International Journal of Current Research and Academic Review

ISSN: 2347-3215 Volume 3 Number 8 (August-2015) pp. 427-436

www.ijcrar.com

Effects of Pantoprazole on Serum Glucose Level in Type Two Diabetic Patients

Farzad Najafipour[1], Mohammah Hasan Omidvar[2]* and Mahmoud Reshadatjoo[2]

[1]Endocrine Research Center, Faculty of Medicine, Tabriz University of Medical Sciences, Iran
[2]Resident of Internal Medicine, Internal Medicine Department, Faculty of Medicine, Tabriz University of Medical Sciences, Iran.
Corresponding author

KEYWORDS

Type II Diabetes,
Pantoprazole,
Fasting Blood Glucose,
Gastrin,
Insulin

A B S T R A C T

Type II diabetes is a heterogeneous and complex combination of metabolic condition caused by high levels of blood glucose and insulin resistance or insulin deficiency. Some studies suggest the increased levels of gastrin following the administration of PPIs who seek to improve glycemic status and increased pancreatic insulin content. The purpose of this study was to determine the effect of Pantoprazole on glycemic control in patients with type II diabetes. In this double-blind clinical trial, 40 patients with type II diabetes under treatment with oral hypoglycemic drugs and HbA1C levels less than 8.5% were evaluated in two group (each with 20 patients). Patients were treated for 12 weeks with placebo or 40 mg Pantoprazole tablets twice a day. Glucose, HbA1C, insulin and gastrin levels, before and after treatment, were measured. The mean fasting blood glucose at baseline in the intervention and control groups was 164.6 ± 11.3 and 138.5 ± 4.6 mg per deciliter respectively and at the end of intervention was 126.5 ± 3.8 and 151.2 ± 9.4 *mg/dl*. In the within group analysis, the lower the blood glucose in the intervention group and increased in the control group was seen. The within group changes in the intervention group was statistically significant (P = 0.001). The statistical analysis between groups after intervention showed a significant differences (P = 0.02). HbA1C reductions in the intervention and control groups in the study was 5.12% and 10.25%, respectively, but decreased in the intervention group was statistically significant (P = 0.01). Mean 2hpp in the intervention and control groups at baseline was 233.5 ± 15.9 and 189.1 ± 13.01 *mg/dl*, respectively and at the end of the intervention was 162.1 ± 7.6 and 203.8 ± 13.2 *mg/dl*. In the group, 2hpp reduction in the intervention group and increased in the control group. The within-group changes in the intervention group was statistically significant (P <0.0001). In the intervention group, in the end, the two groups were statistically significant differences (P = 0.009). Mean plasma insulin levels before the intervention and control groups, respectively, versus 8.1 ± 1.2 and 9.9 ± 2.4 *µm/ml* and after the intervention to 10.2 ± 1.3 and 10.7 ± 1.4 *µm/ml*, respectively. After the intervention in both groups there was an increase in insulin levels (20.5% and 8.08% in the intervention and control groups, respectively), but this increase was statistically significant in the intervention group (P = 0.003). Based on our results, consumption of Pantoprazole by reduction in fasting blood glucose, 2hpp and HbA1C and increased levels of insulin and gastrin, have a positive effect on diabetes type two. Therefore, in this study, we recorded a significant effect of taking Pantoprazole in patients with diabetes type two.

Introduction

Type II Diabetes is a complex heterogeneous combination of metabolic conditions. It is characterized by high levels of blood glucose and results from either resistance to insulin or insulin deficiency (1). However, recent studies have mostly focused on reinforcing the enteroinsular axis and incretins. The presence of the enteroinsular axis, which includes gastrin, insulin, and beta islet cells, is acknowledged. Gastrin has long been known as an incretion hormone and an intestinal factor. As compared to the condition in which venous glucose is administered to adjust the blood glucose levels to the peripheral glucose level, this hormone doubles the secretion of insulin when glucose is consumed orally.

In healthy individuals, acute administration of gastrin with low levels of glucose for achieving super-physiological levels leads to little secretion of insulin but if gastrin is administered with glucose it causes more insulin secretion. There is evidence on the role of gastrin as an incretin in this process (2).

Although resection of the gastric antrum as part of Whipple surgery reduces gastrin to very insignificant undiscoverable amounts, it does not reduce the incretin effects whatsoever. Hence, it is concluded that the role of gastrin is negligible at least in non-diabetic peoples (3).

Similar to gastric inhibitory polypeptides and glucagon-like peptides, gastrin plays a significant role in the stimulation of proliferation and neogenesis of β-cells and seemingly it also increases the insulin contents of beta-cells.

PPIs (Proton Pump Inhibitors) which are normally used for the treatment of peptic ulcer and the associated symptoms increase the level of serum gastrin indirectly. After blocking the production of gastric acid, the proton-pump inhibitors eliminate the negative feedback on the production of gastrin by enterochromaffin cells.

Research results showed that there is a dosage- and time-dependent relationship between PPIs and gastrin level (4-5). In a study that was carried out to treat Type II Diabetes in rats, administration of PPI increased gastrin levels and the increase finally led to the improvement of the glycemic condition and pancreatic insulin content (6).

Considering the above discussion and the restrictions on the relevant studies in Iran and other countries (which have not conducted significant studies in this regard), it was decided to carry out a study to examine the effects of Pantoprazole on blood sugar control in patients with Type II Diabetes.

Methods and Materials

The present research was a Clinical trail Placebo-Controlled study in which 40 patients with Type II Diabetes were selected randomly and were included in the study after the research plan was explained to them and their written consent was obtained. The participants were divided into two 20-member groups based on Random list.
After putting patients into the medicine and placebo groups, they were exposed to treatment with a placebo or Pantoprazole-40mg/BID for 12 weeks.

The researchers were blind to the grouping of patients. The levels of glucose, HbA1C, insulin, and serum gastrin were measured and recorded prior to the treatment and after treatment.

In addition to the placebo and the aforementioned drug the patients also received oral drugs as before. Prior to the study, all of the research details were explained to the patients and their written consent was obtained. The names of patients were mentioned in none of the phases of the study during the research and confidentiality was fully ensured. The patients were allowed to leave the study and avoid participating in the study at any phase. It is worth mentioning that all of the information in the patients' files completely remained secret. This research was registered with www.irct.ir as IRCT201306049626N2.

Result and Discussion

Of the 20 patients in the intervention group 9 were male (45%) and 11 were female (55%). Of the 20 patients in the control group, 10 were male (50%) and 10 were female (50%) (P=0.5).

The mean age of patients in both groups was 58.05±1.4 years and varied from 42 to 74 years. The mean age of patients in the intervention group was 60.2±1.7 years and varied from 44 to 74 years. In addition, the mean age of participants in the control group was 55.9±2.1 years and varied from 42 to 72 years (P=0.12).

Type II Diabetes is the most common endocrine disease which causes metabolic disorders and vascular and neurological conditions. These disorders result in undesirable complications in most organs such as retinopathy, nephropathy, and neuropathy (21).

Considering the complications of this disease, in this study it was tried to examine the effect of Pantoprazole on serum glucose levels in patients with type II diabetes and members of the control group.

Proton pump inhibitor is known as the factor regulating the glucose-insulin homeostasis. This regulation occurs by increasing the plasma gastrin levels. This trial may be the first trial of this type to assess the effects of Pantoprazole on the glucose-insulin homeostasis in patients with Type II Diabetes.

Jensen et al. studied patients with hypogastrinemia caused by resection of antrum, duodenum, and a part of jejunum. These researchers observed a drastic decrease in glucose variations in the response to insulin (22). Due to the existence of such contradictory findings the authors of this manuscript decided to conduct further studies of the effects of gastrin.

In our study, 40 patients with Type II Diabetes were randomly divided into two 20-member groups. Of the 20 patients in the intervention group 9 were male (45%) and 11 were female (55%). Of the 20 patients in the control group, 10 were male (50%) and 10 were female (50%) (P=0.5).

The mean age of patients in both groups was 58.05±1.4 years and varied from 42 to 74 years. The mean age of patients in the intervention group was 60.2±1.7 years and varied from 44 to 74 years. In addition, the mean age of participants in the control group was 55.9±2.1 years and varied from 42 to 72 years (P=0.12). Therefore, the participants in the two groups had similar demographic properties at the beginning of the research.
The research by Cowey et al. (2005) showed the development of central obesity and insulin resistance in rats with damaged gastrin-related genes. This finding reflects the existence of a relationship between gastrin and the glucose-insulin homeostasis (23).

Table.1 Demographics finding of patients in two groups

		Group		P
		Intervention	Control	
Age		60.2±1.7	55.9±2.1	0.12
Sex	Male	9(45%)	10(50%)	0.5
	Female	11(55%)	10(50%)	

Table.2 Evaluation of FBS, Bs 2hpp and HbA1C at two groups

		Group		P¥
		Intervention	Control	
FBS	Before	164.6±11.3	138.5±4.6	0.04
	After	126.5±3.8	151.2±9.4	0.02
	Change	38.1±7.5	12.7±4.8	
	P*	0.001	0.2	
Bs 2hpp	Before	233.5±15.9	189.1±13.01	0.03
	After	162.1±7.6	203.8±13.2	0.009
	Change	71.4±8.3	14.7±0.19	
	P*	<0.0001	0.42	
HbA1C	Before	7.9±0.3	7.8±0.2	0.89
	After	7.09±0.1	7.4±0.3	0.11
	Change	0.81±0.2	0.4±0.1	
	P*	0.01	0.21	

¥_P_Value: Between Group *_P_Value: Within Group

Table.3 Evaluation of Insulin and Gastrin level at two groups

		Group		P¥
		Intervention	Control	
Insulin	Before	8.1±1.2	9.9±2.4	0.52
µm/ml	After	10.2±1.3	10.7±1.4	0.83
	Change	2.1±0.1	0.8±1	
	P*	0.003	0.63	
Gastrin	Before	184.8±22.2	158.5±15.5	0.33
pg/ml	After	378.3±36.4	186.2±23.3	<0.0001
	Change	193.5±14.2	27.7±6.8	
	P*	<0.0001	0.17	

¥-P-Value: Between Group *-P-Value: Within Group

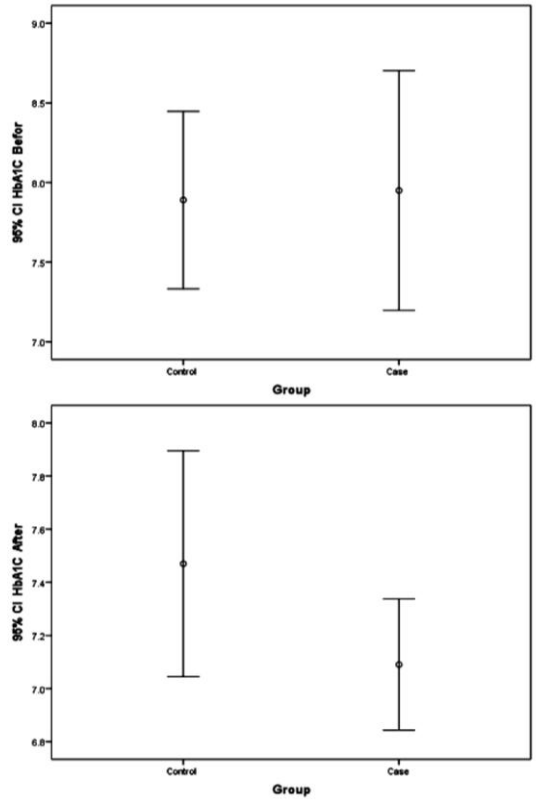

Figure.1 Distribution of HbA1C level at before-after study in two groups

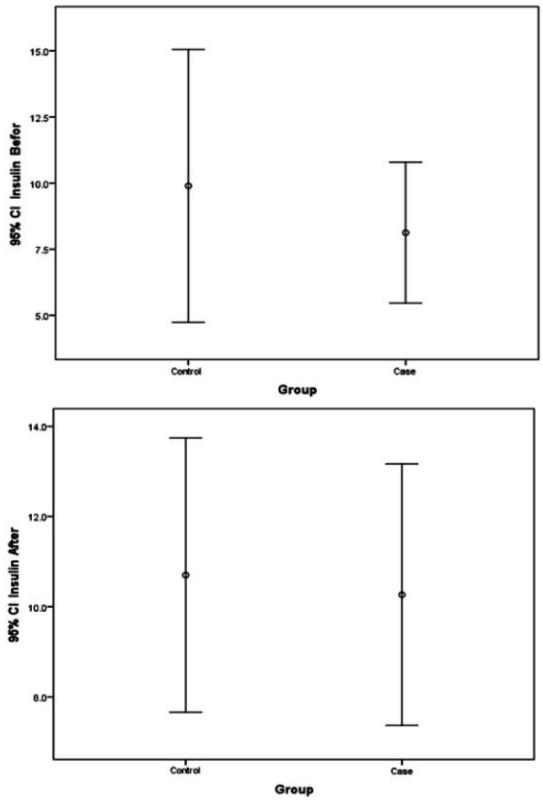

Figure.2 Distribution of Insulin level at before-after study in two groups

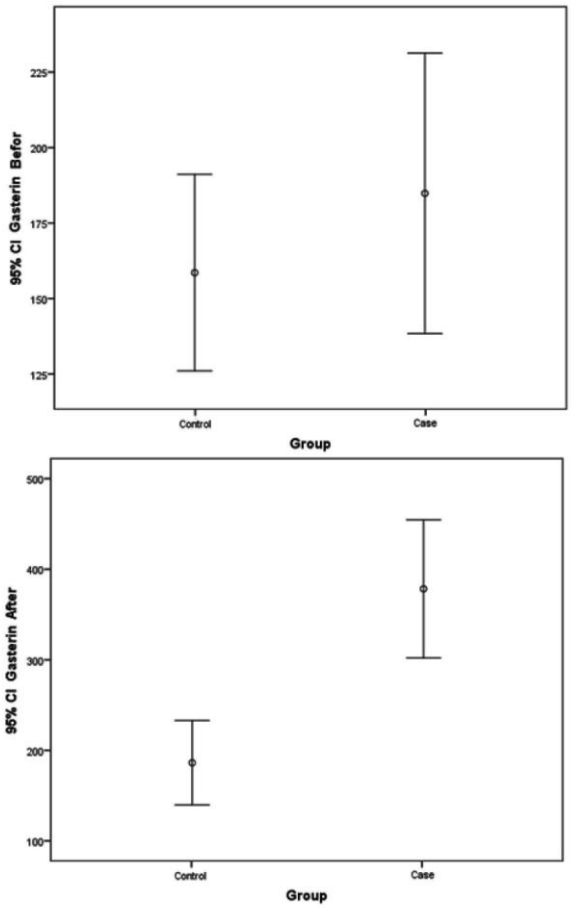

Figure.3 Distribution of Gasterin level at before-after study in two groups

In our study, the mean fasting blood sugar (FBS) in the intervention and control groups was 164.6±11.3 *mg/dl* and 138.5±4.6 *mg/dl* at the beginning of the study, respectively. There were significant inter-group and intra-group differences (P=0.001) and therefore it is concluded that administration of Pantoprazole considerably contributes to the reduction of FBS in Type II Diabetes patients.

In another research, in a group of patients with hypergastrinemia –related malignant anemia, a consideration insulin response to glucose changes was observed. However, in patients with hypogastrinemia the insulin response was lower than patients in the control group (3).

In a study by Singh et al., 31 male and female patients with type II diabetes were studied. The patients had been suffering from Type II Diabetes for less than 5 years and had HbA1C levels of lower than 8.5%. The patients were divided into two 15- and 16-member groups. In addition, the patients were examined for 12 weeks through the double-blind random intervention method using Pantoprazole-40mg/BID and a placebo. Finally, a reduction in HbA1C level was seen in patients of the intervention group (24).

In our study, the reduction in HbA1C levels in the intervention and control groups was 10.25% and 5.12% at the end of the study, respectively. Unlike the study by Singh, in

our study a higher reduction was observed in the intervention group which reflects the effect of administration of Pantoprazole.

Moreover, in Singh's research, the mean level of FBS after 12 weeks was 145.1 *mg/dl* and 109.2 *mg/dl* in the control and intervention groups, respectively. However, the levels of FBS in the control and intervention groups were 134 *mg/dl* and 126.3 *mg/dl* prior to the study, respectively (P<0.05). The level of gastrin was 54.7 *pg/dl* in the control group and 75.6 *pg/dl* in the intervention group. The level of insulin was 11 *µm/ml* in the control group and 13.9 *µm/ml* in the intervention group (24).

In our study, the increase in gastrin was higher than the increase observed by Singh et al. However, the level of insulin in both groups was lower than Singh's study. In our study, the pre-study insulin levels of the two groups did not show a statistically significant difference whereas following the within-group study a higher increase was observed in the intervention group in spite of the growth of insulin levels in both groups (P=0.003). In the intergroup examinations, at the beginning of the study no difference was observed between the insulin levels of the two groups, and following the intervention no significant difference was observed between the insulin levels in spite of the changes in the insulin levels of both groups (P=0.83).

Moreover, in our study the mean level of Bs2hpp in the intervention and control groups was 15.9±233.5 *mg/dl* and 189.1±13.1 *mg/dl* at the beginning of the study, respectively. The mean levels of Bs2hpp in the intervention and control groups were also 162.1±7.6 *mg/dl* and 13.2±203.8*mg/dl* at the end of the study, respectively. In the within-group investigations a decrease in Bs2hpp was observed in the intervention group and an increase in Bs2hpp was seen in the control group (P<0.0001). In the intergroup investigations at the end of the intervention, the differences between the results of the two groups were statistically significant (P=0.009).

According to the research report recently published by the Clinical Endocrinology and Metabolism Journal, administration of PPI can be useful for patients with Type II Diabetes. In this study, patients received Pantoprazole for 12 weeks. Following the examinations an increase in the plasma gastrin levels and insulin levels as well as improvement of β-cells performance were observed. Moreover, the levels of HbA1C declined significantly (24).

In our study, the mean level of HbA1C in patients of the intervention and control groups was 7.9±0.3% and 7.8±0.2%, respectively. Following the intervention phase, the mean levels of HbA1C in patients of the intervention and control groups were 7.09±0.1% and 7.4±0.3%, respectively. Therefore, the reduction of HbA1C in the intervention and control groups was 10.2% and 5.1%, respectively. As seen, both groups showed a decrease in HbA1C levels, but the reduction was statistically significant in the intervention group (P=0.01). However, the reductions in the two groups did not differ significantly (P=0.11).

In the study by Mulder et al. within 12 weeks of a Clinical trail Placebo-Controlled study, Type II Diabetes patients received Pantoprazole or placebo. The levels of HbA1C, FBS, insulin and gastrin were measured at the beginning of the experiment and after 12 weeks. In addition to the positive effects of Pantoprazole on the levels of gastrin, insulin, and β-cells performance, this drug also drastically reduced the HbA1C levels. This finding confirms the findings of our study (24).

Furthermore, Mulder et al. concluded that treatment with Pantoprazole results in an increase in plasma insulin and gastrin levels and consequently improves blood sugar control in Type II Diabetes patients (25).

In the present research, the mean level of plasma insulin in the intervention and control groups before the intervention was $8.1\pm1.2\ \mu m/ml$ and $9.9\pm2.4\ \mu m/ml$, respectively. In addition, the mean level of plasma insulin in the intervention and control groups was also equal to $10.2\pm0.3\ \mu m/ml$ and $10.7\pm1.4\ \mu m/ml$ following the intervention, respectively. As seen, the levels of insulin increased in both groups following the intervention. However, the increase was only statistically significant in the intervention group (P=0.003) and this finding complies with results of the research by Mulder et al(25).

Concerning the levels of gastrin it can be said that the mean level of gastrin in patients of the intervention and control groups was 184.8±22.2pg/ml and 15.5±15.5pg/ml before the intervention, respectively. In addition, the level of gastrin in the intervention and control groups following the intervention was 378.3±36.4 pg/ml and 186.6±22.3 pg/ml, respectively.

As seen, following the intervention the levels of gastrin increased in both groups and the increase was 104.7% and 17.47% in the intervention and control groups, respectively. However, the increase was only statistically significant in the intervention group ($p<0.0001$). This finding also complies with the results of previous research in this field.

Conclusion

According to the results of this study, intake of Pantoprazole leads to a decrease in FBS, Bs2hpp and HbA1C levels and an increase in the insulin and gastrin levels. Therefore, this drug can have a positive effect on Type II Diabetes patients and the significant effect of Pantoprazole on Type II Diabetes patients was observed in this research. Hence, considering the significant difference in the values of each of the study parameters in the control and intervention groups and also considering the zero complications caused by the intake of Pantoprazole, this drug can be used to control blood glucose levels in diabetics. This drug can also be used to reduce the complications caused by the improper use of glucose in such patients.

Research results suggest that Type II Diabetes patients shall not solely rely on the consumption of diabetes control drugs as a change in lifestyle also contributes to the improvement of glycemic conditions in such patients. Hence, in addition to medical treatments, teaching lifestyle changes is highly important.

References

1.Das SK, Elbein SC. The Genetic Basis of Type 2 Diabetes. Cell science. 2006 Apr 30;2(4):100-131.

2.Rehfeld JF, Stadil F. The effect of gastrin on basal- and glucose-stimulated insulin secretion in man. J Clin Invest. 1973 Jun;52(6):1415-26.

3.Rehfeld J F, Stadil F, Baden H, Fischerman K. The enteral insulin-stimulation after Whipple's operation. Diabetologia. 1975 Jun;11(3):207-10.

4.Hu YM[1], Mei Q, Xu XH, Hu XP, Hu NZ, Xu JM. Pharmacodynamic and kinetic effect of rabeprazole on serum gastrin level in relation to CYP2C19 polymorphismin Chinese H ans. World J Gastroenterol. 2006 Aug 7;12(29):4750-3.

5.Rickels MR, Elahi D. Raising serum gastrin to improve glycemic control in

(type 2) diabetes: another limb of the enteroinsular axis? J Clin Endocrinol Metab. 2012 Nov;97(11):3915-6.

6.Bödvarsdóttir T B, Hove KD, Gotfredsen CF, Pridal L, Vaag A, Karlsen AE, Petersen JS. Treatment with a proton pump inhibitor improves glycaemic control in Psammomys obesus, a model of type 2 diabetes. Diabetologia. 2010 Oct;53(10):2220-3.

7.Shea JJ, Kitabchi AE. Management of fluctuant hearing loss. Arch Otolaryngol. 1973 Feb;97(2):118-24.

8.Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. Diabetes Res Clin Pract. 2010 Jan;87(1):4-14.

9.Malucelli DA, Malucelli FJ, Fonseca VR, Zeigeboim B, Ribas A, Trotta Fd, Silva TP. Hearing loss prevalence in patients with diabet es mellitus type 1. Braz J Otorhinolaryngol. 2012 Jun; 78(3): 105-15.

10.Conlin AE, Parnes LS. Treatment of sudden sensorineural hearing loss: I. A systematic review. Arch Otolaryngol Head Neck Surg. 2007 Jun;133(6):573-81.

11.Holcát M. Tinnitus and diabetes. Vnitr Lek. 2007 May;53(5):534-6.

12.Elamin A, Fadlallah M, Tuevmo T. Hearing loss in children with type 1 diabetes. Indian Pediatr. 2005 Jan;42(1):15-21.

13.Kasemsuwan L, Sriwanyong S, Krittiyawong S, Sunetrworakul J, Jiamsuchon K. Hearing in young diabetic patients. J Med Assoc Thai. 2001 Oct;84(10):1389-94.

14.Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving HH, Steffes MW; American Diabetes Association. Nephropathy in diabetes. Diabetes Care. 2004 Jan;27 Suppl 1:S79-83.

15.Sheetz MJ, King GL. Molecular understanding of hyperglycemia's adv erse effects for diabetic complications. JAMA. 2002 Nov 27;288(20):2579-88.

16.Leehey DJ, Singh AK, Alavi N, Singh R. Role of angiotensin II in diabetic nephropathy. Kidney Int Suppl. 2000 Sep;77:S93-8.

17.Huang XR, Chen WY, Truong LD, Lan HY.
Chymase is upregulated in diabetic nephropathy: implications for an alternative pathway of angiotensin II-mediated diabetic renal and vascular disease. J Am Soc Nephrol. 2003 Jul;14(7):1738-47.

18.Carey RM, Siragy HM. The intrarenal renin-angiotensin system and diabetic nephropathy. Trends Endocrinol Metab. 2003 Aug;14(6):274-81.

19.Zollinger R M, Ellison E H. Primary peptic ulcerations of the jejunum associated with islet cell tumors of the pancreas. Ann Surg. 1955 Oct; 142(4):709-23; discussion, 724-8.

20.Meier J.J, Butler A.E, Galasso R, Rizza RA, Butler PC. Increased islet beta cell replication adjacent to intrapancreatic gastrinomas in human. Diabetologia. 2006 Nov; 49(11): 2689-96. Epub 2006 Sep 23.

21.Shea JJ, Kitabchi AE. Management of fluctuant hearing loss. Arch Otolaryngol. 1973 Feb;97(2):118-24.

22.Jensen SL, Nielsen OV, Kühl C. The enteral insulin-stimulation after pancreas transplantation in the pig. Diabetologia. 1976 Dec;12(6):617-20.

23.Cowey S L, Quast M, Belalcazar L M, Wei J, Deng X, Given R, Singh P. Abdominal obesity, insulin resistance, and colon carcinogenesis are increased in mutant mice lacking gastrin gene

expression. Cancer. 2005 Jun 15;103(12):2643-53.

24.Singh PK, Hota D, Dutta P, Sachdeva N, Chakrabarti A, Srinivasan A, Singh I, Bhansali A. Pantoprazole improves glycemic control in type 2 diabetes: a randomized, double-blind, placebo-controlled trial. J Clin Endocrinol Metab. 2012 Nov;97(11):E2105-8.

25.Mulder C J, Westerveld BD, Smit JM, Oudkerk Pool M, Otten MH, Tan TG, van Milligen de Wit AW, de Groot GH; Dutch omeprazole MUPS study group. A double-blind, randomized comparison of omeprazole Multiple Unit Pellet System (MUPS) 20 mg, lansoprazole 30 mg and pantoprazole 40 mg in symptomatic reflux oesophagitis followed by 3 months of omeprazole MUPS maintenance treatment: a Dutch multicentre trial. Eur J Gastroenterol Hepatol. 2002 Jun; 14(6):649-56.