Changes in circulatory I-FABP in elderly persons in daily life: a pilot study.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal vascular conditions
Study type	Observational invasive

Summary

ID

NL-OMON44117

Source
ToetsingOnline

Brief title
Circulatory I-FABP changes in elderly people.

Condition

- Gastrointestinal vascular conditions
- Appetite and general nutritional disorders

Synonym
intestinal ischemia, malnutrition

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: ageing, elderly, I-FABP, intestinal integrity

Outcome measures

Primary outcome

50% increase of I-FABP concentration in plasma compared to baseline value.

Secondary outcome

NA

Study description

Background summary

In 2010, 326.202 patients aged 65 years or older underwent surgery in the Netherlands, which is 25% of all operations executed that year. Since the elderly population will double in the next years, more and more older patients will undergo surgery. Older age is associated with increased mortality and morbidity after surgery. Fifty-one percent of cancer patients of 70 years and older requiring surgery have a postoperative complication. Also, major surgery is associated with a significant reduction in physiologic and functional capacity. A major cause of increased adverse outcomes in elderly patients undergoing surgery is the high prevalence of malnutrition. In a cohort study that explored the nutritional state in 4500 elderly (both clinical and in the general population), 23% was in a state of malnutrition and a further 46% was at risk to develop malnutrition. The percentage malnourished elderly in hospitals and geriatric rehabilitation units was even higher. Malnutrition increases the vulnerability of elderly in general, and is an independent risk factor impacting on higher complications and increased mortality, length of hospital stay and costs. Preliminary data of onco-geriatric studies in the UMCG show a fourfold increased risk for development of postoperative complications in patients with pre-operative malnutrition. Thus, prevention and treatment of malnutrition is of major clinical and economical importance. There are multiple causes of malnutrition in the elderly including decreased smell and taste, age-related changes in the brain causing a dysregulation of the energy balance, delayed gastric emptying, spontaneous gastroesophageal reflux and social factors such as depression and stress. We hypothesize that low grade intestinal damage, resulting in a decreased uptake of nutrients, is another important contributor to the malnourished state of many elderly patients.

Intestinal integrity

The bowel harvests the largest immune system of our body. The intestinal wall is the major barrier between host and environment and the intestinal barrier plays an important role in health and disease. Recently certain diseases, such as inflammatory bowel disease and celiac disease, were shown to be associated with increased intestinal permeability. Therefore, preserving intestinal integrity forms a potential new target for disease prevention and therapy. Until now insight in gut barrier integrity and function loss was limited because of a lack of practical, non-invasive measurement methods; the measurements were often cumbersome and demanding for the patient. However, lately there is more interest in serologic biomarkers to determine intestinal integrity. One of these serologic biomarkers is I-FABP, which is released upon enterocyte damage.

I-FABP

Fatty acid binding proteins (FABPs) are small cytoplasmic proteins involved in cellular long-chain fatty acid metabolism and are abundantly expressed in tissue with an active fatty acid metabolism like heart and liver. After cell damage, these cellular proteins are released into the interstitium and will diffuse through endothelial clefts into the circulation and are therefore sensitive novel biomarkers. Until now 9 different FABP types are known, each type has a characteristic pattern of tissue distribution. Heart FABP has been reported the most sensitive marker for myocardial injury. In the bowel, 3 different FABP types are present: intestinal FABP (I-FABP), liver FABP (L-FABP) and ileal bile ABP (I-BABP). I-FABP is solely present in the entire intestine and not in other organs, which makes it the most specific FABP subtype to analyze intestinal damage. I-FABP is present in the cytoplasm of enterocytes on top of the bowel villi. During normal circumstances, the I-FABP value in plasma is low to negligible and reflects the physiological turnover rate of enterocytes. The effect of decreased intestinal perfusion followed by reperfusion, as studied in a human translational ischemia-reperfusion model, led to damage on the tip of the villi and increase of I-FABP. Even after a short period of ischemia, with morphologic hardly noticeable intestinal ischemic damage, there was a tenfold increase in I-FABP. This emphasizes the high sensitive nature of I-FABP and indicates that enterocyte membrane integrity loss alone is sufficient to cause increased plasma I-FABP levels.

I-FABP as a marker for acute intestinal damage has been studied in multiple patient groups. Patients who underwent open aortic aneurysm repair, during which the aorta is clamped resulting in temporarily closure of the intestinal circulation, showed an I-FABP increase during surgery with a peak at the end of the surgery and a decrease to baseline after the first postoperative day. Patients who developed intestinal necrosis, a known and severe complication of open aorta repair, displayed exceptionally high I-FABP levels at the end of surgery and on the first postoperative day, thus assessment of plasma IFABP levels enables early identification of patients developing intestinal necrosis after open aortic repair. Also for trauma patients and neonates suffering from

necrotizing enterocolitis (NEC), high I-FABP values are related to intestinal ischemia. In otherwise healthy children undergoing spinal fusion surgery because of scoliosis, plasma I-FABP increased significantly during surgery and quickly returned back to baseline postoperative. Plasma I-FABP was significantly negatively correlated with mean arterial pressure. During a further study it was demonstrated that this increase in I-FABP didn*t occur if the mean arterial pressure was *60mmHg which indicated that an adequate intestinal perfusion prevents damage of the enterocytes.

The usefulness of I-FABP as a marker for gut dysfunction was also studied in healthy individuals and patients with a chronic disease. Young, healthy volunteers who cycled for one hour showed a significant I-FABP increase, without any complaints such as nausea or abdominal pain. I-FABP is significantly elevated during the transient postprandial ischemic episode in chronic gastro intestinal ischemia patients. COPD patients (mean age 64 years old) showed a significant I-FABP increase during the performance of activities of daily living, such as walking, dressing, doing the laundry and cleaning. This implicates that the impaired gas exchange characteristic for COPD, worsens during exercise. Patients with moderate to severe COPD are often cachexic which raises the question if the compromised bowel in these patients contributes to this malnourished state.

The control group of the fore cited study in COPD patients ,constituting of a group of healthy volunteers matched for age, sex and BMI, showed no I-FABP increase during these activities of daily living. The control group in the study of Mensink et al, consisting of healthy volunteers, showed undetectable or within normal serum levels of I-FABP before and after a standard test meal in all healthy participants.

Intestinal atherosclerosis in the elderly
We postulate that occurrence of intestinal damage in elderly under daily circumstances is associated with atherosclerotic changes in the intestinal circulation, a condition with a high prevalence in the older population. Fifteen percent of individuals had at least two stenotic mesenteric arteries as evaluated in an unselected Finnish autopsy series of 120 cases. The occurrence of mesenteric artery stenosis was strongly associated with aging. Sixty-seven per cent of the subjects aged 80 or more presented with mesenteric artery stenosis, whereas the rate was 6% among those aged less than 40 years. Mesenteric artery atherosclerosis was strongly associated with atherosclerosis in coronary arteries and cerebral arteries in the skull base. In the Netherlands, 21% of men and 11% of women are suffering from a coronary heart disease as a result of atherosclerosis. Generalized peripheral arterial disease is also a frequent condition, 7% of women and 10% of men aged 55-59 and 52% of women and 60% of men aged 85 years or older are affected.

Purpose:
Our hypothesis is that, analogous to the fore cited COPD patients, low grade

intestinal ischemia is present in part of the elderly under daily circumstances. Atherosclerosis affects blood flow redistribution, thereby redistribution of the cardiac output during exercise or postprandial, as appears in the physiological state in healthy individuals, might be compromised in the elderly. Low mesenteric blood flow subsequently leads to injury of the cells at the most distal point from the mucosal blood supply, being the mature enterocytes, evidenced by I-FABP release into the circulation. This disturbed membrane may reduce the digestive and absorptive capacity of the intestinal tract and contributes to malnutrition in elderly patients. Before performing extensive studies in vulnerable onco-geriatric patients, we perform the present pilot study in elderly persons in the general population.

Study objective

We will investigate the effect of the combination of moderate physical activity and a standard meal on the onset of low grade intestinal ischemia. Will will use the serological biomarker I-FABP to determine the occurrence of low grade intestinal ischemia.

Study design

A minimal invasive study design was set up to obtain a proof of concept in the general elderly population before performing more extensive experiments in a vulnerable onco-geriatric patient cohort. This study will be performed in elderly people aged 75 years and older receiving person-centered and integrated care and support by Embrace. Thirty volunteers of >75 years will be included. This study consists of an intake interview and one testing day.

Intake interview: General characteristics of the volunteers are recorded including gender, medical history and medication. A nutritional assessment including a short questionnaire (Patient Generated Subjective Global Assessment; PG-SGA) is taken.

Testing day: Volunteers perform a walking test. No fasting is required before this test. After the walking test volunteers will eat a standard meal. The plates are weighed and a picture of the plate is taken before and after the meal to calculate the ingested macronutrients and calories. A drip is placed in a vein in the forearm, through which 8 samples of blood are taken in 2,5 hours. In total, 48ml of blood is taken, constituting <1% of total blood volume. The drip is removed following the last blood withdrawal.

Study burden and risks

Burden:
- intake interview, max 1 hour

- drip placement for 2.5 hours. Risk: pain, bleeding

- walking test. No risks involved

- consumption of a standard meal. No risks involved

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age 75 years or older (both sexes)
2. Signed written informed consent
3. Able to comply with the protocol

Exclusion criteria

1. Previous gastrointestinal resections
2. Chronic inflammatory gastrointestinal disease

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	04-07-2016
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	21-06-2016
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	24-08-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL54574.042.16