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Review

Hypoglycaemia in cystic fibrosis in the absence of diabetes: A systematic review

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Abstract

Background: Hypoglycaemia in CF in the absence of diabetes or glucose lowering therapies is a phenomenon that is receiving growing attention in the literature. These episodes are sometimes symptomatic and likely have variable aetiologies. Our first aim was to conduct a systematic review of the literature to determine what is known about hypoglycaemia in CF. Our second aim was to assess evidence based guidelines for management strategies.
Methods: A comprehensive search of databases and guideline compiler entities was performed. Inclusion criteria were primary research articles and evidence based guidelines that referred to hypoglycaemia in CF in the absence of insulin treatment or other glucose lowering therapies.
Results: A total of 11 studies (four manuscripts and seven abstracts) and five evidence-based guidelines met the inclusion criteria. Prevalence rates of hypoglycaemia unrelated to diabetes varied between studies (7–69%). Hypoglycaemia was diagnosed during oral glucose tolerance testing or continuous glucose monitoring (CGM). Associations between hypoglycaemia and clinical parameters of BMI, lung function, liver disease and pancreatic insufficiency were measured in some studies. There was no unifying definition of hypoglycaemia in the absence of diabetes. Only two evidence based guidelines reported possible management strategies.
Conclusion: The systematic review found limited data on this clinical problem and supports the need for high quality methodological studies that are able to describe the experience and the aetiology(ies) of hypoglycaemia in CF.

Keywords: Cystic fibrosis; Hypoglycaemia; Oral glucose tolerance test; Continuous glucose monitoring

Contents

Abbreviations: CF, Cystic fibrosis; CFRD, Cystic fibrosis related diabetes; CGM, Continuous glucose monitoring; FPG, Fasting plasma glucose; IFG, Impaired fasting glucose; IGT, Impaired glucose tolerance; OGTT, Oral glucose tolerance test.

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1. Introduction

Cystic fibrosis (CF) is a multisystem recessive genetic disorder, that primarily affects the lungs, pancreas, gut and liver. Improvements in medical and surgical management, and nutrition have led to a rise in survival rates. Consequently, complications, such as abnormalities in glucose metabolism, have increased in prevalence. Cystic fibrosis related diabetes (CFRD) is the leading co-morbidity in patients with CF, although patients present with varying states of abnormal glucose tolerance, which varies over time and between sexes [1,2]. A novel complication is the phenomenon of hypoglycaemia in the absence of established diabetes and glucose lowering therapies. This phenomenon has been described in a clinical setting in relation to an oral glucose tolerance test (OGTT) with reactive hypoglycaemia [3]. Anecdotally patients also describe symptoms suggestive of hypoglycaemia in relation to exercise and to inadequate food intake. These episodes are physically unpleasant and it is unknown how these may affect glucose metabolism. There is no apparent unifying hypothesis for their aetiology.

Hypoglycaemia in the absence of a diagnosis of diabetes and the use of glucose lowering therapies is documented in a number of clinical scenarios. Episodes of hypoglycaemia unrelated to diabetes have been described in impaired glucose tolerance (IGT) [4–6], liver disease [7,8], malnutrition [9,10] and gastrointestinal disorders such as dumping syndrome following gastric surgery [11]. Collectively, these conditions may also occur in CF and some of the proposed mechanisms for hypoglycaemia might arguably also be extended to explain the origins of hypoglycaemia in CF.

We were unable to identify a systematic analysis of the literature around hypoglycaemia in CF, although it is a well-recognised phenomenon in both paediatric and adult clinics. The aim of this systematic review was to determine what is already known about hypoglycaemia unrelated to diabetes in CF. A supplementary aim was to determine whether CF related hypoglycaemia had been included in clinical guidelines.

2. Methods

2.1. Search strategy

The following databases were searched: Medline, Pre-Medline, Cochrane database for systematic reviews, Embase (via OvidSPWeb), Scopus and Web of Science. No limits were placed on publication date, study type, or language. The search strategy for Medline is included in Appendix A with search terms modified as required for other databases. Reference lists of relevant articles were hand searched to supplement results.

Additionally, evidence based guidelines in the area of CF were retrieved with direction from experts in the field and using the following tools:

1. Websites of guideline compiler entities, registries or clearing houses: National Guideline Clearinghouse [12], International Centre for Allied Health Evidence [13] and National Health Service Evidence – National Library of Guidelines [14].
2. The databases TRIP and Informit.

2.2. Inclusion and exclusion criteria

Only human CF related studies were included. Hypoglycaemia was required to be an outcome of the study. Study participants must not have had a confirmed diagnosis of CFRD prior to participation in the study. Manuscripts that did not explicitly state that all participants with confirmed diagnosis of CFRD were excluded at baseline were also excluded from this systematic review. The use of glucose-lowering treatments, insulin and oral hypoglycaemic medications were also criteria for exclusion. While the common clinically accepted definition of hypoglycaemia is a blood glucose level of ≤ 3.9 mmol/L [15] we included all studies which reported episodes of hypoglycaemia to be present in participants.

For the supplementary CF evidence based guideline study, CF clinical guidelines published by scientific bodies or similar were specifically searched for from countries where CF is prevalent: Europe, The Americas, Australia, New Zealand, United Kingdom and the Republic of Ireland, as well as the reference lists of these guidelines.

The Institute of Medicine (IOM), defines clinical practise guidelines as "…statements that include recommendations, intended to optimize patient care, that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options" [9]. The tools used, as outlined in the methodology, confirmed that retrieved guidelines reflected this definition. Clinical guidelines were included in the review if these provided an explanation of hypoglycaemia