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Lipoprotein Insulin Resistance Score in non-diabetic patients with obesity and following bariatric surgery

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Abstract

Background—Lipoprotein insulin resistance (LPIR) is a composite biomarker representative of atherogenic dyslipidemia characteristic of early insulin resistance. It is elevated in obesity and may provide information not captured in hemoglobin A1c (A1C) and homeostatic model assessment for insulin resistance (HOMA-IR). While bariatric surgery reduces diabetes incidence and resolves metabolic syndrome, the effect of bariatric surgery on LPIR is untested.

Objectives—We sought to assess the effects of Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) on LPIR in non-diabetic women with obesity.

Settings—Non-smoking, non-diabetic, premenopausal Hispanic women, age 18 years, undergoing RYGB or SG at Bellevue Hospital (New York, NY) were recruited for a prospective observational study.

Methods—Anthropometric measures and blood sampling were performed preoperatively and at six, and 12 months postoperatively. LPIR was measured by Nuclear Magnetic Resonance (NMR) spectroscopy.

Results—Among 53 women (RYGB, n=22; SG, n=31), mean age was 32±7 years and body mass index (BMI) 44.1±6.4 kg/m². LPIR was reduced by 35±4% and 46±4% at six and 12 months after surgery, respectively, with no difference by procedure. Twenty-seven of 53 subjects met International Diabetes Federation (IDF) criteria for metabolic syndrome preoperatively and had concomitant higher HOMA-IR, A1C, non-high density lipoprotein-cholesterol (nonHDL-C) and

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Conflict of interest:

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

LPIR. Twenty-five of 27 subjects experienced resolution of metabolic syndrome postoperatively. Concordantly, the preoperative differences in HOMA-IR, A1C and nonHDL-C between those with and without metabolic syndrome resolved at six and 12 months. In contrast, subjects with metabolic syndrome preoperatively exhibited greater LPIR scores at six and 12 months postoperatively.

Conclusion—This is the first study to demonstrate improvement in insulin resistance, as measured by LPIR, following bariatric surgery with no difference by procedure. This measure, but not traditional markers, was persistently higher in subjects with a preoperative metabolic syndrome diagnosis, despite resolution of the condition.

Keywords

lipoprotein insulin resistance score; insulin resistance; metabolic syndrome; bariatric surgery; dyslipidemia; cardiometabolic risk

Introduction

Preclinical insulin resistance often precedes the diagnosis of Type II diabetes (T2D) by many years [1]. Among nondiabetic individuals, insulin resistance is associated with not only incident T2D, but also increased risk of atherosclerosis, myocardial infarction and overall mortality [2,3] – outcomes that are at least partially due to atherogenic dyslipidemia of insulin resistance [4]. There are at least four sets of varied clinical diagnostic criteria for the insulin resistance syndrome [5] (more commonly known as the metabolic syndrome), which is a strong independent risk factor for cardiovascular disease [6]. Sensitive techniques for identifying insulin resistance are thus of critical importance.

A number of laboratory methods are used to assess insulin resistance. The gold standard remains glucose disposal rate (GDR) measured with a hyperinsulinemic-euglycemic clamp [7]. However, as this test is invasive and labor intensive, it is not routinely performed clinically. The most commonly used clinical marker is hemoglobin A1c (A1C), a measurement of the mean blood glucose level over the previous three months. Despite its ubiquitous use for assessing glycemia and diabetes management, A1C has several limitations. For example, A1C does not reflect glycemic variation [8]. Additionally, changes in hemoglobin features and erythrocyte turnover can influence A1C values. Another measure, the homeostatic model assessment of insulin resistance (HOMA-IR), reflects changes in insulin resistance in the liver [9]. It is widely employed in clinical and epidemiologic studies as the components (insulin and glucose) can be measured in fasting plasma samples, but limited due to the variability of each individual component [7]. For the assessment of insulin resistance-associated dyslipidemic risk, the use of non-high density lipoprotein-cholesterol (nonHDL-C) is widely recommended [10], although there is debate about its adequacy [11].

Recently, the lipoprotein insulin resistance (LPIR) score has been developed as a composite biomarker that demonstrates alterations in lipoprotein metabolism – one of the earliest manifestations of insulin resistance [12]. LPIR is calculated as a weighted combination of size and concentration of small low density lipoprotein (LDL), large very low-density

lipoprotein (VLDL), and large high density lipoprotein (HDL) particles measured by nuclear magnetic resonance (NMR) spectroscopy [13]. The score was initially derived from HOMA-IR in 4972 nondiabetic subjects in the Multi-Ethnic Study of Atherosclerosis and then validated independently using GDR [12], which is highly associated with the individual components of LPIR [14].

LPIR has been shown to be robustly associated with incident T2D [13], independent of blood glucose, HOMA-IR, and other established risk factors [11]. Notably, LPIR is elevated in obesity and weight loss via caloric restriction reduces LPIR levels [15,16]. Bariatric surgery is the most effective intervention in the management of severe obesity and is known to cause remission of prevalent diabetes and reduce diabetes incidence [17]. However, different bariatric surgical techniques have differing effects on lipid profile, insulin resistance, and rates of diabetes remission [18–20]. To date, the effects of bariatric surgery on LPIR have not been studied. We thus sought to assess the effects of the two most common bariatric surgical techniques, Roux-en-Y gastric bypass (RYGB) and Sleeve gastrectomy (SG), on LPIR in non-diabetic women with obesity.

Patients and Methods

Non-smoking, non-diabetic, premenopausal Hispanic women, age 18 years, undergoing RYGB or SG at Bellevue Hospital (New York, NY) were recruited for a prospective observational study approved by the NYU School of Medicine Institutional Review Board. Informed consent was obtained from all individual participants included in the study. To reduce confounding, patients taking medications known to affect blood glucose or lipid levels were excluded. Seventy-seven subjects enrolled and presented for preoperative anthropometric and clinical measurements and blood sampling. Seventy-one, sixty-seven and fifty-three subjects presented for follow-up testing at one, six and 12 months postoperatively. Data presented in this study include the fifty-three subjects who underwent laparoscopic RYGB (n=22) or SG (n=31) and presented for all postoperative visits.

LPIR was calculated as a weighted score of VLDL, LDL and HDL particle sizes and their subset concentrations measured by NMR spectroscopy (LabCorp Inc., Raleigh, NC). Fasting glucose, A1C and typical lipid panels were measured on a Beckman-Coulter AU5832 chemistry analyzer. Plasma insulin was measured using multiplex immunoassays (Millipore, Darmstadt, Germany) in the Immune Monitoring Core Lab of NYU Langone Medical Center. HOMA-IR was calculated using the formula of Matthews et al. [21]. A diagnosis of metabolic syndrome was made based on International Diabetes Federation (IDF) criteria [22].

Comparisons of preoperative values between the two surgical groups were performed with independent samples t-tests. Unpaired t-tests and Pearson's tests of correlation were used to assess associations between LPIR and A1C and HOMA-IR, as well as associations between changes in LPIR pre- and post-surgery and with changes in anthropometric and blood measures. Comparisons of outcomes stratified by surgical procedure or pre-operative metabolic syndrome diagnosis were prespecified. Two-way repeated measures ANOVA, with post-hoc t-tests, was used to test for effects of time and/or surgical procedure or pre-

operative metabolic syndrome diagnosis on measures of insulin resistance. SPSS (Armonk, NY) was used for statistical analyses. A p-value <0.05 was considered statistically significant.

Results

The 77 subjects enrolled in this study were predominantly young adults (32 ± 7 years) with severe obesity (44.1 ± 6.4 kg/m²). They did not differ from the 71, 67 and 53 women who attended follow-up visits at one, six and 12 months after surgery, respectively. There were no significant differences in age, body mass index (BMI), waist or hip circumference, lipid parameters, HOMA-IR or LPIR between surgical groups pre-operatively (Table 1, Figures 1A, 1B). Women undergoing RYGB had slightly greater A1C prior to surgery than those women undergoing SG (Table 1, Figure 1C).

LPIR was reduced by $35 \pm 4\%$ and $46 \pm 4\%$ at six and 12 months after surgery, respectively (Figure 1D). The improvements in LPIR post-operatively did not differ by surgical procedure (Figures 1A, 1D). Similarly, post-operative reductions of HOMA-IR did not differ between procedures and continued to occur from six to 12 months after surgery (Figures 1B, 1E). In contrast, reductions in A1C in our subjects were no different at six and 12 months, with RYGB exhibiting greater reductions than SG at both time points (Figure 1F). Of note, while reductions in body weight and BMI were similar at one and six months following each procedure, subjects undergoing RYGB exhibited greater reductions in weight (% total body weight loss RYGB= 37 ± 1 , SG= 31 ± 1 , $p=0.0013$) and BMI (% change BMI RYGB= -37 ± 1 , SG= -31 ± 1 , $p=0.0013$; % excess BMI loss RYGB= 89 ± 4 , SG= 74 ± 4 , $p=0.012$) by 12 months after surgery (Supplemental Figure 1).

Pre-operatively, LPIR modestly correlated with HOMA-IR ($r=0.28$, $p=0.04$) and A1C ($r=0.35$, $p=0.01$) (Supplemental Figures 2A, 2D). Post-operatively, LPIR correlated with HOMA-IR at 12 months but not six months post-operatively (Supplemental Figures 2B, 2C). In contrast, the association with A1C was lost following surgery (Supplemental Figures 2E, 2F). Post-operative associations did not vary by surgical procedure. Although LPIR was not associated with measures of adiposity preoperatively (BMI, $r=0.03$, $p=0.82$ - Figure 2A; waist circumference, $r=0.17$, $p=0.22$ - Supplemental Figure 3A), post-operative reductions in LPIR were strongly correlated with reductions in these measures (Figures 2B, 2C, Supplemental Figures 3B, 3C).

Twenty-seven of the 53 subjects described in this study met IDF criteria for the metabolic syndrome prior to surgery. As expected, these subjects exhibited higher blood pressure, fasting triglycerides, and lower HDL-C than those not meeting metabolic syndrome criteria (Supplemental Table 1). However, there was no difference in age, BMI, waist or hip circumferences by metabolic syndrome diagnosis (Supplemental Table 1). Subjects with the diagnosis also exhibited higher HOMA-IR, A1C, nonHDL-C and LPIR at baseline. Twenty-five of 27 subjects experienced resolution of the metabolic syndrome diagnosis at six and 12 months following surgery. Subjects with metabolic syndrome tended to experience greater decreases in triglycerides and increases in HDL-C post-operatively (Supplemental Figure 4). Concordantly, the pre-operative differences in HOMA-IR, A1C and nonHDL-C between

those with and without metabolic syndrome were lost at six and 12 months (Figures 3A–C). In contrast, subjects with the metabolic syndrome prior to surgery continued to exhibit higher LPIR scores at six and 12 months postoperatively (Figure 3D, Supplemental Figure 5).

Discussion

This is the first study to demonstrate the effect of bariatric surgery on the novel composite lipoproteomic marker of insulin resistance, LPIR. In this study of 53 women followed for over one year, we demonstrate that bariatric surgery markedly reduces LPIR, with no significant difference in effect between RYGB and SG. Importantly, we also show that despite substantial weight loss similar to that of patients without the metabolic syndrome, a pre-operative metabolic syndrome diagnosis is associated with persistently higher LPIR score over the 12 months following surgery. In contrast, pre-operative differences in HOMA-IR and A1C, as well as nonHDL-C, between subjects with and without the metabolic syndrome were nullified by 6 months.

Insulin resistance is common in obesity and mechanistically drives the metabolic syndrome [23]. Accordingly, our subjects with IDF-defined metabolic syndrome exhibited higher pre-operative LPIR, HOMA-IR, A1C and nonHDL-C than those without the diagnosis. It is established that both RYGB and SG improve traditional markers of insulin resistance [19,24–26] and levels of each marker decreased similarly after SG or RYGB in our study, although the degree of improvement was larger in patients with the metabolic syndrome. Notably, proportionally similar reductions occurred in LPIR regardless of pre-operative metabolic syndrome status, leading this measure to remain different between groups throughout the post-operative follow-up period. We did not anticipate the unique potential of LPIR to discriminate subjects with the metabolic syndrome prior to surgery at a year post, despite resolution of metabolic syndrome criteria. This observation suggests that despite improvements in insulin resistance as indicated by reduced HOMA-IR and A1C, non-diabetic patients with obesity and the metabolic syndrome prior to bariatric surgery still harbor residual, potentially unappreciated, cardiometabolic risk in the post-operative period. RYGB and SG-induced weight loss conferred similar degrees of LPIR score improvement, suggesting improvement in this score is weight loss dependent and independent of surgery type. While we cannot exclude that larger numbers of subjects might allow for differentiation of post-operative nonHDL-C levels between metabolic syndrome groups, the discriminatory ability of LPIR within our small cohort is quite impressive. Our data suggest that LPIR could serve as a useful marker of atherogenic dyslipidemia-related risk in obesity and following bariatric surgery, but this will require validation in larger prospective cohorts.

In addition to the above novel observations, this is also the first study to assess the dynamic associations of LPIR with other established measures of insulin resistance in the setting of weight loss. Notably, the association between LPIR and HOMA-IR was strongest at surgery and weakened postoperatively. Given its original derivation from HOMA-IR [27], the persistent associations with this measure are perhaps not surprising, but nonetheless important to demonstrate for the first time. Further, the absence of association at six months, highlights the limitations of each of these markers, particularly in the setting of active weight

loss which is occurring at this point after surgery. The breakdown in associations of LPIR with A1C at all points post-operatively demonstrates the lack of sensitivity for acute metabolic changes in the latter marker, and its reduced utility in the absence of diabetes.

Finally, there was no association of pre-operative BMI with LPIR in our subjects. Previous reports have highlighted the superior specificity of waist circumference as an indicator of insulin resistance [28]. Although waist circumference suggested a slight correlation with LPIR in our cohort, this did not achieve statistical significance. Our findings may suggest the overall lack of specificity of both of these measures as indicators of cardiometabolic risk within a morbidly obese population. However, it should be noted that the ranges of pre-operative BMI and waist circumference are narrow given our population was composed solely of individuals with obesity, and therefore may not reveal meaningful statistical correlations with LPIR. In contrast, improvements in LPIR following bariatric surgery strongly correlated with reductions in both BMI and waist circumference. The correlation between change in LPIR and change in BMI during weight loss are consistent with prior work [16], whereas the association with reductions in waist circumference is novel. Overall, the varied associations of different markers with hematological and anthropometric measures of adiposity and insulin resistance serve to highlight the complex condition that is insulin resistance and the importance of varied methods for assessing for the presence and risk of insulin resistance in individuals with obesity. Given the ease of measuring LPIR and the combination of atherogenic lipoprotein features represented in this measurement, as stated above, this marker may provide additional prognostic value in persons with obesity who are undergoing weight loss.

This study has a number of limitations. In order to reduce confounding in this sample of limited size, the cohort was homogenous in age, gender and ethnicity. Therefore, it is not known if these findings can be extrapolated to older individuals, men, and other ethnicities. Since this study, by design, includes only individuals that exhibited relatively mild obesity-related metabolic abnormalities that did not necessitate medical treatment, it is unclear how common medications such as statins or diabetes agents may influence LPIR in obesity. However, the exclusion of potentially confounding lipid-lowering and diabetes medications in this study allows for a clean comparison of the effects of weight loss via the two most common bariatric surgical procedures on LPIR free of confounders. Furthermore, findings from this 12-month study may not reflect changes that occur beyond one year. Finally, of the 77 patients initially enrolled into our study, only 53 completed all study visits and were included in this analysis. High rates of loss to follow-up plague prospective studies of bariatric surgery and our attrition rate, unfortunately, does not appear out of line with other reports [29, 30]. While we detected no difference in our comparisons of baseline characteristics of the cohort as a whole and those completing follow-up, we cannot exclude some degree of systematic bias from attrition.

While this study is small and of limited duration, our observations suggest 1) that patients with obesity and the metabolic syndrome may possess persistent and unappreciated residual cardiovascular risk despite marked weight loss following bariatric surgery, and 2) investigation of LPIR's utility of a complementary marker of cardiovascular risk in other populations is warranted.

Conclusions

In conclusion, our study is the first to demonstrate the ability of bariatric surgery to reduce insulin resistance as indicated by LPIR in non-diabetic individuals with obesity and that these changes are highly associated with anthropometric measures of adiposity. We also found that a pre-operative metabolic syndrome diagnosis is associated with persistently higher LPIR scores following either RYGB or SG.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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- LPIR improves after bariatric surgery regardless of surgical procedure
- Preoperative MetSyn is associated with persistently elevated LPIR postoperatively
- Postop A1C, HOMA-IR & nonHDL-C do not differentiate those with preop MetSyn
- Persistent postop LPIR elevations suggest unappreciated residual dyslipidemia

Figure 1.

Markers of insulin resistance before and after bariatric surgeries. Pre-operative, 6 month and 12 month post-RYGB and post-SG levels of (A) LPIR, (B) HOMA-IR, and (C) A1C.

Percent change in (D) LPIR, (E) HOMA-IR, (F) A1C levels compared to baseline at 6 and 12 months post-surgery. Error bars represent mean ± SEM. NS, not significant; *p<0.05, **p<0.01. LPIR, lipoprotein insulin resistance; HOMA-IR, homeostatic model assessment for insulin resistance; A1C, hemoglobin A1c; RYGB, Roux-en-Y gastric bypass; SG, sleeve gastrectomy.

Figure 2.

Associations of LPIR with BMI. Pairwise Pearson correlations between (A) LPIR and BMI at baseline. Pairwise Pearson correlations between percent change in LPIR and BMI at (B) 6 months, and (C) 12 months after surgery. BMI, body mass index; LPIR, lipoprotein insulin resistance.

Figure 3.

Post-operative changes in markers of insulin resistance and nonHDL-C in those with and without pre-operative metabolic syndrome diagnosis. Pre-operative, 6 month and 12 month post-operative levels of (A) HOMA-IR, (B) A1C, (C) nonHDL-C, (D) LPIR stratified by pre-operative metabolic syndrome status. Error bars represent mean $\pm$ SEM. NS, not significant; *p<0.05, **p<0.01, ****p<0.0001. LPIR, lipoprotein insulin resistance; HOMA-IR, homeostatic model assessment for insulin resistance; A1C, hemoglobin A1c; nonHDL-C, non-high-density lipoprotein cholesterol.

Table 1.

Baseline characteristics of subjects with obesity undergoing surgery and completing 12 months of follow-up (mean $\pm$ standard deviation)

	Sleeve Gastrectomy (n = 31)	Roux-en-Y Gastric Bypass (n = 22)
Age (years)	35 $\pm$ 9	32 $\pm$ 8
BMI (kg/m ²)	44.6 $\pm$ 6.9	44.3 $\pm$ 6
Body weight (kg)	110.6 $\pm$ 16.2	114.7 $\pm$ 17
LPIR score	45 $\pm$ 14.1	48.5 $\pm$ 15
A1C (%)	5.4 $\pm$ 0.4	5.8 $\pm$ 0.7 *
HOMA-IR score	5.9 $\pm$ 3.8	6.7 $\pm$ 4.2
SBP/ DBP (mmHg)	122 $\pm$ 10/ 74 $\pm$ 9	122 $\pm$ 8/ 74 $\pm$ 7
waist circumference (cm)	115 $\pm$ 14	118 $\pm$ 11
hip circumference (cm)	135 $\pm$ 13	136 $\pm$ 11
VLDL concentration (nM)	46.3 $\pm$ 20.2	54.8 $\pm$ 30.3
LDL concentration (nM)	1102 $\pm$ 279	1242 $\pm$ 359
HDL concentration (nM)	33.3 $\pm$ 6.8	30.9 $\pm$ 5.0
VLDL size (nm)	48.1 $\pm$ 6.7	47.1 $\pm$ 5.1
LDL size (nm)	20.4 $\pm$ 0.4	20.5 $\pm$ 0.5
HDL size (nm)	9.1 $\pm$ 0.3	9.2 $\pm$ 0.4
nonHDL-C (mg/dL)	134.1 $\pm$ 37.7	117.4 $\pm$ 22.6
hsCRP (mg/L)	9.3 $\pm$ 8.0	11.9 $\pm$ 7.5
Fasting Glucose (mg/dL)	104.4 $\pm$ 17.7	107.4 $\pm$ 15.3
Metabolic Syndrome	50%	50%

*
p<0.05

BMI, body mass index; LPIR, lipoprotein insulin resistance; A1C, hemoglobin A1c; HOMA-IR, homeostatic model assessment for insulin resistance; SBP, systolic blood pressure; DBP, diastolic blood pressure; VLDL, very low density lipoprotein; LDL, low density lipoprotein; HDL, high density lipoprotein.