PRELIMINARY ANALYSIS OF INTERLEUKIN-6 CHANGES IN PRE- AND POSTOPERATIVE IN DIABETIC PATIENTS WITH BMI<35 SUBMITTED TO PARTIAL DUODENAL SWITCH

ABSTRACT – Background: Studies related to obesity have shown association with metabolic syndrome. Data showing that obesity is capable to cause low grade chronic inflammation, without its classic signs and symptoms, call attention to researches to study different cells types and the mechanism of the inflammatory process. Aim: To evaluate the variation of glycated hemoglobin (HbA1c) and the pro-inflammatory cytokine interleukin-6 (IL6) in diabetic patients with BMI <35 kg/m² in the pre and postoperative of partial duodenal switch. Method: Nine patients were studied before and one year after the operation and the variation of the serum IL6 was measured by Elisa. The changes of HbA1c were also registered. Results: The pre-operative IL6 levels reached 65,50436±2,911993 pg/ml and one year after de operation 39,47739±3,410057 pg/ml and the HbA1c average of 10,67 and 5.8 in the same period. Conclusion: The partial duodenal switch was efficient to control one year after the procedure the chronic inflammatory process caused by the diabetes mellitus type 2 with BMI <35 by dropping the IL6 levels and bringing the HbA1c to normal.

Correspondence: Luciano Dias de Oliveira Reis E-mail: reisluciano@uol.com.br

INTRODUCTION

Medicine has been faced to astonished raise rate of obesity. Today, according to the WHO one billion person are overweight and tree hundred thousands are obese. 30% of the USA population has BMI>30. Studies related to obesity have shown wide association to insulin resistance, diabetes mellitus type 2 (DM2), hypertension, cardiovascular diseases, hypertriglyceridemia, the sum of these is known as metabolic syndrome (MS).

Data showing that obesity is capable to cause low grade chronic inflammation, without its classic signs and symptoms, call attention to researches to study different cells types and the mechanism of the inflammatory process.

The International Diabetes Federation indicates that the “obesogenic society” resulted from the sedentary habits associated to high caloric intake are responsible
for the diabetic epidemic with impaired insulin function or low production on insulin by the pancreatic islet cells causing hyperglycemia and interacting with other lipid dysfunctions, oxidative stress and inflammatory response.

Cytokines are signaling polypeptides used in cellular communication by the immune system and in the inflammatory response, acting virtually in all types of cells and in the synthesis of RNAm. Among the cytokines, the IL6, object of this study, has been found in elevated levels in chronic diseases including DM2. IL6 mediated inflammation is implicated in age related disorders including atherosclerosis, peripheral vascular disease, coronary artery disease, dementia and Alzheimer ‘disease, some forms of arthritis, cancer and DM2, the last one related to this paper.

Different surgical procedures upon obese subjects have been very efficient not only to reduce the BMI but also to improve the diseases linked to MS. Several publications are incise in showing the benefits of bariatric procedures in DM2. These surgical procedures are also improving the inflammatory status of the patients allowing a new fied for researchers. Even diseases not related to MS, as asthma, have improved after the DM2 patients reached BMI below 30.

The objective of this study is to be the initial part of the evaluation of the anti-inflammatory effect achieved in diabetic patients with BMI below 35 kg/m² operated by the technique of partial duodenal diversion (PDS), analyzing the variation of levels of IL-6 and hemoglobin glucose levels in pre and one year postoperative diabetic patients with BMI <35.

**METHODS**

This study has been approved by the Ethics Committee on the State University of Ponta Grossa under protocol 37/2010. All patients signed an informed consent.

**Patients**

Nine patients with BMI below 35, with DM2 at least for 2 years, with difficult controlled disease, were submitted to PDS. The surgical procedures were done at Vicentinho Hospital, in Ponta Grossa, PR, Brazil. All patients were diagnosed as DM2 according to WHO criteria. Patients with chronic infectious disease, cancer, pregnancy and drug or alcoholic addicts were excluded. Blood samples were obtained just before surgery, after 8 h fasting and one year after the operation, aiming to measure HbA1c and IL6.

**Surgical procedure**

Patients were admitted the day before surgery for clinical and endocrinological evaluation. The operation was performed under general anesthesia. Laparotomy with a 10 cm midline incision was done. The greater omentum was separated from the transverse colon and removed. A vertical gastrectomy was started 6 cm proximal to the pylorus, after liberation of posterior adhesions and ligature with ultrasonic scalpel of the short gastric vessels. Using stapling devices, casted by Fouchet tube 32F, the vertical gastrectomy was progressive performed aiming the The intestine was severed 260 cm from the duodenojejunal angle and the distal stoma sutured to the antrum (gastroileostomy). A distal anastomosis as performed at 80 cm from the ileoceleval valve, end to side, in two planes, with the proximal severed small bowel to distal ileum. Both anastomoses were fashioned with poliglactin 000. The mesenteric spaces were closed (Figure 1).

**RESULTS**

One of the nine patients was excluded due to the fact of having BMI just above 25. The others had BMI between 30-35 kg/m². The BMI and laboratory data are shown at Table 1. The HbA1c analysis showed a progressive drop from the operation to one year after. The medium pre-operative level was 10.67 and after 12 months the medium level dropped to 5.88 (Table 2).

The pre-operative IL6 levels reached 65.50436±2.911993 pg/ml and one year after de operation 39.47739±3.410057. T Student test showed significant decrease p<0.05 (Figure 2).

**DISCUSSION**

Obesity and DM2 are very common in the modern society. Criteria for definition for both are well stabilized by the International Diabetes Federation and by the American Diabetes Association. Even though, the real mechanisms that conduct to the development of metabolic syndrome is unknown. Genetics and epigenetic factors in association to sedentary style of life and hyper alimentation are frequently mentioned in studies related do DM2 development.

The capacity of fatty cells to in promoting insulin resistance makes the obesity an important risk factor to the development of DM2 even though the disease may occur in mild obese and may not in morbid obese patients.

The majority of reports on the effects of surgery in DM2 patients are in morbid obese patients since the criteria to bariatric/metabolic surgery has as main target the treatment...
TABLE 1 – Laboratory data and patients BMI

| Patients | Pre 3m | 6m | 12m | Pre/3m | Pre/6m | Pre/12m |
|----------|--------|----|-----|--------|-------|--------|
| BMI      |        |    |     |        |       |        |
| % of BMI loss |        |    |     |        |       |        |
| Fasting glucose |        |    |     |        |       |        |
| Post prandial glucose |        |    |     |        |       |        |
| Triglycerides |        |    |     |        |       |        |
| Interleukin 6 levels |        |    |     |        |       |        |
| Preoperative |        |    |     |        |       |        |
| IL-6 (pg/mL) |        |    |     |        |       |        |
| Postoperative |        |    |     |        |       |        |
| IL-6 (pg/mL) |        |    |     |        |       |        |

Table 2 – Means (%) of glycated hemoglobin in the different periods

| Patients | Pre 3m | 6m | 12m | Pre/3m | Pre/6m | Pre/12m |
|----------|--------|----|-----|--------|-------|--------|
| % of BMI loss |        |    |     |        |       |        |
| Fasting glucose |        |    |     |        |       |        |
| Post prandial glucose |        |    |     |        |       |        |
| Triglycerides |        |    |     |        |       |        |
| Interleukin 6 levels |        |    |     |        |       |        |
| Preoperative |        |    |     |        |       |        |
| IL-6 (pg/mL) |        |    |     |        |       |        |
| Postoperative |        |    |     |        |       |        |
| IL-6 (pg/mL) |        |    |     |        |       |        |

of obesity. The most important criteria to choose patients to surgery are related to BMI and not the comorbidities as hypertriglyceridemia, hypertension, and DM2. But the majority of DM2 patients are mild obese or obese grade I, since the pattern of these patients is abdominal obesity, excluding a great deal of DM2 patients with refractive disease as possible candidate to surgery.

In our study we are dealing with patients excluded from the classic protocol to bariatric surgery, since they obese I, with BMI below 35 or overweight, BMI >25 and <35, all with DM2 of difficult clinical control. Treating this group of not obese morbid patients the PDS caused a complete loss of excess of weight, with a drop of the BMI of 28% on average after one year.

Recent papers are suggesting to lower the BMI to treat patients with MS. According to the consensus of International Diabetes Federation, procedures to treat patients with MS may be indicated to patients with BMI of 35 or to patients between 30 and 35 if they have DM2 of difficult clinical control. In some Asian population with higher risks BMI of 27.5 is acceptable. In this study 8 (88%) patients were in the group with BMI between 30-35.

The results of metabolic surgery is consistently better in obese patients when compared to clinical treatment and has stimulated trials using different technics aiming the glycemic control in patients with BMI under 35, seeking to establish surgery as an effective and definitive treatment to MS patients resistant to clinical treatment, a commoner growing problem in worldwide population.

Most of the surgical bariatric procedures used today were described more than 20 years ago and designed to treat morbid obese patients before the knowledge of the enterohormones. Santoro et al. published and staged evolutive adaptive procedure to treat MS patients and from his group arouse the concept of the operation used in this study, PDS. This procedure innovates not excluding any segment of stomach or bowel, allowing a rapid transit of the alimentary bolus without dumping or iron or calcium deficiency and an early stimulus to distal ileum.

In this study, the results of PDS in DM2 patients were very satisfactory. From the 9 patients in this group, six were on daily use of insulin and one refused to use insulin despite of his endocrinologist recommendation. The indication of insulin was suspended in all patients after the operation and the patients were orientated to measure regular fasting glycemic levels and return if it reached >200 ml/dl. None of these patients need to return to insulin during the first year. Only one patient was kept on oral hypoglycemic drug (a DPP IV inhibitor) according to the endocrinologist to improve the MS, despite of the Hba1c below 7 mg%. The average of pre-operative Hba1c was 10.67%. A significant drop of the Hba1c (p<0.05) follow de operation, below 7 in the first trimester and and reaching an average of 5.88% one year after the surgery. The average fasting glycemic level before PDS was 269 mg% and 94.3 mg% one year post-operative, considered very acceptable.

Cohen at al. reported 37 patients submitted to laparoscopic gastric bypass (RYGB) and De Paula et al. published the results with sleeve gastrectomy and ileal interposition (ileal break) in 30 patients. Both studies were in patients with BMI under 35 kg/m² and reached diabetes control level s above 90% of patients.

When RYGB is used the segment of small bowel in contact with the ingested food is the jejunum, being the results not as expressive as when bilipancreatic bypass with duodenal switch is used, when the ileum is in contact to food. It has
been suggested that the size of proximal excluded segment (biliopancreatic loop) is very important in the antidiabetogenic final result of the procedure. Valezi reported in a prospective study in obese patients submitted to RYGB that the size of the alimentary or biliopancreatic loop did not interfere with the weight loss of their patients. PDS do not only interfere in the amount of food ingested due to the vertical gastrectomy but also places the ileum in contact to the alimentary bolus via gastroileostomy improving the release of incretins, mainly GLP-1. In our study 88% of patients reached DM2 control without exclusion of any gastrointestinal segment.

Aiming to set up a pattern, Nassif et al. in 2013 described a technique for vertical gastrectomy placing a Fouchet's tube 32 F in the lesser curvature to cast the neo stomach, starting stapling the greater curvature just proximal to the pylorus, creating a narrow and long stomach. In 55 patients submitted to vertical gastrectomy, Nassif obtained control of 84.6% of the DM2 in the first year and 91.6% in the second year. In a long revision of 27 reports, when vertical gastrectomy was used as the only procedure, an average of 66% remission rate for the DM2 patients was obtained.

Early publication of this group of researches using PDS has shown, using small metal radiopaque spheres mixed to a meal, that 40% of ingested content exited through the pylorus to duodenum and 60% via gastroileostomy. Keeping the duodenum in the PDS is responsible for avoiding lacking of absorption of important substances, essentials to human metabolism. Chronic anemia is common after RYGB and demands oral or parenteral iron replacement. Keeping the pylorus intact also avoids dumping syndrome, a frequent complication of gastric operations. In our patients submitted to PDS, none had nutritional deficits or dumping and after one year of the procedure the median hematocrit was 39 mg/dl.

The duodenum and proximal jejunum is rich in K cell, responsible for the production of GLP. Evidence suggesting that the duodenum is important in controlling glycemic levels (foregut hypothesis) linked to this incretin enterohormone action. The greater capacity of distal small bowel, rich in GLP 1 producing L cells, is also very important in regulating glycemic levels (hindgut hypothesis) after metabolic procedures.

Visceral fat, mainly the omentum, is responsible to secrete resistin, a peptide that acts on mioctes, liver and even on the adipocites, impairing insulin sensitivity and inducing to DM2. The metabolic operation associated to resection of a large part of the omentum also results in lesser secretion of PAI-1 and decrease cardiovascular risks and improves lipid profile. In this study we also measured the fasting triglycerides before and one year after the PDS. There was a significant drop in triglycerides (p<0.05). The pre-operative median levels were 325.11 mg/dl and one year after the operation only 105.78 mg/dl, considered normal. Santoro comparing two surgical techniques - RYGB and gastroentero omentectomy - found a second report, was 98% in the biliopancreatic group, 83% in RYGB group and in the adjustable gastric band 47.9%. The second report, in 2009 confirmed the previous findings.

In our review we did not find any study using PDS for the treatment of DM2 patients with BMI below 35, neither measuring IL6 as parameter for DM2 low rate chronic inflammatory resolution. The PDS controlled the MS and induced DM2 remission parallel to IL6 drop to normal. This procedure is technically simple, safe, and efficient in controlling the DM2 and excess of weight, without iron and calcium deficiency by keeping the duodenum in the alimentary transit.

According to Santoro et al., the PDS, referred by him as vertical gastrectomy with transit bipartition, has been designed to work primarily through metabolic ways, avoiding restriction and malabsorption. Absence of prosthesis or excluded segment, full endocrine production, and easy feasibility associated with a metabolic corrective intervention bring benefits to patients. PDS is simple, reversible, and improves the results of vertical gastrectomy (with is the commonest bariatric-metabolic procedure performed in USA since 2015). We believe that PDS is one more step toward the excellence of metabolic surgery.

### Conclusion

The partial duodenal switch was efficient to control one year after the procedure the chronic inflammatory process caused by the DM 2 with BMI < 35 by dropping the IL6 levels and bringing the HbA1c to normal.

### References

1. Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JL, Donato KA, Frucht JC, James WP, Loria CM, Smith SC Jr; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity. Circulation. 2009 Oct 20;120(16):1640-5. doi: 10.1161/CIRCULATIONAHA.109.1926444.strap A, Finer N, Redefining type 2 diabetes: “diabetes” or “obesity dependent diabetes mellitus”? Obes Rev 2000 Oct;1(2):57-.

2. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories WJ, Fahrbach K, Schoelles K. Bariatric surgery: a systematic review and meta-analysis. JAMA. 2004 Oct 13;292(14):1724-37. Review.

3. Buchwald H, Estok R, Fahrbach K, Bannel D, Jensen MD, Pories WJ, Bantle JP, Sledige W. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. Am J Med. 2009 Mar;122(3):248-256.e5. doi: 10.1016/j.amjmed.2008.09.041.
4. Cohen R, Pinheiro JS, Correa JL, Schiavon CA. Laparoscopic Roux-en-Y gastric bypass for BMI < 35 kg/m²: a tailored approach. Surg Obes Relat Dis. 2006 May-Jun;2(3):401-4.

5. Cummings DE, Arterburn DE, Westbrook EO, Kusma JN, Stewart SD, Chan CP, Bock SN, Landers JT, Kratz M, Foster-Schubert KE Flum DR. Gastric bypass surgery vs intensive lifestyle and medical intervention for type 2 diabetes: the CROSSROADS randomized controlled trial. Diabetologia 2016; 59:945-953.

6. DePaula AL, Macedo ALV, Schraibman V. Hormonal evaluation following laparoscopic treatment of type 2 diabetes mellitus patients with BMI 20-34. Surg Endosc. 2009; 23:1724-32.

7. Dixon JB, Zimmetta P, Albertib K G, Rubino F. Bariatric surgery: an IDF statement for obese Type 2 diabetes. Surgery for Obesity and Related Diseases. 2011;7:433-447.

8. Domene CE, Volpe P, Heitor FA. Robotic Roux-en-Y gastric bypass: operative results in 100 patients. Arq Bras Cir Dig. 2014;27 Suppl 1:9-12 (D).

9. Faria SL, Faria OP, Cardeal Mde A. Comparison of weight loss, food consumption and frequency of vomiting among Roux-en-Y gastric bypass patients with or without constriction ring. Arq Bras Cir Dig. 2014;27 Suppl 1:43-6. (C)

10. Kao YH, Lo CH, Huang CK. Relationship of bypassed limb length and remission of type 2 diabetes mellitus after Roux-en-Y gastric bypass. Surg Obes Relat Dis. 2012;Nov-Dec;8(6):e82-4. doi: 10.1016/j.soard.2011.10.011.

11. Kaur J. A comprehensive review on metabolic syndrome. Cardiol Res Pract 2014;2014:943162.

12. Lee WJ, Almulaihi A, Chong K, Chen SC, Tsou JJ, Ser KH Lee IC, Chen JC. The Effect and Predictive Score of Gastric Bypass and Sleeve Gastrectomy on Type 2 Diabetes Mellitus Patients with BMI < 30kg/m². Obes Surg, 2015

13. Lima WC, Lucas RWC, Nassif PAN, Boop DS, Malafaia o. Análisa da relação entre a estatura e o perímetro abdominal em indivíduos portadores de percentuais normais de gordura. Arq Bras Cir Dig 2010; 23(1):24-28.

14. Lindegaard KK, Jorgensen NB, Just R, Heegaard PM, Madsbad S. Effects of Roux-en-Y gastric bypass on fasting and postprandial inflammation-related parameters in obese subjects with normal glucose tolerance and type 2 diabetes. Diabetes Metab Syndr. 2015 Feb 24;7:12. doi: 10.1016/s1398-015-0012-9.

15. Lyssenko V, McCarthy ML, Groop L, Salehi A, Gloyn AL, Renström E, Ahlin S, , Anveden Å, Bengtsson C, Bergmark G, Bouchard C, Carlson B, Dahlgren S, Karlsson J, Lindroos AK, Lonroth H, Narbro K, Näslund I, Olbers T, Svensson PA, Carlsson LM. Bariatric surgery and long-term cardiovascular events. JAMA. 2012 Jan 4;307(1):56-65.

16. Shuai X, Tao K, Mori M, Kanda T. Bariatric surgery for metabolic syndrome in obesity. Metab Syndr Relat Disord. 2013;15(4):149-60.

17. Sjöström L, Peltonen M, Jacobsson P, Sjöström CD, Karason K, Wedel H, Ahlin S., Arveden A., Bengtsson C, Bergmark G, Bouchard C, Carlson B, Dahlgren S, Karlsson J, Lindroos AK, Lonroth H, Narbro K, Näslund I, Olbers T, Svensson PA, Carlsson LM. Bariatric surgery and remission of type 2 diabetes mellitus after Roux-en-Y gastric bypass. Arq Bras Cir Dig. 2015;28(Supl.1):19-22. doi: 10.1590/S0102-6720201500S100010. (B)

18. Souza MDG, Vilar L, Andrade CB, Albuquerque RO, Cordeiro LHO, Campos JM , Ferraz AAB, Obesity prevalence and metabolic syndrome in a park users. Arq Bras Cir Dig. 2015;28(Supl 1):31-35. doi: /10.1590/S0102-6720201500S100010. (E)

19. Valezí AC, Cabrera EJ, Delfino VDA, Barbosa DS, Málí Júnior J, Menezes MA. Derivação gástrica em Y-de-Roux: comprimento das alças e emagrecimento. Rev. Col. Bras. Cir. 2014 27:56-58.

20. Volp ACP, Bressan J, Heimsotht HHM, Zuleit MA Martinez JA. Efeitos anti oxidantes do selênio e seu elo com a inflamação e síndrome metabólica. Ver Nutr. 23(4):581-590, 2010