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CLINICAL REPORT

Studies in Insulin Resistance following Very Low Calorie Diet and/or Gastric Bypass Surgery

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Abstract The explanation for the rapid improvement in insulin resistance after Roux-en Y gastric bypass (RYGB) may involve mechanisms additional to caloric restriction and improvements in peripheral glucose disposal. 8 severely obese patients underwent a 6-day very low calorie diet (VLCD) (456 kcal/day) followed 1-3 weeks later by RYGB. Insulin resistance was measured by short intravenous insulin tolerance test (IVITT) and by homeostasis model assessment (HOMA) before and again 6 days after the VLCD and after RYGB. In a group of 24 matched patients, HOMA assessments were made before and six days after RYGB. HOMA-IR fell significantly from 6.84.9 to 4.32.9 ($p<0.05$) following VLCD, but this was less than the subsequent fall following RYGB (6.8±4.9 to 1.50.4, $p<0.01$). Control patients who underwent RYGB alone, reduced their HOMA-IR to 1.50.9 following the operation which was not significantly different from the VLCD then RYGB group. Following VLCD, IVITT showed no significant change. However, 6 days after RYGB, IVITT showed worsened insulin induced glucose uptake ($p<0.05$). Patients undergoing VLCD over six days had a reduction in HOMA-IR which was half that of patients undergoing RYGB. Patients who underwent both VLCD and RYGB had a total reduction in HOMA similar to those who underwent the RYGB alone. In contrast, IVITT showed a worsening in insulin induced glucose disposal following RYGB, which suggests worsening peripheral insulin resistance. This study supports the hypothesis that mechanisms other than caloric restriction are involved in the acute improvement in HOMA-IR following RYGB.

Keywords Insulin resistance · Calorie restriction · Gastric bypass surgery

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Introduction

Insulin resistance is believed to be a key step in the pathogenesis of type 2 diabetes mellitus (T2DM) [1]. Treatment of T2DM focuses on either reducing insulin resistance or increasing insulin levels or a combination of both. Non-pharmaceutical treatments such as weight loss and lifestyle modifications may improve insulin resistance [2, 3], whereas pharmaceutical treatments focus on improving insulin resistance or elevating insulin levels. It is now widely accepted that metabolic procedures such as gastric bypass surgery (RYGB) have a rapid effect on insulin resistance and can induce remission of T2DM within 6 days of surgery [4–6]. Understanding how insulin resistance can be ameliorated or resolved over this time frame may be a key step in developing new paradigms for the treatment of T2DM.

Our understanding of the relationship between insulin resistance and obesity has changed considerably since the realisation that some bariatric procedures induce rapid

improvement in insulin resistance well ahead of any weight loss [4, 6]. Furthermore, such improvements have been shown to be compartment specific [7, 8], with measures of hepatic insulin resistance improving without change being noted in peripheral insulin resistance [7–9]. It has been noted that different bariatric surgical procedures have varying early effects on insulin resistance. Thus, purely restrictive procedures such as gastric banding appear to have less effect than Roux-en Y gastric bypass [4, 10]. In a similar fashion, restrictive procedures have a lower resolution rate of type 2 diabetes compared to gastric bypass procedures [11].

These observations have led to a variety of hypotheses on possible underlying mechanisms. Caloric restriction has always been considered to be a contributing factor [12]; however, it remains unclear whether this is the predominant mechanism involved in the immediate improvements following surgery. In the standard post-operative period following gastric bypass, individuals have minimal calorie intake during the first week. Several studies have shown that short-term starvation of 4 to 7 days increases insulin resistance [13, 14], which quickly reverts upon resumption of food intake [15]. Whereas the zero energy intake of starvation induces insulin resistance, lesser degrees of energy restriction have been shown to improve insulin sensitivity [16, 17]. The oral intake and, therefore, the degree of energy restriction are similar across all bariatric procedures in the initial post-operative phase, and yet, early improvements in insulin resistance are greater following RYGB compared to restrictive procedures such as gastric banding and gastric sleeve [4, 10]. This suggests that RYGB may confer an additional effect over that produced by energy restriction alone.

Some studies in both humans and rodents suggest that rather than reduced energy intake, it is either the bypass of the foregut [18–20] or rapid exposure of nutrients to the hindgut [19, 21] that is responsible for improved insulin sensitivity (or lower insulin resistance). Thus, in man, it is unclear whether the benefits of gastric bypass are partly or wholly due to energy restriction or whether there is a fundamental change in the physiological status of the gut that is independent of energy restriction.

Although the medium- and long-term benefits of gastric bypass on insulin resistance are well documented, relatively few studies have looked at the immediate post-operative period prior to any significant loss of body weight. Yet, the changes that occur in this timeframe may have enormous implications for the future management of insulin-resistant states. In particular, any mechanisms not related to energy restriction are worthy of thorough investigation. In this study, we examine changes in insulin resistance in a group of patients undertaking very low calorie diet (VLCD), then again in the same group following RYGB and in yet another group of patients undergoing RYGB, without prior VLCD. The aim is to determine if mechanisms additional to caloric restriction contribute to the improvements in insulin resistance and glucose homeostasis following RYGB.

Patients and Methods

Measures of insulin resistance were undertaken before and after VLCD and before and after RYGB using both the Homeostasis Model Assessment Method (HOMA) and the short intravenous insulin tolerance test (IVITT). Eight severely obese patients scheduled for gastric bypass surgery agreed to undertake a VLCD diet for 6 days. Between 1 and 3 weeks following the completion of the VLCD, a RYGB procedure was performed on these patients (VLCD+RYGB group). A further 24 patients, matched for initial HOMA, BMI and age, who underwent RYGB, without prior VLCD were used as a comparison group (RYGB-only group). In this group, insulin resistance was measured solely by HOMA. The study was approved by the Central Regional Ethics Committee, and all patients gave their written informed consent. The inclusion criteria were patients between the ages of 18–70 with a BMI $\geq$ 35 kg/m^2. Subjects were excluded if they had known diabetes mellitus, significant cardiovascular, renal or liver disease.

Each patient undergoing a VLCD diet was given three sachets of Optifast 40 g (Novartis) to replace their normal diet for each of 6 days. This provided a total of 2,736 kCal over 6 days or 456 kCal per day. Patients were encouraged to take a further 2 l of water per 24 h. One to three weeks following the completion of the VLCD, patients underwent an open RYGB procedure which was performed by a single surgeon (RSS). The technique employed was the "Fobi pouch," which entails a silastic ring Roux-en Y gastric bypass with a gastric transection described in detail elsewhere [22]. Following surgery, patients received 2–3 l of intravenous fluid per day for 4–5 days, including 1 l of normal saline and the remainder of 5% dextrose. Oral caloric intake was resumed on day 5 or 6 when up to 20 ml of puree food was offered per meal. The caloric intake (intravenous and oral) during the 6 days in hospital following surgery was calculated to be approximately 2,000 kCal.

Insulin Resistance Measurements

Insulin resistance was assessed in the VLCD+RYGB group before and at the conclusion of 6 days of VLCD by HOMA-IR and IVITT and again by both measures before and 6 days after RYGB. HOMA-IR assessments were made

before and 6 days after RYGB in all 24 patients from the RYGB-alone group, and in seven of these patients, IVITT was also performed before and 6 days after RYGB.

Biochemical Analysis

Insulin, C-peptide, glucose and non-esterified fatty acid (NEFA) assays were conducted by Canterbury Health Laboratories (Christchurch). A Roche Elecsys 2010 automated analyser was used for insulin and C-peptide assays (coefficient of variation 3.1% and 11%, respectively). For insulin assays, plasma was extracted with an equal volume of 25% PEG 6000 to precipitate immunoglobulins prior to analysis. Day 0 and Day 6 samples were analysed in the same batch. Plasma glucose was assayed using a standard Abbott reagent with a coefficient of variation of 1%. NEFAs were analysed using an Abbott C8000 analyser (coefficient of variation 6.3%). Fasting insulin resistance was assessed using the Homeostatic Model Assessment (HOMA) method according to the formula: HOMA-IR= (fasting insulin (pmol/l)×fasting glucose (mmol/l)) ÷ 135 [23].

Short Intravenous Insulin Tolerance Test

The short IVITT was performed in the usual manner [24] to assess whole body insulin sensitivity. In brief, a bolus of human insulin (0.1 U/kg of body weight to a maximum of 16 units) was administered intravenously, and blood was sampled at 10 and 5 min before and at 0, 3, 6, 9, 12 and 15 min after insulin administration. Capillary glucose was measured every 10 min for 2 h following insulin administration. If capillary glucose concentration fell below 3.0 mmol/l after the conclusion of the test (15 min blood sample), glucose was administered intravenously. Plasma glucose t1⁄2 was calculated from the slope of least-square analysis of plasma glucose concentrations from 3 to 15 min after insulin injection, when plasma glucose declined linearly. Kitt values represent the percent decline in plasma glucose concentration per minute, and they were calculated according to the formula: Kitt=(0.693 ÷ t1⁄2)*100, in which t1⁄2 represents the half-life of plasma glucose decay. A rise in insulin-sensitivity index (Kitt) score indicates a reduction in whole body insulin-induced glucose uptake and hence insulin sensitivity.

Statistical Analysis

Mann–Whitney (non-parametric) testing was used to compare data between VLCD+RYGB and matched RYGB-alone patients. The Wilcoxon sign rank test was used to compare data from the same patient. All data are presented as mean±SD. GraphPad Prism 5 software was used for statistical analysis.

Results

Baseline biochemical and demographic data for the two groups of patients are shown in Table 1. The RYGB-alone group had been selected to provide three matched patients for every VLCD+RYGB patient. There was no significant difference in baseline weights in the two groups nor in measurements of fasting insulin, fasting glucose, HbA1c or HOMA-IR. Six days after VLCD, there had been a mean weight loss of 4.4±1.9 kg, but by the time of surgery 1 to 3 weeks later, the mean weight of this group had returned to 144.4±34.9 kg, which was not significantly different from the pre-VLCD weight of 145.6±34.1 kg (p=0.195).

Changes in Glycaemic Control, Insulin, HOMA-IR and NEFA

HOMA-IR decreased from 6.8±4.9 to 4.3±2.9, p<0.05, after 6 days of VLCD (Table 2). This decrease was significantly smaller than the decrease seen in the matched control patients who underwent RYGB-alone, where HOMA-IR fell from 6.8±4.9 to 1.5±0.9. However, in the VLCD+RYGB group, the values fell further to 1.5±0.4 following RYGB (Table 2). Thus, a comparable improvement in HOMA-IR was seen in both groups after the RYGB had been performed (1.5±0.4 vs 1.5±0.9, p=0.587).

As shown in Table 2, there were decreases in fasting glucose and fasting insulin after 6 days of VLCD. Whilst the decrease in fasting glucose was not statistically significant (p>0.05), the decrease in fasting insulin was significant (p<0.01). Levels of both these indices decreased further after RYGB. After VLCD alone, the changes were smaller than after RYGB in either group (Fig. 1). At 12 months following surgery, in both the VLCD+RYGB and RYGB-only groups, measures of fasting insulin, fasting glucose and HOMA-IR were not statistically significantly different from those at day 6 post-RYGB in all patients or

Table 1 Baseline demographics and biochemical data in 32 severely obese insulin-resistant patients. All baseline variables presented here were not significantly different between groups (p>0.05)

	VLCD+RYGB (n=8)	RYGB-only (n=24)
Gender (M/F)	3/5	7/17
Age (years)	40±7	41±9
BMI (kg/m^2)	48.6±7.7	48.0±6.2
Weight (kg)	144.2±35.4	142.7±19.2
Fasting glucose (mmol/l)	4.8±0.5	5.2±0.6
Fasting insulin (pmol/l)	199±104	172±116
HbA1c (%)	5.7±3.5	5.6±0.4
Day 0 HOMA-IR	6.8±4.9	6.8±4.9

Table 2 Weight, fasting glucose, fasting insulin and HOMA-IR before and after intervention in the VLCD+RYGB and RYGB-only groups of severely obese insulin-resistant patients

	VLCD+RYGB day 0 VLCD	VLCD+RYGB day 6 VLCD	VLCD+RYGB day 0 RYGB	VLCD+RYGB day 6 RYGB	RYGB-only day 0	RYGB-only day 6
Weight (kg)	145.6±34.1	141.2±33.7	144.4±34.9	140.5±11.9	142.7±19.2	–
Fasting glucose (mmol/l)	4.8±0.5	4.4±0.6	5.0±0.6	3.5±1.8**	5.3±0.6	4.2±0.5***
Fasting insulin (pmol/l)	199±104	130±74*	116±52*	50±10*	172±116	49±29***
HOMA-IR	6.8±4.9	4.3±2.9*	4.3±2.0	1.5±0.4**	6.8±4.9	1.5±0.9***

*$p<0.05$; **$p<0.01$;***$p<0.0001$ from baseline

either group (Table 3). By 12 months, the VLCD+RYGB group had a BMI of 30.9±6.1 vs the RYGB-only group's BMI of 29.5±5.1. There was no statistical difference between the two groups ($p=0.559$).

Mean NEFA concentrations were within the normal range at baseline in both groups of patients (<0.6 mEq/l).

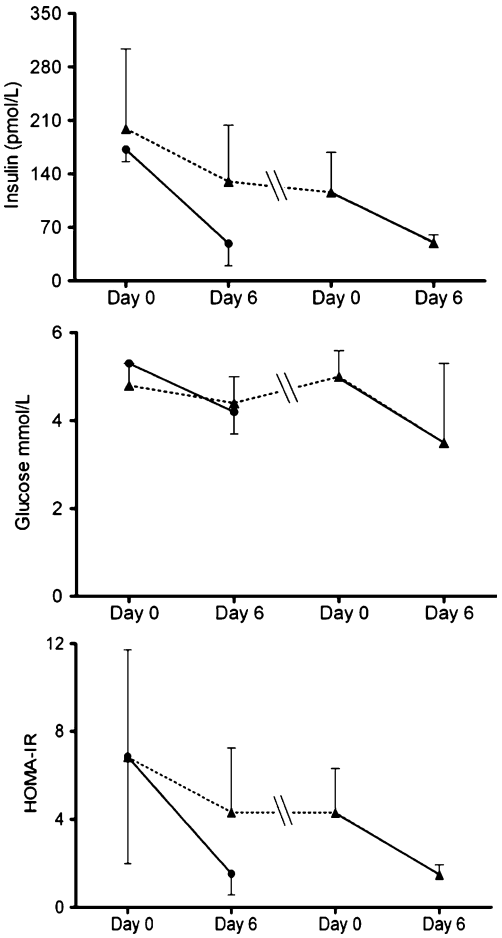

Fig. 1 Fasting plasma insulin, glucose and HOMA-IR following VLCD diet ($n=8$) compared to matched patients undergoing RYGB ($n=24$). Post-VLCD, patients then underwent RYGB. The *filled triangles* denote VLCD+RYGB, and the *filled circles* denote matched RYGB-only patients. The *solid lines* denote changes following RYGB in both groups. The *dashed lines* denote changes following VLCD in the VLCD+RYGB group

Levels became elevated after 6 days of VLCD and 6 days after RYGB, but the changes were not significantly different between the interventions ($p=0.324$), as shown in Fig. 2.

Insulin Tolerance Test

No significant change was noted in Kitt value after 6 days of VLCD. There was, however, a marked and significant reduction in Kitt value following RYGB, as shown in Fig. 3, indicating that whole body insulin resistance had increased 6 days after this surgery.

Discussion

The underlying mechanisms of the early improvements in glycaemic homeostasis following bariatric procedures have been the source of much debate. Energy-restricted diets and gastric restrictive procedures, such as laparoscopic gastric banding, which result in restricted energy intake without bypass of any of the gut, have been shown to lead to improvement in insulin resistance [5, 12, 25, 26]. Similarly, RYGB has been shown to improve insulin resistance [6, 27–29]. The question remains whether the improvement seen after RYGB is largely due to energy restriction or whether there is a more fundamental change occurring in gut physiology contributing to the improvement in insulin resistance. Clarification of this point is important as we consider new paradigms for managing insulin-resistant states such as type 2 diabetes.

Table 3 BMI, HOMA-IR, fasting glucose and fasting insulin at 12 months after surgery in the VLCD+RYGB and RYGB-only groups

	VLCD+RYGB ($n=8$)	RYGB-only ($n=24$)	p
Fasting glucose (mmol/l)	4.6±0.5	4.6±0.3	0.45
Fasting insulin (pmol/L)	51±26	39±28	0.15
HbA1c (%)	5.3±0.3	5.3±0.3	0.61
HOMA-IR	1.8±1.2	1.3±0.9	0.25
BMI	30.9±6.1	29.5±5.2	0.56

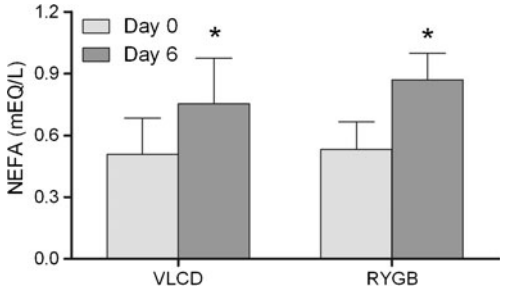

Fig. 2 Fasting non-esterified free fatty acid concentrations (mEq/l) day 0 and day 6 of a VLCD (n=8) and in matched RYGB patients (n=7). *p<0.05 compared to baseline

The current study used two separate measures of insulin resistance to examine changes in a non-diabetic population after 6 days of a VLCD or 6 days after a RYGB. HOMA-IR was used to assess hepatic insulin resistance, for which it is an accepted correlate [30], and an IVITT was used to assess whole body insulin sensitivity in a dynamic phase. Although there are those who may question the use of HOMA-IR as an valid indicator of insulin resistance, this measure has been shown by us [6] and many others to consistently change in the early post-operative period, during the period in which striking improvements in glycaemic control are seen to occur, and should not, for that reason, be ignored.

Both VLCD and RYGB led to a significant decrease in HOMA-IR within 6 days, which is consistent with Isbell's previous work [31]. Previous studies have not, however, examined the sequential and comparative changes in HOMA-IR following VLCD and RYGB. In this study, calorie restriction was demonstrated to reduce HOMA-IR significantly, which was then further and significantly reduced by subsequent RYGB. The change in HOMA after VLCD followed by RYGB was not different from the change after RYGB alone. It seems that RYGB has a beneficial effect on insulin resistance over and above that seen with calorie restriction alone (Fig. 1). This is in accordance with those studies which have found greater

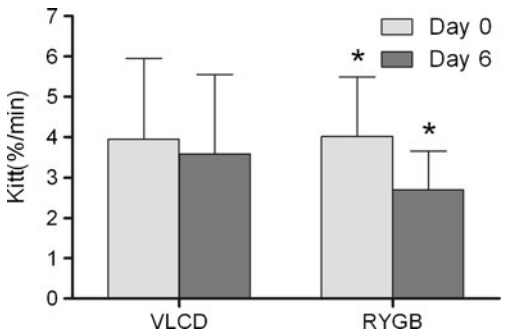

Fig. 3 Difference in glucose Kitt at day 0 and day 6 of a VLCD (n=8) and in matched RYGB patients (n=7). *Paired p<0.05

improvements in insulin resistance after RYGB than after restrictive procedures such as sleeve gastrectomy and gastric banding [4, 27]. Our findings are consistent with Pournaras and colleagues who studied the early changes in insulin resistance in RYGB, gastric band and diet patients [10]; however, they are at odds with a recent study comparing RYGB and VLCD in which no difference in HOMA was found in nine patients approximately 4 days (range 2–7 days) post-RYGB compared to nine patients undergoing a VLCD diet for 4 days [31]. The findings of marked reduction in HOMA-IR by 6 days after RYGB are in keeping with our previous published work in 71 patients [6] and our unpublished observations in over 600 patients. Major abdominal surgery is known to increase whole body insulin resistance and is a factor which must be allowed for in the management of patients post-surgery [32]. Acute effects of surgery may last between 4 and 6 days [32]. The beneficial effects of the surgery, whether due to energy restriction or some other factor, are balanced against the detrimental effects of the surgery on insulin resistance. Thus, the timing of insulin resistance measurement post-surgery is important and should be delayed until the major effects of the surgery on insulin resistance have abated. There is some evidence that surgical stress-related insulin resistance only begins to return to pre-operative levels 5 days post-surgery [32]. Therefore, at only 4 days after RYGB, it is likely that there was still some residual surgical stress-related insulin resistance, which may have masked the true magnitude of the benefit of the operation itself in the study of Isbell et al [31].

Based on our findings and those of others [4, 10], there appear to be additional mechanisms over and above caloric restriction, involved in the early changes in insulin resistance seen after RYGB. In this context, there have been considerable research undertaken and interest shown by many groups in the possible role of gut peptides and their influence on glucose homeostasis [18, 19, 33, 34]. Many groups have considered the role of the hindgut [19, 20, 33] and, in particular, the enhanced incretin response to food seen after RYGB to be of paramount importance. Others, including ourselves, have favoured the importance of putative and perhaps unknown peptides arising from the foregut [35]. Influential in our thinking is the observation that whilst profound changes in insulin resistance are seen in the fasting state after RYGB (e.g. HOMA-IR), incretin levels are not surprisingly unchanged in the fasting state following surgery as they are largely post-prandial signals [4]. This suggests that the incretins are unlikely to be responsible for the improvements in insulin resistance noted in the fasting state, within 1 week of RYGB, despite having been demonstrated to be an important contributor to post-prandial benefits.

Interestingly and somewhat unexpectedly, the insulin tolerance test demonstrated a significant deterioration in

overall insulin sensitivity 6 days after RYGB in the face of marked improvement (even normalisation) of HOMA-IR. This disparity between two measures of insulin resistance suggests that in the acute post-operative state, either the validity of various measures of insulin resistance may be altered or HOMA-IR and IVITT may be measuring different "compartments" of insulin resistance. If HOMA-IR is improved whilst insulin sensitivity measured by IVITT deteriorates following surgery, it may be assumed that peripheral insulin resistance has worsened 6 days after surgery, whilst hepatic insulin resistance has improved and even resolved. This is a very significant observation since it suggests that resolution of insulin resistance in the liver may be central to the improvements in glucose metabolism with insulin resistance in muscle and fat perhaps being of secondary or even little importance. The changes in IVITT that we have noted are consistent with previously published work of others demonstrating that improvements in peripheral glucose uptake following Roux-en Y gastric bypass surgery correlate with and relate to substantial weight loss [7] rather than being an early effect. In a similar vein, it has recently been noted that improvements in fasting glucose metabolism in the post-operative period are independent of changes in peripheral insulin sensitivity [9].

NEFA levels were included in the present study as these are known to inhibit insulin- and glucose-induced stimulation of peripheral glucose uptake as well as increasing hepatic glucose output through gluconeogenesis. NEFA levels have previously been found to increase following gastric bypass surgery in the acute post-operative phase [36] and also following VLCD [37]. This was confirmed in the present study. It is noteworthy that the rise in NEFA following RYGB was very similar to that after VLCD, which suggests that the elevation occurs as a result of calorie restriction rather than as a result of the surgery itself. It seems, however, that whatever impact this post-operative elevation of NEFA might have on gluconeogenesis and hepatic glucose output, this is overridden by the effect of the operation on hepatic insulin resistance. Peripheral glucose uptake, on the other hand, does deteriorate 6 days after surgery, which is in line with the elevated NEFA levels and again suggests that the liver is the central lesion which is addressed by the surgery.

There are imperfections in the design of the current study and, therefore, some possible limitations to the interpretation of the results. The sample set of patients undergoing VLCD and subsequent RYGB is relatively small, but the findings were nevertheless consistent and highly significant. The caloric intake of those receiving the VLCD was not perfectly matched with that of patients after RYGB, but was very similar. Neither were all other circumstances for these two groups able to be matched because of the surgical intervention. We had hoped to allow a 3-week "washout" period between the end of the VLCD study and the RYGB surgery to see return to baseline of HOMA-IR and other parameters, but this proved impractical because of patient wishes and practicalities around timing of surgery. As a result, the interval between the two interventions was between 1 and 3 weeks for all eight patients, and not all the parameters of fasting glucose, fasting insulin and HOMA-IR had returned to baseline levels. Ideally, we would have employed dynamic testing such as the hyperinsulinaemic euglycaemic clamp as a measure of insulin resistance and separately determined hepatic insulin resistance and peripheral insulin resistance using isotopic measurements. Unfortunately, the costs of these studies and the increased demands on patients made these approaches impractical. Instead, we rely on the knowledge that HOMA-IR primarily reflects hepatic glucose output in the fasting state, and therefore, it can reasonably be regarded as a measure of hepatic insulin resistance [30]. IVITT, on the other hand, is a global measure of insulin resistance, and in the face of incongruent changes in hepatic insulin resistance (HOMA-IR), it may be assumed to reflect peripheral (muscle or fat) insulin resistance.

To conclude, this study provides further support for the growing acceptance that there are numerous mechanisms contributing to the improvements in insulin resistance and resolution of type 2 diabetes which occur following RYGB surgery. Whilst there can be no doubt that caloric restriction is a contributor to this important phenomenon, our measurements of insulin resistance suggest that there also appears to be a significant contribution made by altered gut physiology, impacting particularly on hepatic insulin resistance.

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