Received: 05 August 2023 / Accepted: 17 October 2023 / Published online: 31 October 2023
DOI 10.34689/SH.2023.25.5.004
UDC 617-089

STUDY OF THE RELATIONSHIP BETWEEN TRIMETHYLAMINE N-OXIDE (TMAO) LEVELS AND CLINICAL PARAMETERS IN PATIENTS WITH ST-SEGMENT ELEVATION ACUTE CORONARY SYNDROME

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Summary

Relevance: There are classic risk factors for atherosclerosis - gender, ethnicity, family history, diabetes mellitus, chronic kidney disease, obesity, hypertension, smoking. Research continues into traditional theories of atherosclerosis such as dyslipidemia, infection, and inflammation. Based on these theories, appropriate studies of blood lipids, C-reactive protein, and homocysteine are carried out in clinical practice. However, new factors are currently being identified in the pathogenesis of atherosclerosis - air pollution with microparticles, disruption of clonal hematopoiesis and changes in the proatherogenic metabolic biomarker trimethylamine N-oxide. Large studies have shown that TMAO may be a predictor of cardiovascular disease risk. TMAO is synthesized by intestinal microflora and studies are being conducted on these metabolic pathways and the factors influencing TMAO levels. In this regard, it is necessary to study the correlating relationship between the level of TMAO and a number of clinical indicators.

The aim: Based on clinical studies of patients with acute coronary syndrome with ST segment elevation, analyze possible predictors of changes in TMAO levels.

Materials and methods: The study was conducted as part of a larger body of research on the effects of dietary remodeling of the gut microbiota on oxidative status, trimethylamine oxide (TMAO) levels, and recurrent cardiovascular events after STEMI. The work hypothesized that there is a relationship between the resulting TMAO variable and a number of clinical indicators.

Results: To the greatest extent, changes in TMAO concentrations depend on the composition of the intestinal microbiome. Plasma TMAO levels have previously been shown to be determined by several factors, including consumption of its metabolic precursors, medications, and hepatic flavinmonooxygenase FMO activity.

Conclusion: The work analyzed the dependence of TMAO levels on 43 clinical indicators. It was revealed that there was a statistically significant correlation between the level of the coronary SYNTAX Score I scale, the presence of peptic ulcer disease and social status.

Key words: *trimethylamine N-oxide (TMAO), ST-segment elevation myocardial infarction (STEMI), cardiovascular disease (CVD).*

Резюме

ИССЛЕДОВАНИЕ ЗАВИСИМОСТИ УРОВНЯ ТРИМЕТИЛАМИНА N-ОКСИДА (TMAO) ОТ КЛИНИЧЕСКИХ ПОКАЗАТЕЛЕЙ У ПАЦИЕНТОВ С ОСТРЫМ КОРОНАРНЫМ СИНДРОМОМ С ПОДЪЕМОМ СЕГМЕНТА ST

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Введение: существуют классические факторы риска атеросклероза - пол, этническая принадлежность, семейный анамнез, сахарный диабет, хроническая болезнь почек, ожирение, артериальная гипертензия, курение. Продолжается исследование таких традиционных теорий атеросклероза, как дислипедемий, инфекций и воспаление. На основе этих теорий в клинической практике проводятся соответствующие исследования липидов крови, С- реактивного белка, гомоцистеина. Однако, в настоящее время обозначаются новые факторы в патогенезе атеросклероза - загрязнение воздуха микрочастицами, нарушение клонального гемопоэза и изменение проатерогенного метаболического биомаркера триметиламин N-оксида. В крупных исследованиях показано, что ТМАО может быть предиктором риска сердечно-сосудистых заболеваний. ТМАО синтезируется с помощью кишечной микрофлоры и проводится изучение этих метаболических путей и факторов, влияющих на уровень ТМАО. В этой связи необходимо изучение коррелирующей зависимости между уровнем ТМАО и рядом клинических показателей.

Цель: на основе клинических исследований пациентов с острым коронарным синдромом с подъемом сегмента ST провести анализ возможных предикторов изменения уровня ТМАО.

Материалы и методы: исследование проведено в рамках другой более обширной научной работы по влиянию диетическогоремоделирования кишечной микробиоты на оксидативный статус, уровень триметиламиноксида (ТМАО) и частоту повторных сердечно-сосудистых событий после ИМST. В работе была выдвинута гипотеза о наличии зависимости между результирующей переменной ТМАО и рядом клинических показателей.

Результаты: в наибольшей степени изменение концентраций ТМАО зависит от состава кишечного микробиома. Ранее доказано, что уровни ТМАО в плазме крови определяются несколькими факторами, включая потребление его метаболических предшественников, лекарства и активность флавинмонооксигеназыFMO в печени.

Вывод:в работе проведен анализ зависимости уровня ТМАО от 43 клинических индикаторов. Выявлено, наличие статистически значимой корреляций уровня от шкалы состояния коронарного русла SYNTAXScoreI, наличия язвенной болезни и социального статуса.

***Ключевые слова**: триметиламина N-оксида (ТМАО), инфаркт миокарда с подъемом сегмента ST (ИМST), сердечно-сосудистые заболевания (ССЗ).*

Түйіндеме

ST СЕГМЕНТІ КӨТЕРІЛГЕН ЖЕДЕЛ КОРОНАРЛЫҚ СИНДРОМЫ БАР ЕМДЕЛУШІЛЕРДЕ ТРИМЕТИЛАМИН N - ОКСИДІ (ТМАО) ДЕҢГЕЙІНІҢ КЛИНИКАЛЫҚ КӨРСЕТКІШТЕРГЕ ТӘУЕЛДІЛІГІН ЗЕРТТЕУ

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Кіріспе: атеросклероздың классикалық қауіп факторлары бар - жынысы, этникалық тегі, отбасылық тарихы, қант диабеті, созылмалы бүйрек ауруы, семіздік, артериялық гипертензия, темекі шегу. Дислипедемия, инфекциялар және қабыну сияқты атеросклероздың дәстүрлі теорияларын зерттеу жалғасуда. Осы теориялардың негізінде клиникалық тәжірибеде қан липидтері, С – реактивті ақуыз, гомоцистеин бойынша тиісті зерттеулер жүргізіледі. Алайда, қазіргі уақытта атеросклероздың патогенезінде жаңа факторлар белгіленуде – ауаның микро бөлшектер мен ластануы, клондық гемопоэздің бұзылуы және триметиламин N-оксидінің проатерогенді метаболикалық биомаркерінің өзгеруі. Ірі зерттеулерде ТМАО жүрек – қан тамырлары ауруларының қаупін болжай алатындығы көрсетілген. ТМАО ішек микрофлорасы арқылы синтезделеді және осы метаболикалық жолдармен ТМАО деңгейіне әсер ететін факторларды зерттейді. Осыған байланысты ТМАО деңгейімен бірқатар клиникалық көрсеткіштер арасындағы корреляциялық байланысты зерттеу қажет.

Мақсаты: ST сегментінің жоғарылауы бар жедел коронарлық синдромы бар науқастардың клиникалық зерттеулеріне сүйене отырып, ТМАО деңгейінің өзгеруінің ықтимал болжаушыларына талдау жасау.

Материалдар мен әдістер: зерттеу ішек микро биотасын диеталық қайта құрудың тотығу күйіне, триметила миноксид деңгейіне (ТМАО) және ИМST – ден кейінгі қайталанатын жүрек-қантамырлары оқиғаларының жиілігіне әсері туралы тағы бір ауқымды ғылыми жұмыстың бөлігі ретінде жүргізілді. Жұмыста алынған ТМАО айнымалысымен бірқатар клиникалық көрсеткіштер арасында тәуелділіктің болуы туралы гипотеза жасалды.

Нәтижелері: ТМАО концентрациясының өзгеруі көбінесе ішек микро биомасының құрамына байланысты. Қан плазмасындағы ТМАО деңгейлері бірнеше факторлармен, соның ішінде оның метаболикалық прекурсорларын тұтынумен, дәрі-дәрмектермен және бауырдағы FMO флавинмоно оксигеназа белсенділігімен анықталатыны бұрын дәлелденген.

Қорытынды: Жұмыста ТМАО деңгейінің 43 клиникалық индикаторға тәуелділігі талданды. SYNTAX ScoreI коронарлық арнасының жай-күйі шкаласынан, ойық жара ауруының болуынан және әлеуметтік мәртебеден деңгейдің статистикалық маңызды корреляциясы анықталды.

***Түйінді сөздер**: триметиламин N-оксиді (ТМАО), ST сегментінің жоғарылауы бар миокард инфарктісі (STEMI), жүрек-қан тамырлары аурулары (CFS).*

Bibliographic citation:

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Сергазы Ш.Д., Жашкеев А.К., Жумадилов Ж.Ш. Исследование зависимости уровня Триметиламина N-оксида (ТМАО) от клинических показателей у пациентов с острым коронарным синдромом с подъемом сегмента ST// Наука и Здравоохранение. 2023. 5(Т.25). С. 34-44. *doi 10.34689/SH.2023.25.5.004*

Сергазы Ш.Д., Жашкеев А.К., Жумадилов Ж.Ш. ST сегменті көтерілген жедел коронарлық синдромы бар емделушілерде Триметиламин N-оксиді (ТМАО) деңгейінің клиникалық көрсеткіштерге тәуелділігін зерттеу // Ғылым және Денсаулық сақтау. 2023. 5 (Т.25). Б. 34-44. *doi 10.34689/SH.2023.25.5.004*

Introduction

Due to the numerous links between trimethylamine-N-oxide (TMAO) and various disorders and diseases, this is a very popular topic and is often addressed by researchers [1-10]. TMAO is a low molecular weight compound belonging to the class of amine oxides. It is formed during the oxidation of trimethylamine (TMA) by hepatic flavinmonooxygenases (FMO1 and FMO3). TMAO is mainly formed from dietary substrates through the metabolism of phosphatidylcholine/choline, carnitine, betaine, dimethylglycine and ergothioneine by gut microflora in the colon. Its level is determined by many factors, such as age, gender, diet, intestinal microflora composition, kidney function, and liver flavinmonooxygenase activity [11-19]. The Stanley Hazen group at the Cleveland Clinic found in a large clinical trial that serum TMAO levels may be a predictor of cardiovascular disease. Since that time, a number of independent cohort projects have confirmed the relationship between TMAO levels and the risk of cardiovascular diseases, in particular the risk of atherosclerosis [20-29]. However, stratification of the risk of cardiovascular events in coronary heart disease using assessment of TMAO levels remains a clinical problem [30-34].

Our study aimed to analyze possible predictors of changes in TMAO levels which are based on clinical studies of patients with acute coronary syndrome with ST segment elevation.

Materials and methods. This study was conducted on patients with STEMI admitted to the intensive care unit of Multidisciplinary Hospital No. 2, Karaganda, Kazakhstan in 2021-2022. Ethical approval was obtained from the local ethics committee of the Karaganda Medical University. Informed consent was obtained directly from the participants. Upon admission to all patients, the level of general clinical tests and troponin was determined, coronary angiography was performed with stenting of the infarct-related arteries; echocardiography was performed on days 1-2, SYNTAX Score I and Logistic Clinical Syntax Score were calculated according to the official versions. 61 patients (25 women and 36 men) aged from 35 to 75 years were examined.

Inclusion criteria:

- acute stage of myocardial infarction in patients in a specialized cardiology hospital after stenting of the coronary arteries.

- participants who are willing and able to comply with all scheduled appointments, treatment plan, laboratory test schedule, recommended lifestyle and other study procedures.

Exclusion criterion:

-other acute or chronic illnesses or psychiatric disorders.

Blood samples were collected by venipuncture. The blood was immediately transferred into a test tube. Blood samples were frozen for further determination of TMAO. To determine the level of TMAO in blood plasma, an Agilent 1260 Infinity chromatography system was used. The analysis was carried out using a validated method, with mass spectrometric detection, in SIM mode. The average time of TMAO release on the chromatogram was 1.29 minutes, the average TMAO level was 0.678 μmol/L, the maximum value was 7.401 μmol/L, the minimum value was 0.010 μmol/L.

Statistical analysis and results obtained. Statistical processing of the collected information was carried out using the universal integrated system STATISTICA

The influencing factors and their designations are presented in Table 1. Also, during the modeling, dummy variables were used, the coding of which is given in the same Table.

Table 1.

Study indicators

Indicator	Unit	Meaning
TMAO	μmol/l	y
age	years	x_1
gender		$x_2 = \begin{cases} 0, men \\ 1, women \end{cases}$
race		$x_3 = \begin{cases} 0, european \\ 1, mongoloid \end{cases}$
smoking		$x_4 = \begin{cases} 0, yes \\ 1, no \end{cases}$
height	cm.	x_5
weight	kg.	x_6
BMI	kg/cm	x_7
time to stenting	hour	x_8
cTnI	ng/ml	x_9
total protein	g/l	x_{10}
creatinine clearance	ml/min per 1,73	x_{11}
creatinine	μmol/l	x_{12}
urea	μmol/l	x_{13}
total bilirubin	μmol/l	x_{14}
ASAT	unit	x_{15}
ALaT	unit	x_{16}
glucose	μmol/l	x_{17}
cholesterol	μmol/l	x_{18}

Continuation of Table 1.

TG	μmol/l	x_{19}
Lipoproteins	μmol/l	x_{20}
Creatine kinase	unit	x_{21}
HGB	g/l	x_{22}
HCT	%	x_{23}
RBC	10x12/l	x_{24}
PLT	10x9/l	x_{25}
WBC	10x9/l	x_{26}
NEUT	%	x_{27}
LYM	%	x_{28}
MON	%	x_{29}
EOS	%	x_{30}
urine reaction	unit	x_{31}
urine density	g/l	x_{32}
urine glucose	μmol/l	x_{33}
urine protein	g/l	x_{34}
Q1	microcoulomb	x_{35}
Q2	microcoulomb	x_{36}
QT	microcoulomb	x_{37}
ECHOKS, FV	%	x_{38}
SYNTAX Score I	score	x_{39}
Logistic Clinical Syntax Score	risk of death in % over 2 years	x_{40}
main diagnosis		$x_{41} = \begin{cases} 1, anterior\ infarction \\ 0, other \end{cases}$ $x_{42} = \begin{cases} 1, inferior\ infarction \\ 0, other \end{cases}$ if $x_{41} = 0$, $x_{42} = 0$– lateral infarction
concomitant diagnosis		$x_{43} = \begin{cases} 1, SD \\ 0, other \end{cases}$ $x_{44} = \begin{cases} 1, arrhythmia \\ 0, other \end{cases}$ $x_{45} = \begin{cases} 1, PU \\ 0, other \end{cases}$ $x_{46} = \begin{cases} 1, \text{Ar}\ 3d\ degree \\ 0, other \end{cases}$ $x_{47} = \begin{cases} 1, COPD \\ 0, other \end{cases}$ $x_{48} = \begin{cases} 1, anemia \\ 0, other \end{cases}$ Ifx_{43}, x_{44}, x_{45}, x_{46}, x_{47}, $x_{48} = 0$– no concomitant diagnosis
social status		$x_{49} = \begin{cases} 1, working \\ 0, other \end{cases}$ $x_{50} = \begin{cases} 1, pensioner \\ 0, other \end{cases}$ $x_{51} = \begin{cases} 1, unemployed \\ 0, other \end{cases}$ if x_{49}, x_{50}, $x_{51} = 0$– disabled person

To determine the strength of the relationship, a matrix of pairwise correlation coefficients was calculated. Statistically significant (with a probability of 95%) correlation coefficients are highlighted in red in the table. Next, using a process of sequentially eliminating variables, a statistically reliable (95% probability) multiple linear regression equation was constructed. A flowchart of the process carried out in the Statistica program is presented in Table 2.

As a result of econometric modeling, a multiple linear regression equation was obtained:

$$y = -0{,}336 + 0{,}058x_{36} + 0{,}018x_{39} + 3{,}107x_{45} + 0{,}390x_{50}$$

The regression equation as a whole and its parameters before the regressors are statistically significant and reliable with a 95% probability.

Table 2.

Scheme of the process of sequential elimination of variables.

Step 1.

Statistic	Summary Statistics; DVy (Spreadshee Value
Multiple R	0,851476696
Multiple R?	0,725012564
Adjusted R?	0,64895221
F(13,47)	9,53206922
p	0,00000000302422598
Std.Err. of Estimate	0,394508839

N=61	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,85147670 R?= ,72501256 Adjusted R?= ,64895221 F(13,47)=9,5321 p<,00000 Std.Error of estimate: ,39451 b*	Std.Err. of b*	b	Std.Err. of b	t(47)	p-value
Intercept			-0,555175	1,068242	-0,519709	0,6057
x11	0,076004	0,109905	0,002337	0,003379	0,691543	0,4926
x12	0,217579	0,134559	0,008518	0,005268	1,616977	0,1125
x22	-0,135454	0,381106	-0,005212	0,014664	-0,355422	0,7238
x23	0,309500	0,575906	0,046728	0,086951	0,537414	0,5935
x24	-0,330403	0,631342	-0,454326	0,868136	-0,523335	0,6032
x26	0,007535	0,085321	0,002290	0,025934	0,088315	0,9300
x30	0,204628	0,082049	0,092893	0,037247	2,493977	0,0162
x36	0,170237	0,079441	0,057370	0,026771	2,142936	0,0373
x38	-0,014307	0,088714	-0,001319	0,008179	-0,161268	0,8725
x39	0,198009	0,083990	0,019317	0,008194	2,357535	0,0226
x43	0,133676	0,089164	0,276964	0,184739	1,499216	0,1405
x45	0,372666	0,117070	1,938022	0,608811	3,183291	0,0025
x50	0,179426	0,094274	0,249379	0,131029	1,903228	0,0631

Step 2

Statistic	Summary Statistics; DVy (Spreadsheet14) Value
Multiple R	0,851449899
Multiple R?	0,724966931
Adjusted R?	0,656208664
F(12,48)	10,5437057
p	0,000000000901785757
Std.Err. of Estimate	0,390410132

N=61	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,85144990 R?= ,72496693 Adjusted R?= ,65620866 F(12,48)=10,544 p<,00000 Std.Error of estimate: ,39041 b*	Std.Err. of b*	b	Std.Err. of b	t(48)	p-value
Intercept			-0,534454	1,031330	-0,518218	0,606687
x11	0,077003	0,108184	0,002367	0,003326	0,711777	0,480048
x12	0,217137	0,133069	0,008501	0,005210	1,631763	0,109274
x22	-0,127694	0,366987	-0,004913	0,014120	-0,347953	0,729397
x23	0,300691	0,561310	0,045398	0,084747	0,535696	0,594643
x24	-0,327866	0,624135	-0,450837	0,858227	-0,525312	0,601784
x30	0,203578	0,080340	0,092416	0,036471	2,533963	0,014596
x36	0,169612	0,078303	0,057159	0,026388	2,166090	0,035301
x38	-0,015045	0,087401	-0,001387	0,008058	-0,172141	0,864051
x39	0,198073	0,083114	0,019323	0,008108	2,383138	0,021172
x43	0,134806	0,087325	0,279305	0,180928	1,543735	0,129220
x45	0,372931	0,115815	1,939397	0,602289	3,220046	0,002301
x50	0,181230	0,091077	0,251887	0,126586	1,989847	0,052321

Step 3

Statistic	Summary Statistics; DVy (Spreadsheet14) Value
Multiple R	0,851350187
Multiple R?	0,724797141
Adjusted R?	0,663016907
F(11,49)	11,7318614
p	0,000000000257175253
Std.Err. of Estimate	0,386525074

N=61	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,85135019 R?= ,72479714 Adjusted R?= ,66301691 F(11,49)=11,732 p<,00000 Std.Error of estimate: ,38653 b*	Std.Err. of b*	b	Std.Err. of b	t(49)	p-value
Intercept			-0,613946	0,912994	-0,672454	0,504454
x11	0,074428	0,106079	0,002288	0,003261	0,701630	0,486229
x12	0,215307	0,131324	0,008429	0,005141	1,639516	0,107511
x22	-0,142402	0,353351	-0,005479	0,013596	-0,403006	0,688697
x23	0,300602	0,555724	0,045385	0,083903	0,540919	0,591014
x24	-0,312304	0,611408	-0,429439	0,840727	-0,510795	0,611788
x30	0,204827	0,079216	0,092983	0,035961	2,585690	0,012743
x36	0,168568	0,077291	0,056807	0,026047	2,180947	0,034017
x39	0,201528	0,079852	0,019660	0,007790	2,523770	0,014902
x43	0,135643	0,086322	0,281039	0,178849	1,571372	0,122532
x45	0,375767	0,113497	1,954145	0,590232	3,310808	0,001751
x50	0,185336	0,087024	0,257593	0,120953	2,129703	0,038244

Step 4

Statistic	Summary Statistics; DVy (Spreadsheet14) Value
Multiple R	0,850814295
Multiple R?	0,723884964
Adjusted R?	0,668661957
F(10,50)	13,1083945
p	0,00000000007369267
Std.Err. of Estimate	0,383273919

N=61	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,85081429 R?= ,72388496 Adjusted R?= ,66866196 F(10,50)=13,108 p<,00000 Std.Error of estimate: ,38327 b*	Std.Err. of b*	b	Std.Err. of b	t(50)	p-value
Intercept			-0,482528	0,845599	-0,570635	0,570803
x11	0,075383	0,105160	0,002318	0,003233	0,716838	0,476810
x12	0,219534	0,129803	0,008595	0,005082	1,691282	0,097008
x23	0,262671	0,543089	0,039658	0,081996	0,483661	0,630738
x24	-0,416131	0,549815	-0,572207	0,756032	-0,756856	0,452688
x30	0,208101	0,078135	0,094469	0,035470	2,663338	0,010383
x36	0,167943	0,076626	0,056597	0,025823	2,191739	0,033083
x39	0,200024	0,079094	0,019513	0,007716	2,528949	0,014641
x43	0,136837	0,085545	0,283512	0,177241	1,599588	0,115991
x45	0,369994	0,111642	1,924123	0,580587	3,314099	0,001715
x50	0,183150	0,086125	0,254555	0,119702	2,126575	0,038414

Step 5

Statistic	Summary Statistics; DVy (Spreadsheet14) Value
Multiple R	0,850054789
Multiple R?	0,722593145
Adjusted R?	0,673638994
F(9,51)	14,7606103
p	0,0000000000205443718
Std.Err. of Estimate	0,380384444

N=61	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,85005479 R?= ,72259315 Adjusted R?= ,67363899 F(9,51)=14,761 p<,00000 Std.Error of estimate: ,38038 b*	Std.Err. of b*	b	Std.Err. of b	t(51)	p-value
Intercept			-0,584351	0,812799	-0,71894	0,475461
x11	0,088940	0,100592	0,002734	0,003093	0,88416	0,380759
x12	0,233227	0,125723	0,009131	0,004922	1,85508	0,069369
x24	-0,153603	0,086932	-0,211214	0,119537	-1,76694	0,083222
x30	0,214645	0,076375	0,097440	0,034671	2,81042	0,007001
x36	0,164229	0,075665	0,055345	0,025499	2,17047	0,034651
x39	0,204278	0,078011	0,019928	0,007610	2,61859	0,011597
x43	0,126889	0,082409	0,262900	0,170744	1,53973	0,129808
x45	0,371240	0,110771	1,930603	0,576057	3,35141	0,001520
x50	0,187270	0,085056	0,260281	0,118217	2,20172	0,032234

Step 6

Statistic	Summary Statistics; DVy (Spreadsheet14) Value
Multiple R	0,833054893
Multiple R?	0,693980455
Adjusted R?	0,647788826
F(8,53)	15,023944
p	0,0000000000318620234
Std.Err. of Estimate	0,394460766

N=62	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,83305489 R?= ,69398045 Adjusted R?= ,64778883 F(8,53)=15,024 p<,00000 Std.Error of estimate: ,39446 b*	Std.Err. of b*	b	Std.Err. of b	t(53)	p-value
Intercept			-0,099508	0,663948	-0,14987	0,881433
x12	0,114020	0,100698	0,004433	0,003915	1,13230	0,262605
x24	-0,126156	0,088885	-0,174550	0,122982	-1,41931	0,161662
x30	0,171502	0,077814	0,076813	0,034852	2,20400	0,031889
x36	0,175665	0,078028	0,059404	0,026387	2,25130	0,028537
x39	0,190989	0,080224	0,018504	0,007773	2,38069	0,020907
x43	0,120002	0,084637	0,249990	0,176317	1,41784	0,162089
x45	0,435218	0,109326	2,277743	0,572164	3,98093	0,000210
x50	0,205689	0,085686	0,286532	0,119363	2,40051	0,019916

Step 7

Statistic	Summary Statistics; DVy (Spreadsheet14) Value
Multiple R	0,828599801
Multiple R?	0,68657763
Adjusted R?	0,645948804
F(7,54)	16,898781
p	0,0000000000134809186
Std.Err. of Estimate	0,395489795

N=62	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,82859980 R?= ,68657763 Adjusted R?= ,64594880 F(7,54)=16,899 p<,00000 Std.Error of estimate: ,39549 b*	Std.Err. of b*	b	Std.Err. of b	t(54)	p-value
Intercept			0,162764	0,623858	0,26090	0,795162
x24	-0,114847	0,088553	-0,158904	0,122522	-1,29694	0,200167
x30	0,168991	0,077985	0,075688	0,034928	2,16696	0,034668
x36	0,175758	0,078232	0,059436	0,026455	2,24664	0,028774
x39	0,207890	0,079029	0,020142	0,007657	2,63054	0,011085
x43	0,126609	0,084656	0,263753	0,176356	1,49557	0,140587
x45	0,503835	0,091231	2,636854	0,477464	5,52263	0,000001
x50	0,212269	0,085711	0,295698	0,119399	2,47656	0,016430

Step 8

Statistic	Summary Statistics; DVy (Spreadsheet14) Value
Multiple R	0,822687555
Multiple R?	0,676814814
Adjusted R?	0,641558248
F(6,55)	19,1968446
p	0,00000000000644219487
Std.Err. of Estimate	0,397934455

N=62	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,82268756 R?= ,67681481 Adjusted R?= ,64155825 F(6,55)=19,197 p<,00000 Std.Error of estimate: ,39793 b*	Std.Err. of b*	b	Std.Err. of b	t(55)	p-value
Intercept			-0,560692	0,281077	-1,99480	0,051030
x30	0,161056	0,078225	0,072134	0,035036	2,05887	0,044255
x36	0,172094	0,078664	0,058197	0,026602	2,18771	0,032958
x39	0,204614	0,079477	0,019824	0,007700	2,57449	0,012761
x43	0,103683	0,083302	0,215994	0,173535	1,24467	0,218530
x45	0,539862	0,087436	2,825404	0,457603	6,17435	0,000000
x50	0,256980	0,078958	0,357982	0,109991	3,25465	0,001945

Step 9

Statistic	Summary Statistics; DVy (Spreadsheet14) Value
Multiple R	0,817136159
Multiple R?	0,667711503
Adjusted R?	0,638042887
F(5,56)	22,5056506
p	0,000000000000266656272
Std.Err. of Estimate	0,399881034

N=62	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,81713616 R?= ,66771150 Adjusted R?= ,63804289 F(5,56)=22,506 p<,00000 Std.Error of estimate: ,39988					
	b*	Std.Err. of b*	b	Std.Err. of b	t(56)	p-value
Intercept			-0,495649	0,277528	-1,78594	0,079523
x30	0,152869	0,078329	0,068468	0,035083	1,95162	0,055992
x36	0,166528	0,078921	0,056314	0,026689	2,11006	0,039334
x39	0,190872	0,079092	0,018493	0,007663	2,41330	0,019106
x45	0,581293	0,081248	3,042237	0,425215	7,15458	0,000000
x50	0,258970	0,079328	0,360754	0,110506	3,26456	0,001872

Step 10

Statistic	Summary Statistics; DVy (Spreadsheet14) Value
Multiple R	0,803188052
Multiple R?	0,645111047
Adjusted R?	0,620206559
F(4,57)	25,9034054
p	0,00000000000291820756
Std.Err. of Estimate	0,409615119

N=62	Regression Summary for Dependent Variable:y (Spreadsheet14) R= ,80318805 R?= ,64511105 Adjusted R?= ,62020656 F(4,57)=25,903 p<,00000 Std.Error of estimate: ,40962					
	b*	Std.Err. of b*	b	Std.Err. of b	t(57)	p-value
Intercept			-0,335834	0,271626	-1,23638	0,221387
x36	0,172146	0,080788	0,058214	0,027320	2,13084	0,037429
x39	0,190664	0,081017	0,018473	0,007850	2,35338	0,022076
x45	0,593575	0,082975	3,106516	0,434257	7,15363	0,000000
x50	0,280063	0,080501	0,390137	0,112141	3,47900	0,000971

Discussion

The results obtained can be interpreted as follows:

1) If Q2 before the dietary supplement increases by 1 microcoulomb, then we can expect an increase in TMAO before the dietary supplement by an average of 0.058 μmol/l;

2) If SYNTAX Score I before dietary supplement increases by 1 point, then we can expect an increase in TMAO before dietary supplement by an average of 0.018 μmol/l;

3) The presence of a concomitant disease of ulcer (peptic ulcer?), increases TMAO to BAA by an average of

3.107 μmol/l compared with other diseases or their absence;

4) In sick pensioners, TMAO before dietary supplementation is on average 0.390 μmol/l higher than in other patients. This study revealed a statistically significant relationship between plasma TMAO concentrations and the degree of atherosclerotic coronary lesions in patients with STEMI. These data can be used to predict the incidence of major adverse cardiovascular events (MACE) in patients with CAD. Our analysis also showed a relationship between TMAO concentration, social status and peptic ulcer disease.

Conclusion

The presence of an evidence-based relationship between the level of TMAO and the state of the coronary artery provides opportunities for the development of both new diagnostic tests as biomarkers of susceptibility to myocardial infarction and stroke and new therapeutic approaches for the prevention of cardiovascular events. Our results are based on limited data from studies but clearly show that TMAO concentrations have prognostic value in patients with CAD. More prospective studies are needed to evaluate this relationship and the mechanisms that drive it.

Funding: *This research has been funded by the Ministry of Health of the Republic of Kazakhstan (Program №AP09259661).*

Acknowledgements: *We thank all the participants in this study.*

Conflict of interest: *the authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*

Publication details: *This material has not been published in other publications and is not pending review by other publishers.*

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