ESR1 gene and insulin resistance remission are associated with serum uric acid decline for severely obese patients undergoing bariatric surgery

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Abstract

Background: Hyperuricemia is associated with obesity. Few studies have reported the effects of different types of bariatric surgery on uric acid metabolism. The aim of our study was to determine the relationships between serum uric acid reduction and estrogen receptor-α (ESR1) gene polymorphism, as well as the type of bariatric surgery received. The potential physiological pathways involved in postsurgery serum uric acid reduction were also discussed.

Methods: A total of 508 severely obese Han Chinese patients, aged 20 to 50 years, with a body mass index (BMI) ≥ 35 kg/m² were selected. Patients received either laparoscopic adjustable gastric banding (LAGB; n = 164) or laparoscopic mini-gastric bypass (LMGB; n = 344). A 12-month follow-up was performed to explore the effects of the type of bariatric surgery and ESR1 polymorphism on serum uric acid reduction.

Results: The rs712221 polymorphism of ESR1 affects serum uric acid reduction after bariatric surgery. The LMGB group exhibited a greater reduction in serum uric acid level compared with the LAGB counterpart after adjusting for sex, age, and metabolic confounders (−2.3 ± 2.1 mg/dL versus −1.2 ± 1.1 mg/dL; P = .002). Patients with the rs712221 genotype exhibited better glycemic control and a greater serum uric acid reduction at 12 months after surgery. The effects of the rs712221 polymorphism in LMGB patients resulted in the greatest serum uric acid reduction (−2.7 ± 1.4 mg/dL).

Conclusions: For severely obese Han Chinese patients, bariatric surgery appears to reduce serum uric acid levels, potentially mediated by synergic effects of surgery type, BMI reduction, rs712221 locus, insulin sensitivity, and changed dietary factors via an unknown mechanism. (Surg Obes Relat Dis 2014;10:14–22.) © 2014 American Society for Bariatric Surgery. All rights reserved.

Keywords: Uric acid; Estrogen receptor-α (ESR1); Bariatric surgery; Hyperuricemia

Hyperuricemia is a major indicator of cardiovascular disease [1], which is an independent risk factor for mortality from all causes, total cardiovascular disease, and ischemic stroke [2]. The higher prevalence of hyperuricemia in Taiwan [3] may reflect a combination of risk factors that are unique to the Taiwanese population, including genetic variation, metabolic co-morbidities, and environmental factors.
Numerous studies have shown that obesity and insulin resistance are closely associated with various metabolic co-morbidities, including hyperglycemia, hyperlipidemia, hypertension, and hyperuricemia [4–7]. Thus, obesity is a major predictor for an unfavorable serum uric acid profile [8,9]. Pan et al. [10] reported a higher prevalence of hyperuricemia in Taiwanese people than in white Americans. Therefore, the obese candidate genes and the dietary patterns of Taiwanese people may be the pivotal factors in the development of hyperuricemia.

Obese patients benefit from various weight loss programs, including lifestyle modification, oral medication, and bariatric surgery [11,12]. Bariatric surgery is currently the only effective weight loss approach for severely obese patients. Metabolic disorders can be improved by weight reduction in severely obese patients undergoing bariatric surgery [13]. Our previous study found that the rs712221 polymorphism of estrogen receptor-α (ESR1) gene, the rs660339 polymorphism of the uncoupling protein 2 (UCP2) gene, the rs9939609 polymorphism of the fat mass and obesity-associated protein (FTO) gene, and the rs4684846 and the rs1822825 polymorphisms of the peroxisome proliferator-activated receptor gamma (PPARγ) gene were significantly associated with obesity in Han Chinese patients [14] and interacted with bariatric surgery, contributing to weight reduction and glycemic control in severely obese patients [15]. The association of the ESR1 gene with insulin resistance [16] and serum estrogen level has been reported [17]. Moreover, both serum estrogen concentration and insulin resistance have been shown to affect serum uric acid and lipid metabolism [5,18,19]. The ESR1 gene is associated not only with obesity but also with serum estrogen level and insulin resistance, which indirectly contributed to serum uric acid abnormality.

The first step of our present study was to determine the relationships between the polymorphisms of the ESR1, the UCP2, the FTO, and the PPARγ genes and hyperuricemia. The second step, the major aim of the present study, was to explore the genetic effect on serum uric acid reduction in obese Han Chinese patients after different types of bariatric surgery. We also discussed the possibly physiologic factor involved in the serum uric acid reductions in these patients after bariatric surgery.

Methods

Participants

This multicenter study included 3 hospitals in Taiwan. Between May 2008 and April 2010, a total of 523 obese patients underwent bariatric surgery for weight reduction; 508 patients were willing to participate in the start of study. Each patient had a body mass index (BMI) ≥35 kg/m². The patients ranged in age from 20 to 50 years. Patients had been previously recommended for either laparoscopic adjustable gastric banding (LAGB) or laparoscopic mini-gastric bypass (LMGB) bariatric surgery. The serum blood urea nitrogen (BUN), serum creatinine, and urine protein of all patients were within the normal range as evaluated by their attending physicians before undergoing surgery.

Our study protocol was approved by the ethics committees of Min-Sheng General Hospital, Taipei Medical University Hospital, and Chang Jung Christian University. All participants signed informed consent forms before participating in our study. A follow-up was performed at 12 months after bariatric surgery.

Study design

This is a 2-staged candidate gene research for impaired serum uric acid metabolism. Possible physiologic factors associated with serum uric acid reduction after the LAGB and LMGB surgeries were explored. In the first-stage study, allelic association analysis was initially performed to identify polymorphisms associated with hyperuricemia in severely obese Han Chinese patients. Polymorphisms that were identified during the initial genetic analysis (P < .05) were considered the candidate genetic markers for impaired uric acid metabolism. The reference ranges of serum uric acid for men and women are 3.6 to 8.3 mg/dL and 2.3 to 6.6 mg/dL, respectively. Hyperuricemia is diagnosed based on a serum uric acid level ≥7.0 mg/dL in men and ≥6.0 mg/dL in women [20]. Participants were assigned to hyperuricemia or nonhyperuricemia groups according to their serum uric acid levels before surgery. In the second stage, the candidate genetic markers with statistical significance were assessed whether they impaired serum uric reduction in obese patients after bariatric surgery.

Data collection

Anthropometric and serum biochemical data were collected before and 12 months after bariatric surgery to assess indicators of impaired uric acid metabolism according to the Standard Operation Procedures manual at Min-Sheng General Hospital and Taipei Medical University Hospital. Homeostatic assessment for insulin sensitivity (HOMA-IR) was used to quantify the insulin resistance and the β-cell function for each patient in our study [21]. Anthropometric data included BMI and waist circumference. Blood pressure was also recorded. Biochemical data included serum uric acid, serum triglycerides (TG), glycated hemoglobin (HbA1c), serum total cholesterol (TC), and fasting serum glucose (FPG) levels. A registered dietician collected dietary intake data on a 3-day, 24-hour dietary recall (2 usual days and 1 weekend day) before surgery and 12 months after surgery. The dietary data were transformed to estimate the total intakes of the 3 macronutrients—carbohydrate, fat, and protein—using the food exchange list. The daily intake shown in the tables, including the intake of energy, carbohydrate (CHO), protein, and fat, represents the average of the total intake during the 3-day period.
Genotyping

The ESR1-rs712221, the UCP2-rs660339, the FTO-rs9393609, the PPAR-rs4684846, and the PPAR-rs1822825 single-nucleotide polymorphisms (SNPs) were selected based on the results of previous studies on genetic influences in obesity and bariatric surgery efficacy in Han Chinese patients [14,15,22]. Genomic DNA was extracted from cells in the buffy coat layer of centrifuged whole-blood samples by using a modified phenol-chloroform method [23]. The quality of the DNA was assessed by the ratio of the absorbance readings at 260 nm to 280 nm. DNA samples were diluted to 2.5 to 3.0 ng/μL for use in the multiplex polymerase chain reaction (PCR) procedure. The PCR products were genotyped using the SNPstream genotyping system (Beckman Coulter, Brea, CA). The sequence information for the 5 SNPs was retrieved from the dbSNP database.

Statistical analysis

SAS 9.2 software (SAS Institute Inc., Cary, NC) was used for data analysis in our study. Allele association analysis was performed using the PROC ALLELE procedure. The paired Student t test was performed to compare the presurgery and postsurgery data. The Mantel-Haenszel χ² analysis was used to evaluate dichotomy data for adjusting the sex distribution. ANCOVA was used to compare the risk genotype and the nonrisk genotype as defined in the previous studies [14,15,22]. To explore the possible physiologic factors involved in serum uric acid reduction, multivariable linear regression analysis was performed to adjust for confounding factors that may influence serum uric acid reduction, including age, sex distribution, and other factors that showed significant differences between presurgery and postsurgery data. Pearson’s correlation coefficient was used to investigate whether gene expression was correlated with genotype and/or serum uric acid level. P values < .05 were considered statistically significant differences.

Results

Allele association analysis showed that, among the 5 SNPs of the ESR1 gene, only the rs712221 polymorphism was significantly associated with hyperuricemia (Appendix 1). Thus, rs712221 was used as the genetic marker for impaired uric acid metabolism in subsequent analyses.

All patients showed normal renal function before surgery as assessed by serum creatinine, BUN, and urine protein levels (Table 1), and no significant differences existed in presurgery serum uric acid levels between the LAGB and LMGB patients (7.5 ± 2.5 mg/dL versus 7.7 ± 3.0 mg/dL, respectively; P = .408). Likewise, no significant differences between the LAGB and LMGB patients were observed among the other variables before surgery, as assessed using ANCOVA, adjusting for age and sex, except for the sex distribution (P = .008). The distribution of hyperuricemia and follow-up rates were further analyzed using the Mantel-Haenszel model to adjust for the sex distribution (Table 1).

Changes in anthropometric and biochemical data are expressed separately for the LAGB and LMGB patients as the difference (e.g., ΔBMI reduction) between the data at 12 months after surgery and the data before surgery (Table 2). The paired t test was used to investigate the effects of surgery on the changes in these variables. The results indicated a significant difference in surgical efficacy. Compared with the patients’ presurgery data, both the LAGB and LMGB patients had significant declines in BMI, serum TG, HbA1c, HOMA-IR, and serum uric acid, as well as the energy, protein, and CHO intakes at 12 months after surgery (Table 2). However, significant

Table 1

<table>
<thead>
<tr>
<th></th>
<th>LAGB (n = 164)</th>
<th>LMGB (n = 344)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>31.4 ± 8.1</td>
<td>30.3 ± 7.6</td>
<td>.076</td>
</tr>
<tr>
<td>Male/female</td>
<td>69/95</td>
<td>102/242</td>
<td>.008</td>
</tr>
<tr>
<td>Body Mass Index BMI, kg/m²</td>
<td>42.3 ± 6.6</td>
<td>42.7 ± 6.5</td>
<td>.573</td>
</tr>
<tr>
<td>Serum Lipid, mg/dL</td>
<td>190.5 ± 160.3</td>
<td>210.5 ± 177.5</td>
<td>.078</td>
</tr>
<tr>
<td>TC</td>
<td>198.0 ± 39.0</td>
<td>195.8 ± 35.0</td>
<td>.546</td>
</tr>
<tr>
<td>Serum Glucose Profiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose, mg/dL</td>
<td>6.9 ± 1.8</td>
<td>7.0 ± 1.1</td>
<td>.149</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>120.6 ± 111.1</td>
<td>135.7 ± 105.6</td>
<td>.405</td>
</tr>
<tr>
<td>Blood Pressure, mm Hg</td>
<td>136.7 ± 20.0</td>
<td>134.3 ± 17.7</td>
<td>.159</td>
</tr>
<tr>
<td>Systolic</td>
<td>865.6 ± 13.7</td>
<td>866.6 ± 13.7</td>
<td>.964</td>
</tr>
<tr>
<td>Diastolic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Indicators of Renal Function</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>7.5 ± 2.5</td>
<td>7.7 ± 3.0</td>
<td>.408</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>8 ± 4</td>
<td>8 ± 3</td>
<td>.681</td>
</tr>
<tr>
<td>Urea nitrogen, mg/dL</td>
<td>15.8 ± 5.1</td>
<td>17.2 ± 3.9</td>
<td>.122</td>
</tr>
<tr>
<td>Food Intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy Intake, kcal</td>
<td>2512 ± 423</td>
<td>2680 ± 548</td>
<td>.192</td>
</tr>
<tr>
<td>Protein Intake, g</td>
<td>91.6 ± 16.4</td>
<td>94.3 ± 20.0</td>
<td>.369</td>
</tr>
<tr>
<td>CHO Intake, g</td>
<td>321.1 ± 102.3</td>
<td>358.8 ± 126.4</td>
<td>.100</td>
</tr>
<tr>
<td>Follow-up Rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At month 12, % (n)</td>
<td>72.0% (118)</td>
<td>70.3% (242)</td>
<td>.586</td>
</tr>
</tbody>
</table>

LAGB = Laparoscopic adjustable gastric banding; LMGB = laparoscopic mini-gastric bypass; BMI = body mass index; TG = triglyceride; TC = total cholesterol; HbA1c = glycated hemoglobin; HOMA-IR = homeostatic assessment for insulin sensitivity; CHO = carbohydrate.

Data were expressed as mean ± SD.

All P values were derived from an ANCOVA model and adjusted for sex and age.

*t test analysis was performed.

χ² analysis was performed.

Mantel-Haenszel model to adjust for gender distribution.

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changes in selected indicators in severely obese patients at 12 months postsurgery (compared with presurgery)

<table>
<thead>
<tr>
<th></th>
<th>LAGB (n = 118)</th>
<th>LMGB (n = 242)</th>
<th>P value of LAGB versus LMGB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female, n</td>
<td>53/65</td>
<td>68/174</td>
<td>.002</td>
</tr>
<tr>
<td>ΔBMI reduction</td>
<td>9.2 ± 4.0</td>
<td>14.9 ± 3.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>ΔSerum TG, mg/dL</td>
<td>102.5 ± 92.9</td>
<td>125.3 ± 100.6</td>
<td>.037</td>
</tr>
<tr>
<td>ΔSerum TC, mg/dL</td>
<td>8.4 ± 28.7</td>
<td>19.8 ± 29.5</td>
<td>.117</td>
</tr>
<tr>
<td>ΔHbA1c, %</td>
<td>.6 ± .4</td>
<td>.8 ± .6</td>
<td>.087</td>
</tr>
<tr>
<td>ΔHOMA-IR, %</td>
<td>60.6 ± 86.7</td>
<td>141.0 ± 88.0</td>
<td>.003</td>
</tr>
<tr>
<td>Blood pressure, mm Hg</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic decrease</td>
<td>15.0 ± 27.7</td>
<td>12.3 ± 22.8</td>
<td>.186</td>
</tr>
<tr>
<td>Diastolic decrease</td>
<td>12.5 ± 17.7</td>
<td>11.8 ± 14.2</td>
<td>.115</td>
</tr>
<tr>
<td>ΔSerum uric acid decline, mg/dL</td>
<td>1.2 ± 1.1</td>
<td>2.3 ± 2.1</td>
<td>.002</td>
</tr>
<tr>
<td>ΔEnergy intake decline, kcal</td>
<td>871.0 ± 456.2</td>
<td>867.5 ± 362.4</td>
<td>.901</td>
</tr>
<tr>
<td>ΔProtein intake decline, g</td>
<td>47.3 ± 11.6</td>
<td>60.8 ± 17.3</td>
<td>.001</td>
</tr>
<tr>
<td>ΔCHO intake decline, g</td>
<td>132.9 ± 113.9</td>
<td>95.4 ± 80.7</td>
<td>.037</td>
</tr>
</tbody>
</table>

LAGB = Laparoscopic adjustable gastric banding; LMGB = laparoscopic mini-gastric bypass; BMI = body mass index; TG = triglyceride; TC = total cholesterol; HbA1c = glycated hemoglobin; HOMA-IR = homeostatic assessment for insulin sensitivity; CHO = carbohydrate.

Data were expressed as mean ± SD.

χ² analysis was performed.

Derived from an ANCOVA model and adjusted for sex and age.

Derived from paired t test analysis.

patients with the risk genotype had greater declines in BMI (P = .041), HOMA-IR (P = .001), and serum uric acid (P = .050) than those with the nonrisk genotype (Table 4).

We focused on exploring potential factors responsible for the postsurgery reduction in serum uric acid. The decrease in serum uric acid level was defined as an independent variable in the linear regression model. The dependent variables included age, sex, presurgery serum uric acid level, rs712221 polymorphism, ΔBMI, ΔTG, ΔHbA1c, ΔHOMA-IR, and Δprotein intake declines. The Δwaist circumference was not selected for this analysis because of colinearity with ΔBMI in linear regression models. The results of this analysis (model 1) found that surgery efficacy, ΔBMI reduction, rs712221 polymorphism, Δprotein intake decline, and presurgery serum uric acid level were significantly associated with Δserum uric acid decline in obese patients at 12 months after surgery (Table 5). The results of LAGB analysis (model 2) found that the risk genotype had a greater Δserum uric acid (β = 2.33; P = .014) compared with patients with the nonrisk genotype AT/AA (Table 5). The model 3 analysis of the LMGB patients also showed that the risk genotype was associated with the Δserum uric acid decline (β = .943; P = .024). The ΔBMI reduction (β = .055; P = .023), the ΔHOMA-IR decline (β = .002; P = .050), and the Δprotein intake decline (β = .024; P = .014) also were significantly associated with the Δserum uric acid decline at 12 months after surgery in the LMGB patients (Table 5).
As shown in Table 6, both the LAGB and the LMGB and bariatric surgery on the dual and synergistic effects of the rs712221 polymorphism.

Table 5

<table>
<thead>
<tr>
<th>Model</th>
<th>Surgery LMGB versus LAGB</th>
<th>ΔBMI decline</th>
<th>ΔHOMA-IR decline</th>
<th>rs712221 R versus NR</th>
<th>ΔSerum TG decline</th>
<th>ΔProtein intake decline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1, n = 360</td>
<td>—</td>
<td>.960</td>
<td>.019</td>
<td>.262</td>
<td>.001</td>
<td>.940</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>.050</td>
<td>.050</td>
<td>.203</td>
<td>.111</td>
<td>.016</td>
</tr>
<tr>
<td>Model 2, n = 118</td>
<td>—</td>
<td>—</td>
<td>.050</td>
<td>.546</td>
<td>.001</td>
<td>2.33</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>—</td>
<td>.638</td>
<td>.369</td>
<td>.564</td>
<td>.014</td>
</tr>
<tr>
<td>Model 3, n = 242</td>
<td>—</td>
<td>—</td>
<td>.055</td>
<td>.263</td>
<td>.002</td>
<td>.943</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>—</td>
<td>.023</td>
<td>.206</td>
<td>.050</td>
<td>.024</td>
</tr>
</tbody>
</table>

LMBG = Laparoscopic mini-gastric bypass; LAGB = laparoscopic adjustable gastric banding; BMI = body mass index; HbA1c = glycated hemoglobin; HOMA-IR = homeostatic assessment for insulin sensitivity; TG = triglyceride.

In this linear regression model, LAGB was defined as 1 and LMBG was defined as 2; nonrisk genotype (NR) was defined as 1 and risk genotype (R) was defined as 2 on rs712221 of the ESR1 gene.

Model 1: Total obese cases were involved. Model 2: Obese cases undergoing LAGB were enrolled. Model 3: Obese cases undergoing LMBG were enrolled.

ΔBMI reduction: The reduction of BMI value between presurgery and month 12 postsurgery.
ΔHOMA-IR: The decline of homeostatic assessment for insulin sensitivity between presurgery and month 12 postsurgery.
ΔSerum TG: The decline of serum triglyceride level between presurgery and month 12 postsurgery.
ΔProtein intake: The decline of serum triglyceride level between presurgery and month 12 postsurgery.

Further analysis was performed to determine the individual and synergistic effects of the rs712221 polymorphism and bariatric surgery on the serum uric acid decline. As shown in Table 6, both the LAGB and the LMBG patients carrying the risk genotype had greater serum uric acid decline than patients with the nonrisk genotype (−1.7 ± 1.0 mg/dL versus −.8 ± 1.2 mg/dL, P = .033 for LAGB; and −2.7 ± 1.4 mg/dL versus −2.1 ± 1.3 mg/dL, P = .050 for LMBG). Comparisons of the serum uric acid decline in LAGB and LMBG patients with the nonrisk genotype indicated that the LMBG group had a greater serum uric acid decline than did the LAGB patients (−.8 ± 1.2 mg/dL in LAGB versus −2.1 ± 1.3 mg/dL in LMBG; P < .001). Furthermore, the LMBG patients with the risk genotype had greater serum uric acid decline than did the LAGB patients (−1.7 ± 1.0 mg/dL in LAGB versus −2.7 ± 1.4 mg/dL in LMBG; P < .001). Thus, the greatest serum uric acid decline was observed in the LMBG patients with the risk genotype.

Discussion

Gastric bands (restrictive-type surgery) and gastric bypass (malabsorptive surgery) are the 2 most commonly performed bariatric surgeries worldwide [24]. Different types of bariatric surgeries produce different outcomes for improving metabolic abnormalities [25,26]. However, few studies have examined the effect of the type of bariatric surgery on hyperuricemia. Obesity often causes hyperuricemia [8,27,28], and some studies have reported that bariatric surgery may correct hyperuricemia [29] for up to 10 years [30]. However, the relationships between reduced serum uric acid and weight loss for the different types of bariatric surgery have remained unclear. Therefore, we sought to compare the effects of the LAGB and LMBG.
surgeries on reductions in serum uric acid and to identify the physiologic pathways responsible for postsurgery reductions in serum uric acid.

LMGB surgery has been reported to be more effective in weight reduction and glycemic control than LAGB surgery [31]. However, its application is limited by short-term weight reduction and glycemic control than LAGB surgery [11]. The uric acid metabolic pathway, including genetic effect and dietary abnormalities [34], higher serum uric acid levels [5,6], and inflammatory processes [35]. Furthermore, hyperuricemia is also associated with hyperlipidemia [36] and the inflammatory response [37]. Research has suggested that decreased insulin resistance (improved insulin sensitivity) may be associated with decreased serum uric acid levels [38] and improvements in other metabolic abnormalities [39].

The uric acid metabolic pathway, including genetic effect and other factors, may be far more complicated than currently known. To date, there is scarce information concerning serum uric acid reduction and bariatric surgery. We supposed that the difference of serum uric acid decline in patient undergoing bariatric surgery mainly resulted from declined protein intake and insulin resistance remission.

Table 6:
The single and synergic effects of rs712221 and bariatric surgery on serum uric acid reduction at month 12 postsurgery

<table>
<thead>
<tr>
<th>Surgery type</th>
<th>Genotype</th>
<th>ΔSerum uric acid change, mg/dL n = 360</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LAGB</td>
<td>LMGB</td>
<td></td>
</tr>
<tr>
<td>Risk genotype (TT)</td>
<td>−1.7 ± 1.0 (35)</td>
<td>−2.7 ± 1.4 (57)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>Nonrisk genotype (AA/AT)</td>
<td>−8.8 ± 1.2 (83)</td>
<td>−2.1 ± 1.3 (185)</td>
<td>&lt; .001*</td>
</tr>
<tr>
<td>P</td>
<td>.033†</td>
<td>.050‡</td>
<td></td>
</tr>
</tbody>
</table>

LAGB = Laparoscopic adjustable gastric banding; LMGB = laparoscopic mini-gastric bypass. Genotype frequency was expressed in parenthesis.

The P value indicated the combined effect of rs712221 polymorphism and bariatric surgery and the comparison of declined serum uric acid levels in individuals carrying risk genotypes between LAGB and LMGB.

The P value indicated the bariatric surgery effect and the comparison of declined serum uric acid levels in individuals carrying nonrisk genotypes between LAGB and LMGB.

The P value indicated the rs712221 polymorphism effect and the comparison of declined serum uric acid levels between risk and nonrisk genotypes in LAGB and LMGB, respectively.

Stratum analysis was used to clarify the effect of the rs712221 genotype on the serum uric acid levels in the LAGB and LMGB patients. We found that the Δserum uric acid decline was significantly different between the risk and nonrisk genotypes in both LAGB and LMGB patients. In addition, an extreme significance (P < .001; Table 4) in HOMA-IR was observed between the risk and nonrisk genotypes in LMGB obese patients. Our previous studies also indicated that rs712221 was associated with better glycemic control in severely obese patients after LMGB [15]. Tsunoda et al. [38] also reported that serum uric acid decline is mediated by decreased insulin resistance. Therefore, the genetic effects of the rs712221 risk genotype after LMGB surgery may contribute to reduced serum uric acid and diminished insulin resistance, which thereby improves insulin sensitivity. This might explain why serum uric acid decline and HOMA-IR were both associated with rs712221 in LMGB patients. However, the HOMA-IR response (insulin sensitivity) did not show a significant difference between risk and nonrisk genotype in LAGB, where the serum uric acid decline displayed a significant difference between the 2 genotypes (Table 3). Thus, the variation of rs712221 locus might contribute to serum uric acid decline not only through improvement of insulin sensitivity but also through other mechanisms such as genetic effect and dietary factors.

Our study indicated that surgery type, rs712221, and Δprotein intake decline (Table 5, model 1) may affect Δserum uric acid decline. Further linear regression analyses, models 2 and 3, were conducted to analyze the effects of the LAGB and LMGB surgeries, respectively. The rs712221 polymorphism, ΔBMI reduction, decreased HOMA-IR, and Δprotein intake decline may contribute to Δserum uric acid decline. Decreased HOMA-IR was significantly associated with Δserum uric acid decline in LMGB patients, which can be attributed to LMGB treatment [40], BMI reduction, and the genetic effect of rs712221 via a currently unknown physiologic pathway. Ishizaka et al. [41] suggested that the reduction in serum uric acid after LAGB surgery may be derived from obesity reduction. Our results for the patients who underwent LAGB were consistent with the observations made by Ishizaka et al. [41]. We also found that both BMI and serum uric acid parameters differed significantly between LAGB patients with the risk and nonrisk genotype on rs712221 locus. Thus, serum uric acid decline in LAGB might be mainly through obesity reduction mediated by the rs712221 locus effect and dietary intake.

Some discrepancies were found in the present study compared with our previous study [15], such that Hba1c decline exhibited a significant association with the rs712221 polymorphism at month 6, but not at month 12, after LMGB. We also found that all LMGB patients
decreased their dietary intake at month 6, compared with month 12 after surgery, which is probably due to the long recovery time for obese patients who underwent bypass surgery. Therefore, the recovery status and impaired dietary intake might be the major reason for this discrepancy.

The rs712221 polymorphism was significantly associated with serum uric acid decline in both the LAGB ($P = .014$) and LMGB ($P = .024$) patients (Table 5) after adjusting confounders. We speculated that estrogen and its receptor may play a fundamental role in uric acid metabolism. Previous studies have reported that uric acid homeostasis is affected by sex and serum estrogen level [42,43]. Moreover, xanthine oxidase plays a key role in uric acid metabolism [44–47], in which estrogen modulates the activities of xanthine dehydrogenase (XDH) and xanthine oxidase by a receptor-independent mechanism [48]. Estrogen receptors mainly include ESRI and estrogen receptor-β (ESR2). Previous studies have reported that ESRI allelic variations were significantly associated with serum estrogen levels [17,49,50], insulin sensitivity [15,16], and metabolism co-morbidities, such as hyperlipidemia and obesity [16,17,51,52]. Because obesity, insulin resistance, and hyperlipidemia are associated with hyperuricemia [36,53], we propose that certain ESRI polymorphisms may play a pivotal role in uric acid metabolism.

Uric acid metabolism is affected by dietary protein intake. Jeffreys et al. [54] reported that relatively lower protein intake was observed in obese patients undergoing laparoscopic Roux-en-Y gastric bypass surgery within 1 year after surgery. Thus, lower protein intake contributes to greater serum uric acid decline in obese patients after LMGB surgery, compared with LAGB patients. Dodsworth et al. [55] indicated that short-term lower protein intake was observed in obese patients after LAGB surgery. However, the LAGB patients in the Dodsworth et al. study also exhibited a reduction in serum uric acid, which is consistent with our present findings.

ESRI gene product is a ligand-activated transcription factor that is composed of several domains. Previous studies have reported that polymorphisms within the PvuII and XbaI cleavage sites of ESRI were associated with serum estrogen levels [49,50]. The ESRI-rs6902771 and the ESRI-rs7774230 polymorphisms within intron 2 were also significantly associated with insulin resistance [16]. Moreover, ESRI-rs3798577 was reported to be associated with a lower circulating estrogen level, contributing to an approximate 1% variation in the concentration of circulating estrogen [17]. Our present study found that rs712221, a tag-SNP, was significantly associated with reduced serum uric acid levels in severely obese Han Chinese patients after either LAGB or LMGB surgery. Therefore, rs712221 may represent a unique marker for serum uric acid reduction that is mediated by surgery, insulin sensitivity, and estrogen-related mechanism.

We found that the ESRI-rs712221 polymorphism was associated with BMI reduction in LAGB ($P < .044$) and LMGB ($P < .041$) (Tables 3 and 4). The association between the ESRI-rs712221 allele and insulin resistance remission showed a strong statistical significant difference in LMGB ($P < .001$; Table 4) and a borderline significance in LAGB ($P < .097$; Table 3). Moreover, a significant association between serum uric acid reduction and rs712221 polymorphism was observed in obese patients undergoing either LAGB or LMGB surgery after adjusting for other confounders by a linear regression model (Table 5). Although a direct link concerning ESRI-rs712221 polymorphism, insulin resistance, serum estrogen level, and serum uric acid reduction was not identified in the present study, we inferred that the ESRI-rs712221 polymorphism was associated with serum uric acid decline through insulin resistance remission, BMI reduction, protein intake, and unknown pathways. Therefore, further studies of ESRI genetic effect on serum uric acid are warranted to explore the underlying mechanism.

Both the LAGB and LMGB patients with the rs712221 risk genotype TT had a greater serum uric acid ($0.9$ mg/dL and $0.6$ mg/dL, respectively), compared with the nonrisk genotype in LAGB and LMGB patients. Moreover, the LMGB procedure and rs712221 genotype exhibited individual and synergistic effects on serum uric acid reduction (Table 6).

We validated our results by reanalyzing data retrieved from a human genome-wide gene-related study [56]. The preliminary analysis showed that the correlation coefficients (data not shown) were $-0.1$ for serum uric acid–ESRI expression ($P = .04$), $-0.3$ for ESRI-XDH expression ($P = 1 \times 10^{-4}$), and $-0.1$ for serum uric acid level–XDH expression ($P = .03$) using a whole human RNA-tag platform (Human OneArray v5 platform, Phalanx Biotech, Taiwan). Lacking evidence of a direct association between rs712221 and ESRI expression represents an additional limitation in the present study; our data nevertheless indicate that allelic variation in ESRI is associated with uric acid metabolism in obese Han Chinese patients.

**Conclusion**

Our study showed that bariatric surgery maybe an effective therapy to improve uric acid metabolism in severely obese Han Chinese patients. The serum uric acid decline was associated with synergic effect of surgery type, protein intake, BMI reduction, insulin sensitivity, and rs712221 locus on ESRI gene mediated by an unknown mechanism. Further studies elucidating the connection between the ESRI gene and uric acid metabolism might be helpful to treat hyperuricemia in obese patients receiving bariatric surgery.

**Table 5**

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<th>SNP</th>
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<tr>
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**Table 6**

<table>
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Appendix 1. The allelic association between hyperuricemia and 5 polymorphisms in 508 severely obese individuals

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</tr>
</tbody>
</table>

SNPs = Single-nucleotide polymorphisms.

References

[23] Paramsothy P, Knopp R, Bertoni AG, Tsai MY, Rue T, Heckbert SR. Combined hyperlipidemia in relation to race/ethnicity, obesity, and


