

Conference on ‘Malnutrition matters’ Nutrition Society Symposium: Muscle wasting with age: a new challenge in nutritional care; part 1 – the underlying factor

Ageing and the gut

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The goal of this brief review is to address the role of the ageing gut in the genesis of malnutrition in the elderly. We assess the burden of malnutrition in the elderly, exploring the role of comorbid conditions and neurohumoral changes that take place to contribute towards the process of anorexia associated with ageing. Following this, the review assesses physiological changes that occur in each part of the gastrointestinal (GI) tract and what implication they may have in clinical practice. In the oropharynx and the oesophagus, changes in swallowing and oesophageal motility associated with ageing can be demonstrated using physiological testing. However, in the absence of comorbid disease, they often have little, if any, clinical significance. In the stomach, reduced fundal compliance may contribute to early satiety; however, the primary change is hypochlorhydria, which may predispose to malabsorption or bacterial overgrowth further along the GI tract. Almost uniquely, the small bowel, particularly its absorptive function, is unaffected by age and we review the literature demonstrating this. In the colon, there is evidence of a prolonged transit time related to a reduction in both neurotransmitters and receptors. Although this may cause symptoms, this aspect is unlikely to contribute to malnutrition. In addition, we assess the potential changes in the gut microbiome and how this may interact with the immune system in the process of ‘inflamm-ageing’. We conclude by summarising the main changes and their impact for the clinician along with recommendations for future areas of research.

Ageing: Gastrointestinal tract: Nutrition in ageing

The process of ageing involves complex physiological changes that are not fully understood but are thought to come about because of accumulated lifelong molecular, tissue and organ damage. It is clear, however, that the proportion of the population defined as old or elderly by the WHO is continuing to increase. According to the United Kingdom Office of National Statistics, the average life expectancy is now 78 years for males, 82 years for females and the percentage of persons aged over 75 years has increased by 8% from 2000 to 2009. Furthermore, it is anticipated that, by 2050, the size of the population aged over 65 years will double in size.

Understanding the normal physiological process of ageing within the gut will assist in managing the clinical and nutritional needs of an ageing population and should be a key strategic focus for research. This review article attempts to address physiological changes within the gastrointestinal (GI) tract that occur with ageing. It is also intended to assist the clinician in delineating pathology from the normal ageing process. We will review the problem of malnutrition and anorexia related to ageing along with the physiological changes which occur throughout the different sections of the GI tract. Finally, we will briefly assess the changes to the

Abbreviation: GI, gastrointestinal.

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immune system within the GI tract and the changes to the microbiome.

Malnutrition in the elderly

Malnutrition in the ageing population is one of the most commonly implicated factors in decline in independence, well-being and health. Malnutrition costs £7.3 billion per year, it affects 10% of the population over the age of 65 years and over half of the cost is in this age group⁽¹⁾. Furthermore, the elderly population is less likely and less able to recover from malnutrition, as demonstrated in a study of older men *v.* younger men. After a few weeks of a hypoenergetic diet, both elderly and young subjects lost weight; however, the elderly were unable to regain that weight and lacked the compensatory hyperphagia observed in young adults⁽²⁾. Malnutrition in the elderly is often multifactorial and related to social circumstances, the morbidity associated with chronic disease and poly-pharmacy. The majority of factors contributing to malnutrition in this age group, therefore, occur before nutrition reaches the gut for the complex process of digestion and absorption. There are, however, physiological changes within the ageing process that can contribute to this malnutrition which, when present, may need to be addressed along with social aspects to correct malnutrition.

Anorexia of ageing

The majority of causes of malnutrition in the elderly are related to problems that occur before the food even reaches the gut to undergo the process of digestion and absorption. Reduced energy intake in the healthy elderly and physiological changes that lead to anorexia in ageing have been described in the literature for over 20 years. The process of anorexia of ageing involves multiple small changes in taste and smell, gastric fundal compliance, GI and adipose-derived (adipokine) hormone secretion and altered autonomic nervous system feedback. All these factors contribute to a reduction in intake⁽³⁾.

During ageing, olfactory function declines, including the ability to discriminate between smells. Much of the overall flavour sensation of food is produced by food stimulating the retronasal olfactory receptors. Therefore, what is often labelled as a loss of taste is, in fact, due to decline in olfactory receptors^(3,4). Fukunaga *et al.*⁽⁵⁾ demonstrated significant age-associated deterioration in taste discrimination between sweet, salty, sour and bitter but not somatic sensations. This loss of smell and associated taste leads to a reduction in the amount of food ingested owing to loss of enjoyment and a reduction in variety choice. Both of these increase the risk of quantitative malnutrition due to hypoenergetic intake and qualitative malnutrition related to a monotonous diet and low intake of single nutrients⁽⁶⁾.

Gastric distension is known to play a key role in appetite and satiety response⁽⁷⁾. The ageing process is thought to reduce gastric compliance particularly of the fundus leading to earlier arrival of food at the antrum with earlier antral stretch and early satiety. Furthermore, there may be an element of hypersensitivity of the antrum in the elderly

as Di Francesco *et al.*⁽⁸⁾ demonstrated prolonged satiety post-prandially related to a relatively small antral volume.

Neuroendocrine changes also contribute to the process of ageing-associated anorexia. The orexigenic factors, neuropeptide Y and agouti-related peptide, are produced by neurons in the nucleus arcuatus. The axons release these neuropeptides into the paraventricular nucleus and are some of the most potent hunger stimulants⁽⁹⁾. However, many of these orexigenic peptides exhibit their effects via NO which has been shown to decline during ageing^(10,11).

Cholecystokinin is a potent anorexigenic hormone. It is secreted by duodenal enteroendocrine cells in response to the presence of duodenal fat. Studies have demonstrated an increased cholecystokinin release in response to fat that is associated with ageing⁽¹²⁾.

Leptin is principally produced from adipocytes, but is also produced in the stomach. It produces potent satiety, although body fat percentage can decrease with ageing and chronic disease, leptin levels have been shown to increase particularly in men. This is thought to be related to a decrease in testosterone⁽³⁾.

Although the majority of anorexia in the elderly is related to comorbid disease and illness, there are subtle changes in the mechanisms of appetite and satiety that can further contribute to the loss of appetite associated with age. Although these physiological changes may exert a clinical effect in reducing intake and contributing to malnutrition, none, as yet, have proved useful as a therapeutic target.

Oropharyngeal and oesophageal motility

In 1964, a study by Soergel *et al.*⁽¹³⁾ coined the term 'presbyoesophagus' to describe the physiological changes of reduced peristaltic velocity and efficiency of oesophageal contractions with age, thus suggesting that dysphagia and reflux were consequences of the normal ageing process. However, the small study numbers and co-existing disease in the patients studied make it difficult to extrapolate these findings to the wider population.

Studies have demonstrated changes with oropharyngeal and oesophageal motility which are commonly associated with ageing, but in the absence of disease, they seem to have little clinical significance. In the oropharyngeal phase, there is a reduction in tongue propulsion and increased pooling in the valleculae, but this is probably in part compensated for by relaxation of the upper oesophageal sphincter and well-preserved pharyngeal peristalsis leading to minimal clinical change in swallow function^(14,15). Furthermore, it has been demonstrated that in the healthy elderly, there is well-preserved timing of glottal closure protecting against aspiration⁽¹⁶⁾. However, neurological disease in the elderly frequently affects swallowing, and should be actively sought before attributing related issues merely to ageing.

In the oesophageal body, there is a reduction in the amplitude of peristaltic contractions and a reduction in the lower oesophageal sphincter pressure. There is, however, no conclusive evidence that these changes have any clinical correlation to symptoms or disease⁽¹⁷⁾.

Changes in swallowing and oesophageal motility associated with ageing can be demonstrated using physiological and functional testing. However, in the absence of comorbid disease, they have little, if any, clinical significance. More importantly, we recommend all patients with dysphagia or aspiration be thoroughly investigated to ascertain an underlying cause rather than attributing the change solely to ageing.

Stomach

Alterations in fundal compliance, the role of antral distension and delayed emptying have already been discussed with regard to their role in the anorexia of ageing. In addition, these may predispose to reflux via delayed emptying, particularly if cholecystokinin secretion is enhanced. Other changes in gastric motility are usually secondary to disease process such as diabetes mellitus, neurological or connective tissue disease rather than a consequence *per se*.

Changes to acid secretion are, however, particularly common in relation to ageing. Hypochlorhydria is the most frequent change and at its highest prevalence in those previously or currently affected by *Helicobacter pylori*. The process of hypochlorhydria can predispose to Fe malabsorption, small bowel bacterial overgrowth and vitamin B₁₂ deficiency if associated with autoimmune atrophic gastritis and loss of the parietal cells which also secrete intrinsic factor.

Overall, reduced fundal compliance may contribute to early satiety, and hypochlorhydria can impact on the development of other conditions which can contribute to malabsorption and subsequent malnutrition.

Small bowel

Perhaps uniquely, there is little evidence to show any structural or functional change in the small bowel mucosa attributable to the normal healthy ageing process. Studies of small bowel biopsies from healthy elderly volunteers and from mice models have demonstrated no correlation between age and areas of duodenal surface epithelium, crypts and lamina propria, height of villi and surface epithelium, depths of crypts, crypt to villus ratio, the number of intraepithelial lymphocytes, duodenal architecture, enterocytes or brush borders^(18–20).

The maintenance of a tight barrier and low intestinal permeability plays an important role in preventing pathogenesis, although the paracellular route also plays a limited role in nutrient absorption. Some small studies have demonstrated no significant change to the permeability of lactose and mannitol associated with ageing^(21–23). Further studies are needed to explore changes in intestinal permeability with ageing as these are likely to affect how the mucous membrane interacts with the luminal contents including the small- and large-intestinal microbiome to cause disease or inflammation.

There is little conclusive evidence to support malabsorption related to ageing. Morley hypothesises multiple small, but probably clinically insignificant, changes in

Table 1. Changes in intestinal absorption with ageing

Reduced	No change	Increased
Carbohydrate	Thiamine	Cholesterol
Protein	Riboflavin	Vitamin A
TAG	Niacin	Vitamin C
Folate	Vitamin K	
Vitamin B ₁₂	Zn	
Vitamin D	Mg	
Ca	Fe	

small intestinal nutrient absorption as demonstrated in Table 1⁽³⁾. Fat malabsorption is a key indicator of gut dysfunction, but despite demonstrable reductions in bile acid levels in human subjects related to ageing, there are no changes in the faecal fat excretion⁽²⁴⁾. This is not surprising, however, since cholecystectomy and idiopathic bile acid malabsorption, for example, are not causes of steatorrhoea despite clear depletion of the bile salt pool.

Amino-acid absorption, for example, tyrosine, arginine and aspartic acid, has been shown to decline in ageing rodents, but no studies have corroborated this in human subjects⁽²⁵⁾. Furthermore, there is no evidence to support significant changes in the brush border enzymes or small intestinal motility without the presence of concurrent disease^(26,27). As a result, there are no clinically significant changes in small intestinal function attributable to ageing.

In the absence of comorbid disease, there is currently no evidence within the literature to support any significant alteration in small bowel function associated with ageing. Therefore, in patients presenting with clinical features suggestive of small bowel malabsorption, active investigation for underlying pathology is indicated.

Colon

Colonic transit time appears to increase with age due to a decline in propulsive activity in the colon⁽²⁸⁾. This is hypothesised to be related to a reduction in colonic enteric neurons which begins early in life alongside a diminution in the expression of neural transmitters including NO. As a result, there is less neurotransmitter and fewer neurons to respond to signals leading to a reduction in the peristaltic ability of the colon^(29,30). Other neurotransmitters implicated have included acetylcholine. Roberts *et al.*⁽³¹⁾ demonstrated up to a 50% reduction in acetylcholine release in response to electrical stimuli in rat models. Further studies in progeric mice created by depletion of the anti-ageing peptide, Klotho, have demonstrated reduced myocontractile proteins within the colonic wall, suggesting a possible cause for increased transit time⁽³²⁾. In all, these changes appear to increase colonic transit time allowing increased water absorption and making individuals more prone to constipation. However, the colon plays little role in nutrition beyond salvage of fibre-derived energies via bacterial fermentation. Indeed, slowed transit may enhance this salvage capacity via increased dwell time, although the increased complaints of wind and flatulence in the elderly may be a parallel consequence.

In summary, the main change within the colon is an increased transit time related to a reduction in both neurotransmitters and receptors. Although this may cause symptoms of constipation and flatulence, it is unlikely to affect an individual's nutritional status.

Gut microbiome

The GI tract has two conflicting roles. It must efficiently handle digestion and absorption while maintaining its barrier function to keep pathogens and toxins excluded in the lumen. The GI tract is not a sterile organ with the number of colony-forming units present increasing from mouth to anus from 10^1 to 10^2 colony-forming units in the stomach and upper small bowel to 10^7 colony-forming units in the distal small bowel and 10^{12} colony-forming units in the colon⁽³³⁾. The gut microbiome is key to maintaining the natural barrier against pathogens and facilitating absorption. However, changes to the microbiome associated with ageing could trigger the host immune response and precipitate a luminal and systemic inflammatory response. This initiation of an inflammatory response may be a key feature in the initiation of pathogenesis.

The data surrounding alterations to the microbiome with ageing are conflicting. One recent study, investigating the microbiome across the ages, found no significant changes between the young and a population of 70 year olds⁽³⁴⁾. However, when investigating centenarians, they found a change in the microbiome with a rearrangement in the Firmicutes population and enrichment in facultative anaerobes, notably pathobionts. These changes appeared to lead to a host inflammatory response and a process coined 'inflamm-ageing'⁽³⁴⁾.

Changes in the gut microbiome with ageing still require further investigation. The role alterations in the microbiome may play in contributing to onset of disease, or in disease activity, is yet to be defined. Although this may be demonstrated in future, there are no commercially available tools to investigate changes to the microbiome in a clinical setting or any evidence that the use of probiotics in ageing alter disease activity or onset.

Immune response and the gut

Ageing is associated with a natural decline in both innate and adaptive immunity attributable to both a decline in T-cell function and numbers alongside reductions in Ig diversity and B-cell numbers. There is, however, little known about the process of immunosenescence in the human gut. Animal and human studies, to date, present conflicting evidence; some studies report age-related decline in mucosal IgA while others have demonstrated that it is well maintained. Natural killer T-cells appear increased in ageing gut mucosa, but conflicting studies have reported reduction in chemotaxis and phagocytosis^(35–37).

The interaction between the immune system and the alteration in the microbiome with ageing may have a key role in both systemic and luminal inflammation and disease

pathogenesis. What is clear is that further work is needed to explore this interaction in both human and experimental models to better understand the changes associated with ageing.

Conclusion

The natural healthy ageing process produces many small changes in gut function that can give rise to functional symptoms. These include alterations in motility of the oesophagus gastric antrum and colon. Although reduced antral and fundal compliance lead to potential symptoms including early satiety or inability to undertake compensatory hyperphagia after a period of malnutrition, it is unlikely to be the sole cause of disease. Flatulence and constipation associated with reduced colonic motility and the associated increased fermentation may be a cause for symptomatic complaint, but again is unlikely to be a cause for malnutrition or red flag colonic symptoms. However, more importantly, some of the small changes associated with ageing can predispose to pathological states. The hypochlorhydria, which can occur with ageing, increases the likelihood of *H. pylori*-associated atrophic gastritis, vitamin B₁₂ deficiency, small bowel bacterial overgrowth and Fe malabsorption. However, in the presence of Fe deficiency, we would still recommend investigating in line with present guidelines rather than attributing the change to ageing.

The small bowel is the primary site for nutrient absorption and there is no change in small bowel absorption or physiology reinforcing that, although there are physiological changes of the gut associated with ageing in the absence of any comorbid disease, these are unlikely to affect nutritional status.

There are still large gaps in knowledge related to ageing and the gut particularly in relation to the microbiome, the immune system and the role these may play in either disease onset or disease activity. As our ageing population increases, more research studies may help us to better understand and manipulate the gut to support nutrition and controlling symptoms and disease.

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