Loss of Insulin Resistance after Roux-en-Y Gastric Bypass Surgery; a time course study

Kusal Wickremesekera, MBChB, FRACS; Geoff Miller, BSc; Tissa DeSilva Naotunne, MBBS, PhD; Graham Knowles, BSc, PhD; Richard S Stubbs. MD, FRCS, FRACS

Wakefield Gastroenterology Centre, Wakefield Hospital, Private Bag 7909, Wellington 6039, New Zealand.

Correspondence to Richard S. Stubbs, Wakefield Gastroenterology Centre, Wakefield Hospital, Private Bag 7909, Wellington 6039, New Zealand.

Email: rsstubbs@wakefieldclinic.co.nz

This work was presented as a poster at the International Federation for the Surgery of Obesity, September 8-11, 2004, Tokyo, Japan.

ABSTRACT

Background: Gastric bypass has repeatedly been shown to improve and even cure type 2 diabetes by substantially improving insulin resistance. The mechanism by which it achieves this is not currently known, but some have hypothesized that there may be important humoral effects brought about by the bypass of the stomach, duodenum or proximal jejunum. A better understanding of the time course of the changes in insulin resistance after surgery might assist our understanding of potential mechanisms.

Methods: Intravenous glucose tolerance tests were performed in 26 severely obese patients on the morning of gastric bypass surgery and again 6 days later. In addition insulin resistance was assessed in 71 patients undergoing gastric bypass surgery by the homeostasis model assessment method before surgery, and again at 6 days, 3, 6, 9, and 12 months. Patients were divided into three groups for analysis: diabetics, impaired glucose tolerance and normal glucose tolerance.

Results: All three groups of patients were noted to have insulin resistance prior to surgery. This was greatest in the diabetic patients as indicated by HOMA. There was marked loss of/improvement in insulin resistance within six days of gastric bypass by both IVGTT and HOMA methods in all groups which was maintained over the 12 month period. The study included 31 diabetic patients of whom only 3 required medication following hospital discharge.

Conclusion: The changes in insulin resistance seen after gastric bypass, which are responsible for the resolution or improvement of type 2 diabetes occur within 6 days of the surgery, before any appreciable weight loss has occurred. This finding has implications for our understanding of the mechanism of insulin

resistance in severely obese patients and is consistent with a humoral mechanism emanating from the gastrointestinal tract.

INTRODUCTION

The prevalence of type 2 diabetes is increasing alarmingly, "hand-in-hand" with the prevalence of obesity. It has been estimated that between 1995 and 2025 the prevalence of type 2 diabetes will increase by 42% in developed countries and by 170% in developing countries.[1] This is occurring at a time when the treatment of type 2 diabetes remains highly unsatisfactory, principally because of our poor understanding of the underlying mechanisms responsible for insulin resistance and the lack of effective drugs for treating the condition. The need to discover new targets for treatment and develop novel, cost effective therapies, are high priorities.

It has been known for sometime that type 2 diabetes can be cured by gastric bypass and some other forms of bariatric surgery.[2-4] Initial reports of this phenomenon indicated cure or much improved control of type 2 diabetes was seen some or many months after surgery, by which time significant weight loss had occurred. More recently it has become apparent that this improvement may occur very soon after surgery before weight loss has taken place.[3,5,6] Such knowledge has important implications in terms of understanding the mechanism or mechanisms by which gastric surgery improves insulin resistance. Several hypotheses have been proposed including energy restriction which follows surgery, the weight loss itself, and humoral effects from known or unknown gut peptides.

Whereas early reports focused on the clinical effect of improvement in diabetes, recent work has focused on glycaemic control and measurements of insulin resistance.[5-7] Insulin resistance is conveniently measured by the intravenous glucose tolerance test (IVGTT) and the homeostasis model assessment method (HOMA). Both of these correlate with insulin resistance as measured by the more demanding euglycaemic insulin clamp technique.[8,9]

The improvement in insulin resistance following gastric bypass surgery offers opportunities to study the molecular basis for insulin resistance and devise new therapies. In this study we report improvement in insulin resistance six days after Roux-en-Y gastric bypass (RYGB), as observed by IVGTT. We also report on improvement in glycaemic control and HOMA values over the first 12 months following RYGB.

METHODS

Patients and Methods

The Wakefield Gastroenterology Centre runs an active bariatric surgery programme for patients with severe obesity (BMI over 35). The operation performed is the Fobi Pouch, which is a RYGB, the specifics of which have been described elsewhere.[7,10] All patients undergoing RYGB after 1 February 2000 were considered for inclusion in this study. Patients not known to be diabetic prior to surgery underwent an oral glucose tolerance test in the course of pre-operative assessment. Thus, prior to surgery, the diabetic status of the patients was classified as; diabetes, impaired

glucose tolerance or normal glucose tolerance. Clinical and laboratory data were collected prospectively and stored on a computerized database. The study was approved by the Wellington Ethics Committee and all those included gave written informed consent.

Intravenous Glucose Tolerance Test (IVGTT)

On the morning of surgery and again six days later, after an overnight 10-12 hour fast, a short intravenous glucose tolerance test was undertaken. A cannula was placed in the radial artery to allow for rapid blood sampling. A second, large bore cannula was placed in a vein on the contra-lateral arm for rapid administration of a 25 g glucose load in 50 ml of normal saline. This was warmed to reduce viscosity in order to permit rapid administration in less than 60 seconds. Blood was drawn from the arterial line at 0, 3, 5, 10, 20, 30, 40, 60 and 90 min after completion of the glucose administration. Blood for glucose estimation was collected in tubes containing fluoride oxalate, and that for insulin estimation was collected in tubes containing EDTA. These latter samples were kept on ice until plasma was prepared following which they were stored at -70^{o}C until assayed in batches by radioimmunoassay, in an accredited medical laboratory. Samples from the IVGTT before and after surgery for any one patient were assayed in the same batch.

All patients underwent open surgery, under general anaesthesia. Ice chips by mouth were permitted on day 1 after surgery, progressing to 30 ml of water per hour by day 2, and 60-90 ml of water per hour by day 4. Patients were generally taking free fluids by mouth on day 5 and had often taken a few teaspoons of pureed food by late on day 5. They were then fasted for 10-12 hours overnight for the post-operative IVGTT on

the morning of day 6. On this occasion the IVGTT was conducted in identical fashion to that done prior to surgery, except blood sampling was venous (rather than arterial) and taken through a large bore central venous catheter, which had been retained, *in situ,* since surgery, for this purpose.

HOMA assessment

Fasting blood samples were drawn from all patients on the morning of surgery, six days later, and again at 3, 6, 9, and 12 months after the surgery prior to follow-up visits. Plasma glucose and insulin levels were measured by the same methods as for the IVGTT. HOMA values were calculated according to the following formula.[11]

$$\text{HOMA} = \frac{[\text{glucose}]\ \text{mM} \times [\text{insulin}]\ \text{pM}}{22.5 \times 6}$$

Analysis of data

The total area under the curve (AUC_{total}) was calculated for insulin and glucose using trapezoidal rules. The AUC_{total} comprises two components. The first component is due to the contribution made by the fasting concentrations of insulin, or glucose, at time zero. We call these the basal concentrations. The second component is due to the changes in concentrations following the injection of glucose, we call this the incremental response. The incremental response is obtained by subtracting the basal estimate from the total, to give a value termed $AUC_{incremental}$. The best estimate of the contribution due to basal insulin or glucose is the value obtained at time zero of the IVGTT multiplied by time period of the IVGTT (i.e. 90 min).

Statistical tests

Variables that were not normally distributed were logarithmically transformed to achieve normality and statistical tests were performed on the transformed data, although for clarity, the graphs contain the means of the untransformed data. Data were analysed by ANOVA repeated measures using Statistica version 6. The ANOVA tested for significant differences in the values before and after RYGB (the repeated measure) and tests for the effect of surgery and concomitant procedures. Diabetic status was tested as a factor.

RESULTS

Patient profile

Data were collected from 71 patients (47 female, 24 male). Ages ranged from 21 to 68 years with a median of 45 years. Pre-operative BMI ranged from 34 to 99 with a median of 45. Those studied included 31 type 2 diabetics (9 insulin dependent, 11 on oral hypoglycaemic agents, 2 diet controlled, 9 previously unrecognized), 11 with impaired glucose tolerance and 29 with normal glucose tolerance. None of the impaired glucose tolerant have become diabetic since surgery, and only 3 of the 31 with type 2 diabetes still require medication for glycaemic control following discharge from hospital six days after surgery.

Intravenous Glucose Tolerance Test

Paired IVGTT data is available on 26 patients, including 14 diabetics, 4 with impaired glucose tolerance and 8 with normal glucose tolerance.

Insulin IVGTT

The data for the insulin AUC_{total} and $AUC_{incremental}$ were logarithmically transformed prior to analyses. The mean insulin AUC_{total} before surgery was greater in each patient group, than the corresponding value six days after surgery, (p=0.00012) Figure 1. The greatest reduction after surgery was observed in the four impaired glucose tolerant patients. ANOVA reveals a significant effect of the diabetic status of the patients on AUC_{total} (p=0.045). This effect is probably due to the high values for AUC_{total} before surgery in the impaired glucose tolerant patients. The diabetic patients had the lowest AUC_{total} both before and after surgery.

If the contribution by the plasma insulin concentration at the start of the IVGTT is subtracted from the AUC_{total}, to give $AUC_{incremental}$ then the picture changes slightly, Figure 2; now the values for insulin $AUC_{incremental}$ before and after surgery are very similar and are not significantly different within each group (p=0.104). However, both the AUC_{total} and the $AUC_{incremental}$ are affected by the diabetic status of the patient. Thus for the $AUC_{incremental}$ the diabetic patients have the lowest values, the glucose intolerant the highest and those with normal glucose tolerance being in between (p=0.038 for a difference between $AUC_{incremental}$).

Glucose IVGTT

The values for glucose AUC_{total} and $AUC_{incremental}$ were logarithmically transformed prior to statistical analyses. There were no significant differences between the before and after surgery values for the glucose AUC_{total}, figure 3 (p=0.249). However, the AUC_{total} values were significantly greater in the diabetic patients than in the group with normal glucose tolerance (p=0.0001). Thus the mean glucose AUC_{total} for diabetics, irrespective of operation was 1020, whereas for normal glucose tolerant

patients, the corresponding value was 674. As was the case for insulin, basal concentrations of glucose fell during the six day interval following surgery. If glucose $AUC_{incremental}$ values before and after surgery are compared (figure 4) statistical significance is almost achieved (p=0.061) with glucose $AUC_{incremental}$ being greater six days after surgery. The glucose $AUC_{incremental}$ for the diabetic patients was greater than the comparable value for those with normal glucose tolerance (p=0.035) which was also the case for glucose AUC_{total} .

Fasting plasma glucose and insulin concentrations

Prior to analyses by ANOVA, the blood glucose concentrations were logarithmically transformed. Six days following gastric bypass surgery there were marked falls in the mean concentrations of both plasma glucose and insulin as shown in Figure 5 and 6 respectively. These falls occurred in all three patient groups. Repeated measures ANOVA revealed that the falls in glucose and insulin concentrations were statistically significant (p=0.006 for glucose and p=0.0000 for insulin). The magnitude of the reduction in plasma glucose and insulin concentrations six days after surgery was similar in all three groups. As expected, the plasma glucose concentrations were higher before surgery for the diabetics than for the non-diabetics (p=0.001) and this difference persisted after the operation. The mean fasting plasma glucose concentration six days after surgery in the diabetics was 7.47 mM, which is above 7.0 mM, which is one of the criterion for diagnosing diabetes.

HOMA

The untransformed means for each patient group before and after surgery are shown in Figure 7. All three patient groups had mean HOMA values greater than 2.2 before surgery indicating the presence of insulin resistance. The HOMA values were logarithmically transformed for statistical analysis and repeated measures ANOVA indicate statistically significant differences between the patient groups ($p=0.0002$) and a fall six days after gastric bypass surgery ($p<0.0001$). After surgery the mean HOMA for the diabetic, impaired glucose tolerance and normal glucose tolerance groups were 3.67, 1.95 and 1.29 respectively. The magnitude of the falls in the HOMA values six days after surgery were similar in the three patient groups and were not statistically significantly different ($p=0.52$).

In the normal and impaired glucose tolerant patients there was a small but statistically significant ($p=0.027$) increase in HOMA values between six days and three months after surgery (Figure 7). However, in the diabetic patients HOMA values were unchanged in this time period. After three months HOMA values remained virtually unchanged in all three groups from 3 to 12 months, despite continuing loss of weight during this period.

Loss of Weight

Weight was lost rapidly after gastric bypass (Figure 8) with approximately one third occurring in the first three months, another third in the next three months and the final third occurring in the next six months. The median BMI for all 71 patients at 12 months was 29, with a range of 21-58.

DISCUSSION

There is abundant evidence from many centres indicating that type 2 diabetes can be cured by gastric bypass and by other forms of bariatric surgery.[2-4] That this is achieved before appreciable loss of weight is an important clue to improving our understanding of insulin resistance. Whereas obesity is conventionally thought to produce insulin resistance, it may emerge that obesity is another manifestation of insulin resistance. Put simply, insulin resistance may cause obesity, not vice versa. It has been postulated that gastric bypass improves diabetes through influences on the entero-insular axis, through a humoral effect[5,12]. Our understanding of the changes in insulin resistance following surgery has been assisted by the documentation of marked falls in plasma insulin levels within days of gastric bypass. [5,6] In addition, a small but important literature is emerging in which insulin resistance is assessed in the early post-operative period before there has been appreciable loss of weight.[6] We have measured insulin resistance using an IVGTT before RYGB surgery and again six days later.

The IVGTT clearly demonstrate substantial loss of insulin resistance within six days of gastric bypass. The same conclusion is drawn from the reduction in HOMA values over this time period. We had initially thought that patients with normal glucose tolerance would serve as a comparative group for the diabetic patients and were mildly surprised to find that the majority of these patients also had marked insulin resistance as indicated by elevated HOMA values. Interestingly, all patients showed loss of insulin resistance following surgery. This contrasts with the expected worsening of insulin resistance which occurs after major abdominal surgery (not gastric bypass) - a phenomenon thought to be related to surgical stress. [13,14] This

suggests that the bypass of the stomach and duodenum results in physiological changes that either inhibit the stress response to surgery, or more likely, alleviate insulin resistance to such an extent that post surgical insulin resistance is not manifest. What cannot be certain from these results is whether the improvement may be due to the period of fasting after the surgery and/or the re-introduction of a very low calorie diet on or about day 5 after the surgery. Both fasting and calorie restriction reduce the concentrations of glucose and insulin in the blood.[15,16] The fact that HOMA values increase slightly between 6 days and 3 months suggests that fasting has contributed at least a little to the improvement seen after six days. It is interesting that we did not observe this effect in patients who were diabetic prior to surgery. Without a sham operation being performed on severely obese individuals it will be hard to resolve the role of fasting on insulin resistance in these patients. However, sham operations can be performed on animals and experiments in a non-obese diabetic rat model support the hypothesis that the loss of insulin resistance is related to surgical bypass of components of the gut.[17] These authors compared sham operated rats with those in which the duodenum and proximal jejunum had been bypassed. This was done by performing an anastomosis between the pre-pyloric stomach and the distal jejunum. Glycaemic control was much improved in those rats in which duodeno-jejunal bypass had been performed but was not altered in the sham operated group and only marginally affected in a group of un-operated rats subjected to major food restriction.

Scopinaro's group has also reported reduced HOMA values, and by inference improved insulin sensitivity, four days after biliopancreatic diversion (BPD).[5] The improvement in insulin sensitivity after BPD was greater than that achieved in a comparable group of obese individuals who had fasted for 3 days.

In our patients the biochemical loss of insulin resistance was mirrored by a clinical effect. Of the 31 diabetics in the study only three required medication for diabetes at the time of, or subsequent to, leaving hospital. All three patients were insulin dependent prior to RYGB and 2 remain so following surgery, though on markedly reduced doses.

Although insulin AUC_{total} for all three groups of patients is markedly reduced 6 days after surgery, $AUC_{incremental}$ is not significantly altered, indicating the insulin secreted in response to the glucose challenge is not altered by the surgery or the loss of insulin resistance which follows the surgery. Thus it appears one effect of RYGB is to modify the secretion of insulin in the fasting state. Fasting plasma insulin and liver gluconeogenesis are inversely related, and in diabetics gluconeogenesis is unusually high and not subjected to the normal inhibition by insulin.[18,19] Our evidence indicates that although fasting glucose in diabetics has fallen six days after RYGB, it is still higher in diabetics compared to non-diabetics. Thus it appears the rates of gluconeogenesis have narrowed between the diabetics and non diabetics, although at this stage, it is not clear whether this is a direct or indirect effect of gastric bypass surgery.

In conclusion we have followed changes in insulin resistance following RYGB and demonstrated a rapid improvement in insulin resistance within six days of surgery. The improvement is maintained throughout the initial 12 months after surgery and is clearly unrelated to weight loss, which proceeds much more slowly. This finding taken in conjunction with other published clinical and experimental data leads us to believe that gastric bypass surgery fundamentally alters the physiology of the foregut.

REFERENCES

1. King, H., Aubert, R. E., and Herman, W. H. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care 1998; 21: 1414-31.

2. Scheen, A. J. , Luyckx, F. H., and Lefebvre, P. J. The place of bariatric surgery in the management of the obese type 2 iabetic patient. Int Diab Monitor 1998 ; 10: 1-7.

3. Dhabuwala, A., Cannan, R. J., and Stubbs, R. S. Improvement in co-morbidities following weight loss from gastric bypass surgery. Obes Surg 2000; 10: 428-35.

4. O'Brien, P. E., Dixon, J. B., Brown, W., Schachter, L. M., Chapman, L., Burn, A. J., Dixon, M. E., Scheinkestel, C., Halket, C., Sutherland, L. J., Korin, A., and Baquie, P. The laparoscopic adjustable gastric band (Lap-Band): a prospective study of medium-term effects on weight, health and quality of life. Obes Surg 2002; 12: 652-60.

5. Adami, G. F., Cordera, R., Camerini, G., Marinari, G. M., and Scopinaro, N. Recovery of insulin sensitivity in obese patients at short term after biliopancreatic diversion. J Surg Res 2003; 113: 217-21.

6. Rubino, F., Gagner, M., Gentileschi, P., Kini, S., Fukuyama, S., Feng, J., and Diamond, E. The early effect of the Roux-en-Y gastric bypass on hormones involved in body weight regulation and glucose metabolism. Ann Surg 2004; 240: 236-42 .

7. Stubbs, R. S. and Wickremesekera, S. K. Insulin resistance in the severely obese and links with metabolic co-morbidities. Obes Surg 2002; 12: 343-8.

8. Emoto, M., Nishizawa, Y., Maekawa, K., Hiura, Y., Kanda, H., Kawagishi, T.,

Shoji, T., Okuno, Y., and Morii, H. Homeostasis model assessment as a clinical index of insulin resistance in type 2 diabetic patients treated with sulfonylureas. Diabetes Care 1999; 22: 818-22.

9. Bonora, E., Targher, G., Alberiche, M., Bonadonna, R. C., Saggiani, F., Zenere, M. B., Monauni, T., and Muggeo, M. Homeostasis model assessment closely mirrors the glucose clamp technique in the assessment of insulin sensitivity: studies in subjects with various degrees of glucose tolerance and insulin sensitivity. Diabetes Care 2000; 23: 57-63.

10. Fobi, M. A. Surgical treatment of obesity: a review. J Natl Med Assoc 2004; 96: 61-75.

11. Matthews, D. R., Hosker, J. P., Rudenski, A. S., Naylor, B. A., Treacher, D. F., and Turner, R. C. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-9.

12. Pories, W. J. Why Does the Gastric Bypass Control Type 2 Diabetes Mellitus? Obes Surg 1992; 2: 303-313.

13. Brandi, L. S., Santoro, D., Natali, A., Altomonte, F., Baldi, S., Frascerra, S., and Ferrannini, E. Insulin resistance of stress: sites and mechanisms. Clin Sci (Lond) 1993; 85: 525-35.

14. Thorell, A., Nygren, J., and Ljungqvist, O. Insulin resistance: a marker of surgical stress. Curr Opin Clin Nutr Metab Care 1999; 2: 69-78.

15. Greenfield, M., Kolterman, O., Olefsky, J. M., and Reaven, G. M. The effect of ten days of fasting on various aspects of carbohydrate metabolism in obese diabetic subjects with significant fasting hyperglycemia. Metabolism 1978; 27:

1839-52 .

16. Verrillo, A., de Teresa, A., Martino, C., di Chiara, G., and Verrillo, L. Somatostatin response to glucose before and after prolonged fasting in lean and obese non-diabetic subjects. Regul Pept 1988; 21: 185-95.

17. Rubino, F. and Marescaux, J. Effect of duodenal-jejunal exclusion in a non-obese animal model of type 2 diabetes: a new perspective for an old disease. Ann Surg 2004; 239: 1-11.

18. Newsholme, E. A. and Dimitriadis, G. Integration of biochemical and physiologic effects of insulin on glucose metabolism. Exp Clin Endocrinol Diabetes 2001; 109 Suppl 2: S122-34.

19. Link, J. T. Pharmacological regulation of hepatic glucose production. Curr Opin Investig Drugs 2003; 4: 421-9.

Legends to figures

Figure 1. The AUC_{total} for insulin before and six days after RYGB.

$p<0.0001$ for the difference between the AUC_{total} before and after RYGB in all patients.

$p=0.045$ for the differences between the AUC_{total} for the different patient groups

Figure 2. The $AUC_{incremental}$ for insulin before and six days after RYGB.

$p=0.104$ for the differences between the $AUC_{incremental}$ before and after RYGB in all patients.

$p=0.038$ for the differences between the $AUC_{incremental}$ for the different patient groups

Figure 3. The AUC_{total} for glucose before and six days after RYGB.

$p=0.249$ for the difference between the AUC_{total} before and after RYGB in all patients

$p=0.0001$ for the differences between the AUC_{total} for the different patient groups

Figure 4. The $AUC_{incremental}$ for glucose before and six days after RYGB

$p=0.061$ for the differences between the $AUC_{incremental}$ before and after RYGB in all patients

$p=0.035$ for the differences between the $AUC_{incremental}$ between diabetic and normal glucose tolerant patients

Figure 5. Time course of changes in fasting plasma insulin concentrations after RYGB.

$p<0.0000$ for the differences between fasting plasma insulin concentrations before and 6 days after RYGB in all patients.

$p=0.171$ for the differences between fasting plasma insulin concentrations between the different patient groups.

Figure 6. Time course of changes in fasting plasma glucose concentrations after RYGB.

p=0.006 for the differences between fasting plasma glucose concentrations before and 6 days after RYGB in all patients.

p=0.001 for the differences between fasting plasma glucose concentrations between the different patient groups.

Figure 7. Time course of changes in HOMA values after RYGB.

p<0.0000 for the differences between HOMA values before and 6 days after RYGB in all patients.

p<0.0000 for the differences between HOMA values between the different patient groups.

Figure 8. Changes in median body weight after RYGB in all patients

Figure 1
Wickremesekera et al

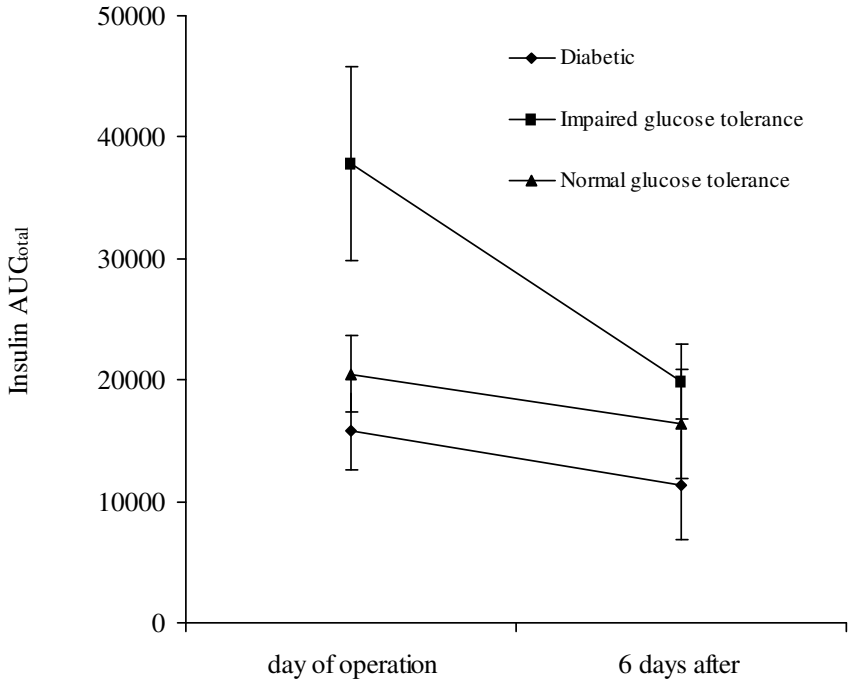

Figure 2
Wickremesekera et al

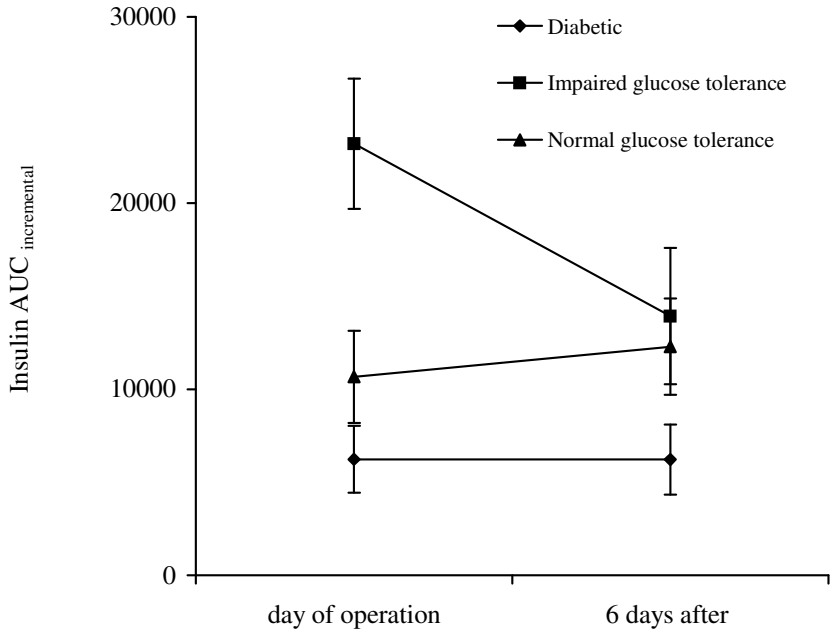

Figure 3
Wickremesekera et al

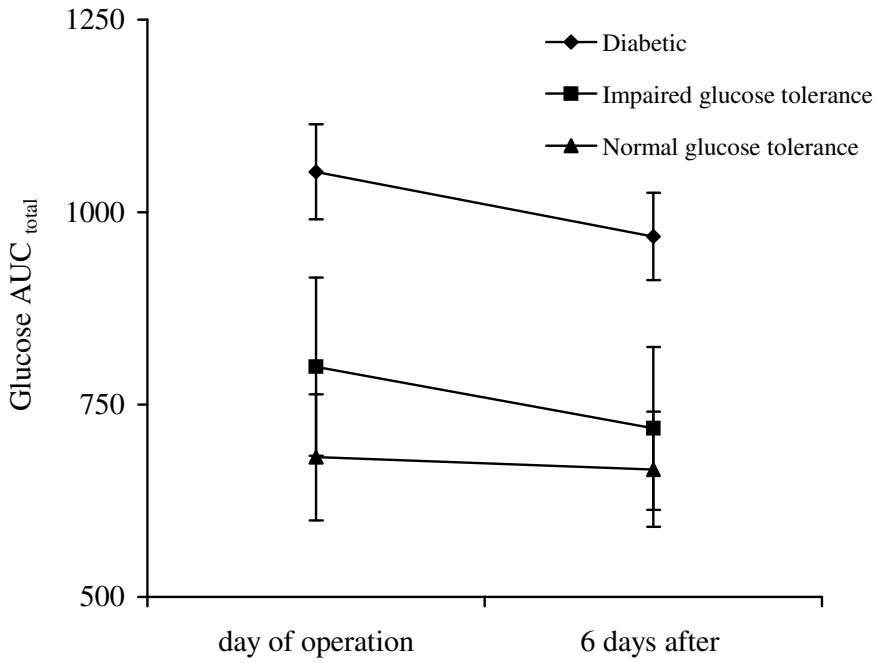

Figure 4
Wickremesekera et al

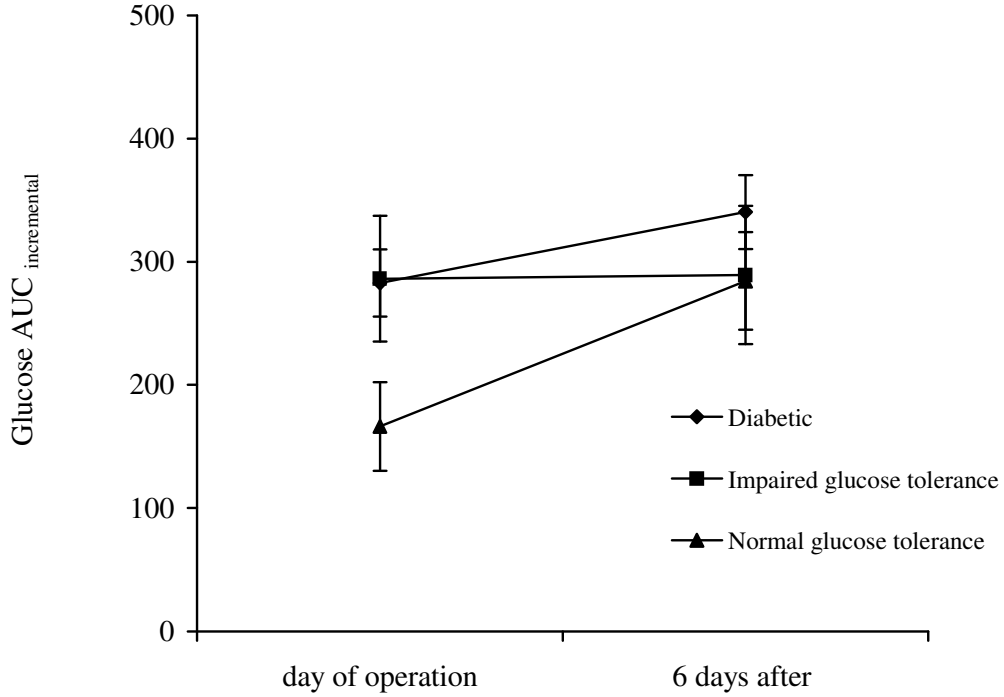

Figure 5
Wickremesekera et al

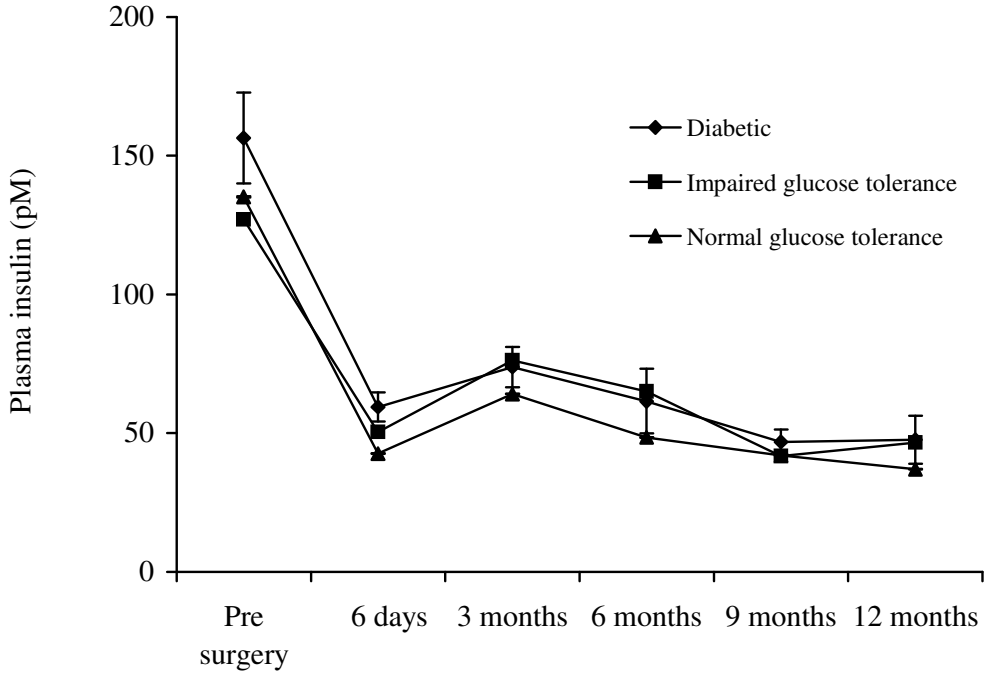

Figure 6
Wickremesekera et al

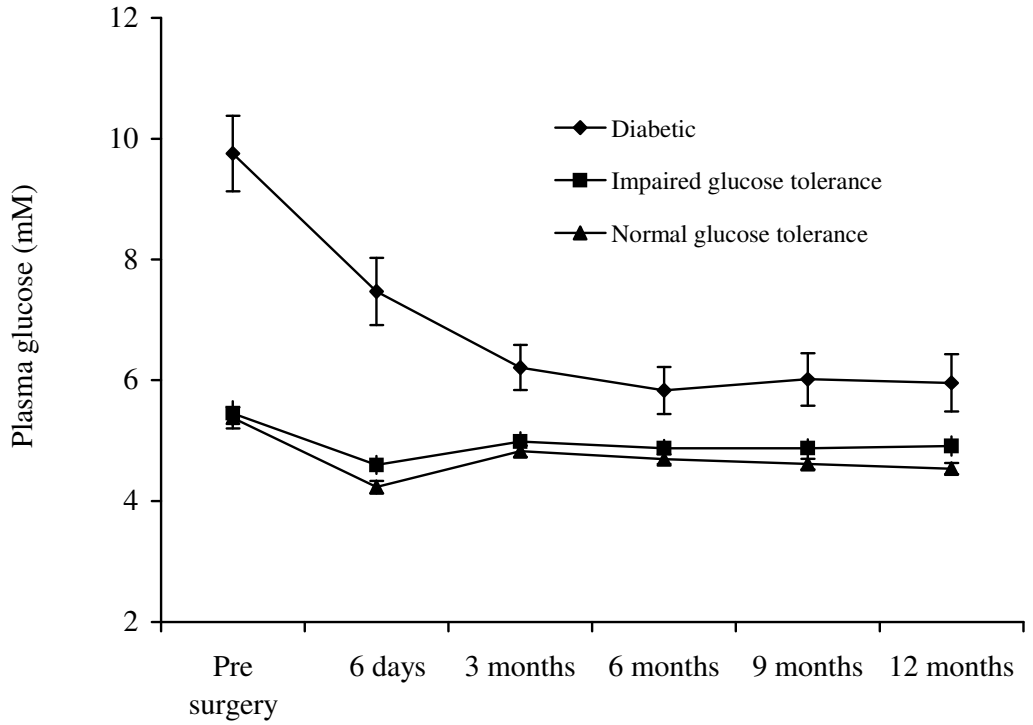

Figure 7
Wickremesekera et al

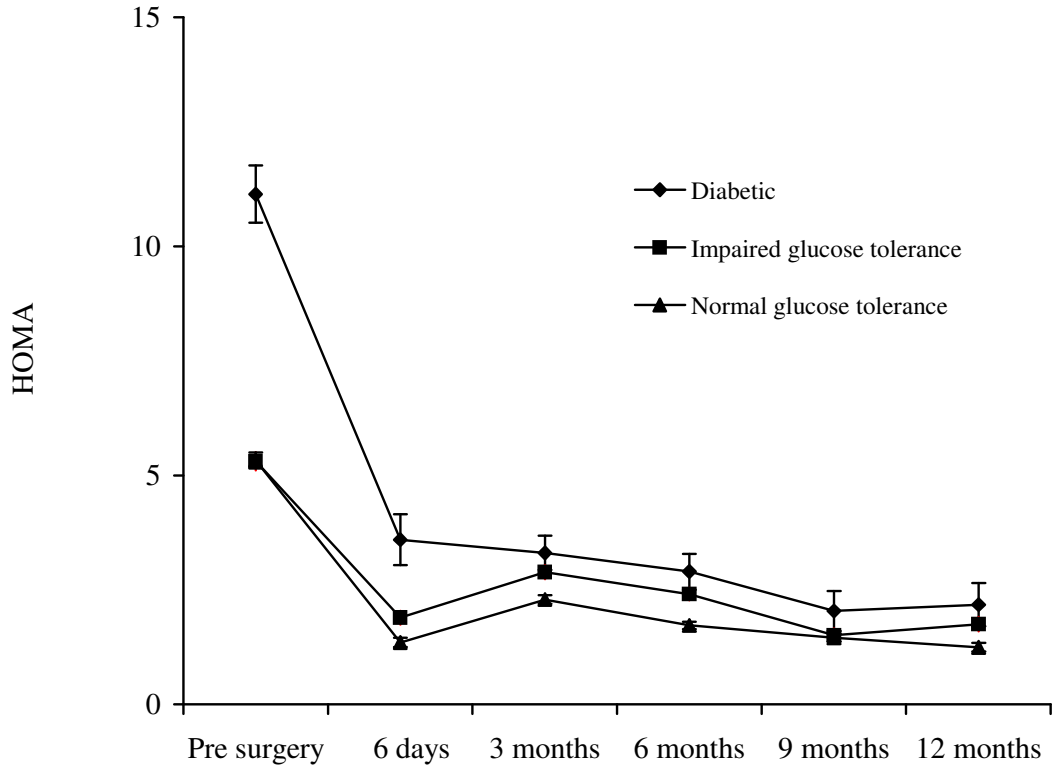

Figure 8
Wickremesekera et al