

Third Gastroenterology and Nutrition Conference, Worcester, UK. September 12, 2014

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This day-long conference was organised by Kamran Rostami and David Aldulaimi who pulled together an impressive line up of speakers. The first session was devoted to gluten related disorders and the gluten free diet. This is timely because the market for gluten free products in the USA alone is huge and out of all proportion to those who have coeliac disease. It is a multi-billion dollar industry. Who is consuming all these gluten free products? Clearly many people think that they are gluten sensitive and on little or no objective evidence begin a gluten free diet. Dr Rostami summarised what is known about the three conditions that are now grouped under the heading gluten related disorders – wheat allergy, non-coeliac gluten sensitivity and coeliac disease. Wheat allergy is an uncommon adverse reaction to wheat proteins, the site of exposure determining the clinical manifestations e.g. in the skin, the gastrointestinal or respiratory tracts. IgE antibodies play a central role in the pathogenesis of these disorders. Non coeliac gluten sensitivity is defined as a reaction to gluten in which allergic and autoimmune mechanisms have been excluded. The morphology of the small intestinal mucosa is grossly normal. Symptoms should resolve on gluten free diet and reappear on gluten challenge. There are no specific tests and the diagnosis is one of exclusion. Recent research suggests that gluten itself may not be the only culprit and the role of FODMAPS which are short-chain indigestible carbohydrates that coexist with gluten in cereals, have been highlighted in provoking symptoms. Coeliac disease is by far the best known and researched of gluten related disorders and now recognised as a chronic immune mediated enteropathy triggered by exposure to dietary gluten in genetically susceptible subjects.

Geoffrey Holmes discussed the epidemiology of coeliac disease and pointed out that figures from his large data base from Derby, UK, indicated in recent years a 15-fold increase in prevalence has occurred. This has been mainly due to better case finding with the advent of endoscopic biopsy and reliable screening tests but there is also evidence that coeliac disease is becoming more common. An increased intake of gluten containing foods or a reduction in infections might explain this. The increase in prevalence through the years has been found in many adult and paediatric coeliac centres. It is interesting that while coeliac disease is increasing in prevalence, dermatitis herpetiformis is decreasing. A possible explanation is that the earlier diagnosis and treatment of coeliac disease is preventing the skin lesions from appearing. The diagnosis of coeliac disease in Derby and elsewhere is increasingly being made in the elderly who improve on and are well able to manage a gluten free diet. A survey in Derby showed that coeliac disease is more common in Asians than in their white counterparts and this could be attributed to a significantly higher prevalence in Asian women ≥ 16 years and < 60 years. Dietary factors may be responsible for these observations. Of concern coeliac disease was not being diagnosed in elderly Asian men so this group needs special attention. Strategies need to be developed to help this group adhere to a gluten free diet. Coeliac disease in India is potentially a huge problem with perhaps 10,000,000 undiagnosed patients.

Heidi Unwin drew attention to recent legislation concerning the gluten free diet and the implications of using the term gluten free. She

pointed out that the diet has more dimensions than just being gluten free. It should be adequate in terms of calories, iron, calcium, vitamins and importantly in fibre to try and offset constipation which can be a problem for those on gluten free diet. Oats are a valuable source of fibre and the evidence is that pure oats are safe in the diet. She emphasised that to enjoy good health patients need to adhere to a strict diet and can be helped by better understanding of the diet, clearer food labelling, fuller information when eating out and having access to a skilled dietitian.

The role of diet in the treatment of Irritable bowel syndrome was discussed by Robin Spiller and Marianne Williams. Irritable bowel syndrome is common and costs the NHS a considerable amount of money annually. Many patients have a miserable existence and any advances in treatment are to be welcomed. A low FODMAP diet has been shown to benefit symptoms. A pilot study set up by the Somerset Partnership NHS Trust in 2010 to implement this form of treatment was so successful that a county-wide service was commissioned in 2012 whereby patients could be referred to a dietetic primary care gastroenterology clinic rather than to a secondary care clinic for patients with irritable bowel syndrome but without red-flag symptoms. Two thirds of those referred in the first year had symptom relief and three quarters had an improved quality of life. This experience has shown that with specialist and dedicated dieticians good results can be achieved and other areas are likely to go down this road.

The prescribing of medications has been the mainstay of treating inflammatory bowel disease and this still prevails as discussed by Nicola Burch under a series of important headings that all those caring for patients will have to consider at some point such as rescue and combination therapy and de-escalating treatment. The aim of treatment is mucosal healing as this reduces complications and the risk of colorectal cancer. To monitor healing, biopsies must be taken even when the mucosa looks macroscopically normal. She discussed some emerging therapies presently under evaluation. Inflammatory bowel disease presents a great challenge to gastroenterologists and a patient centred approach is the best way forward to help those with this lifelong often very debilitating condition.

In a fascinating presentation John Hunter showed what can be accomplished when enteral feeds are used as a primary treatment for Crohn's disease. Over three quarters of patients achieve remission and of these 40% receive little or no other treatment. Not all patients can tolerate the regime required and adding foods after remission is achieved needs considerable expertise. This approach is not widely used by gastroenterologists because to be successful, dedicated specialist dieticians must be part of the management team caring for the patients. If the methods of Dr Hunter were to become generalised the benefits for patients across the NHS would be considerable. This should be the aim. Colin Whately presented the results of a study that compared the effectiveness of steroids and standard nutritional advice against steroid treatment with adjunct exclusive enteral nutrition in a group of patients with ulcerative colitis. The symptom score was lower post intervention in the diet group than in the control group but further work is required in patients with better characterisation of their symptoms.

The last session was devoted to Barrett's oesophagus and oesophageal carcinoma. Barrett's oesophagus has intrigued gastroenterologist since it was first described over 50 years ago and recognised to have malignant potential. Oliver Old outlined current controversies surrounding diagnosis and surveillance. He pointed to current trials designed to answer some difficult questions which have yet to report but thought that in the future there will be greater intervention in those patients with early dysplastic changes in the mucosa. Mohammed Derakhshan drew attention to the rising incidence of oesophageal carcinoma and the factors that might be involved and can be manipulated such as smoking, obesity, hiatal hernia and the consumption of red meat. Diets enriched with fruit and vegetables have been shown to be protective as has H pylori.

This was an interesting and informative day with much practical advice for those dealing with a range of disorders. It lived up to expectations.

The widening perspective of gluten-related disorders

Kamran Rostami

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Gluten is one of the most abundant and diffusely spread dietary components for most populations, particularly those of European origin. In Europe, the mean consumption of gluten is 10 g to 20 g per day, with segments of the general population consuming as much as 50 g of daily gluten or more. It is increasingly evident that undiagnosed gluten related disorders presenting with a multitude of symptoms and complications inside and outside the small bowel are highly prevalent. To better define gluten related disorders, a group of experts met in London in 2011 and proposed three forms of reactions to gluten – coeliac disease (CD), wheat allergy (WA) and non-coeliac gluten sensitivity (NCGS) (1). NCGS is defined as a reaction to gluten in which allergic and autoimmune mechanisms have been excluded. More specifically, patients have negative serological tests for CD (endomysial and/or tissue transglutaminase antibodies) but anti gliadin antibodies may be present. The duodenal mucosa is grossly normal. Symptoms should resolve on a gluten free diet and reappear on gluten challenge. It is essentially a diagnosis of exclusion (2-3).

Wheat allergy is defined as an adverse immunologic reaction to wheat proteins. Depending on the route of allergen exposure and the underlying immunologic mechanisms, WA is classified into classic food allergy, affecting the skin, gastrointestinal tract or respiratory tract; wheat-dependent, exercise-induced anaphylaxis, occupational asthma (baker's asthma) and rhinitis and contact urticaria. IgE antibodies play a central role in the pathogenesis of these diseases. Skin prick tests and *in vitro* IgE assays are first-level diagnostics for WA. However, the positive predictive value of these tests is less than 75%, particularly in adults due to cross-reactivity with grass pollens.

Coeliac disease is an autoimmune disorder generated in genetically susceptible subjects via the ingestion of gluten containing grains such as wheat, rye and barley. The immune response to these grains leads to

progressive damage to the small intestine and to the production of serum antibodies directed against tissue transglutaminase. Environmental factors associated with complex genetics lead to destruction of the small intestinal villi resulting in the malabsorption syndrome in CD. The association between CD and other disorders has been clearly established and there have been many reports of numerous intestinal and extra intestinal coexistent disorders with CD. Extra intestinal symptoms are also common in NCGS. The high frequency and wide range of adverse reactions to gluten indicate that the dietary protein is toxic for a high number of individuals resulting in a variety of reactions from allergic, unexplainable intolerance to autoimmunity.

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Epidemiology of coeliac disease

Geoffrey Holmes

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Patients with coeliac disease (CD) are being diagnosed in increasing numbers. In Derby in the quinquennium 1972-1976, 23 cases were diagnosed by biopsy but during 2004-2008, 361 were diagnosed, an increase of 15-fold. The advent of accurate serological screening tests and the technique of endoscopic biopsy have been the main drivers of this increase by promoting case finding. There is also evidence however, that CD is becoming more common as shown in a study from Finland where between 1978 and 2001 the prevalence increased 2-fold(1). This might be due to an increasing consumption of gluten in the diet. The prevalence of CD and dermatitis

herpetiformis (DH) has been studied in adults in the UK in a large population-based investigation (2). Over a 22 year period the prevalence increased by a factor of four. At the same time the prevalence of DH has been falling by about 4% per year. It may be that diagnosing and treating CD earlier might prevent the skin lesions from occurring. In the UK in 2011 it was estimated that there were 150,000 cases of CD and 19,000 of DH giving a point prevalence of 1:420 for CD and 1:3,300 for DH. In 2011 there were 12,000 new patients with CD and 500 with DH. The increase in prevalence has been noted in children in Scotland (3) and Wales (4).

Coeliac disease is being increasingly diagnosed in later life. In the Derby series of 1315 patients diagnosed by biopsy, 29% were ≥ 60 years of age while 20% were ≥ 65 years at diagnosis. These patients readily accept and respond to gluten free diet (GFD). The diagnosis in the elderly is often delayed because it is not immediately considered a possibility.

A study in Derby showed that CD is more common in Asians than in their white counterparts and this could be attributed to the significantly higher prevalence in Asian women ≥ 16 and < 60 years (5). Of concern no Asian male ≥ 65 years was diagnosed with CD which may be a cultural phenomenon whereby elderly Asian men are reluctant to discuss their health problems. Asians find adhering to a GFD difficult compared to whites. The increasing prevalence raises important questions about follow up of patients. Is it necessary? If so who should do it and how frequently? What tests should be carried out? In addition strategies need to be developed to diagnose the disorder in Asians and help them adhere to the GFD.

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There is more to the diet than gluten-free

Heidi Unwin

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Coeliac disease (CD) is an auto-immune condition triggered by the ingestion of gluten found in wheat, barley and rye. The only current treatment for CD is lifelong strict adherence to a gluten free diet (GFD); but there is more to the diet than GF legislation - food labelling, nutritional adequacy, supplementation and support. Codex Alimentarius, Commission of the World Health Organisation issued a revised standard for the gluten content of processed food in 2008. Following this, a law around the use of the term GF was published in Europe in 2009 and implemented on 1 Jan 2012, based on the revised Codex standard. This is the first ever EU law on GF, translated as less than 20 parts per million gluten, that is less than 20 mg gluten per kilogram. Since then, the Food and Drug Administration has introduced the same standard in North America, and there is discussion to follow suit in Australia, although currently GF remains to be defined as 'no detectable gluten'.

The GFD can be made up of naturally GF foods such as meat, fish, fruit, vegetables, rice, tapioca, beans and pulses but also specially manufactured GF substitute foods where the traditional gluten-containing ingredients have been replaced with GF alternatives such as teff, quinoa, polenta, rice or potato. The nutritional adequacy of the GFD is difficult to assess because intake is so variable between individuals and in a life-time; there is limited research in this area. A systematic review of the literature by the UK Foods Standards Agency was completed by Coeliac UK in 2008 and found that the GFD was not deficient in iron, calcium or vitamins but due to the paucity of data available a conclusive assessment could not be made (1). Three further published studies since the review have also been small in size and varied in

their methods of assessment but conclude that in addition to ensuring a GFD there should be a focus on adequate fibre and micronutrient intakes (2-4). There are currently no separate nutritional recommendations other than for calcium intake in adults with CD to be at or above 1000 mg/d compared with 700 mg/d for the general population (5).

Naturally GF cereals include rice, maize and oats. Oats are a good source of fibre, vitamins and contain twice as much protein as that found in rice. Pure uncontaminated oats can provide variety to the GFD but they contain avenin, a similar protein to gluten and although the majority of people with CD are able to tolerate GF oats there is a small percentage who appear to remain sensitive. The guidelines for the use of oats in the GFD of people with CD vary across the globe and from one region to another within the UK. In the UK the British Society of Gastroenterology Guidelines on the diagnosis and management of CD recommend that oats may be included in the diet from diagnosis (5), they are also included in the GFD in Scandinavia and Canada, whereas in Australia and North America they are not recommended. This remains a controversial area.

Strict adherence to the GFD by people diagnosed with CD is poor, despite high rating of self reported adherence. The range for strict adherence is 42-91% (6) and is found to be lower in ethnic minority groups compared with white Caucasians (7). Common factors associated with compliance to a GFD are access to GF food on prescription, affordability of GF foods, understanding food labelling, clearer information when eating out and follow-up with a dietitian (8). The implementation of the EU Food Information for Consumers Regulation in December 2014, which applies to food manufacturers and caterers, should be a benefit. Where additional dietary support has been provided there is evidence of further improvements in histological recovery and dietary adherence.

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The Role of Diet in IBS

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Many patients believe that food is responsible for their symptoms but proving this is difficult owing to the many variables that determine the GI response to food. Exclusion diets have been demonstrated to help around 1/3 of patients with IBS (1). Commonly implicated foods include onions, dairy products, wheat and coffee. Food allergy is rare in a GI clinic since most patients with obvious allergy see immunologists (2). Earlier studies suggested that gluten-free diets (GFD) may help but more recently a high quality study suggests the benefit relates to a reduction in poorly absorbed wheat starch rather than gluten exclusion (3).

Activation of TRPV1 receptors via chilli has been shown to sensitise patients to rectal distension

which may account for the symptoms of urgency (4). Caffeine in coffee activates colonic motility (5) and in excess can cause diarrhoea. Lactose malabsorption is the norm world wide, adult lactose tolerance being a genetic mutation arising in NW Europe with an incidence which falls from 90% in the NW Scotland to <10% in China. Lactose intolerance is aggravated by rapid transit which increases delivery of lactose to the colon where it is fermented to SCFAs and gas. This may explain its correlation with anxiety (6). Other poorly absorbed carbohydrates, mainly fructose and fructans described collectively as “FODMAPs” also cause symptoms and low FODMAP diets have been shown in double blinded studies to benefit IBS symptoms (7).

Recent MRI studies show that fructose ingestion rapidly increases small bowel water content but only transiently increases colonic fermentation while fructans, being less osmotically active do not affect the small bowel but do increase colonic gas over many hours (8). IBS patients appear particularly sensitive to this distension which is usually well tolerated by healthy subjects.

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Dietary therapy in Irritable bowel syndrome

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IBS is a chronic and debilitating gastrointestinal disorder which affects 10-20% of the population and costs the UK in excess of £45.6 million per year. In 2010 Somerset Partnership NHS Trust set up a pilot study using the newly recognised low FODMAP Diet as a treatment for IBS patients in a community setting. This pilot showed 69% success rate with patients and Somerset CCG went on to commission the first UK dietetic-led primary care gastroenterology clinic in 2012. This is a countywide service which is commissioned for primary care as an alternative to referral into secondary care for non-red flag IBS patients. As the aim is to prevent secondary care referral, this dietetic-led clinic will check for red flags that may not have been reported to the GP and will also check for a differential diagnosis of coeliac disease, gluten sensitivity or gastrointestinal allergy.

The first year audit of this fully commissioned service showed that 74% of patients had an improved quality of life and 65% had satisfactory relief of their IBS symptoms. The FODMAP diet is complex and needs thorough input from a specialist dietitian with the correct patient resources. Poor support and resources will often lead to a confused patient and to poor outcomes.

Inflammatory bowel disease update

Nicola Burch

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IBD comprising Crohn's disease and ulcerative colitis are common with approximately 260,000 people in the UK currently affected. Since there is no cure, patients require a lifetime of care resulting in a substantial burden for the patient, family, and healthcare providers. Although they have a similar underlying pathophysiology, the distribution and degree of mucosal damage differ considerably; requiring patient centred tailored management to ensure the best outcome. In recent years there has been significant progress with both emerging therapies and diagnostic tools to facilitate evaluation of disease and ongoing patient monitoring. Some of these developments are considered and how these may help improve outcomes via a tailored, patient centred approach.

Rescue Therapy in Acute Severe Colitis

There has been much debate in recent years about the use of Ciclosporin versus Infliximab for rescue therapy in patients with steroid refractory acute severe colitis. The CYSIF trial, the first randomised controlled trial comparing Ciclosporin versus Infliximab rescue therapy in acute severe colitis, found equivalent response rates at both 7-days (84% versus 86%, p 0.76) and long-term colectomy rates at 98 days (18% versus 23%). Accelerated dosing with infliximab might be considered in patients with ulcerative colitis who fail to demonstrate significant response following the initial rescue Infliximab infusion.

Combination Therapy in IBD

It is generally accepted that combination therapy with Infliximab and a 2nd line immunosuppressant (Azathioprine/6-mercaptopurine) improves remission rates in Crohn's disease although this benefit has not been found when using methotrexate in combination with Infliximab in Crohn's. In ulcerative colitis the use of combination therapy is less well established.

Optimising Treatment with the use of Drug monitoring & Metabolites

Many centres are now utilising drug levels to help tailor treatment strategies in the IBD population. Measurement of azathioprine metabolites can help to determine compliance with treatment and also

enable specific targeted dose reduction in those with toxic levels of metabolites. Measurement of anti-TNF trough levels and antibodies may be similarly effective at helping to tailor individual treatment regimens.

Using Faecal Calprotectin (FCP) for disease monitoring & treatment escalation

FCP is a protein of s100 family occurring in large amounts of neutrophil granulocytes and is released following neutrophil degranulation as a result of mucosal inflammation. It is therefore a highly useful tool for monitoring disease activity in IBD.

Mucosal Healing

In IBD the ultimate aim of treatment is to establish mucosal healing as this has been shown in numerous trials to reduce long term complications and risk of colorectal cancer. In one trial it was found that in 12% with macroscopic remission of colitis there was evidence of ongoing active inflammation on histology. This reinforces the importance of taking colonic biopsies even in a macroscopically normal colon.

De-escalating Treatment

The choice of when, how, and whether to de-escalate treatment in IBD once the patient is in clinical remission is a challenge for Gastroenterologists and it is therefore important to establish the potential risk of relapse following treatment cessation.

Emerging Therapies

There are several new and exciting agents currently under evaluation for the management of UC and Crohn's. These include budesonide MMX, vedolizumab, golimumab, tofacitinib, ustekinumab and briakinumab.

Conclusions

Overall success of treatment in IBD is dependent upon a patient centred approach. Measurement of drug levels and antibody titres in patients on immunosuppression or anti-TNF treatment may help direct dose optimisation or therapy switch in order to enhance patient outcomes. Faecal calprotectin may also be utilised as a guide to early escalation of treatment. A risk stratification strategy may be a useful adjunct to guide de-escalation of treatment in patients on combination anti-TNF and immunosuppression in clinical remission.

The role of diet in Inflammatory Bowel Disease

John Hunter

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Inflammatory bowel disease may lead to nutritional deficiencies whose prevention and correction are crucial to successful management of the condition. The role of diet as a primary treatment for Crohn's Disease (CD) remains, however, controversial.

It is now over 30 years since the effectiveness of enteral feeds in CD was first reported. Remission may be achieved in as many as 80% of compliant patients, yet diet is not used widely. This may partly be because of lack of understanding of its method of action, although it is now recognised that food intolerance in CD is not due to allergy, but to the interaction between undigested food residues and the intestinal microbiota. Further difficulties include poor compliance by as many as 25% of patients, disagreements about how food should be reintroduced when remission is achieved, and a lack of experienced gastrointestinal dietitians in many centres. Gastroenterologists often have little confidence in dealing with nutritional problems.

The long term results of dietary treatment are however, excellent. It is cheap, provides extended remissions, is safe in pregnancy and does not produce side effects such as osteoporosis. Often invaluable in difficult cases refractory to pharmacological treatment, it should be available in all tertiary referral centres for IBD.

The Role of Diet Intervention in the Treatment of ulcerative Colitis

Colin Whatley

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Introduction: It is accepted that corticosteroids are the primary tool in managing severe inflammation in Ulcerative Colitis (UC). This presentation summarises guidance for nutritional management of UC and will discuss findings of a case study from an Acute Hospital Trust. The case study compared the effectiveness of steroid treatment alongside standard nutritional advice against steroid treatment with adjunct exclusive enteral

nutrition (EEN) - in improving subjective feelings of gastrointestinal (GI) symptoms.

Method: UC patients ($n=30$) were chosen for inclusion in the study, and these were divided into 2 branches: Control – steroid treatment + nutritional advice ($n=15$); and Diet – steroid treatment + adjunct EEN ($n=15$). Gastrointestinal symptoms were recorded, with consent, during dietetic assessment and were rated according to the Subjective Gastrointestinal Rating Scale (GSRS), in respect of severity and frequency. The symptoms were recorded prior to dietetic assessment (and intervention) and after assessment and intervention. On collation of average symptom scores, statistical analysis was carried out with Student *t*-test using Microsoft Excel 2010 software package.

Results: Pre vs. Post Overall Symptom Score; Control – ($p<0.01$) and Diet – ($p<0.01$) indicating improvement in symptoms. Pre-intervention Control vs. Diet overall symptom scores were not dissimilar ($p=0.18$). However post-intervention diet cohort overall symptom score statistically significantly lower compared to Control group ($p=0.02$).

Discussion: Corticosteroid treatment is the main protagonist in managing acute flare-ups of UC. There is no evidence to show that diet therapy and EEN has a role in inducing clinical remission in UC. However, diet intervention and EEN appears to improve subjective feelings of GI symptoms in the present study. Moreover, overall symptom scores were lower in the diet group compared with the control group post-intervention. This raises the question of whether manipulation of these symptoms may lead to enhanced patient compliance to medical management and increased engagement with local IBD teams, therefore resulting in better outcomes. Overall, further research may be warranted in this area, with emphasis on use of polymeric diets and liquid diets in managing global GI symptoms associated with flare-ups of UC.

Barrett's oesophagus

Oliver Old

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The role of Barrett's oesophagus as the first step in progression towards oesophageal adenocarcinoma has been recognised for over 50

years. The metaplasia-dysplasia-adenocarcinoma sequence is well characterised, and in this time a wealth of research has informed our understanding of this condition, but nonetheless there are many topics surrounding Barrett's which remain uncertain. Current controversies include the definitions required for histopathological diagnosis and the significance of intestinal metaplasia, the natural history of progression and risk of malignancy, the role of chemoprevention, the effectiveness of surveillance programmes, timing of intervention for those who progress, and optimal management for dysplastic Barrett's.

Developments in endoscopic therapy have provided many tools for advanced endoscopic imaging to aid diagnosis, and have revolutionised treatment options. More recently there has been much work towards developing biomarkers that identify those at risk of progression. At present, the main goals of the multiple strands of research in Barrett's oesophagus can be summarised as follows: firstly, to improve identification of those with high risk of progression, and secondly to provide effective, minimally invasive treatment to prevent progression (through both chemoprevention and endotherapy). Large scale trials are under way to address these key questions, and it seems likely that the future will bring greater intervention for those with early dysplastic disease, a continued increase in endotherapy, and a reduction in patients requiring radical surgery or presenting with disseminated disease.

Prevention of oesophageal adenocarcinoma and Barrett's oesophagus.

Mohammad Derakhshan

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Although oesophageal cancer of all histological types stands in eighth position in terms of global cancer statistics, incidence of oesophageal adenocarcinoma has risen faster than any other malignancy in recent decades. Oesophageal adenocarcinoma results from a multi-step cascade starting with gastro-oesophageal reflux disease, moving to columnar metaplasia and glandular dysplasia and leading to invasive adenocarcinoma.

Many environmental and life-style factors contribute to the development of inflammatory and precancerous changes and cancer itself. Smoking, obesity, male gender, hiatus hernia and dietary factors are well established. Strong linkage between obesity and alterations of lower oesophageal sphincter function make these risk factors plausible targets for preventative measures. Protective effects of healthy diet enriched with frequent vegetables and fruit portions have been shown in several high quality studies. Micronutrient deficiencies and inflammation are among the most important factors in pathogenesis of oesophageal adenocarcinoma and have attracted several prevention trials involving nutritional supplements and non-steroidal anti-inflammatory agents. Finally, the protective effects of *H.pylori* infection should be noted.

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