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Review: Surgical Treatment of Type 2 Diabetes

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ABSTRACT

In the last decades we have witnessed a significant increase in the incidence of type 2 diabetes mellitus, and obesity in parallel. So 90% of patients with Diabetes Mellitus type 2 (DM2) are obese. Changes in lifestyle (diet and exercise), behavioral therapies or the use of certain anti-obesity drugs have shown a limited effect and are not maintained over time. Currently, bariatric surgery is the most effective anti-obesity treatment, which is durable and resolves associated comorbidities. The surgical treatment of obesity for the modification of the anatomy of the digestive system is to produce gastric capacity constraints alone or associate with varying degrees of intestinal malabsorption and reduce body weight, improve and maintain the comorbidities associated weight loss by reduced food intake alone or in combination with malabsorption of this. The development of these surgical techniques has occurred in stages. With these techniques, setting to bariatric surgery is an effective, safe and proven procedure for the treatment of obesity and its complications especially DM2, as their post surgery referral mechanisms provide us with information for potential therapeutic treatment aimed at optimizing the control DM2 patients metabolic obese. In this review, we expose the evidence in treatment of DM2 with bariatric surgery and the actual hypothesis trying to explain how it is possible.

KEYWORDS

DM2; Bariatric Surgery; Gastric Bypass

1. Introduction

In recent decades we have witnessed a significant increase in the incidence of type 2 diabetes mellitus (DM2), and obesity in parallel. Thus it is estimated that from 1986-2000 the prevalence of BMI > 30 kg/m^2 has doubled, from morbid obesity, BMI > 40 Kg/m^2 has quadrupled and extreme obesity, BMI > 50 Kg/m^2 has multiplied by 5 [1].

In parallel what has exponentially increased the prevalence of DM2 is considered as obesity, the major risk factor for its developing. So 90% of patients with DM2 have overweight or obesity [2]. The mechanism of interrelationship is the accumulation of abdominal fat, which causes an inflammatory state, insulin resistance and a lipotoxic effect in the β cell [3,4]. Weight loss reduces the inflammatory state associated with abdominal obesity by decreasing the concentration of inflammatory markers such as reactive Protein C [5]. Changes in lifestyle (diet and exercise), behavioral therapies or the use of certain anti-obesity drugs have shown limited effect and are not maintained over time. Bariatric surgery is currently the most effective anti-obesity treatment, which is durable and meets the associated comorbidities.

2. Background

Surgical treatment of obesity is considered as the modification of the anatomy of the digestive system to produce gastric reduction alone or associated with varying degrees of intestinal malabsorption reducing body weight and improvement associated comorbidities [6-9].

The development of these surgical techniques has occurred in stages. In the 50's *Kremer* noted that patients undergoing abdominal surgery for various reasons experienced considerable weight loss. Although these techniques produced significant weight loss, were accompanied by complications such as acute liver failure, cirrhosis, renal failure, autoimmune disorders and electrolyte abnormalities severas [10]. In view of the side effects was not considered justified these procedures. Later in the 60's, *Mason* developed 2 techniques as effective for weight loss as above but with better security: gastric banding and gastric bypass [10]. During the 70's, Hess *and Scopinaro* spread these techniques and making some variants. The first used the biliopancreatic bypass [11] while the second set point the duodenal [12] exclusion technique. Another important step came in 1994 when *Clark and Wittgrove* demonstrated the posibility to perform by laparoscopic, improving the safety of the procedure [13]. In recent years the number of laparoscopic bariatric surgery procedures has increased exponentially following a few indications. In 1991 The National Institute of Health (NIH), developed a consensus document which indicated the patients eligible for bariatric surgery: BMI greater than or equal to 40 kg/m^2 who have had failure of medical treatment and lifestyle measures, or BMI greater than or equal 35 kg/m^2 with complications: DM2, HT or cardiovascular disease.

3. Surgical Techniques

Currently, bariatric surgery techniques are divided into 3 groups: restrictive, mixed and malabsorptive [1,4]:

- Restrictive techniques: Their intention is to produce a decrease of food intake by decreasing the volume of the stomach, so as to produce a feeling of fullness and satiety with small intakes. It does not interfere with the absorption of food. The most common techniques are:
  - Adjustable gastric banding: technique consisting of a horizontal restraint silicone band in subcardial situation that causes a narrowing and leaving a small gastric outlet, added to a portion adjustable. This regulates the size of the hole from a subcutaneous reservoir.
- Mixed: Combine the gastric reduction with some type of intestinal bypass. Are currently being made more frequently.
  - Gastric bypass, involves creating a small gastric chamber which connects the distal jejunum and yeyunoyeyunostomía to 50,150 cm gastrojejunal union.
- Malabsortives:
  - Biliopancreatic diversion: We performed a distal gastrectomy with gastrointestinal anastomosis in Roux en Y to 50 - 75 cm iliocecal valve.
  - Duodenal switch: Same as above with the difference that gastrectomy is performed longitudinally.

4. Effects on Weight and Mechanism Inducing Weight Loss

Weight loss after surgery occurs rapidly in the postoperative period, reaching a nadir at 18 - 24 months. It is common to produce a partial recovery of weight from the 2 years after surgery [15]. The most effective treatment for severe obesity, resulting in significant weight loss, which remains long time. In some series with a follow up to 16 years-showed a mean weight loss of 48.2 kg [10], but results differ depending on the techniques used. Expressed as a percentage of excess weight lost, average data have been published until 61.2% for all techniques: 47.5% for patients undergoing gastric banding, 61.6% gastric bypass, 68.2% for gastroplasty and 70.1% for biliopancreatic diversion or cross duodenal [16]. Furthermore, the effect is maintained and in studies with follow-up 10 years, weight loss for patients undergoing gastric banding, vertical gastroplasty and gastric bypass are 14% ± 14%, 16% ± 11% and 25% ± 11% respectively. At 15 years, the differences remained at similar values of 13% ± 14%, 18% ± 11% and 27% ± 12% respectively [17]. Other factors that influence the response to surgery: age, sex, race, body composition, educational level, emotional state and level of activity. In general, best results are obtained with younger patients, women, Caucasians, who have a high percentage of muscle mass, motivated to follow a program of physical activity, regular medical supervision, which followed the recommendations of vitamin supplementation and are able to follow a dietary program [18].

The mechanism by which weight loss occurs is not fully clarified. Different theories have been postulated [9], mainly in patients undergoing gastric bypass. In the first weeks malabsorption occurs in response to the gastrointestinal anatomical changes, although this phenolmenon is followed by a rapid intestinal adaptation. The restriction of gastric volume accompanied by a decreased intake and increased satiety is an important element in weight loss but would not explain the differences observed between the different techniques, because the volume remains after the gastric bypass and gastroplasty stomach is similar. Other alterations studied are the phenomena of dumping in that after the intake of rapidly absorbed sugars, it produces its influx into the intestine and induce intense osmotic effect which leads to the passage of fluids from the bloodstream into the intestine and a exaggerated incretin response, producing a hypoglycemic effect with a clinical response (hypoglycemia and tachycardia) [20]. Finally, we have the taste changes that refer these patients. However, none of them has been clearly correlated with the lost wheight [21]. So, it is

postulated that changes in enteroendocrine axis may play a role. *Cummings and colleagues* (2002) found that there was a sudden drop in ghrelin levels after bariatric surgery, which contrasts with the increase, as a counterregulatory, when patients experience loss of weight due to caloric restriction and exercise [22]. Also described increased levels of PYY and GLP-1 which induces an increased sense of fullness after surgery [23]. These hypotheses are currently under study, as well as other proposed mechanisms, including increased basal energy expenditure at multiple levels or decrease in leptin levels [19].

5. Effects of Alterations Hydrocarbon in Diabetes Mellitus Type 2 and Its Regulation

From the 70's, have been published data resolution for DM2 after bariatric surgery without being able to specify which was the mechanism of remission. *Pories* (1995), published data of resolution of DM2 in bariatric surgery patients over 10 years. In these cases showed that the effect on blood glucose levels observed in the first days after surgery and before the commencement weight [23] loss. On the other hand, different studies have shown that the homeostasis of glucose control varies with different surgical techniques including pre-term equality of DM2, BMI and weight loss after surgery [24]. In the literature, provides data resolution and better control of DM2 rises to 85.4% of patients, although there are notable differences in the different técnicas16. In the meta-analysis by *Buchwald et al* (2004), the resolution of DM2 amounted to 76.8% of patients. In addition, decreases were more marked in the number of fasting glucose levels and glycosylated hemoglobin in patients with intolerance to carbohydrates and diabetics than in the total population of the study [16]. The malabsorptive techniques, such as biliopancreatic diversion or duodenal switch, had the highest resolution, 98.9% versus 83.7% of patients undergoing gastric bypass, 71.6% for gastroplasty or 47.9% for purely restrictive techniques such as gastric banding. This work was criticized because the average age of patients was very young with DM2 of early diagnosis [26]. *Schauer et al*. published a series of 240 patients with obesity and DM2 that over 80% patients normalized both fasting plasma glucose and glycated hemoglobin after bariatric surgery. Patients with shorter duration of DM2 (less than 5 years) and greater weight loss getting better results [27].

In other studies also show a sustained effect over time. Thus the *SOS study*, with follow up at 10 years, provides data for recurrence of diabetes. This rate was lower in surgery group than the control group (search rates) [8].

In this sense, the techniques are not compared. For the equal weight loss, gastric bypass, vertical gastrectomy and gastric banding banded, have shown different rate of DM2 resolution [25-27]. These data make us think of an independent mechanisms of weight loss may be contributing to an improvement of the metabolism of carbohydrates. The above data have led to controversy over whether improved glycemic control is due to increased insulin sensitivity or a change in the secretion of gastrointestinal hormones. Is known to increase up to 4 or 5 times insulin sensitivity after gastric bypass due in part to increased concentrations of adiponectin, with decreasing adipose tissue after surgery. This increase in insulin sensitivity has been studied primarily in liver and muscle tissue. In parallel, the liver is reduced fatty acid content, thus reducing insulin resistance associated with hepatic steatosis. To explain these phenomena and why they occur have been postulated several hipótesis [25,28,29].

- Theory of acute weight loss: After bariatric surgery, patients substantially reduced their intake during the first postoperative weeks. Following this premise, the acute effect on glycemic control is due to the drastic reduction in intake of these patients. Thus different authors as *Isbell et al.* [30] explain that drastically reducing intake without changes in body weight, which occurs in the early weeks is the most important factor in the increased insulin sensitivity. Now the action protocol is similar to all surgical techniques, so that remains important to clarify the differences observed between the different thecniques [16]. Moreover, an acute ruduced intake is frequently observed in other abdominal surgeries, however, there is a worsening diabetes control due to inflammation or contraregulatory hormones [25].
- Ghrelin assumption: 90% of which is secreted ghrelin is produced in the stomach and duodenum, two of the organs affected by bariatric surgery. As we discussed above, there have been studies that ghrelin levels decrease dramatically after surgery, although these data are currently not clarificated [22]. Ghrelin has effects on carbohydrate metabolism mainly at 3 levels: it inhibits the action and secretion of adiponectin and its insulinsensibilized effect and inhibits itd effect in liver [25]. Therefore, decreases in ghrelin levels may induce an increase in insulin secretion and increased insulin sensitivity.
- Foregut: This theory states that the proximal intestine (mainly duodenum) that contacts with food producing an antidiabetic effect by action of some unrecognized factor now called anti-incretinic factor [31]. The theory contemplates that prevent contact of food with the duodenal, inhibits the production of this factor so it improves glycemic control in obese patients.
- Hindgut: This effect and described in the 60's as the amplification of the insulin response that occurs after oral ingestion of glucose in the administration of an

equivalent amount by way intravenosa [32]. This effect is responsible for up to 60% of the increased secretion of insulin after ingestion. Is primarily mediated by the gastrointestinal hormones GLP-1 and GIP, which produce K and L cells of the intestinal tissue, known as incretins. GLP-1 is an incretin hormone family, glucose-dependent secretion and increases insulin sensitivity, reduces postprandial glucagon levels, increased pancreatic β cell number, reduces gastric emptying, and regulates appetite. Nauck *et al.*, (1986) showed that the incretin effect was decreased in patients with DM2 because the decrease in concentrations of GIP and GLP-1 mainly after food intake [33]. Exogenous administration of GLP-1 lowers blood glucose in a process glucosadependient because, increases insulin levels and decreases glucagón concentration [33]. In obese patients with DM2 underwent bariatric surgery, biliopancreatic diversion especially, has been shown an increase levels of GLP-1 and GIP from the first week. Later this effect is maintained. This increase is accompanied by incretins stimulate insulin secretion and the consequent reduction plasma glucose [35]. It is thought that the anatomical disorder after gastric bypass makes the bolus reaches the distal portions of the intestine undigested, thereby producing an increase in intestinal secretion of incretins. On the other hand other authors have shown increased concentrations of GLP-1 but other gastrointestinal peptides direct effect on carbohydrate metabolism (PYY), [30,36].

- There are also other factors under study could explain this rapid improvement in blood sugar levels after surgery: bile acids, other gastrointestinal factors or the role of insulin sensitivity of certain nutrientes [37].

6. Mortality and Safety of Bariatric Surgery

The American Association of Metabolic and Bariatric Surgery, founded a program for certification of good practice. This certification is known as Center of Excellence to develop standards and quality standards for good practice of these surgical techniques. In 2008, the total of 339 accredited centers published their mortality rates, with a hospital mortality of 0.14% and 0.35% at 90 days [10]. Moreover, the published data on mortality from surgery, considering only those patients who die after less than 30 days after surgery are less than 0.1% for all surgical techniques were distributed in 0.1% for pure restrictive techniques, 0.5% for gastric bypass and 1.1% for biliopancreatic diversion or cross duodenal [16].

On the other hand, in 2007, Swedish Obese Subject (SOS), comparing mortality data published in obese patients divided them into 2 groups, those who underwent bariatric surgery and those treated with standard measures. Monitoring carried out at 15 years. A reduction in overall mortality of patients undergoing surgery of 24% compared to the other group, and the values were independent of age, sex and cardiovascular risk factors. The most common causes of death were myocardial infarction and cancer [17]. In addition, other groups such as *Adams et al.* have reported a decrease in the incidence of cancer in patients versus the control group underwent a follow-up to 12.5 años [38].

7. Conclusion

There is no doubt that bariatric surgery is an effective, safe and proven procedure for the treatment of obesity and its complications, especially type 2 diabetes, particularly in those young patients and a short development time. In-depth study of the mechanism of remission after surgery DM2, it will give us information to potential therapeutic targets in order to optimize the metabolic control of obese DM2 patients.

REFERENCES

[1] C. L. Ogden, M. D. Carroll, L. R. Curtin, M. A. McDowell, C. J. Tabak and K. M. Flegal, “Prevalence of Overweight and Obesity in the United States, 1999-2004,” *JAMA*, Vol. 295, No. 13, 2006, pp. 1549-1555. http://dx.doi.org/10.1001/jama.295.13.1549

[2] H. Kolb and T. Mandrup-Poulsen, “The Global Diabetes Epidemic as a Consequence of Lifestyle-Induced Low-Grade Inflammation,” *Diabetologia*, Vol. 53, No. 1, 2010, pp. 10-20. http://dx.doi.org/10.1007/s00125-009-1573-7

[3] R. H. Unger, “Minireview: Weapons of Lean Body Mass Destruction: The Role of Ectopic Lipids in the Metabolic Syndrome,” *Endocrinology*, Vol. 144, No. 12, 2003, pp. 5159-5165. http://dx.doi.org/10.1210/en.2003-0870

[4] A. Gastaldelli, E. Ferrannini, Y. Miyazaki, M. Matsuda and R. A. DeFronzo, “San Antonio Metabolism Study. Beta-Cell Dysfunction and Glucose Intolerance: Results from the San Antonio Metabolism (SAM) Study,” *Diabetología*, Vol. 47, No. 1, 2004, pp. 31-39. http://dx.doi.org/10.1007/s00125-003-1263-9

[5] G. Schernthaner, J. M. Brix, H. P. Kopp and G. H. Schernthaner, “Cure of Type 2 Diabetes by Metabolic Surgery? A Critical Analysis of the Evidence in 2010,” *Diabetes Care*, Vol. 34, No. 2, 2010, pp. 355S-360S.

[6] W. J. Pories, K. G. MacDonald Jr., E. J. Morgan, M. K. Sinha, G. L. Dohm, M. S. Swanson, *et al.*, “Surgical Treatment of Obesity and Its Effect on Diabetes: 10-y Follow-Up,” *The American Journal of Clinical Nutrition*, Vol. 55, No. 2, 1992, pp. 582S-85S.

[7] C. D. Sjostrom, L. Lissner, H. Wedel and L. Sjostrom, “Reduction in Incidence of Diabetes, Hypertension and Lipid Disturbances after Intentional Weight Loss induced by Bariatric Surgery: The SOS Intervention Study,” *Obesity Research*, Vol. 7, No. 5, 1999, pp. 477-484. http://dx.doi.org/10.1002/j.1550-8528.1999.tb00436.x

[8] L. Sjostrom, A. K. Lindroos, M. Peltonen, J. Torgerson, C. Bouchard, B. Carlsson, *et al*., "Lifestyle, Diabetes, and Cardiovascular Risk Factors 10 Years after Bariatric Surgery," *New England Journal of Medicine*, Vol. 351, No. 26, 2004, pp. 2683-2693. http://dx.doi.org/10.1056/NEJMoa035622

[9] W. J. Pories, "Bariatric Surgery: Risks and Rewards," *Journal of Clinical Endocrinology & Metabolism*, Vol. 93, No. 11, 2008, pp. S89-S96. http://dx.doi.org/10.1210/jc.2008-1641

[10] D. R. Cottam, S. G. Mattar, E. Barinas-Mitchell, *et al*., "The Chronic Inflammatory Hypothesis for the Morbidity Associated with Morbid Obesity: Implications and Effects of Weight Loss," *Obesity Surgery*, Vol. 14, No. 15, 2004, pp. 589-600. http://dx.doi.org/10.1381/096089204323093345

[11] N. Scopinaro, F. Papadia, G. Camerini, G. Marinari, D. Civalleri and A. Gian Franco, "A Comparison of a Personal Series of Biliopancreatic Diversion and Literature Data on Gastric Bypass Help to Explain the Mechanisms of Resolution of Type 2 Diabetes by the Two Operations," *Obesity Surgery*, Vol. 18, No. 8, 2008, pp. 1035-1038. http://dx.doi.org/10.1007/s11695-008-9531-x

[12] D. S. Hess, D. W. Hess and R. S. Oakley, "The Biliopancreatic Diversion with the Duodenal Switch: Results beyond 10 Years," *Obesity Surgery*, Vol. 15, No. 3, 2005, pp. 408-416. http://dx.doi.org/10.1381/0960892053576695

[13] A. C. Wittgrove and G. W. Clark, "Laparoscopic Gastric Bypass, Roux-en-Y-500 Patients: Technique and Results, with 3 - 60 Month Follow-Up," *Obesity Surgery*, Vol. 10, No. 3, 2000, pp. 233-239. http://dx.doi.org/10.1381/096089200321643511

[14] B. Z. A. Moreno, "Cirugía Bariatrica: Situación Actual," *Revista de Medicina de la Universidad de Navarra*, Vol. 48, No. 2, 2004, p. 6.

[15] J. J. Arrizabalaga, A. Calañas-Continente, J. Vidal, *et al*., "Guía Práctica Clínica Para el Manejo del Sobrepeso y la Obesidad en Personas Adultas," *Endocnologia y Nutrición*, Vol. 50, Suppl. 4, 2003, pp. 1-38.

[16] H. Buchwald, Y. Avidor, E. Braunwald, M. D. Jensen, W. Pories, K. Fahrbach, *et al*., "Bariatric Surgery: A Systematic Review and Meta-Analysis," *JAMA*, Vol. 292, No. 14, 2004, pp. 1724-1737. http://dx.doi.org/10.1001/jama.292.14.1724

[17] L. Sjostrom, K. Narbro, C. D. Sjostrom, K. Karason, B. Larsson, H. Wedel, *et al*., "Effects of Bariatric Surgery on Mortality in Swedish Obese Subjects," *New England Journal of Medicine*, Vol. 357, No. 8, 2007, pp. 741-752. http://dx.doi.org/10.1056/NEJMoa066254

[18] P. R. Schauer, B. Burguera, S. Ikramuddin, D. Cottam, W. Gourash, G. Hamad, *et al*., "Effect of Laparoscopic Roux-en Y Gastric Bypass on Type 2 Diabetes Mellitus," *Annals of Surgery*, Vol. 238, No. 4, 2003, pp. 467-484.

[19] J. A. Tadross and C. W. le Roux, "The Mechanisms of Weight Loss after Bariatric Surgery," *International Journal of Obesity* (*London*), Vol. 33, Suppl. 1, 2009, pp. S28-S32. http://dx.doi.org/10.1038/ijo.2009.14

[20] D. E. Cummings, J. Overduin and K. E. Foster-Schubert, "Gastric Bypass for Obesity: Mechanisms of Weight Loss and Diabetes Resolution," *Journal of Clinical Endocrinology & Metabolism*, Vol. 89, No. 6, 2004, pp. 2608-2615. http://dx.doi.org/10.1210/jc.2004-0433

[21] D. S. Tichansky, J. D. Boughter Jr. and A. K. Madan, "Taste Change after Laparoscopic Roux-en-Y Gastric Bypass and Laparoscopic Adjustable Gastric Banding," *Surgery for Obesity and Related Diseases*, Vol. 2, No. 4, 2006, pp. 440-444. http://dx.doi.org/10.1016/j.soard.2006.02.014

[22] D. E. Cummings, D. S. Weigle, R. S. Frayo, P. A. Breen, M. K. Ma, E. P. Dellinger, *et al*., "Plasma Ghrelin Levels after Diet-Induced Weight Loss or Gastric Bypass Surgery," *New England Journal of Medicine*, Vol. 346, No. 21, 2002, pp. 1623-1630. http://dx.doi.org/10.1056/NEJMoa012908

[23] J. Korner, M. Bessler, L. J. Cirilo, I. M. Conwell, A. Daud, N. L. Restuccia, *et al*., "Effects of Roux-en-Y Gastric Bypass Surgery on Fasting and Postprandial Concentrations of Plasma Ghrelin, Peptide YY, and Insulin," *Journal of Clinical Endocrinology & Metabolism*, Vol. 90, No. 1, 2005, pp. 359-365. http://dx.doi.org/10.1210/jc.2004-1076

[24] W. J. Pories, M. S. Swanson, K. G. MacDonald, S. B. Long, P. G. Morris, B. M. Brown, *et al*., "Who Would Have Thought It? An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus," *Annals of Surgery*, Vol. 222, No. 3, 1995, pp. 339-350. http://dx.doi.org/10.1097/00000658-199509000-00011

[25] D. E. Cummings, "Endocrine Mechanisms Mediating Remission of Diabetes after Gastric Bypass Surgery," *International Journal of Obesity* (*London*), Vol. 33, Suppl. 1, 2009, pp. S33-S40. http://dx.doi.org/10.1038/ijo.2009.15

[26] S. R. Chipkin and R. J. Goldberg, "Obesity Surgery and Diabetes: Does a Chance to Cut Mean a Chance to Cure?" *American Journal of Medicine*, Vol. 122, No. 3, 2009, pp. 205-206.

[27] M. Hempen, H. P. Kopp, M. Elhenicky, *et al*., "YKL-40 Is Elevated in Morbidly Obese Patients and Declines after Weight Loss," *Obesity Surgery*, Vol. 19, No. 11, 2009, pp. 1557-1563. http://dx.doi.org/10.1007/s11695-009-9917-4

[28] C. W. le Roux, S. J. Aylwin, R. L. Batterham, C. M. Borg, F. Coyle, V. Prasad, *et al*., "Gut Hormone Profiles Following Bariatric Surgery Favor an Anorectic State, Facilitate Weight Loss, and Improve Metabolic Parameters," *Annals of Surgery*, Vol. 243, No. 1, 2006, pp. 108-114. http://dx.doi.org/10.1097/01.sla.0000183349.16877.84

[29] J. Korner, M. Bessler, W. Inabnet, C. Taveras and J. J. Holst, "Exaggerated Glucagon-Like Peptide-1 and Blunted Glucose-Dependent Insulinotropic Peptide Secretion Are Associated with Roux-en-Y Gastric Bypass but Not Adjustable Gastric Banding," *Surgery for Obesity and Related Diseases*, Vol. 3, No. 6, 2007, pp. 597-601. http://dx.doi.org/10.1016/j.soard.2007.08.004

[30] J. M. Isbell, R. A. Tamboli, E. N. Hansen, *et al*., "The Importance of Caloric Restriction in the Early Improvements in Insulin Sensitivity Following Roux-en-Y Gastric Bypass Surgery," *Diabetes Care*, Vol. 33, No. 7, 2010, pp. 1438-1442. http://dx.doi.org/10.2337/dc09-2107

[31] F. Rubino, A. Forgione, D. E. Cummings, M. Vix, D. Gnuli, G. Mingrone, *et al*., "The Mechanism of Diabetes Control after Gastrointestinal Bypass Surgery Reveals a Role of the Proximal Small Intestine in the Pathophy- siology of Type 2 Diabetes," *Annals of Surgery*, Vol. 244, No. 5, 2006, pp. 741-749. http://dx.doi.org/10.1097/01.sla.0000224726.61448.1b

[32] M. J. Perley and D. M. Kipnis, "Plasma Insulin Responses to Oral and Intravenous Glucose: Studies in Normal and Diabetic Sujbjects," *Journal of Clinical Investigation*, Vol. 46, No. 12, 1967, pp. 1954-1962. http://dx.doi.org/10.1172/JCI105685

[33] M. Nauck, F. Stockmann, R. Ebert and W. Creutzfeldt, "Reduced Incretin Effect in Type 2 (Non-Insulin-Dependent) Diabetes," *Diabetologia*, Vol. 29, No. 1, 1986, pp. 46-52. http://dx.doi.org/10.1007/BF02427280

[34] M. A. Nauck, N. Kleine, C. Orskov, J. J. Holst, B. Willms and W. Creutzfeldt, "Normalization of Fasting Hyperglycaemia by Exogenous Glucagon-Like Peptide 1 (7-36 Amide) in Type 2 (Non-Insulin-Dependent) Diabetic Patients," *Diabetologia*, Vol. 36, No. 8, 1993, pp. 741-744. http://dx.doi.org/10.1007/BF00401145

[35] C. Guidone, M. Manco, E. Valera-Mora, A. Iaconelli, D. Gniuli, A. Mari, *et al*., "Mechanisms of Recovery from Type 2 Diabetes after Malabsorptive Bariatric Surgery," *Diabetes*, Vol. 55, No. 7, 2006, pp. 2025-2031. http://dx.doi.org/10.2337/db06-0068

[36] D. J. Pournaras, A. Osborne, S. C. Hawkins, *et al*., "The Gut Hormone Response Following Roux-em-Y Gastric Bypass: Cross-Sectional and Prospective Study," *Obesity Surgery*, Vol. 20, No. 1, 2010, pp. 56-60. http://dx.doi.org/10.1007/s11695-009-9989-1

[37] A. Keidar, "Bariatric Surgery for Type 2 Diabetes Reversal: The Risks," *Diabetes Care*, Vol. 34, No. 2, 2011, pp. 361S-366S.

[38] T. D. Adams, A. M. Stroup, R. E. Gress, *et al*., "Cancer Incidence and Mortality after Gastric Bypass Surgery," *Obesity*, Vol. 17, No. 4, 2009, pp. 796-802. http://dx.doi.org/10.1038/oby.2008.610