical and biochemical variables of patients with Angina and MI were compared with control as shown in (Table 2). There have been no significant variations were observed in BMI, Diastolic & Systolic blood pressure, and HDL-c ($P < 0.05$) in patient groups compared to control. The levels of TC (total cholesterol), FBS (fasting blood sugar), TG (triglycerides), and cardiac troponin were significantly increased in the serum of patient groups in comparison to the control (Table2).

Table 1: Clinical and hemodynamic variables were compared between study groups

Variables	***Groups***		
	IHD		***Control***
	Angina	***MI***	
Total Number	30	30	60
Sex			
Females, N (%)	6 (20%)	7 (23.3%)	9 (15%)
Males, N (%)	24 (80%)	23 (76.6%)	51 (85%)
Age(years)			
mean ± SEM	58.4±3.13	57.25±3.90	52.0±2.1
Family history with CVDs			
Yes	3(10%)	21 (35%)	0
NO	27(90%)	39 (65%)	60(100%)
Smoking			
Yes	9 (21%)	15(50%)	0 (0%)
NO	21 (79%)	15(50%)	60 (100%)

Table 2: Comparison of the biochemical parameters in study groups

Parameters Mean ± SEM	*Groups*			
	IHD			
	Angina	MI	*Control*	*P-value*
BMI(Kg)	27.64±3.13	27.08±1.9	24.873±0.34	$P \geq 0.05$
Diastolic blood pressure (DBP) (mmHg)	80.898+2.98	80.125±1.57	75.55±1.40	$P \geq 0.05$
Systolic blood pressure(SBP) (mmHg)	133.33±4.44	131.25±3.43	120.475±2.73	$P \geq 0.05$
FBS(mg/dl)	115.33±7.63*	114.62 ± 8.84*	98.57± 4.47	$P \leq 0.05$
TG (mg/dl)	157.34±11.2*	163.8 ±18.7 *	109.77 ± 4.47	$P \leq 0.05$
TC (mg/dl)	220.66±4.67*	230.75± 18.71*	157.78 ±10.17	$P < 0.05$
HDL-c (mg /dl)	42.73± 9.7	38.9 ± 5.7	51.5 ± 8.2	$P \geq 0.05$
CTnI (ng / ml)	1.125±0.28*	1.185±0.28*	0.38±0.01	$P \leq 0.05$

*represents statistically significant differences in comparison to the control.

Recently, it was suggested that an association between Vit-D deficiency and cardiovascular diseases. Vitamin D3 levels in this study were measured using ELISA. The results were showed low Vit-D levels in patient groups with IHD in comparison (P<0.01) to the control (Figure 1). Significant decreases were found in the patient group (angina and MI) compared to control, a high decrease was indicated in the group with MI (P<0.01). There were no significant differences between the patient groups (Figure 2).

The metabolic effects of Vit-D3 were mediated by the Vit-D3 receptor (VDR). The results were demonstrated that VDR levels were decreased significantly in the patient with IHD compared to control, indicating the mechanism by which Vit-D3 was acted in IHD (P < 0.001, figure 3). There has been a marked decline in angina and MI groups compared to the control, MI group declared a great decrease (P< 0.001). There was no significant change between patient groups (Figure 4).

Tyrosine kinase-2(TK-2) and its inhibitor were the targeted therapy for inflammatory diseases. Serum level of TK2 was decreased significantly in the patient with IHD compared to control (p <0.01, Figure 5). This suggested that measuring tyrosine kinase in serum could be an indicator of IHD prognosis. TK2 level decreased in angina and MI in comparison to control (P<0.01, 0.001 respectively), while no significant changes were found in TK2 between patient groups (P>0.05, Figure 6).

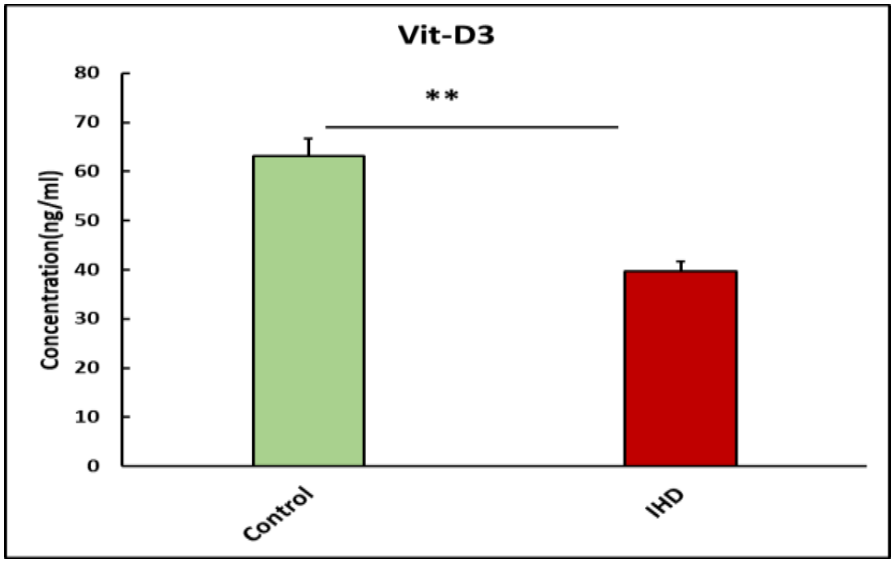

Fig.1: Serum Vit-D level in patients with IHD, and control. The data are presented as mean ± SEM. **represents a significant change between patients and control (P < 0.01).

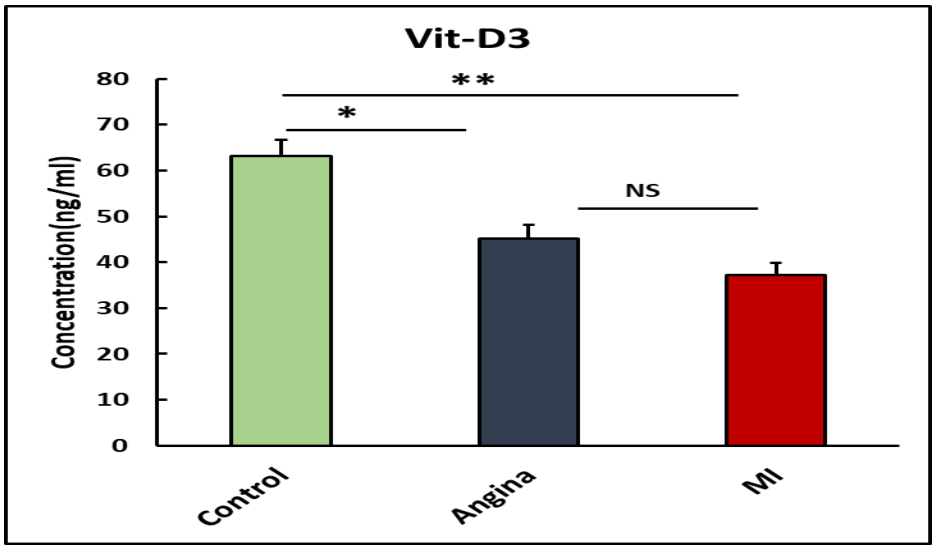

Fig.2: Serum Vit-D levels in patients with angina, MI, and control. The data are presented as mean ± SEM. *exhibited a significant change between patient groups and control (P < 0.05), ** exhibited a significant change between patient groups and control (P < 0.01), and NS is non-significant.

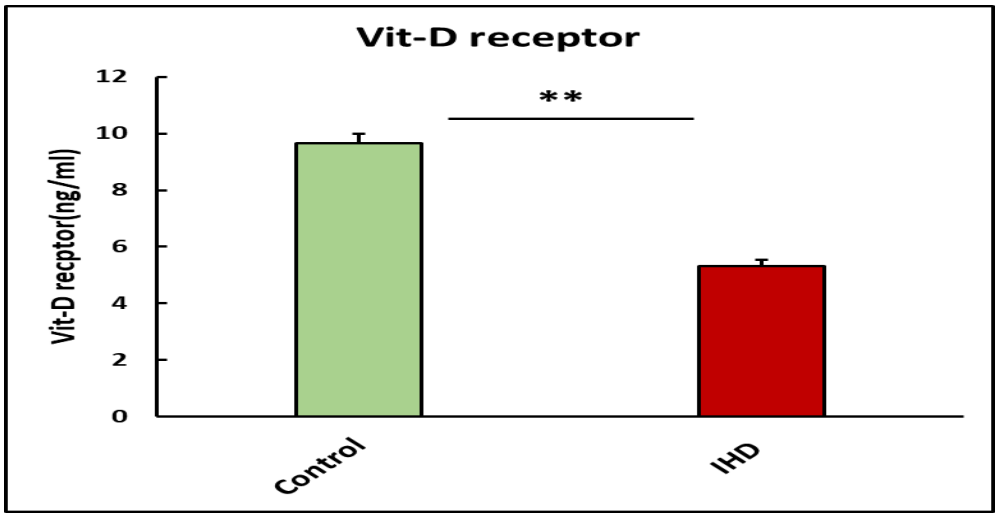

Fig.3: Vit-D receptor levels in patients with IHD and control groups. The data are presented as means ± SEM, ** exhibited significant differences compared to the control (P < 0.01).

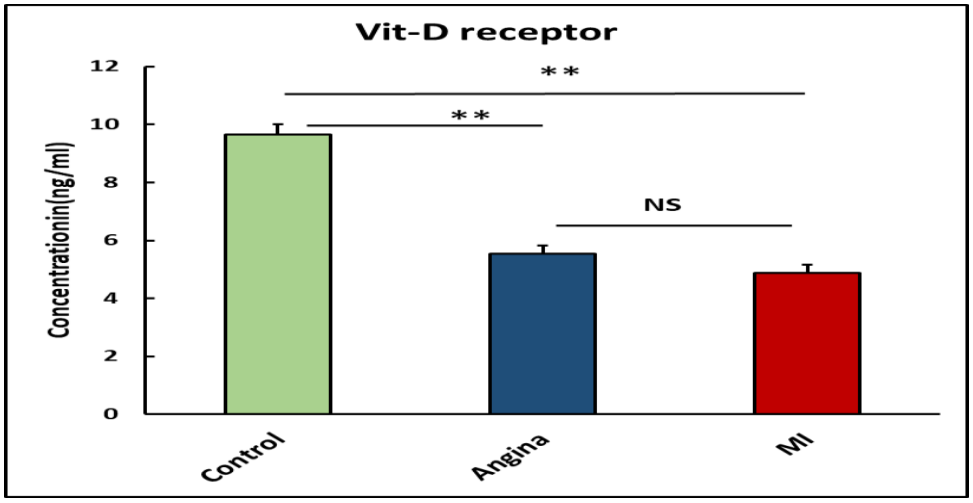

Fig.4: Vit-D receptor levels in angina, MI patients, and control. The data are presented as mean ± SEM. ** exhibited a significant change between patient's groups and control (P < 0. 01) and NS non-significant.

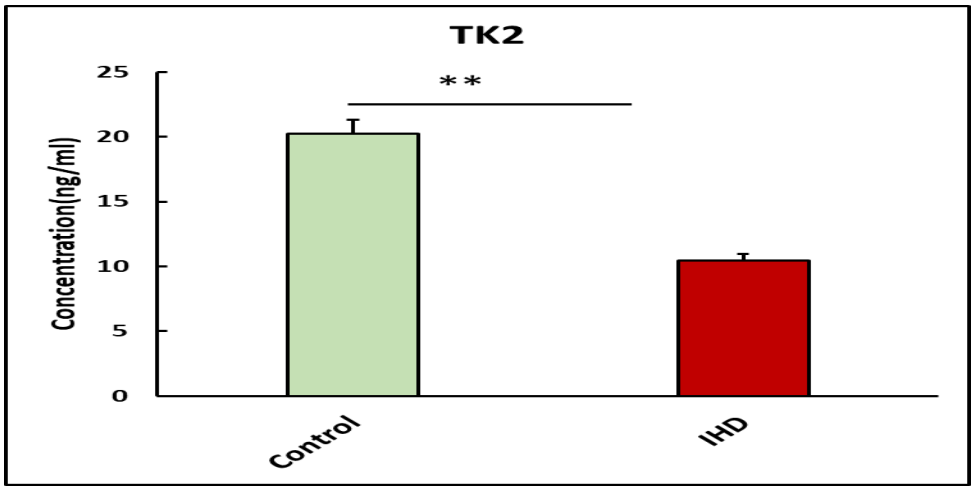

Fig.5: Serum tyrosine kinase-2 (TK-2) activity in patients with IHD and control. The data are presented as means ± SEM, (**) exhibited significant changes in comparison to the control (P < 0.01).

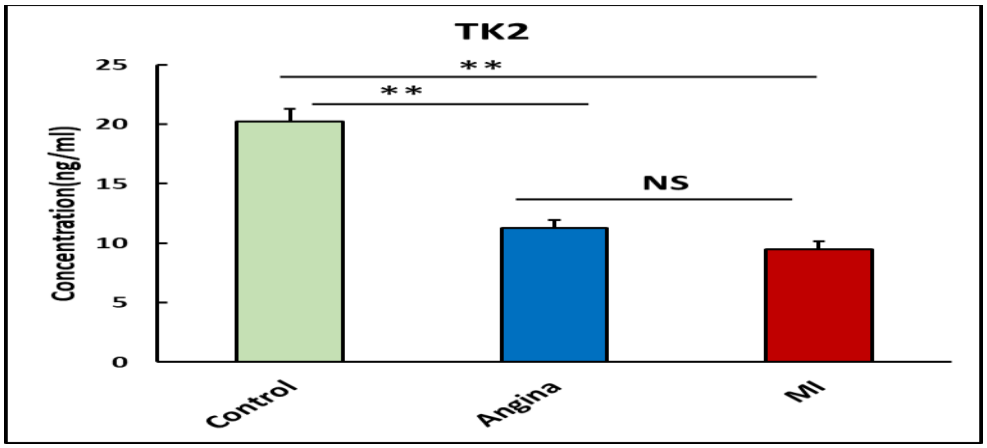

Fig.6: Serum tyrosine kinase2 (TK-2) levels in patients with angina, MI, and control. The data are presented as mean ± SEM. ** exhibited a significant change between patients and control (P < 0.01), and NS non-significant.

Discussion

Vitamin D deficiency has been linked to the incidence of IHD, however, the pathophysiological mechanisms underlying this link are still unclear. The main findings of the current study presented a decrease in the levels of vitamin D and VDR in patients with IHD compared to the control group (figure1, 2, 3, 4). The expression of VDR and 1α-hydroxylase enzyme in both the myocardium and vascular cells is the key evidence for such a link, and epidemiological studies have shown the incidence of both IHD and vitamin D insufficiency rises during the winter months and in areas farthest from the Equator[10].

Our study results are in agreement with several recent studies that revealed the association between vitamin D levels and IHD. A Follow-up study by Health Professionals monitored 18,225 men for ten years and showed a relationship between insufficient vitamin D and an increased risk of AMI, even after controlling for other risk factors[29]. In a study from the TRIUMPH database, 96% of patients hospitalized to 20 American clinics for acute MI (n = 239) had inadequate vitamin D levels[30]. furthermore, Karur et al. (2014) [31] observed that 83.5% (n = 314) of acute MI patients had low vitamin D levels. In contrast, a study by John Sluyter et al., (2017) [32] found that a monthly dosage of 100,000 IU of vitamin D had no impact on the risk of cardiovascular disease.

The present findings may be explained by a different number of possible pathophysiological mechanisms, direct and indirect, by which vitamin D levels are involved in the development of IHD. Firstly, in vascular health and the development and stability of atherosclerotic plaques, endothelial cells, SMCs, and immune cells can all play a significant role. Vitamin D also may protect endothelial cells from oxidative stress and inhibit the expression of genes involved in the induction of apoptosis[14], [33]–[35]. Interestingly, an increasing body of data demonstrates that VDR is expressed in the cardiovascular system and has an important role in the control of this system, VDR activation has been shown to maintain appropriate endothelial cell function[36], decreased the proliferation of VSMCs (vascular

smooth muscle cell)[37], and prevented macrophage-cholesterol accumulation[38]. VDR activation in the myocardium reduced ventricular hypertrophy and protected from heart failure [39][40].

There was additional evidence from animal studies, such as VDR-lacking mice (VDR −/−) that imitate vitamin D deficiency. In two investigations, VDR −/− animals had increased renin activity, high blood pressure, and myocardial hypertrophy, which atherosclerotic risk factors [41], [42]. Heart failure biomarkers, apoptosis, inflammation, and fibrosis were all significantly increased in VDR knockout (KO) mice[39]. Furthermore, new data suggest that VDR act as a cardioprotective receptor that protects against MI/R damage by minimizing oxidative stress and suppressing apoptosis and autophagy dysfunction-mediated cell death[43]. As a result, VDR might be a potential target for the therapy of ischemic heart disease[43].

Secondly, Vitamin D is important in reducing oxidative stress and supporting mitochondrial respiratory processes[44]. When vitamin D insufficiency is present, the amount of proteins and nuclear mRNA components that participate in respiration process of mitochondria decreases, these result in declines in respiration rate in mitochondria[45], [46]. In particular, because of a vitamin D deficiency results in decreased expression of complex I of the ETC (electron transport chain), the synthesis of ATP declines, this decline result in an increase in the generation of ROS [47]. A growing body of data promotes the concept that mitochondrial dysfunction in mitochondria contributes to the pathogenesis of disorders in cardiovascular system [48]. Down - stream consequences of mitochondrial dysfunction involve decreased ATP synthesis, increased ROS production, and, when dysfunction is overt, induction of apoptosis, additionally, atherosclerosis, ischemia-reperfusion damage, and heart failure have all been linked to mitochondrial dysfunction[49][50]. Mitochondrial dysfunction has significant metabolic effects and may lead to the development of atherosclerosis[51]. Cardiovascular disorders, on the other hand, may cause mitochondrial dysfunction by inhibiting oxidative substrate and oxygen delivery to cells, leading in hypoxic damage, involving ischemia/reperfusion events which lead to the buildup of calcium in mitochondria [49].

The present study showed that serum TyK2 activity was significantly decreased in IHD groups when compared with healthy control subjects (figure 4, 5). Phosphorylation of TyK2 in the mitochondria decreased with an increased mitochondrial ROS level and apoptosis[52]. Additionally, Receptors of TyK2 play an important role in regulating TyK2 activity, expression, and phosphorylation of these receptors were found to be downregulated in cardiomyocytes in response to hypoxia. This may explain the lower levels of Tk2 in patients with IHD[53].

Our study results are in agreement with several immunologically recent, observed that naïve Tyk2-null animals are vulnerable to infection, likely due to a reduction in IL-12-induced IFN-γ, which results in decreased Th1 responses[54]. A study by Ramesh Potla et al., (2006) [55] demonstrate that Tyk2-null B cells had lower baseline mitochondrial respiration and ATP generation, as well as a reduction in the activity of complex I, complex III, and complex IV of the ETC. Another study found that tyrosine kinase inhibitors result in mitochondrial injury and apoptosis in mice and cultured rat cardiomyocytes[56][26].

Additionally, besides the direct benefits on cells participating in the atherogenic cascade, vitamin D has a protective action against Insulin resistance, β-cell dysfunction, and hyperlipidemia all of them involved in atherosclerosis[16].

Conclusions

According to the main findings in the present study, Vitamin D abnormalities (low levels of Vit-D level & VDR) associated with IHD can explain several mechanisms by which involved in the pathogenesis of IHD. The levels of TK2 are decreased in IHD, this suggests to consider an important target to regulate extracellular signal in IHD with Vit-D deficiency.

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