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Changes in Albuminuria after Bariatric Surgery in Obese Patients with Normal Renal Function are Associated with Reduced Adipocyte Insulin Resistance

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Abstract

Background: Obesity induces insulin resistance, increases serum free fatty acids (FFAs), and causes renal problems including albuminuria. Adipocyte insulin resistance has an important effect on occurrence of whole-body insulin resistance, which is correlated with fasting free fatty acids and fasting insulin levels. Bariatric surgery (BS) improves albuminuria, free fatty acid and insulin levels. We investigated whether albuminuria associates with adipocyte insulin resistance and whether following BS a reduction in albuminuria relates to the improvement of adipocyte insulin resistance.

Methods: We included patients aged >18 years receiving BS in Beijing Chao-Yang Hospital between January 1st, 2020 and December 31st, 2022. A 6-month follow-up was conducted in these patients following BS.

Results: Fifty-seven patients were analysed, including 26 men. Of them, 16 developed diabetes, whereas 15 suffered from hypertension. No obvious abnormality was detected in renal function (creatinine≤1.0 mg/dL), with an estimated glomerular filtration rate of 120.24 ± 14.22 mL/min/1.73m^2. Significant reductions existed in FFA levels, serum insulin levels, HOMA-IR, adipo-IR, and urine albumin-to-creatinine ratio (ACR) at 6 months post-BS. Besides, delta ACR showed a positive relationship to delta adipo-IR ($r = 0.371$, $p = 0.004$). As revealed by linear stepwise regression, delta adipo-IR ($\beta = 0.006$, $p = 0.028$) independently predicted the risk of delta ACR.

Conclusions: This study indicates that BS can decrease albuminuria in obese patients with normal renal function partly through decreasing adipocyte insulin resistance.

Keywords: Albuminuria; Bariatric Surgery; Adipocyte Insulin Resistance

Introduction

Obesity, the chronic disorder, results from excess fat accumulation, which is associated with metabolic abnormalities such as glucose and lipid metabolic impairment and insulin resistance [1]. Such abnormalities can lead to complications, including stroke, hypertension, type 2 diabetes mellitus, and coronary artery disease [2]. Obesity can also lead to renal damage, including proteinuria, chronic kidney disease (CKD), or even end-stage renal disease [3,4]. Obesity-related glomerulopathy (ORG) is a common complication of obesity, with microalbuminuria or clinically dominant albuminuria as the primary manifestation. The mechanisms of obesity-related kidney damage are correlated with insulin resistance and altered renal haemodynamics [5].

Insulin resistance indicates the reduced insulin response in certain tissues, including hepatic tissue, peripheral muscle tissue and adipose tissue [6]. Adipocytes are the key insulin-responsive tissue, which is important for the whole-body metabolism of glucose and lipid. Recently, adipocyte insulin resistance has gained much attention regarding the effects of lipid and glucose metabolism. However, the effect of adipocyte insulin resistance on obesity-related kidney damage has been less investigated. The gold standard for measuring adipocyte insulin sensitivity is the adipose tissue insulin index, which can be calculated through multiplying fasting FFA by insulin contents [7].

In obesity, free fatty acids (FFAs) can be released by adipose tissues through unsuppressed lipolysis, which accounts for a major characteristic of adipose insulin resistance. FFAs in circulation have an important effect on the decreased insulin sensitivity [7]. Excessive FFAs released from adipose tissue escape into other organs based on the circulatory system and result in lipotoxicity, insulin resistance and beta-cell dysfunction [8]. It has been indicated that high FFA levels are related to the increased urinary albumin excretion and impaired glomerular filtration function [9,10]. Excessive triglycerides and FFAs can result in glomerular and tubular lesions. Reduction of triglycerides by fenofibrate can lead to improvements in insulin resistance and microalbuminuria in mice [11].

Bariatric surgery is identified with the highest efficacy in treating severe obesity and the relevant comorbidities [12]. Metabolism is greatly improved following bariatric surgery, including reduction of microalbuminuria and FFA [13]. Besides, bariatric surgery is found to enhance glycaemic control and insulin resistance among obese patients who develop diabetes [14].

Although recent evidence sheds substantial lights on metabolic improvements in FFA and renal damage postoperatively, the underlying mechanism between FFA-related adipocyte insulin resistance and obesity-related glomerulopathy has not been completely elucidated. Therefore, the current prospective study attempted to explore the association between adipocyte insulin resistance and obesity-related albuminuria.

Materials and Methods

Subjects

The present prospective cohort study recruited obese patients (BMI ≥ 30 kg/m^2) aged >18 years receiving bariatric surgery (laparoscopic Roux-en Y gastric bypass surgery or gastric sleeve surgery) at the General Surgery Department of Beijing Chao-Yang Hospital between January 1st, 2020 and December 31st, 2022. Patients below were eliminated, including overt proteinuria evidenced by undetectable or trace dipstick test results and CKD (creatinine ≥ 1.0 mg/dL). One physician was responsible for 6-month follow-up of all patients after discharge. This study was carried out in line with the Declaration of Helsinki of the World Medical Association. Informed consent was acquired from every subject. This work gained approval from the Ethics and Research Committee of Beijing Chao-yang hospital, Beijing, China.

Data Collection

The perioperative clinical data were age, gender, blood pressure, height, weight, BMI, and surgery mode. In addition, we also measured FFAs, serum albumin, fasting glucose, aspartate transaminase (AST), alanine aminotransferase (ALT), total cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), blood urea nitrogen, serum creatinine, uric acid, fasting serum insulin and urine ACR. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was employed for calculating glomerular filtration rate (GFR) [15]. The formula below was used to determine the homeostasis model assessment of insulin resistance (HOMA-IR) index, namely, HOMA-IR=fasting blood glucose levels (mM) × fasting blood insulin levels (mUI/L)/22.5 [16]. At the same time, we determined the adipocyte insulin resistance (adipo-IR) index as (fasting FFAs × fasting insulin [17].

Statistical Analysis

Continuous variables were represented by mean ± standard deviation or median (interquartile range), whereas categorical variables by frequencies (sample percentage or number). The paired t-test or Wilcoxon signed-rank test was applied in evaluating differences in continuous variables before and after surgery. Abnormally-distributed continuous variables were subjected to log transfection prior to analysis. To obtain delta values, we subtracted the value determined 6 months following BS from the baseline value. Correlation coefficient was evaluated by Pearson's correlation analysis. Independent risk factors affecting alterations of proteinuria, such as values verified as $p<0.05$ upon Pearson's correlation analysis or those with clinical significance (age, gender, smoking history, alcohol history, hypertension history, diabetes history, surgical technique) were assessed through multivariate linear stepwise regression. Statistical analysis was completed with SPSS26.0 (SPSS Inc., Chicago, IL, USA).

Results

Baseline Characteristics of the Obese Patients

Table 1 displays basic features for those obese patients. Totally 57 obese patients were finally analysed, with the age ranging from 19 to 50 (median, 31) years and the follow-up period of 6 months. Twenty-six patients were male. In addition, there were 15 patients with hypertension and 16 patients suffering from diabetes. Among them, there were 6 patients receiving laparoscopic Roux-en-Y gastric bypass, while 51 undergoing laparoscopic sleeve gastrectomy.

Table 1: Baseline characteristics of the patients (n=57)

| Parameters	Characteristics
Age, years	30.89 ± 7.81
Sex (M/F), n (%)	Male 26 (45.61%)Female 31 (54.39%)
Smoking, n (%)	5 (8.87%)
Alcohol, n (%)	7 (12.28%)
Hypertension, n (%)	15 (26.32%)
Diabetes, n (%)	16 (28.07%)
Surgical technique, n (%)	SG 51 (89.47%)LRYGB 6 (10.53%)

LRYGB, laparoscopic Roux-en Y gastric bypass; SG, laparoscopic sleeve gastrectomy

## Changes in Various Clinical Parameters before and after BS

Changes in various clinical parameters before and after BS are shown in Table 2. All the enrolled patients had normal creatinine levels (≤1.0 mg/dL) without overt proteinuria, and estimated GFR (eGFR) was estimated to be 120.24 ± 14.22 mL/min/1.73m^2 with CKD-EPI equation (Table 2). There was no obvious abnormality of ACR (<30 mg/g) for 43 patients, 14 patients had microalbuminuria (30–300 mg/g). No patient had macroalbuminuria (>300 mg/g). Following BS, just 3 cases still had microalbuminuria, while none of these patients had macroalbuminuria. BS significantly declined body weight, BMI, FFAs, AST, ALT, TC, triglycerides, uric acid, creatinine, ACR, eGFR, fasting glucose, fasting insulin, HOMA-IR index and adipo-IR index. The average delta ACR was 16.74 mg/g. ACR was positively related to adipo-IR both before and after BS (r = 0.338, p = 0.010, Figure 1; r = 0.337, p = 0.010, Figure 2). Moreover, there were also positive associations between delta ACR and delta adipo-IR (r = 0.371, p = 0.004, Figure 3).
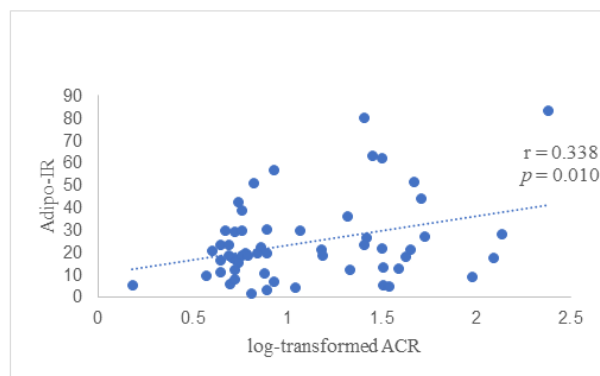
Figure 1: Plot showing the correlation between adipo-IR and ACR before BS (r=0.338, p=0.010)
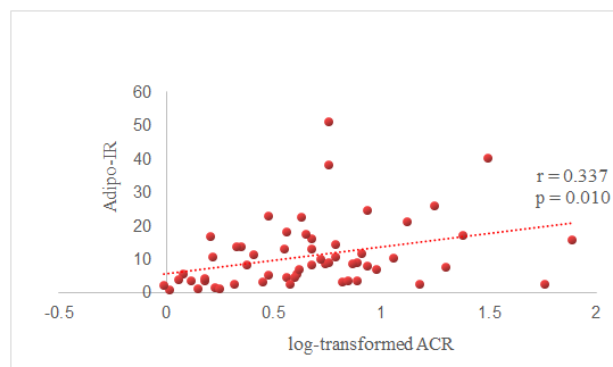
Figure 2: Plot showing the correlation between adipo-IR and ACR after BS (r=0.337, p=0.010)
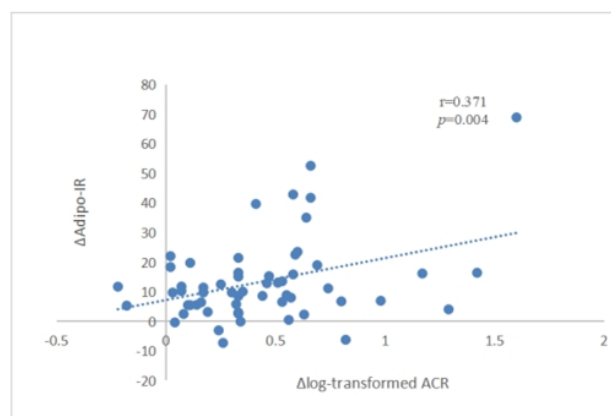
Figure 3: Plot showing the correlation between delta adipo-IR and delta ACR (r = 0.371, p<0.001)

Table 2: Changes in parameters between baseline and 6 months after BS

Parameters	Baseline	After 6 months	p value
Body weight (kg)	111.5 ± 19.34	82.6 ± 15.21	< 0.001
BMI (kg/m2)	38.97 ± 5.43	28.91 ± 4.81	< 0.001
SBP (mmHg)	125.91 ± 11.55	123.88 ± 8.50	0.056
DBP (mmHg)	83.16 ± 8.17	81.95 ± 6.19	0.011
Albumin (g/L)	47.87 ± 8.17	46.26 ± 3.70	0.121
Glucose (mmol/L)	7.10 ± 2.96	5.03 ± 1.13	< 0.001
AST (U/L)	32.63 ± 29.21	19.28 ± 10.48	0.001
ALT (U/L)	51.16 ± 37.6	28.46 ± 18.22	< 0.001
Total cholesterol (mmol/L)	4.73 ± 0.97	4.47 ± 0.89	0.026
LDL-c (mmol/L)	3.01 ±0.77	2.79 ± 0.87	0.038
HDL-c (mmol/L)	1.05 ± 0.22	1.12 ± 0.23	0.020
Triglycerides (mmol/L)	2.13 ± 1.99	1.31 ± 0.77	< 0.001
Uric acid (μmol/L)	444.4 ± 119.2	374.6 ± 96.53	< 0.001
FFA (mmol/L)	0.85 ± 0.31	0.63 ± 0.39	< 0.001
Fasting insulin (μIU/ml)	28.53 ± 18.82	17.5 ± 12.64	< 0.001
Blood urea nitrogen (mg/dL)	4.80 ± 1.20	4.85 ± 1.27	0.644
Creatinine (μmol/L)	61.00 ± 14.25	60.86 ± 17.25	0.933
UACR (mg/g creatinine)	7.80 (5.30, 31.65)	4.47 (2.18, 7.77)	< 0.001
eGFR (mL/min/1.73 m2)	120.24 ± 14.22	117.49 ± 14.56	0.039
HOMA-IR	8.65 ± 6.88	3.93 ± 2.98	< 0.001
Adipo-IR	24.24 ± 18.20	10.89 ± 10.09	< 0.001

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, AST aspartate aminotransferase, ALT alanine aminotransferase, LDL-c low-density lipoprotein cholesterol, HDL-c high-density lipoprotein cholesterol, FFA free fatty acid, UACR urine albumin-to-creatinine ratio, eGFR estimated glomerular filtration rate.

Pearson's Correlation Analysis Between Δ Log-ACR and the Changes in Other Metabolic Parameters

Table 3 exhibits correlation between delta log-transformed ACR and the changes in other metabolic parameters. There existed a significant positive relationship between delta ACR and the changes in fasting glucose (r = 0.404, p = 0.002), triglycerides (r = 0.282, p = 0.034), fasting insulin (r = 0.345, p = 0.009), HOMA-IR (r = 0.482, p < 0.001) and adipo-IR (r = 0.371, p = 0.004). Nevertheless, there was no association observed between delta ACR and delta BMI, cholesterol, FFAs, or blood pressure.

Table 3: Pearson's correlation analysis of Δ log-ACR

parameters	r-value	p-value
Δ Body weight	-0.207	0.123
Δ BMI	-0.192	0.153
Δ SBP	0.135	0.317

Δ DBP	0.184	0.170
Δ Glucose	0.404	0.002
Δ LDL-c	0.041	0.764
Δ HDL-c	0.064	0.637
Δ Triglycerides	0.282	0.034
Δ FFA	0.063	0.641
Δ Fasting insulin	0.345	0.009
Δ HOMA-IR	0.482	< 0.001
Δ Adipo-IR	0.371	0.004

Table 4: Effect of parameters on Δ log-ACR: results of stepwise regression model

	b-value	**95%CI**	*p-value*
Hypertension history	0.31	(0.141, 0.480)	0.001
Δ Glucose	0.035	(0.008, 0.063)	0.013
Δ Triglycerides	0.054	(0.006, 0.102)	0.029
Δ Adipo-IR	0.006	(0.001, 0.012)	0.028

BMI body mass index, SBP systolic blood pressure, DBP diastolic blood pressure, LDL-c low-density lipoprotein cholesterol, HDL-c high-density lipoprotein cholesterol, FFA free fatty acid

Multiple Linear Stepwise Regression Analysis of Delta ACR

Linear stepwise regression model was adopted for exploring the independent risk factors that affect the changes in albuminuria. We found hypertension history was associated with delta ACR and changes in fasting glucose, triglycerides, and adipo-IR were still correlated with delta ACR after regression analysis.

Discussion

According to our results, BMI, metabolic parameters and renal function (including eGFR and ACR) significantly improved at 6 months after BS in obese patients. ACR was associated with adipo-IR both before and after BS. Moreover, the changes of the two indicators were still positively correlated. Besides, the change of ACR was also associated with the change of glucose, fasting insulin, triglycerides and HOMA-IR. Linear regression model showed hypertension history and the changes in fasting glucose, triglycerides, and adipo-IR could predict the change of ACR after BS.

BS is a choice of treatment in severe obese patients and significantly reduces body weight and insulin resistance after surgery [18]. Former study has found that there were different mechanisms of metabolic improvements in diabetic patients during different phases after BS. Early glycemic amelioration was mainly due to the changes in neuroendocrine pathways and adipose factors might contribute to long-term insulin sensitivity [19]. Further studies found insulin kinetics altered after BS, resulting an increase in hepatic insulin clearance [20]. Weight loss after surgery was related to a decrease of ectopic fat deposition in pancreas, which correlated with the improvement of glucose homeostasis [21]. Besides, the expression of glucose and lipid metabolism genes altered after BS in white adipose tissue of diabetic rats [22]. DNA methylation has a critical effect on metabolic improvement post-BS [23]. These results might explain the improvements in metabolic parameters after BS and were consistent with our finding that fasting blood glucose, serum insulin levels and blood lipids were notably decreased.

Our study also proved that FFAs were significantly decreased six months after BS. FFAs, adipocyte-derived secreted products formed via triglyceride (TG) hydrolysis, are the primary energy source during fasting and play a vital role in regulating energy metabolism [24]. However, sustained FFA elevation was correlated with obesity and insulin resistance [25,26]. A previous study indicated that circulating FFA levels were higher in subjects with morbid obesity in relative to lean subjects [27]. BS enhanced plasma GLP-1 level reducing fat load and increasing fatty acid -oxidation by activated autophagy to control the hepatic lipid pathway by mTOR/p70S6K signaling pathway [28].

Previous studies showed that renal function was improved after BS [29-31], conforming to our findings. We found glomerular hyperfiltration improved after surgery, manifested as decreased ACR and eGFR. The degree of reduction in log-transformed ACR was significantly correlated with changes in adipo-IR index. These results might suggest that insulin resistance of adipose tissue improved by BS subsequently leads to reduced albuminuria. Previous studies found renal FFA uptake was ~50% higher in the obese as a result of higher circulating FFA levels [27] and saturated fatty acids could inhibit insulin-stimulated glucose uptake in human podocytes causing podocytes insulin resistance, which presented a link between fatty acids and nephropathy [32]. Besides, the reduction in FFA plasma levels by thiazolidinediones or fenofibrate has been shown to be related to reducing microalbuminuria [33,10]. Our study also proved that the changes of TG and adipo-IR could predict the change of ACR after BS. Indicating that Obesity-related renal damage could be associated with excessive triglycerides accumulation and adipocyte insulin resistance. The improvement of adipo-IR could reduce urinary microalbumin excretion, which implied the amelioration of the pathological process in obesity-related nephropathy.

BS can effectively treat weight loss and the relevant comorbidities among severe obesity patients. Prior studies reported that BS was an effective strategy for blood pressure control and hypertension remission [34]. According to our results, BS caused obvious weight loss and remarkably declined the diastolic blood pressure. However, there existed no statistically significant change in systolic blood pressure after BS. This could be resulted from the small number of hypertensive patients in the current work. Only 15 patients (26.3%) had hypertension, and their blood pressure was stable before BS (125.91 ± 11.55mmHg). Moreover, we also found patients with hypertension history had a greater improvement in ACR after BS. A former study found the severity of hypertension increased in parallel with the rise in albuminuria among diabetic patients [35]. Obese patients might achieve improvement in blood pressure following BS by decreasing fat accumulation in renal sinus [36]. Besides, as in previous reports, serum uric acid, AST and ALT levels decreased in our study [37].

Certain limitations should be noted in the present work. At first, the sample size of this study was relatively small, making it challenging to determine the applicability of our results in all the Chinese obese individuals. Second, another limitation was the approach for measuring albuminuria level and determining GFR. We evaluated albuminuria based on spot ACR, rather than 24-h urine. GFR was analyzed according to CKD-EPI equation, rather than 24-h creatinine clearance. Third, the observation period was relatively short in our study. A longer follow-up duration is needed. However, we found adipocyte insulin resistance was associated with albuminuria and a decrease in ACR following BS was correlated with the improvement of adipocyte insulin resistance in patients who had normal renal function. Moreover, our findings may provide a new idea for understanding obesity-related glomerulopathy and shed light on new thoughts for the treatment.

To sum up, BS decreases albuminuria among the obese patients who have normal renal function, which is achieved through decreasing the adipocyte insulin resistance.

Acknowledgments

References

1. Yazici D, Sezer H (2017) Insulin Resistance, Obesity and Lipotoxicity. ADV EXP MED BIOL, 960: 277-304.

2. Haslam DW (2005) James WP Obesity LANCET, 366: 1197-209.

3. Navarro-Diaz M, Serra A, Lopez D, Granada M, Bayes B, Romero R (2008) Obesity, inflammation, and kidney disease. KIDNEY INT SUPPL, S15-8.

4. de Jong PE, Verhave JC, Pinto-Sietsma SJ, Hillege HL (2002) Obesity and target organ damage: the kidney. Int J Obes Relat Metab Disord, 26: S21-4.

5. D'Agati VD, Chagnac A, de Vries AP, Levi M, Porrini E, Herman-Edelstein M, et al. (2016) Obesity-related glomerulopathy: clinical and pathologic characteristics and pathogenesis. NAT REV NEPHROL, 12: 453-71.

6. Hershkop K, Besor O, Santoro N, Pierpont B, Caprio S, Weiss R (2016) Adipose Insulin Resistance in Obese Adolescents Across the Spectrum of Glucose Tolerance. J Clin Endocrinol Metab, 101: 2423-31.

7. Groop LC, Bonadonna RC, DelPrato S, Ratheiser K, Zyck K, Ferrannini E et al. (1989) Glucose and free fatty acid metabolism in non-insulin-dependent diabetes mellitus. Evidence for multiple sites of insulin resistance. J CLIN INVEST, 84: 205-13.

8. Oh YS, Bae GD, Baek DJ, Park EY, Jun HS (2018) Fatty Acid-Induced Lipotoxicity in Pancreatic Beta-Cells During Development of Type 2 Diabetes. Front Endocrinol (Lausanne), 9: 384.

9. Hou N, Han F, Wang M, Huang N, Zhao J, Liu X et al. (2014) Perirenal fat associated with microalbuminuria in obese rats. INT UROL NEPHROL, 46: 839-45.

10. Sun X, Yu Y, Han L (2013) High FFA levels related to microalbuminuria and uncoupling of VEGF-NO axis in obese rats. INT UROL NEPHROL, 45: 1197-207.

11. Gai Z, Wang T, Visentin M, Kullak-Ublick GA, Fu X, Wang Z (2009) Lipid Accumulation and Chronic Kidney Disease. NUTRIENTS, 11.

12. Sjostrom L, Lindroos AK, Peltonen M, Torgerson J, Bouchard C, Carlsson B et al. (2004) Lifestyle, diabetes, and cardiovascular risk factors 10 years after bariatric surgery. N Engl J Med, 351: 2683-93.

13. Alkharaiji M, Anyanwagu U, Donnelly R, Idris I (2020) Effect of Bariatric Surgery on Diagnosed Chronic Kidney Disease and Cardiovascular Events in Patients with Insulin-treated Type 2 Diabetes: a Retrospective Cohort Study from a Large UK Primary Care Database. OBES SURG, 30: 1685-95.

14. Schauer PR, Kashyap SR, Wolski K, Brethauer SA, Kirwan JP et al. (2012) Bariatric surgery versus intensive medical therapy in obese patients with diabetes. N Engl J Med, 366: 1567-76.

15. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AR, Feldman HI et al. (2009) A new equation to estimate glomerular filtration rate. ANN INTERN MED, 150: 604-12.

16. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC (1985) Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. DIABETOLOGIA, 28: 412-9.

17. Saponaro C, Gaggini M, Carli F, Gastaldelli A (2015) The Subtle Balance between Lipolysis and Lipogenesis: A Critical Point in Metabolic Homeostasis. NUTRIENTS, 7: 9453-74.

18. Magouliotis DE, Tasiopoulou VS, Sioka E, Chatedaki C, Zacharoulis D (2017) Impact of Bariatric Surgery on Metabolic and Gut Microbiota Profile: a Systematic Review and Meta-analysis. OBES SURG, 27: 1345-57.

19. Almby KE, Katsogiannos P, Pereira MJ, Karlsson FA, Sundbom M, Wiklund U et al.(2021) Time Course of Metabolic, Neuroendocrine, and Adipose Effects During 2 Years of Follow-up After Gastric Bypass in Patients With Type 2 Diabetes. J Clin Endocrinol Metab, 106: e4049-61.

20. Salehi M, DeFronzo R, Gastaldelli A (2022) Altered Insulin Clearance after Gastric Bypass and Sleeve Gastrectomy in the Fasting and Prandial Conditions. INT J MOL SCI, 23.

21. Salman AA, Salman MA, Said M, El SM, Elkassar H, Hassan MB et al. (2022) Improvement of Pancreatic Steatosis and Indices of Insulin Resistance After Metabolic Surgery. Front Med (Lausanne), 9: 894465.

22. Zhang LH, Wang J, Tan BH, Yin YB, Kang YM (2022) The Association of lncRNA and mRNA Changes in Adipose Tissue with Improved Insulin Resistance in Type 2 Obese Diabetes Mellitus Rats after Roux-en-Y Gastric Bypass. DIS MARKERS, 2022: 8902916.

23. Morcillo S, Martin-Nunez GM, Garcia-Serrano S, Gutierrez-Repiso C, Rodriguez-Pacheco F et al. (2017) Changes in SCD gene DNA methylation after bariatric surgery in morbidly obese patients are associated with free fatty acids. Sci Rep, 7: 46292.

24. Rosen ED, Spiegelman BM (2006) Adipocytes as regulators of energy balance and glucose homeostasis. NATURE, 444:847-53.

25. Prentki M, Joly E, El-Assaad W, Roduit R (2002) Malonyl-CoA signaling, lipid partitioning, and glucolipotoxicity: role in beta-cell adaptation and failure in the etiology of diabetes. DIABETES, 51: S405-13.

26. Lytle KA, Bush NC, Triay JM, Kellogg TA, Kendrick ML, Swain JM et al. (2021) Adipocyte Proteins and Storage of Endogenous Fatty Acids in Visceral and Subcutaneous Adipose Tissue in Severe Obesity. Obesity (Silver Spring), 29:1014-21.

27. Rebelos E, Dadson P, Oikonen V, Iida H, Hannukainen JC, Iozzo P et al. (2019) Renal hemodynamics and fatty acid uptake: effects of obesity and weight loss. Am J Physiol Endocrinol Metab, 31: E871-8.

28. Ma N, Ma R, Tang K, Li X, He B. Roux-en-Y (2020) Gastric Bypass in Obese Diabetic Rats Promotes Autophagy to Improve Lipid Metabolism through mTOR/p70S6K Signaling Pathway. J DIABETES RES, 2020: 4326549.

29. Nehus EJ, Khoury JC, Inge TH, Xiao N, Jenkins TM, Moxey-Mims MM et al. (2017) Kidney outcomes three years after bariatric surgery in severely obese adolescents. KIDNEY INT, 91: 451-8.

30. Fathy E, Aisha H, Abosayed AK, ElAnsary A, Al AA (2022) Effect of Bariatric Surgery on Albuminuria in Non-Diabetic Non-Hypertensive Patients with Severe Obesity: a Short-Term Outcome. OBES SURG, 32: 2397-402.

31. Mahmoudieh M, Keleidari B, Hadipour P, Sheikhbahaei E, Chang AR, Ramtin S et al. (2021) Comparative Effectiveness of Roux-en-Y Gastric Bypass vs. One Anastomosis Gastric Bypass on Kidney Function. OBES SURG, 31: 2464-70.

32. Lennon R, Pons D, Sabin MA, Wei C, Shield JP, Coward RJ et al. (2009) Saturated fatty acids induce insulin resistance in human podocytes: implications for diabetic nephropathy. Nephrol Dial Transplant, 24: 3288-96.

33. Wyne KL (2003) Free fatty acids and type 2 diabetes mellitus. AM J MED, 115: 29S-36S.

34. Schiavon CA, Bhatt DL, Ikeoka D, Santucci EV, Santos RN, Damiani LP et al. (2020) Three-Year Outcomes of Bariatric Surgery in Patients With Obesity and Hypertension: A Randomized Clinical Trial. ANN INTERN MED, 173: 685-93.

35. Georgianou E, Markakis K, Georgianos P, Zografou I, Sachinidis A, Sabanis C et al. (2022) Prevalence and Control of Hypertension In Diabetic Patients with Versus Without Chronic Kidney Disease. J Hypertens, 40: e211.

36. Moritz E, Dadson P, Saukko E, Honka MJ, Koskensalo K, Seppala K et al. (2022) Renal Sinus Fat Is Expanded in Patients with Obesity and/or Hypertension and Reduced by Bariatric Surgery Associated with Hypertension Remission. Metabolites, 12.

37. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K et al. (2004) Bariatric surgery: a systematic review and meta-analysis. JAMA, 292:1724-37.