Evidence Synthesis

Pancreatic enzyme replacement therapy for chronic pancreatitis. Systematic review and meta-analysis

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Chronic pancreatitis is a condition predominantly associated with deprivation. Excess alcohol consumption is the major cause of this disease and it can exacerbate most of symptoms such as abdominal pain, pancreatic insufficiency and malnutrition. Furthermore, treatment adherence in determinant social groups could be lower than in others. For this reason is fundamental to evaluate the effect of the pancreatic enzyme replacement therapy in patients from different socioeconomic status and different aetiologies to assess the impact of health inequalities in the treatment of this disease. With this approach we could identify specific groups of patients at risk and planning specific interventions.

Chronic pancreatitis is a long-term toxic process that damages the pancreatic exocrine parenchyma, with variable amounts of chronic inflammation and progressive fibrosis. There are few studies that document the prevalence of chronic pancreatitis in the UK, however some studies have demonstrated dramatic increases in incidence over successive time periods. This entity is characterized by intermittent or constant abdominal pain, pancreatic insufficiency (endocrine and/or exocrine) and malnutrition. The condition is caused by alcohol excess (~65% of cases), hypertriglyceridaemia, genetic mutations (e.g. of the cationic trypsinogen gene) or may be idiopathic. In addition, smoking is strongly associated and considered a contributor factor. Both excess alcohol consumption and smoking are associated with socioeconomic status (SES). SES also can exacerbate malnutrition that results from chronic pancreatitis. It is therefore important to determine the role of health inequalities in aetiology, presentation, management and outcome of chronic pancreatitis. Furthermore, identification of the impact of health inequalities on disease burden and management is essential for full evidence synthesis to inform commissioning. Nevertheless to our knowledge there has been no systematic assessment of the impact of health inequalities in chronic pancreatitis. There have been trials to address components of deprivation in pancreatitis, e.g. alcohol excess, but not specifically focused on health inequalities, rather the life style issue associated with deprivation.
A formal assessment of the literature is therefore necessary, extracting those data that identify the actual or potential role of health inequalities, prior to any proposal for specific interventions designed to address these.

Aims and objectives of the project

- To determine how and to what extent health inequalities influence the management of chronic pancreatitis, using pancreatic enzyme therapy as the primary focus for a disease that already represents deprivation
- To determine if pancreatic enzyme supplements are:
  - Superior to placebo for treating fat malabsorption
  - Superior to placebo in improving bowel symptoms as a stool frequency, stool consistency abdominal pain, flatulence,
  - Superior to placebo in improving vitamin deficiency, quality of life and weight
- To determine what is the most appropriate dose and timing of enzyme administration
- To compare the efficacy of PERT to avoid malnutrition according to different place of residence, race/ethnicity, gender and socioeconomic status
- To evaluate the treatment adherence according to place the residence, race/ethnicity, gender and socioeconomic status
- To evaluate the efficacy of gastric acid secretion inhibitors associated to PERT
- Adverse events attributed to pancreatic enzyme replacement
- To ensure full patient and public involvement in this research through the NIHR Liverpool Pancreas BRU Patient Advisory Group, with input into the questions asked, the methods used and the dissemination of results

One of the most important outcomes in the management of chronic pancreatitis is the treatment of pancreatic exocrine insufficiency (PEI) that can lead to malnutrition and related complications such as osteoporosis and impaired of quality of life due to steatorrhea, weight loss, abdominal discomfort and other PEI-related symptoms. In order to avoid malabsorption and improve the nutritional status of patients with PEI, the cornerstone of treatment is pancreatic enzyme replacement therapy (PERT), however the efficacy and safety of PERT remains unclear. Similarly, the impact of health inequalities on identification of patients with the disease, delay in diagnosis, efficacy of management and long-term outcome has not been systematically addressed.

The optimal dose of PERT in CP has not been investigated systematically in clinical trials. There are recommendations from different national societies that range from 20000 to 50000 lipase units per main meal. Despite such treatment, fat digestion does not become normal in almost half of patients with PEI. The most important reason to optimize PERT is to improve the nutritional status and quality of life in people with CP.
Enzyme replacement may differ in formulation (non-enteric coated or enteric coated microsphere preparations) or timing of administration (with food, before or after food). There is need to evaluate differential efficacy of these enzyme preparations, with or without treatments to reduce gastric acid output. Additionally, the dosing schedule of the enzyme may also influence the clinical outcome and needs to be evaluated in a systematic review. The impact of health inequalities in these various elements of PERT remain to be evaluated, as proposed here.

In our approach to address health inequalities in chronic pancreatitis we are going to evaluate the therapy with pancreatic enzymes in order to reduce the differences in treatment adherence and nutritional status between different socioeconomic groups. With this approach we are going to be able to identify specific groups that are going to require specific interventions in order to improve their quality of life and avoid complications.

For more information regarding the project, please contact Evidence Synthesis Theme Leader, Professor Rumona Dickson via R.Dickson@liverpool.ac.uk