**Endocrine,** *vol. 17, no. 3, 229–232, April 2002* 0969–711X/02/17:229–232/$11.00 

# A Meal Stimulation Test in the Diagnosis of Pancreatic Endocrine Tumors in Multiple Endocrine Neoplasia Type 1

M. Migliori, P. Tomassetti, D. Campana, S. Boschi,[1] R. Pezzilli, L. Piscitelli, R. Corinaldesi, and L. Gullo

[1]*Department of Internal Medicine and Gastroenterology, and Department of Internal Medicine and Gastroenterology, University of Bologna, S. Orsola Hospital, Bologna, Italy*

**Background: The diagnostic value of the determination of the serum pancreatic polypeptide (PP) and gastrin concentrations after a standard meal for early diagnosis of patients with multiple endocrine neoplasia type 1 (MEN 1) is controversial. The aim of this study was to clarify this issue. Thirteen patients with MEN 1, seven healthy family members, and eight healthy controls were studied. Plasma PP and serum gastrin were measured before and after the ingestion of a standardized meal. The meal caused a statistically significant ($p < 0.05$) increase of both PP and gastrin in all three groups studied. Concerning PP, no statistically significant difference was observed between patients and controls. In family members, the values were significantly ($p < 0.05$) lower than in the other two groups. On the whole, no significant differences in gastrin levels were noted between patients and controls; in family members, the values were significantly ($p < 0.05$) lower than in patients. All patients who had abnormally high postprandial values of PP and gastrin also had abnormally high basal values of these two peptides. The determination of serum PP and gastrin levels after a meal stimulation test in patients with MEN 1 adds no information about the presence of pancreatic endocrine tumors over that provided by basal values of the two peptides.**

**Key Words:** MEN 1; meal test; gastrin; pancreatic polypeptide; gastrinoma; hyperparathyroidism.

## Introduction

Multiple endocrine neoplasia type 1 (MEN 1) is an autosomal dominant inherited syndrome characterized by the development of parathyroid, pituitary, pancreatic, and duodenal tumors, in various combinations *(1,2)*. It is a rare hereditary syndrome that is now much better understood than previously, especially as regarding the underlying genetic defect responsible for the disease *(3,4)*. From a clinical point of view, this syndrome often poses problems of diagnosis, especially early diagnosis, of the various tumors. Pancreatic endocrine tumors (PETs) develop in about 80% of patients with MEN 1, in about half of whom they are malignant *(2,5)*. These tumors are usually small and can be multicentric and so they are often not visualized by imaging examinations, especially in their early phase. For this reason, various biological markers have been proposed for their recognition *(6)*. Among these, the determination of serum pancreatic polypeptide (PP) and gastrin in basal conditions seems particularly useful for the diagnosis of endocrine pancreatic involvement *(6–8)*. More recently, it has been reported that detection of PETs in MEN 1 is enhanced by the determination of serum PP and gastrin responses to stimulation by a standardized meal *(9)*. According to the proponent's studies *(9)*, this test is particularly sensitive for the early detection of PETs, capable of giving a diagnosis at least 5 yr earlier than imaging procedures.

Very recently, however, a prospective controlled trial of a standardized meal stimulation test in the detection of PETs in patients with MEN 1 has shown that this test does not reliably indicate the presence of these tumors *(10)*.

Because of these conflicting results and considering that early discovery of PETs has great clinical and therapeutic importance for these patients, we performed the present study in order to help determine the utility of the meal stimulation test for the detection of these pancreatic tumors in patients with MEN 1.

## Results

The meal caused a significant ($p < 0.05$) increase of PP in the three groups of subjects studied (Fig. 1); the increase was much more marked in healthy controls than in the other two groups. The differences between the values in healthy controls and those in patients with MEN 1 were not statistically significant. The values in the seven healthy family members were significantly ($p < 0.05$) lower than were those in the healthy controls or patients.

The mean basal value of PP (Fig. 1) was higher in patients with MEN 1 than in the control subjects, but the difference was not statistically significant. On the whole, eight of the 13 patients (61.5%) with MEN 1 had basal values greater than the highest normal value of the peptide.

Received February 15, 2002; Accepted March 28, 2002.

Author to whom all correspondence and reprint requests should be addressed: Prof. P. Tomassetti, Department of Internal Medicine and Gastroenterology, S. Orsola Hospital, Via Massarenti, 9, 40138 Bologna, Italy. E-mail: tomasset@med.unibo.it

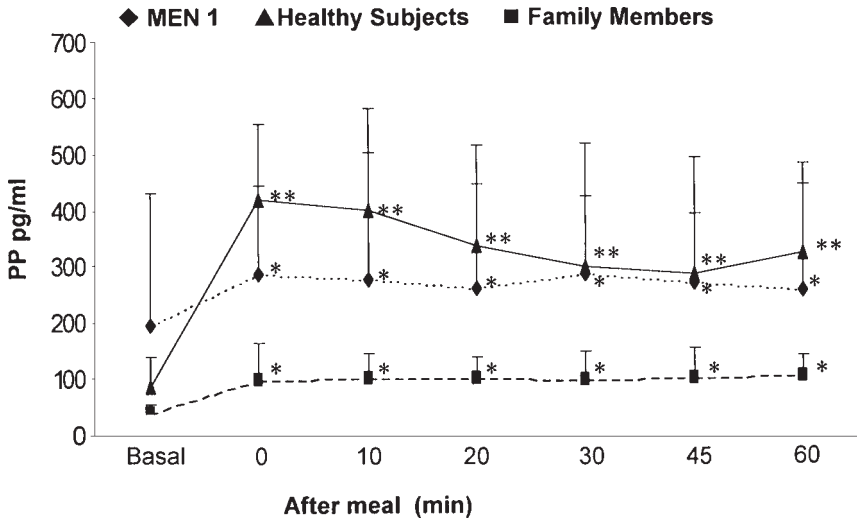


**Fig. 1.** Basal and postprandial values of plasma PP in the three groups of subjects studied. Means ± SD. *$p < 0.05$; **$p < 0.001$, compared to basal values.

Figure 2 shows the mean values ± SD of PP in the 13 patients with MEN 1 divided into those with pancreatic tumor ($n$ =6) and those apparently without pancreatic tumor ($n$ = 7). The concentrations of PP were higher in the six patients with pancreatic tumor, but the differences with the values in the remaining seven patients without pancreatic tumor were not statistically significant, apart from the values at 45 min ($p < 0.05$). The basal value of PP was higher than normal in five of the six patients with pancreatic tumor and in three of the remaining seven; this difference was not statistically significant.

After the meal, there was a moderate increase of gastrin in all three groups of subjects studied (Fig. 3). The increase was statistically significant ($p < 0.05$) in healthy controls and in family members, in patients with MEN 1, it was statistically significant ($p < 0.05$) only at 10 and 20 min after the meal. Five of the 13 patients with MEN 1 also had Zollinger Ellison Syndrome (ZES) and these five patients had very high values (>500 pg/mL) of postprandial gastrin. The difference between patients with MEN 1 and the normal subjects was not statistically significant, while the values in family members were significantly ($p < 0.05$) lower than in patients.

The basal values of gastrin were in the normal range in healthy subjects and in family members. Concerning the patients with MEN 1, these values were very high (>500 pg/mL) in the five patients who also had ZES. Of the remaining eight, seven had normal basal values and only one a raised value. The difference between these patients with MEN 1 and healthy subjects was not statistically significant.

## Discussion

Pancreatic endocrine tumors are present in most of the patients with MEN 1, and their diagnosis, especially early diagnosis, is of great practical importance. In recent years, it has been reported that a meal stimulation test with determination of serum PP and gastrin is useful for early detection of pancreatic lesions in patients with MEN 1 *(8,9)*. According to these investigators, early pancreatic lesions such as hyperplasia or small tumors in patients with MEN 1 *(8,9)* could be discovered even 5 yr before they could be visualized by imaging procedures. These findings, however, have not been confirmed by a more recent study *(10)*. Because of this discrepancy, we performed this study in an attempt to clarify the clinical value of this test in the early diagnosis of PETs in patients with MEN 1. Our results have clearly shown that the determination of both PP and gastrin after a standard meal is of no value in the detection of these tumors, either in the patients who were known to have these tumors or in those in whom none were detected by ultrasonography (US) and computed tomography (CT). Concerning PP, there was an increase of this hormone after the meal in all three groups of subjects studied; however, the values of PP in patients with MEN 1 did not differ significantly from those of normal subjects. Family members had postprandial values that were lower than those of the other two groups; this could be attributed to the fact that they were young subjects, because it has been shown that PP concentrations increase progressively with age *(11–13)*.

Among the 13 patients with MEN 1, none of the seven patients who had no PET by CT or US had postprandial values of PP higher than controls. Among the remaining six patients with pancreatic tumor, only two had very high values of PP (more than 500 pg/mL) after the meal.

Concerning the basal values of this peptide, five of the six patients with pancreatic tumor and three of the seven with no apparent pancreatic tumor had values higher than the highest limit of normal. In particular, these values were very high (more than 500 pg/mL) in the two who also had very high postprandial values. Thus, these results clearly show that the postprandial values of PP have no greater diagnostic value than do the basal values of the peptide.

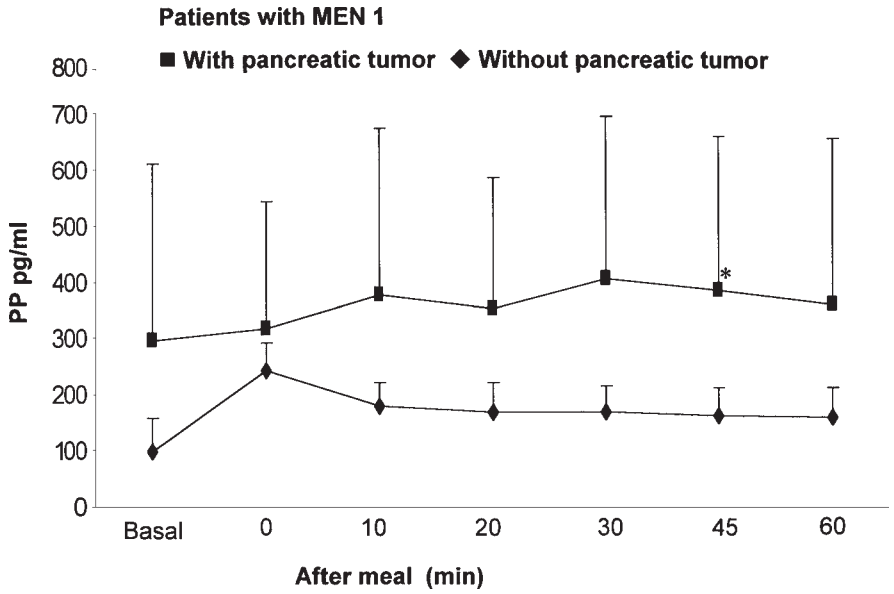


**Fig. 2**. Basal and postprandial values of plasma PP in patients with MEN 1, with pancreatic tumor and without pancreatic tumor. Means ± SD. *$p < 0.05$, compared to the corresponding value in the other groups of patients.

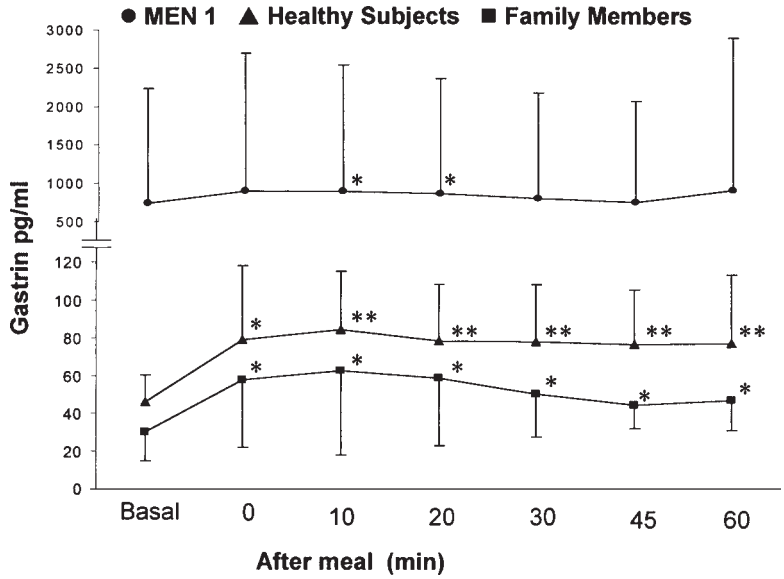


**Fig. 3.** Basal and postprandial values of serum gastrin in the three groups of subjects studied. Means ± SD. *$p < 0.05$; **$p < 0.01$, compared to basal values.

Concerning gastrin, the meal caused a slight but statistically significant increase of the peptide in control subjects and in family members, whereas in patients with MEN 1, the increase was slight and it was significant only at 10 and 20 min after the meal. Five of these latter 13 patients had MEN 1 and ZES: In these patients, postprandial values of gastrin were very high, but the basal values of gastrin were very high as well, limiting the diagnostic significance of elevated postprandial values. Markedly elevated values of serum gastrin in patients with MEN 1 and ZES have been also reported by others *(14)*.

Thus, these results do not agree with those of Skogseid et al. *(9)*, who found an exagerated response of PP and gastrin to a meal in patients with MEN 1 with and without PETs. Our results agree with those of Langer et al. *(10)*, who found no diagnostic utility for postprandial PP and gastrin values as compared with fasting values in these patients.

Our results do confirm that basal plasma PP and serum gastrin concentrations are often higher in patients with MEN 1 and PETs than in control subjects, but that the standardized meal stimulation test does not add any further useful information for the diagnosis of these tumors.

## Materials and Methods

Three groups of subjects were studied. Group 1 consisted of 13 patients with MEN 1 (8 men, 5 women; mean age =

41 yr; range = 20–56 yr). All of these patients had hyperparathyroidism, four had a pituitary tumor, and six had PETs (insulinoma in one and nonfunctioning pancreatic tumors in the remaining five). Seven did not have pancreatic tumors at ultrasonography and computed tomography. These seven patients were included in the study in order to assess whether the test is useful for early diagnosis of these tumors [i.e., even before they are detectable by imaging procedures, as suggested by Skogseid et al. *(9)*].

Group 2 consisted of seven apparently healthy family members, without clinical, biochemical, or radiological evidence of pancreatic or other tumors (two men and five women; mean age = 22 yr; range = 17–29 yr). Group 3 consisted of eight healthy subjects studied as controls (five men and three women; mean age = 48 yr; range = 31–65 yr).

The test was performed in the morning after an overnight fast. All subjects received a 563-Kcal mixed meal composed of 66 g of carbohydrates, 18 g of protein, and 22 g of fat, which was consumed in 20 min. The composition of this meal is identical to the meal used in the previous studies *(7, 8)*. Blood samples were drawn at 10 and 5 min before the meal and at 0, 10, 20, 30, 45, and 60 min after the meal. Serum and plasma were stored at –80ºC until analysis. Plasma PP was measured by radioimmunoassay (RIA) (Phoenix Pharmaceutical Inc., USA) and serum gastrin by RIA using a commercial kit. The highest normal basal value for PP is 100 pg/mL and 80 pg/mL for gastrin.

Results are expressed as mean ± SD. Statistical analysis of the data was carried out using the Mann–Whitney *U*-test and the Wilcoxon test. $p < 0.05$ was considered to indicate a statistically significant difference.

## References


1. Wermer, P. (1954). *Am. J. Med.* **16,** 363–371.
2. Ballard, H. S., Frame, B., and Hartsock, R. J. (1964). *Medicine (Baltimore)* **43,** 481–516.
3. Larsson, C., Skogseid, B., Oberg, K., Nakamura, Y., and Nordenskiold, M. (1987). *Nature* **332,** 85–87.
4. Chandrasekharappa, S. C., Guru, S. C., Manickam, P., Olufemi, S.-E., Collins, F. S., Emmert-Buck, M. R., et al. (1997). *Science* **276,** 404–406.
5. Shepherd, J. J., Challis, D. R., Davies, P. F., McArdle, J. P., Teh, B. T., and Wilkinson, S. (1993). *Arch Surg.* **128,** 1133–1142.
6. Oberg, K., Walinder, O., Bostrom, H., Lundqvist, G., and Wide, L. (1982). *Am. J. Med.* **73,** 619–630.
7. Friesen, S. R., Tomita, T., and Kimmel, J. R. (1983). *Surgery* **94,** 1028–1037.
8. Oberg, K. and Skogseid, B. (1998). *J. Intern. Med.* **243,** 471–476.
9. Skogseid, B., Oberg, K., Benson, L., et al. (1987). *J. Clin. Endocrinol. Metab.* **64,** 1233–1240.
10. Langer, P., Wild, A., Celik, I., Kopp, I., Bergenfelz, A., and Bartsch, D. K. (2001). *Br. J. Surg.* **88,** 1403–1407.
11. Floyd, J. D., Fajans, S. S., and Pek, S. (1976). *Trans. Assoc. Am. Physician* **98,** 146–158.
12. Berger, D., Crowther, C., and Floyd, J. C. Jr. (1978). *Clin. Endocrinol. Metab.* **1,** 845–848.
13. Taylor, I. L., Walsh, J. H., Rotter, J., and Passaro, E. Jr. (1978). *Lancet* **1,** 845–848.
14. Mignon, M., Jais, P. H., Cadiot, G., Yedder, B., and Vatier, J. (1995). In: Mignon, M. and Jensen, R. T. (eds.). *Endocrine tumors of the pancreas*. Frontiers of Gastrointestinal Research, Vol. 23. Karger: Basel, pp. 223–229.