

Symposium 4

SY3-6

Antioxidants and atherosclerosis

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Risk factor, of current interest in the etiology of heart disease is the accumulation of oxidation products the body, and the role of antioxidants in minimising this oxidative damage. Since it is modified LDL and not LDL, that is atherogenic, interest is focused on antioxidants which inhibit LDL oxidation. There are many antioxidants in addition to vitamin E, vitamin C and carotenoids.

Recently we have addressed polyphenols as an important component among antioxidants. Tea, red wine, vegetables and so on are rich in polyphenols.

Possibly, polyphenols in red wine inhibit LDL oxidation. Possibly, it is due to a diet enriched in polyphenols, including red color components such as anthocyanidin. All of these substances may inhibit LDL oxidation.

Thus we examined the association between LDL oxidation and red wine in 10 male volunteers. They drank vodka for 14 days and then red wine for 14 days. All subjects received a standard diet. Oxidation of LDL was measured by the lag time method.

We observed a 10% longer lag time after consumption of red wine than before but no difference in lag time during consumption of vodka. This suggests that red wine intake rather than alcohol per se inhibits LDL oxidation and may reduce atherosclerosis.

Despite a high smoking rate, we still have a low incidence of coronary heart disease. The "Japanese paradox" referred to above may be influenced by other contributing factors. Perhaps other dietary components, including Japanese green tea, also rich in polyphenols, especially catechins, are involved. To test this hypothesis, I requested volunteers to consume green tea and I then measured the lag time before and after at 1, 2, 4 and 6 hours after consuming tea.

The LDL oxidation lag time was significantly prolonged at 1 and 2 hours after consuming green tea and serum polyphenols (epigallocatechin gallate and epicatechin gallate) levels also significantly increased during this time, suggesting that, catechins in green tea are absorbed in the intestine and enter the blood stream and inhibit LDL oxidation.

Only a few epidemiological studies exist that address these issues. One example, that of the Zutphen elderly study where flavonoid intake was more than 19 mg per day, it was found that coronary heart disease risk decreased by one-third compared to those with a lower flavonoid consumption. It is also known that differences in other nutrients such as black tea, onions and apples contributed to the outcome in this study.

SY4-1

Therapeutic Efficacy of Sliding-Scale based Cyclic Home Elemental Enteral Alimentation in Patients with Crohn's disease: Its Beneficial and Adverse Effects.

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Drug treatment may not be sufficient enough to prevent flare-up of Crohn's disease (CD). We, therefore, developed a sliding-scale based home elemental enteral alimentation (S-S-b-HEEA) in order to prevent its flare-up. The S-S-b-HEEA was also designed to prevent a development of essential fatty acid deficiency in patients with CD because elemental diet (ED) contains a minimal amount of fat. The long-term S-S-b-HEEA may also precipitate the deficiency of selenium (Se) because ED does not contain a sufficient amount of Se. So far, we have experienced 2 patients of possible Se-deficient cardiomyopathy with long-term S-S-b-HEEA. It is critical to detect the cardiomyopathy in the subclinical stage because it cannot be completely reversed when it becomes clinically full-blown. However, there are no practical methods to detect subclinical stage of Se-deficient cardiomyopathy at present.

AIM: Aims of this study were three folds: 1) to re-evaluate the therapeutic efficacy of S-S-b-HEEA in our patients, 2) to define whether or not the S-S-b-HEEA can prevent essential fatty acids deficiency, and 3) to establish the practical method to detect subclinical Se-deficient cardiomyopathy.

SUBJECTS & METHODS: 1. Cumulative remission and non-hospitalization rates were compared between S-S-b-HEEA treated CD patients (n=85) and drug-treated CD patients (n=35). 2. Fat composition of serum and red blood cell (RBC) membrane were measured in CD patients (n=18) who were on long-term S-S-b-HEEA (>1 year) and they were compared to that of control. 3. Eleven consecutive patients with CD on long-term S-S-b-HEEA (>1 year) were analyzed for plasma Se and their 12-lead ECGs were taken. Then, the correlation between the plasma Se concentration and the QTc interval of the ECGs were evaluated.

RESULTS: 1. Cumulative remission and non-hospitalization rates of S-S-b-HEEA treated group were significantly higher than those of drug-treated group (p<0.001). 2. Fat composition (18:2, 18:3, 20:3, 20:3/20:4) of serum and RBC membrane showed no significant difference between S-S-b-HEEA treated patients and control. 3. Nine out of 11 patients (81.8%) had low plasma Se concentrations (<100 µg/l = the lower limit of the reference value). Average plasma Se concentration was 48.8(±13.1) µg/l. Plasma Se concentration had an inverse correlation independently only with QTc interval among 3 parameters of ECG changes, patients' age and duration of S-S-b-HEEA (p<0.05).

CONCLUSIONS: The above results suggest that the therapeutic efficacy of S-S-b-HEEA was superior to that of drug treatments in CD. Moreover, it can prevent essential fatty acids deficiency in spite of the long-term use of ED. On the other hand, it may precipitate Se deficiency in patients with CD on long-term S-S-b-HEEA, and the prolongation of the QTc intervals in ECG is a feasible indicator to detect low plasma Se concentration possibly with early cardiac change.

SY4-2

Controlled trial of low fat versus high fat diet in treatment of Crohn's disease

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Aim: To determine whether low fat diet or high fat diet would be more effective for preventing flare-up of Crohn's disease, we conducted a prospective randomized clinical controlled 12-months trial.

Methods: Two hundred and twenty patients with inactive Crohn's disease after nutritional therapy with elemental diet (Elental) were enrolled into this study. They had never received treatment with prednisolone or immunosuppressive drug before and after maintenance therapy of this trial. These patients received 12-months elemental diet course with either a low fat diet or a high fat diet. Patients were assessed using Crohn's Disease Activity Index (CDAI), body weight, erythrocyte sedimentation rate, C-reactive protein, retinol binding protein, serum albumin, and serum fatty acid levels.

Results: Fifteen patients were intolerant of the elemental diet and were withdrawn from the trial within 3 months. Two hundred and five patients completed 12 months treatment on each regimen. Clinical remission due to Crohn's Disease Activity Index (CDAI) was maintained in 84 of the 101 patients on low fat diet (<30g/day) compared with 40 of the 104 patients assigned to high fat diet (>50g/day). There was a trend for patients receiving high fat diet an increase in the value of their CDAI. There was significant difference in outcome between the two groups, including symptoms, need for hospitalization, need for surgery, new complication, nutritional status, or recurrence.

Conclusions: The present study strongly suggests that low fat diet with an elemental diet plus omega-3 fatty acid is superior to high fat diet for preventing relapse of Crohn's disease.

SY4-3

Glutamine Prevents Intestinal Ischemia-Reperfusion Injury - *in vivo* and *in vitro* study-

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Aim: We investigated whether glutamine (Gln) prevents intestinal ischemia-reperfusion (I/R) injury in both *in vivo* and *in vitro* models.

Methods: *in vivo* study: Male Wistar rats were randomized to the four groups: group A; laparotomy+total parenteral nutrition (TPN) with standard amino acid formula (S-AA), group B; laparotomy+TPN with alanyl-glutamine (Ala-Gln), group C; I/R+TPN with S-AA, and Group D; I/R+TPN with Ala-Gln. Superior mesenteric artery was occluded for 1 hour, then reperfusion and TPN were started. Twenty-four hours after reperfusion, blood samples and small intestine were obtained for morphologic and biochemical analysis. *in vitro* study: A human intestinal epithelial cell line, Caco-2, was used for study. After getting 100% cell confluence, the cells were incubated in hypoxic condition (5% CO₂ + 94% N₂) and culture medium was changed from DMEM to phosphate-buffered saline (ischemia). Two hours later, the cells were returned to the standard culture condition (5% CO₂ + 95% air) with or without 2 mM Gln supplementation. After 4 hours, intracellular glutathione and 3H-thymidine incorporation (DNA synthesis) were measured.

Results: (*in vivo*) Villous epithelium was damaged and mild edema was observed in lamina propria in group C. Villous architecture was fully restored in group D. In group C, mucosal wet weight, DNA and RNA content, and mucosal protein content decreased significantly compared with group A ($p < 0.05$), however, these parameters improved significantly in group D ($p < 0.05$). Plasma FITC-dextran concentrations were significantly increased in group C than in group A ($p < 0.01$), but in group D they decreased to the equal levels observed in group A and B. (*in vitro*) In the group without Gln supplementation, glutathione and DNA synthesis decreased compared with control ($p < 0.01$). Gln supplementation returned them to the levels found in control.

Conclusions: Gln prevents intestinal mucosal injury induced by intestinal I/R, presumably by maintaining glutathione levels and DNA synthesis.

SY4-4**Nutritional Management of Intestinal Failure
in Children in Developing Countries**

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Intestinal failure in infants & children in developing countries is a challenging problem because of limited resources & facilities, & socio-economic factors. This problem is further aggravated by delay in seeking treatment, & pre-existing malnutrition & an acute insult leads to severe nutritional failure. Intestinal failure may be acute or chronic & also may be reversible or irreversible. The neonatal causes of intestinal failure are similar to other countries. Other major causes being chronic infantile diarrhoea, acute tropical inflammatory bowel disease of the small bowel or colon, high output gastrointestinal fistulas, Necrotizing enterocolitis due to Hirschsprung's disease & tuberculosis. Crohn's disease & ulcerative colitis are extremely rare in our environment. This discussion is based on experience at three centres – two in Madras, India (1981 to 1990) & one in Malaysia (1991 to 2001). Both parenteral & enteral nutrition were used initially & in chronic cases cyclic nutrition, home enteral & parenteral nutrition were used. The duration ranged from 90 days to 5 years. The problems in management, complications & limitations are discussed. Parental acceptance, cost, growth, psycho-social development, quality of life & longterm results will be discussed.

SY4-5**Bowel Lengthening Procedure Combined with
Growth Hormone and Glutamine for Short Bowel
Patients**

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Aim : Longitudinal intestinal lengthening (LIL) procedure has shown a limited promise for long-term outcome in the patients with short bowel syndrome (SBS). This study is to examine the feasibility of the LIL procedure before adaptation period of the short bowel, and the nutritional outcome in combination with growth hormone (GH) and glutamine.

Methods : Ten patients of adults (2) and children (8, aged one week to 6 years) had critical lengths of remaining intestine from necrotizing enterocolitis (4), mesenteric vein thrombosis (1), strangulation (2), atresia (2) and volvulus (1). Remaining lengths after massive bowel resection were 40 cm of jejunum and descending colon in adults, and 18 to 30 cm of jejunum with (6) or without (2) ileocecal valve in children. All of these patients are partially or totally dependent on parenteral nutrition. LIL procedure was performed at the time of bowel resection (2) or within 3 months after resection (5). GH (0.5 IU/kg/day) and glutamine (5 to 20 g/day) were supplied for three months after LIL surgery.

Results : The combined therapy resulted in significant improvement in nutritional status and stool counts. At six months after LIL operation, 6 patients have been gradually weaned from PN. Two patients who had antiperistaltic anastomosis were lost from repeated stagnation, sepsis and severe metabolic acidosis in 9 and 15 months. Two of four patients, applied with hand-sewing sutures, had leakages at the suture sites, and one suffered from repeated episodes of massive gastrointestinal bleeding. Only two patients are alive, and free from parenteral nutrition.

Conclusions : Simultaneous LIL procedure with initial resection was feasible even in neonatal patients. GIA stapler is preferred to hand sewing for safety of sutures. Isoperistaltic one site anastomosis is more desired than antiperistaltic two sites anastomosis. Even with the improvement of nutritional status, stool count and weaning from total parenteral nutrition, long term survival is limited. Continued effort for repeated stagnations, sepsis and metabolic acidosis seems to be limiting factor for success.

Panel Discussion

SY4-6

Nutritional treatment of intestinal failure: Clinical outcome in children

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In children intestinal failure can be roughly divided into two categories including short bowel syndrome (SBS) characterized an absolute reduction in normally functioning gut mass after massive intestinal resection or intestinal atresia, and allied disorders of Hirschsprung's disease, which shows bowel dysfunction. The later includes morphologically abnormal intestinal ganglia such as immaturity, hypogenesis and hypoganglionosis. The other forms consists of non functioning morphologically normal intestinal ganglia including megacystis, microcolon, intestinal hypoperistalsis syndrome (MMIHS) and chronic idiopathic intestinal pseudo obstruction syndrome (CIIPS). The key to successful treatment of these intestinal failure is how to utilize nutritional management including parenteral nutrition (PN) and enteral nutrition (EN).

During the past 31 years, we encountered 7 patients with SBS, whose small intestine measured less than 75cm, 7 patients with an immaturity of ganglion cells, two with hypogenesis of the ganglion cells, two with MMIHS and two with CIIPS. In SBS, 5 patients tolerated to PN well and then thereafter started EN at average 87 days of PN. One patient with 30cm of small intestine died because of catheter-related infection after 10 month of PN. The other one with 37 cm of small intestine and biliary atresia died because of liver failure. In the immaturity group, the patients started EN on average 21 days of life and required 104 days of PN, because the ganglion cells matured between 3 to 6 months of age. All patients are presently alive and well. Two patients with hypogenesis of ganglion cells started EN on 110 and 430 days of life and required 138 and 1332 days of PN support, respectively. At present they demonstrate growth retardation and both still depend on either an elemental diet or intermittent PN support. Two patients with MMIHS could not undergo EN and eventually died from complications related to PN. One patient with CIIPS is doing well with intermittent ileus and the other one with CIIPS has been on elemental diet and PN for 17 years.

Owing to advances in PN, the prognosis of patients with intestinal failure has shown great improvement. However, the longer the period of PN, the higher the incidence of PN induced complications, which sometimes induce lethal complications. Therefore, the prognosis of the patients with intestinal failure is how they can tolerate the EN. We should make very important decisions when we start EN, how aggressively we advance and what kind of EN we choose.

PD1

Measuring the impact of Nutrition Support: a cost-benefit approach

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Malnutrition in the hospitalised patient is associated with an increased risk of complications and a higher mortality rate. Malnourished patients also incur higher hospital-related costs and charges, and have increased length of hospital stay (1). Although the provision of nutrition support to patients at risk of malnutrition or with established malnutrition is intuitively beneficial, the cost of effectiveness of providing nutrition support has been documented in only a few publications and for specific disease and nutritional indications.

Due to the limitation of resources, many healthcare organizations are under increasing pressure to justify current clinical practice and to support the introduction of new nutritional options (2). The cost of providing nutrition support can be clarified as direct costs (the cost of inpatient and outpatient care), indirect costs (infrastructure costs) and opportunity costs (cost of a patient's lost opportunities; i.e. lost earnings). The benefit of nutrition therapy can be estimated by using objective outcome measures (i.e. length of hospital stay, functional outcomes, quality of life) and subjective outcome measures (i.e. patient satisfaction and perception of quality of care).

The balance of the cost-benefit analysis will vary on the type of nutrition support provided (dietary counselling, energy or micronutrient supplements, enteral or parenteral nutrition, specialised nutritional products), method of nutrition delivery (tube, IV), patient characteristics, disease factors (i.e. cancer, critical illness) and the site of administration (hospital versus home). Nutrition support teams have been evaluated and proved to be cost-effective in a number of healthcare settings.

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