Annals of Parasitology 2022, 68(1), 9–16
doi: 10.17420/ap6801.402

Original paper

The role of PCSK9 in blood lipids recycling in women with acute toxoplasmosis

Rajaa ABD ALI[1], Azhar Hatif AL-KURAISHI[1], Fatin Shallal FARHAN[2]

[1]Department of Microbiology, College of Medicine, Al-Mustansiriya University, Bagdad, Iraq
[2]Department of Obstetrics and Gynecology, College of Medicine, Al-Mustansiriya University, Bagdad, Iraq

Corresponding Author: Rajaa Abd Ali; e-mail: rajaaaeali@gmail.com

ABSTRACT. *Toxoplasma gondii* is intracellular parasite; it is considered one of the most important causes of miscarriage and can inhibit the development of the fetus, especially at the beginning of pregnancy. Host lipids have an important role in the pathogenesis of *T. gondii* infection. Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a liver secreted protein that has the unusual ability to interfere and block the natural recycling of lipid receptors, resulting in impaired lipid clearance from the plasma. This study designed to investigate the role of PCSK9 in recycling blood lipid levels in women with acute toxoplasmosis and to evaluate the relationship between them. Forty serum blood samples were collected from aborted women, who were having acute toxoplasmosis (IgM and IgA positive result) for the period October 2020 to March 2021. In addition, 25 samples were collected from apparently-healthy women (negative control group) and 25 samples collected from other aborted women (positive control group). Both groups gave negative result for the presence of IgM, IgA and IgG-*Toxoplasma* antibodies. Finally, PCSK9 and blood lipids levels were measured for all groups. Positive relations were found between lipid profile values and *T. gondii* infected women. There were an increased in triglycerides (149.65 mg/dl), HDL (38.5 mg/dl), VLDL (140.53 mg/dl) values, while there was a decreased in LDL values (41.7 mg/dl). The PCSK9 was a highly significant increase in PCSK9 in *T. gondii* infected women (3.23) compared with aborted and healthy control groups (1.57, 1.15 respectively). The measurement of PCSK9 can be used as a biomarker and may be useful in screening for acute toxoplasmosis. In spite of a highly significant increase in PCSK9 and blood lipids in acute toxoplasmosis, there was a decrease in BMI. This may be due to toxoplasmosis infection.

Keywords: acute toxoplasmosis, PCSK9, blood lipids

Introduction

Toxoplasmosis is worldwide distribution disease approximately a third one of population, caused by an obligate intracellular protozoan, *Toxoplasma gondii* [1]. This parasite can be infecting a broad range of warm-blooded vertebrates, humans and animals as intermediate hosts, while Felidae (cats) serve as intermediate, and definitive host [2]. *T. gondii* is mainly transmitted through consuming contaminated water and food with cat faeces containing mature oocyst, or via ingested under-cooked meat containing tissue cysts [3], and can be transmitted congenitally from mothers to their fetus [4]. Asymptomatic or presents only mild symptoms at other infected human population. However, the infection can cause significant morbidity and mortality in immunocompromised individuals. *T. gondii* replicates in a specialized vacuole known as the parasitophorous vacuole (PV), within a host cell cytoplasm. So, inside the PV, the replication needs significant amount of the specific lipids for membrane biosynthesis [5].

It is unable to synthesize cholesterol, and based on acquisition of low-density lipoprotein (LDL) derived from the host cell, through endocytosis mediated by the LDL receptor (LDLR) [6]. Latest researchers indicated that the levels of high-density lipoprotein (HDL) and triglycerides are elevated in patients with chronic *T. gondii* infection, while cholesterol levels are showing a different pattern, so host lipid metabolism pathway may be potential strategies for *T. gondii* infection [7].

Proprotein convertase subtilisin/kexin type 9

(PCSK9) was first recognized for auto-dominant hypercholesterolemia in French families in 2003 [8]. It is a liver secreted enzyme expressed in many tissues, and cell types, and binds to LDLR, which typically transport 3,000 to 6,000 fat molecules per particle, within extracellular fluid. The LDLR on liver, and other cell membranes, binds, and initiates ingestion of LDL particles from extracellular fluid into cells, thus reducing LDL particle concentrations. If PCSK9 is blocked, more LDLRs are recycled, and present on the surface of cells to remove LDL-particles from the extracellular fluid. Therefore, blocking PCSK9 can lower blood LDL-particle concentrations [9].

Materials and Methods

Samples collection

Forty serum blood samples were collected from aborted women with acute toxoplasmosis, for the period October 2020 to March 2021. These were collected from aborted women who had attended at the Obstetrics and Gynecology Department of Al-Yarmouk Teaching Hospital, Kamal Al-Samaraie Hospital, and private laboratories in Baghdad City. Patients who had diabetes mellitus, hypertension, and takes any drugs were excluded. The acute toxoplasmosis infection was confirmed for IgM, IgG by rapid Test-Cassette (Bio-Medical Co., Ltd., Beijing, China) followed by IgM and IgG ELISA test (Foresight Co., USA), and IgA ELISA test (MyBioSource Co., USA). Sera that giving positive result for IgM and IgA and negative result for IgG were used as acute toxoplasmosis group. In addition, 25 serum samples from apparently healthy women (use as negative control group) and 25 serum samples from other aborted women (used as positive control group) were collected. Both control groups should give negative results for IgM, IgG and IgA by rapid Test-Cassette and ELISA test.

Measurements of body mass index (*BMI*)

The BMI was achieved using tape measurement and an electronic weight measuring instrument by measuring weight in kilos and height in meters, and the following equation was applied: BMI = weight (kg)/height (m^2) [10].

Lipid profile tests

Cholesterol, triglycerides, and HDL levels were measured by using a traditional enzymatic assay (Linear Chemicals, Biosystem-Barcelona, Spain). The LDL and VLDL levels were measured indirectly from Friedewald's equation [11].

LDL = Total cholesterol – HDL – (TG/5); VLDL = Triglyceride/5

Estimation of PCSK9 level

The PCSK9 ELISA kit (Elabscience Bio-technology Co., Ltd., USA) based on sandwich enzyme-linked immune-sorbent assay technology was tested and measured in each group.

Statistical analysis

The data was carried out using available statistical package of SPSS-27 (Statistical Package for the Social Sciences version 27), whenever the *P*-value was equal or less than 0.01 and receiver operating characteristic (ROC) curve technique to determine the "cut-off value" which of optimum sensitivity and specificity for diagnosing disease. Area under the curve (AUC) of the ROC was explanted as follows, Perfect (0.9), Good (0.8), Fair (0.7), Poor (0.6), and Failure 0>0.6. The sensitivity and specificity were calculated according to the following equations:

Sensitivity = (True Positive/Total Disease) × 100

Specificity = (True Negative/Total Healthy) × 100

Authorizations and ethical approvals

All authorizations and permissions were obtained before starting work in hospitals including patients' ethical approval for samples and data collection.

Results

BMI value confirmed that toxoplasmosis group were significantly associated with normal weight 27(67.5%), as compared with positive and negative control groups 9(36%), 7(28%) respectively, while overweight was significantly decreased 11(27.5%) in infected group, and 13(52%), 10(40%) in positive and negative control groups respectively, followed by obese was 2(5%) in toxoplasmosis group, and 3(12%), 8(32%) in positive and negative control groups, respectively (Tab. 1).

Positive relations were found between lipid profile values and *T. gondii* infected women as compared with two control groups, except in cholesterol value showed no significant differences of total serum cholesterol 145.90 in toxoplasmosis group, when compared with positive, and negative control groups; 131.84, 147.56 respectively.

Table 1. The relationship between BMI and toxoplasmosis

		Toxoplasmosis group		Positive control		Negative control		*P*-value
BMI (kg/m^2)	Normal (18.5–24.9)	27	67.5	9	36.0	7	28.0	0.002**
	Overweight (25–29.9)	11	27.5	13	52.0	10	40.0	
	Obese (=>30)	2	5.0	3	12.0	8	32.0	
	Mean±SD (Range)	24.5±2.1 (21.2–30.46)		26.5±4.0 (20.9–7.8)		28.89±7.33 (20.96–57.8)		0.002**

** highly significant difference at 0.01 level

Table 2. The lipid profile values of women infected with *Toxoplasma gondii* compared with control groups

	Toxoplasmosis group	Positive control	Negative control	*P*-value
Cholesterol (mg/dl)	145.90±29.83 (100–186)	131.84±29.10 (91–230)	147.56±38.70 (75–222)	0.158
Triglycerides (mg/dl)	149.65±51.34 (103–383)	89.16±29.13 (56–193)	88.44±21.38 (54–135)	0.0001**
HDL (mg/dl)	38.50±16.03 (11–63)	7.48±3.73 (3–20)	7.08±3.34 (2–17)	0.0001**
LDL (mg/dl)	41.70±9.00 (19.6–76.6)	106.53±28.17 (71.4–203.4)	122.79±39.43 (42.4–204.6)	0.0001**
VLDL (mg/dl)	140.53±38.30 (10.8–199.6)	17.83±5.83 (11.2–38.6)	17.69±4.28 (10.8–27.0)	0.0001**

**highly significant difference at 0.01 level

Triglycerides values were significantly increased in toxoplasmosis group 149.65, when compared with positive and negative control groups; 89.16, 88.44 respectively. Regarding the HDL values were significantly increased in toxoplasmosis group 38.50, when compared with positive and negative control groups; 7.48, 7.08 respectively. While in LDL values, there was a significant decrease in toxoplasmosis group 41.70 as compared with positive and negative control groups; 106.53, 122.79 respectively. VLDL values were highly significant increase in toxoplasmosis cases 140.53, when compared with both control groups; 17.83, 17.69 respectively (Tab. 2).

PCSK9 serum level was a highly significant increase 3.23 in toxoplasmosis group as compared with positive and negative control groups; 1.57, 1.15 respectively (Fig. 1).

Regarding the relation between PCSK9 levels and lipid profile values, there was an increasing value with all types of lipids in toxoplasmosis cases when compared with positive and negative control groups, however there were none significantly differences between these values of different study groups (Fig. 2).

The receiver operating characteristic (ROC) analysis that was done to each parameter used in the present study to be a useful tool in evaluating the ability of continuous markers in discriminating between two states of binary out-come such as diseased or not diseased. The resulting ROC curve and its functional area under the curve (AUC), had shown that ELISA IgM still the best tool for diagnosis of toxoplasmosis, and PCSK9 as simple analytical form working parameter for diagnosis of acute toxoplasmosis (Tab. 3 and Fig. 3).

A comparison of each test showed that cut-off value suggested for ELISA IgM is > 0.895 IU/ml

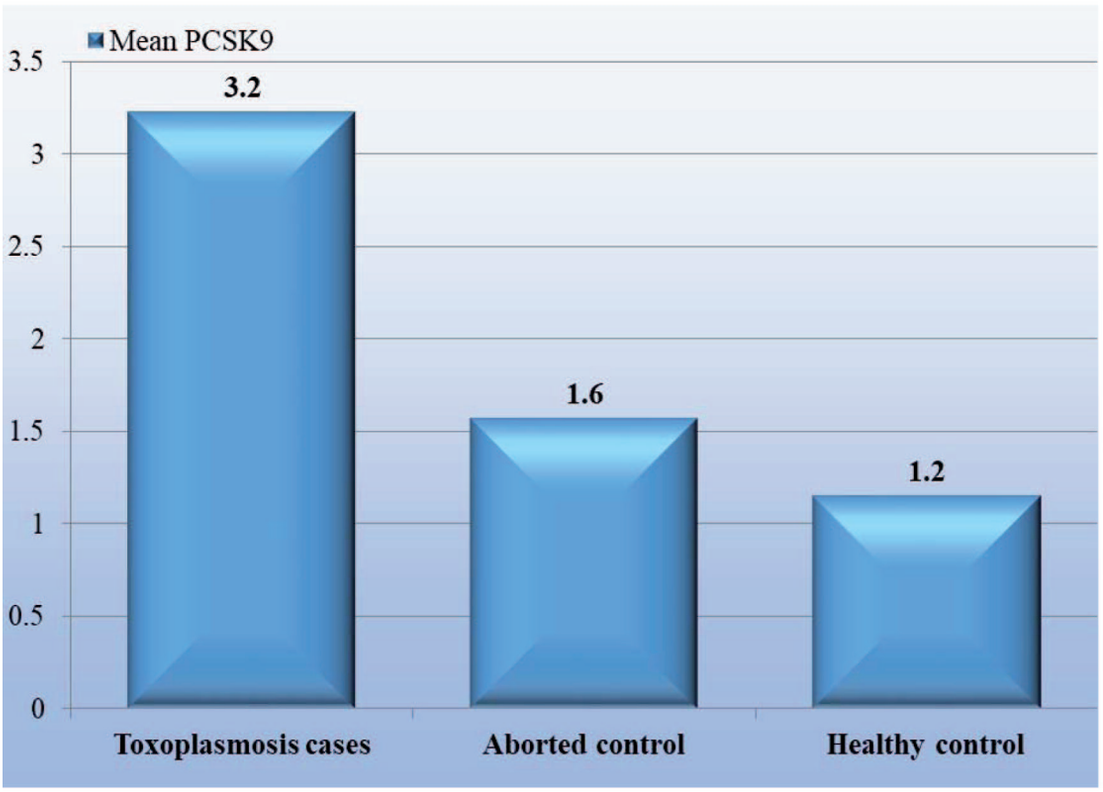

Figure 1. The PCSK9 levels of women infected with *Toxoplasma gondii* compared with control groups

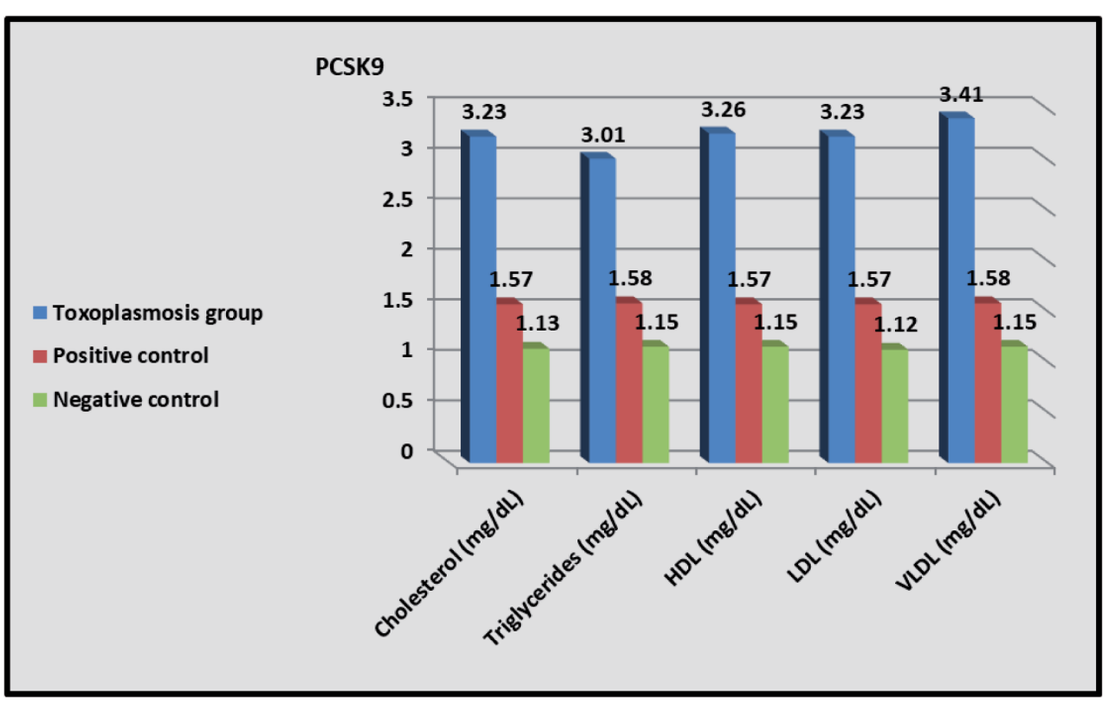

Figure 2. The relation between PCSK9 levels and lipid profile of women infected with *Toxoplasma gondii* compared with control groups

(100% sensitivity and 100% specificity), while for PCSK9 a cut-off value of > 1.713 IU/ml for 100% sensitivity and > 2.537 IU/ml for 100% specificity while the optimal suggested cut-off value is > 1.9995 IU/ml (97.5 sensitivity and 94% specificity) (Tab. 4).

Table 3. The ROC analysis area for selected parameters when used to diagnosis of acute toxoplasmosis as compared with non-toxoplasmosis (both positive and negative control groups)

Test results variables	Area under the curve (AUC)	SE	*P*-value	95% Confidence Interval	
				Lower bound	Upper bound
ELISA IgM	1.000	0.001	0.0001**	1.000	1.000
ELISA IgA	0.566	0.065	0.284	0.440	0.692
PCSK9	0.992	0.006	0.0001**	0.980	1.000

**highly significant difference at 0.01 level

Discussion

This study was conducted to demonstrate the efficacy of toxoplasmosis on blood lipids and PCSK9. There was a highly significant increase in triglycerides, HDL and VLDL values in toxoplasmosis group. These results were compatible with that of Al-Hadraawy et al. [12]. The opposite result was obtained from LDL value in which showed a significant decrease values in toxoplasmosis group as compared with control groups. This result was consistent with Al-Kuraishi et al. [13]. For cholesterol value, it showed no significant differences in toxoplasmosis infected women. This finding was in agreement with studies of both of Kadir in Erbil [14] and Ali and Al-Warid in Baghdad [15]. So, these lipid profile difference results can be explained by the change in blood lipids during acute infection when compared to control due to the dependence of *T. gondii* on host lipid droplet for its intracellular development and the parasite's ability to scavenger neutral lipids from host lipid droplet [16]. The mean

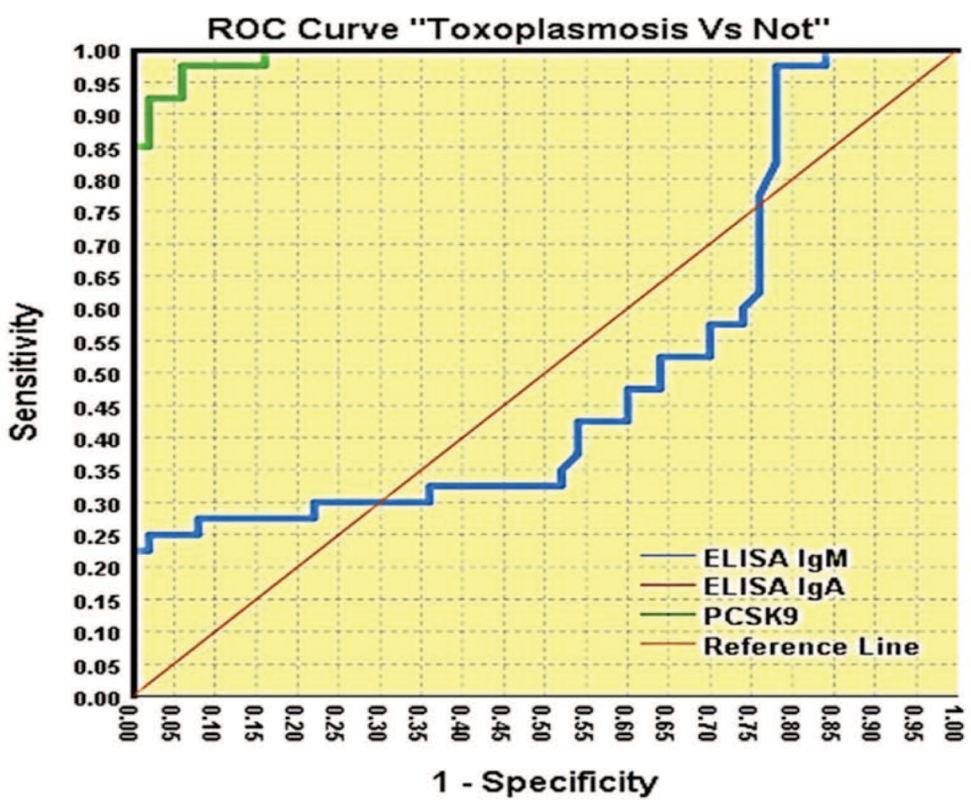

Figure 3. The ROC curve when use to diagnosis of acute toxoplasmosis as compared with non-toxoplasmosis (both positive and negative control groups)

Table 4. The cut-off values, sensitivities, and specificities for early detection of acute toxoplasmosis as compared with non-toxoplasmosis (both positive and negative control groups)

Variables (cut-off values)		Sensitivity (%)	Specificity (%)
ELISA IgM	≥ 0.895	100.0	100.0
ELISA IgA		–	–
PCSK9	≥ 1.713	100.0	84.0
	≥ 1.9995	97.5	94.0
	≥ 2.537	85.0	100.0

of BMI in women with acute toxoplasmosis was significantly associated with normal weight 27(67.5%), as compared with both control groups 9(36%), 7(28%) respectively. These results are consistent with many studies done previously, such as studies done in Germany [17,18], and a study done in Baghdad [19]. They showed a positive relationship between BMI and toxoplasmosis, and the normal or overweight people with positive results of *T. gondii* have a weak chance of gaining weight compared to healthy people. The reverse results were observed by other studies prepared in Nigeria and Mexico [20,21], they found that there is no association between BMI and *T. gondii* infection. These differences in results might be explained, that the serological or molecular evidence is not sufficient to find much relationship.

Regarding the PCSK9, it worth noting that no published studies are comparing the effect of PCSK9 on *T. gondii* infection, and this study may be the first of its type to measure the serum PCSK9 level in women with acute toxoplasmosis, but a previous study (in Italy) showed the beneficial role of PCSK9 in promotes inhibition of pathogens lipids [22]. Other related studies showed high levels of PCSK9 seen in patients with a lower respiratory tract infection and in bacteremia caused by *Streptococcus pneumoniae* [23], and the same results obtained from a study done in San Francisco, which indicated that PCSK9 level is increased in HIV, and hepatitis C infected individuals [24]. These results can be explained as; several investigators have been observed that the proliferation of intracellular pathogen requires an increase in cholesterol uptake during the cells infection [25]. *In vivo* studies were observed that intracellular parasite enhances intracellular cholesterol graft by expressing LDLR on infected cells and thus increases their proliferation [26]. So, to clarify the role of the intracellular parasite in changing the levels of lipids in the body, this can be done through PCSK9 level change. The PCSK9 promotes LDLR degradation and regulation of intracellular and plasma cholesterol [27], thus the present study confirmed the relationship between them through the relative increase of PCSK9 and decrease of LDL level during acute toxoplasmosis.

Concerning the relation between PCSK9 levels and lipid profile values the study recorded an increase in the value of PCSK9 in all types of blood lipids (cholesterol, triglyceride, HDL, LDL, and VLDL) during infection acute with *T. gondii* when a comparison with positive and negative control groups. This result can be explained as PCSK9 has a key role in lipoprotein homeostasis and has a significant effect on cholesterol. PCSK9 increased LDL-C plasma concentrations intakes by connecting to LDLR on liver cells and stimulating degradation, thus increasing LDL-C [28]. This result has been compatible with previous studies [29,30], which showed a positive correlation between PCSK9 on lipid metabolism. Therefore, these present results contributed to the associate between circulating PCSK9 levels and lipid profile values during toxoplasmosis infection, especially the acute form.

In conclusion, positive relations were found between lipid profile values and *T. gondii* infected women as compared with two control groups, except in cholesterol value showed no significant differences of total serum cholesterol. Triglycerides, HDL, VLDL values were significantly increased, while there was a significant decrease in LDL values in acute toxoplasmosis infected women. Also, there was a highly significant increase in PCSK9 in toxoplasmosis infected women, as compared with positive and negative control groups. The measurement of PCSK9 can be used as a biomarker and may be useful in screening for

acute toxoplasmosis. In spite of a highly significant increase in PCSK9 and blood lipids in acute toxoplasmosis, there was a decrease in BMI. This may be due to toxoplasmosis infection.

References

[1] Al-Kuraishi A.H., Al-Windy S.D., Al-Kuraishy H.M., Al-Gareeb A.I. 2020. Endothelial dysfunction in acute acquired toxoplasmosis. *Tropical Parasitology* 10(1): 29–33. doi:10.4103/tp.TP_26_19

[2] Sevgili M., Babür C., Nalbantoğlu S., Karaş G., Vatansever Z. 2005. Determination of seropositivity for *Toxoplasma gondii* in sheep in Şanlıurfa province. *Turkish Journal of Veterinary and Animal Sciences* 29(1): 107–111.

[3] Pereira K.S., Franco R.M.B., Leal D.A.G. 2010. Transmission of toxoplasmosis (*Toxoplasma gondii*) by foods. *Advances in Food and Nutrition Research* 60: 1–19. doi:10.1016/S1043-4526(10)60001-0

[4] Elsheikha H.M. 2008. Congenital toxoplasmosis: priorities for further health promotion action. *Public Health* 122(4): 335–353. doi:10.1016/j.puhe.2007.08.009

[5] Al-Khamesi M.B. 2016. Effect of toxoplasmosis on lipid profile and thyroid hormones in aborted women. *Al-Nahrain Journal of Science* 19(4): 122–126. http://jour.coie-nahrain.edu.iq/index.php/anjs/article/view/189/151

[6] Coppens I., Sinai A.P., Joiner K.A. 2000. *Toxoplasma gondii* exploits host low-density lipoprotein receptor-mediated endocytosis for cholesterol acquisition. *Journal of Cell Biology* 149(1): 167–180. doi:10.1083/jcb.149.1.167

[7] Xu F., Lu X., Cheng R., Zhu Y., Miao S., Huang Q., Xu Y., Qiu L., Zhou Y. 2020. The influence of exposure to *Toxoplasma gondii* on host lipid metabolism. *BMC Infectious Diseases* 20(1): 1–9. doi:10.1186/s12879-020-05138-9

[8] Shapiro M.D., Tavori H., Fazio S. 2018. PCSK9: from basic science discoveries to clinical trials. *Circulation Research* 122(10): 1420–1438. doi:10.1161/circresaha.118.311227

[9] Joseph L., Robinson J.G. 2015. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibition and the future of lipid lowering therapy. *Progress in Cardiovascular Diseases* 58(1): 19–31. doi:10.1016/j.pcad.2015.04.004

[10] Allison C., Colby S., Opoku-Acheampong A., Kidd T., Kattelmann K., Olfert M.D., Zhou W. 2020. Accuracy of self-reported BMI using objective measurement in high school students. *Journal of Nutritional Science* 9: e35. doi:10.1017/jns.2020.28

[11] Palmer M.K., Barter P.J., Lundman P., Nicholls S.J., Toth P.P., Karlson B.W. 2019. Comparing a novel equation for calculating low-density lipoprotein cholesterol with the Friedewald equation: a VOYAGER analysis. *Clinical Biochemistry* 64: 24–29. doi:10.1016/j.clinbiochem.2018.10.011

[12] Al-Hadraawy S.K.A., AL-Hadraawy M.K.A., AL-Shebly F.M. 2015. Study of lipid profile in women infected with *Toxoplasma gondii* in Al-Najaf Governorate, Iraq. *World Journal of Pharmaceutical Research* 4(7): 145–154.

[13] Al-Kuraishi A.H., Hasan H.H., Al-Kateeb S.M. 2013. Lipid profile changes in toxoplasmosis aborted women. *Baghdad Science Journal* 10(1): 168–175. doi:10.21123/bsj.2013.10.1.168-175

[14] Kadir M.A.A. 2013. Biochemical parameters in patients with *Trichomonas vaginalis* and *Toxoplasma gondii* in Erbil-Iraq. *Tikret Journal of Pharmaceutical Sciences* 9(2): 327–337.

[15] Ali H.Z., Al-Warid H.S. 2021. Changes in serum levels of lipid profile parameters and proteins in *Toxoplasma gondii* seropositive patients. *Iraqi Journal of Science* 62(3): 801–810. doi:10.24996/ijs.2021.62.3.11

[16] Nolan S.J., Romano J.D., Coppens I. 2017. Host lipid droplets: an important source of lipids salvaged by the intracellular parasite *Toxoplasma gondii. PLoS Pathogens* 13(6): e1006362. doi:10.1371/journal.ppat.1006362

[17] Reeves G.M., Postolache T.T., Mazaheri S., Snitker S., Langenberg P., Giegling I., Hartmann A., Konte B., Friedl M., Okusaga O. 2013. A positive association between *T. gondii* seropositivity and obesity. *Frontiers in Public Health* 1: article number 73. doi:10.3389/fpubh.2013.00073

[18] Wilking H., Thamm M., Stark K., Aebischer T., Seeber F. 2016. Prevalence, incidence estimations and risk factors of *Toxoplasma gondii* infection in Germany: a representative, cross-sectional, serological study. *Scientific Reports* 6(1): 1–9. doi:10.1038/srep22551

[19] Hassan A.J., Mohammed N.S., Shweash M., Hadeed H.M. 2020. Impact of anti-*Toxoplasma gondii* and adipose hormones with insulin resistant on obese aborted women. *International Journal of Drug Delivery Technology* 10(1): 114–118. doi:10.25258/ijddt.10.1.24

[20] Gyang V.P., Akinwale O.P., Lee Y.L., Chuang T.W., Orok A., Ajibaye O., Liao C.W., Cheng P.C., Chou C.M., Huang Y.C. 2015. *Toxoplasma gondii* infection: seroprevalence and associated risk factors among primary schoolchildren in Lagos City, Southern Nigeria. *Revista da Sociedade Brasileira de Medicina Tropical* 48(1): 56–63. doi:10.1590/0037-8682-0310-2014

[21] Alvarado-Esquivel C., Maldonado-Soto E., Sanchez-Anguiano L.F., Hernandez-Tinoco J., Ramos-Nevarez A., Cerrillo-Soto S.M., Sandoval-Carrilo A.A., Salas-Pacheco J.M., Antuna-Salcido E.I., Estrada-Martinez S. 2017. Lack of serological

and molecular association between *Toxoplasma gondii* exposure and obesity: a case-control study. *International Journal of Biomedical Science* 13(2): article number 74.

[22] Paciullo F., Fallarino F., Bianconi V., Mannarino M.R., Sahebkar A., Pirro M. 2017. PCSK9 at the crossroad of cholesterol metabolism and immune function during infections. *Journal of Cellular Physiology* 232(9): 2330–2338. doi:10.1002/jcp.25767

[23] Rannikko J., Jacome Sanz D., Ortutay Z., Seiskari T., Aittoniemi J., Huttunen R., Syrjänen J., Pesu M. 2019. Reduced plasma PCSK 9 response in patients with bacteraemia is associated with mortality. *Journal of Internal Medicine* 286(5): 553–561. doi:10.1111/joim.12946

[24] Kohli P., Ganz P., Ma Y., Scherzer R., Hur S., Weigel B., Grunfeld C., Deeks S., Wasserman S., Scott R. 2016. HIV and hepatitis C coinfected patients have lower low-density lipoprotein cholesterol despite higher proprotein convertase subtilisin kexin 9 (PCSK 9): an apparent "PCSK 9-lipid paradox". *Journal of the American Heart Association* 5(5): e002683. doi:10.1161/JAHA.115.002683

[25] Allen P.E., Martinez J.J. 2020. Modulation of host lipid pathways by pathogenic intracellular bacteria. *Pathogens* 9(8): article number 614. doi:10.3390/pathogens9080614

[26] Norata G.D., Tavori H., Pirillo A., Fazio S., Catapano A.L. 2016. Biology of proprotein convertase subtilisin kexin 9: beyond low-density lipoprotein cholesterol lowering. *Cardiovascular Research* 112(1): 429–442. doi:10.1093/cvr/cvw194

[27] Deng S., Alabi A., Gu H., Adijiang A., Qin S., Zhang D. 2019. Identification of amino acid residues in the ligand binding repeats of LDL receptor important for PCSK9 binding. *Journal of Lipid Research* 60(3): 516–527. doi:10.1194/jlr.M089193

[28] Spolitu S., Dai W., Zadroga J.A., Ozcan L. 2019. Proprotein convertase subtilisin/kexin type 9 and lipid metabolism. *Current Opinion in Lipidology* 30(3): 186–191. doi:10.1007/978-981-15-6082-8_9

[29] Bae K.H., Kim S.W., Choi Y.K., Seo J.B., Kim N., Kim C.Y., Lee W.K., Lee S., Kim J.G., Lee I.K. 2018. Serum levels of PCSK9 are associated with coronary angiographic severity in patients with acute coronary syndrome. *Diabetes and Metabolism Journal* 42(3): 207–214. doi:10.4093/dmj.2017.0081

[30] Li T., Zhang Y., Cong H. 2021. Effect of PCSK9 inhibitor on lipoprotein particles in patients with acute coronary syndromes. *BMC Cardiovascular Disorders* 21(1): article number 19. doi:10.1186/s12872-020-01827-0

Received 12 August 2021
Accepted 01 October 2021