Can J Diabetes 39 (2015) 398–404

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Original Research

Pancreatic Lipid Content Is Not Associated with Beta Cell Dysfunction in Youth-Onset Type 2 Diabetes

Brandy A. Wicklow MD, MSc [a,b,*], Angella T. Griffith BSc [a], Jacqueline N. Dumontet BSc [a], Niranjan Venugopal PhD [c], Lawrence N. Ryner PhD [c], Jonathan M. McGavock PhD [a,b]

[a] Manitoba Institute of Child Health, Winnipeg, Manitoba, Canada
[b] University of Manitoba, Department of Pediatrics and Child Health, Faculty of Medicine, Winnipeg, Manitoba, Canada
[c] National Research Council Canada Institute for Biodiagnostics, Winnipeg, Manitoba, Canada

ARTICLE INFO

Article history:
Received 18 December 2014
Received in revised form
31 March 2015
Accepted 6 April 2015

Keywords:
adolescent
lipotoxicity
nuclear magnetic resonance (NMR) spectroscopy
pancreas
steatosis
type 2 diabetes

Mots clés :
adolescent
lipotoxicité
spectroscopie par résonance magnétique nucléaire (RMN)
pancréas
stéatose
diabète de type 2

ABSTRACT

Objective: To determine whether pancreatic lipid content is associated with type 2 diabetes and beta cell function in Indigenous and Caucasian adolescents.
Methods: This was a cross-sectional study comparing ^{1}H-magnetic resonance spectroscopy-derived pancreatic triglyceride content in adolescents 13 to 18 years of age with type 2 diabetes (n=20) and body mass index-matched normoglycemic controls (n=34). Beta cell function was measured by the acute insulin response and disposition index derived from intravenous glucose tolerance tests.
Results: Pancreatic lipid content was not significantly different in youth with type 2 diabetes and their normoglycemic body mass index-matched peers (2.41 [95% CI: 0.63, 5.60] vs. 1.22 [0.08, 5.93]; p=0.27). Pancreatic triglyceride levels were not associated with measures of beta cell function in the cohort. In subgroup analyses, pancreatic lipid content was ∼4-fold higher in youth with type 2 diabetes who were carriers of the G319S mutation in the HNF-1alpha gene (7.45 [2.85, 26.8] vs. 2.20 [0.350, 3.30] % Fat to Water Ratio F/W; p=0.032).
Conclusions: Pancreatic lipid content is not elevated in Indigenous or Caucasian youth with type 2 diabetes compared to normoglycemic youth, nor is it associated with beta cell function. The presence of the G319S mutation in the HNF-1alpha gene in Indigenous youth with type 2 diabetes is associated with higher pancreatic lipid content. Further research is needed to understand the mechanisms that explain beta cell failure in overweight youth with type 2 diabetes.

RÉSUMÉ

Objectif : Déterminer si la teneur en lipides dans les cellules pancréatiques est associée au diabète de type 2 et au fonctionnement des cellules bêta chez les adolescents autochtones et caucasiens.
Méthodes : Il s'agissait d'une étude transversale comparant la teneur en triglycérides dans les cellules pancréatiques obtenue par la spectroscopie par résonance magnétique ^{1}H chez des adolescents de 13 à 18 ans souffrant de diabète de type 2 (n=20) et des témoins normoglycémiques appariés selon l'indice de masse corporelle (n=34). Le fonctionnement des cellules bêta était mesuré par la réponse insulinique aiguë et l'indice de disposition obtenu par les épreuves d'hyperglycémie provoquée par voie intraveineuse.
Résultats : La teneur en lipides dans les cellules pancréatiques n'était pas significativement différente chez les jeunes souffrant du diabète de type 2 et les pairs normoglycémiques appariés selon l'indice de masse corporelle (2,41 [IC à 95 % : 0,63, 5,60] *vs* 1,22 [0,08, 5,93]; p=0,27). Les concentrations en triglycérides dans les cellules pancréatiques n'étaient pas associées aux mesures du fonctionnement des cellules bêta dans la cohorte. Dans les analyses en sous-groupes, la teneur en lipides dans les cellules pancréatiques était ∼4 fois plus élevée chez les jeunes souffrant du diabète de type 2 qui étaient porteurs de la mutation G319S sur le gène HNF-1alpha (7,45 [2,85, 26,8] *vs* 2,20 [0,350, 3,30] %F/W; p=0,032).

* Address for correspondence: Brandy A. Wicklow, MD, MSc, Department of Pediatrics and Child Health, Faculty of Medicine, University of Manitoba, FW306, 3rd Floor, Community Services Building, 685 William Avenue, Winnipeg, Manitoba R3E 0Z2, Canada.
E-mail address: bwicklow@hsc.mb.ca

1499-2671/$ – see front matter © 2015 Canadian Diabetes Association
http://dx.doi.org/10.1016/j.jcjd.2015.04.001

Conclusions : La teneur en lipides dans les cellules pancréatiques n'est pas élevée chez les jeunes autochtones ou caucasiens souffrant du diabète de type 2 comparativement aux jeunes normoglycémiques, et n'est pas associée au fonctionnement des cellules bêta. La présence de la mutation G319S sur le gène HNF-1alpha chez les jeunes autochtones souffrant du diabète de type 2 est associée à une teneur en lipides plus élevée dans les cellules pancréatiques. D'autres recherches sont nécessaires pour comprendre les mécanismes qui expliquent l'insuffisance des cellules bêta chez les jeunes souffrant du diabète de type 2 qui ont un excès de poids.

Introduction

The hallmark pathophysiologic feature of type 2 diabetes is a relative deficit in insulin secretion by pancreatic beta cells (1). The mechanisms to explain the loss of insulin secretory capacity in type 2 diabetes remain poorly understood (2,3). Conventional wisdom suggests that following years of insulin resistance, compensatory hyperinsulinemia results in beta cell exhaustion and eventual failure (1,2). This theory, however, does not explain the rapid loss of glucose-stimulated insulin secretion seen in children and adolescents who develop type 2 diabetes early in life (4).

One theory to explain the loss of insulin secretion in the setting of type 2 diabetes is an excessive accumulation of lipid moieties within beta cells. The additional lipid disrupts the energy status of the beta cells (i.e. the adenosine triphosphate:adenosine diphosphate [ATP:ADP] ratio) and leads to the production of toxic lipid intermediates that accelerate cell death (5,6). To explore this pancreatic lipotoxicity theory in a clinical setting, noninvasive imaging modalities have emerged to quantify lipid content in the human pancreas (7–12). Studies in adults with type 2 diabetes and children with genetic disorders involving triglyceride synthesis have demonstrated that 1) noninvasive imaging tools can quantify triglyceride accurately in the pancreas (13); 2) pancreatic lipid content is elevated in human obesity and in type 2 diabetes (14,15); and 3) the degree of lipid within the pancreas is negatively associated with beta cell function (14). Although these results implicate lipotoxicity in the natural history of beta cell dysfunction, the studies did not control for differences in visceral fat content between the groups, which may contribute to both pancreatic lipid content and defects in glucose-stimulated insulin secretion (16). Our cohort represents a clinical model of early, accelerated beta cell failure in the absence of aging and insulin resistance (4,17).

We recently demonstrated that adolescents with type 2 diabetes are 4 to 6 times more likely to display ectopic lipid accumulation, in the form of hepatic steatosis, than normoglycemic adolescents matched for body mass index (BMI) (17). In addition, we found that the presence of hepatic steatosis in overweight normoglycemic adolescents predicts metabolic abnormalities, including metabolic syndrome and increased glucose dispersion, following oral glucose challenges (18). Based on these findings, we hypothesized 1) that youth with type 2 diabetes would display a significantly higher proportion of lipid within the pancreas compared to normoglycemic adolescents, independent of adiposity; and 2) that the degree of lipid accumulation in the pancreas would be negatively associated with glucose-stimulated insulin secretion. Finally, because a number of patients with type 2 diabetes in our clinical program are carriers of a private polymorphism in the HNF-1alpha gene G319S (19), resulting in reduced insulin secretory capacity (20–22), we also performed an exploratory subgroup analysis to determine levels of pancreatic lipid among carriers of the G319S polymorphism in the HNF-1alpha gene.

Methods

Study design and study population

This was a cross-sectional study comparing pancreatic triglyceride content between adolescents with type 2 diabetes and age-, sex- and BMI-matched normoglycemic adolescents. Participants with type 2 diabetes were recruited through the Diabetes Education Resource for Children and Adolescents (DER-CA) in Winnipeg, Manitoba, Canada. Overweight and obese normoglycemic adolescents were recruited through radio advertisements and posters in local community health centers and in the Manitoba Institute of Child Health Research Center. Type 2 diabetes was diagnosed according to the criteria published by the American and Canadian Diabetes Associations (23,24). Participants were classified as overweight or obese according to the age- and sex-specific guidelines established by the International Obesity Task Force (25). Adolescents were excluded from the study if they 1) had used antidiabetes medications in the 12 months prior to participation in the study or 2) had been treated with medication known to affect glucose handling or lipid metabolism, including statins, atypical antipsychotics or corticosteroids. Three youth recruited as normoglycemic controls demonstrated impaired glucose tolerance during a 75 g oral glucose tolerance test and were excluded from further participation. Two participants with type 2 diabetes failed to obtain magnetic resonance imaging (MRI) due to size restrictions and, therefore, were excluded from final analysis. Three normoglycemic participants failed to receive MRI due to scheduling problems with the MRI acquisition and were excluded from the final analysis. A total of 20 adolescents with type 2 diabetes and 34 healthy overweight/obese controls were included in the final analysis. All participants and parents provided written informed consent to participate in the study, which was approved by the biomedical research ethics board at the University of Manitoba and performed according to the Declaration of Helsinki.

Pancreatic triglyceride content

All MRIs were performed using a 3.0-T whole-body magnet (Siemens USA, Malvern, PA, US) as previously described (17,18). In vivo magnetic resonance spectroscopy with a single voxel volume of 3 cm (axial) × 3 cm (coronal) × 3 cm (sagittal) (27 cm^3) was used to collect 64 consecutive ^1H spectra from the tail of the pancreas (15,26). We chose the tail of the pancreas because preliminary analyses revealed that this location provided the most reliable acquisition of spectra, and it is also the anatomic location of the islets of Langerhans. Axial, coronal and sagittal high-resolution images of the pancreas were obtained by using standard clinical techniques. To reduce contamination from surrounding visceral fat, spatial saturation bands were manually placed around the voxel. The use of spatial saturation bands improves the baseline of collected spectra by dramatically reducing the signals from surrounding contaminating lipids (27). In addition, spectra and imaging were collected using respiratory gating to reduce motion