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# Pancreatic polypeptide and exocrine pancreatic function in the elderly

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## SUMMARY

*The relationship between exocrine pancreatic function and plasma pancreatic polypeptide levels was studied in 14 normal elderly subjects and in ten elderly patients with exocrine pancreatic insufficiency determined by the para-amino-benzoic acid test. There was a decrease in the total pancreatic polypeptide response after a standard mixed meal in the group with pancreatic insufficiency ($t = 2 \cdot 753$, $p = 0 \cdot 01$). An increase above basal of less than 100% in plasma pancreatic polypeptide levels 30 min after a standard mixed meal is strongly associated with exocrine pancreatic insufficiency (Fisher's exact test, $p = 0 \cdot 005$).*

## INTRODUCTION

The para-aminobenzoic acid test is a standard non-invasive test for exocrine pancreatic insufficiency. Its high sensitivity and specificity in identifying cases of severe exocrine pancreatic insufficiency merit its use as a screening tool, although it is less accurate for moderate cases.[1] Elderly people have difficulty coping with this test, and a simpler, equally reliable, initial screening test for exocrine pancreatic insufficiency would be welcome.

Plasma levels of pancreatic polypeptide are related to exocrine pancreatic function in both normal and diseased states.[2-4] Pancreatic polypeptide, a 36 amino acid peptide, inhibits exocrine pancreatic secretion.[5] In healthy adults (aged 18 – 46 years) plasma pancreatic polypeptide levels following nutrient and hormonal stimulation are closely related to exocrine pancreatic function.[4] Stimulated levels of pancreatic polypeptide are reduced in exocrine pancreatic insufficiency.[3] This suggests that plasma pancreatic polypeptide measurement may be a useful screening test for exocrine pancreatic insufficiency.[6] It is not known whether such a relationship between pancreatic polypeptide secretion and exocrine pancreatic function also exists in the elderly. If it did, plasma pancreatic polypeptide levels

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after a standard mixed meal could be used as a screening test before proceeding to para-aminobenzoic acid or more invasive testing. The present study investigated the relationship between the plasma pancreatic polypeptide response to a standard mixed meal in elderly subjects with normal and abnormal para-aminobenzoic acid (PABA) tests.

## SUBJECTS AND METHODS

Fourteen elderly subjects (group 1), mean (±SE) age 74·7 ± 1·4 years with normal para-aminobenzoic acid (PABA) tests, and five asymptomatic subjects (group 2), with a para-aminobenzoic acid excretion index of less than 55% were recruited from a previous study. In that study a sample of 21 healthy subjects, over the age of 65 years and living independently in the community, were screened for evidence of pancreatic insufficiency by para-aminobenzoic acid testing. Those with significant hepatic or renal disease or a history of gastrointestinal surgery, alcohol excess or diabetes mellitus were excluded from the study.[7] Five additional subjects, aged over 60 years, with moderate to severe exocrine pancreatic insufficiency (para-aminobenzoic acid excretion index less than 55% and symptoms/signs of malabsorption) diagnosed in the previous 12 months and studied pre-treatment were also included in group 2. The mean age of the ten patients in group 2 was 68·5 ± 1·5 years.

The modified para-aminobenzoic acid test[8] consists of two stages. On day 1, after overnight fasting, N-benzoyl-l-tryosyl-para-aminobenzoic acid is given along with a standard mixed meal of 50 g of carbohydrate, 18 g of protein and 20 g of fat and the urine is collected over the next 6 hours. N-benzoyl-l-tryosl-para-aminobenzoic acid requires pancreatic chymotrypsin to liberate para-aminobenzoic acid which is then absorbed and excreted in the urine. On day 2 the procedure is repeated with para-aminobenzoic acid to exclude causes of malabsorption other than pancreatic insufficiency. The para-aminobenzoic acid excretion index is then calculated as the percentage of day 1/day 2 urinary para-aminobenzoic acid excretion, a figure of less than 55% indicating exocrine pancreatic insufficiency. To ensure that all urine was collected, a named nurse accompanied each patient throughout each 6 hour period, a single toilet was set apart for each subject and urine was collected using a urinal. Blood samples for insulin and pancreatic polypeptide levels were taken at −15, 0, 15, 30, 60, 90 and 120 min following ingestion of a standard mixed meal. The samples were centrifuged and plasma was stored at −20°C until the study had been completed. The hormones were measured by radioimmunoassay.[9]

Statistical analysis: The unpaired t-test was used to compare the area under the curve and individual results for the log transformation of pancreatic polypeptide and insulin responses over the first hour (which covers the initial rise in plasma pancreatic polypeptide) after a standard mixed meal between groups 1 and 2. (The log transformation was applied to the data as the response for pancreatic polypeptide and insulin over time was skewed). Fisher's exact test was used to examine the association between para-aminobenzoic acid testing and the percentage rise in plasma pancreatic polypeptide levels at 30 minutes after a standard mixed meal compared with basal (−15 min) plasma pancreatic polypeptide levels (a rise of less than 100% was taken as indicating abnormal exocrine pancreatic function).

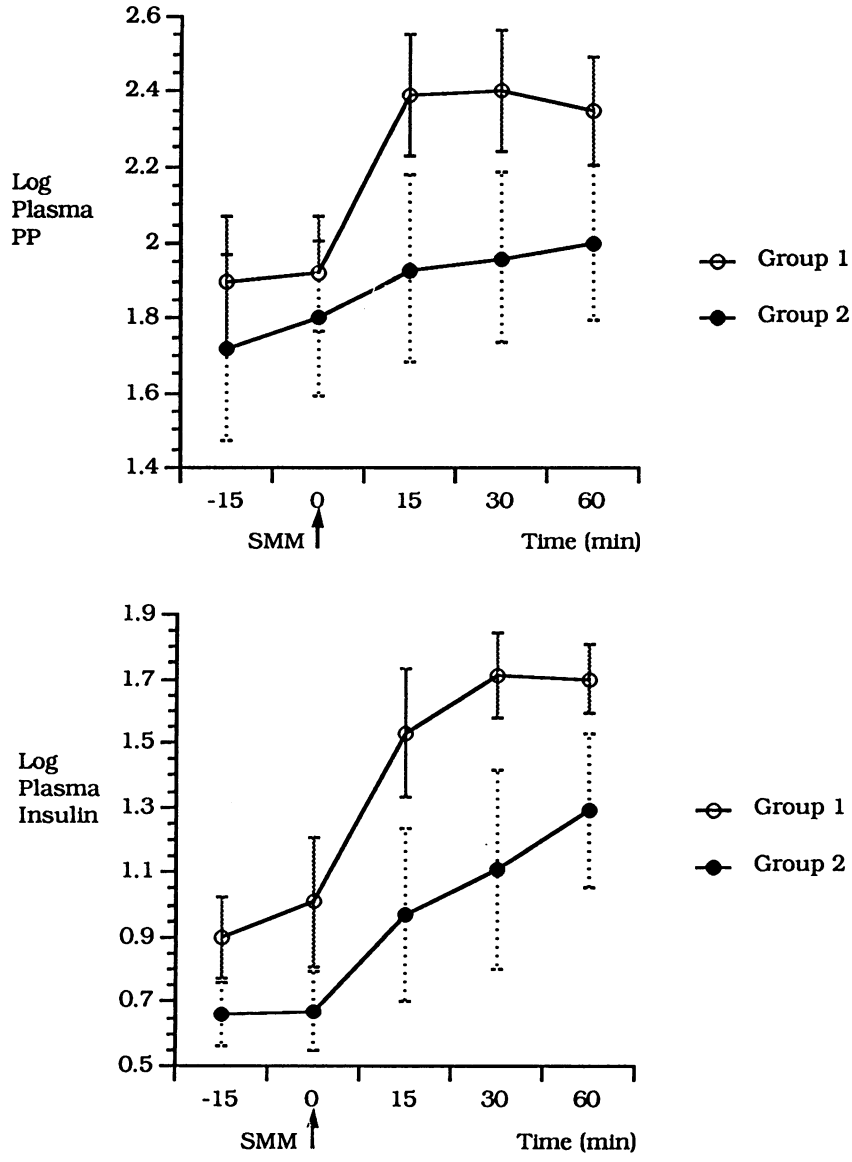


Fig 1. Log transformation, with 95% confidence limits, of plasma pancreatic polypeptide (PP) and insulin responses to a standard mixed meal (SMM) in elderly subjects with normal (group 1) and abnormal (group 2) responses to the para-aminobenzoic acid (PABA) test for exocrine pancreatic insufficiency.

## RESULTS

All subjects had a serum creatinine of $\leq$131 umol/l. Urine volumes (mean ± SE) in group 1 on day 1 and day 2 of the para-aminobenzoic acid test were 794 ± 102 ml and 1233 ± 144 ml and in group 2, 708 ± 77 ml and 988 ± 106 ml, respectively. Basal (15 minutes prior to a standard mixed meal) and stimulated (15 to 60

minutes after a standard mixed meal) plasma pancreatic polypeptide and insulin levels were compared between groups 1 and 2 (Fig 1). The basal pancreatic polypeptide levels (mean SE) were 99·9 18·5 pg/ml and 69·5 17·1 pg/ml, respectively. The total area under the curve for log pancreatic polypeptide and log insulin responses over time was significantly less in group 2 (pancreatic polypeptide $p = 0{\cdot}01$, insulin $p = 0{\cdot}007$). The log pancreatic polypeptide and log insulin levels in group 2 at 15, 30, and 60 min after the standard mixed meal were also significantly less compared with group 1.

If the 30 minute plasma pancreatic polypeptide level was less than 100% greater than fasting, the patient very probably had an abnormal para-aminobenzoic acid test (Fisher's exact test $p = 0{\cdot}005$). (Fig 2).

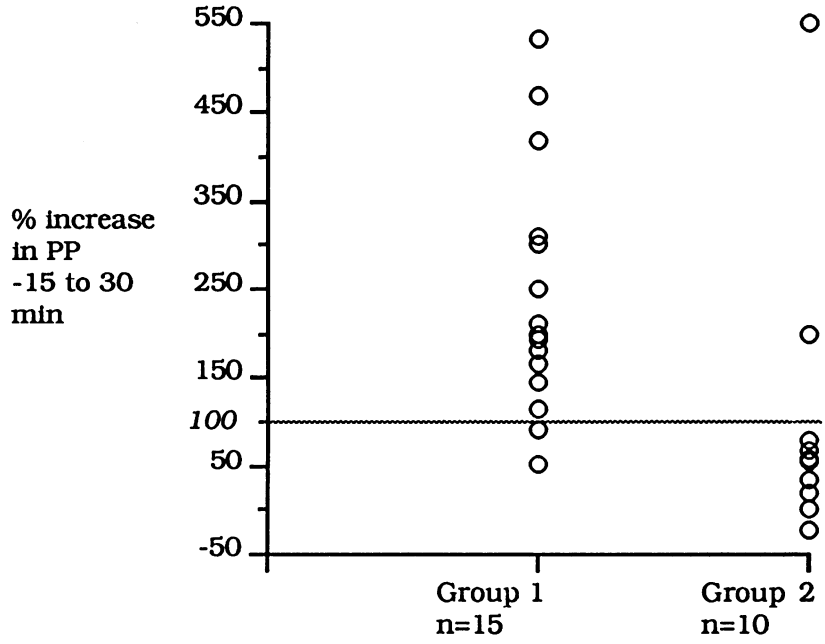


Fig 2. Rise in plasma pancreatic polypeptide (PP) from 15 minutes before to 30 minutes after a standard mixed meal in group1 (normal) and group 2 (abnormal PABA test). $p = 0{\cdot}005$, Fisher's exact test.

## DISCUSSION

Within a few minutes of ingesting food there is a rapid initial rise in plasma pancreatic polypeptide, which tails off after 30–60 minutes. This is followed by a secondary rise lasting for several hours.[10] The initial rise, closely related to exocrine pancreatic secretion, is due to vagal stimulation,[11] the secondary rise may be neurohormonal.[12] In man, pancreatic polypeptide storage cells are located mainly in the head and uncinate process of the pancreas. They are widely distributed between the exocrine acinar and the endocrine islet cells.[13] Functionally, both pancreatic polypeptide and exocrine pancreatic enzyme secretion require an intact vagal pathway.[11, 14] They can be stimulated by ingestion of food or the intravenous injection of secretin/cholecystokinin.[6, 15, 16]

In animal models of exocrine pancreatic insufficiency the reduction in exocrine pancreatic secretion in response to food is associated with a decline in pancreatic polypeptide response in the first 60 minutes and a normal secondary rise due to an intact endocrine axis.[17] In patients with moderate to severe exocrine pancreatic insufficiency reduced pancreatic enzyme output is associated with low basal levels of plasma pancreatic polypeptide and a flat or attenuated rise following a standard mixed meal or cholecystokinin infusion[2,3] related to the degree of exocrine pancreatic insufficiency.[4] In normal elderly subjects basal levels of plasma pancreatic polypeptide are elevated.[18] The cause and the significance of this elevation are unclear.

In the present study the basal plasma pancreatic polypeptide levels in group 1 and group 2 subjects were within the normal range (0–200 pg/ml). There was no significant difference in basal plasma pancreatic polypeptide levels between the two groups. In both groups there was an initial rise in plasma pancreatic polypeptide levels in response to a standard mixed meal, but the magnitude of this response over time was significantly diminished in those with exocrine pancreatic insufficiency. This may in part be due to a decrease in pancreatic exocrine secretions in the duodenum or a decrease in the number or the function of pancreatic polypeptide producing cells.[4] Along with the flattened pancreatic polypeptide response in these patients there was a lower plasma insulin response, indicating concomitant beta cell damage or malfunction.

This reduced pancreatic polypeptide response in the elderly subjects with exocrine pancreatic insufficiency agrees with studies in younger subjects.[2-4] In this study, a strong association was found between a rise in plasma pancreatic polypeptide levels at 30 min of less than 100% and the presence of exocrine pancreatic insufficiency as determined by para-aminobenzoic acid testing, which may prove to be a simpler screening test for exocrine pancreatic insufficiency in the elderly. Para-aminobenzoic acid testing cannot be used to quantify the degree of exocrine pancreatic insufficiency, but it does help to differentiate patients with moderate to severe pancreatic insufficiency from those with normal exocrine pancreatic function or only mild impairment.[1,19] A similar limitation may also apply to pancreatic polypeptide measurement for assessing exocrine pancreatic function.[4]

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