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Correlation of CD40 and DPP-4 Concentration With Corrected TIMI Frame Count in Patients With Coronary Slow Flow

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Abstract

Introduction: Microvascular and endothelial disorders play a significant role in the pathophysiology of coronary slow flow phenomenon (CSFP). However, according to previous studies, the etiology of CSFP is not completely understood. As CD40 and dipeptidyl peptidase-4 (DPP-4) are reported to play an important role in atherosclerosis process as well as microvascular and the endothelial dysfunction, this study evaluated the role of these two biomarkers in the pathophysiology of CSFP.

Methods: One-hundred twenty-nine volunteers who were candidates for angiography and fulfilled the inclusion criteria were selected, including 29 patients with coronary artery diseases (CADs) which had less than 50% stenosis (CAD+, <50%) and without CSF, 22 CAD+patients which had 50-90% stenosis (CAD+, 50%-90%) without CSF, 16 CAD+patients with CSF, 22 patients with CSF without stenosis in their arteries, and 40 healthy individuals as controls. The serum levels of CD40 and DPP-4 were measured by an enzyme-linked immunosorbent assay kit.

Results: There was no significant correlation between the serum concentration of CD40 and the thrombosis in myocardial infarction (TIMI) frame count ($P=0.571$). However, the serum concentration of CD40 in CAD+patients with CSF was significantly higher than the values in patients without CSF ($P=0.022$). Moreover, the concentration of DPP-4 in different coronary vessels did not exhibit any significant relation with TIMI score ($P=0.763$).

Conclusion: In the present study, no significant correlation was found between the serum concentrations of CD40 and DPP-4 and the mean corrected TIMI frame count (CTFC). Accordingly, further studies with larger population sizes are needed to investigate the correlation between CD40 and DPP-4 serum levels and CSFP.

Keywords: DPP-4, CD40, TIMI frame, Coronary slow flow

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Introduction

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of morbidity and mortality all over the world.[1] The coronary slow flow phenomenon (CSFP) is an angiographic finding that is characterized by the slow movement of contrast media forward to the end of branches of coronary arteries while there is not any obstructive coronary artery disease (CAD).[2,3] The exact mechanism of CSFP is still unknown. However, possible proposed mechanisms may include microvascular disorders, endothelial dysfunction, subclinical atherosclerosis, inflammation, and anatomical factors.[3] It has been reported that reduced endothelium-dependent flow-mediated dilatation of the brachial artery was detected in patients with CSFP, suggesting that endothelial dysfunction is implicated in the etiology of CSFP.[3]

As the small vessels with a diameter of less than 400 μm (resistive vessels) can mainly regulate the blood flow to the heart in the absence of significant obstructive epicardial stenosis, the pathogenesis of CSFP can include the dysfunction of resistive vessels. Moreover, endothelium plays an important role in regulating

vascular tone, platelet activity, leukocyte adherence, smooth muscle growth, and the development of atherosclerosis.[4,5]

CD40 and its ligand belong to the tumor necrosis factor family. They are expressed on different kinds of cells like endothelial, smooth muscle cells, macrophages, T lymphocytes, B lymphocytes, and platelets.[6] Some studies suggested that CD40 has an important effect on the cardiovascular system and the interaction of CD40 and CD40L could play a significant role in atherogenesis via several pathways including excessive overexpression of transcription factors in endothelial cells, increased expression of cytokines, chemokines, growth factors, the release of pro-thrombin intermediates (tissue factors), excessive expression of the enzymes producing active oxygen specie, activating of smooth muscle cells and fibroblasts, and matrices metalloproteinase expression.[6,7] Further, previous studies have shown that the interaction of CD40/CD40L can regulate some steps in the progression of atherosclerosis, and it has also been proven that there is a gradual increase in sCD40L concentration in advanced atherosclerosis.[8]

Dipeptidyl peptidase-4 (DPP-4) is a type 2 membrane glycol-protein, also known as CD26, which could be found in different organs and glands such as thymus, lymph nodes, salivary and milky proximal tubules, and kidney glomeruli.[9,10] Hyperglycemia, insulin resistance, dyslipidemia (DLM), oxidative stress, and inflammation are well-known risk factors for subclinical atherosclerosis. DPP-4 is a newly identified adipokine that is related to the abovementioned risk factors, and its inhibitors improve the endothelial cell function and potentially have a cardiovascular protective effect.[11] To be more precise, vasculoprotective endothelial progenitor cells are regulated by the stromal cell-derived factor 1, which is a substrate of DPP-4. DPP-4 inhibitors increase endothelial progenitor cells with concomitant upregulation of stromal cell-derived factor 1, suggesting that this class of drug might play a significant role in endothelial cell biology.[11]

The latest studies demonstrated that in addition to the antidiabetic effect of DPP-4 inhibitors, they could deactivate some of the inflammatory factors such as chemokines, cytokines, and neuropeptides which are effective in the coronary arteries' function.[11] Moreover, human studies indicated that the inhibitors of DPP-4 could improve cardiac function by protecting it against ischemic injuries and recover endothelial function by improving the ability of endothelial pioneer cells.[12,13] Last advances regarding the non-catalyst effects of DPP-4 suggested that DPP-4 plays an essential role in cardiometabolic disease.[9]

The classification of CSF based on thrombosis in myocardial infarction (TIMI) score provides a quantitative assessment of the coronary blood flow, which represents the full passage rate of the contrast media injected through the coronary arteries. Currently, the use of corrected TIMI frame count as a quantitative indicator of blood flow in coronary angiography is the only CSFP diagnostic tool. However, due to its aggressiveness, this method is not clinically used in follow-up and long-term evaluations.[3]

Since no study has been conducted on the role of CD40 and DPP-4 in CSFP, this study strived to evaluate the correlation between CD40 and DPP-4 serum levels and TIMI frame count in patients with a CSF.

Materials and Methods

Study Design and Population

This research was a cross-sectional study performed between July 2019 and October 2021 at Quaem hospital, a tertiary teaching hospital in Mashhad, Iran. Patients with CAD who were candidates for angiography were included in the study, and patients with coronary arteries aneurysm, hyper-homocysteinemia, myocarditis, pericarditis, cardiomyopathy, and taking a DPP-4 inhibitor such as Sitagliptin and those who were on hemodialysis were excluded.

According to the result of the angiography, the patients were divided into five groups (Table 1), including 29 patients with CAD which had less than 50% stenosis (CAD +, < 50%) and without CSF, 22 CAD + patients who had 50-90% stenosis (CAD +, 50-90%) without CSF, 16 CAD + patients with CSF, 22 patients with CSF without stenosis in their arteries, and 40 healthy individuals as controls.

The existence of coronary obstructive artery disease, the number of involved arteries, and CSF arteries were evaluated as the visual findings during the angiography by a cardiologist. Different definitions for the slow blood flow of the coronary arteries are available, and this study used the corrected TIMI frame counts more than two standard deviations from the normal range in the absence

Table 1. Distribution of Patients in the Studied Groups

		Number	%
CAD-, SF-	Patients with no CAD and no epicardial arteries slow flow	40	31
CAD -, SF +	Patients with no CAD and with the slow flow of epicardial arteries	22	17.05
CAD + < 50%, SF -	Patients with CAD (< 50%) having no slow flow of epicardial arteries	29	22.4
CAD + 50-90%, SF-	Patients with CAD) between 50 to 90%) having no slow flow of epicardial arteries	22	17.05
CAD +, SF +	Patients with CAD having the slow flow of epicardial arteries	16	12.4

Note. CAD: Coronary artery disease; SF: Slow flow.

of an obstruction in the coronary arteries.[3]

Patient's demographic data, including gender, age, body mass index (BMI), past medical history (e.g., hypertension, diabetes mellitus [DM], and DLM), smoking, and family history were collected using patients' records in a pre-designed checklist.

CD40, Dipeptidyl Peptidase-4, and Coronary Blood Flow Rate Measurement

Twenty milliliters of patients' blood was taken in the morning of angiography from the brachial vein of all fasting patients and handed to the Qaem hospital's emergency lab. The samples were centrifuged at 3000 rpm for 10 minutes. Then, the plasma fraction was isolated and stored at -80°C until the time for analysis.

Baseline serum CD40 and DPP-4 concentrations were measured by enzyme-linked immunosorbent assay (ELISA) method using commercially available ELISA kits (ab99991-CD40L, UK/ ab119513-DPP-4, UK), and they were read by ELISA reader at 450 nm wavelength.

Sample Size and Statistical Analysis

Since to the best of our knowledge, this is the first study on the correlation between CD40 and DPP-4 serum concentrations and CSFP, we considered it as a pilot study. Thus, we included all eligible patients referred during the study period. Statistical analysis was carried out by SPSS 22. The results were exhibited as mean ± standard deviation or median (interquartile range) for normally and non-normally distributed continuous variables, respectively, and as numbers (percentages) for nominal variables. Further, the Kolmogorov–Smirnov test was used to assess the normality of the variable distributions.

An independent sample t-test and the Mann–Whitney U-test were used to compare normally and non-normally distributed variables between the two groups, respectively. Moreover, for the comparison of more than two groups in normally and non-normally distributed variables, one-way ANOVA and Kruskal–Wallis tests were used, respectively.

The Pearson correlation test (in the case of normal distribution) and Spearma's correlation test (in the case of non-normal distribution) were employed to examine the intensity and correlation between the two quantitative variables. All tests were conducted at a significant level of 0.05.

Results

Patients' Characteristics

Among 129 patients who underwent angiography, 39.53 % were males, and the mean age of the studied population was 54.58 ± 10.3 years old. Table 2 summarizes several patients' demographic information. Most of the patients with coronary artery involvement (50 to 90% of obstruction) had one artery involvement (36.3%) followed by two vessels (31.8%).

Comparison of Mean Serum Concentration of CD40 and DPP-4 in Different Studied Groups

The serum concentration of CD40 was significantly different between various studied groups. However, the serum concentration of DPP-4 showed no significant

Table 2. Patients' Characteristics

Demographic Data	
Gender	
Male, No. (%)	51 (39.53)
Female, No. (%)	78 (60.47)
Age (year) (mean ± SD)	54.58 ± 10.3
BMI (kg/m²) (mean ± SD)	28.1 ± 4.74
FBS (mg/dL) (mean ± SD)	116.38 ± 50.75
Hypertension, No. (%)	81(62.79)
DLM, No. (%)	75 (58.14)
Diabetes, No. (%)	28 (21.71)

Note. SD: Standard deviation; BMI: body mass index; FBS: Fasting blood sugar; DLM: Dyslipidemia.

Table 3. CD40 and DPP-4 Serum Concentration in Different Groups

Parameter	DPP-4 (ng/mL)		CD40 (pg/mL)	
	Concentration	*P* Value[a]	Concentration	*P* Value[a]
CAD (-), SF (-)	633.41 ± 549.68	0.889	4278 ± 3802.05	0.03
CAD (-), SF (+)	673.82 ± 515.61		4551.7 ± 3412.35	
CAD (+, < 50%), SF (–)	633.07 ± 270.05		3462.5 ± 3170.78	
CAD (+, 50-90%), SF (-)	617.23 ± 294.16		2452.5 ± 2741.34	
CAD (+, 50-90%), SF (+)	753.11 ± 487.59		5835.5 ± 2311.31	

Note. DPP-4: Dipeptidyl peptidase-4; CAD: Coronary artery disease; SF: Slow flow.
[a] One-way ANOVA test.

Table 4. The Comparison of CD40 Serum Level in Paired Groups

Studied Groups		*P* Value[a]
CAD (-), CSF (-)	CAD (-), CSF (+)	0.998
CAD (-), CSF (-)	CAD (+, < 50%), CSF (-)	0.846
CAD (-), CSF (-)	CAD (+, 50-90%), CSF (-)	0.257
CAD (-), CSF (-)	CAD (+), CSF (+)	0.498
CAD (-), CSF (+)	CAD (+, < 50%), CSF (-)	0.758
CAD (-), CSF (+)	CAD (+, 50-90%), CSF (-)	0.230
CAD (-), CSF (+)	CAD (+), CSF (+)	0.750
CAD (+, < 50%), CSF (-)	CAD (+, 50-90%), CSF (-)	0.827
CAD (+, < 50%), CSF (-)	CAD (+), CSF (+)	0.145
CAD (+, 50-90%), CSF (-)	CAD (+), CSF (+)	0.022*

Note. CAD: Coronary artery disease; CSF: Coronary slow flow.
[a] Tukey post hoc test.

difference between the groups (Table 3).

The post hoc Tukey test was used to determine that the difference between the pairs of groups caused a significant difference in CD40 average serum level. As illustrated by the *P* value in Table 4, the serum level of CD40 in CAD (+, 50-90%) patients without CSF was significantly lower than in CAD (+, 50-90%) patients with CSF ($P = 0.022$), while the other groups did not exhibit any considerable difference (*P* value > 0.05).

Relation Between CD40 and DPP-4 and Coronary Flow Based on TIMI Frame Count in Different Coronary Arteries

The correlation between CD40 and DPP-4 serum levels and TIMI frame count were measured and compared in different coronary arteries in CAD patients with or without CSF (Table 5).

In CAD patients with a CSF, TIMI was measured in different coronary arteries (e.g., left circumflex, left anterior descending, and right coronary artery. Since some patients had two or three vessels with slow flow, the average TIMI was also calculated for each individual.

Considering the Pearson coefficient (r = 0.095) and *P*-value (*P* value = 0.571), there was no significant correlation between the serum concentration of CD40 and TIMI frame count. Moreover, the concentration of DPP-4 in different coronary vessels did not show any significant correlation with the TIMI score (r = 0.051, *P* value = 0.763).

The Comparison of CD40 and DPP-4 Serum Levels in Patients With Cardiovascular Risk Factors

The serum concentration of CD40 and DPP-4 in CAD patients with or without cardiovascular risk factors such as old age, DM, DLM, tobacco use, hypertension, and high BMI were evaluated in this study. As the variables were distributed normally, an independent t-test and ANOVA variance analysis were used. The results are presented in Table 6.

The comparison of CD40 and DPP-4 levels in CAD patients with or without cardiovascular risk factors displayed no significant difference in CD40 and DPP-4 serum levels in CAD patients with or without DM, high blood pressure, high BMI, and tobacco use, while the concentration of DPP-4 in patients with and without DLM and age risk factor was almost significantly different.

Table 5. The Correlation Between CD40 and DPP-4 Serum Level and TIMI Scale

Mean CTFC in Different Vessels	DPP-4		CD40	
	Correlation Coefficient*	*P* Value	Correlation Coefficient*	*P* Value
LAD	-0.06	0.759	0.1	0.583
LCX	0.27	0.293	0.06	0.813
RCA	0.21	0.395	-0.19	0.447
Average	0.05	0.763	0.1	0.571

Note. DPP-4: Dipeptidyl peptidase-4; TIMI: Thrombosis in myocardial infarction; LAD: Left anterior descending; LCX: Left circumflex; RCA: Right coronary artery; CTFC: Corrected TIMI frame count.
* Pearson correlation.

Discussion

Although the role of CD40 and DPP-4 in the development of microvascular, endothelial dysfunction, and atherosclerosis has been approved, there is not enough data about their probable role in CSFP occurrence.[3] In atherosclerosis, the interaction of CD40/CD40L, their entrance to the cell, and stimulating the expression of some inflammatory factors accelerate the binding of monocytes to vascular endothelium. Endothelial damage is also exacerbated by active oxygen species, and plaque rupture occurs by the expression of extra matrix metalloproteinase (MMPs).[8] Furthermore, the previous studies evidenced that the DPP-4 had an efficient role in cardiovascular diseases by deactivating incretin hormones[11] and increasing insulin secretion after digestion.[14] In addition, DPP-4 is known as an adipokine that is related to high blood glucose, insulin resistance, hyperlipidemia, oxidative stress, and inflammation.[15] the findings of the present study showed that DPP-4 and CD40 concentration were not significantly related to CSFP based on TIMI frame count. However, the results indicated that the level of DPP-4 increased almost significantly in patients with age risk factors (men > 45 years, women > 55 years) and DLM compared to the control groups (without DLM in males under 45 years old and females under 55 years old). Further, the concentration of CD40 significantly increased in patients with CAD + with CSF compared to patients with CAD + group without CSF.

Demir et al reported that TIMI frame count in left anterior descending, left circumflex, and right coronary artery in patients with CSF was significantly higher than that in patients with normal coronary flow patterns.[16] Moreover, the sCD40L level in patients with CSF was considerably higher than that in patients without CSF, suggesting that sCD40L could play an important role in the pathogenesis of CSF. Despite the similarity of the average age and the number of patients in the present study and the previous one, the TIMI frame count was not related to CD40 concentration in the present study. Moreover, the present study indicated that the serum concentration of CD40 in CAD + patients with CSF was significantly higher than that in CAD + patients without CSF which is consistent with data reported in previous studies.[16]

Numerous studies reported that sCD40 concentration increased in CAD + patients with CSF,[16,17] and they supposed that CD40 could be introduced as a predictive biomarker for CAD diagnosis.[7] Some other studies

Table 6. The Comparison of CD40 and DPP-4 Level With CAD's Risk Factors

Risk factor		DPP-4 (ng/mL)		CD40 (pg/mL)	
		Concentration	*P* Value	Concentration	*P* Value
HTN	HTN +	696.52 ± 519.63	0.104	4176 ± 3144.52	0.499[a]
	HTN -	585.61 ± 250.55		3733 ± 3729.52	
DM	Diabetic	632.87 ± 461.13	0.750	4331.1 ± 3542.80	0.576[a]
	Non-diabetic	662.38 ± 437.95		3926.3 ± 3320.09	
DLM	DLM +	710.99 ± 521.95	0.063	4123.8 ± 3207.49	0.665[a]
	DLM -	577.56 ± 280.93		3859.3 ± 3595.36	
Smoking	Smoker	640.22 ± 365.79	0.821	3964.9 ± 3210.48	0.831[a]
	Non-smoker	658.67 ± 478.46		4099.2 ± 3475.17	
BMI	< 25	609.66 ± 342.17	0.563	4424.9 ± 3195.19	0.656[b]
	25-26.9	620.45 ± 299.78		3253.8 ± 3542.55	
	27-29.9	768.35 ± 642.37		3652.2 ± 3586.54	
	≥ 30	628.09 ± 443.31		4071.1 ± 3329.15	
Age	Risk factor + (> 55 for females, > 45 for males)	708.49 ± 484.95	0.073	4038.7 ± 3390.9	0.957[a]
	Risk factor – (< 55 for females, < 45 for males)	567 ± 353.83		4071.5 ± 3377.96	

Note. DPP-4: Dipeptidyl peptidase-4; CAD: Coronary artery disease; HTN: Hypertension; DM: Diabetes mellitus; DLM: dyslipidemia; BMI: body mass index.
[a] Independent samples *t* test; [b] One-way ANOVA test.

reported data that show the relation between sCD40L and acute coronary syndrome (ACS). Olenchock et al designed a study that included 2403 patients with ACS and measured the sCD40L level for 10 months. They found that there is not any correlation between ACS and sCD40L concentration. Additionally, the rise of the sCD40L level did not increase the risk of MI or death.[18] Sanghvi et al found that cardiovascular risk factors such as high blood pressure, DLM, DM, and tobacco use could be considered risk factors in the pathophysiology of CSFP.[19]

Overall, there has never been a study to assess the association between DPP-4 and CSF disease or patients and CAD; however, some studies approved the relationship between DPP-4 and cardiovascular disease. A randomized, double-blind, placebo-controlled trial on 40 volunteers demonstrated that 12-week treatment with linagliptin, as a DPP-4 inhibitor, tended to improve the endothelial and neurovascular microvascular function in patients with type 2 DM.[11] Further, the inhibition of DPP-4 affected a group of cytokines, chemokines, and neuropeptides involved in inflammation and immune function that can have a protective effect on the cardiovascular system.[11]

Moreover, Advani et al suggested that because of the ability of DPP-4 inhibitors in reducing weight, they may be associated with the prevention of cardiovascular problems.[20] In the present study, no significant relationship was observed between DPP-4 concentration and CSF. Although in most of the previous animal studies, an association was found between this biomarker and cardiac disease, there are few human studies on patients with severe risk factors for heart disease.[21] Conversely, there are some contradictory results suggesting that the use of DPP-4 inhibitors in 36 620 diabetic patients for 24 weeks increased the heart failure risk by about 21% in comparison to the placebo group.[22]

Several recent studies concluded that in diabetic patients, DPP-4 inhibitors can help eliminate inflammation and endothelial dysfunction.[23] In addition, a study conducted in 2018 detected the relationship among DPP-4 activity, inflammatory biomarkers, and microvascular response in overweight and non-diabetic individuals. Forty subjects with a BMI of greater than 25 kg/m^2 and nondiabetic subjects were investigated, and DPP-4 activity was found to be related to the activity of primary endothelial pro-inflammatory markers and microvascular function in overweight and non-diabetic patients.[23] The previous study only sought to examine non-diabetic and high-weight patients; therefore, the difference between the results of that study and the current one can be reasonable.

This study confronted with various limitations, including a relatively small sample size. Moreover, in the current study, coronary obstructive disease and the slow flow of the epicardial microvessels were measured visually, dependent on the physician. However, all angiographies were done by only one cardiologist to reduce errors and bias risk. Considering the above limitations, conducting a study with a larger sample size is recommended. In conclusion, the present study suggested that the serum level of CD40 and DPP-4 was not related to the CSF based on the TIMI frame count. Although the concentration of DPP-4 did not show any significant relationship with CSF, the results indicated that the serum concentration of CD40 in CAD + patients with 50-90% stenosis with CSF was higher than that in CAD + patients without CSF, so

its serum level might be related to the CSF. Furthermore, the results revealed that the average serum concentration of CD40 was not significantly different in patients with cardiac risk factors, including hypertension, DLM, tobacco use, high BMI, and old age, but the concentration of DPP-4 in patients with DLM and age risk factor was almost significant in both groups.

Conclusion

In the present study, no significant correlation was observed between the serum concentration of CD40 and DPP-4 and CSF based on TIMI frame count. According to the results, it seems that more studies are needed to illuminate the relation between CD40 and DPP-4 based on TIMI frame count.

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Authors' Contribution

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Competing Interests

The authors declare that they have no competing interests.

Data Availability Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

The Ethics Committee of Mashhad University of Medical Sciences approved the study protocol (Code: IR.MUMS.REC.1395.314), and all of the participants signed a written informed consent form before the start of the study.

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