Review Article

Anti-Aging Medicine for Liver and Gastroenterology

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Abstract

Anti-Aging Medicine is a branch of preventive medicine that aims to promote a healthy long life. Given that aging itself is a root cause of several diseases of the gut and liver, advances in Anti-Aging Medicine and research may help improve the accuracy of gastroenterological diagnosis and efficacy of treatment. Digestive organ function degrades with age, in line with changes in secretion of hormones such as growth hormone/insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone-sulfate (DHEA-s). This degradation can be exacerbated by risk factors such as mental, physical, oxidative, and glycation stress, which have direct and indirect effects on digestion and absorption in the alimentary tract. The liver, which influences IGF-I production and lipid and sugar metabolism, is also affected by aging. Here, we note age-related diseases of the liver and intestine, outline aspects of Anti-Aging Medicine relevant to digestive organs and the liver, and argue that traditional therapy should be combined with lifestyle guidance, such as that developed by Anti-Aging Medicine, to treat the underlying causes of gastrointestinal functional decline.

KEY WORDS: DHEA (dehydroepiandrosterone), IGF-I (insulin-like growth factor-I), melatonin, AGEs (advanced glycation end products)

Introduction

Anti-Aging Medicine belongs to a category of preventive medicine that aims to improve the quality of life (QOL) for people of all ages. Morbid aging can be diagnosed via a medical checkup, such as the “Anti-Aging dock”, a questionnaire developed through research into the aging process. This information can then be used to select treatments that will promote and prolong a healthy life. Although geriatric gastroenterology is well established, treatment methods derived from this branch of medicine are not well known.

In both genders, gastrointestinal and hepatic functions deteriorate with age, and Anti-Aging treatments help maintain optimal metabolic and nutritional conditions. However, the whole body should be treated, and the effect of gastrointestinal condition on whole body function and vice versa evaluated. We believe that inclusion of Anti-Aging treatments in geriatric gastroenterology will increase the success rates of other treatments for gastroenterological conditions.

A holistic therapeutic regimen may include lifestyle guidance, alimentotherapy, ergotherapy, counseling, conventional medical therapies, dietary guidance, functional food, nutritional supplements, anti-oxidation, immune response enhancement, hormone replacement, and aesthetic dermatology. However, the success of any of these therapies depends on accurate identification of the risk associated with aging and individual patient needs.

Evaluating aging and risk factors

Functional age and QOL should be accurately assessed before prescribing any Anti-Aging treatment. The Anti-Aging dock estimates the functional age of several body tissues and systems, including bone, blood vessel, muscle, neural, and hormone systems. If any of these tissues or systems present with an older-than-expected functional age, the tissue can be treated to maintain bodily balance.

A balance between bodily systems maintains health and protects the body from disease. Several authors have reported that the balance between the functional ages of different body systems appears to be the most important factor contributing to the longevity of centenarians. Balance in functional age should be pursued throughout the whole body, including mental and physical systems, as dysfunction in any one system can in turn affect the health of the entire body. The risk of functional change in any bodily system may be increased by stressors derived from physical, mental, oxidative, or glycation causes, and these are influenced by patient lifestyle, diet and exercise habits.

Functional age can be measured for each body system; for example, we can measure hormone concentration to judge hormonal age. Immune condition, oxidative and mental and physical stress can be measured by other methods. Taken together, these measurements enable clinicians to identify serious risk factors and plan priorities for Anti-Aging medical treatment.
Evaluation of functional age

1. Aging-related hormones involved with gastrointestinal function

A study of 229 patients (52.5 ± 14.0 years), receiving Anti-Aging medical dock, investigated the relationship between the subjective assessment of alimentary system conditions and serum hormone concentration. Five symptoms (anorexia, early satiety, epigastralgia, diarrhea, constipation) were evaluated using the Anti-Aging QOL Common Questionnaire (AAQol). Standard laboratory methods were used to measure the concentration of serum hormones, including estradiol, progesterone, insulin-like growth factor-I (IGF-I) and dehydroepiandrosterone-sulfate (DHEA-s). Adverse digestive symptoms and chronological age were not correlated, but the frequency of several symptoms was correlated with the female hormones (i.e. estrogen, progesterone) and DHEA-s, suggesting that hormonal age – not chronological age – might be useful in predicting gastroenterological health in middle-aged and older individuals.

Female hormones

Female hormones such as estrogen control several processes in the uterus, ovaries, and mammary glands, including maturation and sexual development of the embryo and development of external genitalia and secondary sex characteristics. After puberty, estrogen induces ovulation, maturation of the endometrium, secretion of cervical mucus, and enables embryo implantation after fertilization.

The rapid decrease in estrogen secretion from approximately age 50 can induce unpleasant menopausal symptoms, such as hot flashes, irritability, and palpitations. Deficient estrogen secretion also causes premature ovary insufficiency from age 20 to the early 30s and is also connected with infertility.

In our previous study cited above, epigastralgia was correlated with estrogen concentration, and diarrhea was correlated with estrogen, progesterone, and DHEA-s concentrations. In particular, the symptoms were more pronounced when the serum concentration of female hormones was high.

Melatonin

Melatonin, which is secreted by the pineal gland, controls the sleep-wake cycle and has direct anti-oxidative action. This hormone can be transported across the blood-brain barrier, thereby providing defense against oxidative stress injury during sleep. Melatonin secretion is highest during teen-age years and declines with age. This decreased secretion of melatonin may reduce sleep quality and cause other bodily changes.

Bowel motions and gastric acid secretion are influenced by the biological clock. Eating habits and sleep act together to influence the function of the digestive organs. Sleep disorders or irregular sleep arising from shift work are linked to irritable bowel syndrome (IBS) or gastroesophageal reflux disease (GERD) and peptic ulcers. Clinical trials have shown that the administration of melatonin relieves symptoms of IBS and GERD, and melatonin may also be used to treat obesity and non-alcoholic steatohepatitis (NASH).

Animal experiments have found melatonin prevents ischemia re-perfusion gastric mucosal injury, flood stress-induced gastric mucosal injury, and gastric mucosal injury induced by bile duct ligation. The anti-oxidative and anti-inflammatory actions of melatonin may be linked with the control of interleukin-8 (IL-8) production or with another mechanism through the peripheral and central nervous systems.

Other animal experiments have shown melatonin protects the liver against cadmium and carbon tetrachloride toxicity, morphological changes induced by magnetic field exposure, radiation-induced injury, and ischemia re-perfusion; melatonin also protects against hepato cellular injury following experimentally induced acute pancreatitis. The evidence suggests that melatonin not only acts directly as an antioxidant but also increases the activity of liver superoxide dismutase (SOD). We believe that liver cells are protected directly by the anti-oxidative activity of melatonin as well as by melatonin-induced promotion of other cell protection mechanisms, such as anti-oxidative enzyme action.

Growth hormone (GH) and insulin-like growth factor I (IGF-I)

Sleep, exercise, and eating stimulate the anterior pituitary gland to release GH in pulses, which act on the liver to promote the production of IGF-I, a second messenger hormone. Given that blood serum concentrations of GH and IGF-I begin to decrease around the age of 30, the levels of these hormones are useful indicators of vital activity and decreased QOL.

Most IGF-I is produced by the liver; the liver has an endocrine function as well as detoxification, metabolism, energy storage, and external secretion (bile production and secretion) functions. The first case linking IGF-II production to hepatic cancer was noted by our group in 1992, and since then we have made further investigations into the function of IGF in the gastrointestinal organs and liver.

Other organs also secrete hormones besides the liver. For example, ghrelin, discovered by Kojima and Kangawa in 1999, is secreted primarily by the stomach and is responsible for maintaining energy homeostasis by promoting GH secretion, stimulating appetite, and regulating gastrointestinal function, gastric acid secretion, and glucose and fat metabolism. Several studies have reported low plasma levels of ghrelin and IGF-I in patients with chronic atrophic gastritis (Fig. 1) and IGF-I has also been found to promote wound healing in cultured gastric mucosal cells, and low IGF-I levels were implicated in the progression of chronic gastritis from closed to open type, following Helicobacter pylori infection (Table 1). IGF-I is also believed to play an important role in the progression of atrophic gastritis and in the repair of gastric mucosa; portal hypertension gastric disease is characterized by increased venous pressure along with atrophy of gastric mucosa, and the pathology of this disease involves the impairment of microcirculation as well as decreased IGF-I resulting from liver cirrhosis.

Cardio and renal function also affect other facets of gastrointestinal treatments. Although low invasive surgical procedures, such as laparoscopic surgery are common, the number of complex gastrointestinal surgical procedures performed in elderly and high-risk patients has increased; consequently, the prevention and treatment of postoperative complications is important. In particular, cardio and renal function must be monitored in elderly patients, as surgical survival rates are lower in emergency surgeries and patients with dementia.

A combination of old age, severe illness, and malnutrition may lead to postoperative protein catabolism, and organ failure, muscle weakness, and ventilation difficulty, leading to prolonged stays in intensive care units (ICU). Additionally, hypercatabolism may aggravate other conditions, such as the abnormal secretion...
of hormones and reduce secretion of GH/IGF and DHEA-s, which all lead to a poor postoperative prognosis.

Since about 1990, some clinicians have administered GH to control postoperative complications and catabolism, although the effective dosage has not yet been determined. Reports suggest that postoperative GH administration suppresses postoperative hypercatabolism, promotes nitrogen retention, and increases IGF-I secretion, thereby shortening postoperative accommodation in ICUs and increasing survival rates. In Japan, the practice of postoperative administration of GH has also been used in patients with esophageal cancer and short bowel syndrome. However, a multi-center clinical study completed in 1999 (n = 532) found that GH therapy resulted in poor postoperative glycemic control, sepsis, organ failure, and increased death rate, and since then, the frequency of GH administration has been reduced. In that study, high doses of GH (body weight/day 0.10 ± 0.02 mg/kg) induced several complications including abnormally high blood sugar levels, which were difficult to control, and sepsis. Modern practice is to administer postoperative GH dosage under strict regulations, and nutritional supplementation maximizes the efficacy of GH and minimizes its side effects.

Gastrointestinal function can also be maintained by practicing a lifestyle that stimulates GH/IGF-I secretion, such as ensuring quality sleep, moderate exercise, and proper intake of protein amino acids (e.g. arginine). Food intake stimulates ghrelin secretion by the stomach walls, which stimulates the pituitary gland and thereby promotes GH secretion. Food intake is recommended after hunger is felt and may effectively increase GH secretion via ghrelin function. GH secretion can be inhibited by numerous factors, including a lack of sleep or exercise, poor quality sleep resulting from mental or physical stress, excessive intake of carbohydrates, *H. pylori* infections, and atrophic gastritis. Resolution of these situations is therefore needed to restore proper secretion; for example, treating *H. pylori* infections to increase ghrelin levels and thereby promote GH secretion.

**DHEA-s**

DHEA-s is the most abundant steroid hormone in the body and is a precursor for 50 other hormones, including sex and anabolic hormones. DHEA-s is implicated in the immune response and may increase resistance to stress and lifestyle-related diseases, such as diabetes, hyperlipemia, high blood pressure, and osteoporosis. Analysis of five subjective symptoms of alimentary function (anorexia, early satiety, epigastralgia, diarrhea, constipation) in Anti-Aging dock consultations (n = 229, mean age = 52.5 ± 14.0) and serum hormone concentration found a significant correlation.
between adverse digestive symptoms and DHEA-s levels, but none between symptoms and chronological age \(^3\). These data imply that an adverse digestive symptom or disease in middle-aged and older persons may be linked to declining hormone secretion. Measures of DHEA-s secretion may be useful in evaluating physiological health \(^49,50\).

The type of most (99%) blood serum DHEA is sulfate and is converted by the enzyme DHEA sulfotransferase from DHEA to DHEA-s in the liver. The concentration of the enzyme and DHEA-s falls in the blood of patients presenting with liver cirrhosis \(^51\), and this symptom has been reported in cases of NASH \(^52\). In contrast, elevated DHEA-s levels have been reported in male patients with low serum testosterone levels and fatty livers \(^53\). In patients with low testosterone levels caused by reduced testicular function, cases with NASH may show a compensatory increase of DHEA-s. The interaction between DHEA-s and other hormones should always be considered when medical checks present abnormal results for other hormones.

Other studies have reported that reduced serum DHEA-s levels are associated with several alimentary diseases, such as inflammatory bowel disease (IBD) \(^55-57\). Oral administration of DHEA (200 mg/day) provided relief to 8 cases among 13 patients with ulcerative colitis (UC) and 6 cases among 8 patients with Crohn's disease \(^58\). Similar relief was achieved with DHEA medication for pouchitis following treatment for UC \(^59\). We believe the mechanism underlying DHEA action involves nuclear factor-κB (NFκB), the anti-inflammatory effect of IL-6 and IL-12, and peroxisome proliferator-activated receptor α (PPARα). Clarification of the efficacy of DHEA treatment in IBD patients will require further research.

**Table 2** Logistic analysis of factors that contribute to the development of Stage 3 non-alcoholic fatty liver disease

<table>
<thead>
<tr>
<th>Derivatives</th>
<th>Odds ratio</th>
<th>95% CI p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age ≥ 65 years</td>
<td>2.90</td>
<td>0.78 - 10.69</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.95</td>
<td>0.38 - 10.09</td>
</tr>
<tr>
<td>HOMA-IR ≥ 5</td>
<td>2.37</td>
<td>0.63 - 8.93</td>
</tr>
<tr>
<td>BMI ≥ 28</td>
<td>1.04</td>
<td>0.26 - 4.17</td>
</tr>
<tr>
<td>DM (+)</td>
<td>1.60</td>
<td>0.39 - 6.50</td>
</tr>
<tr>
<td>Hypertension (+)</td>
<td>0.42</td>
<td>0.10 - 1.71</td>
</tr>
<tr>
<td>Dyslipidemia (+)</td>
<td>0.25</td>
<td>0.07 - 0.92</td>
</tr>
<tr>
<td>DHEA-s ≥ 66 μg/dl</td>
<td>4.95</td>
<td>1.17 - 21.00</td>
</tr>
</tbody>
</table>

CI: confidence interval; HOMA-IR: homeostasis model assessment-insulin resistance; BMI: body mass index; DM: diabetes mellitus; DHEA-s: dehydroepiandrosterone-sulfate. Data derived from liver biopsies of patients with non-alcoholic fatty liver disease (n = 133). Table is derived from Sumida et al \(^53\).

2. **Muscle age: changes in the muscle system with aging**

Total muscle mass reduces by approximately 1% per year from mid-20s \(^60\). Muscle age measures the functional age of skeletal muscle and estimates the total lean body muscle mass. Body composition of lean muscle mass can be estimated from electrical resistance using bio-electrical impedance analysis, but can also be estimated from magnetic resonance imaging (MRI) of a body cross-section. We measured segmental muscle mass for the brachial, forearm, thigh, and trunk (abdominal and back) muscles of 10,335 individuals via bio-electrical-impedance analysis \(^60\). The results demonstrated that the femoral and trunk muscles weaken more drastically with age compared to the other muscles.

Skeletal muscle accounts for half of all body weight, and approximately 70% of dietary glucose is used by skeletal muscle. As a result, basal metabolism declines with muscle mass and age, thus increasing insulin resistance. Therefore, insulin resistance can be maintained or even improved by retention of skeletal muscle mass. Muscle training is known to protect against other conditions associated with decreased muscle mass, such as non-alcoholic fatty liver disease (NAFLD) and NASH \(^61,62\).

In patients with NAFLD, which is usually regarded as a systemic disease, ectopic fat accumulates in the skeletal muscle \(^63\). We consider this disease to be systematic, relating to the entire body, and treatment should not be restricted to the liver.

Dietetic function is also affecting by chewing, which uses the occlusal muscles, and therefore any deterioration in occlusal muscle function may also cause eating disorders, including malnutrition \(^64\). Negligent oral health care may also allow the proliferation of mouth bacteria and infection by *H. pylori* \(^65\), which has proven difficult to eradicate. An oral cavity treatment program implemented as part of a health promotion program in a health facility for the elderly, exercised the facial muscles and was found to promote salivation and improve adverse digestive symptoms like constipation and nutritional status \(^66\).

3. **Bone age: changes in bone density with aging**

After age 30, bone density decreases in both genders \(^67\), but the decrease is particularly marked in women after menopause when estrogen secretion declines, inducing an increase in bone metabolism \(^68\). Bone age may be expressed as a function of the bone density and measured using either dual energy X-ray absorptiometry or ultrasonography, although the former provides a more precise and repeatable measure than ultrasonography.

Bone age is also reflected in calcium ion (Ca\(^{2+}\)) concentration in blood serum and cytosol. Cytosol levels can be accurately controlled by parathormone (PTH) and vitamin D; these hormones control the calcium ion concentration gradient across the cell membrane, which results in an extracellular concentration of 10\(^{-7}\) M Ca\(^{2+}\) versus an intracellular concentration of 10\(^{-8}\) to 10\(^{-7}\) M Ca\(^{2+}\). The calcium regulatory system responds to chronic calcium shortage caused by malabsorption or malnutrition by translocating calcium from the bone to the serum and simultaneously stimulating PTH secretion. This eventual leads to ectopic calcium accumulation in blood vessel walls and the kidneys \(^69\). In this manner, calcium shortage can stimulate bone aging and blood vascular aging.
This situation is exacerbated when gastric acid secretion is low or inhibited so that gastric pH is close to neutral. This condition may develop if chronic atrophic gastritis or peptic ulcers are treated with proton pump inhibitors as these drugs decrease calcium absorption and increase the risk of calcium deficiency [71-74].

4. Blood vessel age

Age-related arteriosclerosis affects the microcirculatory system of the gastrointestinal mucosa and reduces blood flow, potentially increasing the frequency of hemorrhagic peptic ulcer [75] and ischemic colitis [76,77]; both conditions are associated with arteriosclerosis in elderly persons.

Blood vessel condition may be assessed by either the finger-tip acceleration pulse wave [78] or pulse wave velocity (PWV) methods [79]. The former method compares the form of a patient’s pulse wave to a standard for chronological age, while the latter assumes that the speed at which a pulse wave is transmitted in a blood vessel wall correlates with the grade of arteriosclerosis. Both methods can be used to determine blood vessel organic sclerosis and type, and provide an index of arteriosclerosis that may assist diagnosis of blood vessel condition.

Classic arteriosclerosis is exacerbated by high blood pressure, diabetes, dyslipidemia, and smoking, and may signal the presence of other dangerous conditions, such as abnormal levels of homocysteine, high sensitivity C-reactive protein (CRP), stress hormones (e.g., cortisol), insulin resistance, and adiponectin; abnormal levels of adiponectin indicate oxidative stress or glycation stress. Homocysteine is metabolized to methionine and cysteine in the liver and requires vitamins B6, B12, and folic acid [80]. If available stores of any of these vitamins are limited and homocysteine increases, changes are induced in the vascular endothelium, the activity of renin angiotensin system (RAS) increases, and reactive oxygen species (ROS) production is promoted, thereby increasing the risk of arteriosclerosis [81,82]. H. pylori infection is one source of vitamin deficiency as infection injures the gastric mucosa and mural cells, thereby reducing production of vitamin B12 and promoting arteriosclerosis [83]. One study reported a significant relationship between atherosclerotic cardiovascular disease and atrophic gastritis in association with H. pylori infection and homocysteine metabolism [84]. Maintenance of vitamin levels help ward off these conditions; persons presenting with high levels of homocysteine may be prescribed vitamins B6, B12, and folic acid, but should also be checked for H. pylori infections.

5. Neural age

Given that total cerebral neurons, and nervous and cognitive function are all known to decline with age, evaluation of neural age can help in treatment of functional disorders in the gastrointestinal tract. The Anti-Aging dock tests follow the guideline of the Japan Brain Dock Society and use the Wisconsin card sorting test (http://www.phatima.co.jp/products/wcst.html) [85,86] and Age Management Check software to evaluate neural age [87].

Hirschsprung disease, which is caused by failure of enteric neural cells to migrate correctly during development, causes morphological and functional deterioration in the enteric neural plexus of the large intestine [88-90]. When the myenteric plexus (Auerbach’s plexus) is stimulated, nitric oxide (NO) levels, mediated by neuronal nitric oxide synthase (nNOS), increase, thus inducing peristalsis in the enteric smooth muscle [91]. A reduction in NO production by the Auerbach's plexus reduces peristalsis, which extends gastric emptying time and large intestine holding time. The symptoms of constipation [92] and functional dyspepsia (FD) [93] that are occasionally noted in the elderly may be caused by failure of autonomic or enteric nerves. Several authors have reported that enteric nerve function degrades with aging [94], and we expect further research into these aspects of disease to benefit diagnosis and treatment.

Evaluation of age related risk factors

In the next section of this paper, we explore the risk factors associated with degraded immune function, mental, physical, oxidative, and glycation stress.

1. Immune function

The immune system, including the efficacy of defense and self-recognition mechanisms, degrades with age, thus reducing the body’s resistance against pathogens and decreasing its ability to distinguish internal and external components [95,96]. This degradation increases the risk of developing autoimmune diseases of the digestive organs, such as IBD [97], autoimmune hepatitis [98], autoimmune pancreatitis, and primary biliary cirrhosis. Although mechanisms of several such functional disorders have been clarified, no suitable biomarkers for evaluating immune function as a risk factor have been identified, and these illnesses are difficult to prevent.

Several authors have investigated the role of intestinal bacterial flora in alimentary canal immunity. The quantity of beneficial bacteria, such as Bifidus spp., decreases with age, and consequently the frequency of injurious species, such as the Welch bacillus (Clostridium perfringens), may increase [99]. These injurious species produce several toxins, such as inflammatory cytokines, and enhance the production of Nox1, an ROS-producing enzyme, thus accelerating ROS production through the Toll-like receptor 5 (TLR; expressed in the large intestine epithelial cell basement membrane) [100]. Although the immune response of healthy intestinal mucosa to beneficial bacillus is low and inflammation is rare, injurious bacteria may induce lesions in the gastrointestinal mucosa [101-103].

Intestinal immunity affects the immunological system of the whole body. Functional foods and probiotics (foods containing particular microbe species with beneficial influence on living bodies) improve the health of the intestinal bacterial flora. These dietary supplements reduce the production of inflammatory cytokines, such as IL-6 and tumor necrotizing factor-α (TNF) in laboratory animals [104] and may inhibit the growth of injurious bacteria while stimulating the growth of beneficial species. Consequently, it may be feasible to ease the symptoms of IBD by controlling intestinal mucosal inflammation and immunoreaction [105].

A method of analyzing the genetic composition of the gut flora, based on Terminal Restriction Fragment Length
Polymorphism (T-RFLP), is being developed by Primary Cell, Ltd. (Sapporo-city, Hokkaido, Japan), and may provide clinicians with additional information on the condition of the intestinal tract bacterial flora.

2. Mental and physical stress

Psychosomatic stress affects many body systems, including digestion [106-109]. Secretions of vasopressin, oxytocin, and corticotrophin-releasing factor (CRF), which are secreted from the para-ventricular nucleus, promote adrenalin and cortisol secretion. These hormones respond briefly to psychosomatic stress, but chronic excess cortisol secretion exacerbates blood pressure elevation, arterial sclerosis, and hormonal secretion by depressing the gonadal function and hypercatabolic muscle mass [3]. Thus, stress may cause autonomic nervous system disorders, particularly of the vasomotor nerve, and promote oxidant stress by injuring ischemia-reperfusion.

Psychosomatic stresses act on the alimentary system through CRF or serotonin [100]. CRF, which is found in the brain and intestinal tract, accelerates movement in the lower gastrointestinal tract through the central nervous system and controls stomach motility through the central and peripheral nervous systems [100]. Serotonin, which is secreted from raphe nuclei in the brainstem, acts on the whole body and exerts a calming influence on mood [101]; indeed, mentally instability, depression, irritation, aggression, and impulsive behaviors are associated with low levels of the hormone. In effect, serotonin counteracts stress. Serotonin is also secreted in large amounts by enterochromaffin cells in the gastrointestinal tract.

Some antitumor drugs induce irritable bowel syndrome (diarrheal type), nausea, and vomiting by stimulating serotonin through serotonergic receptor 5-HT3 [111,112]. In a second pathway, locally secreted serotonin stimulates the central nerve, causing nausea and vomiting.

Serotonin generation is mediated by digestion and nutrient assimilation (nutrition), but also effects psychosomatic stress. When tryptophan is metabolized, melatonin is synthesized via serotonin and an intermediate compound [3]. If age alters digestive and absorptive functions, older individuals may produce insufficient serotonin, thereby affecting their mood; i.e. serotonin insufficiency may cause depression [100]. Given these potential consequences, the symptomatic treatment of gastrointestinal diseases, such as peptic ulcer, IBS or IBD, should be combined with treatment of psychosomatic stress.

Although stress was once believed to cause peptic ulcers, recent research suggests that the primary cause is H. pylori. Similarly, although previous findings have suggested that hemorrhagic erosive gastritis is caused by stress, most cases of UC and IBS are caused by immune abnormality. Nevertheless, clinical experience suggests that high stress exacerbates these conditions and that stress control in turn relieves UC symptoms [113]. Given the lack of a clinical biomarker, stress levels are difficult to evaluate objectively, but psychosomatic stress levels can be estimated from serum DHEA-s/cortisol ratio [3]. We suggest a DHEA-s/cortisol ratio ≥ 20 is normal or ideal, between 13 and 20 is borderline and ≤ 13 indicates high stress levels.

Elevated stress levels fatigue the body, and the most effective relief is rest and sleep. We counsel persons suffering from high levels of mental or relationship stress to avoid known sources of stress when possible, and to seek help from families, friends, coworkers, and doctors. Ignoring stress or dealing with stress alone can prove particularly injurious and a stressed patient should be encouraged to seek counseling. Stress also reduces sleep quality, in turn delaying recovery in a vicious cycle.

Low values of blood urea nitrogen (BUN) may indicate protein or amino acid deficiency and apathy, which can reduce stress resistance. Given the abundance of serotonin available in bananas, dairy products, sesame, eggs, and bean products, including bean curd and natto [100], nutritional deficiencies may be corrected by including these products in the diet.

In another biochemical pathway, the metabolism of tryptophan to melatonin is obstructed by iron and vitamin B deficiency. Consequently, the consumption of foods rich in vitamin B and minerals can resolve common issues and disorders.

3. Oxidative stress

We believe our Anti-Aging research indicates that oxidative stress is linked with arteriosclerosis, the accumulation of oxidative products in nerve cells, and gene damage that might lead to cancer induction [114]. Oxidative stress is caused by ROS produced via cellular energy generation, from carbohydrates in mitochondria in addition to exposure to external factors (i.e. smoking, ultra violet radiation, toxic chemicals) that produce free radicals. ROS activity can be countered with antioxidants, such as ubiquinone (CoQ10) and α-lipoic acid, which are also found in mitochondria [114]. However, the quantitative and qualitative antioxidant functions of mitochondria decrease with age, and this decline can be exacerbated by other iatrogenic problems. For example, statins (or HMA-CoA-reducing enzyme inhibitors) used to reduce cholesterol levels in patients with hyperlipidemia, also inhibit CoQ10 synthesis [115-117]. Consequently, older patients who are prescribed statins may be CoQ10-deficient. In these cases, CoQ10 supplements should also be prescribed.

Several diseases of digestive organs are associated with oxidative stress. Initial research into the effect of oxidative stress on gastro-enteric disease found that ischemia-reperfusion injury in the small intestine [118] or stomach [119] increased production of ROS, thereby injuring these tissues. Infections by injurious bacteria, such as H. pylori also increase ROS production in the gastric mucosa, thus increasing oxidative stress and perpetuating the damage.

The progression of several liver diseases, including chronic hepatitis C [120], progression of NAFLD to NASH [121], and alcoholic liver diseases, is also related to oxidative stress. Phlebotomy for hepatitis C patients removes excessive iron and controls ROS production. These findings indicate that oxidative stress is involved in inflammatory and metabolic diseases of the liver.

Lifestyle activities, such as aerobic exercise, antioxidant intake, and detoxification, are known to maintain anti-oxidative capability in the human body [122]. In particular, detoxification may control the intake of food additives and promote waste elimination, thus reducing materials that generate ROS.
4. Glycation Stress

Glycation reactions (Maillard reactions) form advanced glycation end products (AGEs) from proteins and reducing sugars (fructose, glucose, etc.) via intermediate Amadori compounds \(^{123}\). Protein glycation and accumulation of AGEs damage cells by interfering with receptor for AGEs (RAGE) and altering protein structure. Excess glucose has been shown to glycate proteins and alter the TCA cycle, resulting in an excess of fumaric acid which then reacts with cysteine to produce S-(2-succinyl) cysteine (2SC) \(^{124}\). 2SC accumulation subsequently alters the function of several proteins, such as cytoskeleton, heat shock, and adiponectin proteins, in a process called glycation stress (Fig. 2) \(^{125}\).

Glycation stress is associated with several age-related conditions, including atheroma arteriosclerosis (the modification of LDL cholesterol); bone degradation, which increases the risk of fracture; skin deterioration arising from the cross linking of collagen by AGEs; AGE accumulation in brain cells is implicated in Alzheimer’s disease; and AGE-related delays in wound healing in diabetics \(^{126}\).

In addition, healing of postoperative anastomosis injury, incision wounds, and peptic ulcers may all be inhibited by AGE accumulation. Experiments with diabetic rat models have demonstrated that healing of acetic acid-induced ulcers was accelerated by the administration of anti-glycation substances, without affecting blood sugar management \(^{126}\). These findings imply that AGEs produced by glycation stress may delay the healing process of the gastric mucosa; this may also arise from the glycation of lysine and arginine residues of peroxiredoxin 6, a tissue-repairing enzyme \(^{126}\).

Liver function may also be affected by glycation. Several authors have reported that the blood AGES concentration is correlated with the NAFLD activity score (NAS) and stage of hepatic fibrosis \(^{127}\).

Glycated heat shock protein 27 is reported to be a specific cancer tumor marker, particularly abundant in the gastrointestinal region \(^{128}\), which implies that glycation may induce carcinogenesis. Several reports indicate that diabetes mellitus may be associated with an increased risk of colorectal cancer \(^{129-131}\).

AGEs also activate intracellular signals via RAGE, which in turn activates the transcription factors NF-κB and BAP-1 and induces production of inflammatory cytokines MCP-1, PAI-1 and vascular endothelial growth factor (VEGF); VEGF is known to induce platelet aggregation \(^{132}\). Research indicates that of all the AGEs identified so far, pentosidine has the highest activity for inducing NF-κB \(^{133}\). Taken together, these results imply that inflammatory symptoms of gastrointestinal diseases may be exacerbated by glycation stress.

In addition to their effects on intracellular signaling, AGEs also affect the circulatory system. Nitric oxide (NO) production is induced in endothelial cells by nitric oxide synthase (iNO) and stimulates blood vessel dilatation \(^{134}\). If angiotensin II concentration is increased in response to elevated RAS activity, iNO and subsequently NO production fall; this fall leads to a rise in NADPH oxidase activity and an increase in ROS production through the AT1 receptor \(^{132}\). The biochemical sequence is the same as that causing increases in the NADPH oxidase activity and ROS production in the AGES/RAGE system; we believe that

**Fig. 2.** Glycation stress and gastrointestinal and liver diseases. 
AGEs: advanced glycation end products; RAGE: receptor for AGES; NAFLD: non-alcoholic fatty liver disease; NASH: non-alcoholic steatohepatitis.

Figure derived from Ichihashi et al. \(^{125}\).
positive feedback may occur between the two systems (RAS and AGE/RAGE); the interaction between RAS-NADPH pathway and AGEs/RAGE pathway is called “cross-talk”\textsuperscript{132}. These conditions impair the microcirculation in the alimentary canal wall and may exacerbate other alimentary diseases.

Many diseases can be partially treated by adopting habits that reduce the rate of blood sugar increase and insulin secretion. These habits include eating, diet, exercise, and lifestyle. Glycation stress can be managed by eating so that the rate of blood sugar increase after meals is limited; rapid increases in plasma glucose levels lead to excess insulin secretion, which leads to increased insulin resistance and visceral fat storage. Further, the longer a hyperglycemic state (>160 mg/dl glucose) lasts, the likelier glycination is to occur, and we suggest that post-prandial glucose concentrations should be kept below 160 mg/dl.

First – and most importantly – patients should be counseled on good diet, proper nutritional balance, and caloric intake. Second, patients should adopt eating habits that minimize increases in plasma glucose and insulin levels (eat slowly, chew well, and eat fibrous foods, proteins, and carbohydrates in that order), and reduce sugar intake by avoiding confectionery, artificial juices, carbonated drinks, and isomerized syrup (which contains high-fructose corn syrup). Third, patients should exercise to maintain skeletal muscle mass that might otherwise decrease with age\textsuperscript{125}.

Persons experiencing increased glycination stress because of unhealthy eating habits, diabetes, and metabolic syndrome may be treated with any one of several anti-glycation herbal products, such as Houttuynia cordata, chamomile (Anthemis nobilis), kamille (Crataegus oxyacantha) and grape leaf (Vitis vinifera), chrysanthemum flower (Chrysanthemum morifolium), and kumaizasa (Sasa senanensis Rehder)\textsuperscript{135-137}.

5. Lifestyle

Digestive system diseases may also be caused by an unhealthy diet, lack of exercise, poor-quality sleep or sleep deprivation, reduced fluid intake, or smoking and drinking habits\textsuperscript{138}. Smoking and heavy drinking are known to increase oxidative stress, and sleep deprivation and irregular sleep habits may delay recovery from mental and physical stress. Bad eating habits also increase glycination stress, and a lack of exercise causes a decline in GH/IGF-I secretion and muscle mass and degrades carbohydrate and lipid metabolism.

Digestion-related diseases may be improved by changes in lifestyle\textsuperscript{52,63,138}. For example, women who exercise more increased their serum IGF-I and DHEA-s levels\textsuperscript{139}; this increase benefited the functions of the alimentary tract and liver, ameliorated injury to the gastrointestinal mucosa caused by peptic ulcers and IBD, and improved wound healing after surgery. We also believe that exercise may inhibit the onset or development of NAFLD by improving sugar and lipid metabolism. Improvements in lifestyle may also enhance ordinal medical care of digestive organs and liver.

Conclusion – future expectations for Anti-Aging Medicine

Here, we discussed several potential benefits of Anti-Aging Medicine to gastroenterology. Although specialist knowledge of gastroenterology is essential to clinical treatment and research from a systemic point of view, Anti-Aging Medical experience can provide clinicians with additional information on extraneous factors linked to digestive system conditions. Anti-Aging indices assess aging (phenotype) and aging risk factors (inducers). We believe digestive diseases are linked to mental, physical, oxidative and glycination stresses, and the correction of these conditions has potential to prevent disease and promote treatment of existing diseases.

However, individuals age at different rates and in different ways, and a uniform management regimen is not feasible. Consequently, clinicians should assess the functional age of body systems for individual patients and treat the most significant risk factors. We believe that the treatment of digestive organ diseases can be augmented by Anti-Aging premises and methods, and that further development of Anti-Aging Medicine will benefit the specialized field of gastroenterology. This paper was presented as an invited lecture at the 191st Tohoku Branch Meeting of the Japanese Society of Gastroenterology (Morioka-city, Iwate, Japan) in 2011.

Conflict of interest statement:

The authors declare no financial or other conflicts of interest in the writing of this paper.
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