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REVIEW ARTICLE

Insulin therapy in patients with cystic fibrosis in the pre-diabetes stage: a systematic review

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KEYWORDS
Cystic fibrosis;
Insulin;
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Abstract
Objective: To elucidate whether insulin is effective or not in patients with cystic fibrosis before the diabetes mellitus phase.
Data source: The study was performed according to the Prisma method between August and September 2014, using the PubMed, Embase, Lilacs and SciELO databases. Prospective studies published in English, Portuguese and Spanish from 2002 to 2014, evaluating the effect of insulin on weight parameters, body mass index and pulmonary function in patients with cystic fibrosis, with a mean age of 17.37 years before the diabetes mellitus phase were included.
Data synthesis: Eight articles were identified that included 180 patients undergoing insulin use. Sample size ranged from 4 to 54 patients, with a mean age ranging from 12.4 to 28 years. The type of follow-up, time of insulin use, the dose and implementation schedule were very heterogeneous between studies.
Conclusions: There are theoretical reasons to believe that insulin has a beneficial effect in the studied population. The different methods and populations assessed in the studies do not allow us to state whether early insulin therapy should or should not be carried out in patients with cystic fibrosis prior to the diagnosis of diabetes. Therefore, studies with larger samples and insulin use standardization are required.

PALAVRAS-CHAVE
Fibrose cística;
Insulina;
Diabetes melito

Insulinoterapia em pacientes com fibrose cística na fase de pré-diabetes: uma revisão sistemática

Resumo
Objetivo: Elucidar se a insulina é eficaz ou não em pacientes com fibrose cística antes da fase de diabetes.

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Fontes de dados: O estudo foi feito de acordo com o método Prisma entre agosto e setembro de 2014, nas bases de dados PubMed, Embase, Lilacs e SciELO. Foram incluídos estudos prospectivos publicados em inglês, português e espanhol de 2002 a 2014 que avaliaram o efeito da insulina nos parâmetros peso, índice de massa corporal e função pulmonar, em pacientes com fibrose cística, com média de 17,37 anos, antes da fase de diabetes.
Síntese dos dados: Foram identificados oito artigos que incluíram 180 indivíduos submetidos ao uso de insulina. O tamanho das amostras variou de 4 a 54 pacientes, idade média entre 12,4 e 28 anos. O tipo de acompanhamento, o tempo de uso de insulina, a dose e o cronograma de implementação foram muito heterogêneos entre os estudos.
Conclusões: Existem razões teóricas para se acreditar que a insulina tenha um efeito benéfico na população estudada. Os diferentes métodos e populações encontrados não permitem afirmar se a terapia precoce com insulina deve ou não ser feita em pacientes com fibrose cística previamente ao diagnóstico de diabetes. Portanto, são necessários estudos com amostras maiores e uniformidade de uso da insulina.

Introduction

Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity in patients with cystic fibrosis (CF) and affects 20% of adolescents and 40–50% of adults with CF.[1]

Glucose disorders in CF patients typically begin with an intermittent postprandial hyperglycemia, followed by oral glucose intolerance without fasting hyperglycemia and finally diabetes with fasting hyperglycemia.[2,3]

Insulin deficiency and resulting hyperglycemia affect lung disease.[3–5] Insulin is a hormone with anabolic effects and its deficiency may have a negative clinical impact on patients considered ''prediabetic''.[6] Increased serum glucose levels (≥144mg/dL) may have an adverse effect on lung function. Furthermore, increased glucose in the bronchial tree favors the growth of respiratory pathogens.[5] There is still a loss of lean body mass due to the catabolic state caused by insulin deficiency, which leads to a consumption of fat and proteins and also affects pulmonary function.[7]

Therefore, insulin deficiency promotes a clinical deterioration in this population and not only an abnormal glucose metabolism, which may be enhanced by early intervention with insulin.[6] Both diabetes and glucose intolerance reduce the life expectancy of CF patients; insulin is the only treatment that improves clinical outcomes.[8] Early treatment with insulin may reduce the morbidity and mortality of the underlying disease.[9,10]

Moreover, CF patients' classification using the oral glucose tolerance test (OGTT) in intolerant and diabetic patients is based on criteria derived from epidemiological studies in non-CF subjects, it raises doubts whether these conventional diagnostic limits would be appropriate or relevant for CF patients.[11] Thus, the use of conventional glucose evaluation tests in the CF population could underestimate the number of patients with abnormal glucose metabolism, and, consequently, this group could benefit from early intervention with insulin, in glucose levels below those considered abnormal in populations without cystic fibrosis.[12]

To our knowledge, there is no systematic review of early initiation of insulin therapy in CF patients. Therefore, the aim of this study was to identify the effects of this intervention and contribute to clinical practice and future studies.

Method

The search process was developed according to the Prisma method (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).[13] The search was conducted between August and September 2014 in the following electronic databases: PubMed, Lilacs, SciELO, and Excerpta Medica Database (Embase).

The following terms and descriptors (Medical Subjects Headings – MeSH) were used for the search: 'cystic fibrosis', 'early insulin', 'insulin', 'body mass index', 'impaired glucose tolerance', and 'therapy'; in combinations: 'cystic fibrosis and early insulin', 'cystic fibrosis and insulin and body mass index', 'cystic fibrosis and early insulin', 'cystic fibrosis and insulin and body mass index', 'impaired glucose tolerance and cystic fibrosis and insulin and therapy'.

Studies published between 2002 and 2014 were identified through electronic search by two independent reviewers who evaluated the titles and abstracts of articles. References of selected articles were also reviewed in order to identify studies not found in the surveyed bases. Discrepancies between reviewers were discussed and resolved by consensus. The date of the first search was August 28, 2014, and the last, September 22, 2014.

Inclusion criteria were: (I) original articles; (II) prospective studies; (III) articles in English, Spanish or Portuguese; (IV) cystic fibrosis diagnosis; (V) glucose disorders; (VI) insulin use (regardless of type, dose, or implementation schedule); (VII) evaluation of the results in clinical parameters (weight or height or body mass index and pulmonary function). Glucose disorder was considered as an OGTT non-characterized as diabetes by the American Diabetes Association (ADA) criteria and OGTT glucose values above