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Assessment of Vitamin D3 and Selected Interleukins in Atherosclerosis Patients and Their Association with Various Biochemical Markers in Salah al-Din Governorate

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Abstract

This research seeks to assess vitamin D3 and several interleukins in relation to atherosclerosis and their correlation with many biochemical markers. This work sampled (180) men aged (45-75) years with atherosclerosis. The sampled is grouped into five: the initial group comprised of 40 individuals with chronic atherosclerosis; the second group included 40 individuals with acute atherosclerosis; the third group consisted of 40 individuals with atherosclerosis and diabetes; the fourth group contained 35 individuals with atherosclerosis receiving vitamin D; and the fifth group comprised 25 healthy individuals without any disease, serving as the control group. The research was conducted at Salah al-Din General Hospital in Salah al-Din Governorate, including patients admitted to the critical care unit and those in specialized clinics in Tikrit, after a meticulous diagnosis by expert physicians based on clinical manifestations. The level of ($P \leq 0.05$) of Vitamin D3 significantly rose for the group of with atherosclerosis taking Vitamin D3, while significantly dropped at the level of ($P \leq 0.01$) for the study groups, while the level of ($P \leq 0.05$), ($P \leq 0.01$) in IL-1, IL-6, IL-8, CD4 and CD8 significantly rose. In this study, *Distinct letters arranged horizontally indicate substantially different levels at ($P \leq 0.05$) and ($P \leq 0.01$).

Keywords:

Vitamin D3, atherosclerosis, interleukins, biochemical indicators.

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Introduction

Atherosclerosis is a long-term inflammatory condition that impacts the arterial walls, triggered by disturbances in lipid metabolism and an improper immune response. This pathological process includes an endothelial dysfunction, inflammatory migration macrophages in the arterial wall, producing pro-inflammatory cytokines and a series of cellular phenomena including lipidacumulation in the intimate layer. These changes collectively contribute to the auto sessions associated with local vascular inflammation, apoptosis and atherosclerotic development (Yuan et al., 2024; Yaghoobi et al., 2016).

The word atherosclerosis (as) derives from the Greek origin "athero", meaning groel or lime, and refers to lipid -rich deposits and "sclerosis", which means string, which shows rigid of the vessel walls. It is also known as "atherosclerotic sclerosis", a condition that mainly affects the arteries (Adeoye, 2020; Adebayo, 2020). Atherosclerosis is defined by two core pathological properties: lipide generation (atherose) and vascular sclerosis, which together form the base of the term "atherosclerosis" (Larivier et al., 2020; Brondum-Jacobsen et al., 2012).

Vitamin D3 is a member of the 7-dehydrocholesterol (DHS) family of compounds. The term Vit.D3 refers only to the form of cholecalciferol, which is produced by the skin's photoconversion of 7-DHS. Vit.D3 is a crude vitamin, but it can be converted to the Vit.D3 receptor by skin tissue (Goering, 2018). Vit.D3 is considered a multifunctional hormone with multiple effects, including its invisible properties, modulating elements, and anti-inflammatory properties. Vitamin D3 may influence disease progression (Shubham et al., 2023). D3 plays a partial role in regulating blood pressure, and thus partially regulating and preventing heart disease (Nejad, 2015). It supports endothelial cell health, which is essential for proper blood flow, especially preventing plaque formation, a major risk factor for heart attacks. Therefore, it represents a healthy range for reducing the risk of heart disease (National Heart Association, 2022). Vitamin D3 has subsequently been linked to numerous physiological processes, contributing to the regulation, differentiation, and recruitment of immune cells. Vitamin D3 induces the differentiation of cancer cells into Tregs, which help suppress inflammation. It also inhibits the differentiation of immune cells. Vitamin D3 deficiency in humans is associated with cardiomyopathy (Uysal et al., 1999), and several epidemiological studies have found an association between an increased risk of cardiomyopathy and stroke (CVD) (Brundom Ndom et al., 2012). D3 deficiency modulates immune responses, ensuring its integrity and promoting overall strength appropriate for pathological causes. It enhances the ability to fight infection and produces peptides that help defend against bacteria, viruses, and fungi. Vitamin D3 helps prevent the immune system from attacking tissues, thus preventing the formation of hardened plaques in blood vessels (Sanlier et al., 2022; Wang et al., 2024).

Vitamin D3 is recognized as a multicribusion hormone with rapid different biological effects. Due to its antioxidant, anti -inflammatory, immunomodulatory and Features, vitamin D3 can be significant in modifying the initiation and progress of atherosclerosis (Shubam et al., 2023; Gandhi et al., 2024).

The inflammation plays an important role in the patopofizology of atherosclerosis. Chronic vascular inflammation forms and progresses atherosclerotic plaques, mainly congenital immune cells like macrophages and monocytes (Shrivastav & Malakar, 2024; Lariviere et al., 2020). These immune cells infiltrate the intimate and promote inflammatory cascade (Anastasia et al., 2024). Although macrophages are the most important immune cells found in atherosclerotic lesions, adaptive immune cells - especially T

and B -lymphocytes - participate and participate in immunododulation associated with plaque formation (Milutinovic et al, 2020; Li et al., 2017).

Endothelial cells (ECs) reply to the buildup of low-density lipoproteins (LDL) via upregulating chemokines and cytokines including IL-eight and P-selectin, which exacerbate neighborhood irritation and facilitate leukocyte recruitment to lesion web sites (Chistiakov et al., 2018; Roffe-Vazquez et al., 2019). Within the injured arterial intima, various cell kinds contribute to the inflammatory microenvironment, together with dendritic cells, vascular smooth muscle cells, T and B lymphocytes, and exceptional macrophage subtypes (Mohmmad et al., 2021; (Milutinović et al., 2020). Among the proposed mechanisms of atherosclerosis, the inflammatory or immune hypothesis posits that low molecular weight inflammatory mediators—particularly cytokines—are important in plaque growth. Enhanced expression of these mediators accelerates plaque formation (Lysenkov et al., 2021). Since inflammation is a driving force in AS progression, the degree of inflammation—as reflected by biomarkers likr IL-1β and IL-6—can serve as an indicator of plaque instability (Shibiao et al., 2023). Numerous pro-inflammatory cytokines, including IL-6 and one of the IL-1 family, are now recognized as central contributors to the pathogenesis of cardiovascular diseases (Hannah & Naranjan, 2024; Gupta & Verma, 2025). The adaptive innate and immune responses are concerned with atherosclerotic lesion formation. Among adaptive immune cells, CD8+ T lymphocytes play a particularly critical role. Depletion of CD8+ T cells has attenuated atherosclerosis by reducing monocyte production and macrophage accumulation in early lesions. These cells exert cytotoxic effects within plaques, contributing to macrophage apoptosis and the formation of necrotic cores. The activation of CD8+ T cells is tightly regulated by immune checkpoints, and specific regulatory subsets of CD8+ T cells with immunosuppressive functions may help mitigate disease progression (Sarah & Alma, 2020; Poznyak et al., 2024; Chamakuri & Janapana, 2024; Göring, 2018).

Aim of the Study

This study investigates how levels of Vitamin D3 are related to key inflammatory and immune markers—namely IL-1, IL-6, IL-8, CD4, and CD8—in those with atherosclerosis.

Materials and Methods

Sample Collection and Preservation

The study samples 180 male blood from patients admitted to the ICU following thorough diagnosis by specialized physicians. The diagnosis was based on clinical symptoms, evaluation done in specialized clinics in extensive patient interviews and tickets. Diagnosis of all patients with atherosclerosis was at the age of 45 to 75 years. The blood serum was preserved from cold at -20 ° C in the central blood bank to maintain enzymatic activity until suitable biochemical tests were performed.

Immunological Assays

The concentrations of serum of interlucines (IL-1, IL-6, IL-8) as well as CD4 and CD8 markers were set. These concentrations were measured using sandwichenzymes immuneosorbent analysis (sandwich -elisa) technology, which uses the clinical sets produced by the Chinese company sangling. The optical density (OD) was calculated at a wavelength of 450 Nm by a spectrophotometer. OD shows a direct correlation with serum levels of IL-1, IL-6, IL-8, CD4, and CD8. The cytokine concentrations were measured by the comparison of the sample OD to a standard calibration curve.

Biochemical Assays

Estimation of Vitamin D3 Levels

The concentration of Vitamin D3 was assessed using diagnostic kits also produced by the Chinese company Sunlong, following the manufacturer's instructions based on the method described by Scharla (1998). The assay principle involved the use of an ELISA kit based on the Sandwich-ELISA technique.

Results

The result, (Figure, Table 1), revealed a significant rise at ($P \leq 0.01$) in Vitamin D3 in those with atherosclerotic patients who were taking Vitamin D3. Yet, there was a significant decrease in Vitamin D3 in those with lasting and temporary atherosclerotic and in those with atherosclerotic patients with diabetes in comparison with the healthy. In comparison to healthy controls, the concentrations of IL-1, IL-6, and IL-8 in the groups of patients with atherosclerosis, those with short-term atherosclerosis, and those with long-term atherosclerosis increased significantly ($P<0.01$), according to the findings, which are shown in Figures and Tables(4, 2, 3.) The group of atherosclerotic patients receiving vitamin D3 increased considerably at ($P< 0.01$) when compared to the healthy controls. In the groups of patients with long-term atherosclerosis, those with short-term atherosclerosis, and those with diabetes, the concentrations of CD8 and CD4 increased significantly ($P<0.01$), according to the data (Figures and Tables 5, 6). When compared to healthy controls, the group of atherosclerotic patients receiving vitamin D3 showed a significant increase at ($P<0.01$).

Discussion

There is growing evidence that vitamin D deficiency increases the risk of cardiovascular disease, with optimal vitamin D3 concentrations exerting a protective effect (Spiro, 2014). Vitamin D3 is critical in the growth of Type 2 Diabetes Mellitus (T2DM), as it enhances insulin sensitivity by reducing the risk of infrared radiation and also helps regulate insulin production from the pancreas by controlling the insulin receptor gene. Adipose tissue is a major concern regarding Vitamin D3 deficiency (Pereira-Santos et al., 2015). Adipose tissue metabolizes Vitamin D3, and every step of this process requires hormones to activate Vitamin D3 (Landrier et al., 2016). Vitamin D3 is crucial in the prevention of atherosclerosis, particularly in regulating the function of macrophage cells. It has been shown that Vitamin D3 inhibits the recruitment of monocytes or macrophage cells, cholesterol absorption in macrophages, and esterification. It also stimulates lipid droplets autophagy in macrophages, helps cholesterol flux from macrophages, controls macrophage polarization, and has a direct inhibitory result on forming lipid-loaded monocytes and their adhesion and migration (Dongxia et al., 2024; Sun et al., 2023).

Many available studies confirm the involvement of IL-1, as it is crucial in triggering the inflammatory response, not only in plaque formation but also in the stages of monocyte recruitment that eventually become foam cells in plaque formation and progression (Chen et al., 2017). Vitamin D3 has reduced the risk of death in individuals with ischemic stroke, lower levels of inflammatory cytokines, improve insulin sensitivity, and reduce cholesterol levels in monocytes. Emerging evidence suggests that vitamin D3 can suppress supplements atherosclerosis and other disorders (Victoria et al., 2024). The presence of an elevated IL -6 level in plasma is heavily associated with atherosclerotic cardiovascular disease (CVD) phenomena and atherosclerotic heart disease and healthy individuals with all -permanent

risk of all -year -axis mortality in both patients. It underlines the important role of IL-6 as intermediary in the acute diseases of heart growth (Liu and Lee, 2017). In addition, vitamin D3 has anti-inflammatory features and can reduce producing pro-inflammatory cytokines including tumor necrosis factor alpha (TNF-alpha) and IL-6, increasing anti-inflammatory cytokines. This inflammatory reaction modulation contributes to the general immune vitamin D3 impact. In addition, vitamin D3 is used in cell proliferation and discrimination, and controls genes linked to cell cycle control, affecting cell growth and development. Vitamin D3 increases discrimination of different cell types, such as heart muscle cells and vascular smooth muscle cells, both are essential to heart health (shubam et al., 2023). Diabetic patients with type 2 diabetes mellitus (T2DM) and high pot atherosclerosis have a higher level of IL-6 than atherosclerotic patients without diabetes, causing a better prophet of atherosclerosis progress in IL-6 diabetic patients (Wu ET, 2012).

Several studies have reported a collaboration during an increase in cardiovascular disorder, including IL-8 expression and atherosclerosis progression and coronary artery disease (Zhao et al., 2013). Vitamin D3 has a mechanism to reduce the type inflammatory cytokines of the type IL-6 and IL-8 (Zhang et al., 2012). 25oH D are negatively correlated with pro-inflammatory cytokines like IL-1β, TNF-6 and IL-8 (Daniel et al., 2019). Vitamin D3 signaling affects the pathophysiology of atherosclerosis by the modification of the inflammatory responses which decreases TNFα, IL-6, IL-1, and IL-8 in monocytes isolated from blood, reducing C-reactive protein synthesis during the acute atherosclerosis phases (Kassi et al., 2013; Khanolkar et al., 2023).

Plaques in patients with recent cardiovascular events are characterized by CD4+ and CD8+ T cell activation and differentiation (Fernandez et al., 2019). According to studies, patients whose angina is not stable have more CD4+ and CD8+ T cells producing γ-interferon compared to patients whose angina is stable (Liuzzo et al., 1999). Plaques in symptomatic atherosclerotic patients showed some CD4+ T cells that should be activated and differentiated, while plaques in asymptomatic patients also showed activated T cells and macrophages. These combined observations indicate a diversity in the phenotypic features and immune functions of immune cells in atherosclerotic plaques. The interaction between systemic immune responses and local events at the plaque site drives plaque instability (Bornfeldt etal., 2021). The accumulation of total CD8+ T cells contributes to the exacerbation of atherosclerotic lesions (Sarah & Alma, 2020). Studies have confirmed CD8+ T cells primarily in the core and fibrous cap of atherosclerotic plaques (Paul et al., 2016). Notably, localized CD8+ T cell response damages endothelial cell and erosions of plaque in oxidative stresses and local changes in atherosclerotic patients (Liuzzo et al., 2020; Tian et al., 2024).

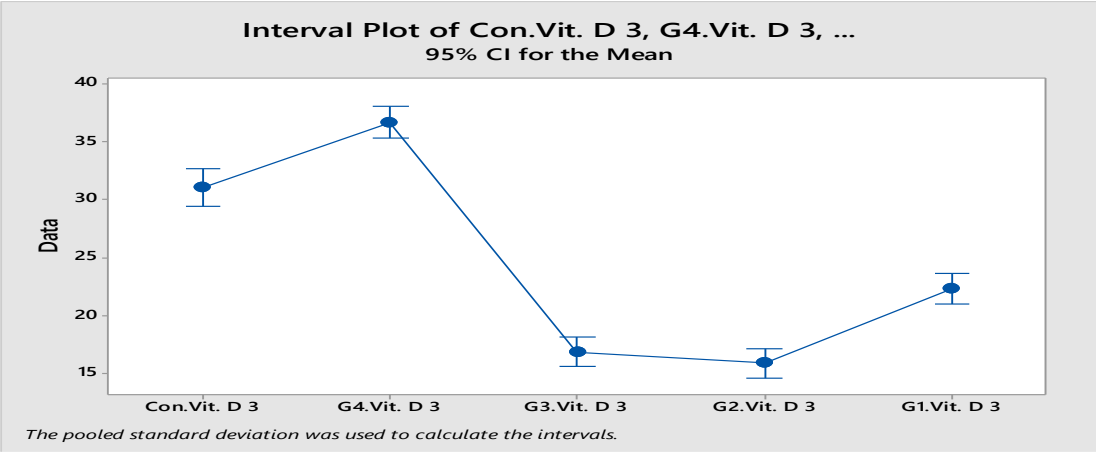

Figure 1. Vitamin D3 concentrations in the patient compared to healthy controls. the concentrations of vitamin D3 are shown for the group of long-term atherosclerotic patients (G1), short-term atherosclerotic

patients (G2), atherosclerotic patients with diabetes (G3), and atherosclerotic patients taking vitamin D3 (G4) compared to healthy controls (G5).

Table 1. Vitamin D3 concentration in patient groups compared to healthy controls. it shows the mean ± standard deviation of vitamin D3 concentrations in the group of long-term atherosclerotic patients (G1), short-term atherosclerotic patients (G2), atherosclerotic patients with diabetes (G3), and atherosclerotic patients taking vitamin D3 (G4) compared to healthy controls (G5).

Sequence	Study Group	Number	Mean ± Standard Deviation	Vitamin D3 ng/ml	P-value
1	G1	40	4.039 ± 22.320	c	0.000007
2	G2	40	2.480 ± 15.880	d	
3	G3	40	2.189 ± 16.865	d	
4	G4	35	5.891 ± 36.657	a	
5	G5	25	5.600 ± 31.000	b	
Total		180			

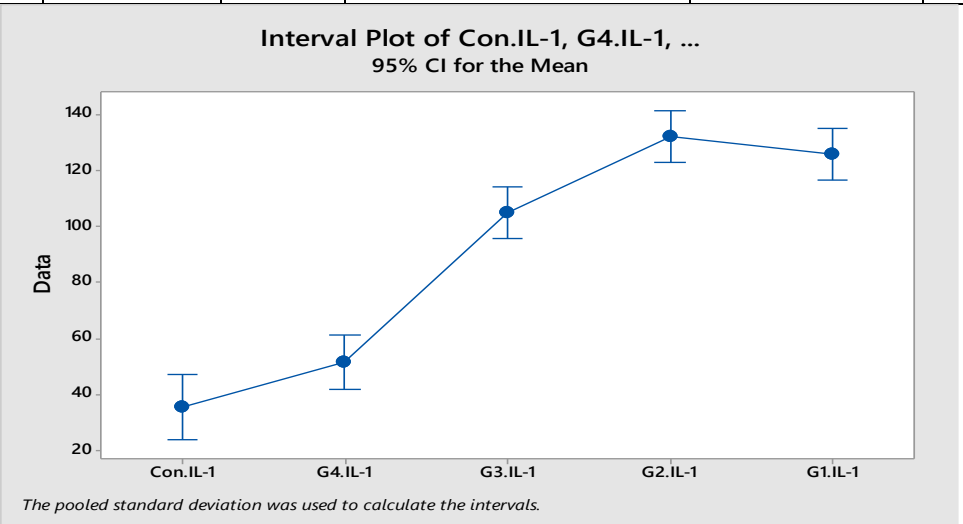

Figure 2. Concentration IL-1 in the patient compared to healthy controls. the concentrations of IL-1 are shown for the group of long-term atherosclerotic patients (G1), short-term atherosclerotic patients (G2), atherosclerotic patients with diabetes (G3), and atherosclerotic patients taking vitamin D3 (G4) compared to healthy controls (G5).

Table 2. IL-1 Concentration in patient groups compared the healthy. the table shows the mean ± standard deviation of IL-1 concentrations in the group of long-term atherosclerotic patients (G1), short-term atherosclerotic patients (G2), atherosclerotic patients with diabetes (G3), and atherosclerotic patients taking vitamin D3 (G4) compared to healthy controls (G5).

Sequence	Study Group	Number	Mean ± Standard Deviation (pg/ml) IL-1	St	P-value
1	Long-term atherosclerotic patients	40	126.11 ± 15.08	A	0.00003
2	Short-term atherosclerotic patients	40	132.07 ± 16.9	A	
3	Atherosclerotic patients with diabetes	40	104.93 ± 14.73	B	
4	Atherosclerotic patients taking Vitamin D3	35	51.43 ± 9.43	C	
5	Healthy controls	25	35.61 ± 8.73	C	
Total		180			

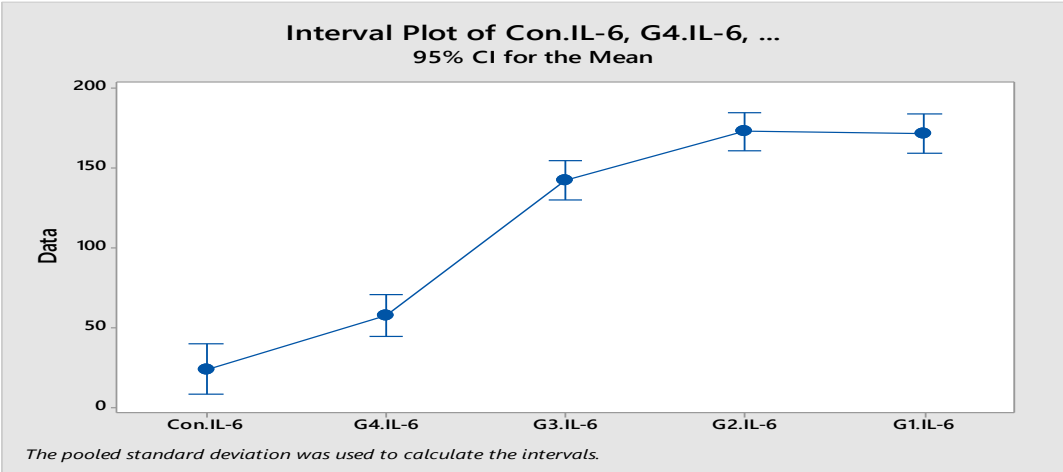

Figure 3. Levels of IL-6 in patient compared to the controls. The concentrations of IL-6 are shown for the group of long-term atherosclerotic patients (G1), short-term atherosclerotic patients (G2), atherosclerotic patients with diabetes (G3), and atherosclerotic patients taking Vitamin D3 (G4) compared to healthy controls (G5).

Table 3. IL-6 Concentration of the patient compared to the controls. The table shows the mean ± standard deviation of IL-6 concentration levels in the group of long-term atherosclerotic patients (G1), short-term atherosclerotic patients (G2), atherosclerotic patients with diabetes (G3), and atherosclerotic patients taking vitamin D3 (G4), compared to healthy controls (G5).

Sequence	Study Group	Number	Mean ± Standard Deviation (pg/ml) IL-6	St	P-value
1	Long-term atherosclerotic patients	40	171.33 ± 25.53	A	0.00006
2	Short-term atherosclerotic patients	40	172.36 ± 26.01	A	
3	Atherosclerotic patients with diabetes	40	141.64 ± 20.24	B	
4	Atherosclerotic patients taking Vitamin D3	35	57.22 ± 8.90	C	
5	Healthy controls	25	23.79 ± 4.74	D	
Total		180			

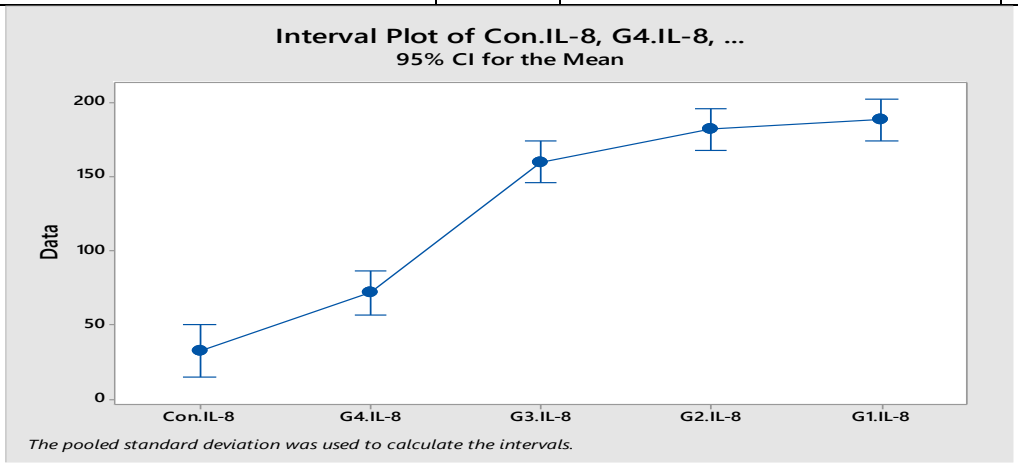

Figure 4. concentration levels of il-8 in patients relative to the controls. the figure shows the IL-8 concentration levels in the group of long-term atherosclerotic patients (G1), short-term atherosclerotic patients (G2), atherosclerotic patients with diabetes (G3), and atherosclerotic patients taking Vitamin D3 (G4), compared to healthy controls (G5).

Table 4. concentration of 8il- in patient groups compared to healthy individuals. this table shows the mean ± standard deviation of 8IL- concentrations in a group of long-term atherosclerosis patients (G1), temporary atherosclerosis patients (G2), atherosclerosis patients with diabetes (G3), and atherosclerosis patients taking vitamin D3 (G4), compared to healthy individuals (G5).

Sequence	Study Group (8IL)	Number	Mean ± Standard Deviation (Pg/ml)	P-value 0.00004
1	Long-term atherosclerotic patients	40	188.41 ± 26.25	A
2	Short-term atherosclerotic patients	40	181.89 ± 23.65	A
3	Atherosclerotic patients with diabetes	40	160.05 ± 22.01	A
4	Atherosclerotic patients taking Vitamin D3	35	71.84 ± 15.88	B
5	Healthy controls	25	32.51 ± 8.680	C
Total		180		

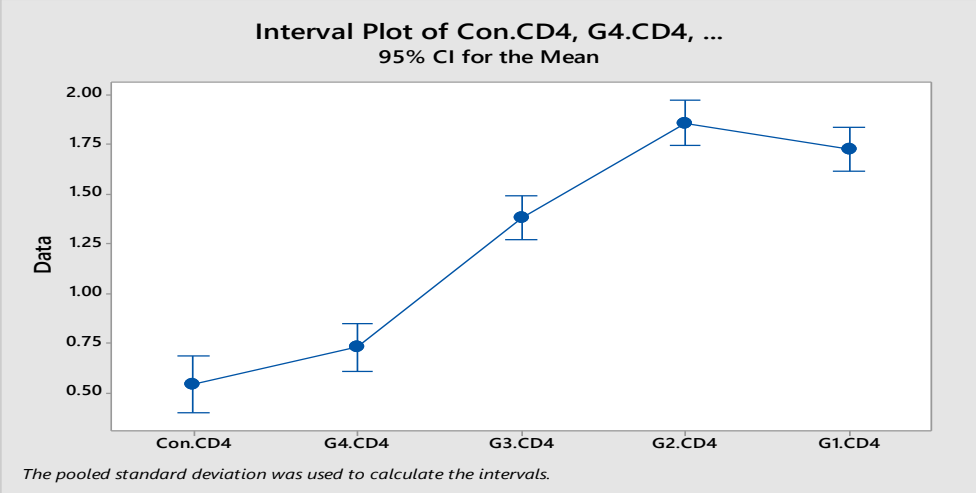

Figure 5. CD4 concentration levels in patient groups compared to healthy individuals. this figure illustrates the CD4 concentration in the long-term atherosclerosis patients (G1), temporary atherosclerosis patients (G2), atherosclerosis patients with diabetes (G3), and atherosclerosis patients taking vitamin D3 (G4), compared to healthy individuals (G5).

Table 5. CD4 Concentration in Patient Groups Compared to Healthy Individuals. This table shows the mean ± standard deviation of CD4 concentration levels in the long-term atherosclerosis patients (G1), temporary atherosclerosis patients (G2), atherosclerosis patients with diabetes (G3), and atherosclerosis patients taking vitamin D3 (G4), compared to healthy individuals (G5).

Sequence	Study Group	Number	Mean ± Standard Deviation (St ± Mean) ng/ml CD4	P-value 0.00080
1	Long-term atherosclerosis patients	40	0.3855 ± 1.7258	A
2	Short-term atherosclerosis patients	40	0.5068 ± 1.8610	A
3	Atherosclerosis patients with diabetes	40	0.3399 ± 1.3824	B
4	Atherosclerosis patients taking Vitamin D3	35	0.1469 ± 0.7279	C
5	Healthy (control)	25	0.2175 ± 0.5424	D
Total		180		

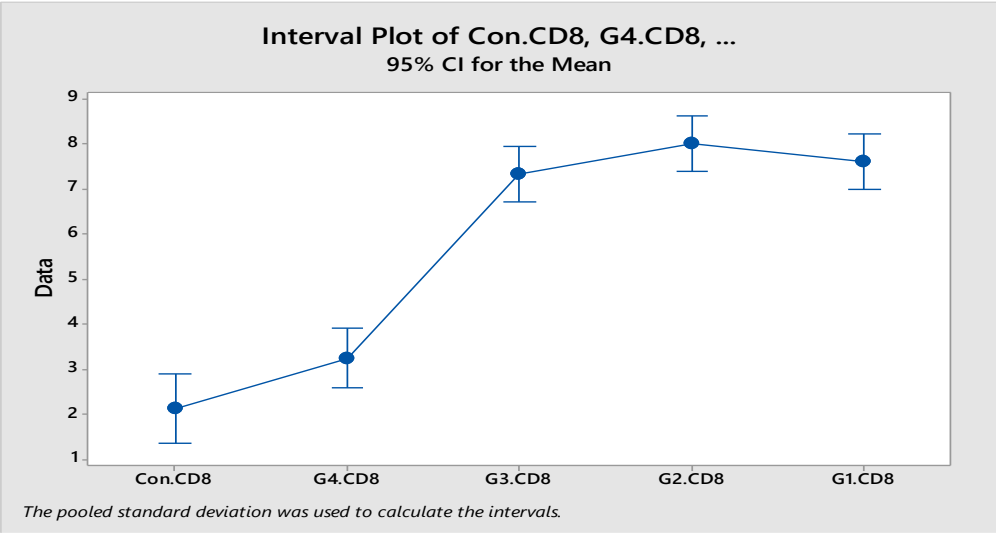

Figure 6.CD8 Concentration Levels in Patient Groups Compared to Healthy Individuals. This figure illustrates the CD8 concentration levels in a group of long-term atherosclerosis patients (G1), short-term atherosclerosis patients (G2), atherosclerosis patients with diabetes (G3), and atherosclerosis patients taking Vitamin D3 (G4), compared to healthy individuals (G5).

Table 6.CD8 Concentration in Patient Groups Compared to Healthy Individuals. This table shows the mean ± standard deviation of CD8 concentration levels in the long-term atherosclerosis patients (G1), temporary atherosclerosis patients (G2), atherosclerosis patients with diabetes (G3), and atherosclerosis patients taking Vitamin D3 (G4), compared to healthy individuals (G5).

Sequence	**Study Group**	**Number**	**Mean ± Standard Deviation (ng/ml St ± Mean) CD8**	**P-value 0.00002**
1	Long-term atherosclerosis patients	40	1.919 ± 7.598	A
2	Short-term atherosclerosis patients	40	2.187 ± 8.020	A
3	Atherosclerosis patients with diabetes	40	2.859 ± 7.341	A
4	Atherosclerosis patients taking Vitamin D3	35	0.737 ± 3.236	B
5	Healthy (control)	25	0.816 ± 2.115	C
Total		180		

Conflict of Interest

The authors declare that they have no competing interests.

Author Contributions

All authors' contributions are equal for the preparation of research in the manuscript

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