The AF protein
A clinical innovation of endogenous origin

Twenty years of Swedish research has led to the discovery of the Antisecretory Factor (AF), an endogenous protein with significance in secretory and inflammatory disease. The research has already resulted in medical foods with clinical use.

CLINICAL STUDIES AND CASE REPORTS

This brochure tells the story of 20 years of Swedish research leading up to the discovery of the endogenous AF protein, an antisecretory factor with the ability to regulate cellular fluid and ion transport over cell membranes in various organs of the body. The effect of the AF protein on different types of secretion is very pronounced. Diseases where the transport of fluid is disturbed, for instance in gastrointestinal diseases, diarrhoea and Mb Ménière, have been studied to assess the clinical significance of AF protein. It has also shown marked anti-inflammatory properties that have been proven in studies of Irritable Bowel Diseases (IBD), rheumatic diseases and mastitis (inflammation of the breast). Recent American studies describe that the AF protein might even have an important role in regulating our immune system.

This brochure focuses on results from multiple clinical trials performed on patients with various diseases in which AF protein most likely is of functional importance. A number of case reports are presented, describing the positive effects of SPC (specially processed cereals) and Egg yolk powder B221® on a number of diseases.

Read more about AF protein and follow the journey from research to finished product in our brochure The AF protein – A clinical innovation of endogenous origin: Research and Development or on our website www.as-faktor.se

The AF protein – a Swedish discovery

Pioneering research

In 1986 the use of antibiotics in animal feed was banned in Sweden, as one of the first countries in the world. The ban resulted in increased diarrhoea and mortality in piglets.

Since the 1980's Stefan Lange and Ivar Lönnroth at the Department of Clinical Bacteriology at the Sahlgrenska University Hospital in Gothenburg, Sweden had been studying mice and cholera disease. They were searching for a substance that immunized mice and rats to diarrhoea caused by cholera toxin. Lange and Lönnroth discovered an endogenous system that reacted faster than the immune system, probably an endogenous substance prone to different types of stimulation. The resistance could be triggered by the addition of enterotoxins or by a combination of amino acids and sugars in defined proportions. The protein was named Antisecretory Factor, in short AF. This regulatory protein affects the intestinal fluid and electrolyte balance in cell membranes in different organs. It is the most potent anti-diarrhoeal substance identified. AF normalises intestinal fluid secretion, an important factor in the treatment of diarrhoeal disease.

An AF-stimulating feed was developed through a patented process involving hydrothermal treatment. The cereals, oats and wheat, are first soaked in water, then heated. No additives are needed in the process. This enzymatically activated specially processed cereal (SPC) stimulates the endogenous production of AF protein. In 1991 an AF-feed intended for piglets and sows was introduced and has become the dominating feed on the Swedish market.

The encouraging results from the animal research led the researchers to look beyond and widen their scope and produce a drug based on a synthetic AF peptide as well as medical food for human use.

The researchers began to test the piglet feed on themselves, preparing it as a porridge and baking bread. Also the gastroenterologists at Sahlgrenska University Hospital became interested and began tests on patients with ulcerative colitis. All patients treated showed favourable results and responded with a significant increase of AF in the blood. This effect remained measurable for four weeks after the intake of piglet feed.

Europe's first medical food

Encouraged by the positive results seen on man the desire became to produce food based on AF protein. Since 1999 it is possible to approve dietary foods for special medical purposes within the EU. The MagiForm® product range was the first to be approved according to the new legislation. The product range includes muesli, rusks and biscuits with AF stimulating effects. The range expanded to also include more potent stimulators in the form of pure SPC and Egg yolk powder B221®, a vehicle for exogenous administration of high dose AF protein.

Regulates fluid transport

The AF-protein is of medium size, 41 kDa, comprised of 380 amino acids with the active region located as a peptide of 8-38 amino acid length in the terminal N-region of the protein. It is possible to produce highly purified protein through microbiological methods as well as chemical synthesis.

The protein has its own pharmacological effect and initiates production of endogenous defence mechanisms against secretion and inflammation.

Within a couple of hours the plasma level of AF rises quickly following exposure to diarrhoea stimulation by e.g. bacterial toxins. An elevated synthesis of AF can also be achieved by the ingestion of AF-inducing specially processed cereals (SPC). It has effect in regulating fluid transport over the intestinal wall in e.g. Crohn's disease and fluid pressure in the inner ear in Ménière's disease. Aside from the highly potent antisecretory activity, AF protein also has important anti-inflammatory effects which have proven clinically important in e.g. ulcerative colitis, Mb Crohn, rheumatoid arthritis and mastitis.

With immunohistochemistry techniques it has been shown that AF is present in most tissues in the body. Eva Jennische, at Gothenburg University, has shown that AF protein is located in three cell types; epithelial cells, lymphatic cells and nervous cells. Research is ongoing to identify a true classical receptor for AF and to develop an analytical method for blood measurement of AF in man.

Diarrhoea in intestinal diseases

"No more diarrhoea thanks to SPC"

Tina, a woman in her 40's, was one of the first persons to try the specially processed cereals (SPC). She had heard about the positive results with SPC in animals thanks to her job as the head of a riding school. She asked if she might try SPC on herself. Ten years earlier during a trip, Tina had been infected by enterobacteria and her situation was worsening. She suffered constant diarrhoeas and tolerated less and less foods. Her joints were aching and she experienced an increasing feeling of feebleness.

A turn of events was seen after one month's treatment with SPC. She has gradually, little by little been able to return to a normal diet. Today she can eat anything, she has returned to work, and her stomach is completely restored. She even dares leave the country, but not without her SPC just in case.

FACTS about diarrhoeal diseases

Gastrointestinal disorders are often characterised by altered bowel activities such as diarrhoea, with or without abdominal pain and increased gas. Of all the symptoms seen in functional gastrointestinal disorders, diarrhoea is the most therapy resistant. Of general importance is information concerning diet and lifestyle. It is important to exclude organic disease when diagnosing functional diarrhoea and the diet should be well balanced as regards nutrients and fat. Diarrhoea can also de caused by an infection of the intestines by virus, bacteria, protozoa or worms.

IBS (Irritable Bowel Syndrome) is a collective term describing a number of symptoms connected with altered bowel activity that are not necessarily of similar origin or mechanism. One group is non-painful diarrhoea. Even in this case it is important to exclude organic disease. It is not uncommon with functional gastrointestinal disorders in children and adolescents; even colon irritable occurs.

In bloodstained diarrhoea ulcerative colitis can be assumed, but identification of Crohn's disease is not as obvious.

AF treatment of short intestines/ intestinal resections

After the encouraging preliminary results seen in healthy subjects it was desirable to test the anti-diarrhoeal effects of the specially processed cereals (SPC) on patients with short intestines and severe hypersecretion. An open pilot study was designed under the guidance and expertise of Ingvar Bosaeus at the Sahlgrenska University Hospital. One aim was to study if an induction of AF could be seen in patients despite a reduced intestinal length.

The study included eight patients with varying extents of intestinal resections due to Crohn's disease. The length of their small intestine varied between 80-400 cm. All patients suffered from chronic diarrhoea without concurrent bowel inflammation. Six healthy controls participated. All subjects received 54 g SPC daily for 2 weeks. The daily dose was divided evenly over the day during at least three occasions in connection with mealtimes. The diet and prior medications in the patient and control groups were kept unchanged.

Plasma AF activity was determined before, during and after the treatment period. The SPC diet increased AF activity in all controls. AF activity was increased from a mean of 0,28 ± 0,37 units/ml

plasma prior to treatment to 1,28 ± 0,23 AF units/ml plasma after the two week treatment period ($p<0,05$). Elevated levels of AF (1,28 ± 0,39) were maintained during at least four weeks after intake of the SPC diet.

In the patients baseline values were low (0,04 ± 0,07), rising during the treatment period to a mean of 0,66 ± 0,45 units. The two patients with the longest remaining small intestine, 300 and 400 cm, achieved elevated AF levels comparable to healthy subjects, i.e. over 1 unit/ml plasma. These patients also lowered the number of daily bowel movements. Analysis showed that there was a significant correlation between the length of the remaining small intestine and AF concentration ($r=0.94$, $p<0.01$).

The study showed that AF activity is strongly associated with remaining length of intestines. A small intestine length of at least 1 metre is needed to induce AF and to maintain the elevated levels after the treatment with AF-inducing diet.

Lange, Bosaeus, Jennische, Johansson, Lundgren and Lönnroth, Food-induced antisecretory factor activity is correlated with small bowel length in patients with intestinal resection, APMIS, 2003; 111:985-988

Secretory diarrhoea due to carcinoid tumours

To test if AF primarily influences the secretory component of the diarrhoea, a study was performed on patients with endocrine tumours. Patients with neuroendocrine tumours may suffer from severe diarrhoea, that may be both difficult to treat, treatment resistant and persistent despite an otherwise optimal treatment regime.

The aim of the study was to investigate if specially processed cereals (SPC) and Egg yolk powder B221® could induce AF-activity and if AF-therapy could reduce the number of bowel movements. The treatment with AF products was administered as a complement to the patients' ongoing medical therapy.

Eight critically ill patients were included. Six patients with the midgut carcinoid syndrome and two with metastasizing medullary thyroid carcinoma (MTC) participated. In an initial open part of the study all patients received Egg yolk powder B221® for 4 weeks. This was followed by randomisation to a double-blind crossover period with SPC and control cereals (CCs) without AF inducing ability for 6 weeks in a dose of 1 g/kg bodyweight divided into four doses daily.

Treatment with SPC and Egg yolk powder B221® resulted in a significant reduction of daily bowel movements (Table 1) and several patients reported firmer stools.

All patients had low levels of AF-activity in serum at baseline. During treatment with Egg yolk powder B221®, the mean level increased slightly. AF-activity was also significantly higher after SPC diet. In four of five patients, the AF concentration reached above a level which in other studies correlated well with positive effects of diarrhoea treatment.

Although these patients had been given optimal medical therapy, an added positive effect could be seen with the addition of the AF-treatment. Treatment with Egg yolk powder B221® was well tolerated by all patients. The two patients with MTC and fully intact intestines responded best to SPC-diet with the highest AF levels.

The positive response to Egg yolk powder B221® indicates that AF protein has a local effect in the intestine, directly interacting with the receptors and its binding proteins in mucosal cells. Therapy with Egg yolk powder B221® may hence be the most suitable treatment alternative for patients with difficulties ingesting large amounts of cereals.

Laurenius, Wängberg, Lange, Jennische, Lundgren and Bosaeus, Antisecretory factor counteracts secretory diarrhoea of endocrine origin, Clinical Nutrition, 2003; 22(6):549-552

Table 1. Number of bowel movements during treatment compared by paired *t*-test

Test period	Mean±SD	n	p
Baseline	5,6±2,6	7	<0,01
Egg yolk powder B221®	4,2±2,4	7	
Control cereals	4,0±1,9	5	<0,05
SPC	2,6±1,3	5	

Ménière's disease

"A little SPC at breakfast relieves me of my dizziness!"

10 years ago, Elisabeth woke up and found the room spinning causing her to vomit. One week later she had a spell of dizziness while out for a walk. After another severe spell lasting an entire week she was diagnosed with Ménière's disease. Elisabeth was offered several treatments – diuretics, antihypertensive drugs and even pills for motion sickness – but nothing seemed to help. The spells continued for a year with a few attacks a week. Finally she hardly dared leave the house in fear that she would not make it home before an attack hit her. She became socially handicapped and her mental health deteriorated.

In the spring of 1998 she came in contact with Per Hanner at the Sahlgrenska University Hospital and was asked to enter a study with specially processed cereals (SPC). As she had nothing to loose she agreed. Immediately after she began treatment with SPC her symptoms disappeared and Elisabeth felt as she had got a new lease of life. She has since gradually been able to lower the dose of SPC that she takes with her yoghurt in the morning.

The disease has made Elisabeth almost deaf on one side and she still has tinnitus, but she is now relieved from the troubling attacks of dizziness.

FACTS about Ménière's disease

Ménière's disease is characterised by recurrent attacks of dizziness, nausea, tinnitus and deafness. Quite a large number of patients also suffer from gastrointestinal disorders and diarrhoea is not uncommon. Attacks of dizziness last between 20 minutes up to a day, but can in some cases last even longer. Attacks are preceded by a few days of tinnitus and reduced hearing in the affected ear. The intensity of the symptoms can vary. Early in the disease the symptoms will disappear in the reverse order they appeared; balance returns to normal, hearing returns and tinnitus disappears. If the disease is in an active phase the attacks may come several times a week and the hearing loss does not have time to heal in between. If the disease is allowed to continue, the loss of hearing and harm to the balance becomes permanent.

The cause of the disease is unknown, although it is believed it may be due to an elevated pressure in the inner ear leading to severe attacks of vertigo and nausea. The elevated pressure may be caused by hypersecretion of fluids by endolymph cells in the section of the ear connecting the cochlea with the balance organ. The elevated pressure may also be caused by insufficient drainage of fluids from the inner ear. Increased pressure in the inner ear will cause rotatory vertigo. Pressure on the cochlea may cause hearing loss and/or tinnitus.

Every year 400 persons are subject to the disease. Many believing they are having a brain aneurysm or something even worse. In total it is estimated that 40 000-50 000 Swedes are currently contracted with the disease.

SPC-treatment of Ménière's disease

Since the AF products have such favourable results in secretory diseases of the gut, it was hypothesised if this could also be applied to other conditions where fluid imbalances are of importance or can be suspected.

After several pilot studies a trial was performed at Sahlgrenska University Hospital under the guidance of Per Hanner. The aim of the study was to examine if AF could be induced in cases of pathologically elevated pressure of the inner ear and to study if stimulated AF production can lessen the clinical symptoms of Mb Ménière patients.

24 patients with Mb Ménière, with a duration between ten months and thirty years, were included in the study. The patients received, in addition to their regular medication, a SPC-diet at a dosage of 1 g/kg bodyweight and day, for 2-4 weeks. The patients kept a diary over their subjective and auditive symptoms, and frequency, duration and characteristics of vertigo. Baseline tone and speech audiometry and neurological status was determined as well as AF plasma level before and after the treatment period.

The concentration of AF in plasma varied between 0-0,6 units before treatment and 0-1,7 units after treatment. 83% of the patients showed an increase of AF above 0,5 units after treatment, the level at which clinical improvement of secretory diarrhoea has been shown in previous studies. In 17% of the patients, little or no increase of AF was seen and they did not experience any improvement of the clinical symptoms either. In 29% of the patients a significant increase of AF was registered but without clinical response.

In 12,5% of the patients hearing ability returned to normal levels and vertigo was completely eradicated. In 54% vertigo was improved. The improvements noted ranged from complete remission to remaining light and diffuse feelings of dizziness without previous attacks of rotatory vertigo.

Symptoms were either reduced or in complete remission in more than half of the patients with severe Ménière's disease who were treated with a simple, inexpensive and well tolerated treatment. Some of the patients, however, did not seem to have the ability to produce AF. They may need AF inducing cereals in higher concentrations or for longer treatment duration.

Hanner, Jennische, Lange, Lönnroth and Wahlström, Increased antisecretory factor reduces vertigo in patients with Ménière's disease: a pilot study, Hearing Research, 2004; 4803:1-6

Treating Mb Ménière with Egg yolk powder B221®

As the study above showed, there are some patients that are non-responders when treated with AF inducing specially processed cereals (SPC). Due to the positive results of Egg yolk powder B221® in the treatment of secretory diarrhoea, it was tested on Ménière's disease as well.

AF-inducing SPC was tested during a two month period on a 67 year old woman with a thirty year history of Mb Ménière. She had frequent attacks lasting for 8 hours up to three days with nausea, vertigo, diarrhoea and vomiting. When the SPC diet did not improve neither the duration of the attacks nor the severity, she was given Egg yolk powder B221® at a dose of 2 g five times daily to see if this exogenous administration of AF in high concentrations could offer positive clinical results.

On day 18 of the treatment the patient was completely relieved of her symptoms and her Ménière status was improved from 6 to 1 (American Academy of Otolaryngology). After six months of symptomatic relief the patient lowered the dosage of Egg yolk powder B221® with the result that her attacks with rotatory vertigo returned. Returning to the original dosage level led to immediate improvement without the need for further medication. No improvement, however, could be seen on her right-sided hearing impairment.

The results show that patients who do not respond to treatment with AF-inducing cereals can be favourably treated with Egg yolk powder B221®. To stimulate the body's own production of AF it is likely that an introduction of AF-inducing cereals in connection with or as a follow-up to Egg yolk powder B221® treatment will be found valuable.

Hanner, Jennische and Lange, Antisecretory Factor: A clinical innovation in Ménière's disease?, Acta Otolaryngol, 2003; 123: 779-780

IBD – Crohn's disease and Ulcerative colitis

"AF treatment gave me a second chance in life"

A 38-year old man with a long history of Crohn's disease, multiple resections and immunosuppressive treatment saw his state deteriorate drastically during the course of a year. He had 15-20 bloodstained diarrhoeas per day and had lost 25% of his weight. He was tired and his joints ached. Despite every imaginable treatment, including infliximab, his state did not improve. The little he had left of his colon was severely inflamed. As he already had lost so much colon he declined further resection and asked if there was something else he might try.

He was offered Egg yolk powder B221®, an exogenous source of highly concentrated AF protein. After a few days treatment he was also given specially processed cereals (SPC) in order to stimulate his own production of AF.

Already within 2 days his diarrhoeas diminished and after 12 days he had none, only a couple of loose stools and none of them bloodstained. His fever went away as well as his abdominal pain and he generally felt a clear improvement. Effect could also be seen on laboratory results and inflammatory markers. The rapid reduction of his intestinal secretion remained. Three months following the treatment the man had regained his previous bodyweight and he could discontinue the use of other medication. Morphologically, his colon was to a great extent completely restored.

FACTS about Crohn's disease (chronic inflammation of the intestines)

Crohn's disease is a chronic inflammation of the intestines that periodically will present itself as abdominal pain, diarrhoea and weight loss; in-between periods of no or little symptoms. The disease affects patients in their twenties and once the disease begins, it tends to be a chronic, recurrent condition with periods of remission and disease exacerbation. At times symptoms are scarce but at present there is no known cure for the disease. It primarily causes ulcerations in the small and large intestines, but can affect the digestive system anywhere between the mouth and the anus. The affected parts of the intestine are red and swollen and sores and bleeding ulcers can arise. When the inflammation heals scarred tissue may result in intestinal constrictions.

The cause of Crohn's disease in not known, although it does seem to run in the family. One theory is that the body's immune system reacts to a virus or bacteria by causing ongoing inflammation in the intestine mucous membrane and deep tears (fistulas) in the intestine wall. The disease is more common in smokers.

Depending on how large part of the intestine is involved the symptoms will vary accordingly. Many patients will have felt weak symptoms for several years before a diagnosis. Symptoms vary from fever, persistent diarrhoea (loose, watery or frequent bowel movements), crampy abdominal pain (due to constrictions in the intestine), fatigue (since the body's ability to absorb nutrients from food is reduced), loss of appetite with subsequent weight loss and a sense of sickness. Some patients may develop tears (fissures), which may cause pain and bleeding, especially during bowel movements. Inflammation may also cause a fistula to develop. A fistula is a tunnel that leads from one loop of intestine to another.

However, the disease is not always limited to the GI tract; it can also affect the joints, eyes, and skin. In certain cases it can also affect the liver and kidneys and there is an increased risk for blood clots and intestinal cancer. In general, though, people with Crohn's disease lead full or almost full, active, and productive lives. Several studies show that the life expectancy is not reduced.

In Sweden 500 patients a year are diagnosed with Crohn's disease and it is believed that the prevalence is 30 000 people. It is slightly more common in women than in men.

AF treatment of inflammatory bowel diseases (IBD) – Mb Crohn and ulcerative colitis

A study was performed to see if AF inducing cereals could promote endogenous AF production in patients with ulcerative colitis and Crohn's disease, and to determine if an elevated AF level was correlated to clinical improvement of intestinal function.

The experimental group consisted of 26 patients given AF inducing cereals as muesli, bread and/or pasta in addition to their regular diet during 30 days. A control group of 24 received a similar diet without the AF inducing properties. Patients were asked to keep a diary over bowel symptoms, and plasma levels of AF and rectal biopsies were evaluated before and after treatment.

Results showed that the patients receiving active treatment significantly improved intestinal function correlating to increased plasma AF levels. Elevated AF levels were sustained one month after treatment (p<0,001). No effect was seen in the placebo group (Fig. 1). A significant accumulation of AF in intestinal epithelial cells of the active treatment group was seen with colonic biopsies.

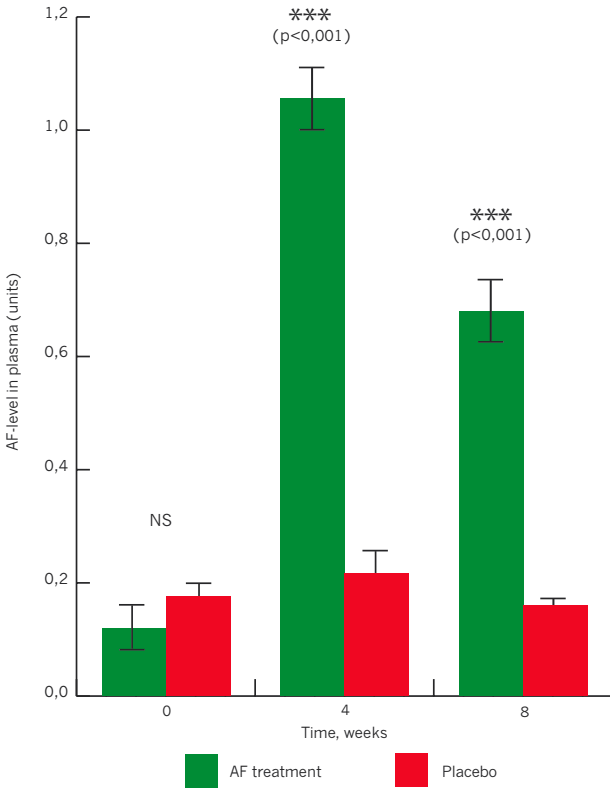

Figure 1. Patients treated with specially processed cereals (SPC) had significantly higher AF-levels in plasma compared to placebo. SPC-treated patients also got a significantly better intestinal function.

Subjective ratings of clinical symptoms according to VAS were significantly improved (p<0,05) in the group receiving active treatment (mean +34,6%) compared with placebo (mean 15,4%) (Fig. 2).

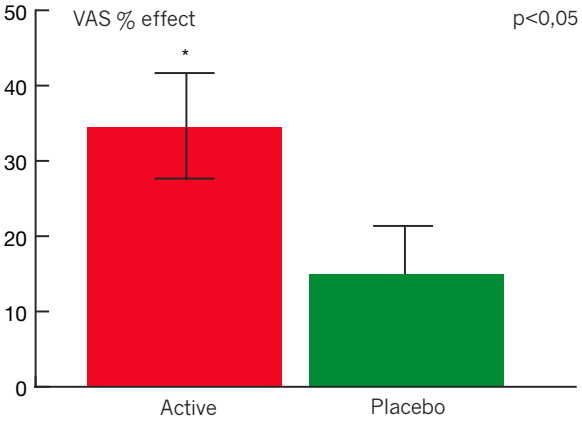

Figure 2. AF-treated patients showed a significant improvement in subjective symptoms as compared to the placebo group.

Due to the findings of this study the surgeons have begun AF-treatment of more patients undergoing GI-surgery in which through experience the outcome is known to lead to reduced intestinal function. Treatment is started very early, in some cases the first day, by giving Egg yolk powder B221® dissolved in ordinary juice. This is a way of administering high amounts of AF directly to the intestines without having the body producing it first. Most of the time the administration of Egg yolk powder B221® can be discontinued after 5-10 days and changed to a maintenance dose of AF inducing cereals, since the desire is to stimulate the patients endogenous production of AF.

Björck, Bosaeus, Ek, Jennische, Lönnroth, Johansson and Lange, Food induced stimulation of the antisecretory factor can improve symptoms in human inflammatory bowel disease: A study of a concept, Gut, 2000; 46:824-829

Treatment of severe Mb Crohn

Prior positive results from AF-treatment on Crohn's patients encouraged an open study on a group of six patients with severe, prolonged treatment resistant Crohn's disease. Patients were treated with AF inducing cereals during three months. Clinical symptoms, blood samples, endoscopic and histological examination, CDAI (Crohn's Disease Activity Index) and quality of life (SF-36) were evaluated.

A continuous and significant improvement of clinical symptoms and quality of life measurements was seen as well as histological improvement. Findings from this and earlier studies show the anti-inflammatory activity of the specially processed AF inducing cereals which has proven to be of clinical importance.

Shafazand, Eriksson, Jennische och Lange, Födoinducerad ökning av antisekretorisk faktor förbättrade det kliniska tillståndet hos sex patienter med svår Crohns sjukdom, Posterpresentation vid Riksstämman, 2003

Treatment of acute onset of ulcerative colitis with Egg yolk powder B221®

The influence of an additive treatment of orally administered AF, through Egg yolk powder B221®, was studied in patients suffering from acute onset of ulcerative colitis. Patients were randomised to either 2 g Egg yolk powder B221® four times daily for 14 days or corresponding placebo egg powder.

A total of 20 patients, 10 in each group, fulfilled this prospective, randomised, double-blind study. The intake of Egg yolk powder B221® was used as an additive treatment to conventional medication, which also included parenteral or enteral nutrition.

Earlier trials performed on patients with chronic IBD, endocrine diarrhoea and diarrhoea due to intestinal resection showed varying, but significant effects on the number of bowel movements following induction of AF. The aim of this study was primarily to measure the histological effects on the intestinal epithelium. In addition other laboratory parameters of inflammation and clinical effect were studied.

During AF treatment, a reduction of inflammation in mucosal biopsies was found. The secretory effect was not significantly different between groups. It is probable that the antisecretory effect of AF in ulcerative colitis is of importance only after the reduction of inflammation. The observation that AF treatment partially restored the intestine supports this hypothesis. It is likely that the antisecretory effect can be achieved by administering AF treatment in higher doses or through AF inducing cereals (SPC), triggering the endogenous production of AF protein.

Eriksson, Shafazand, Jennische and Lange, Effect of Antisecretory Factor in Ulcerative Colitis on Histological and Laborative Outcome: A short Period Clinical Trial, Scand J Gastroenterol, 2003; 38:1045-1049

IBD treatment in children

Recently the first pilot study on children suffering from Crohn's disease and ulcerative colitis was reported. The results show improved clinical symptoms and that treatment with specially processed cereals (SPC) is safe and well tolerated. These positive results will be followed up with a randomised double-blind study.

Finkel, Bjarnason, Lindblad and Lange, Specially Processed Cereals: A clinical innovation for children suffering from inflammatory bowel disease?, Scand J Gastroenterol, 2004; 39: 87-88

FACTS about ulcerative colitis (chronic inflammation of the colon)

The cause of the disease is unknown but there are several theories about hereditary, infectious and immunological factors. Ulcerative colitis is a non-bacterial inflammation in the mucosa of the large intestine causing sores and bleeding ulcers. The disease fluctuates with periods of blood and pus stained diarrhoea and abdominal pain. Typical symptoms are frequent watery diarrhoeas and stool containing blood and/or pus. The diarrhoea is often preceded by strong left-sided abdominal pain that is relieved by bowel emptying. Nausea, fever and weight loss are also common. The symptoms do tend to come and go, with fairly long periods in between flare-ups in which patients may experience no distress at all. The frequency can range from one flare during the entire course of life to daily problems. In more severe cases of ulcerative colitis it may be necessary to surgically remove part of or the entire intestine and replace them with a stoma (an opening on the abdomen through which waste are emptied into a pouch).

During periods of disease activity patients experience milder abdominal pain and less common fever. Symptoms are highly dependant on how widespread the disease is. In approximately ¼ of the patients, the inflammation in limited to the rectum, causing relatively mild symptoms. In 1/3 of the cases it is limited to the lower large intestine, whereas for the remainder the entire large intestine is involved.

Women tend to be affected more often and studies show there is an increasing prevalence in children. Approximately 1000 persons in Sweden are affected yearly with a prevalence of 30 000 totally.

Mastitis

"Imagine if I could have prevented it with SPC"

Karin, aged 31, has just had her first child. Two weeks after giving birth to their daughter, Karin does not feel so well after returning home from an afternoon walk with her husband. One of her breasts feels sore and she can feel a plum-sized mass on one side. Karin lies down to rest but after a few hours she feels febrile. The stiffness has spread and almost half her breast is now affected. She has a temperature of 40° C. When her husband calls the doctor she is recommended to continue breastfeeding, take antipyretic medication and get plenty of rest. The doctor believes it is simply an inflammatory mastitis since Karin does not have any other symptoms or sores on her nipples. If on the other hand the symptoms do not gradually improve then it may be infected and need treatment with antibiotics, in which case they should contact the doctor again.

Karin continues to breastfeed although her daughter finds it more difficult due to the stiff nipple. The milk doesn't come as easily as before and her daughter is unsettled. Karin finds breastfeeding painful and her breast is red and warm.

The next day the swelling has subsided and Karin has been able to breastfeed during the night. She spends the weekend in bed and is tired due to the high fever, but the swelling continues to go down and by the end of the week she is completely recovered and feeling well.

FACTS about mastitis

Mastitis is an inflammation of the breast that may, or may not, be due to infection. Mastitis is caused by a blockage (of milk) in the ducts of the breast. It occurs during the first months following childbirth. It is a common and painful problem for up to one third of all breastfeeding women.

A milk duct can become blocked by a mass of thickened milk. The block is often one-sided. A blocked duct presents as a painful, swollen, firm mass in the breast. Most often the woman is well but some feeling of sickness can be present. A blocked duct can cause slight fever and is often caused by the exposure to a draft, incomplete emptying of a duct during feeding or pressure e.g. from a tight bra.

A blocked duct can go on to become mastitis. Mastitis can be inflammatory or may be due to an infection, most often caused by staphylococci. An infected mastitis can appear without a prior blocked duct if bacteria gains access to the breast through a crack or sore in the nipple. Symptoms can appear suddenly and the woman can feel very sick. It can be difficult to determine if the mastitis is infected and antibiotics are often given as a preventive measure. The difference between blocked ducts and mastitis is primarily that mastitis is associated with high fever, 39-40° C, eventually needing medical care.

Abscess, pusing, occasionally complicates mastitis. Usually the woman's state will improve and fever go down. The infected area is soft but the pus under the skin can be felt and if pressure is applied an indentation will remain. The breast will be severely painful and can be tense and glazed. Abscess should always be looked at by a doctor.

AF-inducing cereals (SPC) can probably increase AF-levels in breast milk, thereby preventing sub-clinical mastitis. This condition increases the risk of transferring virus from an HIV-infected mother to her child.

Prevention of mastitis with SPC

Inflammation of the mammary gland is a painful and common problem for breastfeeding women. Problems can be of a passing inflammatory nature or it may involve long term problems with severe symptoms. In cases where infection cannot be identified, inflammation may be the cause. A new theory has presented the possibility that sub-clinical mastitis may also increase the risk of transmitting HIV-1 from mother to child.

Earlier studies had shown that women in developing countries had measurable amounts of AF in breast milk. The amounts exceeded those measured in women in the industrial world. It was therefore decided to perform a randomised double-blind study on breastfeeding mothers in Sweden at the Karolinska Hospital.

12 women were given AF inducing cereals (SPC) 3-7 days post partum. 16 women acted as controls, given cereals without AF-inducing ability.

In the treated group only one woman developed mastitis compared to six women in the control group. Three women in the control group were diagnosed with mastitis twice and one woman three times. The only woman who developed mastitis in the treatment group had misunderstood the dosage and only ate SPC on weekdays, not weekends as well.

AF levels in breast milk were measured before and after treatment. The median AF level was significantly higher in the AF treated group, 1,1 AF unit/ml breast milk (0,7-1,25), compared to the control group, 0,1 AF unit/ml breast milk (0,0-0,25) ($p<0,0001$). The median AF level in women with mastitis was significantly lower, 0,0 AF units/ml breast milk (0,0-0,1), than the level in women who did not have mastitis, 0,5 units/ml breast milk (0,2-1,1) ($p=0,017$). The one woman in the active treatment group who did develop mastitis had the lowest AF level in the group.

The study showed that an AF level in breast milk above 0,5 units/ml is protective against mastitis. This result is concurrent with the results seen in the animal studies, in which the same level is enough to protect the offspring from developing diarrhoea. These results can be of great importance to developing countries since diarrhoeal diseases are still a great problem. It is of course also of great importance if AF-inducing cereals (SPC) have the ability to reduce sub-clinical mastitis and thereby may reduce the risk of HIV-1 being transferred from an HIV-positive mother to her child.

Svensson, Lange, Lönnroth, Widström and Hanson, Induction of antisecretory factor in human milk may prevent mastitis, Acta Pediatrica, 2004, in press

Rheumatoid arthritis

"SPC improved my situation"

Ian, a man in his fifties, became diagnosed with rheumatic arthritis seven years ago. He couldn't continue his work as a car mechanic and had to find another occupation. The disease came gradually and finally he was not able to handle his tools. Eventually he could hardly walk and the medication he received was causing him gastrointestinal problems.

He was offered a chance to try treatment with specially processed cereals (SPC). Soon he noticed an improvement of the gastrointestinal problems and the inflammation was reduced. The study showed that there is a correlation between inflammation in the gastrointestinal areas and in the joints. However, no improvement of his arthritis was seen during the three-month treatment period.

AF treatment of rheumatoid arthritis

As earlier studies had shown that AF-inducing cereals had a positive effect on symptoms and disease processes in diseases of inflammatory nature, it became of interest to study what effect AF-inducing cereals (SPC) may have on the activity of rheumatoid arthritis.

In a randomised, double-blind, placebo controlled study patients with active rheumatoid arthritis were allocated to either SPC or control cereals. The cereals were given at a daily dose of 0,5 g/ kg bodyweight, divided into three doses daily, for 12 weeks. This dosage is lower compared to normal dosage (1g/kg bw). Prior medication remained unchanged (methotrexate and salazopyrin) and no patients were currently on cortisones. CRP, DAS 28 (Daily Activity Score measured in 28 joints) and HAQ (Health Assessment Questionnaire) was recorded at baseline, and after 4 and 12 weeks of treatment. 16 patients in the treatment group and 18 in the control group followed through.

FACTS about rheumatoid arthritis

Rheumatoid arthritis, in short RA, is one of several chronic diseases affecting the joints, characterized by the inflammation of cartilage, bone and joint lining. The inflammation will eventually result in damage to the involved joint. Inflammation can even affect skin, eyes and internal organs.

RA is an autoimmune disease in which the immune system attacks healthy joint tissue. It is the most common inflammatory rheumatic disease. The cause of RA is not known but there seems to be an inherited tendency. A general theory among experts is that the disease develops due to disturbances in the immune system. What causes the immune system to react and attack body tissue is not yet certain.

RA occurs in approximately one percent of the population and women are three times more prone than men. Although the disease often begins in middle age and occurs with increased frequency in older people, children and young adults also develop it.

Early in the disease, patients may notice general fatigue, soreness, stiffness and aching before symptoms appear in the joints.

Pain and swelling may occur in the same joints on both sides of the body and will usually start in the hands, fingers or wrists. The inflammation causes swelling and pain in joints. The pain and stiffness is most pronounced in the morning and diminishes during the day. Symptoms may recede in periods, but will return. Most joints in the body can be affected but it is not possible to predict which or when.

Surgery is available if the joints become damaged and mobility is reduced. The joint is then either replaced or fixated. The pain is thus reduced and the patient is again able to perform daily chores.

The results show a significant increase of AF-levels in the SPC treated group (Table 2).

Baseline comparisons and after 12 weeks treatment showed a significant difference in CRP between groups. CRP was increased by 66±29% in the control group, whereas it was reduced by 4±12% in the active treatment group (p<0,05). No difference between groups could, however, be seen in status and symptoms of the joints.

Mörck, Ek, Jennische, Laurenius, Tarkowski och Lange, Anti-inflammatorisk effekt av kosttillskott med specialprocessade cerealier vid reumatoid artrit – en dubbel-blind pilotstudie, Posterpresentation vid Riksstämman, 2003

Table 2. Mean plasma AF-concentrations compared by paired *t*-test.

Test period	Mean±SD	n	p
Before treatment, SPC	0,2±0,1	5	ns
Before treatment, control	0,2±0,1	4	
After treatment, SPC	1,1±0,1	5	<0,001
After treatment, control	0,1±0,1	4	

New areas of development

Travel prophylaxis

The AF protein can be induced in healthy individuals and the elevated levels are sustained up to four weeks after treatment with AF-inducing cereals (SPC). It is most likely that the body has a biological memory of AF production.

People living in "dirty" environments have a naturally higher level of AF protein, probably due to an over exposure to bacterial toxins and other factors that have the ability to stimulate the AF system. It has therefore been considered if it could be possible to trigger endogenous defence mechanisms and immunise travellers against diarrhoeal diseases by the prophylactic intake of AF-inducing cereals (SPC) before visiting problem areas, including more severe and chronic diarrhoeas. No clinical trials have been performed yet.

Future clinical studies

Which diseases are caused by inflammatory reactions and which are predominantly of secretory nature? The answer to these questions will lead the way to new areas of research and clinical applications for specially processed cereals (SPC) and administration of highly concentrated Antisecretory Factor (Egg yolk powder B221®).

Considering that patients can continue with their current medication and diet and treatment with AF-products is gentle and well tolerated there are several areas in which clinical research are of interest. Some examples of diseases in which fluid imbalances and/or inflammation plays a part and may become of interest for AF-treatment are listed below.

Secretory diseases/processes	Inflammatory diseases/processes
diabetes (AF in pancreatic cells)	mucositis (following cytotoxic treatment)
diarrhoea in HIV patients	intestinal fistulae
pre-op/acute op. (improve nutritional status)	proctitis
cystic fibrosis	microscopic colitis
oedemas (cerebral oedema)	Mb Bechterew
Sjögren's syndrome	Irritable bowel syndrome
glaucoma	atopic eczema
severe burns	asthma
	chronic sinusitis

Treatment

Dosage

SPC: Normal dosage of AF-inducing cereals (SPC) is 1 g/kg bodyweight daily, divided into 2-3 occasions. When treating children the dose may need to be increased and when treating elderly it may need to be reduced. The dosage should be introduced step by step and reach full dosage after 4-6 days. The cereals can be eaten with yoghurt or boiled to a porridge.

Egg yolk powder B221®: Normal dosage is 2g 5 times daily. The powder is blended with a cold liquid, e.g. water or juice, preferably using a whisk or a blender.

Egg yolk powder B221® is the recommended AF treatment for patients who have difficulties eating large amounts of specially processed cereals. Studies also indicate that patients not responding to treatment with AF inducing cereals may respond to Egg yolk powder B221®.

To stimulate the endogenous production of AF is has been favourable to introduce AF inducing cereals (SPC) during treatment with, or as a follow-up treatment towards the end to, Egg yolk powder B221®.

For seriously ill patients or in patients with suspected low AF-levels, treatment with Egg yolk powder B221® quickly raises AF-levels directly in the intestine. Most often the patients initially treated with Egg yolk powder B221® for 5-10 days can thereafter be transferred to the AF-inducing SPC, in order to stimulate the body's own production of AF.

20 g of SPC is equally potent to 2 g Egg yolk powder B221®.

Expected treatment outcome

A positive therapeutic response can normally be seen after 10-15 days of SPC treatment and within hours after ingestion of Egg yolk powder B221®. After termination of the treatment levels will decline again after a few weeks. If treatment is resumed, AF levels will rise within a matter of days, indicating a biological memory for AF production.

Side effects, interactions and precautions

AF products have been eaten by tens of thousands of individuals and no side effects of medical nature have been reported. A few patients have experienced occasional constipation, but this discomfort can be reduced by a step-by-step introduction of the treatment.

There are no reported interactions with concomitant medications. This is of importance as the patients should continue with their regular medical treatment. Neither SPC nor Egg yolk powder B221® should replace or change the patients' current medication. Persons with celiac disease or gluten intolerance should not be treated with AF inducing cereals and persons with allergy to eggs should not be treated with Egg yolk powder B221®.

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