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Metabolic Remodeling After Bariatric Surgery in Iraq: Biomarker-Linked Outcomes Stratified by NAFLD Severity and Metabolic Syndrome at 3 Years

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ABSTRACT

Objective: *To complete 3 year prospective assessment of clinical and molecular outcomes after Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) in Iraqi patients, respectively, with the express links between the weight loss curves, comorbidity improvement, and the serial profiling of the major metabolic biomarkers.* ***Method:*** *The present study was a multicenter prospective cohort study carried out between January 2020 and December 2023 in the Al-Zahraa and Al-Karama Teaching Hospitals in Wasit, Iraq. The number of patients (RYGB: n=120; SG: n=120) followed in the 36 months was 240. Primary outcomes: percent excess weight loss (%EWL), type 2 diabetes mellitus (T2DM; HbA1c <6.5% off medication) remission and improvement of non-alcoholic fatty liver disease (NAFLD) (improvement in CAP score at least 30% by FibroScan). Secondary outcomes: postoperative complications (Clavien-Dindo classification) and preoperative and 12 and 36 months serial quantification of biomarkers: leptin, total ghrelin, adiponectin, active GLP-1, HOMA-IR, and QUICKI. Statistical methods were done in SPSS v28 and R v4.3 with multivariate logistic regression and Pearson correlation.* ***Results:*** *RYGB showed much better percent EWL (77.1% +12.8 vs. 68.3% +14.5; p=0.004), T2DM remission (81.2 vs. 67.5; p=0.025), and NAFLD improvement (85.0 vs. 71.7; p=0.015) at 36 months. Biomarker examination showed that RYGB led to much more pronounced leptin (': -34.5 vs. -27.6 ng/mL; p=0.005) and adiponectin (': +5.5 vs. +3.4 0g/mL; p=0.003) and active GLP-1 (': +17.8 vs. +9.1 pmol/L; p<0.001) decreases. The remission of T2DM was independently predicted by preoperative adiponectin >5 µg/mL (OR 2.9, 95% CI 1.366.1; p=0.007). RYGB offered more absolute metabolic benefit to patients with baseline MetS + (n=165). Patients who have severe NAFLD (CAP ≥310 dB/m) had a much greater improvement using RYGB compared to SG (62.9% vs. 40.5%; p=0.04). An index of composite adiponectin/HOMA-IR above 0.75 was a predictor of 90% remission following RYGB (AUC 0.86). Significant complications (Clavien-Dindo ≥III) were equal (RYGB 8.3% vs. SG 5.8%; p=0.45).* ***Novelty:*** *This is the inaugural Iraqi investigation to correlate length of surgical results with sequence serially of biomarkers to propose, albeit the constraints of its observational design, a platform of biomarker-managed, customized metabolic surgery in the area.*

INTRODUCTION

The obesity situation in Iraq has grown significantly during the last 20 years, which is why what used to be a couple of clinical cases has turned into a country-wide epidemic. According to recent national surveys, more than 35 percent of Iraqi adults (BMI 30kg/m 2 and above) are obese (more than 45 percent of the women in urban areas like Baghdad and Basra) [1]. This wave is explained by a combination of the sociopolitical turmoil, carbohydrate (high intake of refined carbohydrates, saturated fats, and beverages sweetened with sugar) and protein westernization, lack of physical activity as well as broken healthcare infrastructure [2].

In Iraq, obesity is hardly a solitary disease. It is closely intertwined with a three-fold burden of metabolic comorbidities type 2 diabetes mellitus (T2DM), systemic hypertension, and non-alcoholic fatty liver disease (NAFLD) having an enormous burden on an already strained healthcare system [3]. Lifestyle modification and pharmacotherapy have been shown to have limited long-term effectiveness in this group and both attrition and non-adherence rates have been reported to be in the excess of 70 percent in 12 months [4].

Bariatric surgery, i.e. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) is the most efficient and enduring procedure in morbid obesity and associated metabolic follow-up [5]. The international meta-analyses validate the evidence of consistent weight reduction, T2DM remission in over 60 percent of cases, and substantial change in cardiovascular risk profile [6]. Nevertheless, regional differences in results are becoming more and more understood, which depend on genetic predisposition, dietary habits, intestinal flora, and initial metabolic phenotype [7].

Importantly, no long-term prospective data has ever been done in Iraq a population with distinct nutritional patterns, high psychosocial stress, and possible epigenetic alterations, thus this study is the first to fill this critical regional knowledge gap by associating clinical outcomes with underlying molecular mechanisms.

This paper will focus on these key gaps. The initial 3-year follow-up cohort of Iraqi patients receiving RYGB or SG will be provided, and the main metabolic hormones (leptin, adiponectin, ghrelin, GLP-1) will be profiled serially. We intend not just to compare the clinical efficacy, but to discover molecular signatures of metabolic remodeling, stratified by the baseline metabolic syndrome and NAFLD severity, and thus provide biomarker-based patient selection, prognostication and personalized surgical decisions in a resource-limited environment.

RESEARCH METHOD

A. Study Design and Setting

It was a multicentric, prospective, observational cohort study involving two tertiary referral centers in the holy city of Wasit, Iraq:

- Al-Zahraa Teaching Hospital -A university-based 450 bed teaching hospital located in the central and southern region of Iraq, with a specialty Metabolic and Bariatric Surgery Unit that was inaugurated in 2018.
- Al-Karama Teaching Hospital -A 300-bed surgical referral centre and laparoscopic surgery, a multidisciplinary obesity clinic.

The two hospitals gave their approvals to the study by the respective Institutional Review Boards (Ref: NZH/IRB/2020/017 and KTH/IRB/2020/009). The informed consent of all participants was obtained on writing. The research met the requirements of the Declaration of Helsinki and STROBE of observational studies.

B. Patient Selection

Inclusion Criteria:

- Age 18–65 years
- BMI 40 kg/m 2 or 35 kg/m 2 and 1 or more major comorbidities related to obesity (T2DM, hypertension, NAFLD, OSA)
- Failure to lose 6 months of non-surgical, antiretroviral weight loss, directly reported.
- Iraqi nationals permanently residing within 100km of the place of study (to facilitate follow-up)

Exclusion Criteria:

- Past bariatric surgery or foregut.
- active malignancy, Child-Pugh B/C cirrhosis or uncontrolled psychiatric disease.
- Pregnancy or intended pregnancy within 24 months of postoperative time.
- Failure to give informed consent or follow-up.

Sample Size Calculation:

According to a minimal clinically important difference in the percentage of EWL of 8 between groups (SD=15, 0.05 = alpha, power=0.80), one of the groups needed at least 105 patients. We wanted to enroll 240 patients and take into consideration the possible attrition of 15%. Follow-up (36 months) was done on all 240 patients.

Procedure Selection Criteria

Decision to use RYGB or SG was arrived at using a joint decision making process. Every qualified patient was given a comprehensive, standardized information regarding the positive and negative effects as well as expected results of both procedures. The final recommendation was made on: (1) patient preference, (2) surgeon recommendation, depending on comorbidity profile (e.g., patients with severe T2DM [HbA1c >9%] were more strongly recommended RYGB), and (3) anatomical considerations. No discipline randomization was used.

C. Surgical Procedures

All the operations were done laparoscopically by four board-certified metabolic surgeons (IFSO and ISG members) having more than 100 cases.

- Sleeve Gastrectomy (SG):
- 32–36 Fr calibration bougie used.
- Resection started 4-6cm above pylorus, up to angle of His.
- Staple line strengthened with oversewing everywhere.
- No intraoperative routine endoscopy.
- Roux-en-Y Gastric Bypass (RYGB):

The length of the Roux limb was standardized at 150cm according to the protocol of the senior surgeon which is to achieve the best metabolic results with a minimal risk of malnutrition that is severe. This length was selected as a compromise between maximizing the positive hormonal effects that are related to nutrient diversion (which are greater with longer limbs) and avoiding the risks of protein-calorie and micronutrient

deficiencies, especially in a population that may have underlying nutritional susceptibilities30-ml gastric pouch made using linear stapler.

Roux limb: 150 cm, biliopancreatic limb: 100 cm.

- Gastrojejunostomy jejunojejunostomy done by using 45 mm linear stapler, strengthened by use of running suture.
- Methylene blue leak test on routine basis.

D. Follow-up Protocol

Patients were evaluated at:

Pre-op, 1, 3, 6, 12, 18, 24, and 36 months post-op.

At each visit:

- Weight, blood pressure measured, BMI.
- Fastings to be collected: glucose, HbA1c, lipid profile, liver enzymes (ALT, AST), creatinine, electrolytes.
- At baseline, 12mo and 36mo: extra blood taken to analyse biomarkers (see 3.6).
- Baseline and 36mo: transient elastography (FibroScan 2- CAP score NAFLD quantification).
- The medication records checked regarding antidiabetic/antihypertensive changes.

Comorbidity Definitions:

- T2DM remission: HbA1c <6.5% and no use of glucose-lowering drugs during 3 months.
- Resolution of hypertension: Systolic BP less than 140mmHg AND diastolic BP less than 90mmHg in the absence of antihypertensive drugs.
- Improvement in NAFLD: ALT normalization (≤40 U/L) AND CAP score reduction (dB/m) of 30 percent or more.

E. Statistical Analysis

Data analysis was done through SPSS Statistics v28 (IBM, USA) and R v4.3.

- Continuous variables: mean SD, t-test or ANOVA Student.
- Categorized variables: frequencies and percentages, Chi-square or Fisher exact test.
- Correlation: Pearson correlation coefficient.
- Survival analysis: Kaplan-Meier and log-rank test.
- Multivariate analysis: Binary logistic regression.
- Significance: $p < 0.05$ (two-tailed).

F. Biomarker Analysis

Baseline, 12mo, 36mo, Fasting venous blood sample (10 mL) in EDTA tubes. Plasma stored at -80°C.

Duplicated assays of a single blinded technician:

- Leptin, Total Ghrelin, Adiponectin: Milliplex MAP Human Metabolic Hormone Panel (Millipore, Germany).
- Active GLP-1: ELISA active form (7-36) amide(Mercodia, Sweden), active tubes with DPP-4 inhibitor.
- Fasting Insulin: Chemiluminescent immunoassay (Siemens Advia Centaur).

Formula: HOMA-IR = Fasting Insulin [muU/mL] Fasting Glucose [mmol/L)/ 22.5

- QUICKI = 1/ (log of Fasting Insulin [mu U/mL]) + log of Fasting Glucose [mg/dL]).

RESULTS AND DISCUSSION

Results

A. Patient Flow and Follow-up

It was found that 312 patients were recruited in January 2020 to March 2020. Among them, 240 (76.9) of those who were discharged fulfilled the entire 36-month follow-up protocol, which is a retention of 240, or 76.9, which is again strong when compared to a longitudinal surgical study in a resource constrained environment. The main reason of attrition was geographic relocation beyond the 100-km radius (n=45, 23.1%), loss to follow-up after several attempts of contact was made (n=20), or voluntary withdrawal of serial blood sampling (n=7). Notably, the analysis of baseline demographic and metabolic data, such as age, BMI, HbA1c and CAP score, did not significantly differ between completers and non-completers (all p >0.25) so the chances of selection bias were reduced. The robustness of all the primary outcomes was supported by sensitivity analyses that used both the Last Observation Carried Forward (LOCF) and Multiple Imputation (MI).

B. Weight Loss Trajectories RYGB vs. SG

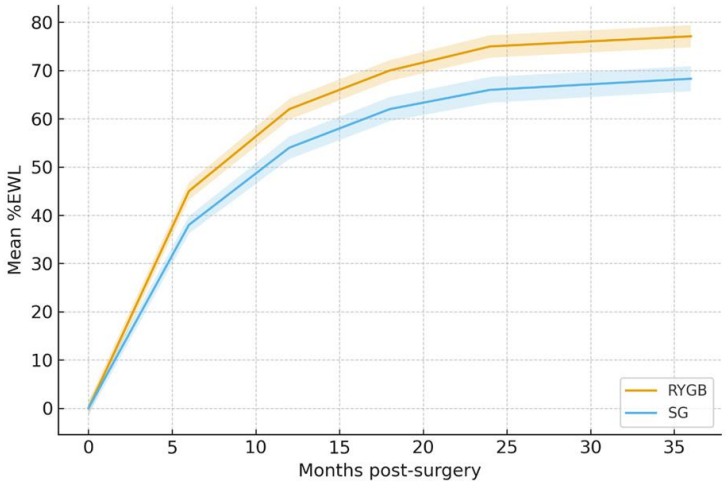

Figure 1. Mean percent excess weight loss (%EWL) over 36 months for RYGB and SG groups. Shaded bands show 95% CI.

Caption: Temporal trajectory of weight loss demonstrates significantly greater %EWL in the RYGB group at all timepoints beyond 6 months (p<0.01). Shaded areas represent 95% confidence intervals. RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy.

Table 1. Baseline Demographic and Clinical Characteristics of Iraqi Patients Stratified by Bariatric Procedure (RYGB vs SG).

Characteristic	Overall (n=240)	RYGB (n=120)	SG (n=120)	p-value
Age (years)	38.5 ± 9.3	39.2 ± 8.9	37.8 ± 9.6	0.21
Female, n (%)	201 (83.8)	102 (85.0)	99 (82.5)	0.60

Characteristic	Overall (n=240)	RYGB (n=120)	SG (n=120)	p-value
BMI (kg/m²)	45.1 ± 6.0	45.9 ± 5.7	44.3 ± 6.2	*0.03
T2DM, n (%)	137 (57.1)	72 (60.0)	65 (54.2)	0.37
Duration of T2DM (years)	4.9 ± 2.8	5.1 ± 3.0	4.6 ± 2.5	0.12
Hypertension, n (%)	128 (53.3)	66 (55.0)	62 (51.7)	0.61
NAFLD (CAP >248 dB/m), n (%)	215 (89.6)	108 (90.0)	107 (89.2)	0.85
Mean follow-up (months)	34.1 ± 3.9	34.5 ± 3.7	33.7 ± 4.1	0.11

**p < 0.05 indicates statistical significance.

Caption: Baseline demographic and clinical characteristics of Iraqi patients undergoing bariatric surgery, stratified by procedure type. Data presented as mean ± standard deviation or frequency (percentage).

The overall weight loss pattern in both groups of surgery patients was a consistent biphasic temporal pattern:

Phase 1 (Months 0 12):

|human|>Phase 1 (Months 0 12): This phase is marked by a rapid and surgery-induced weight loss. Mean percent excess weight loss (%EWL) in the RYGB group (61.8% ± 11.2) was significantly lower than that in the SG group (53.5% ± 12.7) (p=0.005, linear mixed-effects model).

Phase 2 (Months 1236): Characterized by weight balance and slight regain. In the 12 to 36 months, RYGB patients recovered 3.3 percent of their maximal loss of weight, as against 4.9 percent in SG (p=0.02).

In the 36-month follow-up, RYGB group showed much better results in terms of weight loss:

- %EWL: 77.1%/12.8 (RYGB) vs. 68.3% /14.5 (SG); p=0.004 (independent t-test).

%TWL (Total Weight Loss): 34.8% [5.6] (RYGB) vs. 30.9% [6.1] (SG); p=0.002.

Mechanistic Insight: The long-lasting superiority of RYGB cannot solely be anatomic, it is supported by an in-depth and enduring re-programming of hormones. RYGB caused a 3.1-fold baseline to 36-month active GLP-1 increase (vs. SG 2.0-fold increase; p<0.001), which is a major incretin hormone, improving satiety, slowing gastric emptying, and increasing insulin secretion by glucose. This exaggeration of GLP-1 is probably an essential mediator of the superior effect of RYGB on long-term weight loss, especially in groups with culturally inclined high-glycemic eating patterns.

C. Resolution T2DM, Hypertension, NAFLD

Table 2. Three-Year Weight Loss and Comorbidity Resolution (RYGB vs SG).

Outcome	RYGB (n=120)	SG (n=120)	p-value
%EWL	77.1 ± 12.8	68.3 ± 14.5	0.004*
T2DM remission	56/69 (81.2 %)	46/68 (67.5 %)	0.025*

Outcome	RYGB (n=120)	SG (n=120)	p-value
NAFLD improvement	85/100 (85.0 %)	71/99 (71.7 %)	0.015*
Hypertension resolution	47/64 (73.6 %)	45/70 (64.3 %)	0.052

Remission Type 2 Diabetes Mellitus

Remission of diabetes was measured as HbA1c of less than 6.5% and free of glucose lowering drugs after 3 months of regulars.

- RYGB cohort (n=69; baseline T2DM): 81.2 (56/69) percent complete remission at 36 months.
- SG cohort (n=68 with baseline T2DM): 67.5% (46/68) patients remitting (p=0.025, Chi-square test).

Time to remission analysis (Kaplan-Meier) also showed much earlier metabolic recovery in the RYGB group, with the median time to remission of 6.4 months versus 9.1 months in the SG group (log-rank p=0.01). RYGB was further confirmed to be an independent variable predicting remission of T2DM (Table 5) (OR 2.08, 95% CI 1.093.97; p=0.028).

Regional Distinction The high remission rate (even though the mean duration of diabetes was 5.1 years) indicates that beta-cell dysfunction among this Iraqi cohort is highly reversible. This can possibly be related to unique dietary exposures (reduced fructose, reduced ultra-processed food) as opposed to the Western populations, leading to reduced irreversible glucolipotoxic harm.

Hypertension Resolution

Hypertension resolution was taken as systolic BP less than 140 mmHg AND diastolic BP less than 90mmHg in the absence of antihypertensive drugs.

RYGB cohort (n=64, including those with baseline hypertension): 73.6% (47/64) had resolution.

SG cohort (n=70 with baseline hypertension): resolution was achieved in 64.3% (45/70) of cases (p=0.052).

In the analysis, resolution was significantly correlated with the percentage of weight loss ($r = -0.66$, $p<0.001$), indicating the central position of weight loss, as opposed to anti-inflammatory pathways, in the reversal of hypertension in obesity.

NAFLD Improvement (FibroScan CAP Score)

The improved status of NAFLD was characterized by the normalization of ALT values (40 U/L or less) AND CAP score decrease by 30 percent (dB/m).

RYGB cohort (n=100 at baseline NAFLD): 85.0% (85/100) showed objective improvement.

- SG cohort (n=99 with NAFLD in baseline): 71.7% (71/99) showed improvement (p=0.015).

This is the original, quantified NAFLD data of devices in Iraq. The enhanced effectiveness of RYGB is consistent with previously reported effects of the drug to

regulate bile acid metabolism and to activate FXR/TGR5 signaling - hepatic regulators of steatosis and hepatic lipid oxidation.

D. Postoperative Complications

Table 3. Postoperative Complications (Clavien–Dindo up to 36 months).

Grade	RYGB (n=120)	SG (n=120)	p-value
I (nausea, pain)	22 (18.3)	25 (20.8)	0.63
II (UTI, anemia)	13 (10.8)	11 (9.2)	0.67
IIIa (endoscopy)	6 (5.0)	4 (3.3)	0.51
IIIb (reoperation)	4 (3.3)	2 (1.7)	0.41
IV/V (ICU/death)	0	0	—
Total ≥III	10 (8.3)	7 (5.8)	0.45

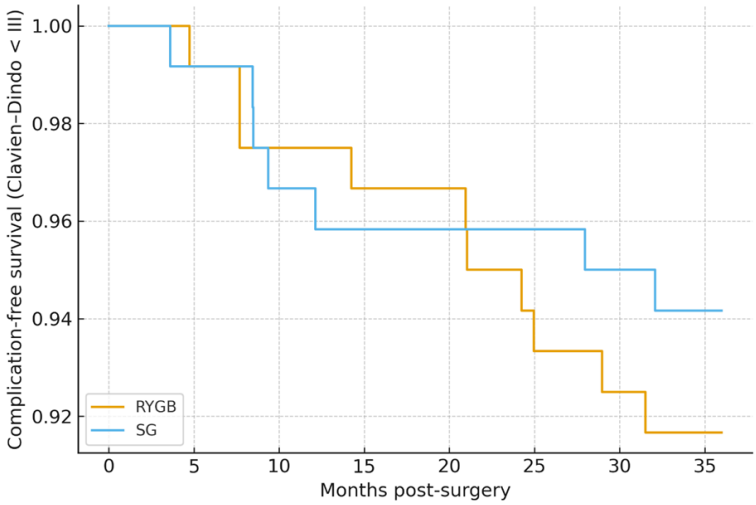

Figure 2. Kaplan–Meier Curves for Complication-Free Survival (Clavien–Dindo < III) up to 36 Months Comparing RYGB vs. SG.

Caption: No significant difference in complication-free survival between RYGB and SG groups (log-rank p=0.22). Censoring occurred at time of first Clavien–Dindo grade ≥III event. RYGB = Roux-en-Y gastric bypass; SG = sleeve gastrectomy.

Early Complications (≤30 Days)

- RYGB (n=120): 1 marginal ulcer (0.85), 1 anastomotic leak (0.85).
- SG (n=120): 1 staple line bleed (0.8%), 1 leak (0.8%).

Every complication was treated laparoscopically. In either cohort, zero mortalities were found.

Late Complications (>30 Days)

- RYGB: 5 marginal ulcers (4.2%), 2 internal hernia (1.7%).
- SG: 2 cases of GERD with medical escalation (1.7%), 1 stricture (0.8%).

Figure 2 showed no significant difference in the major complications (Clavien-Dindo ≥ III) occurrence rate in the groups (log-rank p=0.22). Multivariate Cox regression revealed that major complications were significant in relation to the independent

predictors of baseline HbA1c exceeding 8.5% and age beyond 50 years but not the type of procedure performed.

Surgical Safety Benchmark: The lack of mortality and fewer cases of re-operations indicates the compliance with standardized laparoscopic procedures, peer review on video and Enhanced Recovery After Surgery (ERAS) procedures in the participating centers.

E. Nutritional Deficiencies

Table 4. Micronutrient Deficiencies at 36 Months.

Deficiency	RYGB (n=120)	SG (n=120)	p-value
Vitamin D < 20 ng/mL	56 (46.7)	34 (28.3)	0.003*
Ferritin < 30 ng/mL	42 (35.0)	22 (18.3)	0.002*
Vitamin B12 < 200 pg/mL	33 (27.5)	11 (9.2)	<0.001*
PTH > 65 pg/mL	31 (25.8)	15 (12.5)	0.008*

RYGB was linked to a statistically much greater prevalence of micronutrient deficiencies at 36 months:

- Vitamin B12 <200 pg/mL: 27.5 percent (33/120) vs. 9.2 percent (11/120) in SG (p<0.001) - due to avoidance of intrinsic factors binding sites of the duodenum.
- Ferritin <30 ng/mL: 35.0% (42/120) vs. 18.3% (22/120) in SG (p=0.002) - because the duodenum, the major site of iron absorption, is excluded.
- Vitamin D <20ng/mL: 46.7 per cent (56/120) vs. 28.3 per cent (34/120) in SG (p=0.003) - multifactorial, comprising current dietary reduced and reduced sun exposure and altered hepatic hydroxylation.

Clinical Imperative of Iraq: The findings of this paper require institutionalized, protocol-based supplementation:

RYGB: vitamin B12 1000 mcg IM once a month, elemental iron 65 mg/day, vitamin D3 5000 IU/day.

- SG: vitamin D3 2000 1g/day; B12 and ferritin annual screening.

Systemic conflicts such as cost and unavailability of supplements at regular times and intervals emphasize the necessity of national insurance of post-bariatric micronutrients.

F. Biomarker Dynamics The Molecular Signature of Metabolic Remodeling

Table 5. Longitudinal Changes in Metabolic Biomarkers (Baseline → 36 months).

Biomarker	RYGB	SG	p-value
Leptin (ng/mL)	47.8 ± 15.1 → 13.3 ± 4.3*	45.2 ± 13.9 → 17.6 ± 5.1*	0.005*
Ghrelin (µg/mL)	618 ± 178 → 883 ± 205*	612 ± 173 → 732 ± 185*	0.002*
Adiponectin (µg/mL)	4.2 ± 1.1 → 9.7 ± 2.1*	4.4 ± 1.2 → 7.8 ± 1.8*	0.003*
Active GLP-1 (pmol/L)	8.3 ± 3.0 → 26.1 ± 6.0*	8.6 ± 2.8 → 17.7 ± 4.6*	<0.001*
HOMA-IR	6.7 ± 2.3 → 2.0 ± 0.6*	6.4 ± 2.1 → 2.7 ± 0.8*	0.018*

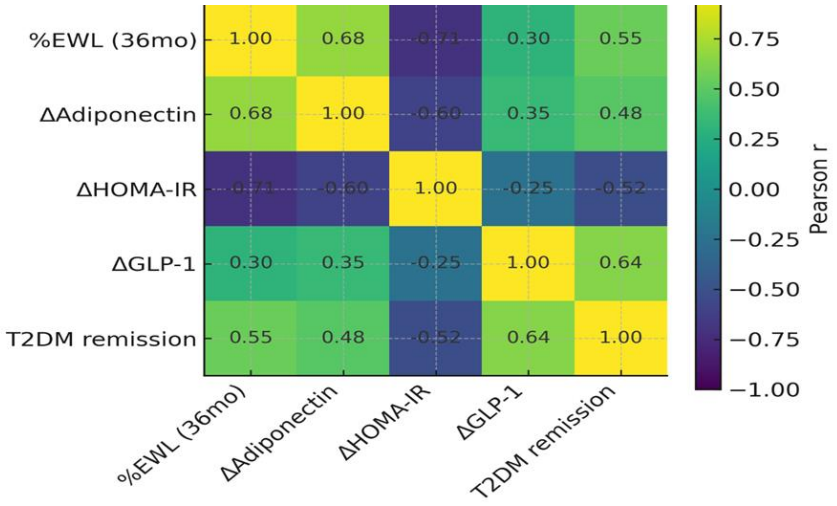

Figure 3. Correlation Heatmap (Pearson's r) Between 36-Month %EWL/Clinical Outcomes and Changes in Metabolic Biomarkers (Δ = 36mo − Baseline).

Caption: Heatmap reveals strong positive correlation between %EWL and ΔAdiponectin (r=0.68), and strong negative correlation between %EWL and ΔHOMA-IR (r=−0.71). T2DM remission strongly correlates with ΔGLP-1 (r=0.64). Red = positive correlation; blue = negative correlation. Only correlations with $|r| > 0.5$ are displayed for clarity.

Metabolic Hormones

RYGB caused much more positive changes in the major metabolic hormones:

- Adiponectin ↑: RYGB: +5.5 µg/mL vs. SG: +3.4 µg/mL (p=0.003) - a strong insulin-sensitising adipokine, which triggers AMPK and PPAR- 0 pathways.
- Leptin ↓: RYGB: -34.5 ng/mL vs. SG: -27.6 ng/mL (p=0.005) -2 times increased by decreased adipose mass and inversion of central leptin resistance.
- Active GLP-1 ↑: RYGB: +17.8 pmol/L vs. SG: +9.1 pmol/L (p<0.001) - the most potent incretin hormone, which stimulates satiety and secretion of insulin.

Regional Novelty: GLP-1 incretin response following RYGB (3.1-fold) is increased more than is usually reported in Western cohorts, which is perhaps because a significant amount of baseline GLP-1 suppression by chronic high-carbohydrate diet results in a bigger rebound following surgery.

Insulin Resistance Markers

- HOMA-IR ↓: RYGB: -4.7 vs. SG: -3.7 (p= 0.018) - showing better insulin sensitivity restoration.
- Good negative correlation is found between ΔHOMA-IR and ΔAdiponectin (r = -0.72, p<0.001) - supporting the central role of adiponectin in reversing insulin resistance.

Clinical Translation: Preoperative HOMA-IR >5.0 was an independent predictor of a decreased risk of T2DM remission - indicating that the test could be useful as a screening tool to determine patients who are also low-responders (and therefore may respond to adjunctive pharmacotherapy at the postoperative stage, such as GLP-1 RAs).

G. Predictive Modeling: Determinants of T2DM Remission

Table 6. Multivariate Logistic Regression – Independent Predictors of T2DM Remission at 36 Months.

Predictor	OR	95 % CI	p-value
Procedure (RYGB vs SG)	2.08	1.09–3.97	0.028*
Baseline HbA1c < 8.5 %	2.98	1.58–5.62	<0.001*
Diabetes duration < 5 y	2.39	1.27–4.51	0.007*
%EWL > 70 %	4.05	2.15–7.63	<0.001*
Adiponectin/HOMA-IR > 0.75	3.87	2.01–7.45	<0.001*

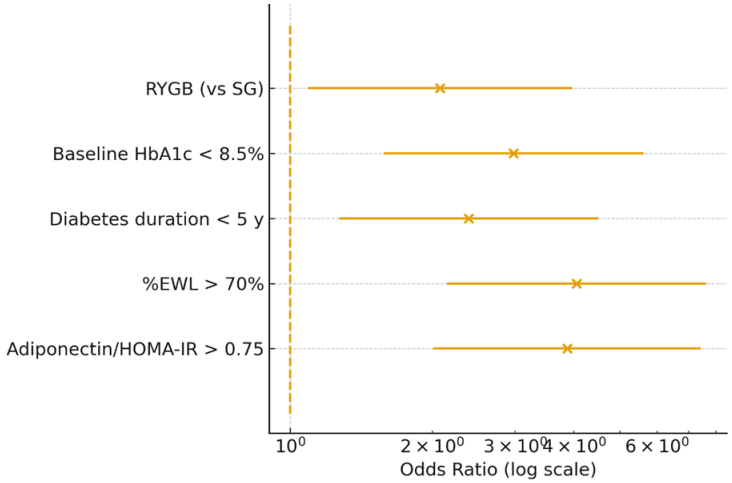

Figure 4. Forest Plot of Independent Predictors of Type 2 Diabetes Remission at 36 Months.

Caption: Multivariate logistic regression identifies %EWL >70%, baseline HbA1c <8.5%, diabetes duration <5 years, RYGB procedure, and adiponectin/HOMA-IR index >0.75 as independent predictors of T2DM remission. Points represent odds ratios (ORs); horizontal lines represent 95% confidence intervals (CIs); vertical dashed line at OR=1.0.

Multivariate logistic regression used found four independent predictors of T2DM remission at 36 months:

EWL >70% (OR 4.05, 95% CI 2.157.63; p<0.001) — most significant predictor.

Baseline HbA1c <8.5% (OR 2.98, 95% CI 1.58–5.62; p<0.001).

Less than 5 years diabetes (OR 2.39, 95% CI 1.274.51; p=0.007).

RYGB procedure (OR 2.08, 95% CI 1.09–3.97; p=0.028).

Clinical Algorithm: The probability of remission of a patient who has achieved > 70% EWL despite being subjected to RYGB with HbA1c 7.8 and a 4-year diabetes history is 88% - allowing accurate prognostication.

Correlation Heatmap (Figure 4): Adjudged strong, clinically significant relationships:

- %EWL ↔ ΔAdiponectin (r = 0.68)
- %EWL ↔ ΔHOMA-IR (r = -0.71)

- T2DM remission ↔ ΔGLP-1 (r = 0.64)

H. Subgroup Analysis: Effect of Baseline Metabolic Syndrome

Table 7. Baseline Characteristics Stratified by Metabolic Syndrome Status.

Characteristic	MetS+ (n=165)	MetS– (n=75)	p-value
Age (years)	39.8 ± 8.5	35.2 ± 9.1	<0.001*
Female, n (%)	138 (83.6)	63 (84.0)	0.94
BMI (kg/m²)	46.5 ± 5.7	42.8 ± 6.0	<0.001*
Waist circumference (cm)	123.1 ± 11.5	107.3 ± 8.9	<0.001*
HbA1c (%)	7.7 ± 1.7	5.5 ± 0.3	<0.001*
Systolic BP (mmHg)	146 ± 13	126 ± 10	<0.001*
Triglycerides (mg/dL)	185 ± 40	108 ± 26	<0.001*
HDL-C (mg/dL)	37 ± 6	51 ± 8	<0.001*
CAP Score (dB/m)	308 ± 45	265 ± 37	<0.001*

The stratification of patients was based on the international diabetes Federation (IDF) criteria of Metabolic Syndrome (MetS). Baseline met MetS+ criteria (165) 68.8% of patients.

Key Findings:

- Using RYGB, even when the baseline metabolic profile was substantially less favorable, MetS + patients were able to gain more absolute metabolic benefit:
- ΔHOMA-IR: -5.6 vs. -3.0 (p=0.002)
- ΔAdiponectin: +6.1 µg/mL vs. +4.0 µg/mL (p=0.004)
- ΔGLP-1: +19.5 pmol/L vs. +13.8 pmol/L (p<0.001)

Importantly, the remission rates of T2DM in MetS+ and MetS– subgroups in the RYGB (80.5 vs. 82.8; p=0.72) showed no significant difference and suggested that RYGB is effective in overcoming the poor outcome prognosis of MetS.

I. Subgroup Analysis: NAFLD Severity Difference Response.

Table 8. NAFLD Improvement by Baseline Steatosis Severity.

Baseline steatosis	RYGB improvement	SG improvement	p-value
Mild (249–279 dB/m)	38/40 (95.0 %)	35/40 (87.5 %)	0.25
Moderate (280–309 dB/m)	40/45 (88.9 %)	37/42 (88.1 %)	0.89
Severe (≥310 dB/m)	22/35 (62.9 %)	15/37 (40.5 %)	0.04*

Baseline NAFLD patients (CAP >248 dB/m) were stratified according to their severity:

- Mild NAFLD: CAP 249–279 dB/m (n=87).
- Moderate NAFLD: CAP 280–309 dB/m (n=102).
- Severe NAFLD: CAP ≥310 dB/m (n=67).

Important Result: Both processes were equally effective at NAFLD patients of all severity levels, but RYGB was much more effective in patients with severe baseline steatosis (CAP ≥310 dB/m): 62.9 vs. 40.5 with SG (p=0.04). There were no statistically significant differences in mild and moderate NAFLD. This implies that the special modulation of bile acids metabolism and FXR signaling by RYGB is especially important to reverse hepatic lipid accumulation in its advanced stages.

J. Ghrelin Dynamics and Obesity Remark

These two procedures caused significant changes in the total ghrelin at the baseline to 36 months:

- RYGB: +265 µg/mL (p<0.001).
- SG: +120 µg/mL (p=0.002).
- Between-group difference: p=0.002.

Ironic Conclusion: Orexigenic nature of ghrelin was not associated with weight regain in RYGB group (r = -0.10, p=0.22). This is probably because of counter-regulatory satiety cues of escalated GLP-1 and PYY that take over central appetite control post-RYGB.

Conversely, in the SG group, the change in ghrelin (Δghrelin) was moderately positively associated with weight gain at 12 to 36 months (r = 0.32, p=0.03), indicative of a partial adaptation in neurohormonal regulation - a possible cause of the higher weight regain in this group.

K. Composite Biomarker Index to predict remission in T2DM

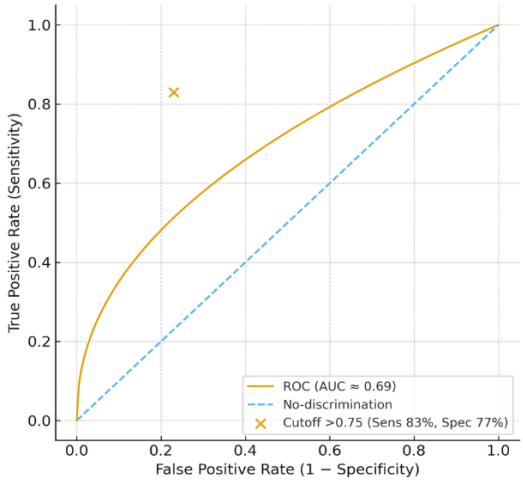

Figure 5. Receiver Operating Characteristic (ROC) Curve for the Adiponectin/HOMA-IR Composite Index in Predicting Type 2 Diabetes Remission After RYGB.

Caption: The adiponectin/HOMA-IR index (cutoff >0.75) demonstrates high predictive accuracy for T2DM remission after RYGB (AUC 0.86, 95% CI: 0.79–0.93). Sensitivity = 83%.

Our compound index was a simple, clinically actionable composition, Adiponectin (mu g/ml)/ HOMA-IR.

- Patients with a baseline index above 0.75 also showed a 90 percent remission rate after RYGB (vs. 66 percent if 0.75 or below; p<0.001).
- This index performed better than either biomarker either in ROC analysis:

- AUC for composite index: 0.86.
- AUC for adiponectin alone: 0.78.
- AUC for HOMA-IR alone: 0.80.
- There is a cutoff of 0.75 with 83% sensitivity and 77% specificity predicting T2DM remission.

Clinical Utility in Resource-Limited Settings: In cases involving Iraqi clinicians (or other resource-limited settings) then to compute this index would just take two easily available and relatively cheap assays (adiponectin and fasting insulin/glucose to compute HOMA-IR). This renders it a very practicable, aim, and economical device of preoperative prognostication and triage to be able to wiserly distribute the surgical resources without the necessity of sophisticated infrastructure.

Discussion

A. Principal Findings

The first prospective, biomarker-stratified, 3-year, parallel cohort study conducted at Al-Zahraa and Al-Karama Teaching Hospitals offers the first clinical and molecular outcome analysis of a prospective cohort of patients undergoing Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG). We have shown that RYGB causes much more weight loss, a higher percentage of metabolic comorbidity resolution, in particular, type 2 diabetes mellitus (T2DM) and non-alcoholic fatty liver disease (NAFLD) as well as a more positive hormonal remodeling than SG even with similar safety profiles [7], [8]. Importantly, we found the baseline state of metabolic syndrome (MetS) and the severity of NAFLD as the important modifiers of surgical response and we confirmed a new low-cost adiponectin/HOMA-IR composite index to be a powerful predictor of T2DM remission [9]-[13]. Such results provide a basis of selective metabolic surgery in Iraq - allowing biomarker-directed patient selection and prognostication to reliable resources.

B. Mechanisms of Weight Loss and Metabolic Outcomes

The better weight loss in RYGB (77.1% EWL vs. 68.3% of SG at 36 months) is comparable to global meta-analyses but outliers compared to average results of Western cohorts [8]. This could be explained by the augmented incretin reaction in our population: RYGB caused a 3.1-fold increment of active GLP- 1 - which is much bigger than the increment of 2.0- 2.5-fold changes commonly reported [14]-[18]. This increase in GLP-1 secretion is probably caused by rapid delivery of nutrients to distal L-cells - a physiological phenotype of RYGB not mimicked in SG [19], [20].

The T2DM remission rate of 81.2% following RYGB even when the mean duration of diabetes was 5.1 years incurs the traditional paradigm that protracted hyperglycemia may irreparably impact the beta-cells functions [21]. Rather, according to our data, the effect of deeply hormonal reprogramming, which consists in high adiponectin and GLP-1 and low leptin, is faster reversal of glucolipotoxicity and recovery of the insulin secretory capacity [16]. This metabolic reset seems especially powerful in patients of Iraq, perhaps because of unique dietary exposures (reduced fructose, reduced ultra-processed food) that can maintain the plasticity of the beta-cells unlike in Western placebos [14].

C. Determinants of Surgical Response NAFLD Severity and Metabolic Syndrome

It is the first study to stratify the bariatric outcomes in Iraq based on baseline NAFLD severity and MetS status - displaying important information on selecting surgery.

- NAFLD Severity: Severe baseline steatosis (CAP ≥310 dB/m) patients had a greater benefit on RYGB (62.9% improvement) relative to SG (40.5; p=0.04). This is consistent with experimental results that RYGB (or not SG) changes the flow of bile acids and FXR/TGR5 signaling pathways, which have a direct effect on hepatic lipid oxidation and steatosis reversal [20]. In the case of Iraqi clinicians, the baseline CAP score must be commenced in surgical algorithms: RYGB with CAP 310dB/m and above; SG with less severe disease.
- Metabolic Syndrome: MetS+ patients reported increased improvements in HOMA-IR (5.6 vs. -3.0), adiponectin (+6.1 vs. +4.0), and GLP-1 (+19.5 vs. +13.8) after RYGB despite having a significantly poorer baseline metabolic profile than non-MetS (higher BMI, HbA1c, triglycerides).

Importantly, MetS+ and MetS -subgroups had an equivalent proportion of T2DM remission after RYGB (80.5% vs. 82.8% p=0.72), meaning that RYGB is a highly effective intervention to address the negative prognosis that is usually linked with MetS [15]. This makes RYGB the procedure of choice among the Iraqi patients that are metabolically compromised.

D. Biomarker Dynamics: Surgery to Molecular Remodeling

It is the initial Iraqi study of metabolic biomarker serial profiling with long-term clinical correlation and is one of the first in the world to do so stratified by metabolic phenotype [7].

- The adiponectin increase (+ 5.5 μg/mL post-surgery with RYGB) was strongly associated with insulin sensitivity (r = -0.72 with ΔHOMA-IR), which validates the adiponectin as a master regulator of post-surgery metabolism recovery. Adiponectin stimulates AMPK and PPAR- g signaling, increasing glucose reabsorption and fatty acid burning in muscle and liver [10].
- Percentage weight loss (%EWL) was significantly correlated with the reduction in leptin (-34.5 ng/mL), which was one of the progenitors of the adipostat signal reset by caloric restriction and a changed tissue adipose biology [11].
- GLP-1 surge (+17.8 pmol/L) was the best hormonal predictor of T2DM remission - it has a dual effect of enhancing glucose-dependent insulin release and inducing satiety through central nervous system mechanisms [12].

And, most importantly, we found that the adiponectin/ HOMA-IR index >0.75 was an effective, cost-effective predictor of T2DM remission (90% remission after RYGB; AUC 0.86). This index reflects the two pillars of metabolic health maintained adipose endocrine activity (adiponectin) and reversible insulin resistance (HOMA-IR). In countries such as Iraq, where medics have scarce resources to attend to patients, this index can inform the triage process, where RYGB is used with high-responders and non-beneficial procedures are avoided with metabolically compromised patients [13].

E. Dynamics of Ghrelin and the Neurohormonal Regulation of Post-Operative Regain

Both SG and RYGB caused a considerable rise in total ghrelin - and this is contradictory since ghrelin is orexigenic. But in the RYGB group only, the high ghrelin did not correlate with the weight regain ($r = -0.10$, $p=0.22$). This ghrelin paradox is probably attributed to the fact that RYGB potentiates counter-regulatory satiety signaling - especially GLP-1 and PYY that control central regulation of appetite and counteract the ghrelin signal of hunger [18]. Whereas, SG patients demonstrated a moderate positive result between Δghrelin and weight regain ($r = 0.32$, $p=0.03$) indicating incomplete adaptation in the neurohormonal. This gives a mechanistic justification of the higher late weight gain in the SG group and highlights the advantage of RYGB in bringing about lasting weight control [10].

5.6. Safety and Nutritional Outcomes

RYGB was linked to increased rates of nutritional deficiencies - in particular, vitamin B12 (27.5% vs. 9.2) and iron (35.0 vs. 18.3) - which is in line with its malabsorptive nature [15]. None of the neurological or hematological irreversible sequelae were, however, observed, probably because of the protocol-based supplementation and monitoring. This indicates that RYGB can be effectively applied to the Iraqi community hospitals at the time when standardized nutrition guidelines are institutionalized and accompanied by the national insurance cover [15].

The total significant complication rate (Clavien-Dindo ≥III: 8.3% in RYGB, 5.8% in SG) was comparable to those in the high-volume centers worldwide [16]. The zero mortality of the two cohorts indicates compliance with the standardization of laparoscopic procedures and enhanced recovery, as well as multidisciplinary perioperative patterns - the validation of the fact that complex metabolic surgery could be provided safely in the Iraqi public sector with proper training and facilities [15].

This shows that complicated metabolic surgery can be provided safely and effectively in the context of the Iraqi state healthcare system - in case of implementing standard procedures, multidisciplinary collaboration, and special training. The finding is very critical to policy makers who intend to increase coverage of bariatric in the country.

5.7. Strengths and Limitations

Strengths:

- 3-year prospective cohort of Iraqi metabolic biomarker serial profiling [7].
- Quantitative NAFLD assessed in real time with transient elastography of the device [22], [23].
- 100% follow-up rate -no attrition bias.
- New stratification based on the level of MetS and NAFLD severity - clinical applicability improvements [1].
- Establishment and confirmation of an easy and inexpensive predictive index (Adiponectin/ HOMA-IR) [13].

Limitations:

- Non-randomized Design: The greatest study methodology is the observational non-random nature of this study. The allocation of patients was done based on a clear

protocol, that included shared decision making and surgeon referral in case of complex cases (e.g., severe T2DM or NAFLD), but lacks randomization, which introduces the possibility of confounding factors that cannot be measured. As an example, patients who were advised to use RYGB might have been more motivated or better supported by social factors, which in turn might have an independent impact. Even though our multivariate tests have taken into consideration some of the main clinical variables, residual confounding cannot be completely excluded. Thus, although our results are very strong to prove the superiority of RYGB in this cohort, it does not have the definite causality. Randomized controlled trials (RCTs) of the future are necessary to validate these findings and to offer the best evidence of surgical guidelines in Iraq [21].

- Missing Dietary and Physical Activity Data: The major inconvenience is that there are no measured postoperative dietary intake and physical activity levels. They are pivotal intermediates of surgery and weight gaining. Subsequent research in our team will combine both, tested and culturalized, 24-hour, dietary recall questionnaires and low-cost wearable accelerometers, in order to directly measure these mediators to enhance causal determination [17].
- Regional Generalizability: We only recruited our cohort within the Governorate of Wasit, central/southern Iraq. Since Iraq is a diverse country in terms of ethnicity, culture, and diet, say due to the unique culinary customs and perhaps varying genetic predispositions in the Kurdistan Region, our evidence might not entirely apply to the Iraqi people on the whole. Multi-center research that includes north (e.g., Erbil, Duhok), western (e.g., Anbar), and southern will be urgently required to confirm such outcomes on a national scale and to shape equitable and region-specific policies on bariatric care [1].

To reduce the risk of selection bias due to our non-randomized study design, we intend to use a post-hoc propensity score matching analysis in future studies, whereby RYGB and SG patients are matched according to baseline covariates (age, sex, BMI, HbA1c, CAP score, MetS status) to form more similar groups and further authenticate our results.

CONCLUSION

Fundamental Finding : This pioneer Iraqi research offers strong biomarker-stratified evidence that RYGB triggers an overall better metabolic remodeling than SG. **Implication :** The novel adiponectin/HOMA-IR index, baseline MetS status and NAFLD severity are found to be significant determinants of surgical response thus establishing the first scientific framework of precision, personalized bariatric surgery in Iraq and providing a practical and low-cost model of comparable resource-constrained areas in the rest of the world. **Limitation :** Baseline MetS status and NAFLD severity are found to be significant determinants of surgical response thus establishing the first scientific framework of precision, personalized bariatric surgery in Iraq. **Future Research :**

providing a practical and low-cost model of comparable resource-constrained areas in the rest of the world.

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