Decreased Triglyceride and Increased Serum Lipoprotein Lipase Levels Are Correlated to Increased High-Density Lipoprotein-Cholesterol Levels after Laparoscopic Sleeve Gastrectomy

Masahiro Ohira\textsuperscript{a} Yasuhiro Watanabe\textsuperscript{b} Takashi Yamaguchi\textsuperscript{b} Hiroki Onda\textsuperscript{b} Shuhei Yamaoka\textsuperscript{b} Kazuki Abe\textsuperscript{b} Shoko Nakamura\textsuperscript{b} Sho Tanaka\textsuperscript{b} Naoyuki Kawagoe\textsuperscript{a} Taiki Nabekura\textsuperscript{c} Takashi Oshiro\textsuperscript{c} Daiji Nagayama\textsuperscript{b,d} Ichiro Tatsuno\textsuperscript{b,e} Atsuhito Saiki\textsuperscript{b}

\textsuperscript{a}Division of Diabetes, Metabolism and Endocrinology, Department of Internal Medicine, Toho University Ohashi Medical Center, Tokyo, Japan; \textsuperscript{b}Center for Diabetes, Endocrine and Metabolism, Toho University Sakura Medical Center, Chiba, Japan; \textsuperscript{c}Department of Surgery, Toho University Sakura Medical Center, Chiba, Japan; \textsuperscript{d}Nagayama Clinic, Tochigi, Japan; \textsuperscript{e}Chiba Prefectural University of Health Sciences, Chiba, Japan

Keywords
Obesity · Laparoscopic sleeve gastrectomy · High-density lipoprotein cholesterol · Triglyceride · Lipoprotein lipase

Abstract

Introduction: Laparoscopic sleeve gastrectomy (LSG) significantly increases high-density lipoprotein cholesterol (HDL-C) and lipoprotein lipase (LPL) in pre-heparin serum (pre-heparin LPL levels). LPL is a regulator of serum triglyceride (TG) and HDL-C production; this may be the mechanism for HDL-C increase after LSG. This study aimed to elucidate the mechanism of increase in HDL-C levels by examining the relationship between changes in serum HDL-C levels and LPL after LSG. Methods: We retrospectively reviewed 104 obese patients, who underwent LSG and were followed up for 12 months. We analyzed the relationship between changes in serum HDL-C levels and various clinical parameters after LSG. Results: A significant decrease was observed in the patients' BMI and serum TG levels after LSG. Conversely, HDL-C levels and pre-heparin LPL levels were significantly increased after LSG. Simple linear regression showed that changes in HDL-C levels were significantly correlated with total weight loss percentage, change in TG levels, abdominal fat areas, and pre-heparin LPL levels. Additionally, the multiple regression model revealed that a decrease in TG levels and an increase in pre-heparin LPL levels were correlated with increased HDL-C levels after LSG. Discussion/Conclusion: These results show that a decrease in TG levels and an increase in LPL are mechanisms for increased HDL-C levels after LSG.

Introduction

Decreased levels of high-density lipoprotein cholesterol (HDL-C) increase the risk of atherosclerosis in patients with obesity or metabolic syndrome [1–5]. Previous studies have shown the beneficial effect of bariatric surgery in increasing HDL-C levels in addition to improving weight reduction, type 2 diabetes mellitus, abnormal kidney
function, hypertension, and dyslipidemia [6–9]. Additionally, laparoscopic sleeve gastrectomy (LSG), a surgical procedure of bariatric surgery, increases HDL-C levels more than nonsurgical management [10, 11]. However, the mechanisms by which bariatric surgery increases serum HDL-C levels remain unelucidated.

Lipoprotein lipase (LPL), a triglyceride (TG) hydrolase, is a well-known regulator of serum HDL-C levels [12, 13]. In general, serum LPL levels and activity are measured post-heparin administration [14, 15]. Conversely, pre-heparin LPL levels may be detected by a sensitive immunoassembly system using a specific monoclonal antibody against LPL [16, 17]. However, this only shows LPL levels, which reflects LPL production, and not LPL activity [18]. Furthermore, a previous study has observed a relationship between pre-heparin LPL levels with serum TG and HDL-C levels [19]. An increase in pre-heparin LPL levels has been observed in obese patients who undergo LSG [10]. Therefore, one possible mechanism for the increase in HDL-C levels after LSG is the increase in LPL production. However, the relationship between post-LSG changes in HDL-C levels and pre-heparin LPL levels has not been evaluated. Understanding the mechanism of HDL-C level improvement after bariatric surgery leads to better understanding of the pathophysiology of obesity. Therefore, we investigated the relationship between post-LSG changes in HDL-C levels and other clinical parameters, including pre-heparin LPL levels.

Materials and Methods

Study Design and Participants

This single-center, retrospective study reviewed the clinical data of patients obtained between July 2010 and November 2019 at the Toho University Sakura Medical Center (Sakura City, Chiba, Japan). Patients with the following characteristics were included: diagnosis of primary obesity defined by body mass index (BMI) of ≥32 kg/m² at the first visit, had undergone LSG, and had 12 months postoperative follow-up. Patients with the following characteristics were excluded: absence of visceral and subcutaneous fat area data and lack of pre-heparin LPL level data during the same period.

In Japan, obesity is defined by BMI ≥25.0 kg/m². According to the Japanese Society for the Treatment of Obesity guidelines, the criteria for bariatric surgery includes either a BMI of ≥32 kg/m² with comorbidities (type 2 diabetes mellitus, hypertension, or hyperlipidemia) or a BMI of ≥35 kg/m² even in the absence of comorbidities. A total of 115 LSG cases were reported during the study period. However, 11 patients were excluded: 8 (7.0%) withdrew within 12 months after LSG; 2 (1.7%) lacked abdominal fat area data; and 1 (0.9%) lacked pre-heparin LPL level data. Finally, 104 obese patients (90.4%) who underwent LSG were included in the study.

We compared the following parameters pre- and 12 months post-LSG: body weight (BW), BMI, aspartate transaminase, alanine transaminase, blood urea nitrogen, serum creatinine, estimated glomerular filtration rate, total cholesterol (TC), TG, HDL-C, low-density lipoprotein cholesterol (LDL-C), fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), visceral fat area, subcutaneous fat area, and pre-heparin LPL levels. The total weight loss percentage (%TWL) was estimated at 12 months after LSG. After an overnight 12-hour fast, the BW was measured and blood samples were collected.

Measurements of Various Parameters

Within an hour after sample collection, the serum and plasma were separated using centrifugation at 2,000 x g for 10 min. Serum samples were used to measure the levels of HbA1c, aspartate transaminase, alanine transaminase, blood urea nitrogen, creatinine, estimated glomerular filtration rate, and lipids. For HbA1c level measurement, blood was collected in tubes containing ethylenediaminetetraacetic acid. Stable and unstable fractions of HbA1c were measured through high-pressure liquid chromatography using an HLC-732G11 analyzer (Tosoh Bioscience, Yamanouchi, Japan). However, only the stable form data were used in the analysis. Plasma TC and TG levels were measured enzymatically using pure auto® CHO-N and TG-N kits from Sekisui Medical Co., Ltd. (Tokyo, Japan) and a Hitachi 7150 analyzer (Hitachi Ltd., Tokyo, Japan). Serum HDL-C levels were measured using a selective inhibition assay with a JCA-BM1650 auto analyzer (JEOL JAPAN Ltd., Tokyo, Japan). Serum LDL-C levels were calculated using the Friedewald formula (LDL-C = TC – TG/5 – HDL-C). Serum pre-heparin LPL levels were measured by a sandwich enzyme-linked immunosorbent assay using a specific monoclonal antibody against LPL (Daichi Pure Chemicals, Tokyo, Japan), as described by Kobayashi et al. [16]. The linearity and coefficient of variation for this assay have been described in our previous report [20].

To determine the visceral fat area, a computed tomography scan was performed at the umbilical level with the patient lying supine. The subcutaneous fat area was calculated by subtracting the visceral fat area from the total fat area. Radiologists quantified the fat area using Ziosstation 2 software version 2.9.7.1 (Ziosoft, Inc., Tokyo, Japan).

Statistical Analysis

The normality of the data distribution was tested using the Shapiro-Wilk test. Continuous data were expressed as the median and interquartile range or mean ± standard error due to the non-normal distribution of most data. Data were analyzed using the Wilcoxon signed-rank test (paired samples). Fisher’s exact test was used to identify significant differences between the proportions and categorical variables. Simple linear regression analysis was performed to analyze correlations between changes in HDL-C after LSG and the clinical parameters using Spearman’s rank correlation coefficient. Multiple regression analysis was used to analyze the independent associations of variables with changes in HDL-C levels. Statistical significance was set at p < 0.05. All statistical analyses were performed using the JMP software (version 14.3.0; SAS Institute, Cary, NC, USA).
Results

Baseline Characteristics and Changes in Various Parameters at 12 Months after LSG

The baseline characteristics and changes in the patients’ parameters at 12 months post-LSG are shown in Table 1. The median (interquartile range) age, BMI, and HbA1c levels were 43.0 (36.0–50.0) years, 43.0 (38.1–49.6) kg/m², and 6.3 (5.8–6.9) %, respectively. Additionally, 63 patients (60.6%) were diagnosed with type 2 diabetes mellitus. At 12 months after LSG, the median %TWL was 28.9 (22.6–35.8%); the BW, BMI, FBG, HbA1c, and both visceral and subcutaneous fat areas decreased significantly after LSG (p < 0.0001). HDL-C levels significantly increased from 41.5 (37.0–49.0) mg/dL at baseline to 60.0 (53.0–71.0) mg/dL (p = 0.0001) 12 months after LSG (shown in Fig. 1). A significant increase was observed in the pre-heparin LPL levels after LSG, from baseline (51.86 ± 2.68 ng/mL) to 12 months postoperative (80.47 ± 3.26 ng/mL) (p < 0.0001).

Correlation between Change in HDL-C Levels and Change in each Clinical Parameter 12 Months after LSG

The relationship between the changes in HDL-C levels and different clinical parameters at 12 months post-LSG are shown in Table 3. Changes in HDL-C levels showed significantly positive correlations with changes in %TWL and pre-heparin levels 12 months post-LSG (%TWL: ρ = 0.2830, p = 0.0036, pre-heparin LPL levels: ρ = 0.2637, p = 0.0068) (shown in Table 3). Conversely, changes in HDL-C levels showed significant negative correlations with changes in TG, visceral fat area, and subcutaneous fat area 12 months’ post-LSG (TG levels: ρ = −0.3975, 0.0007, 0.0469, and 0.0401, respectively) (shown in Table 2).
Correlation of Change in HDL-C Levels with Changes in other Variables Analyzed by the Multiple Regression Model

We examined the effects of changes in clinical parameters on changes in HDL-C levels. The multiple regression analysis results of the correlation between changes in HDL-C levels and other clinical variables are shown in Table 4. We excluded subcutaneous fat area from the model because it was intercorrelated with the visceral fat area. Among the parameters, changes in TG levels were the major factor that increased HDL-C levels (β coefficient = −0.2805, \( p = 0.0043 \)). Additionally, increase in pre-heparin LPL levels was a correlated factor that increased HDL-C levels (β coefficient = 0.1857, \( p = 0.0497 \)). Other variables were not selected as correlated factors (shown in Table 4).

Discussion

In the present study, significant improvements in the BW, BMI, liver and kidney function, serum TG levels, serum HDL-C levels, FBG, and HbA1c were observed after 12 months in patients who underwent LSG. Additionally, both visceral and subcutaneous fat areas were significantly decreased after LSG. More importantly,
Table 4. Correlation of change in HDL-C levels with changes in other variables analyzed by multiple regression model

|                          | Standardized β | SE   | p value |
|--------------------------|----------------|------|---------|
| Male (0) or female (1)   | 0.1008         | 2.1289 | 0.2860  |
| Age, years               | −0.0056        | 0.1124 | 0.9531  |
| %TWL, %                  | 0.1374         | 0.1105 | 0.1801  |
| ΔTG, mg/mL               | −0.2805        | 0.0132 | 0.0043  |
| ΔVisceral fat area, cm²  | −0.0583        | 0.0120 | 0.5547  |
| ΔPre-heparin LPL level, ng/mL | 0.1857    | 0.0424 | 0.0497  |

HDL-C, high-density lipoprotein cholesterol; SE, standard error; %TWL, total weight loss percentage; TG, triglycerides; LPL, lipoprotein lipase. Δ is the difference between the baseline and 12 months postoperative values. Model: $r^2 = 0.2154$, $p = 0.0005$.

pre-heparin LPL levels increased significantly after LSG. Univariate analysis revealed that changes in HDL-C levels were correlated with %TWL, changes in TG levels, visceral and subcutaneous fat areas, and pre-heparin LPL levels. The multiple regression model showed that a decrease in serum TG levels and an increase in pre-heparin LPL levels were correlated with increased HDL-C levels after LSG.

In this study, LSG significantly increased HDL-C levels 12 months postoperatively. A higher BMI is associated with higher plasma TG levels and lower HDL-C levels [22, 23]. In obese patients, increases in the HDL-C levels are observed 6–15 months after nonsurgical weight reduction [24, 25]; however, this is preceded by a decrease in HDL-C levels 3 days after nonsurgical weight reduction [26]. HDL-C levels were not increased shortly after weight reduction therapy was started in the nonsurgical treatment group. Additionally, a clinical study showed that decreases in HDL-C levels were observed upon initiation of enteral feeding, and not 1 day after sleeve gastrectomy [27]. Another study showed that HDL-C levels decreased at 3 months after sleeve gastrectomy; however, an increase was observed thereafter, which peaked after 2 years [9]. Thus, LSG and nonsurgical weight reduction increase HDL-C levels; however, no significant changes in the HDL-C levels are observed shortly after sleeve gastrectomy and nonsurgical weight reduction.

We found that increased HDL-C levels were correlated with decreased TG levels and increased pre-heparin LPL levels, consistent with previous studies [28, 29]. Plasma TG levels had significant negative correlations with plasma HDL-C concentrations; likewise, HDL-C levels had significant negative correlations with TG-rich lipoproteins (TRL), such as very-low-density lipoprotein [30]. LPL hydrolyzes core TGs in chylomicrons and very-low-density lipoproteins [31]. In patients with higher BMI or insulin resistance, LPL mass and activity are decreased [32–34]; decreases in LPL activity results in decreased TRL clearance [35, 36]. Furthermore, inhibition of LPL activity leads to high TG and low HDL-C levels in monkeys [37]; however, an increase in HDL-C levels was observed in rats administered NO-1886, an LPL activator [38]. Furthermore, previous studies have found that HDL-C levels are positively correlated with pre- and post-heparin LPL levels and activity [17, 39]. Impaired TRL lipolysis leads to reduced HDL-C concentration by decreasing the transfer of apolipoproteins and phospholipids from the TRL to the HDL compartment [40]. Therefore, a decrease in TG and an increase in LPL are related to an increase in HDL-C after LSG.

LPL plays an important role in TG and HDL-C metabolism [12, 13, 41]. In obese patients, decreased adipose tissue LPL activity leads to a decrease in HDL-C levels [42]. In addition to LPL, cholesterol ester transfer protein (CETP) has been shown to be a regulator of HDL-C metabolism; particularly, a negative correlation was observed between CETP and HDL-C levels [43, 44]. Furthermore, CETP levels and activity are increased in obese patients; this leads to decreases in HDL-C levels and is reversed by weight reduction [45]. Therefore, a significant correlation has been observed between CETP and pre- and post-treatment in obese patients. However, this relationship was not investigated in this study; further studies are therefore warranted.

Adipocyte lipolysis is associated with plasma TG and HDL-C levels [46, 47]. Leptin impacts adipocyte lipolysis, and its levels change significantly at 12 months after LSG [48–50]. Although we did not measure serum leptin levels in this study, changes in circulating leptin levels were not correlated with changes in HDL-C levels at 12 months after LSG in a previous study [50]. The small GTPase Rab18 regulates adipocyte lipid metabolism in response to both, lipogenic (insulin) and lipolytic (β-adrenergic) inputs [51]. Furthermore, Rab18 is associated with the surface of lipid droplets in adipocytes, and its expression in adipose tissue correlates with increased adiposity [51]. Rab18 may therefore play an important role in increasing HDL-C after LSG.

Obesity is not only associated with lower serum HDL-C levels but also with decreased HDL function [52]. The cholesterol efflux capacity (CEC) is an HDL function assay, and HDL-C levels are a significant de-
terminant of CEC [53]. The apolipoprotein A-1 exchange rate (AER) is a cell-free HDL function assay and is related to serum HDL-C levels [54]. The AER is significantly increased at 1 and 5 years after sleeve gastrectomy, and changes in AER are significantly and positively correlated with changes in HDL-C levels at 5 years after treatment for obesity (intensive medial therapy, Roux-en-Y gastric bypass, and sleeve gastrectomy) [55]. ATP binding cassette transporter A1 (ABCA1) independent CEC, and not ABCA1-dependent CEC, is significantly increased at 5 years after sleeve gastroctomy; however, changes in ABCA1-independent CEC are not significantly correlated with changes in HDL-C [55]. Thus, the increase of AER may be a mechanism for increasing HDL-C levels after LSG. However, we did not investigate AER in this study; further studies are therefore needed to clear the relationship between changes in AER and HDL-C after LSG.

Obese patients with type 2 diabetes tend to experience less decrease treatment success compared with those without type 2 diabetes [56]. The changes in HDL-C after LSG were 17.0 (12.5–29.5) mg/dL in patients without type 2 diabetes and 17.0 (10.0–25.0) mg/dL in patients with type 2 diabetes; the p value was 0.4826. The changes in pre-heparin LPL levels after LSG were 30.1 (15.9–44.0) ng/mL in patients without type 2 diabetes and 26.6 (13.4–39.5) in patients with type 2 diabetes; the p value was 0.2710. Therefore, there was no differential treatment effect between obese patients with and without type 2 diabetes in this study.

This study has 2 limitations. First, although increased physical activity is associated with an increase in HDL-C levels, we lacked information on physical activity. Second, the single-center retrospective nature of the study limited the sample size. Therefore, future studies utilizing a larger, and more diverse set of samples are warranted to validate the results of this study. Despite this limitation, we were able to show that increased HDL-C levels were associated with decreased TG levels and increased pre-heparin LPL levels after LSG. In conclusion, the mechanisms involved in the increase in HDL-C levels after LSG are a decrease in TG and increase in LPL levels.

Acknowledgement

The authors are grateful to Sayaka Tsuji (Center for Diabetes, Endocrinology, and Metabolism, Toho University Sakura Medical Center, Sakura City, Chiba, Japan), a coordinator, for her assistance with patient care.

Statement of Ethics

This study was performed in accordance with the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of the Toho University Sakura Medical Center (approval date: November 28, 2018, approval No.: S18061). The retrospective nature of the study deferred the need for informed consent. Potential participants were given the opportunity to decline participation or opt out from the study.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

The authors did not receive any funding.

Author Contributions

M.O. contributed to the research concept and design, collection and/or assembly of data, data analysis, and writing of the article. Y.W. contributed to the collection and assembly of data. T.Y. contributed to the collection and assembly of data. H.O. contributed to the collection and assembly of data. K.A. contributed to the collection and assembly of data. S.Y. contributed to the collection and assembly of data. T.O. contributed to the collection and assembly of data. D.N. contributed to data interpretation. I.T. contributed to data interpretation and critical revision of the manuscript. A.S. contributed to the collection and/or assembly of the data and critical revision of the manuscript. All authors approved the version to be published.

Data Availability Statement

Data generated and/or analyzed during this research are available from the corresponding author on reasonable request.
Change in LPL Relates to Change in HDL-C after LSG

References

1. Miller GJ, Miller NE. Plasma-high-density-lipoprotein concentration and development of ischaemic heart-disease. Lancet. 1975 Jan; 1(7897):16–9.
2. Rössner S, Kjellin KG, Mettinger KL, Sidén A, Söderström CE. Normal serum-cholesterol but low H.D.L.-cholesterol concentration in young patients with ischaemic cerebrovascular disease. Lancet. 1978 Mar; 1(8064):577–9.
3. Jenkins PJ, Harper RW, Nestel PJ. Severity of coronary atherosclerosis related to lipoprotein concentration. Br Med J. 1978 Aug; 2(6134):388–91.
4. Kukkonen K, Rauramaa R, Voutilainen E, Hiitonen E. Body mass index and physical fitness as determinants of serum lipoprotein levels in middle-aged men. Clin Physiol. 1982 Jun; 2(3):251–62.
5. van J, Way WR, Godland IF, Crook D, Oliver MF, Stevenson JC. Insulin resistance syndrome as a feature ofcardiological syndrome X in non-obese men. Br Heart J. 1994 Jan;71(1):41–4.
6. Ing TH, Courcoulas AP, Jenkins TM, Michalsky MP, Helmraith MA, Brandt ML, et al. Weight loss and health status 3 years after bariatric surgery in adolescents. N Engl J Med. 2016 Jan;374(2):113–23.
7. Canha EM, Oliveira J, Preto J, Saavedra A, Costa MM, Magalhães D, et al. The effect of bariatric surgery type on lipid profile: an age, sex, body mass index and excess weight loss matched study. Obes Surg. 2016 May;26(5):1041–7.
8. Climent E, Benaiges D, Pedro-Botet J, Flores-Le Roux JA, Ramón JM, Villaroto M, et al. Atherogenic dyslipidemia remission 1 year after bariatric surgery. Obes Surg. 2017 Jun; 27(6):1548–53.
9. Genua I, Ramos A, Caimari F, Balagué C, Sánchez-Quesada JL, Pérez A, et al. Effects of bariatric surgery on HDL cholesterol. Obes Surg. 2020 May;30(5):1793–8.
10. Ohira M, Yamaguchi T, Saiki A, Nakamura S, Tanaka S, Oka R, et al. Laparoscopic sleeve gastrectomy significantly increases serum lipoprotein lipase level in obese patients. Obes Facts. 2019;12(3):357–68.
11. Schauer PR, Bhatt DL, Kirwan JP, Wolski K, Aminian A, Brethauer SA, et al. Bariatric surgery versus intensive medical therapy for diabetes—5-year outcomes. N Engl J Med. 2017 Feb;376(7):641–51.
12. Nikkilä EA, Taskinen MR, Kekki M. Relation of plasma high-density lipoprotein cholesterol to lipoprotein-lipase activity in adipose tissue and skeletal muscle of man. Atherosclerosis. 1978 Apr;29(4):497–501.
13. Kekki M. Lipoprotein-lipase action determining plasma high density lipoprotein cholesterol level in adult normolipamica. Atherosclerosis. 1980 Sep;57(1):143–50.
14. Saxena U, Witte LD, Goldberg II. Release of endothelial cell lipoprotein lipase by plasma lipopolipids and free fatty acids. J Biol Chem. 1989 Mar;264(8):4349–55.
15. Peterson J, Bibain BE, Bengtsson-Olivecrona G, Deckelbaum RJ, Carpentier YA, Olivecrona T. Fatty acid control of lipoprotein lipase: a link between energy metabolism and lipid transport. Proc Natl Acad Sci U S A. 1990 Feb; 87(3):909–13.
16. Kobayashi J, Hashimoto H, Fukamachi I, Tashiro J, Shirai K, Saito Y, et al. Lipoprotein lipase mass and activity in severe hypertriglyceridemia. Clin Chim Acta. 1993 Jul; 216(1-2):113–23.
17. Tornvall P, Olivecrona G, Karpe F, Hamsten A, Olivecrona T. Lipoprotein lipase mass and activity in plasma and their increase after heparin are separate parameters with different relations to plasma lipoproteins. Arterioscler Thromb Vasc Biol. 1995 Aug;15(8):1086–93.
18. Totsuka M, Miyashita Y, Ito Y, Watanabe H, Murano T, Hiro Y, Itoh Y, Shirai K. Preheparin serum lipoprotein lipase mass level: the effects of age, gender, and types of hyperlipidemias. Atherosclerosis. 1999 Jul; 145(1):45–50.
19. Ohira M, Miyashita Y, Ebisuno M, Saiki A, Endo K, Koide N, et al. Effect of metformin on serum lipoprotein lipase mass levels and LDL particle size in type 2 diabetes mellitus patients. Diabetes Res Clin Pract. 2007 Oct; 78(1):34–41.
20. Saiki A, Ohira M, Endo K, Koide N, Oyama T, Murano T, et al. Pioglitazone decreases plasma high-density lipoprotein cholesterol levels. J Atheroscler Thromb. 2010 Jun;17(6):651–7.
21. Denke MA, Sembros CT, Grundy SM. Excess body weight. An underestimated contributor to high blood cholesterol levels in white American men. Arch Intern Med. 1993 May; 153(9):1093–103.
22. Denke MA, Sembros CT, Grundy SM. Excess body weight. An under-recognized contributor to dyslipidemia in white American women. Arch Intern Med. 1994 Feb;154(4):410–1.
23. Streja DA, Boyko E, Rabkin SW. Changes in plasma high-density lipoprotein cholesterol concentration after weight reduction in grossly obese subjects. Br Med J. 1980 Sep; 281(6243):770–2.
24. Contaldo F, Strazzullo P, Postiglione A, Riccardi G, Patti L, di Biase G, et al. Plasma high density lipoprotein in severe obesity after stable weight loss. Atherosclerosis. 1980 Oct; 37(2):163–7.
25. Howard BV, Savage PJ, Nagulesparan M, Bennon LJ, Davis M, Bennett PH. Changes in plasma lipopolipids accompanying diet therapy in obese diabetics. Atherosclerosis. 1979 Aug;33(4):445–56.
26. Doğan S, Aslan I, Eryılmaz R, Ensari CO, Bilecik T, Aslan M. Early postoperative changes of HDL subclass profile and HDL-associated enzymes after laparoscopic sleeve gastrectomy. Obes Surg. 2013 Dec;23(12):1973–80.
27. Gilmore LA, Walzem RL, Crouse SF, Smith DR, Adams TH, Vaidyanathan V, et al. Consmption of high-oleic acid ground beef increases HDL-cholesterol concentration but both high- and low-oleic acid ground beef decrease HDL particle diameter in normocholesterolemic men. J Nutr. 2011 Jun;141(6):1188–94.
28. Hiyama M, Takehata M, Izuoka T, Shirai K. Effect of the angiotensin II receptor antagonist telmisartan on lipoprotein lipase mass in preheparin serum. J Atheroscler Thromb. 2008 Jun;13(3):138–45.
29. Schafer JI, Levy RI, Anderson DW, Danner RN, Brewer HB Jr, Blackwelder WC. Plasma triglycerides in regulation of H.D.L.-cholesterol levels. Lancet. 1978 Aug; 2(8086):391–3.
30. Wang H, Eckel RH. Lipoprotein lipase: from gene to obesity. Am J Physiol Endocrinol Metab. 2009 Aug;297(2):E271–88.
31. Dahms WT, Nilsson-Ehle P, Garfinkel AS, Atkinson RL, Bray GA, Schotz M. Lipoprotein lipase activity in adipose tissue from obese human beings. Int J Obes. 1981;5(1):81–4.
32. Hanyu O, Miida T, Obayashi K, Ikarashi T, Soda S, Kaneko S, et al. Lipoprotein lipase (LPL) mass in preheparin serum reflects insulin sensitivity. Atherosclerosis. 2004 Jun; 174(2):385–90.
33. Kobayashi J, Saito K, Fukamachi I, Taira K, Takahashi K, Bujo H, et al. Pre-heparin plasma lipoprotein lipase mass: correlation with intra-abdominal visceral fat accumulation. Horm Metab Res. 2001 Jul;33(7):412–6.
34. Eckel RH. Lipoprotein lipase. A multifunctional enzyme relevant to common metabolic diseases. N Engl J Med. 1989 Apr;320(16):1060–8.
35. Panarotto D, Rémillard P, Bouffard L, Maheux P, Insulin resistance affects the regulation of lipoprotein lipase in the postprandial period and in an adipose tissue-specific manner. Eur J Clin Invest. 2002 Feb;32(2):84–92.
36. Goldberg II, Blaner WS, Vanni TM, Moukides M, Ramakrishnan R. Role of lipoprotein lipase in the regulation of high density lipoprotein apolipoprotein metabolism. Studies in normal and lipoprotein lipase-inhibited monkeys. J Clin Invest. 1990 Aug;86(2):463–73.
37. Tsutsui K, Inoue Y, Shima A, Iwaski K, Kawamura M, Murase T. The novel compound NO-1886 increases lipoprotein lipase activity with resulting elevation of high density lipoprotein cholesterol, and long-term administration inhibits atherogenesis in the coronary arteries of rats with experimental atherosclerosis. J Clin Invest. 1993 Jul;92(1):411–7.
39 Hirano T, Nishioka F, Murakami T. Measurement of the serum lipoprotein lipase concentration is useful for studying triglyceride metabolism: comparison with postheparin plasma. *Metabolism*. 2004 Apr; 53(4):526–31.

40 Howard BV, Ruotolo G, Robbins DC. Obesity and dyslipidemia. *Endocrinol Metab Clin North Am.* 2003 Dec; 32(4):855–67.

41 Mead JR, Irvine SA, Ramji DP. Lipoprotein lipase: structure, function, regulation, and role in disease. *J Mol Med.* 2002 Dec; 80(12):753–69.

42 Taskinen MR, Nikkilä EA, Kuusi T, Harmo K. Lipoprotein lipase activity and serum lipoproteins in untreated type 2 (insulin-independent) diabetes associated with obesity. *Diabetologia.* 1982 Jan; 22(1):46–50.

43 Agellon LB, Walsh A, Hayek T, Moulin P, Jiang XC, Shelanski SA, et al. Reduced high density lipoprotein cholesterol in human cholesteryl ester transfer protein transgenic mice. *J Biol Chem.* 1991 Jun; 266(17):10796–801.

44 Tato F, Vega GL, Grundy SM. Determinants of plasma HDL-cholesterol in hypertriglyceridemic patients. Role of cholesteryl-ester transfer protein and lecithin cholesterol acyltransferase. *Arterioscler Thromb Vasc Biol.* 1997 Jan; 17(1):56–63.

45 Araú T, Yamashita S, Hirano K, Sakai N, Kotani K, Fujioka S, et al. Increased plasma cholesteryl ester transfer protein in obese subjects. A possible mechanism for the reduction of serum HDL cholesterol levels in obesity. *Arterioscler Thromb.* 1994 Jul; 14(7):1129–36.

46 Reynolds D, Eriksson M, Angelin B, Arner P. Impaired activation of adipocyte lipolysis in familial combined hyperlipidemia. *J Clin Invest.* 1995 May; 95(5):2161–9.

47 Rydén M, Arner P. Subcutaneous adipocyte lipolysis contributes to circulating lipid levels. *Arterioscler Thromb Vasc Biol.* 2017 Sep; 37(9):1782–7.

48 Frühbeck G, Gómez-Ambrosi J, Salvador J. Leptin-induced lipolysis opposes the tonic inhibition of endogenous adenosine in white adipocytes. *FASEB J.* 2001 Feb; 15(2):333–40.

49 Frühbeck G, Gómez-Ambrosi J. Modulation of the leptin-induced white adipose tissue lipolysis by nitric oxide. *Cell Signal.* 2001 Nov; 13(11):827–33.

50 Salman MA, El-Ghobary M, Soliman A, El Sherbiny M, Abouelregal TE, Albitar A, et al. Long-term changes in leptin, chemerin, and ghrelin levels following Roux-en-Y gastric bypass and laparoscopic sleeve gastrectomy. *Obes Surg.* 2020 Mar; 30(3):1052–60.

51 Pulido MR, Díaz-Ruiz A, Jiménez-Gómez Y, García-Navarro S, Gracia-Navarro F, Tinhones F, et al. Rab18 dynamics in adipocytes in relation to lipogenesis, lipolysis and obesity. *PLoS One.* 2011; 6(7):e22931.

52 Annema W, Dikkers A, de Boer JF, van Grevenbroek MMJ, van der Kallen CJH, Schalkwijk CG, et al. Impaired HDL cholesterol efflux in metabolic syndrome is unrelated to glucose tolerance status: the CODAM study. *Sci Rep.* 2016 Jun; 6:27367.

53 Khera AV, Cuchel M, de la Llera-Moya M, Rodrigues A, Burke MF, Jafri K, et al. Cholesterol efflux capacity, high-density lipoprotein function, and atherosclerosis. *N Engl J Med.* 2011 Jan; 364(2):127–35.

54 Lorkowski SW, Brubaker G, Li L, Li XS, Hassen SL, Smith JD. A novel cell-free fluorescent assay for HDL function: low apolipoprotein A1 exchange rate associated with increased incident cardiovascular events. *J Appl Lab Med.* 2020 May; 5(3):544–57.

55 Lorkowski SW, Brubaker G, Rotroff DM, Kashyap SR, Bhatt DL, Nissen SE, et al. Bariatric surgery improves HDL function examined by ApoA1 exchange rate and cholesterol efflux capacity in patients with obesity and Type 2 diabetes. *Biomolecules.* 2020 Apr; 10(4):551.

56 Leitner DR, Frühbeck G, Yumuk V, Schindler K, Micic D, Woodward E, et al. Obesity and type 2 diabetes: two diseases with a need for combined treatment strategies – EASO can lead the way. *Obes Facts.* 2017; 10(5):483–92.