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Gut bacterial bile salt hydrolase activity correlates with cardiovascular risk: a case-control study

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Abstract. ***Background.*** *Serum cholesterol may be regulated by bile acid metabolism in the gut that depends on bacterial bile salt hydrolase (BSH) activity. There are limiting data regarding the clear effect of BSH on host lipid metabolism and cardiovascular risk (CVR). The investigation aimed to assess the relationship between the gut bacterial BSH relative activity (RA) and serum cholesterol with CVR levels.* ***Materials and methods.*** *The investigation was conducted as a case-control study and included 26 almost healthy participants (a control group) and 77 patients with dyslipidemia and without anamnesis of major cardiovascular events (a case group). The total RA of gut BSH, lipid profile, and CVR level according to 5 risk scores were assessed.* ***Results.*** *The RA of BSH was higher in healthy adults comparing to participants with dyslipidemia ($p < 0.001$). There were found moderate negative correlation between RA of gut bacterial BSH and total cholesterol (TC) (–0.38) and moderate correlation with low-density lipoproteins (LDL) (–0.36) with linear relationship that is defined by equation: LDL = –5.33 • RA of BSH + 4.479. It was revealed that with increasing of RA of gut bacterial BSH, the risk of dyslipidemia decreased ($p < 0.001$), OR = $1.06 • 10^{-10}$ (95% confidence interval; $2.5 • 10^{-15} – 4.5 • 10^{-6}$). There was found a moderate negative correlation between RA of gut bacterial BSH and CVR levels according to Globorisk score (–0.34), Framingham score (–0.34), 2013 ACC/AHA algorithm (–0.32), PROCAM score (–0.35), and WHO risk chart (–0.34).* ***Conclusions.*** *The total RA of the gut bacterial BSH negatively correlated with TC, LDL, and CVR levels according to 5 risk scores and was negatively associated with the risk of dyslipidemia.*

Keywords: *bile salt hydrolase activity; dyslipidemia; cardiovascular risk*

Introduction

Cardiovascular diseases (CVD) are one of the most prominent contributors to the global burden from noncommunicable diseases in the world [1, 2]. There are a lot of risk factors that may have a different impact on the development and progression of CVD, for example, hypercholesterolemia, arterial hypertension, smoking, diabetes mellitus, metabolic syndrome, etc. Dyslipidemia, especially hypercholesterolemia due to high levels of total cholesterol (TC) and low-density lipoproteins (LDL), is an important influencing factor on cardiovascular risk (CVR) level [3, 4].

The serum level of cholesterol is maintained mainly by the regulation of *de novo* synthesis and partially with food [5]. A newly synthesized cholesterol is required for subsequent cell membrane formation, producing steroid hormones and primary bile acids (BAs) [5, 6]. The latter requires a large proportion of cholesterol [5–7]. Primary BAs with bile enter the small intestine where they play a role in lipid metabolism and after that return to the liver by reabsorption in the ileum (entero-hepatic circulation) [8]. In intestines, bile acid salts may be deconjugated by bile salt hydrolase (BSH) produced by different gut bacteria [8–10]. Deconjugated secondary BAs are less soluble and eliminated with feces leading to a decrease of BA pool of entero-hepatic circulation. Subsequently, this stimulates the liver to increase free cholesterol uptake from the blood to *de novo* synthesis of primary BA [8–11]. Therefore, BSH is considered to have a hypocholesterolemic effect.

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A recent study [12] has shown eight phylogenetic variants of BSH that have different enzymatic activity, distribution, and general activity in different populations, probably due to gut microbiome composition. A correlation was found between certain variants of BSH and atherosclerosis, diabetes, and cardiovascular mortality. The authors noted that BSH maybe had a pleiotropic impact on the atherosclerosis development but further investigations are required to find a clear relationship between BSH and CVD. And we didn't find any data regarding the relationships between the activity of bacterial BSH and CVR assessed using valid risk scores.

The purpose of this investigation was to evaluate the possible relationship between the total relative activity (RA) of gut bacterial BSH and lipid profile values with CVR assessed by valid risk scores in healthy adults and patients with dyslipidemia.

The tasks of the study were:

1. To evaluate and compare the total RA of gut bacterial BSH in the compared groups.
2. To assess the statistical relationship between the total RA of gut bacterial BSH and lipid profile values of the compared groups.
3. To assess the statistical relationship between the total RA of gut bacterial BSH and CVR levels calculated using valid risk scores in the compared groups.

Materials and methods

The clinical investigation was conducted in accordance with the Ukrainian laws, the requirements of Good Clinical Practice, ethical principles of the Declaration of Helsinki. Written informed consent for participation in the investigation had been obtained from all participants before the trial began. The protocol was approved by the Bioethical Committee of Bogomolets National Medical University, Kyiv, Ukraine.

Study design and participants. The study was conducted as a case-control study. The study population included participants of both genders: 26 almost healthy participants aged 22–44 years without dyslipidemia (a control group) and 77 patients aged 40–74 years with dyslipidemia and without anamnesis of major cardiovascular events (a case group). For the case group, the inclusion criteria were as follows: men and women aged 30–74 years; LDL level ≥ 3.0 mmol/l; TC level > 5.0 mmol/l; patients who have not previously received statins or received them more than 6 months before investigation; informed written consent. Exclusion criteria were as follows: administration of any lipid-lowering drugs for 4 weeks before investigation; previous history of major cardiovascular events (myocardial infarction, stroke); chronic liver disease; any acute diseases within 2 months before the investigation; participation in other clinical trials.

Assessment of total RA of gut bacterial BSH. For the evaluation of total RA of gut bacterial BSH, the specimens of participants' feces were collected immediately after defecation. The ultra-performance liquid chromatography — mass spectrometry was used for the assessment of total enzyme activity of gut BSH of fecal samples as it was described before [13, 14]. The relative activity of gut BSH was expressed in units of choloylglycine hydrolase/mL (from *Clostridium perfringens*, EC 3.5.1.24, Sigma-Aldrich). The total RA of gut bacterial BSH of patients' fecal samples was evaluated in the Laboratory of Bioorganic Chemistry and Molecular Imaging, Institute of Chemical Sciences and Engineering, Lausanne, Switzerland (based on the signed memorandum about collaboration between the Laboratory and the Department of Internal Medicine 1 of Bogomolets National Medical University, Kyiv, Ukraine, 14.05.2018).

Biochemical blood analysis. To evaluate TC, LDL, high-density lipoproteins (HDL), triglycerides (TG), liver tests, and creatine phosphokinase, the participants' blood samples were collected. The standard enzymatic methods were used to assess the level of TC, LDL, HDL, TG.

Cardiovascular risk assessment. The levels of CVR were calculated using five valid risk scores: Globorisk [15], Framingham 10-year CVD risk estimation [16], the 10-year risk of heart disease or stroke using the ASCVD algorithm published in 2013 by ACC/AHA [17], Cardiovascular Risk PROCAM Score [18], WHO cardiovascular disease risk chart [2].

Considering the age limit for CVR evaluation, in a control group, for participants younger than 40 years we have assumed their CVR as 1 % according to Globorisk score, 2013 ACC/AHA algorithm and WHO cardiovascular disease risk chart; younger than 35 years — as 20 points according to PROCAM score; younger than 30 years — as 1 % according to Framingham score.

Statistical analysis. The obtained data were analyzed using IBM SPSS Statistics v23 for Windows. Shapiro-Wilk test was used to check the normality of continuous variables. The data were presented as an arithmetic mean with standard deviation (mean ± SD) in case of a normal distribution or as median with first and third quartiles (median (Q1-Q3)) in case of non-normal distribution. The differences between the means of two groups were checked by the unpaired t-test (in case of normal distribution) or Wilcoxon two-samples test (in case of non-normal distribution). The difference between the qualitative variables was checked by the chi-square test. For determining the statistical relationships between variables, the correlation, linear, and logistic regression analysis were used. The difference between the study groups was considered statistically significant with $p < 0.05$.

Results

Baseline characteristics of the compared groups. It was revealed the significant difference between the control and case groups regarding the age, body mass index (BMI), presence of diabetes mellitus (DM), levels of systolic blood pressure (SBP), TC, LDL, and CVR levels according to all scores. There were no differences between the compared groups regarding other values (Table 1).

RA of gut bacterial BSH of the compared groups. It was revealed that RA of gut bacterial BSH of the control group ((0.22 ± 0.12) U/mL) was statistically higher than in the case group ((0.01 ± 0.05) U/mL), $p < 0.001$ (Fig. 1).

Correlation and linear regression model of the relationship between RA of gut bacterial BSH and lipid profile values. There were found a moderate negative correlation between RA of gut bacterial BSH and TC (–0.38) and a moderate re-

Table 1 — Baseline characteristics of the control and case groups

Parameter		Control (n = 26)*	Case (n = 77)*	Difference (p)**
Age		31.5 (28–37)	58 (52–67)	< 0.001
Sex	Men	13 (50 %)	21 (27.3 %)	0.067
	Women	13 (50 %)	56 (72.7 %)	0.067
BMI		23.3 ± 2.4	27.5 ± 3.7	< 0.001
DM	yes	0 (0 %)	36 (46.8 %)	< 0.001
	no	26 (100 %)	41(53.2 %)	–
Smoking	yes	8 (30.8 %)	23 (29.9 %)	0.873
	no	18 (69.2 %)	54 (70.1 %)	–
SBP (mmHg)		120 (110–120)	135 (120–145)	< 0.001
TC (mmol/l)		4.64 (4.19–4.83)	5.88 (5.49–6.52)	< 0.001
LDL (mmol/l)		2.61 (2.17–2.84)	4.01 (3.73–4.52)	< 0.001
HDL (mmol/l)		1.54 ± 0.44	1.39 ± 0.38	0.096
TG (mmol/l)		1.15 (0.8–1.7)	1.31 (0.78–2.18)	0.346
Globorisk (%)		1 (1–1)	37 (15–56)	< 0.001
Framingham (%)		1.25 (1–2.8)	17.9 (9.7–33.5)	< 0.001
2013 ACC/AHA algorithm (%)		1 (1–1)	11.3 (3.4–21.8)	< 0.001
PROCAM (points)		20 (20–20)	50 (41–58)	< 0.001
WHO risk chart (%)		1 (1–1)	19 (9–31)	< 0.001

***Notes:** * — in case of normal and non-normal distribution, the data were presented as mean ± SD and median (Q1-Q3), respectively; ** — t-test or Wilcoxon two-samples test was used for normal and non-normal distribution.*

lationship with LDL (–0.36) (Table 2). There was not found a statistically significant correlation with HDL and TG.

Using the linear regression analysis, it was found a linear relationship between LDL and RA of gut bacterial BSH, line is defined by equation:

$$LDL = -5.33 \cdot RA\ of\ BSH + 4.479.$$

The fitted line plot of this linear model is presented on Fig. 2.

The association between the dyslipidemia risk and RA of gut bacterial BSH. To analyze the association of dyslipidemia risk with RA of gut bacterial BSH, we used the method of constructing and analyzing a one-factor logistic regression model. It was found that with increasing of RA of gut bacterial BSH, the risk of dyslipidemia decreased ($p < 0.001$), OR = $1.06 \cdot 10^{-10}$ (95% CI; $2.5 \cdot 10^{-15} – 4.5 \cdot 10^{-6}$). Fig. 3 shows the ROC curve of this model, AUC = 0.845 (95% CI; 0.746–0.943).

The correlation between RA of gut bacterial BSH and CVR levels. There was found a moderate negative correlation between RA of gut bacterial BSH and CVR levels according to Globorisk score (–0.34), Framingham score (–0.34), 2013 ACC/AHA algorithm (–0.32), PROCAM score (–0.35) and WHO risk chart (–0.34) (Table 3).

Table 2 — Correlation coefficients between RA of gut bacterial BSH and lipid profile values

Lipid profile value	Correlation coefficient, Pearson or Spearman test	Difference from 0, p
TC	–0.38	< 0.01
LDL	–0.36	< 0.01

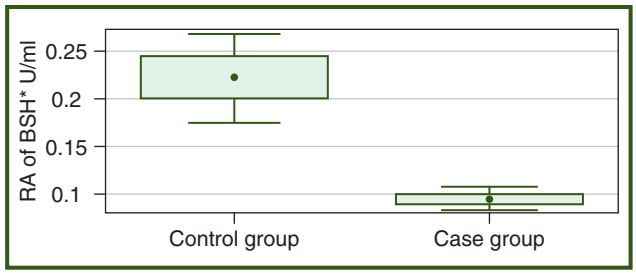

Figure 1 — RA of gut bacterial BSH of the compared groups

***Note.** * — RA — the relative activity of gut bacterial bile salt hydrolase expressed in units of choloylglycine hydrolase/mL from Clostridium perfringens, EC 3.5.1.24, Sigma-Aldrich.*

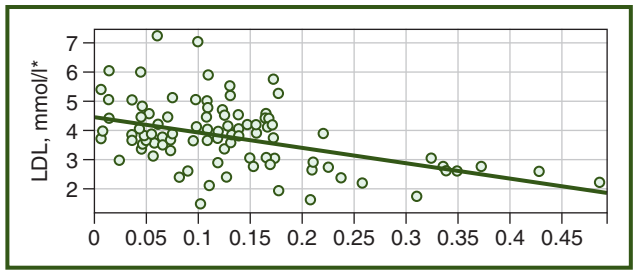

Figure 2 — The fitted line plot of a linear relationship between LDL and RA of gut bacterial BSH

***Note.** * — RA — the relative activity of gut bacterial bile salt hydrolase expressed in units of choloylglycine hydrolase/mL from Clostridium perfringens, EC 3.5.1.24, Sigma-Aldrich.*

Discussion

There are limited world literature data regarding a clear impact of gut bacterial BSH on host lipid metabolism. Some studies [6, 19–21] proposed using the assessment of bile acid excretion with feces to determine the relationship between cholesterol and bile acid metabolism. The investigation on animals [19, 20] revealed the negative correlation between the serum TC and daily excretion of bile salts, while human trials didn't reveal [6, 21] such correlation. But on the other hand, these human investigations [6, 21] have shown that patients with coronary artery disease had lower excretion of bile acids compared with adults without it.

Regarding the evaluation of gut BSH activity, we found a small number of investigations. A recent study [14] using a controlled biological system with *in vivo* study on mice has shown that the increasing of gut BSH activity was associated with lowering of the serum cholesterol. The authors have considered that BSH is the main mechanism by which microbiota has a hypocholesterolemic effect [14]. But another human study on 11 populations [12] used the evaluation of relative abundance of BSH-genes in the human gut microbiome. The authors didn't reveal the correlation between the mean blood cholesterol and the relative abundance of BSH-genes. But this trial didn't use the assessment of BSH-enzyme activity to determine the correlation with the cholesterol levels [12].

In this clinical investigation, we applied the method of quantitative assessment of the relative activity of gut bacterial bile salt hydrolase in healthy adults and participants with dyslipidemia [13, 14]. It was shown that the relative activity of this enzyme is higher in healthy adults and lower in patients with dyslipidemia and negatively correlates with the total cholesterol and low-density lipoproteins. It means that with increasing of BSH activity, the levels of TC and LDL decreased. It was also revealed a linear relationship between RA of gut bacterial BSH and LDL. A logistic regression model has shown that the risk of dyslipidemia decreased with increasing in BSH activity.

There are very limited literature data regarding the association between BSH and cardiovascular risk. The above population investigation [12] has shown eight phylogenetic variants of BSH, genes of which are distributed between the different bacteria strains. The authors revealed a positive correlation between the relative abundance of BSH genes of only T0-phylogenetic variant and CVD mortality [12]. But it wasn't found a correlation between CVD mortality and the relative abundance of other seven phylogenetic BSH variants and total BSH [12]. This investigation didn't assess the BSH enzyme activity and its relation with CVD mortality and also other categories of cardiovascular risk, except for mortality. But in clinical practice, for making the decision of prescribing lipid-lowering therapy and manage its effectiveness, a lot of CVR assessment tools are used that allow assessing the risk of non-fatal and fatal cardiovascular events [2, 15–18]. Most of them include the levels of different lipid profile values. Our investigation was oriented on the evaluation of the possible association between RA of gut bacterial BSH and CVR levels according to five valid risk scores. We have revealed a moderate negative correlation between RA of gut bacterial BSH and absolute levels of CVR according to all risk scores. It means that higher levels of gut bacterial BSH correlated with lower levels of CVR.

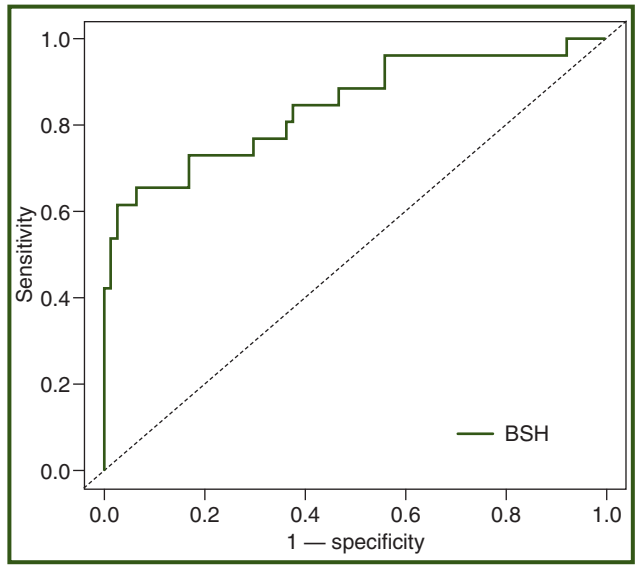

Figure 3 — The ROC curve of the one-factor logistic regression model of association of dyslipidemia risk with the relative activity of gut bacterial bile salt hydrolase

Table 3 — Correlation coefficients between RA of gut bacterial BSH and CVR levels according to five scores

Cardiovascular risk score	Correlation coefficient, Spearman test	Difference from 0, p
Globorisk	–0.34	< 0.01
Framingham	–0.34	< 0.01
2013 ACC/AHA algorithm	–0.32	< 0.01
PROCAM	–0.35	< 0.01
WHO risk chart	–0.34	< 0.01

Conclusions

In summary, the results of this investigation have shown the higher total relative activity of gut bacterial bile salt hydrolase in healthy adults comparing to patients with dyslipidemia. RA of gut bacterial BSH negatively correlated with serum total cholesterol, low-density lipoproteins (with a linear relationship), and cardiovascular risk levels and was negatively associated with the risk of dyslipidemia. But further investigations are needed to confirm the results of the present trial.

Conflicts of interests. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript.

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Authors contribution: *A. Neverovskyi* — concept and design of research; investigation of participants, data collection; analyzing and interpretation of the data obtained; statistical analysis; writing the text of article; final approval; *V. Chernyavskyi* — concept and design of research; analyzing and interpretation of the data obtained; critically re-

vising of the article; final approval; *V. Shypulin* — concept and design of research; critically revising of the article; final approval; *L. Gvozdecka* — investigation of participants, data collection; critically revising of the article; final approval; *N. Mikhnova* — investigation of participants, data collection; critically revising of the article; final approval.

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Активність кишкової бактеріальної гідролази солей жовчних кислот корелює із серцево-судинним ризиком: дослідження «випадок — контроль»

Резюме. ***Актуальність.*** Рівень сироваткового холестерину частково регулюється завдяки метаболізму жовчних кислот у кишечнику, що залежить від активності бактеріальної гідролази солей жовчних кислот (ГСЖК). Існуючі дані щодо чіткого впливу ГСЖК на ліпідний обмін та серцево-судинний ризик є недостатніми та суперечливими. ***Метою дослідження*** було оцінити взаємозв'язок між відносною активністю (ВА) кишкової бактеріальної ГСЖК і рівнями сироваткового хо-

лестерину та серцево-судинним ризиком (ССР). ***Матеріали та методи.*** Дослідження проводилось за дизайном «випадок — контроль» і включало 26 відносно здорових учасників (контрольна група) та 77 пацієнтів із дисліпідемією, без анамнезу тяжких серцево-судинних подій (основна група). В учасників були визначені загальна ВА кишкової бактеріальної ГСЖК, показники ліпідного профілю та рівні ССР за 5 шкалами ризику. ***Результати.*** ВА кишкової бактеріальної ГСЖК була вищою у здорових учасників порівняно з учасниками з дисліпідемією ($p < 0,001$). Було виявлено негативний кореляційний зв'язок помірної сили між ВА ГСЖК та загальним холестерином (ЗХ) (–0,38) і ліпопротеїнами низької щільності (ЛПНЩ) (–0,36) з лінійним співвідношенням, яке визначалось рівнянням: ЛПНЩ = –5,33 · ВА ГСЖК + 4,479. Було виявлено, що зі збільшенням ВА ГСЖК ризик дисліпідемії знижується ($p < 0,001$), ВШ = $1,06 \cdot 10^{-10}$ (95% ДІ; $2,5 \cdot 10^{-15} – 4,5 \cdot 10^{-6}$). Виявлений помірний негативний кореляційний взаємозв'язок між ВА ГСЖК та ССР, оціненим за шкалами Globorisk (–0,34), Framingham (–0,34), алгоритмом ACC/AHA 2013 (–0,32), PROCAM (–0,35) та шкалою ВООЗ (–0,34). ***Висновки.*** Загальна ВА кишкової бактеріальної ГСЖК негативно корелювала із ЗХ, ЛПНЩ, ССР, оціненим за 5 шкалами, та негативно асоціювалася з ризиком дисліпідемії.

Ключові слова: активність бактеріальної гідролази солей жовчних кислот; дисліпідемія; серцево-судинний ризик

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Активность кишечной бактериальной гидролазы солей желчных кислот коррелирует с сердечно-сосудистым риском: исследование «случай — контроль»

Резюме. ***Актуальность.*** Уровень сывороточного холестерина частично регулируется благодаря метаболизму желчных кислот в кишечнике, зависящему от активности бактериальной гидролазы солей желчных кислот (ГСЖК). Существующие данные относительно четкого влияния ГСЖК на липидный обмен и сердечно-сосудистый риск недостаточны и противоречивы. ***Целью исследования*** было оценить взаимосвязь между относительной активностью (ОА) кишечной бактериальной ГСЖК и уровнями сывороточного холестерина и сердечно-сосудистым риском (ССР). ***Материалы и методы.*** Исследование проводилось по дизайну «случай — контроль» и включало 26 относительно здоровых участников (контрольная группа) и 77 пациентов с дислипидемией, без анамнеза тяжелых сердечно-сосудистых событий (основная группа). У участников были определены общая ОА кишечной бактериальной ГСЖК, показатели липидного профиля и уровни ССР по 5 шкалам риска. ***Результаты.*** ОА кишечной бактериальной ГСЖК была выше у здоровых участников по сравнению с участниками с дислипидемией ($p < 0,001$). Была выявлена отрицательная корреляционная связь умеренной силы между ОА ГСЖК и общим холестерином (ОХ) (–0,38) и липопротеинами низкой плотности (ЛПНП) (–0,36) с линейным соотношением, которое определялось уравнением: ЛПНП = –5,33 • ОА ГСЖК + 4,479. Было обнаружено, что с увеличением ОА ГСЖК риск дислипидемии снижается ($p < 0,001$), ОШ = $1,06 \cdot 10^{-10}$ (95% ДИ; $2,5 \cdot 10^{-15} – 4,5 \cdot 10^{-6}$). Выявлена умеренная отрицательная корреляционная взаимосвязь между ОА ГСЖК и ССР, оцененным по шкалам Globorisk (–0,34), Framingham (–0,34), алгоритму ACC/AHA 2013 (–0,32), PROCAM (–0,35) и шкале ВОЗ (–0,34). ***Выводы.*** Общая ОА кишечной бактериальной ГСЖК негативно коррелировала с ОХ, ЛПНП, ССР, оцененным по 5 шкалам, и негативно ассоциировалась с риском дислипидемии.

Ключевые слова: активность бактериальной гидролазы солей желчных кислот; дислипидемия; сердечно-сосудистый риск