Indian J Gastroenterol (March–April 2011) 30(2):63–65
DOI 10.1007/s12664-011-0096-6

EDITORIAL

Chronic pancreatitis in India: untying the nutritional knot

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Received: 15 February 2011 / Accepted: 13 April 2011 / Published online: 18 May 2011

Nutrition is central to human existence from sustenance of cellular life to powering its myriad functions. Contrasting images of Haitian or Ugandan malnourished children and Westerner obese kids mirror not only the economic reality of a nation but also the propensity to diseases albeit of opposite polarity from Kwashiorkor/Marasmus to metabolic syndrome with equal implications for health outcomes. In addition to specific nutritional deficiency states such as scurvy and rickets, indirect effects of nutrition on human health are of greater importance.

In this context, astute clinical observations in 1960s brought attention to a rather typical form of chronic pancreatitis (CP) in Kerala [1]. The picture of a young malnourished patient with chronic calcific pancreatitis and diabetes evoked much interest. Since one of its most peculiar features was malnutrition (undernutrition), it was soon implicated in its etiopathogenesis. At a time when the basic structure of DNA was just about making the headlines, genetic mutation as the cause of disease was not even on the agenda outside of Mendelian disorders. Malnutrition thus made the cut being the striking clinical feature. Since the disease was reported mainly from tropical countries, which ironically were much poorer and undernourished than their temperate counterparts, the term 'tropical pancreatitis' (TP) was coined for want of a more defining terminology.

Protein deficient and high carbohydrate diet was thus implicated in the etiopathogenesis of the thus coined TP. Sandhyamani et al. [2] showed that high carbohydrate and low protein diet, either comprising of cornstarch or cassava, resulted in ductal changes with mucoid metaplasia and parenchymal atrophy in an animal model of bonnet monkey. However, pancreatic changes were rather different from those typically seen in CP and the animals predominantly developed vascular and cardiac changes—features not observed in CP patients. Furthermore, severe malnutrition has been shown to result in pancreatic atrophy and insufficiency and not CP thus disproving the nutritional hypothesis [3]. Since cassava was a staple diet in Kerala, it gained the status of a co-culprit as a logical extension of the nutritional hypothesis. The cassava hypothesis has also been discarded because: (i) cassava consumption was not found as a risk factor in case–control studies including one from Kerala [4], (ii) patients with the TP were reported from areas where cassava was not consumed [5], and (iii) long-term cassava consumption did not produce diabetes or pancreatitis in a rat model [6].

Even though the association of malnutrition with CP was consistent, not many clinical studies examined the cause and effect relationship. Our group first showed that malnutrition was an effect and not a cause of CP. In a prospective study of 120 patients with idiopathic CP, only 20.6% were underweight before the onset of the disease while 67% lost weight following the disease suggesting that malnutrition was an effect and not a cause of CP [5]. A recent study by Sathiaraj et al. [7] has reiterated that malnutrition was not a cause of TP (idiopathic CP) in southern Indian patients as only 15% patients were malnourished before the onset of disease and 52% of patients lost weight subsequently. In this issue of the journal, Regunath et al. [8] have further strengthened these observations. In their study of 54 patients, premorbid BMI in 35 patients with TP (idiopathic CP) was significantly higher than the BMI in the same patients at presentation

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suggesting that the patients were normally nourished before the onset of disease and lost weight afterwards. The authors did not find any particular cause for undernutrition possibly due to a small sample size and a lack of study of dietary intake of patients. We had found diabetes and intake of higher percentage of calories from proteins as two important causes of malnutrition [5]. Thus, these studies from different centers have largely put to rest any doubt that undernutrition is not a cause of idiopathic CP (TP) in India.

Although data are convincing that malnutrition is not causally related to the etiopathogenesis of CP, it is possible that malnutrition modulated the phenotypic expression of the disease. The consistent observations made during the 1960s and 70s cannot simply be brushed aside. At that time, severe protein calorie deficiency resulted in a malnourished patient, early pancreatic atrophy and consequent endocrine failure leading to diabetes. Similarly, absence of steatorrhea and ketosis can be explained by substrate deficiency due to malnutrition. Over the past 3–4 decades, there has been a definite change in the phenotypic profile of idiopathic CP in India: the age at onset has shifted from adolescence to mid twenties, the BMI of most patients is no longer below normal (i.e. <18.5), diabetes is seen in only a third to a half of patients as opposed to 90% reported earlier, and the longevity of patients has increased [9–11]. How does one reconcile with these emerging trends in the disease phenotype? Economic gains by the country during the past four decades have resulted in substantial decline in poverty and malnutrition. In Kerala for example, the headcount index for poverty has declined from 59.8% in 1973–74 to 12.7% in 1999–2000 [12]. The net state GDP was Rs. 1457 crore (~$320 million) and the per capita GDP was Rs. 665 (~$15) in 1972–73; these figures increased to Rs. 62,557 crore (~$13.75 billion) and Rs. 23,865 ($ 525), respectively in 1999–2000, i.e., an almost 40-fold increase [13]. Improvement in nutrition with growing economy has made the difference to the phenotype of patients with chronic pancreatitis—normal BMI, late presentation, delayed onset of diabetes and better outcome—thus making the disease look different. Conventional wisdom will be mistaken if one assumes that the earlier seen variety of CP in India i.e., TP is disappearing because unlike infectious disease, a disease with strong genetic basis cannot just be wished away. Its phenotype can however, certainly change due to environmental factors. For example, pregnant mice with identical genotype gave birth to offspring of a different coat color when maternal diet was supplemented with methyl donors, an epigenetic effect that lasted in the next generation [14]. The conundrum of CP and its changing phenotype further exemplifies this phenomenon [11].

If macronutrient and energy deficiency are not etiologically related to the pathogenesis of CP, it is still possible that micronutrient deficiencies might be playing a role. Indeed, micronutrient deficiencies are common and likely to be related to the pathogenesis through oxidative stress. Oxidative stress has been implicated in the pathophysiology of CP [15]. In this issue of the *Journal*, Girish et al. [16] from Kerala have shown enhanced lipid peroxidation and decreased antioxidant status in both idiopathic CP (TP) and alcoholic CP. The authors have further extended their previous observation that zinc deficiency may have a significant role to play. Zinc deficiency may occur due to pancreatic exocrine insufficiency [17]. Moreover, zincuria has been observed in most cases with pancreatic insufficiency. The authors' suggestion that an early age of onset and rapid course of TP as the reasons for decrease in vitamin C levels and higher thiobarbituric acid reactive substances (TBARS) is however, conjectural. One of the limitations of this study was subgroup analyses without correcting for multiple comparisons which might have impacted the significance of some of the variables.

From a therapeutic standpoint, malnutrition needs to be treated regardless of whether it is a cause or effect. In a randomized clinical trial, we compared the efficacy of MCT-enriched commercially available food supplements with dietary intervention in the form of counseling for regular home-made food [18]. Both commercial food supplementation and dietary counseling improved the nutritional status with significant and comparable improvements in anthropometric parameters including weight, BMI, lean body mass and subcutaneous fat stores at the end of the 3-month study period. Thus, a balanced home-made adequate calorie diet should be prescribed to these patients. Furthermore, in a randomized controlled trial, antioxidant supplementation was associated with relief in abdominal pain and decrease in oxidative stress, thus supporting the oxidative stress hypothesis [19]. Antioxidants should be prescribed in a proper dose as used in that study with a combination of 0.54 g ascorbic acid, 9000 IU β-carotene, 270 IU α-tocopherol, 600 μg organic selenium and 2 g methionine per day in divided doses.

The 2 studies in this issue of the *Journal* from southern India have again emphasized that the clinical profile of TP is much different from that reported earlier and in sync with the idiopathic CP reported elsewhere [20]. The Manipal group diagnosed TP by excluding other causes of CP, suggesting that this was idiopathic CP. The Kochi study also used the term tropical pancreatitis while referring to a study in which the majority of patients were akin to idiopathic CP [21]. The idea that this type of CP is special arose from the earlier observations of severe malnutrition, diabetes and marked calcification—features much mellowed and modified now. A possibly higher prevalence and a rapidly progressive course in a few patients notwithstanding, there is nothing much to suggest that

idiopathic CP in India is a different disease. Further insight into the pathogenesis with mutations in *SPINK1* and *CFTR* genes has shifted the focus to a molecular level for further elucidation of the pathobiomechanism of the disease [11]. In such a scenario, sticking to an old terminology i.e. 'tropical' is an oddity especially since there is nothing to suggest any influence of geographic location either on its pathogenesis, phenotype or disease behaviour [22].

"All is flux, nothing remains the same" (Heraclitus).

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