present, high-risk Caucasian males who at entry endoscopy have macroscopic markers or HGD are obvious candidates. The use of flow cytometry and similar biomarkers may prove a powerful tool to stratify individuals at risk in the future. Targeting individuals at high risk in this way will allow appropriate allocation of endoscopic resources and efficient surveillance strategies. High-risk patients would then be entered into relatively intensive surveillance programs while the frequency of endoscopy for low-risk patients would be curtailed.

References

Malnutrition as a cause of chronic pancreatitis: Myth dispelled?

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A role for protein energy malnutrition in the etiopathogenesis of chronic pancreatitis was postulated several decades ago, based largely on studies of tropical pancreatitis (a chronic calcifying form of pancreatitis) occurring in non-alcoholics from areas where malnutrition is prevalent, such as India, South-East Asia and some parts of Africa.1 A typical patient with this condition presented at a relatively young age with severe abdominal pain, pancreatic calcification and diabetes and, in the majority of cases, belonged to the lower socioeconomic strata of society with its inherent problems of undernutrition. Furthermore, through most of the last century, alcoholic pancreatitis in Western countries was widely thought to be, at least partially, caused by the poor nutrition of heavy drinkers.2,3 Lack of adequate nutrition in alcoholics was thought to be due to: (i) displacement of essential dietary components by alcoholic beverages, which are high in energy value but contain negligible amounts of protein or other nutrients; and (ii) malabsorption of food secondary to the toxic effects of alcohol on gut mucosa and pancreas.

The concept that nutritional deficiency may lead to pancreatitis was supported by some clinical and experimental evidence indicating that protein deficiency, in particular, had adverse effects on the pancreas. In malnourished African children, abnormal histological appearances of the pancreas have been reported; these include acinar atrophy, loss of acinar pattern, fibrosis and cystic dilatation of ducts. In addition, ultrastructural changes were present, such as a decrease in zymogen granules, mitochondria and rough endoplasmic reticulum and an increase in the number of lysosomes.4 However, it must be noted that overt chronic

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pancreatitis has not been reported in these patients. Similarly, experimental studies in rats fed a low protein diet revealed changes in acinar cell structure and function, such as increased fragility of lysosomes and altered digestive enzyme synthesis but, again, without evidence of pancreatitis. These findings are not surprising, given that a decrease in total enzyme content within acinar cells may be seen to be a protective factor against the autodigestive injury that is now well accepted as an initiating mechanism of pancreatitis.

Meanwhile, the well-known increase in dietary intake in Western countries (especially in Western Europe) in the second half of the last century led to reports suggesting that overnutrition, rather than undernutrition, may be a risk factor for alcoholic pancreatitis. In Italy, France and Mexico, higher intakes of protein and/or lipid have been described in alcoholics who develop pancreatitis. A study by Goebell et al. reported higher intakes of calories, fat and alcohol in patients with chronic pancreatitis compared to age- and sex-matched healthy controls. Such studies led to the intuitively reasonable hypothesis that increased protein/lipid intake may result in an adaptive increase in the digestive enzyme content of the gland, thereby increasing the susceptibility of the pancreas to autodigestion.

Experimental support for this notion is furnished by studies showing increased enzyme content and gene expression of pancreatic proteases, amylase and lipase in rats fed high protein, carbohydrate and lipid diets, respectively. Furthermore, studies in rats and dogs have shown that overnutrition worsens experimental pancreatitis. However, in the clinical context, there is no evidence of a role for diet in the pathogenesis of alcoholic pancreatitis, particularly when any variation in alcohol intake is controlled for by comparing alcoholics with pancreatitis to alcoholics without pancreatitis. Thus, while it is possible that diets high in fat and protein may facilitate disease progression, there is little evidence to date to indicate that overnutrition is an initiating factor for pancreatitis.

In this context, the report in this issue of the Journal of Gastroenterology and Hepatology by Midha and colleagues is a welcome attempt to critically examine the influence of dietary deficiency in the pathogenesis of non-alcoholic (idiopathic) chronic pancreatitis. The nutritional status was assessed of 201 patients with chronic pancreatitis before and after the onset of disease. Eighty-one patients were classified as having alcoholic pancreatitis whereas 120 patients were diagnosed with idiopathic chronic pancreatitis. The study focused on the latter group.

Anthropometric analysis and dietary assessment were carried out and compared at both pre-morbid and post-disease onset stages in the same patient. Data were also compared with those from an age- and sex-matched control population. The authors report that nutritional status and dietary intake of patients with idiopathic chronic pancreatitis before disease onset was similar to that of age- and sex-matched population controls. However, after disease onset, two-thirds of patients lost weight, and a significantly higher proportion of patients were malnourished (as indicated by a body mass index [BMI] of < 18.5 kg/m²) compared to controls. The authors conclude that nutritional deficiency does not cause chronic pancreatitis but, rather, is an effect of the disease. The observed lack of a role for malnutrition in chronic pancreatitis is supported by findings of earlier reports, albeit with smaller numbers of patients. Uscanga and colleagues compared nutritional characteristics of Mexican patients with alcoholic and non-alcoholic chronic pancreatitis; the latter resembled patients with tropical pancreatitis in clinical characteristics such as early age of onset. The authors found that neither the alcoholic pancreatitis nor the non-alcoholic pancreatitis cohort was malnourished at the time of onset of the disease.

In view of the above studies, it seems unlikely that a deficiency of macronutrients plays a role in the causation of chronic pancreatitis. However, a factor that has not yet been addressed systematically in any large clinical studies is the micronutrient (particularly anti-oxidant) status of patients before disease onset. Oxidant stress (secondary to excessive production of reactive oxygen species and a concomitant reduction in intracellular anti-oxidant defense systems) has been implicated in the pathogenesis of pancreatitis by both clinical and experimental studies. Thus, it remains possible that an anti-oxidant-depleted state may increase the susceptibility of an individual to the development of pancreatitis. Large multicenter studies will be required to clarify this issue.

Although malnutrition, particularly that of macronutrients, is unlikely to be a cause of chronic pancreatitis, there is little doubt that it can be an effect of the condition, secondary to deficient synthesis of pancreatic digestive enzymes and consequent mal-digestion of dietary fat and protein. Malnutrition in patients with chronic pancreatitis has been assessed by several studies using variable combinations of indices including steatorrhea and weight loss, as well as anthropometric measures such as body mass index, skin fold thickness, mid upper arm circumference and body fat estimation. In the study by Midha et al., it was found that among the 92 patients with idiopathic chronic pancreatitis in whom bodyweight before the onset of disease was known, two-thirds experienced significant weight loss after disease onset. In fact, of 45 patients with a normal pre-morbid bodyweight, almost half the number exhibited a BMI of < 18.5 kg/m² and were classified as malnourished. A significantly higher proportion of idiopathic chronic pancreatitis patients who lost weight also had diabetes and complications, such as pseudocysts, compared to idiopathic chronic pancreatitis patients who exhibited no weight loss.

The cornerstone of therapy for maldigestion due to pancreatic insufficiency is replacement of pancreatic enzymes in the gut sufficient to allow for efficient digestion and absorption of nutrients. The efficacy of enzyme replacement therapy is influenced by a number of factors, such as the type of preparation, enzyme concentrations in the preparation, the dosage schedule and the use of adjuvant therapy to improve bioavailability of enzymes. Although the decision to use replacement enzyme therapy should ideally be based on whether the patient exhibits steatorrhea (> 7 g stool fat/day), in practice, routine 3-day fecal fat tests are not commonly carried out and treatment is largely based on clinical assessment. It is imperative that an adequate dose of enzymes is used in enteric coated formulations (30 000 IU of lipase and 10 000 IU of trypsin to be taken with meals containing 25 g fat). This regimen abolishes azotorrhea (increased stool nitrogen excretion) and significantly reduces (but does not abolish) steatorrhea. With this treatment, most patients report significant symptomatic relief. If this fails to occur, higher doses or adjuvant therapy with acid-reducing agents, such as proton pump inhibitors or H2-receptor blockers, are needed.
In summary, malnutrition is unlikely to play a causative role in the initiation of chronic pancreatitis, but there is little doubt that it is a serious consequence of the disease.17 Even in countries such as India, where the concept of pancreatitis secondary to nutritional deficiency was first proposed, there now appears to be a significant change in the spectrum of disease. Classical tropical pancreatitis (young patient, intraductal calcification, rapid progression to exocrine and endocrine insufficiency) is rapidly being replaced by a more ‘Western’ type of disease (older patient, mild disease, infrequent ductal calcification) associated with environmental factors such as alcohol and/or a genetic predisposition.18 Evidence for a role for smoking as an initiating factor for pancreatitis is unconvincing,19,20 although it is possible that smoking plays a part in disease progression.21 The possible pathogenic role of micronutrient deficiency both before and after onset of disease remains to be clarified. However, available evidence, albeit from studies with design limitations,22 suggests that anti-oxidant supplementation may prove to be a useful component of the therapeutic approach to chronic pancreatitis.

**References**


**Changing landscape of antiviral resistance management in chronic hepatitis B**

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In this edition of the *Journal of Gastroenterology and Hepatology*, Suzuki et al. report the results of a phase II randomized, double-blind multicenter trial comparing the efficacy and safety of 0.5 mg and 1 mg entecavir switch therapy in a cohort of Japanese patients with chronic hepatitis B, who had confirmed genotypic lamivudine resistance.1 Following 48 weeks of entecavir therapy, 90% and 93% of patients treated with 0.5 mg and 1 mg, respectively, achieved the primary endpoint of either a 2 log10 or more reduction in viral load from baseline or undetectable hepatitis B virus (HBV) DNA by polymerase chain reaction (PCR) (Roche Amplicor, Roche Diagnostics, Branchburg, NJ, USA).

In 2008, we are now in the era of highly potent antiviral therapy with agents such as entecavir and tenofovir. What does this mean

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