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INTERPLAY OF SCLEROSTIN AND CYTOKINES OF INTERLEUKIN-6 FAMILY IN THE PATHOPHYSIOLOGY OF CORONARY ARTERY DISEASE

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Sclerostin, a Wnt/β-catenin signaling antagonist, plays a predominant role in bone metabolism and is also expressed in cardiovascular tissues. The level of this glycoprotein is associated with aortic stiffness and vascular calcification in coronary artery disease (CAD). Our study explored the relationship between the levels of sclerostin, cytokines of interleukin-6 family and prostaglandin E2 (PGE2) in the blood serum of CAD patients. The study included two groups of patients : 80 patients aged 46-74 with a stable coronary heart disease, and 80 patients aged 46-70 as a control group. The levels of oncostatin M (OSM), leukemia inhibitory factor (LIF), cardiotrophin-1 (CT-1) and prostaglandin E2 (PGE2) were estimated with ELISA. The result have shown a highly significant decrease of sclerostin in conjunction with the increase of OSM, CT-1, LIF levels and along with the decrease of PGE2 level in the serum of patient with CAD comparing with control group. Pearson correlation analysis showed a significant relationship between sclerostin and OSM, CT-1, LIF, PGE2 concentrations. ROC curve analysis indicated that patients at risk for coronary heart disease could be identified with a specificity of 0.975 when their serum sclerostin level was greater than 88.325 pg/ml. Therefore, sclerostin could play a critical role in CAD and may be useful for monitoring disease progression.

K e y w o r d s: coronary heart disease, sclerostin, oncostatin M, human leukemia inhibitory factor, cardiotrophin-1, prostaglandin E2.

Ischemia, coronary arterial calcification, and myocardial dysfunction all interact in complicated ways to generate coronary artery disease (CAD), which is a major cause of death and disability worldwide [1, 2]. Sclerostin is a glycoprotein that plays a predominant role in bone metabolism and cardiovascular health and inhibits the Wnt signaling pathway [3]. Particularly, aortic stiffness and vascular calcification appear to be mediators of the association between levels of sclerostin and CAD [4].

Oncostatin M (OSM), a member of the IL-6 family, is one of the important regulators of cardiomyocyte (CM) remodeling in disease. OSM activates IL-6 family receptor pathways, initiating acute cardioprotective responses, including angiogenesis and restricted dedifferentiation, while sustaining fibroinflammatory processes and granuloma development, thereby integrating ischaemic, inflammatory, and granulomatous cardiac phenotypes [5].

In the pathophysiology of CVD, Human Leukemia Inhibitory Factor (LIF) has been demonstrated to be an important cytokine that specifically targets endothelial cells that play an essential role in the maintenance of vascular function [6]. LIF helps in the induction of inflammation, coagulation and angiogenesis through several signaling cascades, including JAK/STAT and MAPK.

Leukemia inhibitory factor (LIF) and the cytokine oncostatin M (OSM) are related members of the interleukin-6 (IL-6) family. OSM may have a role in immunological and inflammatory responses, in addition to bone remodeling. However, its role in CAD remains unclear due to contradictory results seen in the subsequent cardiac remodeling and repair procedures [7].

The heart is one of the tissues that synthesises CT-1, which serves a protective function for cardiomyocytes. In the short term, Cardiotrophin-1 (CT-1)

safeguards cardiac cells from injury, particularly during diminished blood flow. Prolonged elevation of CT-1 levels may lead to abnormal remodelling of the cardiac muscle due to sustained activation. These persistent consequences render the heart more vulnerable to heart failure and other cardiovascular disorders [8].

Besides its contribution to cardiovascular disease, prostaglandin E2 (PGE2) may also contribute to MI-induced myocardial remodeling. For the control of immunological reactions, it uses four receptor subtypes [9].

The potential roles of sclerostin, OSM, CT-1, LIF, and PGE2 in the control of these processes have recently been revealed [10-14]. Sclerostin, a Wnt/β-catenin signaling antagonist, is implicated in vascular calcification and atherosclerotic plaque instability [3], while OSM and LIF [11, 12], members of the interleukin-6 (IL-6) cytokine family, regulate inflammation, fibrosis, and endothelial dysfunction.

A member of the IL-6 family [13], CT-1 has two functions: in pathological hypertrophy and in cardioprotection. PGE2 is a lipid mediator derived from the action of cyclooxygenase (COX), and affects inflammatory reaction, platelet aggregation, and vascular tone [14]. Despite the increasing knowledge about their independent roles in CHD, the interactions between these molecules and the combinations that they exert either cooperative or counteractive effects on the development of the disease are largely unknown [3, 7].

There have been no studies investigating whether sclerostin is associated with its potential use as a diagnostic marker of pathogenic role in patients with established CAD. Similarly, its relationship with cytokines such as oncostatin M, cardiotrophin-1, leukemia inhibitory factor, and prostaglandin E has not been studied. To fill this gap, this study aimed to investigate their potential roles in the CAD pathophysiology by evaluating their usefulness as indicators of disease severity and progression.

Materials and Methods

Study design. The study design is a case-control which was included 160 individuals that distribute to two groups: 80 patients with stable coronary heart disease, their aged ranged between 46-74 years, with controlled blood pressure (Table 1) and all cases with moderate calcification, without a history of acute coronary syndrome and without ST segment elevation and 80 sample which are control group with 46-70 years. The patients' samples were collected from Shar hospital in Erbil city and heart center in Mosul city from March to August 2024, after diagnoses of the cases were confirmed by cardiologist who depend on the symptoms, blood tests, stress test, electrocardiogram and coronary angiogram which were carried in the above-mentioned hospitals, in addition to conducting measurement the coronary artery calcification (CAC) by using computed tomography angiography. The sample collection was limited to patients with stable coronary heart disease only and not suffering from diabetes or any other chronic disease by taking information from patients, in addition fasting blood sugar test was done for all patients to ensure that they do not have diabetes.

Serum was collected from patients and control individuals and centrifuged at 2500 rpm for 30 min [15].

Ethics review. The study adhered to all legal and ethical standards and requirements. Approval was obtained from the Ministry of Health/Nineveh Health Directorate, Mosul, Iraq (Protocol Number: 18187). Written informed consent was obtained from all participants, and the consent forms were signed on may13, 2024.

Methods. Sclerostin, oncostatin M, cardiotrophin-1, human leukemia inhibitory factor and prostaglandin E2 concentrations were measured in serum in control and patient groups using enzyme-linked immunosorbent assay (ELISA) kit (Sunlong, China). Also, high-sensitivity C-reactive protein (hs-CRP) was measured in serum using ELISA kit (Sunlong, China), creatine kinase-MB (CK-MB) and fasting blood sugar were spectrophotometrically measured using Biolabo kit (Biolabo, France) and troponin T by Cobas e 411 from Roche company (Switzerland). In addition, Body Mass Indexes (BMI) is a statistical measure calculated by an individual's weight in kilograms by the square of their height in meters [16].

Statistical analysis. By using the SPSS program (version 28), means and standard deviations were found to compare between two groups: control and patient, and *t*-test was used to find the significant change of mean value. In addition, ANOVA test was used for comparing between subgroups, also Pearson test was used to find the correlation between sclerostin and the biochemical cardiac parameters. ROC was drawn using this program for sclerostin.

Results and Disccussion

The study comprised 80 patients with stable coronary heart disease diagnosed with moderate calcification according to computed tomography angiography, with calcium scores (Agatston index) ranging from 100 to 300, and 80 healthy individuals as a control group. The average age of the control group was 53.40 years, which almost matches the average age of the patient group, 55.40 years.

The biocardial markers hs-CRP, troponin T and CK-MB [17], as well as the general anthropometric characteristics, and major cardiac tests of the control group and coronary artery patients, were measured (Table 1). It was observed a significant increase of BMI in patient comparing with control group $P < 0.01$, as well as highly significant increase of hs-CRP, troponin T and CK-MB concentration in patient compared with control group $P < 0.001$. Although troponin levels increase in the case studied, these troponin T remain below the clinical cutoff threshold of < 52 pg/ml, required to classify the cases as acute coronary syndromes [18].

The result showed a highly significant decrease in sclerostin concentration in the sera of the patient group (71.256 pg/ml) compared with the control group (98.426 pg/ml), in conjunction with a highly significant increase in OSM, CT-1 and LIF in the patient group ($P < 0.001$). On the other hand, a highly significant decrease in PGE2 concentration in the sera of the patient group compared with the control group ($P < 0.001$) was observed (Table 2).

Table 3 shows the correlation of sclerostin with OSM, CT1, LIF and PGE2 concentrations in coronary heart patients by using the Pearson coefficient. The results indicate a negative correlation between sclerostin and OSM, CT-1 and LIF concentrations, while the correlation with PGE2 is positive and significant ($P < 0.001$).

The utility of the sclerostin marker for the presence of obstractive stenoses in coronary heart disease was assessed using receiver operating characteristic (ROC) curve analysis. Depending on the value of the area under curves (AUC) (0.941, $P < 0.0001$ for sclerostin), sclerostin can be considered an excellent marker for diagnosing CHD (AUC > 0.9) (Figure). The risk of progression of coronary heart disease in patients could be identified with a sensitivity of 0.85 and a specificity of 0.975 when their serum sclerostin concentration was lower than 88.325 pg/ml, which is the cut off value (Table 4).

Our results showed a decrease in sclerostin level in the patients as illustrated in Table 2, which agrees with Milovanova et. al., who emphasized that dropping sclerostin level is a risk factor for cardiovascular complications in end-stage renal patients [19], also the result agrees with He W et al., who documented a decreased level in elderly patients with CHD [20]. In addition to sclerostin skeletal roles, it is also expressed in cardiovascular tissues, such as the heart and blood arteries [21]. The reduction of sclerostin levels may have substantial ramifications

Table 1. General anthropometric characteristics of a control group and coronary artery patients, (mean ± SD, n = 80)

Characteristics	Control group	Patient group
Sex, M/F	49/ 31	47/33
Age, years	53.40 ± 8.12	55.40 ±6.12
BMI	23.67 ± 1.69	28.33±5.52 *
Blood pressure	120/70 mmHg	130/80 mmHg
Smoking, yes/no	30/50	28/52
Drink alcohol	no	no
Family history, yes/no	30/50	34/46
FBS, mg/dl	93.66 ± 8.22	96.54 ± 9.88
hs-CRP	1.848 ± 0.618	34.161 ± 9.708**
Troponin T, pg/ml	8.640 ± 2.070	19.001 ± 4.049**
CK-MB, IU/l	9.243 ± 1.749	13.397 ± 2.509**

Note. *Significant difference at $P < 0.01$. **Significant difference at $P < 0.001$

Table 2. Comparison of serum sclerostin, OSM, CT-1, LIF and PGE2 concentrations in control and coronary heart patients' groups, (mean ± SD, n = 80)

Parameters	Control group	Patient group
Sclerostin, pg/ml	98.43 ± 11.51	71.26 ± 15.54
OSM, pg/ml	113.37 ± 26.24	183.09 ± 12.48
CT-1, pg/ml	66.88 ± 12.68	208.88 ± 25.35
LIF, pg/dl	152.23 ± 29.05	306.60 ± 26.41
PGE2, pg/dl	82.84 ± 10.98	43.30 ± 10.00

Note. Significant difference at $P < 0.001$

Table 3. Correlation between sclerostin OSM, CT-1, LIF and PGE2 concentrations in coronary heart patients by using the Pearson coefficient, (n = 160)

		Sclerostin, pg/ml	OSM, pg/ml	CT-1, pg/ml	LIF, pg/dl	PGE2, pg/dl
Sclerostin, pg/ml	Pearson correlation	1	-0.670**	-0.781**	-0.751**	0.717**
	Sig. (2-tailed)		0.001	0.001	0.001	0.001
OSM, pg/ml	Pearson correlation	-0.670**	1	0.848**	0.838**	-0.819**
	Sig. (2-tailed)	0.001		0.001	0.001	0.001
CT-1 pg/ml	Pearson correlation	-0.781**	0.848**	1	0.944**	-0.894**
	Sig. (2-tailed)	0.001	0.001		0.001	0.001
LIF, pg/dl	Pearson correlation	-0.751**	0.838**	0.944**	1	-0.863**
	Sig. (2-tailed)	0.001	0.001	0.001		0.001
PGE2, pg/dl	Pearson correlation	0.717**	-0.819**	-0.894**	-0.863**	1
	Sig. (2-tailed)	0.001	0.001	0.001	0.001	

Note. ** Correlation is significant at the 0.01 level (2-tailed)

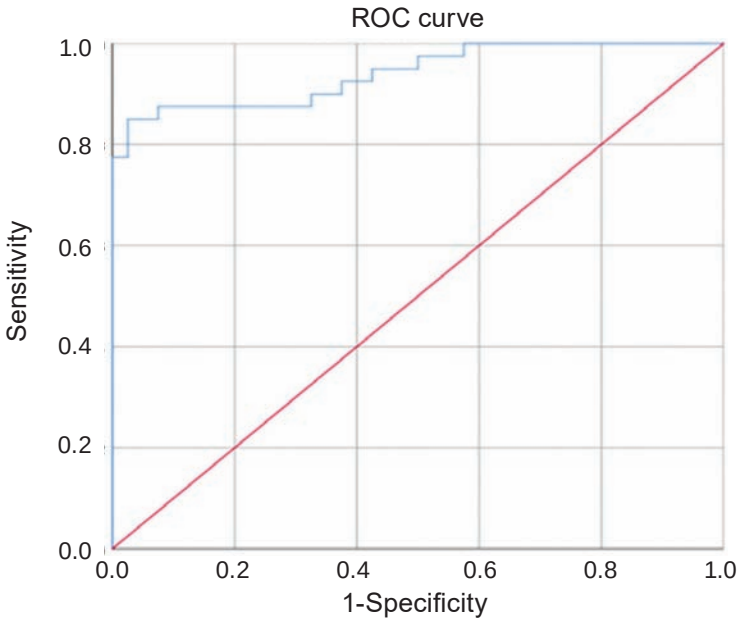

Fig. Sclerostin' receiver operating characteristics (ROC) curve for CHD prediction

Table 4. Sclerostin's receiver operating characteristic (ROC) curve for CHD prediction

Area under the curve	Std. error[a]	Asymptotic Sig.[b]	Asymptotic 95% confidence interval		Cut off value	Sensitivity	Specificity
			Lower bound	Upper bound			
0.941	0.026	0.000	0.891	0.992	88.325	0.85	0.975

Note. [a]Under the nonparametric assumption. [b]Null hypothesis: true area = 0.5

for CHD. First, protective function against vascular calcification: sclerostin has been found at arterial calcification sites, indicating that it plays a regulatory role in maintaining the health of the arteries [22]. Atherosclerosis is a major contributor to the development of CHD [23], and lower levels of sclerostin may lessen its inhibitory effect on vascular calcification processes [3]. Second, impact on post-myocardial infarction cardiac remodeling: research conducted in mouse models has shown that sclerostin can worsen post-myocardial infarction cardiac remodeling by blocking the Wnt/β-catenin signaling pathway [21]. The heart may have negative structural alterations as a result of this inhibition, which could affect how well the heart functions and raise the risk of CHD [24]. The findings indicate that reduced sclerostin levels may lead to a loss of its regulatory effect on vascular and cardiac tissues, thereby playing a role in the development of coronary heart disease [3, 21].

We found a highly significant increase in levels of OSM in the patients with CAD (Table 2), which agrees with Ikeda S. et al. [25], as OSM is recognized for its significant role in the pathophysiology of CAD, this increase can be linked to a number of different reasons, including the following [26]: inflammatory response: During chronic inflammation, activated macrophages and T-lymphocytes create oxidative stress mediators (OSM), which are a significant factor in the development of atherosclerosis [27]. The fact that it is found in atherosclerotic lesions is evidence that it has a role in the course of the disease [27]. OSM promotes the synthesis of extracellular matrix proteins such as fibronectin, which subsequently drives the proliferation and migration of vascular smooth muscle cells, hence affecting blood vessel architecture and repair [25]. This process is referred to as smooth muscle cell activation. These acts are considered to be contributors to the structural alterations that assossiated with atherosclerosis in blood arteries [5]. Cardiomyocyte remodeling: OSM is responsible for mediating the process of cardiomyocyte remodeling under pathological conditions. The activation of OSM receptors for a short period of time can be protective following an acute injury; however, activation over a longer period of time is associated with the development of heart failure [28].

In patients with ischemic heart disease and heart failure, angiogenesis has been shown to be associated with elevated OSM levels, suggesting that OSM promotes angiogenesis [5]. In response to ischemia conditions, OSM stimulates the synthesis of vascular endothelial growth factor (VEGF), which in turn makes it easier for new blood vessels to form [26]. These factors, when taken together, are responsible for the elevated levels of OSM reported in coronary heart disease [29].

A highly significant increase in levels of another cytokine from the interleukin-6 family, cardiotrophin-1, was observed in patients with CAD (Table 2), which agrees with Calabro P. et al. [30], who reported that CT-1 is associated with multiple cardiovascular disorders, including CAD. This increase can be ascribed to multiple factors [13, 30, 31].

CT-1 expression is elevated in cardiomyocytes and cardiac fibroblasts during mechanical, hypoxic, and metabolic stress situations, and this augmentation is crucial to the heart's adaptive mechanisms, facilitating cell survival and remodeling during ischemia episodes [30]. CT-1 exacerbates atherosclerosis by promoting foam cell production and facilitating the migration and proliferation of vascular smooth muscle cells. These processes contribute to the formation and advancement of atherosclerotic plaques, and most CAD develops because of atherosclerosis [32]. Inflammatory activation: CT-1 contributes to the inflammatory processes linked to CAD. It is elicited by several stresses and contributes to the inflammatory environment within the cardiovascular system [30]. These factors collectively result in the heightened levels of CT-1 reported in persons with coronary heart disease.

The results showed a highly significant increase in LIF levels in the patient group (Table 2), which may be a defensive measure to slow the progression of atherosclerosis [33]. This increase may be related to inflammation in atherosclerotic plaques, leading to the defining feature of CAD: ischemia caused by obstruction and unstable plaques that contain deposited lipids and a damaged endothelium. This lesion causes immune cells to secrete LIF, an anti-inflammatory factor [34], to induce myocardial regeneration [35]. In addition, LIF activates the JAK/ STAT signaling pathway in cardiomyocytes, which is considered a protective response to promote adaptive cardiac responses [36]. On the other hand, enhancing LIF concentration can elevate tissue factor expression by stimulating glycoprotein-130 and facilitating the conversion of prothrombin to thrombin in the presence of factors Va and Ca [37]. The occurrence of these events results in fibrin production, platelet activation, and ultimately, thrombus development [38]. Furthermore, the LIF secreted from osteoclasts inhibits the formation of osteocytes, which are the cells that secrete sclerostin [39].

A highly significant decrease of PGE2 levels in the sera of patients with CAD was found in the current study as illuserated in Table 2 which agrees with Suzuki J. et al. [40]. PGE2, although frequently linked to pro-inflammatory functions, also demonstrates anti-inflammatory benefits within the cardiovascular system, the decrease in this study may indicate a weakened anti-inflammatory response, potentially worsening vascular inflammation and the progression of atherosclerosis. The synthesis of PGE2 is facilitated by cyclooxygenase enzymes (COX-1 and COX-2) [41]. A reduction in PGE2 may indicate less COX-2 activity or expression, such modifications may disturb the equilibrium of prostanoids, affecting vascular homeostasis [14].

Emerging studies suggest potential crosstalk between these mediators [42-44]. For instance, OSM and LIF may modulate sclerostin expression in vascular smooth muscle cells, exacerbating calcification [42], while PGE2 could influence CT-1-mediated myocardial remodeling [43]. Such interactions may underlie the transition from stable atherosclerosis to acute coronary syndromes or heart failure [44].

It is clear from the current study, there are a powerful correlation between these cytokines with sclerostin in patients with CHD (Table 3), the increased levels of OSM, CT-1, and LIF could influence sclerostin levels through the following mechanisms: enhanced OSM and LIF signaling via LIF receptor may suppress sclerostin production, promoting bone formation [39, 45], elevated CT-1 levels could stimulate bone formation by modulating sclerostin expression [46]. Meanwhile, in the context of cardiovascular diseases, including CHD, and given the relationship between sclerostin and PGE2, it has been proposed that sclerostin may modulate PGE2 synthesis in vascular cells [47]. PGE_2 has been shown to downregulate sclerostin expression in osteoblastic cells through activation of the EP2 receptor and subsequent cAMP/PKA signaling pathway. This interaction suggests a feedback mechanism where PGE2 can influence sclerostin levels, potentially affecting Wnt signaling and associated cellular functions [21].

Studying these interactions is crucial for understanding the mechanisms behind myocardium injury and the progression of obstruction in the coronary artery, and it may also contribute to exploring new treatment methods.

Conclusion. As far as our current research has shown, this study is the first published to assess sclerostin levels in coronary artery disease (CAD). A significant difference in sclerostin levels was observed in CAD patients compared with healthy individuals. It suggests that low serum sclerostin levels are a risk factor for CAD, so these differences may play a role in the diagnosis and development of CAD, as decreased sclerostin levels could accelerate arterial calcification and unfavourable cardiac remodelling in myocardial ischemia via suppression of Wnt/β-catenin signaling.

Also, we found a significant correlation between sclerostin and oncostatin M (OSM), cardiotrophin-1 (CT-1), leukemia inhibitory factor (LIF) and PGE 2 in patients, paving the way for future research and proposing mechanisms that may have a significant biological impact, which that elevated cytokine levels inhibit the anti-calcification sclerostin, increasing the likelihood of coronary artery calcification associated with inflammation. Hence, further studies are needed to show these cytokines' effects on sclerostin and confirm the results. More comprehensive studies about sclerostin in CHD and its complications may help to clarify its possible role as a therapeutic target.

Conflct of interest. Authors have completed the Unified Conflicts of Interest form at http://ukr-biochemjournal.org/wp-content/uploads/2018/12/coi_disclosure.pdf and declare no conflict of interest.

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ВЗАЄМОДІЯ СКЛЕРОСТИНУ ТА ЦИТОКІНІВ РОДИНИ ІНТЕРЛЕЙКІНІВ-6 У ПАТОФІЗІОЛОГІЇ ІШЕМІЧНОЇ ХВОРОБИ СЕРЦЯ

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Склеростин, антагоніст сигнального шляху Wnt/β-катеніну, відіграє переважну роль у метаболізмі кісток, а також експресується в серцево-судинних тканинах. Рівень цього глікопротеїну пов'язаний з жорсткістю аорти та кальцифікацією судин при ішемічній хворобі серця (ІХС). У нашому дослідженні вивчали зв'язок між рівнями склеростину, цитокінів родини інтерлейкінів-6 та простагландину Е2 (ПГЕ2) у сироватці крові пацієнтів з ІХС. Дослідження включало дві групи пацієнтів: 80 пацієнтів віком 46-74 років зі стабільною ішемічною хворобою серця та 80 пацієнтів віком 46-70 років, які становили контрольну групу. Рівні онкостатину М (ОСМ), фактора інгібування лейкемії (ЛІФ), кардіотрофіну-1 (КТ-1) та простагландину Е2 (ПГЕ2) визначали методом ELISA. Результати показали достовірне зниження рівня склеростину на тлі підвищення рівнів ООСМ, КТ-1, ЛІФ, а також зниження рівня ПГЕ2 у сироватці крові пацієнтів з ІХС порівняно з контрольною групою. Кореляційний аналіз Пірсона показав значний зв'язок між склеростином та концентраціями ООСМ, КТ-1, ЛІФ, ПГЕ2. Аналіз ROC-кривої показав, що пацієнтів з ризиком розвитку ішемічної хвороби серця можна було ідентифікувати зі специфічністю 0,975, якщо рівень склеростину в сироватці крові перевищував 88,325 пг/мл. Таким чином, склеростин може відігравати ажливу роль у розвитку ІХС та бути корисним для моніторингу прогресування захворювання.

Ключові слова: ішемічна хвороба серця, склеростин, онкостатин М, фактор інгібування лейкемії людини, кардіотрофін-1, простагландин Е2.

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