Acta Pharm. Sci. Vol 62:(3), 2024
Research article
DOI: 10.23893/1307-2080.APS6243

Predictive value of lipid profile in predicting the resistance to insulin in apparently healthy adults

Sara Haider KHALID[1*], Zainab Hassan HASHIM[1], Qasim Sharhan AL-MAYAH[2], Hisham AL-MATUBSI[3]

1 Al-Nahrain University, College of Pharmacy, Department of Pharmacology and Toxicology, Baghdad, Iraq
2 Al-Nahrain University, College of Medicine, Medical Research Unit, Baghdad, Iraq
3 University of Petra, Faculty of Pharmacy and Medical Sciences, Department of Pharmacology and Medical Science, Amman, Jordan

ABSTRACT

Insulin resistance (IR) progression can lead to the development of metabolic syndrome and type 2 diabetes mellitus. Objective of the current work was to elucidate how useful lipid profile components were in predicting IR in healthy individuals in cross-sectional study conducted on 100 euglycemic, non-diabetic adults (aged ≥ 45 years). All individuals had their triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), very low-density lipoprotein (VLDL), cholesterol, fasting blood sugar (FBS), fasting insulin and glycosylated hemoglobin (HbA1c) levels tested. The predictive values of lipid profile components separately or as ratios, as well as two obesity-related indicators: lipid accumulation products and visceral adiposity index, were evaluated in relation to the HOMA-IR using the receiver operating characteristic (ROC) curve. Results revealed that thirty (30%) of 100 apparently healthy subjects developed IR. The triglycerides/high density lipoprotein (TG/HDL) ratio had the best predictive value with an area under the curve (AUC) of 0.728, 95% CI = 0.617-0.838, $p<0.001$. The test had 77% sensitivity and 67% specificity, respectively. The optimal TG/HDL ratio cutoff value was 2.96, suggesting that

*Corresponding author: Sara Haider KHALID
E-mail: sarahaydeer@gmail.com
ORCIDs:
Sara Haider KHALID: 0009-0008-1367-8511
Zainab Hassan HASHIM: 0000-0001-7908-0661
Qasim Sharhan AL-MAYAH: 0000-0002-3883-5295
Hisham AL-MATUBSI: 0000-0002-3591-9434
(Received 20 Oct 2023, Accepted 11 Dec 2023)

among healthy adults, the TG/HDL ratio might be utilized as a routine screening test to detect IR.

Keywords: insulin resistance, lipid profile, homeostasis model assessment, healthy adults

INTRODUCTION

Insulin resistance (IR) refers to a diminished ability of target tissues, such as adipose tissue, muscle, and liver, to respond effectively to insulin stimulation. It causes a reduction in the ability of the body to handle glucose, that lead to an induction of insulin production from β-cell to compensate and hyperinsulinemia[1]. Hypertension, visceral obesity, endothelial dysfunction, dyslipidemia, elevated inflammatory markers, Hyperglycemia, and a prothrombotic state are among the metabolic consequences of IR[2]. However, the primary consequence of IR is the development of T2DM, with IR often preceding it by 10 to 15 years[3].

A large amount of data points to the possibility that IR may be linked to the buildup of fatty acid metabolites, or diacylglycerols, in many organs, most notably the skeletal muscles. Conversely, protecting against IR & preventing lipid buildup in muscles is achieved by blocking lipid entry into muscle through the elimination of lipoprotein lipase or other proteins involved in fat transport[4].

The homeostasis model assessment of insulin resistance (HOMA-IR) is now considered the most reliable method for quantifying IR. HOMA-IR was used to quantify IR and β-cell function based on insulin (or C-peptide) and fasting glucose levels[5]. The HOMA-IR model has proved to be a robust clinical and epidemiological tool for the assessment of IR. However, this approach is difficult to apply clinically, primarily due to cost, accessibility, and replicability issues[6]. Therefore, it is of paramount importance to find a practical alternative. Many attempts have been made to find a simple, non-expensive, and feasible alternative for this model. Triglyceride-glucose (TG/Glu) ratios, TG/HDL ratios, triglyceride-glucose indexes, McAuley's indexes, fasting glucose to insulin ratios (FG-I Ratio), and fasting C-peptide indexes are some of the alternatives, with sometimes controversial findings[7,8].

The objective of the current work was to assess the predictive value of lipid profile components and two lipid-rated parameters, visceral adiposity index (VAI) and lipid accumulation products (LAP), in predicting IR in healthy Iraqi adults.

METHODOLOGY

The study population

A cross-sectional study was conducted at Al Nahrain university/ college of medicine, Al Bayan University and Al-Mustafa University College, Baghdad, Iraq from May 2022 to March 2023. The study included 100 apparently healthy adult subjects of both sexes. Subjects enrolled in the study, are euglycemic, non-diabetic adults, ≥45 years old with HbA1C < 5.7%. The exclusion criteria of the volunteers who subjected to the current study are as the following:

- Subjects with diabetes
- Subjects with other severe chronic diseases, such as renal and cardiac diseases,
- Subjects who administered medications that may affect lipid metabolism or IR (such as anti-hyperlipidemic drugs corticosteroids,
- pregnant and breast-feeding women.

Demographic information was obtained from all subjects by direct interview which include age, sex, family history of diabetes, smoking status, and place of residence. All participants also had their body weight (kg), height (m), body mass index (BMI), waist circumference (WC), hip circumference (HC), and waist-hip ratio (WHR) assessed.

Sample collection and laboratory investigations

Fasting participants for eight hours before the collection of blood samples were subjected to the current research. On the next morning, five milliliter of blood was collected from the vein of the subject. FBS, HbA1c, a lipid profile the include the levels of VLDL, LDL, HDL, TC, TG, and fasting insulin were measured using a ready to-use commercial kit for each one (Inear Chemicals/ Spain). Also, HOMA-IR was calculated by multiplying FBS by fasting insulin divided by 405. According to a previous study,[7] the cutoff value of HOMA-IR was determined to be 3.1, beyond which subjects were considered to have IR. LAP and VAI were calculated for all participants according to the following formula[9].

"LAP = [waist circumference (cm) - 58] × triglycerides (mmol/l)."

"VAI = (WC (cm)/(39,68+(1.88*BMI) *(TG/1.03)*(1.31/HDL) for men" and

"VAI = (WC (cm)/(36,58+(BMI *1.89) *(TG/0.81)*(1.52/ HDL) for women."

Statistical analysis

All statistical analysis were performed by The SPSS software, version 25.0 (SPSS, Chicago). The mean and standard deviation of non-numerical data were displayed, and a student t-test was used for analysis. With the Chi-square test, numerical variables that were reported as percentages and numbers were examined. The predictive value of the components of the lipid profile in predicting IR was assessed using the receiver operating characteristic curve (ROC)[10]. For a difference to be considered statistically significant, a p-value of less than 0.05 was used.

RESULTS and DISCUSSION

Baseline characteristics of the patients

The mean age of the included subjects was 53.81 ± 8.78 years, ranging 45-80 years. Males represented 46% of them. Smoking and family history were relatively common and accounted for 39% and 52% of the subjects, respectively. The individuals' mean weight was 82.39 ± 12.4 kg, and their mean height was 167.64 ± 9.16 cm. The average BMI was therefore 29.38 ± 4.29 kg/m^2. Lastly, the average hip and waist circumferences were 104.76 ± 21.68 cm and 91.17 ± 18.91 cm, respectively (Table 1).

Table 1. Patients' baseline characteristics

NON-NUMERICAL VARIABLES		COUNT	%
Sexes	Male Female	46 54	46% 54%
Smoking	Never Ex/current	61 39	61% 39%
Family history of DM	No Yes	48 52	48% 52%
NUMERICAL VARIABLES		**MEAN ± SD**	**RANGE**
Weight (kg)		82.39 ± 12.4	58-112
Age, years		53.81 ± 8.78	45-80
Height (cm)		167.64 ± 9.16	146-198
Hip circumference (cm)		104.76 ± 21.68	64-152
Waist circumference (cm)		91.17 ± 18.91	59-144
WHR		0.88 ± 0.08	0.67-1.01
BMI (kg/m^2)		29.38 ± 4.29	18.37-42.22

Insulin resistance rate

Out of 100 subjects that appeared healthy, 30 subjects (30%) had insulin resistance, while the remaining 70 patients (70%), according to the HOMA-IR model, were insulin sensitive (Figure 1).

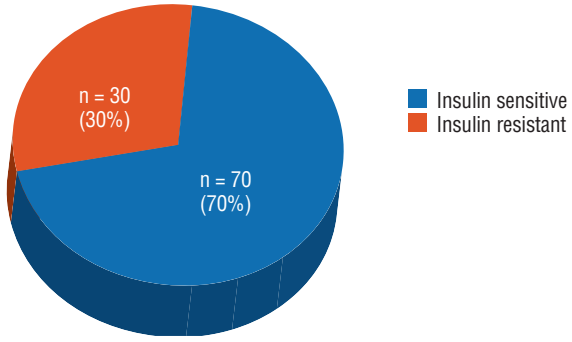

Figure 1. Insulin resistance rate

Association of demographic factors with insulin resistance

The insulin-resistant group had a significantly higher average age than the insulin-sensitive group (56.5 ± 10.44 years versus 52.67 ± 7.74 years). Likewise, females were more common among the insulin resistance group, with a significant difference (p=0.009). Other demographic characteristics did not significantly differ between the two groups; they were comparable (Table 2).

Table 2. Association of demographic factors with insulin status

Variables	Insulin sensitive (70)	Insulin resistance (30)	p-value
Age (years)	52.67 ± 7.74	56.5 ± 10.44	0.045*
Sex			
Male	38(54.2%)	8(26.67%)	0.009*
Female	32(45.71%)	22(73.33%)	
Smoking			
Never	44(62.86%)	17(56.67%)	0.358
Ex/current	26(37.14%)	13(43.33%)	
Family history of DM			
No	37(52.86%)	11(36.67%)	0.102
Yes	33(47.14%)	19(63.33%)	
Weight (kg)	80.97 ± 12.11	85.70 ± 12.64	0.080
Height (cm)	166.99 ± 9.1	169.17 ± 9.28	0.277
Waist circumference	89.31 ± 15.79	96.83 ± 24.22	0.068
Hip circumference	104.09 ± 20.51	106.33 ± 24.52	0.637
BMI (kg/m^2)	28.84 ± 4.22	30.59 ± 4.31	0.062

The association of between lipid profile and insulin status

Results illustrated in Table 3 showed that there was non-significant difference in the levels of TC, VLDL, and VAI between the two studied groups. On the other hand, insulin resistance group showed significantly higher levels of TG and HDL than insulin sensitive group (167.7 ± 56.13mg/dL versus 133.13 ± 40.04mg/dL and 49.66 ± 4.39mg/dL versus 47.22 ± 4.67mg/dL, respectively). Moreover, LDL and LAP were significantly higher in insulin resistance when compared to the insulin-sensitive group (103.9 ± 22.02mg/dL versus 94.22 ± 21.28mg/dL and 34.19 ± 6.63 versus 30.70 ± 7.98, respectively), according to Table 3.

Table 3. Lipid Profile association with insulin status

Variables	Insulin sensitive (n=70)	Insulin resistance (n=30)	p-value
Total cholesterol, mg/dl	178.75 ± 25.74	187.30 ± 29.22	0.147
Triglycerides, mg/dl	133.13 ± 40.04	167.7 ± 56.13	0.002*
HDL, mg/dl	49.66 ± 4.39	47.22 ± 4.67	0.041*
LDL, mg/dl	94.22 ± 21.28	103.9 ± 22.02	0.042*
VLDL, mg/dl	35.40 ± 14.75	34.48 ± 9.51	0.769
LAP	30.70 ± 7.98	34.19 ± 6.63	0.009*
VAI	4.44 ± 1.56	4.95 ± 1.94	0.170

FBS and HbA1c association with insulin status

Fasting blood glucose and fasting insulin, as components of the HOMA-IR equation, were much higher in the insulin-resistance group (92.45 ± 7.94 mg/dL and 17.77 ± 3.49 mIU/L, respectively) than in the insulin-sensitive group (88.06 ± 7.53 mg/dL and 8.57 ± 2.51 mIU/L, respectively) with highly significant differences. Further, HbA1c and HOMA-IR were higher in the insulin-resistant subjects relative to the insulin-sensitive subjects (5.37 ± 0.64% and 4.01 ± 0.78 versus 5.04±0.50% and 1.86 ± 0.54, respectively) as indicated in Table 4.

Table 4. FBS and HbA1c association with insulin resistance

Variables	Insulin sensitive (70)	Insulin resistance (30)	p-value
Fasting insulin, mIU/L	8.57 ± 2.51	17.77 ± 3.49	<0.001*
FBS, mg/dL	88.06 ± 7.53	92.45 ± 7.94	0.010*
HbA1c, %	5.04 ± 0.50	5.37 ± 0.64	0.007*
HOMA-IR	1.86 ± 0.54	4.01 ± 0.78	<0.001*

Diagnostic value of TG, HDL, LDL, and LAP in detecting insulin status

Insulin resistance was detected by evaluating the diagnostic value of LDL, TG, HDL, and LAP using the receiver operating characteristic (ROC) curve. HDL's area under the curve (AUC) was 0.643, 95% CI = 0.524-0.762, p=0.024. The test's results showed that its sensitivity was 63% and its specificity was 57%. For HDL, the optimal cutoff value was 48.5 mg/dL. The AUC for TG was 0.694, p=0.002, 95% CI = 0.584-0.805. The test's sensitivity and specificity were 63% and 68%, respectively. For TG, the optimal cutoff value was 144.5 mg/dL.

The AUC of LDL was 0.596, 95% CI = 0.473-0.720, p=0.048. The test's results showed 57% sensitivity and 57% specificity, respectively. For LDL, a cutoff value of 100.3 mg/dL was ideal. The AUC of LAP was 0.665, 95% CI = 0.553-0.777, and p=0.009. The test's results showed that its sensitivity was 60% and its specificity was 59%. The optimal LAP cutoff value was 30.76, as Figure 2 illustrates.

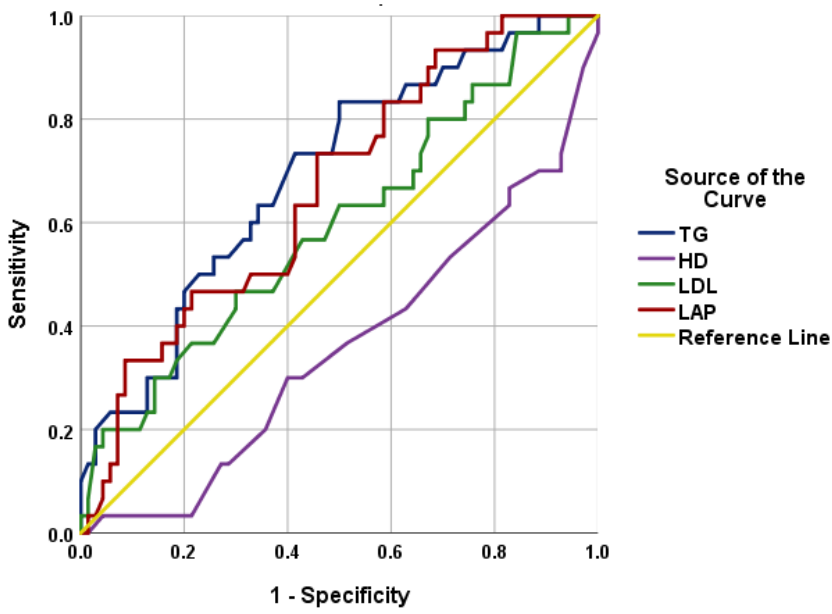

Figure 2. Receiver operating characteristic curve for HDL, TG, LDL, and LAP in detection of insulin status in healthy subjects

Diagnostic value of derived ratios

Two derived ratios were calculated from available data and examined for their diagnostic value of IR. These were the ratios of TG to HDL and TG to FBS. The AUC was 0.728, 95% CI = 0.617-0.838, p <0.001 for the TG/HDL ratio. The test had 77% sensitivity and 67% specificity, respectively. For the TG/HDL ratio, 2.96 was the ideal cutoff value.

The AUC was 0.646, 95% CI = 0.530-0.672, p=0.021 for the TG/FBS ratio. The test's results showed that its sensitivity was 67% and its specificity was 56%. The TG/FBS ratio's ideal cutoff value was 1.5. as Figure 3 illustrates.

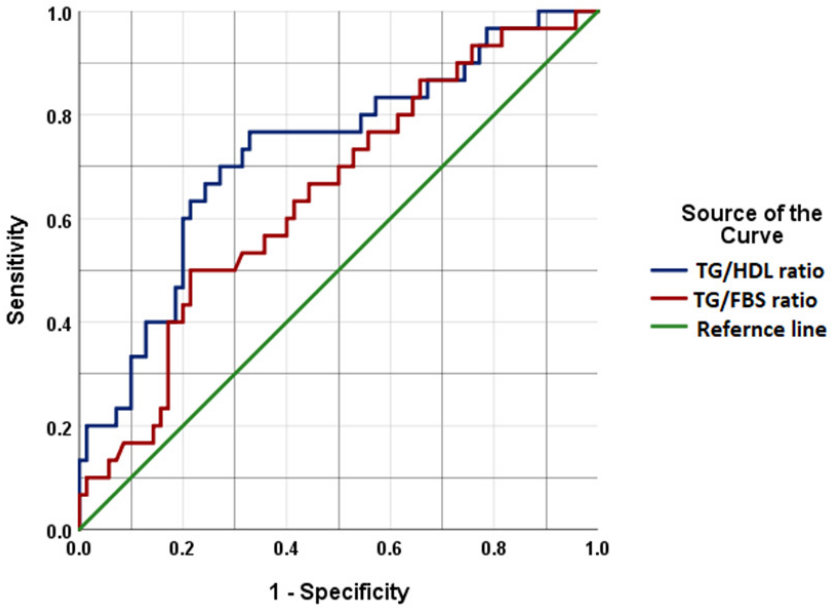

Figure 3. Receiver operating characteristic curve for TG/HDL and TG/FBS ratios in detection of insulin resistance in healthy subjects

The present research has identified a significant correlation between insulin resistance (IR) and advanced age which is consistent with other earlier investigations. Kim et al. discovered a significant relationship between age and IR in the Korean population[11]. In addition, Bermudez et al. discovered that the incidence of IR rose with age and was significantly greater in those aged 30 or older who were obese[12]. Decreased insulin sensitivity in the elderly can be attributed to various mechanisms, including reductions in insulin-stimulated whole-body glucose oxidation, age-related impairments in insulin action at the receptor and post-receptor levels, impaired insulin-mediated glucose uptake, an inability to suppress hepatic glucose output, and reductions in the β-cell response to glucose[13].

Female was also significantly associated with IR in the present study. There have been mixed results from earlier research assessing sex differences in insulin action. While some have observed no difference between men and women[14], others have stated that women are less likely than men to have IR[15]. In the meanwhile, the Greenhill study discovered that women have a lower incidence of IR resistance than men of comparable age prior to menopause[16]. Nevertheless, this protective effect fades after menopause, and the incidence of T2DM and IR in men and women converges, indicating that estrogen may have a preventive role.

Levels of HDL were inversely correlated with IR people in the current study. Multiple tissues' glucose metabolism is modulated by HDL, as demonstrated by Siebel et al.[17]. According to Chiang et al. there is significant variance in TG and HDL between people with and without IR; neither TC nor LDL show the same kind of correlation[18]. In a Chinese study, 1608 adult participants had nearly identical results[19]. Low HDL-C concentrations are hypothesized to be caused by IR through a number of different ways. First, IR is linked to increased exchange of VLDL for cholesterol esters from HDL particles and TG from chylomicrons, which lowers HDL-C. This process is controlled by the cholesteryl ester transfer protein (CETP)[20]. Second, lower hydrolysis of TG from chylomicrons and VLDL is caused by decreased lipoprotein lipase (LPL) activity, which may further restrict the contribution of TG-rich lipoprotein-derived HDL particles[21,22]. Third, higher HDL clearance and consequently lower HDL-C concentrations are linked to elevated HTGL (hepatic triglyceride lipase) activity in IR conditions[23]. Fourth, decreased apo A-I production and release from the liver and intestine may also be the cause of low HDL-C concentrations[24].

According to the result of the current study, LDL level was significantly associated with IR, Mykkänen et al. has been determined that there is a strong correlation between insulin resistance and an abundance of small, dense LDL particles[24]. This can be explained by the fact that the impact of IR on LDL metabolism seems to be less noticeable. In addition to its known ability to increase LDL receptor activity, insulin may be crucial for the metabolism of atherogenic small dense LDL particles[25]. Dannecker et al. found a significant positive correlation between C-peptide-based estimations of insulin secretion and fasting LDL values. Their findings suggested that increased LDL cholesterol levels might encourage pancreatic β cells to secrete more insulin[26]. However, Natali et al. did not discover any connection between LDL-c and insulin secretion[27].

TG levels had a significant correlation with IR people in the current investigation. The 517 Chinese participants in the Ma et al. study was split into four groups: those with normal lipid and glucose levels; those with dyslipidemia alone; those with dysglycemia alone; and those with both dyslipidemia and dysglycemia[28]. They discovered that in people with dyslipidemia alone, TG was connected with both IR and islet β-cell function, as well as the negative impact of hypertriglyceridemia on insulin sensitivity and islet β-cell activity. A different study by Riediger et al. discovered that in Canadian populations, a fasting TG may be helpful as a clinical predictor of IR and the onset of diabetes[29]. The fact that TG builds up in the liver and muscle with hypertriglyceridemia, suggesting lipid ectopic deposition, helps to explain the positive correlation between TG and IR[30]. Hepatocytes and skeletal myocytes produce TG metabo-

lites, such as fatty acyl CoA, diacylglycerol, and ceramides, which can affect insulin signaling and inhibit insulin-induced activation of glycogen synthase and insulin receptor substrate-1-associated PI 3-kinase[31]. Increases in hepatic TG lipase (HTGL) have also been linked to IR, and it has recently been shown that this activity plays a key role in controlling insulin clearance[32]. Since TG is not thought to be a signaling lipid, it is more likely that diacylglycerol, which is TG's synthetic precursor, ceramide, and other lipids are involved in the pathogenesis of hepatic IR through a variety of mechanisms, such as decreased insulin-stimulated glycogen synthase activity, reduced insulin receptor tyrosine kinase activity, and destabilization of the insulin receptor[33,34].

Lipid accumulation product (LAP) level was shown to be significantly correlated with IR in the current investigation. TG levels and WC are combined to create the LAP index, which represents lipid accumulation[35]. In addition to being seen as a sign of central fat accumulation, LAP has also been linked to poor glucose homeostasis, metabolic syndrome, T2DM, cardiovascular disease, and insulin resistance[36]. The body's fat buildup, which is accompanied by elevated TG and assessed WC levels, can be used to explain this substantial variation in LAP[32]. Consequently, elevated LAP can be a sign of lipid overabundance and ectopic lipid deposition[37]. Xia et al. showed that in non-diabetic subjects from China, there was close association between LAP and IR and exhibited stronger predictability of IR than WC and BMI[35]. Bermu´dez et al. showed LAP had a higher predictive capacity and association with IR in the Venezuelan population than VAI[38].

The TG/HDL ratio shown a strong predictive value for IR in the current investigation. The TG/HDL ratio has been reported to be useful in previous research for IR detection[7]. In a cross-sectional study, 258 non-diabetic overweight or obese people were included; 87% of these people were non-Hispanic white people[19].They found that in overweight individuals, the TG/HDL ratio may accurately predict IR. In another study, Gong et al. investigated the association of the TG/HDL ratio with IR in 49696 healthy American populations[39]. Moriyama, proposed a relationship between IR and the TG/HDL-C ratio in a sample of 1068 Japanese subjects in good health[40]. Rodríguez-Gutiérrez et al. also reported findings similar to this one[41]. However, it has been shown that the TG levels and TG–HDL ratio are not accurate indicators of IR in African Americans[42]. Therefore, although not African Americans, the TG/HDL ratio may be a useful diagnostic for identifying IR people of Aboriginal, Chinese, and European ancestry[43]. It is yet unknown how the TG/HDL ratio predicts IR. Nonetheless, adipose tissue is trapped and less fatty acid is retained in the IR by high TG and low HDL. More free fatty acids were therefore carried to

the liver, where they were converted into more TG and TG-containing VLDL. Additionally, as the plasma TG concentration rises, the TG of TG-containing VLDL and the cholesteryl ester of HDL exchange. This process creates the readily catabolized TG-rich HDL. As a result, IR patients had low HDL, high TG, and high TG/HDL[44].

The prevalence of IR among healthy Iraqi adults is 30%. Older ages more than 45 years and female are significantly associated with an increased risk of IR. Higher serum levels of TG, LDL and a lower level of HDL can enhance the development of IR in healthy subjects. The TG/HDL-C ratio has a good predictive value for IR.

STATEMENT OF ETHICS

The study received approval from the "Institute Review Board (IRB) of Al-Nahrain University/College of Medicine" on January, 2022 (58/2022).

CONFLICT OF INTEREST STATEMENT

No conflict of interest was declared by the authors.

AUTHOR CONTRIBUTIONS

Design – Hashim ZH, Al-Mayah QS, Al-Matubsi H; Acquisition of data – Khalid SH; Analysis of data – Khalid SH, Hashim ZH, Al-Mayah QS; Drafting of the manuscript – Khalid SH, Hashim ZH, Al-Mayah QS; Critical revision of the manuscript – Hashim ZH, Al-Mayah QS, Al-Matubsi H; Statistical analysis – Khalid SH, Hashim ZH, Al-Mayah QS; Technical or financial support – Khalid SH, Hashim ZH, Al-Mayah QS, Al-Matubsi H; Supervision – Hashim ZH, Al-Mayah QS, Al-Matubsi H.

REFERENCES

1. Brown JC, Harhay MO, Harhay MN. The value of anthropometric measures in nutrition and metabolism: comment on anthropometrically predicted visceral adipose tissue and blood-based biomarkers: a cross-sectional analysis. Nutr Metab Insights, 2019;12:1178638819831712. Doi: 10.1177/1178638819831712

2. Deacon CF. Physiology and pharmacology of DPP-4 in glucose homeostasis and the treatment of type 2 diabetes. Front Endocrinol, 2019;10:80. Doi: 10.3389/fendo.2019.00080

3. Tangvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. World J Diabetes, 2015;6(3):456-480. Doi: 10.4239/wjd.v6.i3.456

4. Samuel VT, Petersen KF, Shulman GI. Lipid-induced insulin resistance: unravelling the mechanism. Lancet, 2010;26;375(9733):2267-2277. Doi: 10.1016/S0140-6736(10)60408-4

5. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diabetes Care, 2004;27(6):1487-1495. Doi: 10.2337/diacare.27.6.1487

6. Espinel-Bermúdez MC, Robles-Cervantes JA, del Sagrario Villarreal-Hernández L, Villaseñor-Romero JP, Hernández-González SO, González-Ortiz M, et al. Insulin resistance in adult primary care patients with a surrogate index, Guadalajara, Mexico, 2012. J Investig Med, 2015;63(2):247-250. Doi: 10.1097/JIM.0000000000000130

7. Ghani ZA, Qaddori H, Al-Mayah Q. Triglyceride/high-density lipoprotein ratio as a predictor for insulin resistance in a sample of healthy Iraqi adults. J Med Life, 2023;16(5):668-674. Doi: 10.25122/jml-2022-0239

8. Anoop S, Jebasingh FK, Rebekah G, Kurian ME, Mohan VR, Finney G, et al. The triglyceride/glucose ratio is a reliable index of fasting insulin resistance: observations from hyperinsulinaemic-euglycaemic clamp studies in young, normoglycaemic males from southern India. Diabetes Metab Syndr, 2020;14(6):1719-1723. Doi: 10.1016/j.dsx.2020.08.017

9. Bullen AL, Katz R, Kumar U, Gutierrez OM, Sarnak MJ, Kramer HJ, et al. Lipid accumulation product, visceral adiposity index and risk of chronic kidney disease. BMC Nephrol, 2022;23(1):401. Doi: 10.1186/s12882-022-03026-9

10. Mandrekar JN. Receiver operating characteristic curve in diagnostic test assessment. JTO, 2010;5:1315-1316. Doi: 10.1097/JTO.0b013e3181ec173d

11. Kim SG, Lim HS, Cheong HK, Kim CS, Seo HJ. Incidence and risk factors of insulin resistance syndrome in 20-59 year-old Korean male workers. J Korean Med Sci, 2007;22(6):968-972. Doi: 10.3346/jkms.2007.22.6.968

12. Bermudez V, Salazar J, Martínez MS, Chávez-Castillo M, Olivar LC, Calvo MJ, et al. Prevalence and associated factors of insulin resistance in adults from Maracaibo city, Venezuela. Adv Prev Med, 2016;2016:9405105. Doi: 10.1155/2016/9405105

13. Paolisso G, Marrazzo G, de Riu S, Sgambato S, Varricchio M, d'Onofrio F, et al. Effects of mild-to-moderate hyperglycaemia per se on glucose production and uptake in the elderly. Eur J Med, 1992;1(1):6-12.

14. Kim SH, Reaven G. Sex differences in insulin resistance and cardiovascular disease. J Clin Endocrinol Metab, 2013;98(11):E1716-E1721.Doi: 10.1210/jc.2013-1166

15. Moran A, Jacobs DR Jr, Steinberger J, Steffen LM, Pankow JS, Hong CP, et al. Changes in insulin resistance and cardiovascular risk during adolescence: establishment of differential risk in males and females. Circulation, 2008;117(18):2361-2368. Doi: 10.1161/CIRCULATIONAHA.107.704569

16. Greenhill C. Sex differences in insulin resistance. Nat Rev Endocrinol, 2018;14(2):65. Doi: doi10.10:38/nrendo.2017.168

17. Siebel AL, Heywood SE, Kingwell BA. HDL and glucose metabolism: current evidence and therapeutic potential. Front Pharmacol, 2015;6:258.Doi: doi:10.3389/fphar.2015.00258

18. Chiang JK, Lai NS, Chang JK, Koo M. Predicting insulin resistance using the triglyceride-to-high-density lipoprotein cholesterol ratio in Taiwanese adults. Cardiovasc Diabetol, 2011;10:93. Doi: 10.1186/1475-2840-10-93

19. Yang Y, Wang B, Yuan H, Li X. Triglycerides to high-density lipoprotein cholesterol ratio is the best surrogate marker for insulin resistance in nonobese middle-aged and elderly population: a cross-sectional study. Int J Endocrinol, 2021 Apr 30;2021:6676569. Doi: 10.1155/2021/6676569

20. de Vries R, Borggreve SE, Dullaart RP. Role of lipases, lecithin: cholesterol acyltransferase and cholesteryl ester transfer protein in abnormal high density lipoprotein metabolism in insulin resistance and type 2 diabetes mellitus. Clin Lab, 2003;49(11-12):601-613.

21. Bjornstad P, Eckel RH. Pathogenesis of lipid disorders in insulin resistance: a brief review. Curr Diabetes Rep, 2018;18:1-8. Doi: 10.1007/s11892-018-1101-6

22. Garg A, Haffner SM. Insulin resistance and atherosclerosis: an overview. Diabetes Care, 1996;19(3):274-274. Doi: 10.2337/diacare.19.3.274

23. Brinton EA, Eisenberg S, Breslow JL. Human HDL cholesterol levels are determined by apoA-I fractional catabolic rate, which correlates inversely with estimates of HDL particle size. Effects of gender, hepatic and lipoprotein lipases, triglyceride and insulin levels, and body fat distribution. Arterioscler Thromb Vasc Biol, 1994;14(5):707-720. Doi: 10.1161/01.ATV.14.5.707

24. Mykkänen L, Haffner SM, Rainwater DL, Karhapää P, Miettinen H, Laakso M. Relationship of LDL size to insulin sensitivity in normoglycemic men. Arterioscler Thromb Vasc Biol, 1997;17(7):1447-1453. Doi: 10.1161/01.ATV.17.7.1447

25. Gerber PA, Thalhammer C, Schmied C, Spring S, Amann-Vesti B, Spinas GA, et al. Small, dense LDL particles predict changes in intima media thickness and insulin resistance in men with type 2 diabetes and prediabetes--a prospective cohort study. PLoS One, 2013;8(8):e72763. Doi: 10.1371/journal.pone.0072763

26. Dannecker C, Wagner R, Peter A, Hummel J, Vosseler A, Häring HU, et al. Low-density lipoprotein cholesterol is associated with insulin secretion. J Clin Endocrinol Metab, 2021;106(6):1576-1584. Doi: 10.1210/clinem/dgab147

27. Natali A, Baldi S, Bonnet F, Petrie J, Trifirò S, Tricò D, et al. Plasma HDL-cholesterol and triglycerides, but not LDL-cholesterol, are associated with insulin secretion in non-diabetic subjects. Metabolism, 2017;69:33-42. Doi: 10.1016/j.metabol.2017.01.001

28. Ma M, Liu H, Yu J, He S, Li P, Ma C, et al. Triglyceride is independently correlated with insulin resistance and islet beta cell function: a study in population with different glucose and lipid metabolism states. Lipids Health Dis, 2020;19(1):121. Doi: 10.1186/s12944-020-01303-w

29. Riediger ND, Clark K, Lukianchuk V, Roulette J, Bruce S. Fasting triglycerides as a predictor of incident diabetes, insulin resistance and β-cell function in a Canadian First Nation. Int J Circumpolar Health, 2017;76(1):1310444. Doi: 10.1080/22423982.2017.1310444

30. Després JP, Lemieux I, Bergeron J, Pibarot P, Mathieu P, Larose E, et al. Abdominal obesity and the metabolic syndrome: contribution to global cardiometabolic risk. Arterioscler Thromb Vasc Biol, 2008;28(6):1039-1049. Doi: 10.1161/ATVBAHA.107.159228

31. DeFronzo RA. Insulin resistance, lipotoxicity, type 2 diabetes and atherosclerosis: the missing links. The Claude Bernard Lecture 2009. Diabetologia, 2010;53(7):1270-1287. Doi: 10.1007/s00125-010-1684-1

32. Labadzhyan A, Cui J, Péterfy M, Guo X, Chen YI, Hsueh WA, et al. Insulin clearance is associated with hepatic lipase activity and lipid and adiposity traits in Mexican Americans. PLoS One, 2016;11(11):e0166263. Doi: 10.1371/journal.pone.0166263

33. Petersen MC, Shulman GI. Roles of diacylglycerols and ceramides in hepatic insulin resistance. Trends Pharmacol Sci, 2017;38(7):649-665. Doi: 10.1016/j.tips.2017.04.004

34. Petersen MC, Madiraju AK, Gassaway BM, Marcel M, Nasiri AR, Butrico G, et al. Insulin receptor Thr1160 phosphorylation mediates lipid-induced hepatic insulin resistance. J Clin Invest, 2016;126(11):4361-4371. Doi: 10.1172/JCI86013

35. Xia C, Li R, Zhang S, Gong L, Ren W, Wang Z, et al. Lipid accumulation product is a powerful index for recognizing insulin resistance in non-diabetic individuals. Eur J Clin Nutr, 2012;66(9):1035-1038. Doi: 10.1038/ejcn.2012.83

36. Mazidi M, Kengne AP, Katsiki N, Mikhailidis DP, Banach M. Lipid accumulation product and triglycerides/glucose index are useful predictors of insulin resistance. J Diabetes Complications, 2018;32(3):266-270. Doi: 10.1016/j.jdiacomp.2017.10.007

37. Taverna MJ, Martínez-Larrad MT, Frechtel GD, Serrano-Ríos M. Lipid accumulation product: a powerful marker of metabolic syndrome in healthy population. Eur J Endocrinol, 2011;164(4):559-567. Doi: 10.1530/EJE-10-1039

38. Bermúdez V, Salazar J, Fuenmayor J, Nava M, Ortega Á, Duran P, et al. Lipid accumulation product is more related to insulin resistance than the visceral adiposity index in the Maracaibo city population, Venezuela. J Obes, 2021;2021:5514901. Doi: 10.1155/2021/5514901

39. Gong R, Luo G, Wang M, Ma L, Sun S, Wei X. Associations between TG/HDL ratio and insulin resistance in the US population: a cross-sectional study. Endocr Connect, 2021;10(11):1502-1512. Doi: 10.1530/EC-21-0414

40. Moriyama K. Associations between the triglyceride to high-density lipoprotein cholesterol ratio and metabolic syndrome, insulin resistance, and lifestyle habits in healthy Japanese. Metab Syndr Relat Disord, 2020;18(5):260-266. Doi: 10.1089/met.2019.0123

41. Rodríguez-Gutiérrez N, Vanoye Tamez M, Vázquez-Garza E, Villarreal-Calderón JR, Castillo EC, Laresgoiti-Servitje E, et al. Association of the triglyceride/high-density lipoprotein cholesterol index with insulin resistance in a pediatric population in northeast Mexico. Metab Syndr Relat Disord, 2020;18(7):333-340. Doi: 10.1089/met.2020.0046

42. Sumner AE, Finley KB, Genovese DJ, Criqui MH, Boston RC. Fasting triglyceride and the triglyceride-HDL cholesterol ratio are not markers of insulin resistance in African Americans. Arch Intern Med, 2005;165(12):1395-400. Doi: 10.1001/archinte.165.12.1395

43. Gasevic D, Frohlich J, Mancini GB, Lear SA. The association between triglyceride to high-density-lipoprotein cholesterol ratio and insulin resistance in a multiethnic primary prevention cohort. Metabolism, 2012;61(4):583-589. Doi: 10.1016/j.metabol.2011.09.009

44. Yeh WC, Tsao YC, Li WC, Tzeng IS, Chen LS, Chen JY. Elevated triglyceride-to-HDL cholesterol ratio is an indicator for insulin resistance in middle-aged and elderly Taiwanese population: a cross-sectional study. Lipids Health Dis, 2019;18(1):176. Doi: 10.1186/s12944-019-1123-3