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World J Gastroenterol 2006 December 21; 12(47): 7578-7584
World Journal of Gastroenterology ISSN 1007-9327

EDITORIAL

Aging and the intestine

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Received: 2006-07-19 Accepted: 2006-11-04

Abstract

Over the lifetime of the animal, there are many changes in the function of the body's organ systems. In the gastrointestinal tract there is a general modest decline in the function of the esophagus, stomach, colon, pancreas and liver. In the small intestine, there may be subtle alterations in the intestinal morphology, as well as a decline in the uptake of fatty acids and sugars. The malabsorption may be partially reversed by aging glucagon-like peptide 2 (GLP2) or dexamethasone. Modifications in the type of lipids in the diet will influence the intestinal absorption of nutrients: for example, in mature rats a diet enriched with saturated as compared with polysaturated fatty acids will enhance lipid and sugar uptake, whereas in older animals the opposite effect is observed. Thus, the results of studies of the intestinal adaptation performed in mature rats does not necessarily apply in older animals. The age-associated malabsorption of nutrients that occurs with aging may be one of the several factors which contribute to the malnutrition that occurs with aging.

Key words: Aging; Gastrointestinal tract; Intestine; Absorption; Malnutrition

Drozdowski L, Thomson ABR. Aging and the intestine. *World J Gastroenterol* 2006; 12(47): 7578-7584

http://www.wjgnet.com/1007-9327/12/7578.asp

INTRODUCTION

Although each and every one of us is familiar with inevitable age-related changes, the task of clearly defining the term is challenging. Aging is a multi-factorial process which includes both intrinsic and extrinsic factors. To further complicate matters, in humans the term can be considered from sociological, physiological, psychological and molecular perspectives.

While we tend to use the term "ontogeny" to describe development in early life, and "aging" to describe development or sometimes presumed degeneration in later life, it is likely that the better concept is that of development over the lifetime of the animal. Thus, "young" and "old" become descriptive terms describing a process over time. Aging then may be considered to be a continuum that begins at conception and proceeds until death. The definition of aging can be further refined as "chronological age" according to the passage of time. Although advancing age is associated with increases in morbidity and mortality in general, this approach fails to consider the health of the individual. Determining a specific age at which an individual becomes "old" is arbitrary, and the concept of aging has changed over the centuries with humans now experiencing increased longevity and quality of life.

"Biological age" reflects the presence or absence of disease. Because there is not always a direct relationship between age and disease, this definition is considered to be a better marker of health status. The term "functional aging" has also been used to emphasize the limitations of defining health based on chronological age. This definition characterizes people based on what they can do in relation to others in society, but may also be used to characterize the level of functioning of organs and systems in the elderly. Finally, the concept of "successful aging" takes this idea one step further, and suggests that the aging process is variable, and may be characterized as a balance between gains and losses[1]. The compression of morbidity and an enhanced quality of life are cornerstones of the concept of successful aging.

THEORIES OF AGING

A number of theories have been proposed to describe the process of aging. Longevity genes have been identified in many species, suggesting that aging may be at least partially under genetic control. In yeast, overproduction of the enzyme Sir2 prolongs the life of yeast grown under normal nutrient conditions[2]. It has been suggested that increases in Sir2 (seen in response to caloric restriction or resveratrol, a polyphenol found in red wine) may increase gene silencing, and thereby result in greater genomic stability[2]. Research undertaken in Drosophila has identified single gene mutations that extend life span. These include the gene Methuselah (*mth*), a secretion-type receptor that provides resistance to stress[3], and *Indy*

(I'm Not Dead Yet), whose gene product is homologous to Kreb's cycle intermediates[4,5]. In humans, a genetic component to aging has also been suggested. Werner's syndrome, a disorder characterized by an apparent accelerated senescence, has been associated with a single gene locus on chromosome 8[6]. On the other hand, a genome wide scan of elderly subjects suggested that there is a locus on chromosome 4 which influences a person's genetic susceptibility to age well and to achieve exceptional longevity[7].

Cellular theories emphasize that the environment as well as intrinsic properties of the cell, often referred to as a "cellular clock", may limit survival. Pivitol research by Hayflick and Moorhead[8] found that normal human fetal cell strains were limited to 40-60 doublings before they entered senescence. From this finding, they developed the concept of the "Hayflick limit" to explain determination of longevity. From this early work, the concept of telomere shortening was then established as another mechanism of longevity determination. These repetitive DNA sequences found at the end of chromosomes are progressively depleted with age, and may represent a method by which cells enter senescence. However, this theory is not universally accepted, largely due to a lack of correlation between telomere length and life span in many animal species[9].

Aging may be the consequence of oxidative damage. Oxidative damage to DNA, protein, carbohydrates and lipids contribute to degenerative diseases in aging, due to a disruption in cellular homeostasis. The activation of specific stress signalling pathways results in alterations in gene expression mediated by a variety of transcription factors including NF-κB, p53, and heat shock transcription factor 1 (HSF1)[10]. While levels of antioxidants correlate with longevity in primates[11,12], there is no evidence that antioxidant supplementation affects life span. It has been suggested, but not proven conclusively, that the success of calorie restricted diets in extending the lifespan of rodents is related to a reduction in free radical formation[13-15].

The role of insulin/IGF-1 signalling in the regulation of lifespan has been studied. The gene *daf*2, an insulin/IGF-1 receptor homolog has been shown to affect the lifespan of *C. elegans*[16]. Similarly, a related tyrosine kinase receptor, InR, regulates lifespan in Drosophila[17]. Holzenberger *et al*[18] demonstrated the importance of this pathway in mammals. In this study, heterozygous knockout mice ($Igf1r^{+/-}$) were used, as null mutants were not viable. These $Igf1r^{+/-}$ mice had IGF-1 receptor levels that were half of those seen in wild-type animals. These mice lived an average of 26% longer than did their wild-type littermates, without developing dwarfism, or showing adverse changes in physical activity, fertility or metabolism. This suggests that the link between insulin signalling and longevity seen in lower order organisms may also exist in mammals. Furthermore, the $Igf1r^{+/-}$ mice showed a greater resistance to oxidative stress, a known determinant of aging[10]. This lends support to the theory that oxidative stress plays an important role in the aging process.

In addition to increasing resistance to oxidative stress, insulin/IGF-1 signalling may affect aging via effects on Forkhead transcription factors of the FOXO class. Overexpression of FOXO extends life span[19]. Insulin/IGF-1 receptor binding, and subsequent activation of the PI3K/Akt pathway, results in the phosphorylation of Akt, which inactivates FOXO by sequestering it in the cytoplasm[20]. This alters the effects of FOXO on resistance to stress, apoptosis and longevity, and provides another potential link between insulin/IGF-1 and aging.

Other theories of aging focus on neuro-endocrine changes, including reductions in the levels of the steroid hormone dehydroepiandrosterone (DHEA). Both animal and human studies have demonstrated that oral replacement of DHEA may prevent or reduce age-associated events such as cancer and cardiovascular disease, and may stimulate immune function[21-25].

A SOCIETAL PERSPECTIVE

Seniors constitute the fastest growing segment of Canada's population. In fact, the proportion of seniors has risen from one in twenty in 1921, to one in eight in 2001. Within this group, the number of Canadians aged 85 or more is anticipated to increase substantially, up to 4% of the total population by the year 2041 (Health Canada, 2002). Women make up the majority of seniors, with gender differences becoming more pronounced in the oldest age groups.

The aging of the population may be thought of as a modern day success story. For the first time in history human beings have been afforded the opportunity to live an unprecedented number of years, with a reasonable quality of life. This accomplishment is not without challenges, however, as society struggles to adapt to a changing demographic, with a unique set of physiological, psychological, and social needs of the elderly themselves as well as their caregivers.

Several non-genetic factors may influence life expectancy, including improvements in sanitation and nutrition, as well as reductions in maternal mortality and the rates of infectious diseases (An Aging World: 2001, U.S. Census Bureau). These changes, coupled with lower fertility rates, result in a changing demographic that presents society with the challenges of providing quality health care to an aging population, and facilitating the social, economic and community involvement of seniors.

Although most seniors rate their health as "good" or "very good", seniors are more likely to visit health care professionals, to take medication, and to be hospitalized when compared to their younger counterparts. Therefore, increases in this population and the associated increased health care utilization may place a burden on the system. Indeed, health expenditures for seniors in 2000-2001 represented 43% of total health care expenditures (Health Canada, 2002). Of course we recognize that these persons have contributed greatly to our society, and it is our responsibility to provide ready access to quality of healthcare for these special persons, who must be treated with respect and allowed to age with dignity.

MALNUTRITION IN THE ELDERLY

The elderly are at a high risk for malnutrition, yet

unfortunately it is often underdiagnosed[26]. Poor nutritional status is a key determinant of morbidity and mortality in the elderly[27-30]. Because nutrition is a modifiable risk factor, attempts should be made to design preventative nutritional strategies aimed at improving the quality of life and consequently minimizing the use of health care resources.

Why are the elderly malnourished? There are a number of contributing factors including: (1) inadequate intake, attributed to a lack of appetite, or difficulty in preparing food; (2) psychological factors, including depression; (3) social factors, including isolation and low income; and (4) physiological factors, such as reduced sense of smell and taste, drug-nutrient interactions and reductions in nutrient absorption[31]. Sullivan *et al*[29] demonstrated that hospitalization was a risk factor for inadequate food intake in seniors, possibly due to the unattractive and monotonous food choices, or due to the side effects of drug therapies. Reduced food intake is generally accepted as the main cause of undernutrition in the geriatric population, and as such therapies should be aimed at increasing food intake. Many researchers also feel that malnutrition in the elderly is indicative of prevailing social conditions, and that therapies should be aimed at alleviating poverty, isolation and depression in this age group.

Because one of these several factors which may contribute to malnutrition relates to possible age-associated changes in the physiology of the gastrointestinal tract, this topic will be reviewed.

THE AGING PROCESSES AND THE GASTROINTESTINAL TRACT

The aging of the population, coupled with the potential impact on the health care system, has focused attention on the physiological processes associated with aging. Only with an increased understanding of the aging process can we work towards improving the quality of life for the elderly, and reducing disease morbidity in this population.

There are age-related alterations in the gastrointestinal tract but the difficulty lies in excluding concomitant pathological factors as the cause of these changes. Certainly with aging, conditions such as diabetes, pancreatic or liver disease, cancer, or drug-induced enteropathy will have potential adverse effects on the form and function of the intestine. It is necessary to exclude these pathological factors, to consider the physiological changes that occur in the healthy elderly, and to understand how these factors influence the nutritional status of this population.

Dysphagia is more common in the elderly than in younger persons[32]. Selective neurodegeneration may occur in the aging enteric nervous system (reviewed in Saffrey)[33], and may contribute to gastrointestinal symptoms such as dysphagia, gastrointestinal reflux and constipation. Interestingly, caloric restriction in rodents can prevent the neuronal losses that occur with aging, suggesting that diet may influence gastrointestinal aging[34]. Alterations in esophageal motility may be due to reductions in the number of neurons in the myenteric plexus of the elderly[35]. While gastric motility may be impaired with aging[36,37], small intestinal motility is unaffected[38-40]. Aging may affect the signal transduction pathways and cellular mechanisms controlling smooth muscle contraction, which may influence colonic motility and thereby contribute to the development of constipation (reviewed in Bitar and Patil)[41].

The data regarding aging and gastric acid secretion is inconclusive, as early studies were likely confounded by the presence of *H pylori* in some persons. Achlorhydria or hypochlorhydria may result from atrophic gastritis, as a result of the use of medications such as proton pump inhibitors, or as a result of *H pylori* infection[42-44]. This reduction in gastric acidity may increase the risk of small bowel bacterial overgrowth, potentially leading to malabsorption[45]. For example, McEvoy *et al*[46] found that 71% of patients in a general geriatric ward had bacterial overgrowth of the small intestine, while 11% were found to be malnourished. Indeed, bacterial overgrowth in older adults is associated with reduced body weight, which is paralleled by reduced intake of several micronutrients[47].

Although structural changes in the pancreas are seen with aging, no functional age-related alterations are seen using the fluorescein dilaurate test[48]. Some studies demonstrate reduced secretagogue-stimulated lipase, chymotrypsin and bicarbonate concentrations in pancreatic juice with aging[49]. Other research suggests that there is little evidence of reduced pancreatic secretions with age, independent of other factors including the presence of disease and the effect of drugs[50].

There are age-related reductions in liver mass and blood flow, yet microscopic changes are subtle[51-53]. While structural and functional changes do not correlate well, there is evidence that liver function declines with age. For example, Cao *et al*[54] used microarrays to show that aging in mice is accompanied by changes in the expression of genes in the liver involved in inflammation, cellular stress and fibrosis, all of which are linked to age-related liver pathologies. Interestingly, caloric restriction in mice starting at weaning reversed the majority of the age-related changes, once again emphasizing the ability of the diet to influence the aging process.

Holt *et al*[55] looked at age-related changes in the intestinal morphology of Fischer 344 rats. Increases in villous width were noted throughout the small intestine, while increases in villous height were limited to the ileum. Other studies in rats have shown age-related losses in villous and enterocyte heights[56]. Age-related declines in mucosal surface area have also been reported in rabbit jejunum[57]. Human studies generally show no changes in intestinal morphology, as determined from measurements of villous height, crypt depth, crypt-to-villous ratios and enterocyte size[58-60]. Warren *et al*[61] showed a decrease in villous height with age. Martin *et al*[62] described histological changes that occur in aging mice: when old mice were compared to young mice, there were larger villi, a reduced number of crypts, and fewer villi and crypts per mm along the small intestine. These changes were most pronounced in the distal, as opposed to the proximal small intestine. However, even if there are minor age-associated alterations in intestinal morphology with aging, there is not a clear association between intestinal morphology and nutrient

uptake with aging. For example, despite reductions in mucosal surface area, aged rats demonstrated increases in the jejunal uptake of saturated fatty acids[57]. So, while it remains controversial as to whether or not aging is associated with morphological changes, even if such changes were to occur, the impact on nutrient uptake may not be clinically relevant.

Ciccocioppo *et al*[63] suggested that intestinal architecture is maintained with aging by increases in proliferation and differentiation rates. This agrees with work done by Corazza *et al*[64] that showed increased expression of proliferating cell nuclear antigen (PCNA) in older subjects when compared to their younger counterparts.

NUTRIENT DIGESTION AND ABSORPTION

Age-related alterations in the abundance of brush border malease (BBM) enzymes may also impact upon the digestion and subsequent absorption of nutrients. BBM lactase phlorizin hydrolase (LPH) and sucrase-isomaltase (SI) activities fall with age in rats[65]. Bacterial overgrowth, which is common in the elderly, may also negatively impact upon disaccharidase activity, and thereby possibly reduce carbohydrate absorption[66].

Hollander and colleagues demonstrated that intestinal permeability to medium sized probes (mannitol, polyethylene glycol) increased in 28-month old rats when compared to 3-month old rats[67]. However, the lactulose: mannitol (LTM) ratio was not different between young and old subjects, indicating that intestinal permeability to these sugars does not change significantly with age in humans[68]. A study using breath hydrogen analysis following a carbohydrate meal showed evidence of malabsorption with aging. Elderly patients (ranging from 65-89 years, mean age, 79 years) were compared to control subjects (ranging from 20-64, mean age, 35 years). Significantly more subjects in the elderly group (7 out of 21) excreted excess H_2 when compared to controls (0 out of 19)[69]. This suggests that there may be malabsorption of carbohydrates in the elderly. *In vitro* transport experiments using BBM vesicles also demonstrated a reduction in Na^+-dependent D-glucose uptake in patients over the age of 70[70]. In contrast, Wallis and co-workers[71] did not find changes in Na^+-dependent glucose transport in BBM vesicles isolated from duodenal biopsies from patients whose ages ranged from 55 to 91 years.

Experiments using rodent models of aging also demonstrate conflicting results. Several studies show reductions in D-glucose absorption in aged rats[72-74]. Depending upon the intestinal site studied, a normal or increased absorptive capacity was also found in a study using everted intestinal segments from old versus young rats[75]. Results from studies in mice also do not offer conclusive results on the effect of aging on nutrient absorption. Ferraris *et al*[76] showed in aged mice a reduction in uptake and site density of the Na^+-dependent glucose transport in the BBM, SGLT1. This is in contrast to the findings of Thompson *et al*[77] who showed an increase in intestinal glucose uptake in aged mice. Our lab has recently investigated the effect of age on intestinal glucose uptake in Fischer 344 rats using the *in vitro* intestinal sheet method[78]. Glucose uptake was reduced in 9 mo old and 24 mo old rats when compared to 1 mo old animals. When changes in mucosal surface area were accounted for, only ileal glucose uptake was reduced in the older animals. These age-associated changes in glucose uptake were not explained by alterations in the abundance of SGLT1, GLUT2 or Na^+K^+-ATPase.

The variations in the results from human, rat and mouse studies may be due to the differences in the methodologies that were used. While some investigators studied uptake using BBM vesicles[70-74], others used everted intestinal rings[75,77,79] or intestinal sheets[78]. As well, the method of expressing results may influence qualitative differences between studies. Uptake is often expressed on the basis of intestinal weight, and does not taken into account any potential age-associated changes in mucosal weight or surface area. The strain and ages of the animals, and the site of the intestine used also differ between studies, and may explain the variability in the results.

The uptake of fructose has been studied in aging mice. Ferraris and Vinnekota[79] showed that D-fructose uptake per milligram of tissue was higher in the jejunum of young as compared to old animals. Adaptive increases in uptake, in response to increases in carbohydrate levels, were blunted in these mice, and were restricted to more proximal regions of the small intestine

While it is reasonable to speculate that the complexity of lipid absorption may make it susceptible to the effects of aging, experimental findings do not consistently support this notion. While a number of animal studies demonstrate reduced *in vitro* lipid absorption with aging[80,81], others have shown increases in lipid absorption in aged rats using an *in vivo* perfusion model[82]. Aging is associated with a decrease in the thickness and resistance of the unstirred water layer[80], which could partially explain the finding of increased absorption with aging in the *in vivo* model.

Early work using human subjects demonstrated reductions in lipid absorption with age[83]. There also appears to be reduced intestinal absorption of bile acids with age[84], although it is not clear if this negatively impacts lipid absorption in the elderly. When healthy elderly human subjects were studied, however, no correlation between age and 72 h fecal fat excretion was found[85].

More recently, a study by Woudstra *et al*[86] showed that the ileal uptake of several fatty acids including 16:0, 18:0, 18:1 and 18:2, was reduced in 24 mo old rats, when compared to 1 mo old animals. However, when mucosal surface area was considered these differences disappeared, suggesting that the age-related changes in lipid uptake were largely due to non-specific reductions in intestinal surface area. After considering the results of all of these studies, Holt[87] suggested that no important changes in lipid absorption with aging have been described.

MODIFICATION OF AGE-ASSOCIATED DECLINES IN INTESTINAL ABSORPTIVE FUNCTION

Holt *et al*[55] have shown that the intestine of elder rats is capable of adopting its function in response to changes

in dietary protein levels. In adult rats, a diet enriched with saturated fatty acids (SFA) results in increased intestinal sugar uptake when compared to an isocaloric diet enriched with polyunsaturated fatty acids (PUFA)[88-91]. Similarly, Vine *et al*[92] studied the effect of various fatty acids on the passive and active transport properties of rat jejunum, and found that an SFA diet increased Na^+-dependent glucose uptake when compared to a diet enriched with n6 PUFA. Of importance, Woudstra *et al*[93] showed that the intestinal response to dietary lipids may differ with age. In this study, in contrast to what is seen in younger animals, feeding a PUFA diet increased lipid uptake when compared to feeding a SFA diet. Drozdowski *et al* (unpublished observations) have also shown that PUFA rather than SFA increases intestinal sugar uptake in older rats. The mechanism responsible for the age-related alteration in adaptation to daily lipids is not known. But clearly, the results of adoptive studies in young rats do not necessarily apply to older animals. Other factors which may enhance the reduced uptake of sugars that occurs in older animals indicates glucagon-like peptide 2 (GLP2) at the glucocorticosteroid, dexamethasone (Drozdowski *et al*, unpublished observations, 2006).

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