Functional Changes in the Gastrointestinal System

S. Hirsch and M.P. de la Maza

Institute of Nutrition and Food Technology (INTA), University of Chile, Santiago, Chile

Introduction

Aging is associated with a higher risk for nutritional deficiencies which cause adverse functional consequences. Functional and anatomic changes in the gastrointestinal system could explain part of the nutritional alterations observed in the elderly. However, for every study that indicates a decline in gastrointestinal tract efficiency with advancing age, there is another that argues for no age-related effect. Consequently, despite the vast number of studies conducted on this issue, there is no consensus whether healthy old individuals have a reduced capacity for nutrient assimilation.

Taste

Normal aging is associated with taste dysfunction due to significant chemosensory losses such as elevated thresholds for taste and smell, reduced intensity of suprathreshold stimuli, decreased ability to distinguish among the latter, and loss of the ability to identify odor and tastes. The most common manifestations are reduced sensitivity for sweet, sour, salty and bitter compounds as well as amino acids. Individuals usually refer dysgeusia, often complaining about bitter/metallic side tastes not associated with the food that they are eating. These changes in taste could be exacerbated in elderly individuals who take medications (fluvastatin sodium, gemfibrozil, pravastatin, ampicillin, ciprofloxacin, claritromicin, enalapril, nifedipine, propranolol, spironolactone, fluoxetine). In elderly subjects taking an average of 3.4
medicaments, the thresholds for sodium salt increased 11.6 times, for acids 4.3 times, for bitter compounds 7.0 times, for amino acids 2.5 times, for glutamate salt 5.0 times and for sweeteners 2.7 times, compared to young subjects [1].

In sick elderly subjects enhancing food flavor was able to produce an increase in caloric intake, which was associated with an improvement in plasma protein levels and T-lymphocyte count.

Other studies have observed that flavor-enhanced foods increase salivary secretory IgA 30 and 60 min after the meal ingestion, associated with a higher salivary flow [2].

Dry mouth and reduced unstimulated salivary flow is also common in the elderly due to normal aging, medication or diseases. Stimulated salivation remains unchanged in healthy elderly subjects, with or without teeth [1]. However, these subjects frequently report eating difficulties.

**Esophagus**

Advancing age has been associated with some esophageal functional changes. Age correlates inversely with upper and lower esophageal pressure, although within normal limits [3]. Aperistalsis of obscure origin was observed more frequently in aged people (26 in elderly vs. 3 in young subjects, \( p < 0.05 \)) [4]. However, these manometric changes do not seem to have clinical significance.

**Stomach**

Atrophic gastritis is common in healthy elderly people, resulting in hypochlorhydria or achlorhydria and reduced gastric secretion. Its prevalence ranges from 11 to 50\% depending on the sample and the diagnostic test used. Gastritis, which predominantly affects the antrum of the stomach (type B), is a common condition in the urban population. Krasinski *et al*. [5] found that the prevalence of atrophic gastritis was 24\% among people aged 60–69, 32\% between 70 and 79 years old and 37\% among those older than 80.

In animals and human models, basal and post-maximal gastric acid output decreases. This condition is related to an elevated incidence of *Helicobacter pylori* infection and atrophic gastritis [6]. However, other authors have reported that acid secretion increases with aging, an abnormality that could contribute to the age-related increase in the incidence of peptic ulcer in Western countries [7, 8]. To date, there is no consensus whether atrophic gastritis and the decrease in gastric acid secretion are normal processes of aging or a result of *H. pylori* infection, which is frequent among elderly people.
Independent of whether atrophic gastritis is part of the aging process or a consequence of *H. pylori* infection, it may have clinical repercussions in the elderly. The lack of gastric acid can result in bacterial overgrowth. The source of microbiological flora appears to be saliva and food (viridans streptococci, coagulase-negative staphylococci and hemophilus species) [9]. The clinical significance of this colonization in healthy elderly subjects is not clear. For example, Haboudi and Montgomery [10] found that elderly with a presumed bacterial overgrowth, on the basis of an abnormal lactulose breath test, increase their serum D-xylose levels, body weight and improve lactulose breath test after antibiotic treatment. In contrast, Saltzman et al. [9] did not demonstrate that bacterial overgrowth caused by atrophic gastritis or omeprazole is associated with gastrointestinal symptoms or clinically significant fat or carbohydrate malabsorption.

The lack of gastric acid could interfere with the optimal absorption of pH-dependent nutrients. This is the case of vitamin B₁₂ deficiency, which is associated with atrophic gastritis. The mechanism for the reduced absorption is not clear since a stomach with mild to moderate atrophic gastritis (type B) continues to secrete sufficient intrinsic factor to prevent vitamin B₁₂ malabsorption. However, protein-bound cobalamin absorption is decreased in elderly subjects with atrophic gastritis or hypochlorhydria. This situation can be reversed by the concomitant ingestion of acidic beverages or free vitamin B₁₂ administration. Nevertheless, other authors have not observed any relationship between free or bound cobalamin absorption and mild to moderate gastritis in middle-aged and older adults, although the serum cobalamin concentration is negatively correlated with age [11]. The frequency of vitamin B₁₂ deficiency again is higher in people with *H. pylori* infection. Eradication of this bacteria may correct vitamin B₁₂ levels and improve anemia in this subgroup of patients [12].

In elderly people without gastric acid secretion, the pH of the small bowel rises and oral folate absorption is reduced. Nevertheless, serum levels are normal, due to the presence of folate-synthesizing bacteria in the small intestine [13].

Atrophic gastritis with a lack of acid secretion is associated with a decreased absorption of calcium carbonate, but calcium from food or soluble sources, such as calcium citrate and calcium from milk, are absorbed normally in elderly subjects with atrophic gastritis. In addition, calcium carbonate, a relatively insoluble calcium salt, is well absorbed in patients with atrophic gastritis if administered with a meal [14].

Both atrophic gastritis and *H. pylori* infection should be considered when evaluating the gastrointestinal tract of elderly patients with iron deficiency anemia, since hydrochloric and ascorbic acid are essential for iron absorption [15].

Functional changes in the stomach have also been also described. Liquid emptying is slowed whereas antrally determined solid emptying is preserved
with aging. However, Nakae et al. [16] observed that gastric emptying of a liquid meal without lipids is similar in elderly subjects compared to young controls. However, when the beverage is enriched with lipids, elderly subjects have a longer gastric emptying time [16], associated with increased cholecystokinin concentration [17].

Evans et al. [18] found that the elderly have slower gastric emptying of mixed meals compared with young subjects. In contrast, Tougas et al. [19] reported that gastric emptying of a low fat meal is faster in older individuals. On the other hand, there are probably changes in intragastric satiety mechanisms in the elderly that could be associated with a reduction in appetite and food intake. In 5 healthy elderly subjects, Rayner et al. [20] found a decrease in the perception of gastric distension without any changes in fasting gastric compliance. There was also a reduction in gastric tone late in the postprandial period when compared with young controls [20].

Contrary reports about changes in gastric motility with aging could be attributed to the presence of atrophic gastritis or *H. pylori* infection and not to the aging process.

**Pancreas**

The pancreas undergoes a continuous aging process leading to alterations such as atrophy, fatty infiltration, fibrosis and ductal epithelial hyperplasia. The pancreatic duct diameter also tends to increase, but a diameter of > 3 mm should be regarded as a pathological finding. Ultrasonography has demonstrated an increasing echogenicity of the pancreas, beginning from the 4th decade of life. Most people over 50 years and individuals over 80 exhibit a marked echogenicity which is distinctly higher than that found in the liver [21].

Functional alterations in endocrine and exocrine pancreas have been described. The predisposition to glucose intolerance in the elderly is probably associated with a declination in β-cell function, demonstrated by disproportionately high proinsulin to C-peptide levels in older subjects [22].

Exocrine pancreatic secretion decreases in parallel to morphologic changes during the aging process in animal models but not in humans. Stimulated production of pancreatic secretion is similar in young and old persons. However, after repeated pancreatic stimulations, elderly people reduce their pancreatic enzyme output. Other studies show that the elderly have a significant reduction in bicarbonate, chymotrypsin, amylase and lipase concentrations in duodenal aspirate. Asymptomatic elderly with normal fecal fat excretion, on a diet containing 85–90 g fat/day, developed mild steatorrhea when the fat content in the diet was raised to a more unphysiological dose of 115–120 g/day. In contrast, younger volunteers did not develop steatorrhea on the higher fat diet [23]. These differences could reflect the diminished
reserve capacity for absorption, which could have clinical significance under minimal injuries.

**Liver**

Studies have shown a decrease in liver volume and portal blood flow with increasing age. The number of mitochondria in hepatocytes decreases with a compensatory increase in their volume. The decrease in perfusion of the hepatocytes may result in alterations in the clearance of many drugs that are metabolized in the liver (isoniazid, acetaminophen, alcohol, etc.). Drug metabolism by microsomal oxidation and hydrolysis (phase 1) are impaired more consistently than glucuronic acid or glutathione conjugation (phase 2) in animal models. However, human studies on drug elimination do not demonstrate alterations in phase-1 or 2 drug-metabolizing enzymes due to aging. In rats, the activity of certain cytochrome P-450 enzymes is inversely related to age. Nevertheless, changes in microsomal function, as measured by aminopyrine breath test, are not different in elderly people as compared with young controls. Other clinical assays have shown that hepatic enzymes and tests of synthetic function are not affected substantially by age [24].

These minimal age-related changes in the liver could be associated with a minor hepatic reserve to injuries such as infections, autoimmune hepatitis, obesity, drugs and alcohol.

Protein synthesis is reduced in *in vitro* systems (hepatocytes, liver slices or perfused liver), but *in vivo* the results are not convincing. Only about 0.2% of the proteins synthesized in the liver have been shown to either increase or decrease with advancing age [24]. Fu et al. [25] have demonstrated that fibrinogen fractional synthesis but not absolute synthesis is age-related, while albumin synthesis remains unchanged. The albumin and fibrinogen synthesis response to feeding is similar in young and elderly subjects. Protein degradation in the liver is apparently not age-related [25].

Cholesterol metabolism in the liver does not change with increasing age. The rise in the plasma LDL concentration during adult life in Western populations is not an inevitable consequence of aging, but rather is probably related to environmental factors such as inactivity, weight gain, and long-term ingestion of a diet rich in calories, cholesterol and saturated fat [26].

**Gallbladder and Biliary Tract**

The sensitivity of the gallbladder to cholecystokinin stimulation may decrease in older people. Fasting and a stimulated concentration of cholecystokinin in plasma seem to be higher in older individuals than in younger
volunteers. However, gallbladder volumes both during fasting and after stimulation and the rate of gallbladder emptying were equal, while elderly people showed an earlier initiation of contraction [27].

**Small Intestine**

There is a consensus that intestinal anatomy does not change as a result of aging. Enterocyte height and intraepithelial lymphocyte counts are unchanged. However, some clinically and functionally insignificant changes have been described which could decrease the adaptive reserve to face minimal injuries [28]. Studies in dogs have not demonstrated age-related alterations in digestibility and absorption of macronutrients. In contrast, old cats decrease their ability to digest fat efficiently due to a reduction in the activity of pancreatic lipase, transport and secretion of bile acid [29]. In humans evaluation of D-xylose absorption through blood tests is not age-related, but urine excretion is lower in the elderly because renal function declines [30]. Weiner et al. [31], using the D-xylose test, observed that the absorption process is normal, but takes place at a slower rate.

Some evidence indicates that there is a reduction in the concentration of brush border enzymes in aging rats, but at levels that are probably not physiologically important. In rats, total intestinal lactase, sucrase and maltase activity decline with age, although most studies in humans indicate that aging is not significantly correlated with a decline in disaccharidase activity [32]. Nevertheless there is some evidence showing that apparently healthy elderly subjects have lower sucrase and maltase activity compared with young adults. Feibusch and Holt [33] observed abnormal breath hydrogen excretion in more than 60% of elderly subjects after ingestion of a 200-gram carbohydrate meal. It is unclear whether these results are a consequence of increased bacterial metabolism of carbohydrate as a result of bacterial overgrowth or enzymatic deficiency [33].

Lactase deficiency is highly prevalent among adults and the elderly. Lactase activity in humans is more related to the phenotype than to age. Caucasians from western Europe have a persistently high lactase activity, while Asian, Hispanic and African American populations exhibit adult-onset lactase deficiency [32].

Intestinal permeability to macromolecules measured by the lactulose/mannitol absorption does not change with increasing age. However, there is a parallel decline in the percentage of urine lactulose and mannitol excretion which is probably attributable to a decline in renal function with advancing age [34].

The effect of aging on zinc absorption remains unclear. Several studies have shown that the absorption of zinc is lower and its excretion is diminished in elderly subjects when a zinc tolerance test or a stable isotope-labeled diet is
used. Nevertheless zinc balance does not differ between elderly and young subjects on the same diets [35]. In contrast, Couzy et al. [36] found that the either high or low ability to absorb zinc from a test meal shows little or no change in healthy elderly compared with young adults of a very similar zinc and global nutritional status.

Intestinal calcium malabsorption in the elderly is predominantly due to vitamin D deficiency. Renal impairment is also common and contributes to calcium malabsorption by increasing the requirements for vitamin D [37]. The intestinal responsiveness to activated vitamin D decreases due to a drop in the concentration of vitamin D receptors in the small bowel [38].

Vitamin A intestinal absorption and retinol intestinal esterification processes are not markedly modified in the elderly, whereas chylomicron clearance and regulation of the postprandial plasma retinol concentration is increased in old subjects [39]. In addition, Krasinski et al. [40] found that long-term vitamin A supplementation in elderly subjects induced higher fasting plasma retinyl esters, which are associated with an increased risk of vitamin A overload and its consequences.

Various indexes of vitamin B₆ status have been shown to be reduced with aging. The cause for the apparently reduced vitamin B₆ status is not well understood. Indices of absorption, phosphorylation, and excretion are not affected by age [41].

**Colon**

Aging is associated with changes in the structure and function of the colon and in continence and defecatory mechanisms. There is a progressive alteration in the mechanical properties of the colonic wall. During aging, collagens, which form a submucosal network of fibrils, become smaller and more tightly packed in the left colon, and these changes are further accentuated in diverticulosis.

Motor dysfunction in the aging colon is frequent. There are age-related changes in the function of smooth muscle, excitatory neurons and inhibitory neurons in animals. In rats, colonic transit decreases by 45% in senescent compared with young rats. Several lines of evidence suggest that older colonic muscle cells respond less to acetylcholine stimuli and electrical field stimulation than do cells from younger animals. In animals and humans, aging is associated with a reduced number of neurons in the ganglia of the myenteric plexus. Studies using radiopaque markers have found a significant increase in colonic transit time with aging, while others have not detected differences in colonic transit time between young and old people. However, it is not clear whether the cause of delayed colonic transit in older adults reflects a primary colonic motility problem or is the result of inadequate rectal evacuation. In general, it is currently thought that colonic motility is largely unaffected by healthy aging and that prolonged transit time in older people
with constipation, reflects factors associated with aging, such as comorbidity, immobilization or medications, rather than aging per se [42].

Conclusions

The elderly may be more prone to nutritional deficiencies which cause significant functionally deleterious consequences. Apart from adverse environmental conditions, the digestive system has been blamed for most of these alterations. However, to date, the mild functional and anatomic age-related changes do not seem to account for malnutrition in healthy elderly subjects, but rather explain a lower functional reserve which, under pathological challenge, brings about nutritional deterioration.

In addition, several age-related diseases and multiple medication intake are the most relevant factors involved in the gastrointestinal dysfunction of elderly subjects, finally leading to malnutrition.

References

Functional Changes in the Gastrointestinal System


Functional Changes in the Gastrointestinal System


**Discussion**

*Dr. Roubenoff:* Is there any evidence that people with less gastric acid secretion eat less protein?

*Dr. Hirsch:* I know of no evidence for that.

*Dr. Meydani:* This is a comment, not a question. We have evidence that the function of intraepithelial lymphocytes decreases with age as far as their ability to proliferate and produce interleukin-2 is concerned. So there do seem to be changes with age in the function of the gut-associated immune system.

*Dr. Jensen:* In the USA, practitioners are leaving patients on proton pump inhibitors for indefinite periods. It is not short-term therapy any more. I think it is very likely that we will see both subclinical and clinical B12 deficiency.

*Dr. Hirsch:* We don’t see clinical B12 deficiency, but when we measure plasma levels we see a lot of subclinical B12 deficiency.

*Dr. Burckhardt:* You gave a possible explanation for food preferences related to the prolonged gastric emptying time for lipids. Do you have any explanation for the low tolerance for meat?

*Dr. Hirsch:* I think that it could be related to reduced perception of the taste of the amino acids. When you enhance the flavor old people readily eat meat.

*Dr. Rosenberg:* What are the age-related changes in saliva secretion? They could affect taste sensitivity as well as some of the preliminary stages of digestion.

*Dr. Hirsch:* There is evidence that salivary flow is reduced in old people, but when you enhance the flavor of their meals the flow increases. There are also many systemic diseases that affect salivary flow that are more common in elderly people.

*Dr. Morley:* I think the changes in gastric emptying with age are somewhat controversial. We have looked at that in some detail, and it appears that if you have small gastric volumes, gastric emptying is unchanged. The study you quoted which found a change in liquid emptying is, I think, the only one that shows that; most others have not found any change in liquid emptying, but as the total amount of energy in the meal or its volume is increased, there tends to be increasing delay in gastric emptying. You can almost divide the studies in half by those that give less
than 500 kcal as a solid meal versus those giving more than 500 kcal. We have also published very preliminary data in the *Scandinavian Journal of Gastroenterology* suggesting a change in the compliance of the fundus, which would inhibit the amount a person could eat in a single meal. I think this is an area that requires a lot more work. This should involve examining the effects of aging on the stressed stomach, which is extremely important—as you know, without stress everything often functions normally, but when you put big volumes in you start to see changes. This would fit with the satiating data and with the CCK data, because with the CCK feedback you would expect to see some decline in gastric emptying, at least for lipids. Again, often the meals given in those studies have not contained adequate amounts of lipid to stress the stomach. As to salivary flow, the dentists have studied this in detail, and in healthy animals there is certainly no change in salivary flow with age. I thought that was the same in humans, except when you develop xerostomia, or alternatively when you are on a drug that alters salivary flow. Changes in salivary flow are important because a lot of people measure hormones in the saliva; when flow is reduced by drug treatment or disease, you run into major troubles with the ability to measure those hormones.

**Dr. Rosenberg:** My understanding is that where there have been reports of a decrease in salivary flow it had to do with the use of drugs or concurrent illness. I was not aware of any good studies that looked at age-dependent changes, but what both of you seem to be saying is that such changes are minor if they occur at all.

**Dr. Morley:** Certainly that is true in healthy animals, which was probably the best study I've seen.

**Dr. Hirsch:** The most important factor in delayed gastric emptying is atrophic gastritis, though we are currently uncertain how much of the problem is due to atrophic gastritis and how much to *Helicobacter pylori* infection. If healthy elderly people have poor gastric emptying and eat too little because of that, then they should become malnourished, but our healthy elderly population appears to be well nourished. They have no overt nutritional problems except for their low vitamin B12 levels and they do not appear to eat less.

**Dr. Morley:** But they do eat less. There are many studies in healthy elderly people showing that food intake is lower in 70+ year olds than in 20–40 year olds. Apart from Roberts’ studies which you quoted, there are several other studies showing this, including some we have done in Australia. So I think there is no question that there is physiological anorexia. In relation to gastritis, in our studies on gastric emptying we took care to exclude people with atrophic gastritis.

**Dr. Hirsch:** Food intake does not seem to decline in our population of healthy elderly people and we've been following them for over 2 years now.

**Dr. Morley:** There may of course be cultural differences in food intake. When de Castro and others looked at different populations, they found big differences in food intake and in the times of day when food was taken. French people are always very different from the rest of the world, and the Spanish too, I am sure, would also be somewhat different, but in the countries whose populations are of northern European origin, which include Australia, food intake declines with age. There are too many careful studies confirming this now to say that it does not happen.

**Dr. Hirsch:** It could be that food intake declines but not because of problems with gastric emptying. There are many other reasons for a decline. I do not accept that delay in gastric emptying is the cause of decreased food intake in healthy elderly people.

**Dr. Morley:** I will accept that you may be right, but that would mean half of my life's work is wrong!

**Dr. Bunout:** I also want to address the issue of decreasing food intake in the elderly. It is very intriguing why every study done on elderly people appears to show that they have a decrease in food intake, but when you try to correlate that with changes in BMI
or other nutritional parameters you find nothing. So we come back to the question: are these tests reliable or is it just that elderly people forget what they have eaten? We are less and less impressed by dietary surveys in elderly people. In fact we don’t do them now because we don’t believe in them.

Dr. Meydani: My question is addressed to Dr. Morley. Could the cultural differences you referred to, which might affect whether there is a decrease in food intake or not, have to do with the fact that in some cultures elderly people eat with the rest of the family while in others they are more likely to be living alone?

Dr. Morley: I agree that eating together could be relevant, but these studies have also been done in a laboratory with healthy people, and when you measure the food intake carefully under those circumstances young people always eat more than older people. When you obtain your data from dietary diaries you certainly get different results at different times. I think that is likely to be related to the ability of people to report their dietary intake, and different populations will report it very differently.

Dr. Hirsch: But remember also that elderly people take a lot of drugs, and medication is also related to food intake. I believe that reduced food intake in elderly people is primarily related to systemic disease or drug treatment affecting gastrointestinal function.

Dr. Morley: These studies have been done without medication. We are extremely careful to ensure that the participants are healthy – they are certainly much healthier than I am at this stage of my life!

Dr. Roberts: I think the only way you can really address such arguments is to do doubly-labeled water experiments, because there are cultural differences in how accurately people report food intake and there may be age-related differences. You have to have a really independent measurement. Isotopes for doing doubly-labeled water studies will soon be available again in plentiful quantities.

Dr. Jensen: Another issue here is what you relate the results to. Food intake is normalized to what? Expressed how? Relative to body cell mass? Relative to daily energy expenditure, including expenditure on physical activity? This is a highly problematic question, and how you express those figures when you talk about ‘anorexia of aging’ or declining energy intakes is very important.

Dr. Planas: I have a practical question. If you assume that there may be a reduction in gastric emptying in elderly patients, then what quantity of liquid in the stomach indicates gastric retention if you are treating a patient with enteral nutrition?

Dr. Hirsch: Our old patients receiving enteral nutrition have duodenal or jejunal intubation. We don’t use nasogastric feeding. These patients usually have other problems, commonly neurological or diabetic, and they have reduced gastric motility. We use prokinetics and a very low flow rate when we give enteral nutrition in such patients.

Dr. Filho: What is the nutritional benefit of treating H. pylori in asymptomatic elderly people?

Dr. Hirsch: There are studies showing that vitamin B12 deficiency is reversed when you treat H. pylori infection, and gastric acid secretion normalizes [1], which is good for the intestine. Gastric motility also improves [2], so there may be overall gains in digestive function.

References
