Atherogenic Index of Plasma is Associated with the Severity of Hidradenitis Suppurativa: A Case Control Study

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Research

Keywords: Hidradenitis suppurativa, atherogenic indexes, atherogenic index of plasma, lipids

Posted Date: July 16th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-41796/v1

Version of Record: A version of this preprint was published on August 29th, 2020. See the published version at https://doi.org/10.1186/s12944-020-01377-6.

Abstract

Background. Hidradenitis suppurativa (HS) is a chronic inflammatory disease associated with several comorbidities and vascular risk factors, such as dyslipidemia. The aim of the present study was to assess the possible associations between the lipid profile and atherogenic indexes and the severity of HS.

Methods. This case-control study enrolled 78 HS patients and 62 healthy controls. Classic lipid profile and lipoprotein ratios, including the atherogenic index of plasma (AIP) (log_{10}[triglycerides/HDL-c]) were evaluated. Severity of HS was measured by the HS Physician Global Assessment (PGA).

Results. HS-patients had lower serum total cholesterol and HDL-c levels and higher AIP than the control group. AIP was positively correlated to BMI, waist perimeter, systolic and diastolic blood pressure, LDL-c, triglycerides, non-HDL-C, ApoB, HOMA and hs-CRP and negatively to HDL-c and ApoA1. For the overall lipid profile, only AIP was related to a more severe HS (PGA≥3) after controlling for age, sex, BMI, insulin resistance (IR), active smoking and statin use (r=0.268; p=0.023). Multivariable logistic regression adjusted for age, sex, BMI, IR, smoking status and statin use, showed that AIP≥0.5 was significantly associated with the severity of HS (OR, 4.38; CI 95%, 1.09-17.50; p=0.037).

Conclusions. In conclusion, our results showed that AIP was significantly and independently associated with HS severity.

Background

Hidradenitis suppurativa (HS) is a recurrent chronic inflammatory disease presenting with painful, suppurating lesions in the apocrine gland–bearing skin areas. Its estimated prevalence varies from 0.05–4.10% across series and it is associated with severe impairment of quality of life [1]. HS has been linked to several comorbidities and metabolic conditions such as insulin resistance (IR), metabolic syndrome and type 2 diabetes mellitus (T2DM) [2–4]. Besides, HS patients have an increased prevalence of subclinical atherosclerosis and a significant risk of major adverse cardiovascular (CV) morbimortality [5–7].

Although the pathogenesis of HS is not fully understood, genetic, environmental, hormonal and lifestyle factors have been implicated [8]. Moreover, during the course of the disease, increased expression of interleukin (IL)-1β, IL-10, IL-17, interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) appear in skin lesions, as well as increased levels of IL-17 in the serum of HS patients [9]. Atherogenic dyslipidemia, i.e. the combined occurrence of high fasting blood concentrations of triglycerides (TG) and low levels of high-density lipoprotein cholesterol (HDL-c), is frequent in patients with HS [10]. Nevertheless, data on the relationship between the values of nontraditional lipid profiles (lipoprotein ratios), including non-HDL-c, TC/HDL-c, LDL-c/HDL-c, non-HDL-c/HDL-c (atherogenic index, AI), log10 (TG/HDL-c) (atherogenic index of plasma, AIP) and ApoB/ApoA-1 ratio, and the severity of HS are lacking. Compared with single lipid parameters, these comprehensive lipid indexes, are considered to be better predictors for coronary artery disease [11,12], mainly the AIP [13–15]. AIP has a good correlation

with smaller LDL-c particles and increased fractional esterification rate for cholesterol in plasma, and it is a strong and independent predictor factor for coronary disease [16–18]. Noteworthy, AIP has also been associated with raised serum C-reactive protein levels, suggesting a lipid-driven immune-inflammatory link [19].

Taking into account the above considerations, we aimed to assess the possible associations between the lipid profile and atherogenic indexes and the severity of HS.

Methods

In this cross-sectional case-control study, we included 78 patients with HS and 62 age- and gender-similar controls. HS-patients were recruited from the outpatient Dermatology clinic of our hospital. The control group was set up with hospital medical staff and subjects who attended the Dermatology Division due to skin disorders other than HS, such as melanocytic nevus, warts or epithelioma. The research protocol was approved by the local Ethics Committee and all study procedures were done under the ethical principles of the Declaration of Helsinki. All the participants provided written informed consent.

For the present study, exclusion criteria were as follows: age < 18 years, documented history of major adverse cardiovascular events, chronic kidney or liver diseases, and the presence of concomitant inflammatory cutaneous or systemic disorders.

Information about HS duration was collected in all the patients. The HS Physician Global Assessment (HS-PGA) and the Hurley scale were used to assessing the severity of HS. Thus, HS was classified as moderate-severe-very severe (PGA ≥ 3) and as minimal-mild HS (PGA < 3) according to HS-PGA [2].

The following variables were collected in all the participants: demographic features, past medical history, current and prior systemic therapy, traditional CV risk factors (defined as previously reported) [2], weight, height, body mass index (BMI), waist circumference (WC), systolic blood pressure (BP) and diastolic BP. Metabolic syndrome was diagnosed according to the criteria proposed by the National Cholesterol Education Program's Adult Treatment Panel III (ATP III) [20].

Blood samples were drawn after an overnight fast, and serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), Apolipoprotein B100 (ApoB), Apolipoprotein A1 (ApoA1) and lipoprotein (a) (Lpa) were analyzed, as well as the following atherogenic indexes: TC/HDL-c; LDL-c/HDL-c; non-HDL-c/HDL-c; ApoB/ApoA1, and AIP (log10 [TG/HDL-c]). Moreover, the homeostatic model assessment for IR (HOMA-IR) was calculated as fasting insulin level (μIU/ml) x fasting glucose level (mg/dl)/405. A value greater than 2.5 was consistent with IR [2]. We have also considered a cut-off point for AIP ≥ 0.50 for both sexes based on previously published data [16,21].

Results were expressed as numbers (percentage), mean ± standard deviation (SD) or median and interquartile range (IQR), as appropriate. Student's T-test or Mann-Whitney U-test was used to compare

quantitative variables and Chi-squared or Fisher test, to compare qualitative data, as appropriate. The Spearman correlations coefficients were calculated to assess the relationship between AIP and demographic and laboratory parameters in cases and controls. The patients were divided into two groups according to disease severity based on the PGA score (< 3 and ≥ 3). To analyze the potential association between AIP and HS severity, forward stepwise multivariable logistic regression models adjusted for confounder variables were built. The strength of the association between the study parameters and HS severity was evaluated via the odds ratio (OR) and corresponding 95% confidence interval (CI). A p-value < 0.05 was considered significant in all the calculations.

Results

The mean age of HS patients and controls was 43 ± 12 years and 46 ± 13, respectively (p = 0.16). Nearly half of the patients and controls were male. Thirteen HS patients and 12 controls were on statins at baseline (p = 0.68). One patient and 4 controls were taking ezetimibe (p = 0.16), and 2 HS patients were on fenofibrate (p = 0.16). There were no differences regarding the dose of statin between patients and controls (p = 0.83).

Patients with HS had significantly higher weight (82.4 ± 17.8 vs. 76.4 ± 16.9 Kg; p = 0.001), BMI (29.4 ± 5.4 vs. 26.5 ± 4.5 Kg/m2; p = 0.001), waist perimeter (99.6 ± 14 vs. 91.4 ± 14 cm: p = 0.001), systolic blood pressure (132.6 ± 16.4 vs. 124.2 ± 15.8 mmHg; p = 0.003), diastolic blood pressure (82.0 ± 13.8 vs. 76.9 ± 8.3 mmHg; p = 0.012), HOMA-IR values (2.15 [1.00-3.73] vs. 1.48 [0.89–2.28]: p = 0.005), high-sensitive C-reactive protein –hs-CRP- (0.42 [0.17–0.89] vs. 0.10 [0.10–0.20]; p < 0.0001) and prevalence of smoking (65.4% vs. 19.4%; p < 0.0001), IR (46.2 vs. 19.4; p = 0.001) and metabolic syndrome (32.7 vs. 11.9; p = 0.004), than controls. Moreover, HS-patients had lower serum total cholesterol and HDL-c levels and higher AIP than the control group (Table 1).

Table 1
Lipid profile and atherogenic indexes in HS patients and controls.

Parameter	HS patients (n = 78)	Controls (n = 62)	p
Total cholesterol, *mg/dl*	186.4 ± 33.6	202.7 ± 44.7	**0.015**
LDL-c, *mg/dl*	116.6 ± 32.4	122.4 ± 29.2	0.28
HDL-c, *mg/dl*	46.0 (41.0-56.3)	52.5 (46.8–69.5)	**0.001**
Triglycerides, *mg/dl*	87.5 (68.8-117.3)	74.0 (57.8-121.5)	0.23
Non-HDL cholesterol, *mg/dl*	138.5 (115.0-155.3)	136.5 (118.3-160.3)	0.45
ApoA1, *mg/dl*	146.0 (127.0-167.0)	151.0 (134.0-173.0)	0.12
ApoB, *mg/dl*	98.0 (79.5-112.3)	90.0 (77.8-104.3)	0.28
Lpa, *mg/dl*	15.0 (7.6–27.5)	15.5 (6.0–36.0)	0.83
Total cholesterol / HDL-c	4.09 (3.09–4.76)	3.51 (2.83–4.40)	0.06
LDL-c / HDL-c	2.49 (1.85–3.12)	2.19 (1.69–3.02)	0.09
Non-HDL-c / HDL-c	3.09 (2.09–3.76)	2.51 (1.83–3.40)	0.06
LDL-c / ApoB	1.22 (1.09–1.29)	1.35 (12.5–1.45)	**< 0.0001**
ApoB / ApoA1	0.65 (0.51–0.82)	0.60 (0.47–0.70)	0.09
AIP [$\log_{10}$ (TG/HDL-c)]	0.29 (0.12–0.41)	0.14 (-0.05-0.38)	**0.016**

BMI: body mass index; LDL-c: low-density lipoprotein; HDL-c: high-density lipoprotein; Lpa: lipoprotein (a); AIP: atherogenic index of plasma. Values are expressed as mean ± SD or median (interquartile range) as appropriate.

The correlations between AIP and several anthropometric and laboratory parameters, in cases and controls, are shown in Table 2. Noteworthy, AIP is significantly and positively related to BMI and waist perimeter, systolic and diastolic blood pressure and several lipid parameters, but also to HOMA and hs-CRP. Correlations were negative, as expected, with serum HDL-c and ApoA1 levels.

Table 2
Bivariate correlations coefficients of AIP and some demographic and laboratory variables in HS patients and controls.

	HS patients (n = 78)		**Controls (n = 62)**	
	r	p	r	p
Age, *years*	0.233	**0.049**	0.210	0.10
BMI, *Kg/m²*	0.352	**0.002**	0.332	**0.008**
Waist perimeter, *cm*	0.399	**< 0.0001**	0.349	**< 0.0001**
Systolic BP, *mmHg*	0.231	**0.042**	0.277	**0.03**
Diastolic BP, *mmHg*	0.230	**0.042**	0.304	**0.016**
Total cholesterol, *mg/dl*	0.035	0.76	0.187	0.15
LDL-c, *mg/dl*	0.136	0.24	0.266	**0.038**
HDL-c, *mg/dl*	-0.655	**< 0.0001**	-0.709	**< 0.0001**
Triglycerides, *mg/dl*	0.884	**< 0.0001**	0.912	**< 0.0001**
Non-HDL cholesterol, *mg/dl*	0.380	**0.001**	0.554	**< 0.0001**
ApoA1, *mg/dl*	-0.408	**< 0.0001**	-0.499	**< 0.0001**
ApoB, *mg/dl*	0.331	**0.003**	0.587	**< 0.0001**
Lpa, *mg/dl*	-0.080	0.48	-0.141	0.27
Fasting glucose, *mg/dl*	0.258	**0.023**	0.128	0.32
hs-CRP, *mg/dl*	0.343	**0.002**	0.362	**0.004**
HbA1c, *%*	0.375	**0.001**	0.181	0.16
HOMA index	0.551	**< 0.0001**	0.400	**0.001**
Insulin, *mIU/L*	0.491	**< 0.0001**	0.370	**0.003**

BMI: body mass index; BP: blood pressure; LDL-c: low-density lipoprotein; HDL-c: high-density lipoprotein; Lpa: lipoprotein (a); AIP: atherogenic index of plasma. Hs-CRP: high-sensitive C reactive protein. HOMA: homeostatic model assessment. Values are expressed as mean ± SD or median (interquartile range) as appropriate.

For the overall lipid profile analyzed, only AIP (r = 0.316; p = 0.005) was related to a more severe HS (PGA ≥ 3). After controlling for age, sex, BMI, IR, statin use and active smoking this relationship persisted significant (r = 0.268; p = 0.023). No relationship between AIP and duration of HS was found. Table 3 shows the significant variables in HS patients according to the PGA score.

Table 3. Significant variables in HS patients according to the PGA score.

Parameter	PGA < 3 (n=32)	PGA ≥3 (n=46)	p
Age, *years*	39.1 ± 11.6	45.1 ± 11.2	**0.023**
BMI, *Kg/m2*	28.0 ± 5.5	30.4 ± 5.2	**0.043**
Duration of HS, *months*	13.5 (5.3-22.5)	19.0 (9.8-27.3)	**0.039**
Triglycerides, *mg/dl*	71.0 (53.0-103.5)	93.0 (75.5-143.3)	**0.003**
AIP [$\log_{10}$ (TG/HDL-c)]	0.17 (-0.07-0.38)	0.32 (0.19-0.54)	**0.006**
hs-CRP, *mg/dl*	0.23 (0.12-0.58)	0.57 (0.31-1.06)	**0.003**
Fibrinogen, *mg/dl*	281.0 (264.5-324.3)	338.0 (289.0-392.8)	**0.007**

BMI: body mass index; LDL-c: low-density lipoprotein; HDL-c: high-density lipoprotein; Lpa: lipoprotein (a); hs-CRP: high-sensitive C reactive protein. AIP: atherogenic index of plasma. Values are expressed as mean ± SD or median (interquartile range) as appropriate.

The results of multivariable logistic regression analysis of the parameters with potential association with HS severity, adjusted for age, sex, BMI, IR, smoking status and statin use are shown in Table 4. Further adjustment for the duration of HS, hypertension, serum fibrinogen levels, and hs-CRP did not change these results. The exclusion of participants on statins (HS-patients and controls) yielded virtually identical results.

Table 4. Adjusted multivariable analysis showing the best set of factors associated with HS severity.

	b-coefficient	OR (CI 95%)	p
Age, *years*	0.050	1.05 (1.005-1.10)	0.03
AIP ≥ 0.50	1.476	4.38 (1.09-17.50)	0.037
AIP: atherogenic index of plasma			

Discussion

Lipids are biological compounds that play multiple roles in human disease. Thus, neutral lipids, such as TG are critical in energy storage and have been involved in the pathogenesis of cardiovascular diseases, metabolic syndrome and T2DM [22]. Lipid signaling pathways in patients with HS are poorly understood as well as the cellular mechanisms of lipid-mediated HS-induced pathogenesis. Gene expression of certain sphingolipids such as ceramide and sphingosine-1, that act as biologically active signaling molecules, have been implicated in the pathogenesis of the disease [23]. In a recent report, Fincher et al. [24], showed an increased localized accumulation of neutral lipids in HS-infected tissue as a result of a

great bacterial load in these lesions. Moreover, recurrence of the disease has been linked to the development of dermic and subcutaneous sinus tracts, and lipids rafts in plasma membranes of keratinocytes also play a role in the regulation of metabolic and proliferative activity of these cells in HS patients [25]. Local steroidogenic activities in the skin have been implicated in the regulation of immune responses at local or systemic levels, and impaired of this cutaneous steroidogenesis has been linked to inflammatory skin disorders [26].

In clinical studies, HS patients often have higher serum TG and lower HDL-c levels than controls. Our study confirms a significant decrease of HDL-c in patients with HS compared with healthy controls. In this sense, Tsaousi et al. [27], found that matrix metalloproteinase 8, a collagen cleaving enzyme involved in the breakdown of extracellular matrix in normal and pathological processes, and in the degradation of ApoA1, a component of HDL particles, is one of the most highly upregulated molecules in HS lesions.

More recently, the AIP value, a logarithmically transformed ratio of molar concentrations of TG to HDL-cholesterol, has been reported as a good marker for the risk of atherosclerosis and cardiovascular disease [28]. AIP is an easily calculated parameter from the standard lipid profile that adds predictive value beyond that of the individual lipids and/or TC/HDL-c ratio. Furthermore, it is considered a subrogate of small LDL-c particle size distribution, with better correlation than LDL-c/ApoB ratio [29]. AIP provides additional information in predicting short and long term outcomes in patients with acute coronary syndrome but also it may be an independent factor for the risk of type 2 diabetes mellitus and metabolic syndrome [30,31].

Interestingly, in our HS patients (even after excluding the few participants on lipid-lowering agents) serum LDL-c, the traditional marker of the atherosclerotic burden, was similar to controls. Nevertheless, AIP was higher in patients with HS than controls. In this sense, since HS is associated with high cardiovascular morbidity, AIP could be used as a good predictor of cardiovascular risk in these patients even in the presence of a normal lipid profile. Further studies on this matter would be interesting to perform.

We found AIP to be related to BMI, waist perimeter, blood pressure, lipid parameters, hs-CRP, and insulin resistance. Nevertheless, in the present study, we have shown that AIP is an independent factor for the risk of a more severe HS, measured by the PGA. Besides, this association seems to be independent of hs-CRP, a well-known marker of inflammation. Besides, a cut-off point of 0.5 for this index has demonstrated to have a 4-fold increased risk for a PGA score ≥ 3. This index could be useful not only to detect patients at high risk for metabolic (obesity, diabetes or metabolic syndrome) or cardiovascular complications (high blood pressure, cardiovascular events) but also to alert the clinician to the presence of a more severe HS.

Our study has the inherent limitations of a case-control study regarding causality. Besides, as an observational study, it may be subject to some bias due to the possible existence of confounders. However, we have adjusted for multiple potential confounding factors, to try to avoid this issue.

Conclusions

In conclusion, we found that AIP was significantly and independently associated with a more severe HS, Further large prospective studies are needed to confirm these results and explore the underlying mechanisms of the lipid-mediated HS-induced pathogenesis.

List Of Abbreviations

AIP = Aterogenic Index of Plasma

ApoA1 = Apolipoprotein A1

ApoB = Apolipoprotein B100

ATP III = Adult Treatment Panel III

BMI = Body Mass Index

BP = Blood Pressure

CI = Confidence Interval

CV = Cardiovascular

HDL-c = High-density Lipoprotein Cholesterol

HOMA = homeostatic model assessment

HS = Hidradenitis Suppurativa

Hs-CRP = High-sensitive C Reaction Protein

IFN-γ = Interferon-gamma

IQR = Interquartile Range

IR = Insulin Resistance

LDL-c = Low-density Lipoprotein Cholesterol

Lpa = Lipoprotein (a)

OR = Odds Ratio

PGA = Physitian Global Assessment

SD = Standard Deviation

T2DM = Type 2 Diabetes Mellitus

TC = Total Cholesterol

TG = Triglycerides

TNF-α = Tumor Necrosis Factor-alpha

WC = Waist Circumference

Declarations

Ethics approval and consent to participate.

This study was approved by the Comité de Ética de Investigación Clínica (CEIC) in Cantabria, with the code 2013.267 on the 10th of February 2014.

Consent for publication.

N/A.

Availability of data and materials.

The datasets generated and/or analyzed during the current study are not publicly available due to protection of patients' identity, but are available from the corresponding author on reasonable request.

Competing interests.

Dr. Hernandez reports grants and personal fees from Amgen, and personal fees from MSD and Bayer. Dr. R. Blanco received grants/research supports from Abbvie, MSD and Roche, and had consultation fees/participation in company sponsored speaker's bureau from Abbvie, Pfizer, Roche, Bristol Myers, Janssen and MSD. Dr. González-López had consultation fees/participation in company sponsored speaker's bureau from Abbvie. The rest of the authors have not conflict of interest to declare.

Funding.

None.

Author's contributions.

José L. Hernández performed the study, contributed to the elaboration of the protocol of study, helped in the interpretation of the data and was responsible of the final drafting and elaboration of the manuscript. Cristina Baldeón performed the study, helped in the interpretation of data and in the elaboration of the manuscript. Ana E. López-Sundh, Gonzalo Ocejo-Vinyals and Ricardo Blanco helped in the interpretation of data and in the elaboration of the manuscript. Marcos A. González-López recruited patients for the

study, contributed to the elaboration of the protocol of study, performed the study, helped in the interpretation of data and was responsible of the final drafting and elaboration of the manuscript.

References

1. Zouboulis CC, Desai N, Emtestam L, Hunger RE, Ioannides D, Juhász I, et al. European S1 guideline for the treatment of hidradenitis suppurativa/acne inversa. J Eur Acad Dermatol Venereol. 2015; 29: 619-644.
2. Vilanova I, Hernández JL, Mata C, Duran C, García-Unzueta MT, Portilla V, et al. Insulin resistance in hidradenitis suppurativa: a case-control study. J Eur Acad Dermatol Venereol. 2018; 32:820-824.
3. Ergun T. Hidradenitis suppurativa and the metabolic syndrome. Clin Dermatol. 2018;36:41-47.
4. Phan K, Charlton O, Smith SD. Hidradenitis suppurativa and diabetes mellitus: updated systematic review and adjusted meta-analysis. Clin Exp Dermatol. 2019; 44:e126–e132.
5. González-López MA, Hernández JL, Lacalle M, Mata C, López-Escobar M, López-Mejías R, et al. Increased prevalence of subclinical atherosclerosis in patients with hidradenitis suppurativa. J Am Acad Dermatol. 2016;75:329–335.
6. Egeberg A, Gislason GH, Hansen PR. Risk of major adverse cardiovascular events and all-cause mortality in patients with hidradenitis suppurativa. JAMA Dermatol. 2016;152:429–434
7. Gremese E, Tolusso B, Gigante MR, Ferraccioli G. Obesity as a risk and severity factor in rheumatic diseases (autoimmune chronic inflammatory diseases). Front Immunol. 2014;11:576.
8. Negus D, Ahn C, Huang W. An update on the pathogenesis of hidradenitis suppurativa: implications for therapy. Expert Rev Clin Immunol. 2018;14:275-283.
9. Vossen ARJV, van der Zee HH, Prens EP. Hidradenitis Suppurativa: A Systematic Review Integrating Inflammatory Pathways Into a Cohesive Pathogenic Model. Front Immunol. 2018 14;9:2965.
10. Tzellos T, Zouboulis CC, Gulliver W, Cohen AD, Wolkenstein P, Jemec GBE. Cardiovascular disease risk factors in patients with hidradenitis suppurativa: a systematic review and meta-analysis of observational studies. Br J Dermatol. 2015;173:1142-1155.
11. Gao M, Zheng Y, Zhang W, Cheng Y, Wang L, Qin L. Non-high-density lipoprotein cholesterol predicts nonfatal recurrent myocardial infarction in patients with ST-segment elevation myocardial infarction. Lipids Health Dis. 2017;16:20.
12. Zhu L, Lu Z, Zhu L, Ouyang X, Yang Y, He W, et al. Lipoprotein ratios are better than conventional lipid parameters in predicting coronary heart disease in Chinese Han people. Kardiol Pol. 2015;73:931–938.
13. Niroumand S, Khajedaluee M, Khadem-Rezaiyan M, Abrishami M, Juya M, Khodaee G, et al. Atherogenic index of plasma (AIP): a marker of cardiovascular disease. Med J Islam Repub Iran. 2015;29:240.
14. Onat A, Can G, Kaya H, Hergenç G. Atherogenic index of plasma" (log10triglyceride/high-density lipoprotein cholesterol) predicts high blood pressure, diabetes, and vascular events. J Clin Lipidol.

2010;4:89–98.

15. Zhan Y, Xu T, Tan X. Two parameters reflect lipid-driven inflammatory state in acute coronary syndrome: atherogenic index of plasma, neutrophil-lymphocyte ratio. BMC Cardiovasc Disord. 2016;16:96.
16. Dobiasova M, Frohlich J. The plasma parameter log (TG/HDL-C) as an atherogenic index: correlation with lipoprotein particle size and esterification rate in apoB-lipoprotein-depleted plasma (FER(HDL)) Clin Biochem. 2001;34:583–588.
17. Frohlich J, Dobiasova M. Fractional esterification rate of cholesterol and ratio of triglycerides to HDL-cholesterol are powerful predictors of positive findings on coronary angiography. Clin Chem. 2003;49:1873–1880.
18. Cai G, Shi G, Xue S, Lu W. The atherogenic index of plasma is a strong and independent predictor for coronary artery disease in the Chinese Han population. Medicine (Baltimore). 2017;96:e8058.
19. Falk E, Nakano M, Bentzon JF, Finn AV, Virmani R. Update on acute coronary syndromes: the pathologists' view. Eur Heart J. 2013;34:719–728.
20. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) Final report (2002). Circulation. 2002;106:3143–3421.
21. Millán J, Pintó X, Muñoz A, Zúñiga M, Rubiés-Prat J, Pallardo LF, et al. Lipoprotein ratios: Physiological significance and clinical usefulness in cardiovascular prevention. Vasc Health Risk Manag. 2009;5:757-765.
22. Hannun YA, Obeid LM. Principles of bioactive lipid signalling: lessons from sphingolipids. Nature Reviews Molecular Cell Biology. 2008;9:139–150.
23. Dany M, Elston D. Gene expression of sphingolipid metabolism pathways is altered in hidradenitis suppurativa. J Am Acad Dermatol. 2017;77:268-273.
24. Fincher JA, Jones DR, Korte AR, Dyer JE, Parlanti P, Popratiloff A, et al. Mass Spectrometry Imaging of Lipids in Human Skin Disease Model Hidradenitis Suppurativa by Laser Desorption Ionization from Silicon Nanopost Arrays. Sci Rep. 2019;9:17508.
25. Gniadecki R, Jemec GB. Lipid raft-enriched stem cell-like keratinocytes in the epidermis, hair follicles and sinus tracts in hidradenitis suppurativa. Exp Dermatol. 2004;13:361-363.
26. Slominski A, Zbytek B, Nikolakis G, Manna PR, Skobowiat C, Zmijewski M, et al. Steroidogenesis in the skin: implications for local immune functions. J Steroid Biochem Mol Biol. 2013;137:107-123.
27. Tsaousi A, Witte E, Witte K, Röwert-Huber HS, Volk HD, Sterry W, et al. MMP8 Is Increased in Lesions and Blood of Acne Inversa Patients: A Potential Link to Skin Destruction and Metabolic Alterations. Mediators Inflamm. 2016;2016:4097574.
28. Dobiásová M, Frohlich J, Sedová M, Cheung MC, Brown BG. Cholesterol esterification and atherogenic index of plasma correlate with lipoprotein size and findings on coronary angiography. J

Lipid Res. 2011;52:566-571.

29. Furuya D, Yagihashi A, Nasu S, Endoh T, Nakamura T, Kaneko R, et al. LDL particle size by gradient-gel electrophoresis cannot be estimated by LDL-cholesterol/apolipoprotein B ratios. Clin Chem. 2000;46(8 Pt 1):1202-1203.
30. Zhu XW, Deng FY, Lei SF. Meta-analysis of Atherogenic Index of Plasma and other lipid parameters in relation to risk of type 2 diabetes mellitus. Prim Care Diabetes. 2015;9:60-67.
31. Zhang X, Zhang X, Li X, Feng J, Chen X. Association of metabolic syndrome with atherogenic index of plasma in an urban Chinese population: A 15-year prospective study. Nutr Metab Cardiovasc Dis. 2019;29:1214-1219.