Changements phénotypiques de la mucoviscidose, à propos du diabète associé à la mucoviscidose : évolution naturelle des troubles du métabolisme glucidique, impact pronostique et stratégie de dépistage

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CHANGEMENTS PHENOTYPIQUES DE LA MUCOVISCIDOSE, A PROPOS DU DIABETE ASSOCIE A LA MUCOVISCIDOSE : EVOLUTION NATURELLE DES TROUBLES DU METABOLISME GLUCIDIQUE, IMPACT PRONOSTIQUE ET STRATEGIE DE DEPISTAGE

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TITRE : Changements phénotypiques de la mucoviscidose, à propos du diabète associé à la mucoviscidose : évolution naturelle des troubles du métabolisme glucidique, impact pronostique, et stratégie de dépistage.

RESUME : L'amélioration de l'espérance de vie des patients atteints de mucoviscidose est associée à l'apparition de comorbidités dont le diabète est la plus fréquente. L'objectif de ce travail est de mieux déterminer l'impact pronostique du diabète et des valeurs élevées des temps précoces du test d'hyperglycémie provoquée par voie orale (HGPO).

Nous présentons et discutons quatre études sur l'évolution naturelle et l'impact pronostique des troubles du métabolisme glucidique associés à la mucoviscidose. Nous présentons ensuite deux études sur l'impact du diabète dans des situations spécifiques : la grossesse et la transplantation pulmonaire.

Nous retenons les éléments suivants : les variations du statut glucidique intra-individuel sont très importantes au cours du temps, et nos résultats nuancent l'impact péjoratif du diabète décrit dans la littérature, et celui des valeurs élevées de glycémie et d'insulinémie à 1 heure du test HGPO.

Les perspectives de recherche sont de poursuivre l'implémentation de la cohorte GLYCONE pour gagner en effectif et durée de suivi, d'évaluer l'association entre apports alimentaires et trouble du métabolisme glucidique, d'élaborer un processus de décision médicale partagée pour l'instauration d'une insulinothérapie pour les profils de patients stables, de déterminer la consommation de soins et les coûts de prise en charge des patients diabétiques, et d'évaluer les changements épidémiologiques induits par les modulateurs du CFTR sur la prévalence et l'âge d'apparition du diabète et son pronostic.

MOTS-CLES : mucoviscidose ; diabète associé à la mucoviscidose ; hyperglycémie, hypoinsulinémie, HGPO.

TITLE: Phenotypic changes in cystic fibrosis, about cystic fibrosis-related diabetes: evolution of glucose tolerance disorders, prognosis impact and screening strategy.

ABSTRACT: Life expectancy improvement for cystic fibrosis patients is associated with comorbidities with diabetes being the most common. The objective of this work is to better determine the prognosis impact of diabetes and high values of early times of the oral glucose tolerance test (OGTT).

We present and discuss four studies on the natural evolution and prognosis impact of glucose metabolism disorders associated with cystic fibrosis. We then present two studies on the impact of diabetes in specific situations: pregnancy and lung transplantation.

The following elements are important: changes in intra-individual glucose status are very important over time, and our results qualify the pejorative impact of diabetes described in the literature, and that of high blood glucose and insulin levels at one hour of the OGTT.

The research perspectives are to continue the implementation of the GLYCONE cohort to increase the number of participants and the duration of follow-up, to evaluate the association between dietary intake and carbohydrate metabolism disorder, to develop a shared medical decision-making process for the introduction of insulin therapy for stable patient profiles, to determine the consumption of care and the costs of management of diabetic patients, and evaluate the epidemiological changes induced by CFTR modulators on the prevalence and the age of onset of diabetes and its prognosis.

KEY-WORDS: cystic fibrosis, cystic fibrosis-related diabetes, hyperglycemia, hypoinsulinemia, OGTT.

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A Benoit,

A Bertille, Côme et Victoire,

A mes parents et à ma famille.

Table des matières

INTRODUCTION : Le diabète de la mucoviscidose (DAM), un diabète spécifique

La mucoviscidose est la plus fréquente des pathologies génétiques engageant le pronostic vital, dans les populations d'Europe et d'Amérique du Nord. C'est une maladie autosomique récessive liée à une mutation du gène *CFTR* (Cystic Fibrosis Transmembrane Conductance Regulator), situé sur le bras long du chromosome 7. Depuis son identification en 1989, plus de 2 000 mutations du gène ont aujourd'hui été identifiées. La plus fréquente est la mutation F508del. Ce gène code une protéine dite CFTR, normalement présente au pôle apical des cellules épithéliales de l'organisme. Il s'agit d'un canal ionique transmembranaire dont la dysfonction concerne plusieurs tissus (voies aériennes, canaux pancréatiques, tube digestif, voies biliaires, tractus génital, glandes sudoripares). Le pronostic reste essentiellement lié à l'atteinte respiratoire et à l'état nutritionnel (1,2). Son incidence est de 1/4 500 naissances. En France, 120 enfants environ naissent chaque année avec la mucoviscidose. La France compte environ 7000 patients d'après le Registre Français de la mucoviscidose (3). Aujourd'hui, grâce aux progrès thérapeutique et à l'organisation des soins pour la prise en charge de cette maladie, l'espérance de vie moyenne d'un patient est approximativement de 40 ans, alors qu'elle n'était que de 5 ans dans les années 1960 (4). Il est probable que les enfants malades nés ces dernières années voient leur espérance de vie encore améliorée, à fortiori si de nouveaux traitements font prochainement leur apparition (5). L'amélioration de l'espérance de vie des patients atteints de mucoviscidose est malheureusement associée à l'apparition de comorbidités plus fréquentes. Le diabète associé à la mucoviscidose (DAM) est la comorbidité extra respiratoire la plus fréquente après l'insuffisance pancréatique exocrine. Le DAM est présent chez 40 à 50 % des adultes atteints de mucoviscidose âgés de plus de 30 ans et un pourcentage similaire présente un état de pré-diabète (6,7).

Prévalence

La prévalence du diabète chez les patients atteints de mucoviscidose augmente régulièrement avec l'âge. L'âge médian de découverte du diabète est de 20 ans

(8,9), la tranche d'âge 15-30 ans est particulièrement exposée. La prévalence est proche de 40% à 30 ans (10,11). Le risque de DAM augmente avec l'âge du patient de 5% par an après 10 ans et 9,3% par an après 20 ans (11). Ces données épidémiologiques sont extraites des Registres et des études de cohorte (3,12). Elles sont donc dépendantes de la stratégie diagnostique appliquée et du critère de recueil du DAM des différents registres. La stratégie de dépistage du DAM à partir de l'âge de 10 ans, a fait augmenter le diagnostic de DAM de 25% dans la tranche d'âge 10-16 ans (13,14). Peu d'études donnent des informations sur la prévalence des troubles du métabolisme glucidique précédant le DAM ou état pré-diabétique.

Physiopathologie

L'origine des troubles du métabolisme glucidique associés à la mucoviscidose n'est pas encore totalement élucidée, elle est à priori multifactorielle. Le diabète de type 1 (DbT1) est dû à une insulinopénie liée à une destruction auto-immune des cellules bêta des îlots pancréatiques. Le diabète de type 2 (DbT2) est principalement la conséquence d'une diminution progressive de l'insuline associée à une insulino-résistance. Le DAM est une forme spécifique de diabète, ayant à la fois des caractéristiques d'un DbT1 et d'un DbT2 (14). Il est précédé d'une longue phase d'états pré-diabétiques avec des anomalies de tolérance glucidique (15). Le marqueur pronostique du DAM est essentiellement le déclin respiratoire alors que la préoccupation est plutôt la prévention du risque cardio-vasculaire pour le diabète de type 1 et 2.

Dommages pancréatiques ou défaut intrinsèque des cellules endocrines ?

La diminution de la sécrétion d'insuline par le pancréas est le mécanisme le plus important pour le DAM. Cela a été historiquement attribué à la destruction du pancréas exocrine (16). Selon cette « hypothèse de dommage collatéral » ou « hypothèse de voisinage », une obstruction du canal pancréatique par des sécrétions visqueuses liées à la mucoviscidose provoque l'autodigestion des tissus par les enzymes digestives piégées, et la destruction progressive et la fibrose du pancréas exocrine endommagent finalement les cellules endocrines adjacentes. L'insuffisance

pancréatique exocrine, ou la nécessité d'une supplémentation en enzyme pancréatique, est une conséquence facilement objectivable de la destruction du pancréas. Environ 3% seulement des patients atteints de mucoviscidose naissent avec une insuffisance pancréatique exocrine, alors que la plupart sont suffisants pancréatiques à la naissance avec des lésions relativement bénignes, telles que la dilatation du canal et de la lumière acineuse. À la fin de la première année, environ 85% des patients atteints de mucoviscidose auront développé une insuffisance pancréatique exocrine (17). Ces individus présentent généralement deux mutations CFTR qui entraînent une absence complète de la fonction protéique CFTR (mutation F508del ou à fonction minimale). Les 15% restants possèdent au moins une copie du gène CFTR avec une fonction protéique résiduelle et resteront suffisants pancréatiques ou développeront une insuffisance pancréatique exocrine à un âge plus avancé. Les patients présentant une insuffisance pancréatique exocrine présentent généralement une déficience en insuline plus sévère, mesurée par la réponse de l'insuline et du glucose à un test d'hyperglycémie provoquée par voie orale (HGPO) (15). Des études ont régulièrement montré que les patients atteints de mucoviscidose avec une insuffisance pancréatique exocrine et qui présentent une tolérance normale au glucose sur un test HGPO, ont une capacité de sécrétion d'insuline par les cellules β inférieure aux patients suffisants pancréatiques ou à des contrôles sains (18). Les personnes atteintes de maladie pancréatique exocrine néonatale plus sévère in utero, comme en témoigne la réduction des taux de trypsine immuno-réactive en circulation à la naissance, présentent un risque plus élevé de DAM (19). Ces observations corroborent l'idée selon laquelle l'insuffisance pancréatique exocrine est intimement liée à la pathogenèse du DAM. Alternativement, cela pourrait être un marqueur de génotypes de CFTR plus graves responsables du diabète via des mécanismes non liés.

D'autres données suggèrent que des mécanismes en plus de la destruction des îlots et de la fibrose pourraient être en jeu dans le développement du DAM. L'apparition d'une insuffisance pancréatique exocrine ne s'accompagne effectivement pas immédiatement d'un DAM, semblable au diabète secondaire à une pancréatite chronique. Le DAM survient généralement tardivement, plusieurs décennies après l'insuffisance exocrine, ce qui traduit une très lente diminution de la masse et de la capacité fonctionnelle des cellules β. Il est important de noter que l'ampleur de la

destruction des îlots et de la fibrose n'est pas plus importante chez les patients atteints de DAM que chez les autres patients non diabétiques (20), renforçant ainsi la notion selon laquelle les dommages structurels ne sont probablement pas le seul facteur déterminant de la pathogénie du DAM. Des études d'autopsie ont montré que le DAM était en corrélation avec la présence de dépôts amyloïde dans les îlots ; les dépôts amyloïdes sont absents dans les îlots de patients atteints de mucoviscidose sans diabète (21). Le fait que les dépôts amyloïdes des îlots contribuent ou non à la pathogénie du DAM n'a pas été déterminé. L'accumulation de dépôts amyloïdes dans les îlots est également fréquemment observée dans le diabète de type 2 mais généralement pas dans le diabète de type 1. Fait intéressant, l'analyse des familles atteintes de mucoviscidose a montré que les antécédents familiaux de diabète de type 2 constituaient un facteur de risque de DAM, et des études d'association portant sur l'ensemble du génome ont identifié plusieurs gènes de susceptibilité connus du diabète de type 2, à savoir TCF7L2, CDKN2A / B, CDKAL1 et IGF2BP2, en tant que gènes modificateurs pour le DAM (22). Ces observations suggèrent que le dysfonctionnement des îlots dans le DAM pourrait partager certains mécanismes communs avec celui du diabète de type 2. En effet, l'altération initiale de la sécrétion d'insuline observée dans la mucoviscidose est également retrouvée dans le diabète de type 2 (16). D'autre part, bien que la résistance à l'insuline soit la principale caractéristique du diabète de type 2, son rôle dans le développement du DAM est discuté. Des études de clamp euglycémique hyperinsulinémique (méthode de référence de mesure de l'insulinosensibilité in vivo) chez des sujets non diabétiques atteints de mucoviscidose ont rapporté des données contradictoires, révélant une sensibilité accrue, normale et diminuée à l'insuline (23). Il a été suggéré que la résistance à l'insuline trouvée dans le DAM pourrait être une conséquence secondaire d'une hyperglycémie prolongée au lieu d'un défaut principal de la sensibilité à l'insuline (20). Les infections aiguës tendent à être associées de manière plus systématique à une résistance accrue à l'insuline dans la mucoviscidose (23), probablement à cause de niveaux élevés de cytokines inflammatoires et d'hormones de stress. En cas de réduction de la sécrétion d'insuline, les modifications de la résistance à l'insuline peuvent être un facteur déterminant de la tolérance au glucose (24).

Outre la perte de cellules β résultant de la destruction du pancréas et de gènes modificateurs partagés avec le diabète de type 2, certains chercheurs se sont déclarés favorables à la possibilité qu'un défaut autonome des cellules β contribue directement au processus pathologique (25). Les anomalies intrinsèques des cellules β dues aux mutations du gène CFTR pourraient impliquer des mécanismes tels que des altérations du potentiel de la membrane cellulaire affectant l'appareil sécréteur d'insuline (26), l'accumulation d'agrégats de protéines CFTR mal repliées produisant un stress du réticulum endoplasmique (27), ou un transport anormal réduit de glutathion avec augmentation du stress oxydatif (28,29). La protéine CFTR est principalement exprimée dans les cellules canalaires pancréatiques, alors que son expression dans les cellules d'îlots a fait l'objet de débats. Des travaux récents utilisant l'immunolocalisation confocale ont signalé la présence de la protéine CFTR dans les cellules β (30,31). Le traitement par antagonistes de CFTR inhibe significativement la sécrétion d'insuline stimulée par le glucose dans les cellules β humaines et de souris en culture (30). Dans les îlots humains et les cellules de souris, les antagonistes de CFTR ont augmenté la sécrétion de glucagon (31). Dans une étude, les souris mutantes F508del présentaient un potentiel membranaire et une sécrétion d'insuline atténués dans les cellules β, qui étaient corrigés sous traitement correcteur de la protéine CFTR lumacaftor (26).

En plus des cellules β, les cellules **α** peuvent potentiellement contribuer à la dys-glycémie dans la mucoviscidose. Une inhibition de la suppression du glucagon après une prise de glucose par voie orale a été décrite chez des patients atteints de mucoviscidose, prédisposant éventuellement à une altération précoce de la tolérance au glucose (32). Dans plusieurs études, des patients atteints de mucoviscidose présentant une insuffisance pancréatique exocrine ont présenté une réponse réduite du glucagon à l'arginine et à l'hypoglycémie induite par l'insuline (18). La possibilité d'un défaut intrinsèque des cellules **α** a été évoquée par l'observation selon laquelle le traitement d'îlots de souris avec des inhibiteurs de CFTR augmente la sécrétion de glucagon, peut-être via une altération du potentiel de la membrane des cellules **α** (31). L'axe incrétine est un autre système hormonal impliqué dans la pathogenèse du DAM. Le taux de GLP-1 (glucagon-like peptide-1) actif dans la mucoviscidose est diminué dans certaines études (33). Les réponses du GLP-1 et du polypeptide inhibiteur gastrique (GIP-1) à un repas mixte ont été atténuées au cours des 30

premières minutes chez les patients présentant une insuffisance pancréatique par rapport aux patients suffisants pancréatiques (18). On ignore si la protéine CFTR est exprimé dans les cellules entéro-endocrines de l'intestin et si elle peut affecter la sécrétion de GLP-1 ou de GIP-1. Le traitement des patients atteints de mucoviscidose avec l'ivacaftor (potentialisateur de CFTR) a amélioré la sécrétion d'insuline mais pas la sécrétion d'incrétine (34), suggérant que la protéine CFTR pourrait ne pas moduler directement la sécrétion d'incrétine. Enfin, le taux de clairance de l'insuline augmente dans la mucoviscidose en raison de mécanismes obscurs (35).

Aperçus des modèles de furet et de porc

Les modèles de furet et de porc reflètent plus fidèlement la maladie humaine, y compris le développement du diabète en fonction de l'âge (36). Les furets nouveaux-nés CFTR -/- ont une maladie relativement bénigne du pancréas exocrine et ne présentent principalement qu'une dilatation des canaux acineux, mais la plupart développent une inflammation sévère et une insuffisance pancréatique exocrine au cours des premiers mois de leur vie. En revanche, les porcs CFTR -/- développent une inflammation pancréatique en fin de gestation et sont tous nés avec une insuffisance pancréatique exocrine. En termes de pathologie des îlots, les furets CFTR -/- présentent une tolérance anormale au glucose et une diminution de la sécrétion d'insuline de première phase à la naissance, avant l'insuffisance pancréatique exocrine (37). Les porcs CFTR -/- et F508del présentent également une altération de la tolérance au glucose et des anomalies de la sécrétion d'insuline à la naissance, puis développent une hyperglycémie spontanée sans perte appréciable de masse cellulaire d'îlots (38). Ces dernières observations impliquent que la destruction structurelle du pancréas endocrinien peut ne pas être nécessaire au développement du DAM.

Comment les nouvelles données humaines et animales affectent les points de vue sur la pathogenèse du CFRD

Des études récentes chez l’homme confirment la présence d'anomalies précoces dans le métabolisme du glucose. Des nourrissons et jeunes enfants atteints de

mucoviscidose âgés de 3 mois à 5 ans présentaient une tolérance anormale au glucose (39). Les niveaux d'insuline n'ont pas augmenté ou n'ont que légèrement augmenté par rapport aux témoins après une charge en glucose par voie orale, ce qui suggère une incapacité à augmenter la sécrétion d'insuline pour maintenir l'euglycémie. Dans d'autres études cliniques, des patients atteints de mucoviscidose traités par ivacaftor (potentiateur de CFTR), ont significativement amélioré la sécrétion d'insuline de première phase ainsi que la réponse insulinique à la charge de glucose par voie orale, indiquant une réversibilité partielle du défaut de sécrétion (40–42). De telles observations pourraient être compatibles avec un défaut primitif des cellules **β** résultant de mutations de CFTR, car ivacaftor corrige également les défauts du canal dans d'autres cellules pancréatiques. Pour exclure l'influence des cellules non-**β**, une souris nulle CFTR inductible spécifique des cellules **β** a été générée, présentant une masse normale de cellules **β**, une sensibilité accrue à la sécrétion d'insuline induite par le glucose. Aucune expression de CFTR n'a été détectée dans les cellules pancréatiques endocrines humaines ou de furet par hybridation in situ (43), ce qui est en contradiction avec d'autres rapports sur la détection de protéines dans les cellules **β** humaines par immunolocalisation confocale (30). Cependant, les îlots des furets nouveaux-nés nuls pour le CFTR présentaient toujours une diminution de la sécrétion d'insuline. Il a été suggéré que CFTR pourrait contrôler la fonction des cellules **β** indirectement via un mécanisme paracrine impliquant des cellules non endocrines associées aux îlots, telles que des cellules canalaires ou des cellules étoilées. Des neuropeptides tels que le peptide lié au gène de la calcitonine pourrait jouer un rôle dans ce contexte (44). Un mécanisme paracrine pourrait expliquer les défauts fonctionnels de la cellule **β** sans qu'il soit nécessaire d'invoquer des effets autonomes de la cellule ou une destruction extensive des îlots. Des travaux récents sur les furets ont également démontré la survenue d'une crise glycémique transitoire au début de la vie, qui s'accompagne d'une perte de masse de cellules **β** et d'une inflammation et d'une fibrose pancréatique. Ceci est suivi d'une réponse compensatoire, avec un doublement de la masse de cellules **β** résiduelles et une augmentation de l'expression des gènes de l'insuline pancréatique, du glucagon et de la somatostatine (39). Il est concevable que les patients atteints de mucoviscidose puissent subir une crise glycémique similaire tôt dans la vie en cas d'insuffisance pancréatique exocrine, mais des mécanismes compensatoires permettent une récupération fonctionnelle suffisante

pour retarder l'apparition du DAM à des décennies plus tard. Des études expérimentales sur des îlots d'êtres humains et de souris traités avec des inhibiteurs de CFTR ont confirmé le rôle d'un défaut intrinsèque des cellules **β**. Chez les furets, cependant, ces inhibiteurs ont réduit la sécrétion d'insuline dans les îlots de type sauvage et nuls, suggérant un effet hors cible. Il pourrait être intéressant de mener des études sur l'expression et l'inhibition de CFTR en utilisant des tissus d'autres modèles animaux nuls avec le gène CFTR et des patients porteurs de mutations non-sens du gène CFTR.

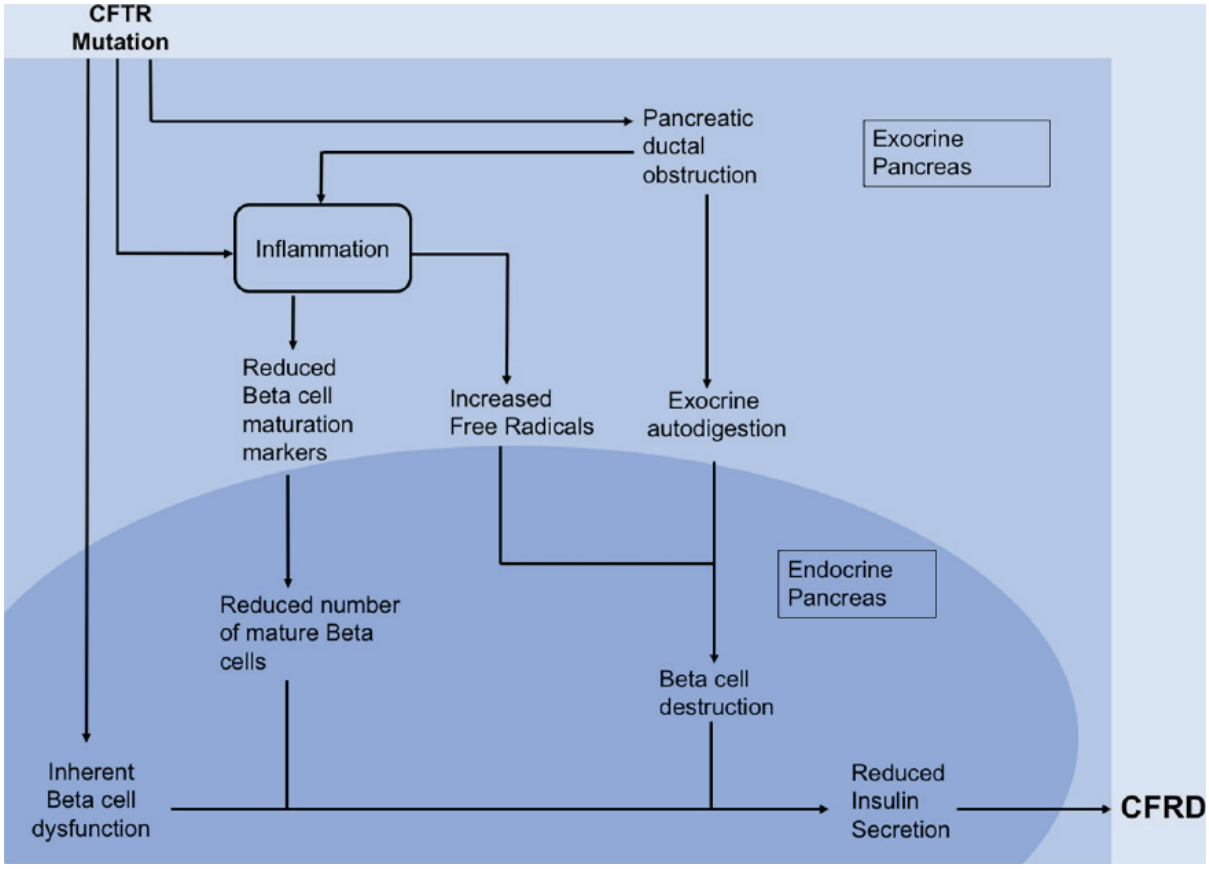

Figure 1 : Résumé des différentes hypothèses pour les mécanismes physiopathologiques du DAM (d'après Kessmey R et al., Cystic Fibrosis-Related Diabetes: Pathophysiology and Therapeutic Challenges. Clin Med Insights Endocrinol Diabetes. 2019 May 28;12:1179551419851770. doi: 10.1177/1179551419851770. eCollection 2019.)

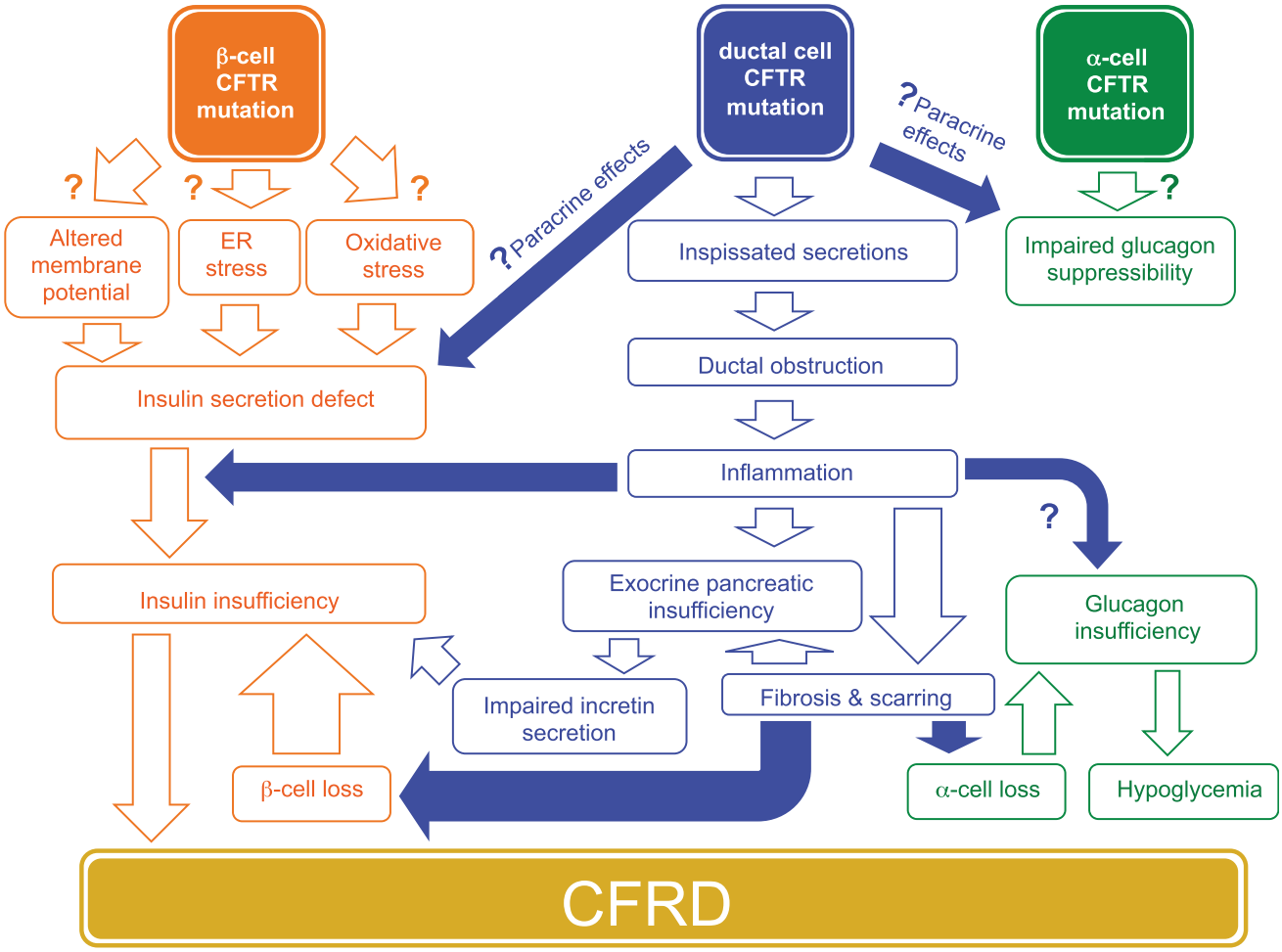

Figure 2 : Mécanismes pathogéniques du DAM. L'insulino-résistance peut aussi jouer un rôle en cas d'exacerbations. Les gènes modificateurs influencent aussi l'évolution du DAM. (ER : réticulum endoplasmique (d'après Yoon JC, Evolving Mechanistic Views and Emerging Therapeutic Strategies for Cystic Fibrosis-Related Diabetes. J Endocr Soc. 2017 Oct 30;1(11):1386-1400. doi: 10.1210/js.2017-00362. eCollection 2017 Nov 1.)

Facteurs prédictifs de survenue du DAM

Les facteurs de risque pour le développement d'un DAM sont : l'âge, le sexe féminin, l'insuffisance pancréatique exocrine (favorisant une insuffisance pancréatique endocrine), le génotype (classe de mutation I et II) (45,46). L'âge est un facteur reconnu car il existe une augmentation de la prévalence et du taux d'incidence du diabète avec l'augmentation de l'âge. Le sexe féminin favoriserait une apparition plus précoce du diabète et la survenue de celui-ci aurait des conséquences plus marquées avec une mortalité plus élevée chez les femmes (45,47). Néanmoins, il reste difficile de montrer si le diabète aggrave la fonction respiratoire ou si une altération sévère de la fonction respiratoire entraîne l'apparition d'un diabète (48). Les antécédents familiaux de diabète sont également identifiés comme facteur prédictif de l'apparition du diabète (22). Enfin, les traitements par corticoïdes accélèrent la survenue de troubles glucidiques. Les études ayant étudié les facteurs prédictifs de troubles de la tolérance glucidique se sont attachées à comparer les patients diabétiques aux patients non diabétiques, dans le cadre d'analyses rétrospectives. Elles ont principalement porté sur de petits échantillons de patients. Les facteurs associés aux troubles du métabolisme glucidique en cas de mucoviscidose semblent nombreux mais le poids de chaque facteur reste à préciser de même que le rôle de ceux-ci dans l'évolution ultérieure des troubles.

Impact pronostique du DAM

Le DAM est associé à une dégradation clinique plus importante. De nombreuses études ont montré que les patients diabétiques ont un statut nutritionnel moins bon, des atteintes pulmonaires plus sévères et une mortalité plus élevée (7,14,45,49–51). L'accélération de la dégradation de la fonction pulmonaire et le déclin nutritionnel commencent 3 à 4 ans avant le début du DAM (52–54). La principale hypothèse pour expliquer l'association entre la glycémie élevée et une fonction pulmonaire plus basse est que l'hyperglycémie plasmatique favorise une hyperglycémie dans les sécrétions bronchiques. Cette hyperglycémie bronchique favoriserait la colonisation bronchique par *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Stenotrophomonas maltophilia* (55,56). Les patients diabétiques comparés aux non diabétiques ont une fréquence d'exacerbation multipliée par deux (57,58).

L'hyperglycémie bronchique induit l'acidification superficielle des épithéliums bronchiques déficitaires pour la protéine CFTR. Il en résulte une augmentation de la production de lactate, qui est encore exacerbée par la colonisation à *Pseudomonas* (59). *Pseudomonas* a par ailleurs montré une meilleure croissance dans les milieux riche en lactate, ce qui signifierait que le milieu bronchique des patients mucoviscidose avec DAM serait particulièrement favorisant pour sa croissance (59).

L'impact clinique des anomalies glucidiques préalables au DAM est par contre peu évalué dans la littérature (durée de suivi courte, petits effectifs) (60), alors que le nombre de patients atteints de mucoviscidose présentant ces anomalies est important.

La transplantation pulmonaire est la stratégie thérapeutique en cas d'insuffisance respiratoire terminale dans la mucoviscidose. Malgré un âge jeune au moment de la transplantation pulmonaire, les patients atteints de mucoviscidose ont un risque de diabète après la transplantation plus élevé par rapport au reste de la population transplanté pulmonaire (61,62). Le diabète préexistant à la transplantation est identifié comme un facteur de mauvais pronostique avec une mortalité post-greffe plus importante chez les patients diabétiques en pré-transplantation (63,64). Il apparait donc indispensable de bien contrôler le DAM avant la transplantation pulmonaire pour en limiter les risques après la transplantation. Pour les patients non diabétiques avant la transplantation, le risque de DAM directement lié à la mucoviscidose persiste après la transplantation et il est probablement majoré par d'autres facteurs comme la corticothérapie et les anticalcineurines.

Les atteintes microangiopathiques à type de rétinopathie, néphropathie et neuropathie diabétiques sont retrouvées chez les patients atteints de mucoviscidose. La rétinopathie diabétique est présente chez 40% des patients diabétiques depuis plus de 10 ans, la neuropathie chez 50% des patients diabétiques depuis plus de 10 ans (65,66). Le risque de néphropathie diabétique est multiplié par quatre après dix ans d'évolution du diabète. La fonction rénale doit être particulièrement préservée compte tenu des multiples potentiels facteurs aggravants : médicaments néphrotoxiques (aminosides) utilisés avant la transplantation, immunosuppresseurs en cas de transplantation. Les complications microvasculaires devraient être dépistées annuellement mais le taux d'adhérence au dépistage est faible (67).

Compte tenu de l'allongement de l'espérance de vie, l'attention portée aux complications du diabète doit être augmentée et des stratégies de dépistage robustes mises en place. Les atteintes macroangiopathiques (HTA, cardiopathie) sont beaucoup moins fréquentes, mais cela pourrait aussi évoluer avec les changements épidémiologiques, et surtout après la transplantation pulmonaire.

Traitement

Le traitement et la prise en charge du DAM à un coût direct (financier) et indirect pour les patients avec une augmentation de la charge de soins déjà lourde (« fardeau thérapeutique ») (68).

L'insulinothérapie est le traitement recommandé en cas de DAM (13). Elle permet une amélioration des paramètres nutritionnels et respiratoires en diminuant le nombre d'exacerbations respiratoires (69). Le plus commun est d'utiliser en monothérapie une insuline de longue durée d'action et / ou des bolus d'insuline rapide aux repas. Le régime basal-bolus est plutôt réservé aux patients avec une hyperglycémie à jeun, complication rare et tardive (13). Il existe peu de données pour préférer l'une ou l'autre des stratégies, et chaque décision thérapeutique doit être personnalisée en fonction des possibilités du patient, de son acceptation des contraintes du traitement, et de la surcharge supplémentaire en soins que cela implique.

Des conseils diététiques personnalisés, basés sur une compréhension du DAM, ainsi que sur son interaction avec d'autres complications liées à la mucoviscidose, sont essentiels pour répondre aux besoins nutritionnels tout en optimisant le contrôle de la glycémie. Les recommandations dictant les meilleures pratiques pour l'alimentation en cas de DAM ne sont pas issues d'essais contrôlés randomisés mais surtout de données d'observations cliniques consensuelles (70–72). Le traitement de substitution par enzymes pancréatiques reste aussi une pierre angulaire du traitement pour optimiser l'absorption des graisses et limiter les pics hyperglycémiques. La carence en insuline observée en cas de DAM potentialise l'état catabolique, un apport calorique accru est donc nécessaire pour contrer ce phénomène. Le type de consommation de glucides est également important. La

restriction complète des sucres simples n'est souvent pas appropriée en raison des besoins caloriques nécessaires.

Cependant, l'impact clinique de l'état pré-diabètique (avant que les valeurs de glycémie n'atteignent les valeurs seuils déterminants le DAM sur l'HGPO) reste à déterminer. Peu d'études ont évalué l'impact d'un traitement précoce de cet état pré-diabétique, ce qui semblerait intéressant si l'impact clinique de ce statut sur la fonction respiratoire et la perte de poids était démontré (73). Des études ont exploré cette hypothèse mais avec de petits effectifs et les résultats sont discutables. Des études prospectives sont en cours et apporteront des réponses à cette question ("CF-IDEA Trial" clinicaltrials.gov: CT01100892 and "The Impact of Insulin Therapy on Protein Turnover in Pre-Diabetic Cystic Fibrosis Patients" clinicaltrials.gov: NCT02496780).

Diagnostic et dépistage

Compte tenu de son caractère insidieux, de l'impact clinique et de la morbidité associée au DAM, une stratégie de dépistage annuelle est recommandée chez les patients à partir de l'âge de 10 ans, dans l'objectif de détecter précocement le DAM pour mettre en route un traitement spécifique et en limiter l'impact clinique (13). L'hyperglycémie provoquée par voie orale (HGPO) est le test de dépistage de référence. Il comporte l'ingestion de 1,75g/kg de glucose dans 300ml d'eau (75mg maximum) avec une mesure de la glycémie à T0 et T120 mn (à jeûn depuis la veille, repos strict pendant la durée du test), dans une situation de stabilité clinique (à distance d'une exacerbation respiratoire).

Selon les recommandations françaises, les patients sont classés en 4 catégories en fonction de leurs valeurs de glycémies aux différents temps du test HGPO : normo tolérant, intolérant au glucose et diabétique avec glycémie à jeûn normale ou diabétique avec glycémie à jeûn élevée (Tableau 1). Les recommandations nord-américaines considèrent une autre catégorie (13) : tolérance glucidique indéterminée, définie par des glycémies à jeûn et à 2 heures normales, mais une valeur à 1 heure $\geq$ 11,1 mmol/L durant le test d'HGPO. Ainsi, les patients peuvent

être classés en 4 catégories : tolérance glucidique normale, tolérance glucidique indéterminée (INDET), tolérance glucidique détériorée et DAM (Tableau 1).

	Critères Nord-Américains		Critères France	
	Glucose à jeun (mmol/L)	Glucose à 2h (mmol/L)	Glucose à jeun (mmol/L)	Glucose à 2h (mmol/L)
Tolérance normale	< 7.0	< 7.8	< 7	< 7.8
Tolérance Indéterminée (INDET)	< 7.0	< 7.8 Glucose à 1h ≥11.1 mmol/L	-	-
Intolérance au glucose	< 7.0	7.8-11.0	< 7.0	7,8-11,0
Diabétique	> 7,0 et/ou ≥ 11,1		> 7,0 et/ou ≥ 11,1	

Tableau 1 : Valeurs de glycémies pour les catégories de tolérance au glucose durant l'HGPO.

Le test d'HGPO présente des inconvénients. Il est mené dans des conditions non physiologiques (jeûne, charge en glucides). Il s'agit d'un test lourd à la fois pour l'équipe de soin et pour le patient, ce qui contribue à une faible adhésion à la procédure de dépistage recommandée (74,75). Un travail non publié d'une équipe québécoise montre que les patients interviewés dans huit centres du Québec percevaient l'HGPO comme une procédure envahissante et difficile à intégrer aux soins courants. Un raccourcissement de l'HPGO à 90 minutes a été proposé, les patients intolérants restaient classés dans la même catégorie avec le test raccourci à 90 min qu'avec le test de durée classique d'HGPO (76). Les critères pour établir le diagnostic de DAM sont contestés. En effet, les seuils à jeun et à 2 heures sont basés sur le risque de rétinopathie chez les sujets atteints de diabète de type 2 et non sur le risque de dégradation de la fonction pulmonaire et du statut nutritionnel, critères pronostiques plus pertinents pour les patients atteints de mucoviscidose (77,78). Le dépistage par hémoglobine glyquée (HbA1C) manque de sensibilité dans

la mucoviscidose (79) compte tenu de la faible corrélation entre la glycémie capillaire et les taux d'HbA1C. Parce que l'HbA1C est pratique (simple prélèvement sanguin facile à combiner avec d'autres tests de laboratoire requis pour la surveillance de la mucoviscidose), la plupart des équipes ont tenté de compenser la sensibilité plus faible en proposant un seuil inférieur d'HbA1C spécifique réduit à 5,8% (80–83).

Mainguy et al. ont étudié d'autres méthodes plus simples de dépistage du DAM, notamment des index d'insulino-résistance (HOMA-IR) et d'insulino-sécretion (HOMA-% β) en les comparant à des mesures de glycémies continues (CGM) (84). Ce sont des formules simples car seules les valeurs d'insuline et de glucose à jeun sont nécessaires. Un critère indispensable sera la standardisation de la méthode de dosage de l'insuline plasmatique ce qui n'est actuellement pas le cas.

La mesure de glycémie continue (CGM) est de plus en plus accessible, sans douleur, ne nécessite pas de jeûne et permet un profil glycémique détaillé dans des conditions réelles, ce qui ne peut pas être observé pendant le test HGPO. Elle pourrait donc être utilisée comme test de dépistage dans les populations à risque élevé de diabète (80). Cependant, contrairement aux critères bien acceptés d'évaluation du contrôle glycémique chez les patients présentant un diabète établi, il n'existe pas de consensus sur les critères de diagnostic du diabète en utilisant la CGM (13). Plusieurs groupes de recherche ont comparé le profil glycémique par CGM et les excursions glycémiques à un test HGPO standard (85,86). Ces études conduites sur de petits groupes de patients ont montré qu'un tiers des patients avec HGPO normale présentent des excursions glycémiques supérieures au seuil habituel utilisé pour le diabète (≥ 11,1 mmol/L). Des études prospectives sont nécessaires pour confirmer l'association entre les excursions glycémiques des CGM et la détérioration clinique (72). Ces études devront répondre à de nombreuses questions, notamment pour l'interprétation des excursions glycémiques (seuils, nombre et durée des épisodes), la durée du test CGM (la plupart des données publiées utilisent 3 jours mais les appareils actuels offrent jusqu'à 2 semaines de valeurs avec capteur unique), la précision du CGM spécifique, la recherche de valeurs aberrantes et les exigences minimales pour l'étalonnage du CGM ainsi que pour l'apport en glucides. Le CGM représente un moyen prometteur pour simplifier le dépistage des troubles glycémiques tant du point de vue clinique que pratique, mais il est trop tôt pour recommander son utilisation pour le dépistage du DAM. Bien que le test HGPO

standard présente des lacunes importantes, il reste le test standard recommandé (13).

Dans la mucoviscidose, les effets cliniques délétères de l'hyperglycémie avant que son seuil n'atteigne les seuils conventionnels du diabète selon les critères de l'HGPO, sont mal connus. Ils ont été décrits pour la catégorie de patients INDET par Coriati et al avec une dégradation clinique (87,88). Si ces effets délétères sont confirmés, il serait très utile d'avoir à disposition un test de dépistage qui prendrait en compte non seulement le DAM avéré mais aussi les situations à risque de dégradation clinique (statut pré-diabétique), et qui soit plus acceptable pour les patients et les équipes.

La valeur pronostique de la glycémie à 1 heure durant l'HGPO a été mise en évidence dans plusieurs pathologies. Par exemple, les glycémies obtenues durant le test HGPO pour dépister le diabète gestationnel ont été associées à des effets indésirables pour des seuils plus bas que les critères diagnostiques. Viser la normalisation de la glycémie à 1 heure chez les femmes enceintes est recommandé pour améliorer le pronostic maternel et fœtal (89). Cet intérêt pour la glycémie à 1 heure durant l'HGPO comme marqueur pronostique de l'état de santé s'étend à la population pré-diabétique (meilleure prédiction du risque de diabète de type 2) et chez les patients avec un diabète de type 2 établi (associé à un profil cardio-métabolique défavorable) (90). De nombreuses équipes ont rapporté que, comparés à des témoins, les patients atteints de mucoviscidose présentent un profil glycémique spécifique, et ce, même chez les sujets atteints de mucoviscidose et considérés comme normo-tolérants au glucose. Ce profil est caractérisé par une augmentation rapide de la glycémie au cours de la première heure de l'HGPO (48,91,92). Pour cette raison les chercheurs se sont intéressés à la valeur des temps intermédiaires de l'HPGO chez les patients atteints de mucoviscidose comme pronostic de l'impact clinique. Il est nécessaire de disposer de plus de preuves sur l'intérêt de la glycémie à 1 heure (78). À notre connaissance, il n'y a pas eu d'étude explorant la valeur de la glycémie à 1 heure durant le test d'HGPO pour confirmer chez les adultes, les résultats observés chez les sujets d'âge pédiatrique. Une cohorte prospective observationnelle mettait en évidence le lien entre le déclin de la fonction pulmonaire et la sévérité du déficit en insuline définit lors d'un test HGPO par l'aire sous la

courbe de l'insuline (47,50). Un faible taux d'insuline lors du test d'HGPO pourrait promouvoir un état catabolique favorisant un déclin respiratoire et nutritionnel rapide. Peu d'études ont investigué le rôle de l'insulinémie à 1 heure durant l'HGPO pour prédire la détérioration clinique.

Présentation du travail

Depuis environ cinq ans, en tant que clinicien impliqué dans la prise en charge de la mucoviscidose chez les patients adultes au centre de référence pour la mucoviscidose (site constitutif) de l'hôpital Lyon Sud des Hospices Civils de Lyon, nous avons participé à l'élaboration et à la conduite de projets de recherche évaluant les troubles du métabolisme glucidique dans la mucoviscidose. Ces projets ont été mis en place en collaboration avec l'équipe du pôle de Santé Publique du Dr Touzet, département Information Médicale Evaluation Recherche, l'équipe du Pr Thivollet et du Pr Laville du service d'endocrinologie et nutrition, et avec l'équipe du Pr Rabasa-Lhoret à Montréal, Québec, Canada, avec qui nous avons constitué une cohorte qui continue à être implémentée.

Ces projets nous ont permis d'aborder certains aspects spécifiques des troubles du métabolisme glucidique dans la mucoviscidose et d'étudier leur impact pronostique. Compte tenu des avancées en termes de prise en charge et d'espérance de vie, il nous a paru nécessaire d'approfondir les éléments de réponse à certaines questions importantes en pratique clinique : quel impact pronostique a le DAM et les valeurs élevées des temps précoces de l'HGPO et faut-il les traiter précocement ? Faut-il élaborer une stratégie de dépistage plus adaptée ? Quel impact pronostique a le diabète dans certaines situations spécifiques de l'adulte, à savoir la grossesse et la transplantation pulmonaire ?

Nous présenterons d'abord notre travail sur les troubles du métabolisme glucidique associés à la mucoviscidose : évolution naturelle et impact pronostique, à partir d'analyses de bases de données régionales et internationales. Nous présenterons successivement quatre études : DIAMUCO 1 et 2, et GLYCONE 1 et 2.

Nous présenterons ensuite deux études sur l'impact du diabète de la mucoviscidose dans la grossesse et la transplantation pulmonaire (MUCOG et MUCOTRANSPLAN) à partir de bases de données nationales et régionales.

Les travaux présentés dans cette thèse font l'objet de quatre publications et de deux manuscrits soumis à publication.

TRAVAUX DE RECHERCHE

Les troubles du métabolisme glucidique associés à la mucoviscidose : évolution naturelle et impact pronostique, à partir d'analyses de bases de données régionales et internationales.

1. Evolution naturelle et impact pronostique des troubles du métabolisme glucidique dans la mucoviscidose en Rhône-Alpes

A. Etudes DIAMUCO : contexte

Au cours de ces dernières années, différents facteurs pourraient avoir modifié l'évolution des troubles du métabolisme glucidique : l'amélioration de la prise en charge nutritionnelle, le diagnostic plus précoce des troubles du métabolisme glucidique, l'augmentation du nombre de patients adultes et l'allongement de leur survie. Il semble exister, pour un certain nombre de patients, une réversibilité spontanée des troubles du métabolisme glucidique, que ces troubles soient au stade de l'intolérance glucidique ou de diabète (50). En comparant les résultats annuels d'HGPO, on constate que 40% des patients changent de statut glycémique. Lanng et al. ont montré au cours d'une étude prospective portant sur 191 patients suivis pendant 5 ans bénéficiant d'une HGPO annuelle que 58% des patients diagnostiqués intolérants étaient à nouveau normo-tolérants l'année suivante (11).

L'étude DIAMUCO est une étude de cohorte, constituée de patients atteints de mucoviscidose suivis dans les quatre Centre de Ressources et de Compétence pour la Mucoviscidose (CRCM) de la région Rhône-Alpes. La période de suivi des patients est de 3 années (soit 1 évaluation du statut glucidique à l'inclusion du patient puis 3 évaluations à un an d'intervalle). Le stade de tolérance glycémique : « normo-tolérant », « intolérant au glucose », « diabète » est évalué à l'inclusion et annuellement par un test d'HGPO standard. Les caractéristiques démographiques, cliniques et paracliniques sont recueillies lors des venues des patients en CRCM pour la réalisation de l'HGPO annuellement. Le statut glucidique peut être « normo-tolérant », « intolérant » ou « diabétique » à chaque point de mesure et le profil de

variation de chaque patient sur la durée de l'étude est établi, en rapport avec l'évolution de son statut clinique global (pulmonaire et nutritionnel).

B. Etude DIAMUCO 1

Objectif

L'objectif principal de cette étude a été d'estimer la prévalence des différents statuts glucidiques au cours du suivi, de décrire la variabilité intra-individuelle des troubles glucidiques dans le temps et d'évaluer leur impact pronostique sur le statut clinique respiratoire et nutritionnel.

Résultats

111 enfants et 117 adultes étaient inclus dans l'étude. Le nombre de patients pour chaque statut glucidique était variable à chaque année de suivi. Les patients étaient classés en trois groupes selon la variation de leur résultat annuel d'HGPO au cours du suivi : groupe stable, groupe amélioré, et groupe détérioré. 34.7% des patients étaient dans le groupe stable, 16.6 % étaient dans le groupe détérioré et 48.7% dans le groupe amélioré. A l'inclusion les 3 groupes étaient comparables pour la population pédiatrique et adulte. Aucune différence n'était observée en termes d'évolution respiratoire et nutritionnelle entre les 3 groupes au cours du suivi.

Les résultats de l'étude sont produits dans l'article intitulé "**High variability of glucose tolerance in patients with cystic fibrosis and its impact on clinical evolution"** qui est en révision pour la revue Current Diabetes Reports.

Discussion

Cet article confirme l'importante variabilité intra-individuelle du statut glycémique au cours du temps dans la mucoviscidose. L'absence de différence d'évolution entre les

3 groupes pourrait être expliquée par la durée de suivi de seulement 3 ans. Chez les adultes cette absence de différence pourrait être expliquée par le fait que le groupe détérioration incluait des patients traités par insuline.

Malgré l'absence de différence entre les groupes pour l'évolution de l'IMC, l'IMC à l'inclusion du groupe amélioré était plus élevé. Ce statut clinique meilleur pour le groupe amélioré n'était pas confirmé pour le statut respiratoire, puisque même si la tendance était non statistiquement significative, la fonction respiratoire était meilleure à l'inclusion pour le groupe détérioré.

Current Diabetes Reports

High variability of glucose tolerance in patients with cystic fibrosis and its impact on clinical evolution

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Abstract:	Aim to evaluate within-patient variability of glucose tolerance status over time and determine the impact of glucose metabolism evolution over time on clinical change (pulmonary function and BMI) in children and adult CF patients.Methods 105 children and 94 adult CF patients were included and examined at inclusion then yearly over a three-year follow-up period. At each visit, all subjects underwent a 2-h OGTT. Patients were then classified in 3 groups according to the variation of their OGTT results during follow-up: stable glucose tolerance group, improved glucose tolerance group and deteriorated glucose tolerance group. Clinical status (pulmonary function and BMI) of the 3 glucose tolerance evolution groups (stable, improved and deteriorated) were compared over the follow-up period.Results Sixty-nine patients (34.7%) maintained a similar glucose tolerance status during follow-up (stable group). The remaining patients had either deteriorated (33, 16.6%) or improved (97, 48.7%) their glucose tolerance status. For children and adult at

	inclusion, no significant difference of age, BMI Z-score weight, FEV1 and number of days of intravenous antibiotic per year was observed between the three glucose evolution groups (stable, deteriorated, improved). During follow-up, no significant difference was observed between the three groups for mean FEV1 change per year and mean BMI Z-score change per year in children and adults.Conclusion Recurring glucose abnormalities need enhanced surveillance to evaluate the clinical impact of these abnormalities and before discussion of insulin initiation.

High variability of glucose tolerance in patients with cystic fibrosis and its impact on clinical evolution

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Running head: variability of glucose tolerance in patients with cystic fibrosis

Key messages:

- In a context of very variable glucose tolerance within patient's overtime, more importance should be given to recurring glucose abnormalities.

- Recurring glucose abnormalities need enhanced surveillance before discussion of treatment burden and insulin initiation.

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ABSTRACT

Aim: to evaluate within-patient variability of glucose tolerance status over time and determine the impact of glucose metabolism evolution over time on clinical change (pulmonary function and BMI) in children and adult CF patients.

Methods: 105 children and 94 adult CF patients were included and examined at inclusion then yearly over a three-year follow-up period. At each visit, all subjects underwent a 2-h OGTT. Patients were then classified in 3 groups according to the variation of their OGTT results during follow-up: stable glucose tolerance group, improved glucose tolerance group and deteriorated glucose tolerance group. Clinical status (pulmonary function and BMI) of the 3 glucose tolerance evolution groups (stable, improved and deteriorated) were compared over the follow-up period.

Results: Sixty-nine patients (34.7%) maintained a similar glucose tolerance status during follow-up (stable group). The remaining patients had either deteriorated (33, 16.6%) or improved (97, 48.7%) their glucose tolerance status. For children and adult at inclusion, no significant difference of age, BMI Z-score weight, FEV1 and number of days of intravenous antibiotic per year was observed between the three glucose evolution groups (stable, deteriorated, improved). During follow-up, no significant difference was observed between the three groups for mean FEV1 change per year and mean BMI Z-score change per year in children and adults.

Conclusion: Recurring glucose abnormalities need enhanced surveillance to evaluate the clinical impact of these abnormalities and before discussion of insulin initiation.

Key words: Cystic fibrosis-related diabetes, Oral glucose tolerance test, Pulmonary function, Body mass index

INTRODUCTION

Cystic fibrosis related diabetes (CFRD) is the most common endocrine complication of CF and affects about 20% of adolescents and 40 to 50% of adults [1]. As the average life span of people with cystic fibrosis continues to grow, CFRD is expected to become more common. The diagnosis of CFRD is associated with worse clinical outcomes in patients with CF, reflected in more frequent pulmonary exacerbations, greater reduction in lung function, poorer nutritional status and decreased survival [2–4]. Even impaired glucose tolerance occurring before the diagnosis of diabetes has been linked to major clinical deterioration [5,6]. Recommendations for annual screening using a 75g oral glucose tolerance test (OGTT) and insulin treatment initiation when the diagnosis is confirmed are established by the Cystic Fibrosis Foundation and the European Cystic Fibrosis Society [7,8]. Some studies have reported a high variation in glucose tolerance over time [9–12], and dysglycemia appears to be a dynamic process due to variable insulinopenia and insulin resistance. The impact on clinical status (lung function and BMI) over time of different glucose abnormalities (Normal Glucose tolerance, Abnormal Glucose Tolerance, CFRD) has been evaluated in only a few studies and no important differences were observed between glucose abnormalities subgroups [11,13]. The aim of this study was to evaluate within-patient variability of glucose tolerance status over time and determine the impact of glucose metabolism evolution over time on clinical change (pulmonary function and BMI) in children and adult CF patients.

METHODS

Study design, population, and oral glucose tolerance testing (OGTT)

Inclusion and exclusion criteria, population characteristics, OGTT testing were previously described in the DIAMUCO study [11]. The participants were examined at inclusion then yearly over a three-year follow-up period as part of routine follow-up visits. At each examination, the physicians collected, among other data: weight, height, FEV1, and OGTT results. FEV1 values were expressed as percentage of the predicted normal value given by Knudson formula. At each visit, all subjects underwent a 2-h OGTT. Blood sample were taken at 0 (0), 60 (1), and 120 (2) min to measure plasma

glucose (G0, G1, G2) and insulin values (I0, I1, I2) (immunoradiometric assay, BI-INS-IRMA, Cisbio Bioassays, France). Insulin sensitivity (Stumvoll index) and insulin resistance (HOMA-IR) were calculated. At baseline, patients were classified into different subgroups of glucose tolerance according to international guidelines: Normal Glucose Tolerance (NGT) (G0 ≤ 7.0 mmol/L and G2 ≤ 7.7 mmol/L), Abnormal glucose tolerance (AGT) defined as having either indeterminate glucose tolerance (INDET) (G0 ≤ 7.0 mmol/L and G2 ≤ 7.7 mmol/L, but G1 ≥ 11.1 mmol/L) or impaired glucose tolerance (IGT) (G0 ≤ 7.0 mmol/L and G2 > 7.7 mmol/L but < 11.1 mmol/L) and finally de novo CFRD (G0 > 7.0 mmol/L or G2 ≥ 11.1 mmol/L). Patients diagnosed with CFRD after an OGTT were kept in the cohort and the analysis whenever they had at least 2 OGTT measurements on 2 different visits (before or including the one diagnosing CFRD) including those who required insulin treatment after CFRD diagnosis and those who met strict CFRD criteria but were left untreated. Once CFRD was confirmed on a second OGTT, the test was not redone the year after if the patient was treated with insulin. According to conventional criteria (American Diabetes Association and Cystic Fibrosis Foundation) [1] patients diagnosed with fasting hyperglycemia at any moment during the three-year follow-up received an antidiabetic treatment (insulin). Patients with abnormal OGTTs (impaired glucose tolerance, CFRD without fasting hyperglycemia) were monitored at home with three daily glycemic controls including before- and after-meal glucose level controls during a minimum of 7 days. Patients with after-meal glucose levels < 10 mmol/L were left untreated. In case of clinical worsening, OGTT was repeated and patients found with abnormal OGTT were given insulin when justified. Patients were then classified in 3 groups according to the variation of their OGTT results (at least 2 OGTT tests) during follow-up: stable glucose tolerance group for patients who maintained a similar glucose tolerance status at fourth tests; improved glucose tolerance group for patients who reverted at least once over the four tests from CFRD to AGT or NGT, and from AGT to NGT; deteriorated glucose tolerance group for patients who worsened their glucose tolerance at least once over the 4 tests from NGT to AGT, or AGT to CFRD, or NGT to CFRD without any reversion.

Statistical analysis

Characteristics data were presented as the median with interquartile range (IQR) and percentage, as appropriate. We compared at baseline the 3 subgroups of glucose tolerance (NGT, AGT, CFRD). Glucose tolerance evolution groups (stable, improved and deteriorated) were also compared over the follow-up period using non-parametric tests for quantitative variables (Mann-Whitney test).

To compare clinical changes in FEV1 and BMI of the 3 glucose tolerance evolution groups over time, we used a linear model with random intercept taking into account the repeated data. Analyses were done separately for children and adults.

Analyses were performed using statistical software package (SAS, version 9.3; SAS Institute; Cary, NC). All p-values reported are two-tailed; values ≤ 0.05 were considered statistically significant.

RESULTS

Baseline

The study included 111 children (59 males and 52 females) and 117 adults (65 males and 52 females). Their main inclusion characteristics according to each OGTT classification subgroup are shown in Table 1.

Glucose tolerance status evolution during follow-up

Over the 3-year follow-up period, 199 patients whom completed at least 2 OGTTs were included in the analysis, including 105 children and 94 adults. Sixty-nine patients (34.7%) maintained a similar glucose tolerance status during follow-up (stable group). The remaining patients had either deteriorated (33, 16.6%) or improved (97, 48.7%) their glucose tolerance status during follow-up. During follow-up, 17 participants required insulin treatment in the deteriorated group.

Children

At inclusion, for children, no significant difference of age, BMI Z-score weight, FEV1 and number of days of intravenous antibiotic per year was observed between the three glucose evolution groups (stable, deteriorated, improved),Table 2. Only G2 values of the improved group was higher compared

to the 2 others groups (p = 0.004). Insulin resistance (HOMA-IR) and insulin secretion (HOMA-S) compared at baseline between the 3 groups were not significantly different.

During follow-up, no significant difference was observed between the three groups for mean FEV1 change per year (deteriorated vs stable p = 0.13; deteriorated versus improved p = 0.51; improved vs stable p = 0.32) and mean BMI Z-score change per year (deteriorated vs stable p = 0.22; deteriorated versus improved p = 0.05; improved vs stable p = 0.55) (Figure 1).

Adults

At inclusion in adults, no significant difference of age, BMI, FEV1 and number of days of intravenous antibiotic per year was observed between the three glucose evolution groups (stable, deteriorated, improved) ,Table 2.G1 and G2 values, and I2 insulin were statistically different between the 3 groups at inclusion (p = 0.002, p < 0.0001 and p = 0.005 respectively). Insulin resistance (HOMA-IR) and insulin secretion (HOMA-S) compared between the 3 groups were not significantly different.

During follow-up, the mean FEV1 change per year (deteriorated vs stable p = 0.29; deteriorated versus improved p = 0.15; improved vs stable p = 0.58) and mean BMI change per year (deteriorated vs stable p = 0.53; deteriorated versus improved p = 0.77; improved vs stable p = 0.50) were not statistically different between the 3 groups (Figure 1).

DISCUSSION

This large CF cohort study was designed to evaluate glucose tolerance variability over time and evaluate the relationship between glucose tolerance evolution and clinical deterioration in children and adult CF patients over time. The study confirmed the high variability of glucose tolerance status over the 3-year follow up period, as previously described [9–11,14]. However, no significant decrease of FEV1 or BMI over time was observed in the deteriorate group compared to stable group either in children or adults, taking into account that 17 patients required insulin treatment in the deteriorated group. The absence of a faster FEV1 decline in the deteriorated group compared to others may be

explained by insulin treated patients. This may also be due to the relative shortness of the follow up period and the small sample sizes of the different groups. In children, this may also be due to the relative shortness of the follow-up period; in fact, FEV1 may remain generally stable over a few years, particularly in children.

Despite no significant difference, the improved group (children and adults) has higher BMI at inclusion compared to deteriorated and stable. The nutritional status remained stable over time, which may be explained by better nutritional care in patients with known glucose abnormalities. This better clinical status is not confirmed for FEV1, with surprisingly, although not significant, a higher FEV1 in deteriorated group at inclusion.

In our cohort, insulin resistance (HOMA-IR) and insulin secretion (HOMA-S) compared at baseline between the 3 groups were not significantly different. A recent paper by Boudreau et al. [12] observed insulin secretion and insulin sensitivity for 152 adult patients whom completed 2 OGTTs with a mean of 21.2 ± 5.5 months between the 2 tests. Patients were classified in 3 groups according to the variation of their glucose tolerance between baseline and follow up: stable, improved and deteriorated. They suggested that insulin secretion in their 3 groups of glucose tolerance remained stable whereas insulin sensitivity mirrored changes in glucose tolerance. Our paper support different results as we also included children, and analyzed data over a longer period with a minimum of 2 OGTT over the follow up period. Another point is also that we kept in the cohort non-treated CFRD patients but also patients with CFRD treated with insulin.

In a context of very variable glucose tolerance within patient's overtime, we would recommend giving more importance to recurring glucose abnormalities rather than isolated glucose abnormalities. Recurring glucose abnormalities need enhanced surveillance before discussion of treatment burden and insulin initiation. Continuous glucose monitoring will perhaps allow better assessment of glucose abnormalities over time and contribute to the decision of starting insulin.

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Author contribution statement

Contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work : QR, VB, SPB, ST, MR

Drafting the work : QR, VB, ST, ID

Final approval of the version to be published : QR, VB, SPB, MR, RNJ, ST, ID

Conflict of interest

The authors declare that they have no conflict of interest.

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Author disclosures

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	Children			Adults		
Characteristic	**NGT**	**AGT**	**CFRD**	**NGT**	**AGT**	**CFRD**
Nb. of participants	75	30	6	78	28	11
Males n, [%]	43 [57.3 %]	13 [43.3 %]	3 [50.0 %]	47 [60.3 %]	15 [53.6 %]	5 [45.4 %]
Genotype						
DelF508-homozygous	45 [60 %]	16 [53.3 %]	4 [66.7 %]	39 [50.0 %]	19 [67.8 %]	5 [45.4 %]
Age in years median[IQR]	12.79 [9.89;17.89]	13.70 [9.71;17.93]	15.53 [10.23;17.66]	24.71 [18.09;48.81]	23.55 [18.11;47.87]	28.11 [18.52;28.12]
BMI in Kg/m² median[IQR]*	-0.66 [-3.49;2.16]*	-0.89 [-2.34;1.20]*	-0.91 [-3.36;1.18]*	-0.43 [-3.15;1.77]	-0.83 [-1.83;1.08]	-0.50 [-3.16;0.60]
FEV1 in % median[IQR]	90 [30;126]	80 [37;138]	92 [64;103]	60 [22;110]	66 [27;107]	52 [18;40]

Table 1 – Patient's characteristics at inclusion for each OGTT results subgroup.

* BMI Z-score median [IQR]

At baseline, patients were classified into different subgroups of glucose tolerance according to international guidelines: Normal Glucose Tolerance (NGT) (G0 ≤ 7.0 mmol/L and G2 ≤ 7.7 mmol/L), Abnormal glucose tolerance (AGT) defined as having either indeterminate glucose tolerance (INDET) (G0 ≤ 7.0 mmol/L and G2 ≤ 7.7 mmol/L, but G1 ≥ 11.1 mmol/L) or impaired glucose tolerance (IGT) (G0 ≤ 7.0 mmol/L and G2 > 7.7 mmol/L but < 11.1 mmol/L) and finally de novo CFRD (G0 > 7.0 mmol/L or G2 ≥ 11.1 mmol/L)

Population	Children n=105				Adults n=94		
Glucose evolution groups	Stable n=34	Improved n=54	Deteriorated n=17	p	Stable n=35	Improved n=43	Deteriorated n=16
Median age	13.25 [9.91 ; 17.46]	13.62 [9.71 ; 17.93]	11.86 [10.40 ; 17.36]	0.66	23.83 [18.09 ; 48.81]	24.28 [18.11 ; 47.87]	23.42 [18.34 ; 36.30]
Median BMI*	-0.35 [-3.36 ; 2.16]	-0.88 [-2.34 ; 1.55]	-0.65 [-2.62 ; 1.48]	0.14	-0.38 [-3.15 ; 1.30]	-0.45 [-3.16 ; 1.26]	-0.32 [-2.92 ; 0.77]
Median FEV1	90.00 [48.00 ; 126.00]	83.00 [37.00 ; 138.00]	92.00 [62.00 ; 123.00]	0.13	64.00 [29.00 ; 110.00]	62.00 [30.00 ; 107.00]	70.50 [22.00 ; 108.00]
HOMA-S baseline	69.05 [29.47 ; 400.00]	85.71 [26.67 ; 600.00]	66.67 [22.22 ; 236.36]	0.54	42.00 [16.00 ; 150.44]	54.92 [12.50 ; 225.00]	40.00 [16.00 ; 116.67]
HOMA-IR baseline	1.09 [0.49 ; 5.01]	0.94 [0.16 ; 4.18]	0.92 [0.19 ; 2.66]	0.27	0.55 [0.17 ; 2.24]	0.67 [0.20 ; 1.52]	0.61 [0.20 ; 1.85]
Glycemia G0 [mmol/l]	4.90 [3.50 ; 5.70]	4.70 [3.50 ; 5.80]	4.80 [3.80 ; 5.30]	0.22	4.80 [3.90 ; 6.30]	4.80 [3.80 ; 6.30]	4.95 [4.10 ; 5.80]
Glycemia G1 [mmol/l]	8.70 [5.50 ; 11.50]	9.60 [6.90 ; 14.00]	9.80 [5.80 ; 16.90]	0.06	8.60 [5.00 ; 15.20]	10.50 [4.40 ; 15.80]	10.30 [4.40 ; 12.80]
Glycemia G2 [mmol/l]	6.15 [2.80 ; 12.30]	7.85 [3.70 ; 12.90]	6.50 [4.50 ; 10.70]	**0.004**	5.20 [2.40 ; 13.30]	8.20 [3.40 ; 15.80]	5.30 [3.90 ; 10.0]
Insulin I0 [µIU]	5.00 [2.21 ; 24.00]	4.00 [1.00 ; 20.00]	4.17 [1.00 ; 13.00]	0.33	2.80 [0.90 ; 9.70]	3.20 [1.00 ; 7.00]	2.80 [1.10 ; 8.00]
Insulin I1 [µIU]	35.00 [5.93 ; 180.80]	29.00 [2.00 ; 130.00]	28.00 [7.29 ; 143.00]	0.33	23.15 [6.30 ; 76.00]	17.00 [5.60 ; 107.00]	15.55 [8.90 ; 37.00]
Insulin I2 [µIU]	22.50 [8.39 ; 101.00]	32.50 [3.00 0 ; 196.00]	30.00 [4.00 ; 120.00]	0.26	12.30 [2.30 ; 62.00]	21.00 [3.00 ; 96.00]	15.55 [5.10 ; 38.85]
Number of intravenous antibiotic days/year	0 [0 ; 42]	0 [0 ; 37.00]	0 [0 ; 15.00]	0.5	0 [0 ; 38.00]	0 [0 ; 57.00]	13.0 [0 ; 37.00]
Mean FEV_1 change / year	0.90 [-13.21 ;13.04]	-0.28 [-13.58 ; 8.64]	-2.69 [-10.64 ; 9.67]	0.33	-1.24 [-7.52 ; 4.39]	-0.62 [-9.16 ; 8.94]	-1.27 [-9.29 ; 2.81]
Mean BMI* change / year	0.03 [-0.53 ; 0.67]	0.01 [-0.48 ; 0.37]	0.13 [-0.20 ; 0.45]	0.15	0.01 [-0.55 ; 0.57]	0.03 [-0.53 ; 0.35]	0.04 [-0.35 ; 0.28]

Table 2: Patient's characteristics according to glucose evolution groups at inclusion

Patients were classified in 3 groups according to the variation of their OGTT results (at least 2 OGTT tests) during follow-up: stable glucose tolerance group for patients who maintained a similar glucose tolerance status at fourth tests; improved glucose tolerance group for patients who reverted at least once over the four tests from CFRD to AGT or NGT, and from AGT to NGT; deteriorated glucose tolerance group for patients who worsened their glucose tolerance at least once over the 4 tests from NGT to AGT, or AGT to CFRD, or NGT to CFRD without any reversion.

BMI: Body Mass Index, Forced Expiratory Volum in 1 second: FEV1 [% predicted], median [min ; max],*BMI z-score in children,

Figure

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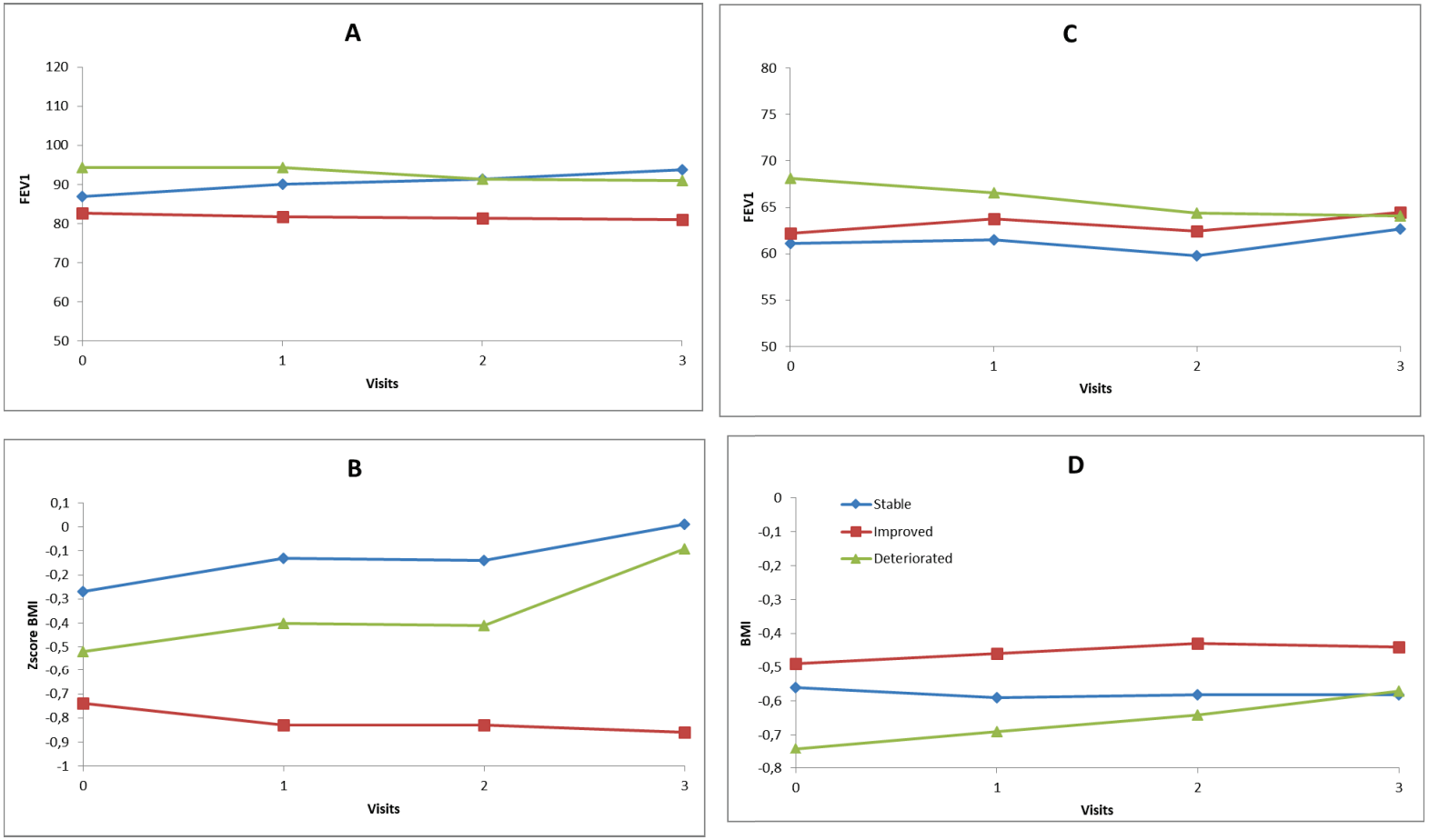

Figure 1: Rate of FEV_1 and BMI Z-score decline in children (A and B) and rate of FEV1 and BMI decline in adults (C and D) according to the three glucose evolution groups (stable, deteriorated, improved) over the follow-up period

Objectif

Les objectifs étaient les mêmes que pour l'étude DIAMUCO 1, c'est-à-dire confirmer la variabilité intra-individuelle des troubles glucidiques dans le temps et évaluer leur impact pronostique, mais en s'affranchissant des seuils diagnostiques de l'HGPO qui sont discutables. L'originalité de cette recherche tient à la méthode statistique utilisée. Une méthode d'analyse en cluster longitudinale, KmL (93), a été utilisée pour diviser les participants en plusieurs sous-groupes homogènes d'évolution de la glycémie à une (G1) et deux heures (G2) du test HGPO annuel au cours des trois années de suivi. Le procédé permet d'identifier des sous-groupes de participants qui suivent des profils similaires d'évolution de glycémie dans le temps, appelés « trajectoires de glycémie ». Pour un nombre donné de sous-groupes (2, 3 ou 4), la partition optimale a été obtenue en maximisant la variance entre sous-groupes. Le nombre de sous-groupes retenus a été déterminé selon le critère de Calinski & Harabasz (94). Une interface graphique a également été utilisée pour permettre un choix à posteriori des sous-groupes en fonction de leur signification clinique, et décrire chaque sous-groupe en fonction du niveau et de la forme de la trajectoire du glucose. Un modèle mixte linéaire a été utilisé pour quantifier la relation entre les changements du VEMS dans le temps et les trajectoires G1 ou G2. Cela a permis de modéliser les modifications du VEMS en tenant compte des mesures successives de glycémie. Le lien entre les trajectoires de glycémie et les modifications du VEMS a été quantifié à l'aide d'un terme d'interaction entre le temps et les sous-groupes. L'analyse a été ajustée sur le sexe et l'âge à l'inclusion. L'âge à l'inclusion était centré sur 13 ans chez les enfants et 25 ans chez les adultes. L'effet de l'âge sur le VEMS moyen à l'inclusion a été exprimé par incrément d'un an. Le modèle d'analyse KmL permet de s'affranchir des valeurs seuils habituelles qui définissent les groupes des différents troubles du métabolisme glucidique grâce à un modèle de trajectoire spécifique.

Résultats

Chez les enfants, pour la glycémie G1, 3 groupes étaient identifiés : « intermediate level and stable over time, low level and stable over time, high level and increasing over time » et 4 groupes pour la glycémie G2 « low level and stable over time, low level and increasing over time, intermediate level and decreasing over time, and high level and increasing over time ». Les différents sous-groupes pour G1 et G2 étaient comparables à l'inclusion. Pour les enfants, il n'était pas retrouvé de différence pour l'évolution de la fonction respiratoire entre les sous-groupes de trajectoire de glycémie pour G1 et G2.

Chez les patients adultes, pour la glycémie G1, 2 groupes étaient identifiés : « low level and stable over time, and intermediate level and stable over time » et 4 groupes pour la glycémie G2 « low level and stable over time, intermediate level and decreasing over time, low level and increasing then decreasing over time, high level and stable over time ». Les différents sous-groupes pour G1 et G2 étaient comparables à l'inclusion. Il n'était pas retrouvé de différence pour l'évolution de la fonction respiratoire entre les sous-groupes de trajectoire de glycémie pour G1 pour les adultes. L'étude a permis de mettre en évidence que pour le groupe de patients ayant une glycémie G2 élevée et augmentant au cours du suivi, le VEMS diminuait en moyenne plus rapidement que pour le groupe de patients ayant une glycémie G2 basse et stable, et ce de façon statistiquement significative.

Les résultats de l'étude sont produits dans l'article intitulé "**Glucose trajectories in cystic fibrosis and their association with pulmonary function"** publié en 2018 dans la revue Journal of Cystic Fibrosis.

Discussion

L'étude DIAMUCO 2 confirme la grande variabilité des valeurs de glycémie au cours du temps chez les enfants et les adultes en s'affranchissant des valeurs seuils de l'HGPO standard. L'impact clinique des différentes trajectoires de glycémie à G1 et G2 chez l'enfant et à G1 chez l'adulte n'est pas significativement différent. Chez

l'adulte, l'impact clinique d'une glycémie G2 élevée et persistante est plus importante que celle d'une glycémie G2 normale et stable. Le statut nutritionnel (IMC) reste stable au cours du suivi dans la population pédiatrique et adulte. A nouveau, l'interprétation des troubles glucidiques doit être faite avec prudence et doit plutôt considérer des anomalies persistantes en lieu et place d'anomalies sur une seule mesure. L'analyse par trajectoire de glycémie sur une population plus importante et pendant une durée plus longue permettra peut-être d'identifier mieux les trajectoires à risque de dégradation clinique et de proposer une stratégie de dépistage spécifique.

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Original Article

Glucose trajectories in cystic fibrosis and their association with pulmonary function

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Abstract

Background: The prevalence of cystic fibrosis-related diabetes is increasing. This condition is potentially responsible for respiratory decline.
Methods: At inclusion, then yearly (over three years), 111 children and 117 adults with cystic fibrosis had oral glucose tolerance and insulin tests at one (G1) and 2 h (G2). KmL analysis identified homogeneous G1 and G2 glucose trajectories. A linear mixed model quantified the relationships between trajectories and FEV1 changes.
Results: In children, there were three G1 and four G2 trajectories and FEV1 decrease was not significantly different between G1 or G2 trajectories. In adults, two G1 and four G2 trajectories were identified and FEV1 change was estimated at −0.85/year (95% CI: [−1.54; −0.17], p = 0.01) whatever the G1 trajectory and found significantly faster in the high and increasing G2 trajectory (−2.1/year, [−3.9; −0.2], p = 0.03).
Conclusions: In case of persistent G2 abnormality, physicians should be alert for clinical deterioration and intensify patient surveillance.

Keywords: Cystic fibrosis-related diabetes; Oral glucose tolerance test; Pulmonary function; Body mass index

1. Introduction

In cystic fibrosis (CF) patients, CF-related diabetes (CFRD) is a highly prevalent non-respiratory comorbidity. Its increasing prevalence may be linked to the increase in screening rates and

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the extension of life expectancy. By the start of the current decade, CFRD was affecting 9% of CF patients aged 5 to 9 years, 26% of those aged 10 to 20 years, and up to 50% of those aged ≥30 [1,2]. Similar prevalence rates were given by the last report of the French CF Registry (2014) [3].

In CF, an annual 75 g oral glucose tolerance test (OGTT) for screening CFRD is now standard care in patients aged ≥10 years. The diagnosis of CFRD is currently recommended by the American Diabetes Association despite some limitations [4]. The strict diagnostic criterion of CFRD is still one OGTT made when patients are clinically stable and confirmed three months later whereas recent studies in CF patients have shown that glucose homeostasis is highly variable over time [5,6]. A recent study suggested a role for decreased insulin sensitivity in the deterioration of glucose tolerance [7].

Screening for CFRD is important because it may be partly responsible for deterioration of pulmonary function [8]. This explains the recourse to OGTT and other markers and thresholds of glucose abnormality as early predictors of CFRD development and clinical deterioration; however, the relative importance of these predictors and their link with the decline of the forced expiratory volume in 1 s (FEV1) are still unclear. In recent cross-sectional studies [9,10], the elevation of 1-h fasting plasma glucose during 75 g-OGTT has been shown associated with poor pulmonary function and, more recently, new subgroups of patients with indeterminate glucose tolerance (INDET) had reduced pulmonary functions [11]. Though, none of these studies has taken into account the high changes of glucose homeostasis over time.

The aim of the present study was to identify patterns of glucose homeostasis change over time in children and adults with CF and explore a possible link between these patterns and pulmonary function.

2. Methods

2.1. Study design and population

This multicenter prospective cohort study considered first all CF patients aged ≥10 years who attended four CF centers (two adult and two pediatric centers) in the French Rhône-Alpes Region between 2009 and 2011. After excluding CF patients with pancreatic insufficiency (defined by the need for pancreatic enzyme supplementation), patients with current antidiabetic treatment (insulin or oral antidiabetic), patients with previous or planned pulmonary transplantation, and pregnant or breastfeeding women, the study kept 228 CF patients as participants: 111 children (aged 10 to 18 years at inclusion) and 117 adults (>18 years).

The main participant characteristics collected at inclusion were: sex, age, genotype, body mass index (BMI) in adults, BMI Z-scores in children, and FEV1. The participants were examined at inclusion then yearly over a three-year follow-up period as part of routine follow-up visits. At each examination, the physicians collected, among other data: weight, height, FEV1, and OGTT results. FEV1 values were expressed as percentage of the predicted normal value given by Knudson formula [12]. All measurements of the same variable were carried out the same way over the whole study period.

The institutional review board of each participating hospital authorized the study in accordance with the current ethical standards. Printed information about the study was given to each participant or legal surrogate and his/her signed informed consent obtained. The study ClinicalTrials.gov Identifier is NCT01072708.

2.2. Oral glucose tolerance testing

Each OGTT was carried out after an overnight fast before a routine clinical visit. The participant was given glucose (1.75 g per kg bodyweight, maximum 75 g); then plasma glucose and insulin were measured at start (G0), 1 h (G1), and 2 h (G2). Insulin was measured with BI-INS-IRMA kit (CisBio Bioassays, Codolet, France).

At the time of OGTT, all participants were clinically stable with no recent pulmonary exacerbation or symptoms of acute infection. Individuals treated with long-term low-dose oral corticosteroids were included in the study. Patients were kept in the cohort and the analysis whenever they had at least two OGTT measurements on two different visits, including those who required insulin treatment, met strict CFRD criteria but were left untreated, underwent pulmonary transplantation, or died during follow-up.

According to conventional criteria (American Diabetes Association and Cystic Fibrosis Foundation) [1] patients diagnosed with fasting hyperglycemia at any moment during the three-year follow-up received an antidiabetic treatment (insulin). Patients with abnormal OGTTs (impaired glucose tolerance, CFRD without fasting hyperglycemia) were monitored at home with three daily glycemic controls including before- and after-meal glucose level controls during a minimum of 7 days. Patients with after-meal glucose levels <10 mmol/L were left untreated. In case of clinical worsening, OGTT was repeated and patients found with abnormal OGTT were given insulin when justified.

2.3. Statistical analysis

The participants' characteristics at inclusion were described using the mean ± standard deviation or the median (range) for quantitative variables and the absolute + relative frequency in each category for qualitative variables.

A longitudinal cluster analysis method, KmL [13], was used to split the participants into several homogeneous subgroups of G1 and G2 glycemia changes over three years of follow-up. The method allows identifying subgroups of participants that follow similar patterns of glucose changes over time, herein called "glucose trajectories". For a given number of subgroups (2, 3, or 4), the optimal partition was obtained by maximizing the between-subgroup variance. The number of subgroups retained was determined according to Calinski & Harabasz criterion [14].

A graphical interface was also used to allow an a posteriori choice of the subgroups according to their clinical significance

and to describe each subgroup according to the level and shape of the glucose trajectory. Missing G1 or G2 data were imputed with the CopyMean method [13].

The characteristics of the participants at inclusion were described by subgroup. Age, FEV1, and BMI at inclusion were compared between subgroups using Kruskal-Wallis test.

A linear mixed model was used to quantify the relationship between changes of FEV1 over time and G1 or G2 trajectories. This allowed modelling FEV1 changes taking into account the within-participant correlation between FEV1 successive measurements (a random intercept and a random slope were introduced in the model). The link between glucose trajectories and changes in FEV1 was quantified using an interaction term between time and subgroups. The analysis was adjusted on sex and age at inclusion. The age at inclusion was centered on 13 years old in children and 25 years old in adults. The effect of age on the mean FEV1 at inclusion was expressed per 1-year increment.

All these analyses were carried out in children and adults separately because the slope of deterioration of the pulmonary function differs between children and adults and because the patterns of glucose changes were expected to be also different between children and adults.

As the results indicated that FEV1 changes over time were significantly different between G2 trajectories in adults, the relationship between insulin changes over the 3-year follow-up and G2 trajectories was analyzed using a linear mixed model. In this model, plasma insulin was measured at 1 h (G1 insulin) and 2 h (G2 insulin) during the OGTT.

The longitudinal cluster analyses used KmL package in R software, version 3.0.3 (http://www.r-project.org/). All other statistical analyses were performed with Stata 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP). All tests were two-tailed and $p < 0.05$ was considered for statistical significance.

3. Results

3.1. Participant characteristics

The study included 111 children (mean age 13.5 ± 2.3, 59 males and 52 females) and 117 adults (mean age 26.3 ± 6.6, 65 males and 52 females). Their main characteristics are shown in Table 1. At inclusion, 7.5% of the participants were receiving systemic corticosteroids at low and stable doses (only adults). During follow-up, 2 participants died, 11 underwent pulmonary transplantation, and 17 required insulin treatment (see Supplementary Table 1). The mean BMI in adults and the BMI Z-score in children was stable during the 3-year follow-up (see Supplementary Table 2).

3.2. Children G1 and G2 subgroups

For G1, the analysis carried out in children (c) yielded three subgroups that correspond to the following glucose trajectories (Fig. 1a): intermediate level and stable over time (subgroup cG1-IS; 50 participants: 27girls and 23 boys), low level and

Table 1
Characteristics at inclusion of the subgroups of patients in each subgroup of OGTT results.

Characteristic	Children							Adults					
	G1 subgroups			G2 subgroups				G1 subgroups			G2 subgroups		
	cG1-LS	cG1-IS	cG1-HI	cG2-LS	cG2-ID	cG2-LID	cG2-HS	aG1-LS	aG1-IS	aG2-LS	aG2-LI	aG2-ID	aG2-HI
Nb. of participants	44	50	17	54	34	15	8	68	46	54	33	20	10
Males (n, %)	27 (61)	23 (46)	9 (53)	35 (65)	14 (41)	7 (47)	3 (37)	35 (51)	30 (65)	33 (61)	15 (45)	12 (60)	5 (50)
Genotype													
DelF508-DelF508	26	30	9	33	18	10	4	36	25	27	21	10	5
DelF508-other	14	16	7	16	13	4	4	23	18	19	11	9	3
Other-other	4	4	1	5	3	1	0	6	2	5	1	1	1
Age*	13.3 ± 2.5	13.6 ± 2.2	13.9 ± 2.3	13.5 ± 2.4	13.3 ± 2.2	13.0 ± 2	15.2 ± 2.4	25.7 ± 6.7	28 ± 6.3	25.8 ± 6.9	26.3 ± 5.6	26.6 ± 7.5	30.1 ± 6.3
BMI or BMI Z-score*	−0.32 ± 1.17	−0.64 ± 0.88	−1.07 ± 1.47	−0.32 ± 1.11	−0.74 ± 0.98	−1.17 ± 1.01	−0.55 ± 1.57	20.4 ± 2	20.1 ± 2.5	20.4 ± 2.1	20.4 ± 2.0	19.4 ± 1.8	20.8 ± 3.4
FEV1 (%)*	84 ± 17	87 ± 19	84 ± 24	85 ± 18	85 ± 17	85 ± 28	90 ± 17	62 ± 23	56 ± 21	61 ± 23	64 ± 23	52 ± 17	57 ± 23
Glycemia at start G0*	4.6 ± 0.4	4.8 ± 0.5	4.8 ± 0.5	4.8 ± 0.4	4.5 ± 0.5	4.8 ± 0.4	5.1 ± 0.5	4.6 ± 0.5	5.1 ± 0.6	4.7 ± 0.4	4.9 ± 0.5	4.8 ± 0.6	5.6 ± 0.8
Glycemia G1*	8.3 ± 1.5	9.9 ± 1.4	11.5 ± 2.8	9.2 ± 1.8	9.45 ± 1.9	9.5 ± 1.8	12 ± 2.7	8.6 ± 1.9	11.8 ± 1.6	8.7 ± 2.1	10.0 ± 2.0	11.1 ± 2.0	12.7 ± 1.4
Glycemia G2*	6.8 ± 1.5	7.1 ± 2.0	8.4 ± 3.2	6 ± 1.3	8.6 ± 1.5	6.1 ± 1.4	11.2 ± 1.8	6.2 ± 2.2	8.1 ± 3.2	5.6 ± 1.7	6.4 ± 1.5	9.8 ± 2.2	11.4 ± 3.2
Insulin G0*	5.5 ± 3.9	5.2 ± 3.2	5.4 ± 2.6	5.1 ± 3.6	5.2 ± 2.4	6.1 ± 4.4	5.9 ± 3.4	3.5 ± 1.9	2.9 ± 1.5	3.2 ± 1.9	3.4 ± 1.7	3.2 ± 1.6	3.7 ± 1.8
Insulin G1*	33.8 ± 26.4	42.3 ± 35.3	45.9 ± 32	45.9 ± 36.4	33.8 ± 22.5	29.9 ± 19.4	40.1 ± 43.6	25.3 ± 17.9	20.2 ± 10.4	27.3 ± 19.1	22.5 ± 11.2	16.8 ± 9.8	18.6 ± 13
Insulin G2*	28.1 ± 18.7	38 ± 25.1	50.3 ± 49.4	29.4 ± 21.8	46 ± 35.2	24 ± 17	57.9 ± 37.9	20.9 ± 16.5	23.6 ± 18.7	19 ± 16.4	23.8 ± 17.2	24.9 ± 13.4	33.2 ± 27.9

* Mean ± standard deviation - G0: glucose value before OGTT – G1 and G2: glucose values at 1 and 2 h – a: adult – c: children – trajectory descriptions: IS = intermediate stable - LS = low stable - HI = high increasing - ID = intermediate decreasing - LID = low increasing then decreasing - HS = high stable - LI = low increasing.

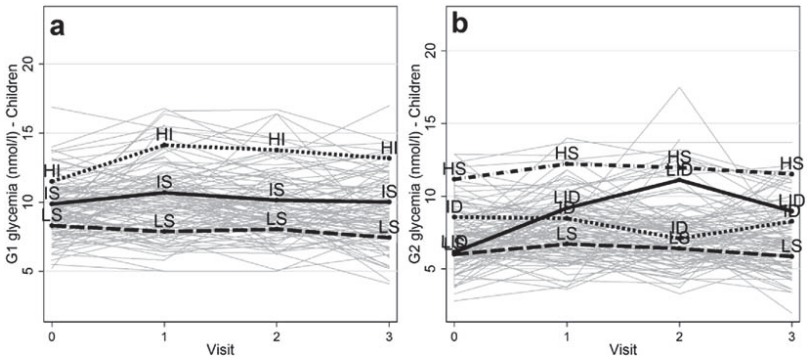

Fig. 1. Glycemic subgroups in children. Panel a - G1 glucose trajectories in children: IS = intermediate stable level (n = 50), LS = low stable level (n = 44), HI = high increasing level (n = 17). Panel b - G2 glucose trajectories in children: LS = low stable level (n = 54), ID = intermediate decreasing level (n = 34), LID = low increasing then decreasing level (n = 15), HS = high stable level (n = 8).

stable over time (subgroup cG1-LS; 44 participants: 17 girls and 27 boys), and high level and increasing over time (subgroup cG1-HI; 17 participants: 8 girls and 9 boys).

For G2, the analysis yielded four subgroups that correspond to the following glucose trajectories (Fig. 1b): low level and stable over time (subgroup cG2-LS; 54 participants: 19 girls and 35 boys), intermediate level and decreasing over time (subgroup cG2-ID; 34 participants: 20 girls and 14 boys), low level and increasing then decreasing over time (subgroup cG2-LID; 15 participants: 8 girls and 7 boys), and high level and stable over time (subgroup cG2-HS; 8 participants: 5 girls and 3 boys).

Details on the children within each glucose trajectory at inclusion are given in Table 1. At inclusion, there were no statistically significant differences regarding age, FEV1, or BMI Z-score between G1 subgroups (p = 0.50, 0.83, and 0.15, respectively) or between G2 subgroups (p = 0.17, 0.85, and 0.10, respectively).

3.3. FEV1 changes in children according to the glucose trajectories

After adjustment on sex and age at inclusion, the change in FEV1 over time was estimated at −1.1% per year (95% CI: [−2.64; 0.45]; p = 0.17) in subgroup cG1-LS (Table 2). The changes in FEV1 over time were not significantly different vs. subgroup cG1-IS or cG1-HI (p = 0.71 and p = 0.98, respectively).

Regarding G2, the changes in subgroups cG2-ID, cG2-LID, and cG2-HS were faster than in subgroup cG2-LS but the differences were not statistically significant (p = 0.28, 0.25, and 0.41, respectively) (Table 2).

3.4. Adult G1 and G2 subgroups

For G1, the analysis carried out in only 114 adults with two measurements yielded two subgroups that correspond to the following glucose trajectories (Fig. 2a): low level and stable over time (subgroup aG1-LS; 68 participants: 33 women and 35 men) and intermediate level and stable over time (subgroup aG1-IS; 46 participants: 16 women and 30 men).

For G2, the analysis carried out on all 117 adults yielded four subgroups that correspond to the following trajectories (Fig. 2b): low level and stable over time (subgroup aG2-LS; 54

Table 2
Relationship between the changes of FEV1 over time and glucose trajectories: results of the linear mixed models.

Covariates	RG coeff [95% CI]	p value
Children - G1		
FEV1 at baseline in girls aged 13	87.95 [83.10; 92.80]	
Time since inclusion in glycemia cG1-LS[a]	−1.10 [−2.64; 0.45]	0.17
Time since inclusion * glycemia cG1-IS	−0.41 [−2.54; 1.73]	0.71
Time since inclusion * glycemia cG1-HI	0.03 [−2.89; 2.95]	0.98
Age at baseline[a]	−0.37 [−1.8; 1.05]	0.61
Boys (vs. girls)	−4.91 [−11.49; 1.67]	0.14
Children - G2		
FEV1 at baseline in girls aged 13	88.05 [83.20; 92.90]	
Time since inclusion in cG2-LS[a]	−0.54 [−1.94; 0.85]	0.45
Time since inclusion * glycemia cG2-ID	−1.25 [−3.50; 1.00]	0.28
Time since inclusion * glycemia cG2-LID	−1.76 [−4.77; 1.25]	0.25
Time since inclusion * glycemia cG2-HS	−1.59 [−5.39; 2.22]	0.41
Age at baseline[a]	−0.39 [−1.81; 1.04]	0.59
Boys (vs. girls)	−5.07 [−11.64; 1.51]	0.13
Adults - G1		
FEV1 at baseline in women at age 25	62.41 [56.42; 68.40]	
Time since inclusion in aG1-LS[a]	−0.85 [−1.54; −0.17]	0.01
Time since inclusion * glycemia aG1-IS	−0.32 [−1.42; 0.79]	0.57
Age at baseline[a]	−1.09 [−1.67; −0.52]	<0.01
Men (vs. women)	−1.38 [−9.04; 6.28]	0.72
Adults - G2		
FEV1 at baseline in women aged 25	63.15 [57.39; 68.91]	
Time since inclusion in aG2_LS[a]	−0.73 [−1.44; −0.02]	0.04
Time since inclusion * glycemia aG2-LI	−1.05 [−2.24; 0.14]	0.08
Time since inclusion * glycemia aG2-ID	1.07 [−0.36; 2.50]	0.14
Time since inclusion * glycemia aG2-HI	−2.06 [−3.93; −0.18]	0.03
Age at baseline[a]	−1.10 [−1.66; −0.53]	<0.01
Men (vs. women)	−2.16 [−9.70; 5.37]	0.57

[a] Per one year increment * interaction - RG coeff: regression coefficient [95% confidence interval] - trajectory descriptions: HI = high increasing - HS = high stable - ID = intermediate decreasing - IS = intermediate stable - LI = low increasing - LID = low increasing then decreasing - LS = low stable.

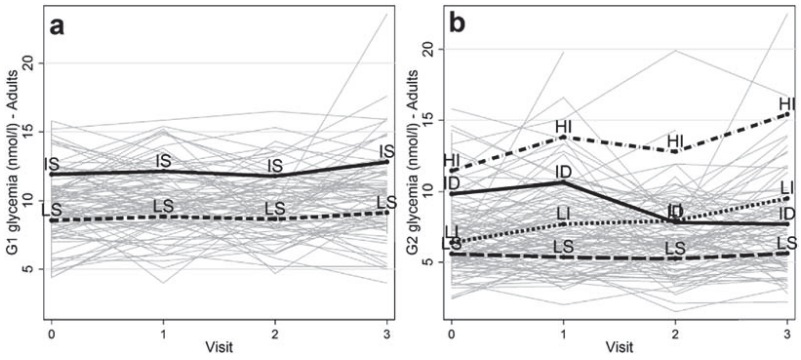

Fig. 2. Glycemic subgroups in adults. Panel a - G1 glucose trajectories in adults: LS = low stable level (n = 68), IS = intermediate stable level (n = 46). Panel b - G2 glucose trajectories in adults: LS = low stable level (n = 54), LI = low increasing level (n = 33), ID = intermediate decreasing level (n = 20), HI = high increasing level (n = 10).

participants: 21 women and 33 men), low level and increasing over time (subgroup aG2-LI; 33 participants: 18 women and 15 men), intermediate level and decreasing over time (subgroup aG2-ID; 20 participants: 8 women and 12 men), and high level and increasing over time (subgroup aG2-HI; 10 participants: 5 women and 5 men).

Details on the adults within each glucose trajectory at inclusion are given in Table 1. Among all age-, FEV1-, and BMI-related comparisons between subgroups at inclusion, only age showed a statistically significant difference between the two G1 subgroups (p = 0.03).

3.5. FEV1 changes in adults according to the glucose trajectories

After adjustment on sex and age at inclusion, the change in FEV1 over time was estimated at −0.85% per year (95% CI: [−1.54; −0.17]; p = 0.01) in subgroup aG1-LS (Table 2). The changes in FEV1 over time were not significantly different vs. subgroup aG1-IS (−0.37; 95% CI: [−1.42; 0.79]; p = 0.57).

In subgroup aG2-LS, the change in FEV1 over time was estimated at −0.73% per year (95% CI: [−1.44; −0.02]; p = 0.04) (Table 2 and Supplementary Fig. 1). In subgroup aG2-HI, the decrease was significantly faster: −2.06% per year (95% CI: [−3.93; −0.18]; p = 0.03) (Table 2 and Supplementary Fig. 1). In subgroup aG2-LI, the decrease was also faster but not statistically significantly different (−1.05% per year; 95% CI: [−2.24; 0.14]; p = 0.08). Interestingly, in subgroup aG2-ID, the decrease of FEV1 was slower (+1.10% per year; 95% CI: [−0.36; +2.50]; p = 0.14) but the difference with subgroup aG2-LS was not statistically significant (Table 2 and Supplementary Fig. 1).

3.6. Insulin changes over time according to G2 trajectories

In aG2-LS subgroup, G1 insulin increased by 2.51 mIU/L per year on average over the 3-year follow-up (p < 0.01) (Supplementary Table 3). In aG2-LI, aG2-ID, and aG2-HI subgroups, G1 insulin was stable over time: the differences in the regression line slopes vs. aG2-LS subgroup were estimated at −2.26 (p = 0.09), −2.92 (p = 0.07), and −2.59 mIU/L (p = 0.30), respectively.

In aG2-LS subgroup, G2 insulin was also stable over time: the slope was estimated at −0.61 per year, which is not significantly different from 0 (p = 0.45). In aG2-LI and aG2-HI subgroups, G2 insulin increased over time: the differences in slope vs. aG2-LS were estimated at 2.82 (p = 0.02) and 4.10 (p = 0.07), respectively. In aG2-ID subgroup, G2 insulin was also stable over time (slope difference vs. aG2-LS estimated at −0.06, p = 0.97).

4. Conclusions

This large CF cohort study was designed to evaluate glucose and insulin changes over time and quantify the relationships between glucose trajectories and changes in FEV1 using an original statistical analysis. The study confirmed incidentally the high variability of glucose tolerance status over the 3-year follow-up period. However, most importantly, it found: i) no link between glucose trajectories and FEV1 in children; ii) no link between one-hour glucose trajectories and FEV1 in adults, but iii) a significant decrease of FEV1 over time in adults of the high and increasing two-hour glucose trajectory vs. adults with low and stable 2-hour glucose trajectory.

The classical 2-hour OGTT thresholds used to diagnose abnormal glucose tolerance in CF are called into question because they are based on the risk of retinopathy in type 2 diabetes. One recent Canadian survey highlighted a new glucose tolerance status called indeterminate glucose tolerance, INDET, with normal G2 values <7.8 mmol/L but elevated G1 values >11.0 mmol/L. This status seems to be associated with reduced pulmonary function and may benefit from early treatment [11]. Concurrently, high plasma glucose levels at non-classical OGTT times (other than 2 h) are common in CF. Brodsky and Coriati [9,15] suggested that early G1 abnormalities may be associated

with worsening of the pulmonary function and would be more relevant than G2 abnormalities in identifying at-risk CF patients; but longitudinal studies are still needed to confirm these results. In the present study, no G1 subgroup had faster impairment of FEV1 than another.

Despite the high prevalence of CFRD, especially in adult CF patients, few studies have examined the natural changes in glucose tolerance over time and their impact. The present study confirmed the high variability of glucose tolerance over time already mentioned by Sterescu et al. [5] and later demonstrated by Scheuing et al. [6] on 4643 standardized OGTTs in 1128 CF patients (the average within-patient coefficient of variation was 11.1% for fasting blood glucose and 25.3% for two-hour blood glucose). This high variability and the fact that some patients who belong to the "low and stable" trajectory group needed insulin at some time point challenge the current idea that CFRD occurs at the term of a process that progresses from normal glucose tolerance to impaired glucose tolerance to CFRD. The latter point requires further observations and discussions.

No significant differences in the decline of pulmonary function were found between children G1 or G2 glucose trajectory subgroups. This may be due to the relative shortness of the follow-up period and the small sample sizes; in fact, FEV1 may remain generally stable over a few years, particularly in children.

In adults, the high and increasing two-hour glucose trajectory subgroup showed faster decrease in FEV1 than other G2 subgroups (the rate of decrease in this subgroup was statistically significantly different from the rate seen in other G2 subgroups). This result should be considered with caution because the faster decrease in this subgroup may be explained by the presence of insulin-treated patients.

The nutritional status remained stable over time, which may be explained by better nutritional care in patients with known glucose abnormalities. In fact, better medical support in children and adults may have participated to the near absence of FEV1 or BMI decline given that, in our experience, CF patients showed better health conditions circa 2010 than circa 2000.

Considering insulin and G2 trajectories in adults, one hypothesis is that G1 insulin level may be a good indicator of insulin secretion and insulin reserve whereas G2 insulin increase in high and increasing G2 subgroup may be explained by a delay in insulin secretion due to insulinopenia.

One strength of the present study is the use of KmL to model the changes in OGTT results over time and generate glucose trajectories. This method allowed identifying typical G1 and G2 trajectories without using the OGTT traditional (and arbitrary) thresholds for subject classification. Given the variability of glucose levels in CF patients, it seems important to assess the effect on FEV1 of a given pattern of change in glucose level over a follow-up period instead of the effect of an occasional measurement. Thus, continuous glucose monitoring could be a very useful tool for CF patient surveillance [16].

The present study admits some limitations. The first is the small sample sizes of high glucose trajectory subgroups in children and adults. Another is the relatively short duration of follow-up that may explain the absence of significant FEV1 decline, especially in children. However, three years is one of the longest homogeneous follow-ups in the field of CF. Furthermore, the absence of detailed nutritional data and the non-use of a criterion for insulin sensitivity (such as the Insulin Sensitivity Index of Matsuda) [17] may have limited the field of interpretation of the present results.

In summary, glucose tolerance is highly variable over time in both adolescent and adult CF patients. Patterns of glucose changes over time (or typical glucose trajectories) were explored and characterized. In this study, the only trajectory associated with a significant FEV1 decline was a high level and increasing over time two-hour glucose value. This supports our opinion and what is already clinically done, that persistent rather than isolated G2 abnormalities are associated with patient's condition deterioration. This situation needs increased surveillance and discussion of insulin initiation.

More generally, we would recommend giving more importance to regular OGTTs over long periods (say, two or three years) with recurring glucose abnormalities, than to occasional tests with isolated glucose abnormalities. If the trajectories we observed are further confirmed over even longer periods and if specific trajectories are shown to correlate with future development of CFRD, these findings will surely lead to preventive measure and changes in the current treatment protocols of patients with specific profiles. The hypothesis of a link between environmental and genetic factors and prediction of CFRD onset will have to be investigated.

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Conflict of interest

None of the authors have any relevant conflicts of interest to disclose.

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D. Etude DIAMUCO : points clés

La variabilité intra-individuelle au cours du temps des troubles du métabolisme glucidique est confirmée par l'étude DIAMUCO. Différents profils d'évolution des anomalies glucidiques au cours du temps ont été identifiés (détérioration, stabilité, amélioration ou trajectoires de glycémies).

Chez l'enfant, l'étude DIAMUCO ne met pas en évidence de différence d'évolution clinique (fonction respiratoire et IMC) entre les différents profils d'évolution des anomalies glucidiques que ce soit pour la glycémie à une heure ou à 2 heures. Chez l'adulte, il n'est pas mis en évidence de différence d'évolution clinique en fonction de la glycémie à 1 heure. Seules les anomalies persistantes de la glycémie à 2 heures sont corrélées à une dégradation clinique chez l'adulte.

Ces résultats suggèrent que l'impact clinique des troubles glucidiques doit être interprété avec prudence en considérant plutôt des anomalies persistantes dans le temps en lieu et place d'anomalies sur une seule mesure.

Compte tenu des effectifs réduits des différents sous-groupes de l'étude DIAMUCO, ces résultats doivent être validés sur un effectif plus important. Les questions auxquelles il faut encore répondre sont les suivantes : l'impact clinique des différentes anomalies du métabolisme glucidique est-il différent dans d'autres cohortes ? peut-on utiliser l'hyperglycémie et l'hypoinsulinémie à 1h comme facteur prédictif de dégradation clinique ?

2. Impact pronostique des troubles du métabolisme glucidique sur la fonction respiratoire et l'état nutritionnel : comparaison Canada – France et intérêt des marqueurs précoces de l'HGPO à 1 heure

A. Etude GLYCONE : contexte

Ce projet de collaboration internationale a pour but de confirmer les résultats des études DIAMUCO. La cohorte DIAMUCO décrite précédemment a permis d'identifier l'histoire naturelle des troubles du métabolisme glucidique et déterminer leur impact clinique. Le suivi annuel des patients (HGPO et collecte des données cliniques) et les valeurs de glycémie et d'insulinémie à jeun, à une heure et deux heures après la prise de glucose a permis d'inclure cette population dans l'étude GLYCONE.

Le Pr Rabasa-Lhoret, professeur en endocrinologie et nutrition à Montréal, Québec, mène des travaux de recherche sur le diabète de type 1 et 2, l'obésité et le diabète secondaire à la mucoviscidose. Il travaille en collaboration sur le sujet avec l'équipe du Pr Berthiaume, qui dirige le centre mucoviscidose adulte de Montréal. Ils sont auteurs de nombreuses publications sur le DAM. L'équipe de recherche du Pr Rabasa-Lhoret a mis en place en 2003 une cohorte prospective observationnelle d'adultes atteints de mucoviscidose : Montreal Cystic Fibrosis Cohort (MCFC), dont le principal objectif est d'étudier les mécanismes et les conséquences de la survenue du DAM. Depuis 2015, cette cohorte compte plus de 260 patients suivis sur une période allant jusqu'à 11 ans. Les suivis (HGPO et collecte des données cliniques) ont lieu à un intervalle de temps de 18 mois (±9 mois). Comme pour la population DIAMUCO, le test HGPO standardisé est effectué lorsque les patients sont stables cliniquement (> 4 semaines d'une décompensation aigue, > 2 semaines de la fin d'une prise d'antibiotique). La glycémie et l'insulinémie sont mesurées à jeun, une heure et deux heures après la prise de glucose.

L'étude GLYCONE consiste en l'association de ces deux cohortes DIAMUCO (cohorte française) et MCFC (cohorte canadienne) pour constituer une cohorte adulte uniquement.

B. Etude Glycone 1

Contexte

A l'aide de Registres nationaux de la mucoviscidose incluant les patients atteints de mucoviscidose de chaque pays, certains auteurs ont pu comparer les données démographiques européennes et nord-américaines des patients atteints de mucoviscidose (95,96), suggérant des différences de poids entre ces populations. Ces différences pourraient impacter les mécanismes du DAM (insulinopénie et insulinorésistance) et ainsi modifier la prévalence et l'impact clinique du DAM, mais très peu de données existent sur ce point (97). Le rôle de l'insulinopénie et de l'insulino-résistance n'a pas été non plus évalué en comparant ces cohortes.

Objectif

L'objectif est de décrire les caractéristiques cliniques des deux populations et l'incidence du DAM pour identifier d'éventuelles différences entre les deux cohortes canadienne et française. Cette étude décrit également les profils d'évolution clinique des deux populations canadienne et française en relation avec leur statut glycémique et insulinique dans un contexte d'accès aux soins et de recommandations de prise en charge similaires pour les deux pays.

Résultats

L'étude rapporte un meilleur statut clinique global pour les patients canadiens avec une meilleure fonction respiratoire et un IMC plus élevé, avec des populations comparables en termes d'âge, sexe, génotype et colonisation bronchique. Cependant l'incidence du DAM était plus élevée dans le groupe canadien avec des valeurs de glycémie et d'insulinémie plus élevées au cours de l'HGPO que dans le groupe de patients français. Aucune corrélation entre insulinémie et IMC n'était

retrouvée. Le groupe normo-tolérant canadien avait une fonction respiratoire plus élevée que le groupe normo-tolérant français, différence qui n'était pas retrouvée pour les groupes intolérants et diabétiques. Il n'était pas observé de différence entre l'évolution de la fonction respiratoire des groupes normo-tolérants et intolérants. Le déclin de la fonction respiratoire du groupe canadien était moins important au cours du temps par rapport au groupe français et cela malgré des valeurs de glycémies plus élevées.

Les résultats de l'étude sont produits dans l'article intitulé "**Glucose abnormalities in Canadian and French cystic fibrosis adults patients"** publié dans la revue Scientific Report en 2019.

Discussion

Les canadiens présentent des glycémies élevées, une sécrétion d'insuline plus importante, une résistance à l'insuline plus élevée mais aussi plus de DAM. Le lien entre hyperinsulinémie, IMC et insulino-résistance n'est pas totalement élucidé. Le taux de DAM plus important dans la population canadienne alors que leur état clinique est meilleur que celui des français est inattendu, de même que la dégradation respiratoire moindre au cours du suivi chez les canadiens. L'alimentation, en qualité et en quantité, et la supplémentation enzymatique pancréatique peuvent contribuer à ces différences et n'ont pas été évaluées dans cette étude. Des facteurs explicatifs autres comme l'étude des gènes modificateurs pourraient aussi être explorés comme nous l'avons suggéré au Pr Harriet Corvol.

SCIENTIFIC REPORTS

OPEN

Glucose tolerance in Canadian and French cystic fibrosis adult patients

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Cystic fibrosis (CF)-related diabetes is associated with increased mortality. We analysed the clinical and glycemic profiles of two cohorts of patients treated according to the same guidelines in France and Canada. To investigate incidence differences in phenotypic and glucose abnormalities and to explore the evolution over a 4-year follow-up period, two cohorts of 224 Canadian and 147 French adult CF patients (≥18 years) without treated CF-related diabetes (CFRD) were followed over a 4 year period. In each of these groups, we investigated the longitudinal relationship between glucose tolerance and pulmonary function. An annual 2-hour oral glucose tolerance test was performed: fasting blood glucose (G0) and 2-h blood glucose (G2) were measured. Patients were classified at inclusion according to their glucose tolerance status: Normal glucose tolerant, abnormal glucose tolerant or de novo CFRD. Age, sex ratio and proportion of F508del homozygous patients were not statistically different between both cohorts. Canadian patients had better pulmonary function (median %FEV1 (IQR): 71.0 (55.0–82.0) vs. 64.0 (40.0–78.0), $p < 0.001$) and greater body mass index (BMI; median BMI in kg/m^2) (IQR) 21.1 (19.5–22.8) vs. 19.9 (18.4–21.4), $p < 0.001$). Glucose values: G0 (5.4 (5.0–5.9) vs. 4.8 (4.5–5.1) mmol/L, $p < 0.001$) and G2 (7.6 (5.8–9.7) vs. 6.5 (5.2–8.5) mmol/L, $p = 0.001$) were higher in the Canadian cohort translating into a higher incidence of *de novo CFRD* diagnosis (19.2 vs. 9.8%, $p = 0.003$). Decline in FEV1 over time was not different between patients according to glucose tolerance groups. Despite higher glucose levels and incidence of *de novo* CFRD, Canadian CF patients have a better lung function and a higher BMI than French patients. In spite of these differences between the cohorts, the decline in FEV1 in patients with abnormal glucose tolerance is similar between these groups.

In the last decade, life expectancy of patients with cystic fibrosis (CF) has significantly improved. While the median life expectancy was 10 years of age in the 1960's, it is now estimated to greater than 50 years both in Canada and France[1,2]. However, along with this better life expectancy, new complications have emerged. Abnormalities in glycemic status and CF-related diabetes (CFRD) have become the main complications after respiratory disease and exocrine pancreatic insufficiency[3].

The prevalence of CFRD increases with age, affecting around 50% of adult CF patients. In adult patients without CFRD, the prevalence of abnormal glucose tolerance is 35%[4]. A progressive loss of beta cell mass with a direct effect from CFTR-mutation and a possible contributory role of insulin resistance lead to abnormal glucose levels and development of CFRD[5–8]. Because of the insidious onset of CFRD and the fact that standard simple screening tests are less reliable for CF patients (e.g. fasting glucose, glycosylated hemoglobin, etc.)[9], annual screening for CFRD is recommended starting at ten years of age, using the 2-h Oral Glucose Tolerance Test (OGTT)[10]. CFRD is still associated with increased mortality despite the progressive improvement in screening and management[11].

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Studies have compared demographic data of European and North American CF children patients using CF registries[12,13], suggesting differences in demographic data (height and weight) between populations. No data are available regarding difference in CFRD prevalence between Europe and North America except data from annual registry reports[14]. Furthermore, registry data concerning specific comorbidities like CFRD are not homogeneously collected, and most of the time registries do not collect data about other glucose metabolic abnormalitites. It is thus possible that both prevalence of CFRD and its impact on clinical CF condition differ between these two populations. The consequences of different glucose tolerance profiles on respiratory function have not been evaluated in large cohorts and over long periods. Similarly, the potential role of insulin deficiency and insulin resistance have not been described and compared in large cohorts[15–17].

The objective of this study was to compare the following parameters between the Canadian and French cohorts: (1) clinical characteristics, (2) glucose and insulin values as well as CFRD incidence and (3) evolution of pulmonary function over a 4-year follow-up period.

Methods

Study population. Data were obtained from the Montreal Cystic fibrosis Cohort (MCFC) for Canada and from the Lyon Cystic Fibrosis Cohort (DIAMUCO) for France. Both research cohorts are investigating mechanisms of glucose intolerance as well as associations between glucose intolerance and clinical outcomes in adult patients with CF. The Montreal Cystic Fibrosis Cohort was established in 2004 and all available data at inclusion from patients included between 2004 to 2016 were considered for this analysis. The DIAMUCO Cohort was established in 2009 and all available data at inlusion from patients included between 2009 to 2012 were considered for this analysis. All available follow-up pulmonary function data were included in both cohorts over a 4-year period.

Informed consents have been obtained for all subjects included. The institutional review board of each participating hospital and research ethics board authorized the cohorts in accordance with the current ethical standards (Comité de Protection des Personnes in France, Comité d'éthique de la recherche in Canada), as well as the French data Protection Agency for DIAMUCO Cohort (Comission Nationale de l'Informatique et des Libertés CNIL).

For both cohorts, all adult patients (>18 years) with CF, pancreatic insufficiency and no previous history of treated CFRD were included. Patients who received a *de novo* CFRD diagnosis during recruitment were however included. Main exclusion criteria were pancreatic sufficiency and previous pulmonary transplantation. In patients with ongoing pregnancy, pulmonary exacerbation or current treatment with medication known to interfere with glucose metabolism (e.g. high dose oral steroids and enteral tube feeding), OGTT was delayed upon resolution of this temporary exclusion factor. OGTT results were accepted in patients taking stable, long-term (≥1 year) low-dose oral corticosteroids (maximal dose of 10 mg prednisone per day). At the time of the OGTT, all patients were clinically stable with no recent (<1 month) pulmonary exacerbation or symptoms of acute infection. Included patients represent around 80% of all patients with CF followed at our respective clinics.

Clinical and biological data. In both cohorts, a harmonized data collection process was used to extract required information from medical charts at inclusion. This included age, sex, CF related genotype, chronic bacteriological colonization and number of intravenous antibiotics courses in the previous year. Chronic bacteriological colonization was defined as follow: 50% or more of samples being positive for a specific bacteria in the preceding 12 months[18]. Other data such as BMI, FEV1, glycosylated hemoglobin (HbA1c) were also collected at inclusion and then between 12 and 18 months during a 4-year follow-up for FEV1. BMI was calculated using weight in kilograms divided by height in square meter (kg/m^2). Pulmonary function was measured by spirometry using the forced expiratory volume in 1 second in L (FEV1) using Hankinson 1999 formula for FEV1(%)[19]. HbA1c was measured using HPLC automate variant II (Biorad) in France, and immunotubidimeter (Bayer Health Care diagnosis) in Canada. Both HbA1c are aligned with international standards.

Oral glucose tolerance test (OGTT). OGTT was realized at the inclusion in both cohorts and was carried out after an overnight fast. Patients were given glucose (1.75 g per kg bodyweight, maximum 75 g) then plasma glucose was measured at start (G0), 1 hour (G1) and 2 hour (G2)[20]. Patients diagnosed with *de novo* CFRD underwent within 2 months a second OGTT to confirm the diagnosis. Plasma insulin was also measured at start (I0), 1 hour (I1) and 2 hour (I2) by immunoradiometric assay (BI-INS-IRMA, Cisbio Bioassays, France) and measures were centralized in Quebec, to obtain comparable values.

Depending on the results of the OGTT at inclusion, patients were classified into different subgroups of glucose tolerance according to international guidelines[10]: Normal Glucose Tolerance (NGT) (G0 ≤ 7.0 mmol/L and G2 ≤ 7.7 mmol/L), Abnormal Glucose Tolerance (AGT) defined as having either indeterminate glucose tolerance (INDET) (G0 ≤ 7.0 mmol/L and G2 ≤ 7.7 mmol/L, but G1 ≥ 11.1 mmol/L) or impaired glucose tolerance (IGT) (G0 ≤ 7.0 mmol/L and G2 > 7.7 mmol/L but <11.1 mmol/L) or de novo CFRD (G0 > 7.0 mmol/L or G2 ≥ 11.1 mmol/L).

Statistical methods. Values are expressed as median (interquartile range [IQR]) or percentage, as appropriate. Demographic and clinical data, insulin and glucose values from both cohorts were compared at inclusion of patients of each cohort, using non parametric tests (Chi^2 or Mann-Whitney tests, as appropriate). Subgroups analyses determined by glucose tolerance subgroup classification were then performed to compare clinical status, glucose and insulin values of both cohorts using non parametric tests (Chi^2 or Mann-Whitney tests, as appropriate). Correlation analysis between BMI and pulmonary function (FEV1), AUC glycemia and AUC insulin were made with Spearman's correlation. A linear mixed regression model with random intercept and random slope was fitted to assess the effect of glucose tolerance subgroup at entry in the cohort on the mean slope of

FEV1 change over 4 years. Effect of glucose tolerance subgroup was controlled for the cohort and age. Interaction between covariates (cohort, NGT and AGT) and time were tested to characterize differences in longitudinal rates of change. The relationship between FEV1 decline and CFRD subgroup (56 patients) was not analyzed due to the small sample size and no available clinical data in the canadian group since confirmed *de novo* CFRD patients are excluded from the cohort after diagnosis.

Analyses were performed using SPSS software (version 24 by IBM, Chicago, USA) and SAS® software (version 9.4, SAS® Institute Inc., Cary, NC, USA). Area under the curve (AUC) for glucose and insulin was calculated using the software GraphPad Prism (GraphPad Software Inc; CA, USA). A probability value ≤ 0.05 was considered as statistically significant.

Results

Characteristics at baseline. Data of 224 Canadian and 147 French patients were included (See Table 1). Demographic and clinical data are detailed in Table 1. No difference of sex ratio, proportion of F508del homozygous patients and age was observed between the 2 cohorts. The clinical status of Canadian group was better with higher BMI (median in kg/m^2 [IQR]) 21.1 [19.5–22.8] vs. 19.9 [18.4–21.4], $p < 0.001$ and higher FEV1 (median in % [IQR]) 71.0 [55.0–82.0] vs. 64.0 [40.0–78.0], $p < 0.001$. Accordingly, a higher proportion of patients with mild to normal predicted FEV1 (>70%) was observed in Canadians cohort (51.3% vs. 38.1%, $p = 0.012$). The proportion of patients colonized with *Pseudomonas aeruginosa (PA)*, *Burkholderia cepacia*, and *Aspergillus* was not statistically different between both cohorts. There was a higher proportion of patients colonized with *Staphylococcus aureus* (SA) in the French cohort (70.1% vs. 55.8%, $p < 0.006$). The number of intravenous antibiotics courses in the year preceding the OGTT was not statistically different between the 2 groups.

The incidence of *de novo CFRD* diagnosis was higher in the Canadian population (19.2% vs. 9.8%, $p = 0.003$). Canadian cohort displayed a lower proportion of patients with normal glucose tolerance (36.6% vs. 53.4%, $p = 0.003$). Both fasting (G0) and 2-hours (G2) OGTT values (median in mmol/L [IQR]) were higher in the Canadian cohort: 5.4 [5.0–5.9] vs 4.8 [4.5–5.1], $p < 0.001$ for G0; 7.6 [5.8–9.7] vs. 6.5 [5.2–8.5], $p = 0.001$ for G2. The AUC OGTT curve for glucose values is higher in Canadian patients ($p < 0.001$). However, there was no statistical difference in HbA1c values between the two groups. Regarding insulin values (median μU/dl [IQR]) in Canadian compared to French patients, fasting (I0) and I2 values were higher in the Canadian cohort: 3.8 [2.3–5.7] vs. 3.2 [2.2–5.0], $p = 0.031$ for I0; and 27.4 [16.6–42.3] vs. 18.1 [11.0–33.0], $p < 0.001$ for I2. For the entire OGTT test area under the curve for insulin values is higher in Canadian patients ($p < 0.001$).

Clinical status comparison among the different glucose tolerance groups. Subgroup analyses determined by glucose tolerance subgroup classification were performed (Table 2). Fourteen French patients were excluded from the analyses because data for either G1 or G2 were not available and their data did not allow classification into glucose tolerance subgroups. %FEV1 (median in % [IQR]) was higher for Canadian patients for the NGT group compared to NGT French patients: 72.0 [56.0–86.0] vs. 64.0[38.0–80.0], $p = 0.006$, while no difference was observed for %FEV1 between Canada and France for the AGT and CFRD groups. BMI (median in kg/m^2 [IQR]) was also significantly higher for NGT and AGT Canadian patients compared to the French patients: 20.8 [19.5–22.7] vs. 20.2 [18.4–21.4], $p = 0.010$ for NGT and 21.1 [19.5–23.1] vs. 19.8 [18.5–21.6], $p = 0.002$ for AGT.

Glucose values according to glucose tolerance group. For each glucose tolerance category (see Table 2), Canadian patients displayed higher G0 median values and higher glucose median AUC as compared to French patients: $p < 0.001$ and $p = 0.005$ in NGT group, $p < 0.001$ and $p < 0.001$ in AGT group, and $p = 0.005$ and $p = 0.006$ in CFRD group.

Insulin values according to glucose tolerance group. NGT and AGT Canadian patients displayed higher insulin median AUC than French patients ($p < 0.001$ and $p = 0.040$), but this difference no longer exists for patients with *de novo* CFRD, $p = 0.278$ (see Table 2).

Insulin sensitivity (Stumvoll index) was higher for NGT French patients ($p = 0.039$) compared to Canadian NGT patients, but no difference was observed in the 2 other subgroups. Insulin resistance (HOMA-IR) was higher for Canadian NGT and AGT patients ($p = 0.004$ and $p = 0.048$) compared to French patients.

Despite higher level of insulin values for Canadian patients, the trends of the curve of insulin profile is similar for both Canadian and French NGT and AGT patients. Patients of both cohorts with NGT present a plasma insulin rise during the first hour of the OGTT (Fig. 1a), followed by moderated reduction at 2-h when glucose levels are trending downward. For all AGT patients, a similar insulin profile as for NGT-patients is observed for the 1st hour of the OGTT (Fig. 1b), but then insulin levels remain high at the second hour. For CFRD patients (Fig. 1c), if insulin values are similar at the end of the test for both cohorts, it is slightly higher in Canadian patients at 1-h. However, the 1 h insulin peak observed in NGT and AGT patients is reduced by approximatively 30% for CFRD patients. Insulin values keep rising during the second hour of the test for Canadian and French CFRD patients.

Insulin sensitivity and resistance and correlation analysis between BMI and pulmonary function, and between glycemic and clinical parameters in the global cohort. We observe higher insulin sensitivity during the OGTT using the Stumvoll index (median [IQR]) in NGT patients 0.111 [0.102–0.119] vs. both AGT 0.093 [0.085–0.104] and CFRD 0.059 [0.047–0.071] groups and in AGT patients 0.093 [0.085–0.104] vs. CFRD 0.059 [0.047–0.071] ($p < 0.001$). For fasting insulin resistance (HOMA-IR, median [IQR]), it is higher in CFRD 1.15 [0.71–1.45] than in NGT 0.76 [0.47–1.16] and AGT patients 0.82 [0.51–1.22] ($p = 0.013$).

After controlling for cohort, we observed a significant positive correlation (Fig. 2) between BMI and pulmonary function (FEV1) for all glucose tolerance groups (respectively $p < 0.001$, $p = 0.001$, $p < 0.001$ for NGT, AGT and CFRD). No significant correlation was observed for all subgroups between BMI and AUC glycemia.

	Canada	France	
	N = 224	N = 147	p value
Gender: woman, %	42.0	43.5	0.764*
Age in year, median (IQR)	22.0 (19.0–28.0)	22.5 (19.0–28.7)	0.831
ΔF508 homozygous, %	57.9	55.1	0.818*
%FEV1, median (IQR)	71.0 (55.0–82.0)	64.0 (40.0–78.0)	**0.001**
%FEV1 > 70%, %	51.3	38.1	**0.012***
BMI in kg/m^2, median (IQR)	21.1 (19.5–22.8)	19.9 (18.4–21.4)	**<0.001**
Colonized with P. Aeruginosa, %	74.5	67.3	0.155*
Colonized with B. Cepacia, %	2.8	2.7	0.968*
Colonized with S. Aureus, %	55.8	70.1	**0.006***
Colonized with Aspergillus, %	42.3	33.3	0.084
Patients requiring IV antibiotics in the year prior the OGTT, %	41.1	49.0	0.238*
Glycemia G0 in mmol/L, median (IQR)	5.4 (5.0–5.9)	4.8 (4.5–5.1)	**<0.001**
Glycemia G2 in mmol/L, median (IQR)	7.6 (5.8–9.7)	6.5 (5.2–8.5)	**0.001**
AUC Glycemia (G0, G1, G2), median (IQR)	1059.5 (914.9–1239.0)	913.5 (761.2–1043.2)	**<0.001**
NGT, %	36.6	53.4	**0.003***
INDET, %	16.5	9.0	
IGT, %	27.7	27.8	
De novo CFRD, %	19.2	9.8	
HbA1c in %, median (IQR)	5.8 (5.5–6.1)	5.7 (5.5–6.0)	0.825
Insulin I0 in μU/dl, median (IQR)	3.8 (2.3–5.7)	3.2 (2.2–5.0)	**0.031**
Insulin I2 in μU/dl, median (IQR)	27.4 (16.6–42.3)	18.1 (11.0–33.0)	**<0.001**
AUC Insulin (I0, I1, I2), median (IQR)	2530.0 (1837.0–3649.0)	1974.0 (1302.0–2910.0)	**<0.001**
Stumvoll Index, median (IQR)	0.096 (0.078–0.111)	0.103 (0.088–0.116)	**<0.001**
HOMA-IR, median (IQR)	0.93 (0.55–1.39)	0.68 (0.47–1.07)	**<0.001**

Table 1. Comparison of demographic characteristics and clinical data at inclusion of the Canadian and French patients. Bold values represent significant differences. Abbreviations: AGT: Abnormal glucose tolerance (INDET: indeterminate glucose tolerance + IGT: impaired glucose tolerance), AUC: area under the curve, BMI: body mass index, CFRD: cystic fibrosis-related diabetes, CRP: C reactive protein, FEV1: predicted forced expiratory volume in 1 second, G0: plasma glucose measured at start of OGTT, G2: plasma glucose measured at 2 hours of OGTT, HbA1c: glycated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance, IV antibiotics: number of days of intravenous antibiotics in the year of OGTT, NGT: normal glucose tolerance, P. Aeruginosa: *Pseudomonas aeruginosa*, S. Aureus: *Staphylococcus aureus*, *: p value was determined by chi^2.

Concerning BMI and AUC insulin, a significant correlation was observed in NGT subgroup (p = 0.004) but not in AGT and CFRD patients. No significant correlation between pulmonary function (FEV1) and AUC glycemia were observed for all glucose tolerance groups (data not shown).

FEV1 evolution during follow-up according to glucose tolerance subgroup. FEV1 measurements during the 4-year follow-up period were obtained in 301 patients (81% of overall cohort: 181 French and 120 Canadian). No interaction for glucose tolerance subgroup with time were observed, indicating that the longitudinal changes in FEV1 were not different between NGT and AGT groups (difference in mean annual FEV1 change in NGT compared to AGT group (0.4% 95% CI [−0.5–1.3], p = 0.375). However in all glucose tolerance subgroup a significant difference in mean change in FEV1 per year was observed when French and Canadian patients were compared with Canadian patients having a slower mean annual decline of their FEV1 (difference in mean annual FEV1 change 0.89%, 95% CI [0.0;1.77], p = 0.049), Fig. 3.

Discussion

To our knowledge, this is the first study that compares the incidence of glucose abnormalities in adult patients with CF, in two large cohorts and their association with clinical status. Despite higher glucose levels and incidence of *de novo* CFRD, Canadian CF patients secrete more insulin and have a better pulmonary and nutritional status according to their FEV1 and BMI than French patients. To explore the mechanisms of these differences, we conducted correlation analyses but we observed no correlation between BMI and glycemia AUC. Canadian patients also have slower annual decrease of their FEV1 than French patients during follow-up. No significant difference was observed for pulmonary function change over time between AGT and NGT patients. These observations challenge the concept of a possible causal role of hyperglycemia and/or hypoinsulinemia favouring clinical status (BMI and/or FEV1) degradation.

In the context of a well-established limited insulin secretion in adult CF patients[21,22], three key factors could contribute to the development of hyperglycemia: progression of insulin secretory deficiency, higher insulin resistance or higher insulin requirements[22,23]. In Canadian patients, we observe higher insulin secretory capacity, higher estimated insulin resistance but also higher CFRD incidence. Recently, insulin resistance variations has

	NGT			AGT (INDET + IGT)			*De Novo* CFRD		
	Canada	France	P value	Canada	France	P value	Canada	France	P value
n	82	71		99	49		43	13	
Age in year, median (IQR)	22.0 (20.0–25.0)	24.0 (19.0–31.0)	0.063	22.0 (19.0–27.0)	22.0 (19.0–26.0)	0.591	25.0 (20.0–30.0)	27.0 (20.0.—37.0)	0.736
%FEV1, median (IQR)	72.0 (56.0–86.0)	64.0 (38.0–80.0)	**0.006**	73.0 (54.7–82.0)	65.0 (42.5–81.5)	0.143	61.0 (51.0–79.0)	51.0 (42.5–67.0)	0.098
%FEV1 > 70%, %	53.6	39.4	0.079*	56.1	42.8	0.129*	35.7	23.1	0.396*
BMI in kg/m^2, median (IQR)	20.8 (19.5–22.7)	20.2 (18.4–21.4)	**0.010**	21.1 (19.5–23.1)	19.8 (18.5–21.6)	**0.002**	21.1 (19.3–22.9)	20.2 (18.8–21.1)	0.178
HbA1c in %, median (IQR)	5.7 (5.3–5.9)	5.7 (5.5–6.0)	0.325	5.7 (5.5–6.0)	5.8 (5.5–6.0)	0.759	6.1 (5.8–6.9)	6.3 (5.6–6.7)	0.796
G0 in mmol/L, median (IQR)	5.2 (4.9–5.5)	4.7 (4.4–5.0)	**<0.001**	5.4 (5.0–5.8)	4.8 (4.5–5.2)	**<0.001**	6.3 (5.4–7.4)	5.0 (4.7–6.3)	**0.005**
G2 in mmol/L, median (IQR)	5.6 (4.8–6.7)	5.4 (4.6–6.5)	0.234	8.3 (6.8–9.5)	8.3 (7.6–9.2)	0.851	13.6 (11.5–16.7)	13.0 (12.3–14.2)	0.437
AUC Glycemia (G0, G1, G2), median (IQR)	881 (783–943)	834 (735–918)	**0.005**	1105 (1041–1212)	1026 (951–1122)	**<0.001**	1513 (1342–1776)	1293 (1212–1447)	**0.006**
AUC Insulin (I0, I1, I2), median (IQR)	2483 (1906–3768)	1866 (1257–2649)	**<0.001**	2652 (2022–3678)	2283 (1318–3247)	**0.040**	2008 (1520–3255)	1833 (1083–2856)	0.278
Stumvoll index, median (IQR)	0.110 (0.099–0.117)	0.114 (0.103–0.121)	**0.039**	0.093 (0.085–0.105)	0.092 (0.087–0.104)	0.735	0.060 (0.048–0.071)	0.065 (0.050–0.074)	0.432
HOMA-IR, median (IQR)	0.88 (0.53–1.40)	0.64 (0.39–1.04)	**0.004**	0.91 (0.54–1.32)	0.65 (0.49–1.04)	**0.048**	1.17 (0.69–1.49)	1.00 (0.53–1.32)	0.331

Table 2. Comparison between glucose tolerance groups of the Canadian and French patients. Bold values represent significant differences. Abbreviations: AGT: Abnormal glucose tolerance (INDET: indeterminate glucose tolerance + IGT: impaired glucose tolerance), AUC: area under the curve, BMI: body mass index, CFRD: cystic fibrosis-related diabetes, CRP: C reactive protein,FEV1: predicted forced expiratory volume in 1 second, HbA1c: glycated hemoglobin, HOMA-IR: Homeostasis model assessment of insulin resistance, NGT: normal glucose tolerance. Mann-Whitney analysis were performed except for p value with * that were determined by chi^2.

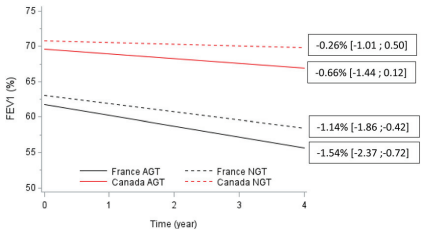

Figure 1. Insulin secretion (μU/dl) at start, 1-h and 2-h of the OGTT for. (**a**) NGT, (**b**) AGT and (**c**) CFRD patients according to their respective cohorts: black dot (●) for Canadian patients and black square (■) for French patients. Values are presented as mean ± SEM. Abbreviations: AGT: abnormal glucose tolerance, CA: Canadian patients, CFRD: cystic fibrosis-related diabetes, FR: French patients, NGT: normal glucose tolerance.

emerged as a possible contributor to hyperglycemia for patients with CF[8,24]. Higher BMI could contribute to higher insulin resistance in Canadian patients[25,26]. As insulin is an anabolic hormone, as long as a certain degree of insulin secretion is preserved, this could allow a higher BMI[27]. Indeed, when insulin secretion further deteriorates leading to *de novo* CFRD, both cohorts do not present anymore differences for BMI and insulin secretion. The frequency of exacerbations which is a good marker of respiratory function stability does not seem to be implicated in observed insulin resistance differences as the number of antibiotic courses is similar in both cohorts. It is also possible that insulin secretion itself might explain clinical differences between cohorts rather than blood glucose. A higher insulin secretion level might allow to reach and/or maintain a higher weight[28]. In a context of a limited insulin secretion capacity, hyperglycemia could also play a role by favoring pulmonary exacerbations[29] and promoting oxidative stress[30]. Both higher insulin as well as lower glucose values can thus contribute to better lung function.

In contrast to previous reports, our results highlight that despite higher glucose values, Canadian CF patients have better pulmonary function and BMI. Despite these higher glucose values, Canadian patients also presented a slower annual FEV1 decline. When both cohorts are combined and the pulmonary evolution of patients with AGT is compared to patients with NGT, there is no difference in annual FEV1 decline. Various factors not related

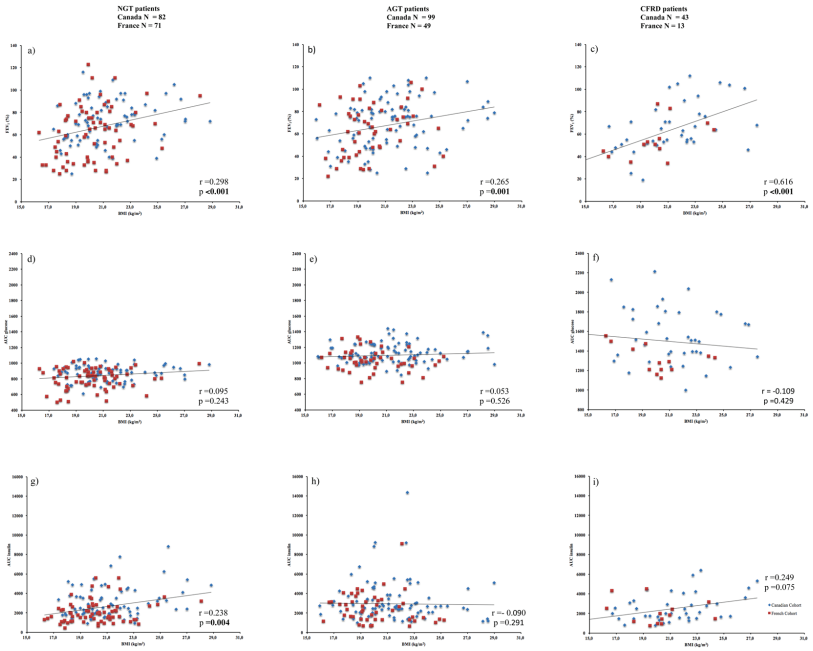

Figure 2. Spearman's correlation for (**a**) BMI and FEV1in NGT patients (**b**) BMI and FEV1 in AGT patients and (**c**) BMI and FEV1 in CFRD patients (**d**) BMI and AUC glucose in NGT patients (**e**) BMI and AUC glucose in AGT patients (**f**) BMI and AUC glucose in CFRD patients (**g**) BMI and AUC insulin in NGT patients (**h**) BMI and AUC insulin in AGT patients (**i**) BMI and AUC insulin in CFRD patients. Blue diamond: Canadian cohort and Red square: French cohort.

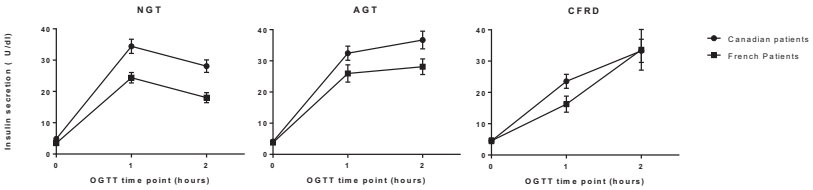

Figure 3. Mean FEV1 change in FEV_1 according to glucose tolerance subgroup and cohort. Values are presented as mean ± SEM. Abbreviations: AGT: abnormal glucose tolerance, CA: Canadian patients, FR: French patients, NGT: normal glucose tolerance.

to cystic fibrosis can also explain this observation. Among them, the role of genetic factors other than CFTR mutations may explain the observed differences between these two cohorts (modifier genes). In the present study, the distribution for F508del CFTR mutation proportions is similar between the two cohorts but it is now well established that other mutations are associated, for some of them, with lung disease severity and for others, with diabetes susceptibility[31,32]. This emerging important factor may also have a role in observed glucose and BMI differences. For example, some mutations in genes involved in a higher risk for type 2 diabetes (e.g. TCF7L2) are also associated with a higher and earlier CFRD prevalence[32]. Further investigations need to be done to compare modifier genes between the 2 cohorts. Secondly, despite comparable nutritional and clinical recommendations for CF care as well as health care systems (universal access) between the 2 cohorts, other factors can still influence glucose values as well as the nutritional status of CF-patients. For example, differences in qualitative and quantitative nutritional intake could impact both glucose tolerance and BMI. Unfortunately, nutritional intake was not assessed in the present study. If done in the future, such assessment could be limited by the precision of available tools (e.g. food journals, 24-hour dietary recall, etc.) as well as the fact that most tools are country specific thus

limiting the ability to compare different populations[33]. In addition, despite merging two large and well characterized cohorts, the sample size of some subgroups, such as de novo CFRD, remains small thus limiting our ability to explore some differences.

In order to interpret our results, the potential mechanisms of higher BMI in Canadian patients should be explored. Key factors involved in energy balance and nutritional intake, absorption and energy expenditure (physical activity, energy demand related to CF exacerbations, etc.) should be evaluated. Nutritional recommendations are similar in North America and Europe with a recommended energy intake range from 120 to 150% of energy needs for the healthy population of similar age, sex and size. Patients included in both countries are also exposed to similar pancreatic enzyme replacement therapy (PERT) protocol, starting at 500 U lipase/kg/meal to a maximal dose of 1000–2500 U lipase/kg/meal which should lead to similar nutrient absorption capacity. Thus the two cohorts should be exposed to similar quantitative nutritional intake and absorption. The frequency of exacerbations necessitating intravenous antibiotics does not seem to play a role on BMI values as the number of antibiotics course is similar in both cohorts. International guidelines for antibiotic use in CF are worldwide applied and this may contribute to the very close use of antibiotics in Canadian and French cohorts. However, chronic higher caloric intake and/or differences in physical activity may still be important factors in explaining the differences and may play a role in the higher BMI of Canadian patients. In addition, backgroud population differences in diabetes and obesity, which are both higher in Canada compared to France[34–37], could also explain the disparities between French and Canadians independently of CF status. As previously reported herein, there is a positive correlation between BMI and FEV1 which could explain the higher FEV1 observed in Canadian patients as well as their lower mean annual FEV1 decline.

Observed association and differences do not imply causality and despite our careful assessement of two large and well characterized cohorts important underlying mechanistic factors were not measured in that study.

In conclusion, Canadian patients present a better clinical status (higher BMI, insulin secretion and FEV1) than French patients, but unexpectedly they also present a higher incidence of glucose abnormalities. In addition, patients in the abnormal glucose tolerance group do not have worse mean FEV1 decline over observed time than patients with normal glucose tolerance. To better understand the complex interplay between glucose tolerance and clincal status (BMI and/or FEV1) of adult patients with CF, further investigations should focus on potential underlying factors that may play a role in the observed differences.

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C. Etude Glycone 2

Contexte

Certains auteurs rapportent que les valeurs de glycémie et d'insulinémie aux temps précoces de l'HGPO (1 heure) seraient mieux corrélées à l'évolution du statut clinique des patients mucoviscidose que les temps tardifs de deux heures. Effectivement nombre de patients avec un profil glycémique spécifique caractérisé par une glycémie à jeûn normale, un pic à 1 heure puis une décroissance rapide avec un temps glycémique à 2 heures normal, entrent dans la catégorie normo-tolérant alors qu'ils ont des glycémies élevées aux temps intermédiaires.

Dans la littérature concernant spécifiquement ce groupe de patients avec un temps intermédiaire à 1 heure de glycémie élevée ou d'insulinémie basse, des auteurs rapportent une dégradation de la fonction pulmonaire et du poids comme dans le cas de DAM (60,87). Cette corrélation entre les temps intermédiaires de l'HGPO et l'évolution du statut clinique des patients au cours du temps n'a jamais été évaluée sur une cohorte importante et une période longue.

Objectif

Dans la cohorte GLYCONE, nous avons modélisé sur quatre ans l'évolution de la fonction respiratoire et de l'IMC, en fonction de la valeur de la glycémie et de l'insulinémie mesurées à 1 heure au cours de l'HGPO. Les valeurs seuils de glycémie et d'insulinémie étaient 11.1mmol/L et 24mU/L.

Résultats

Notre étude ne rapporte pas d'interaction entre les valeurs de glycémie à 1 heure à l'inclusion dans la cohorte et l'évolution de la fonction pulmonaire au cours du suivi dans les deux groupes de patients canadiens et français. Une valeur d'insulinémie

basse à 1 heure à l'inclusion tend à être associée à un IMC plus bas à l'inclusion mais n'est pas associée à une dégradation de l'IMC au cours du suivi.

Les résultats de l'étude sont produits dans l'article intitulé "**Impact of 1h oral glucose tolerance test on the clinical status of adult cystic fibrosis patients over a 4-year period"** qui est en révision pour la revue Scientific Reports.

Discussion

Les résultats ne montrent pas d'association entre l'hyperglycémie à une heure au test d'HGPO et un déclin respiratoire au cours du suivi, ni avec la fonction respiratoire à l'entrée dans la cohorte. L'association entre hypoinsulinémie à une heure et dégradation clinique n'est pas non plus mise en évidence, mais l'hypoinsulinémie à une heure est associée à un IMC plus bas à l'inclusion.

SCIENTIFIC REPORTS

ORIGINAL RESEARCH

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Impact of 1h oral glucose tolerance test on the clinical status of adult cystic fibrosis patients over a 4-year period

Running title: 1h OGTT values impact on clinical status in CF

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Abstract

Objective: To report the clinical profile associated with G60 and I60 over a 4-year prospective observational period in 2 large cohorts of adult patients with CF.

Methods: 319 patients were included (210 Canadian and 119 French) and classified according to their inclusion G60 ($\geq$ or $<$ 11.1 mmol/L) and the median inclusion I60 ($\geq$ or $<$ 24 mU/I). Forced expiratory volume in 1 second (FEV1), body mass index (BMI) were collected on OGTT days. Linear mixed regression models were used to assess the effect of G60 and I60.

Results: High G60 was not associated to a lower FEV1 at inclusion and the follow-up decline was not higher in the high G60 group (Coefficient [95% CI] : -3.4 [-7.4;0.6], p= 0.0995.). There was no significant association between BMI and G60. Patients with high I60 tended to have a higher mean BMI (+0.5 kg/m² [0.0 to 1.1], p=0.05) but no interaction over time was observed.

Conclusions: High G60 is not associated with a lower lung function at inclusion nor its decline over a 4-year follow-up. High I60 is slightly associated to a higher weight at inclusion, but not with BMI evolution over time in adult patients.

1. Introduction

Cystic fibrosis (CF) is a genetic inherited disorder affecting approximatively one in 3800 people in the Caucasian population [1, 2] leading to multiple organ damages with major damages to lung and digestive systems [3]. CFTR dysfunction also plays a role in the exocrine and endocrine pancreas insufficiency resulting, in combination with other factors including inflammation and oxidative stress, in a progressive decrease in insulin secretion [4]. Therefore 20% of young adult CF patients have cystic fibrosis-related diabetes (CFRD) while the prevalence increases to almost 50% of people in their 50s. In addition a similar proportion of patients have glucose intolerance [5]. Hyperglycemia occurrence is associated with accelerated lung function decline as well as weight loss, thereby increasing early mortality [6, 7]. This association is at least partly explained by reduced insulin secretion leading to a reduced anabolic capacity [8].

Because of its frequency and possible impact on weight and lung function it is recommended to screen annually for CFRD from the age of 10 years with a 2-hour oral glucose tolerance test (OGTT) [9]. The current OGTT glucose threshold used for CFRD diagnosis are based on fasting and 2-h glucose values [10] but controversial because they are based on retinopathy risk in patients with type 2 diabetes, while in CF hyperglycemia is mainly associated with altered nutritional and pulmonary status [11]. Many efforts are being made to found if CF-specific glycemic thresholds could help to target patients at higher risk for clinical decline (nutritional and/or pulmonary status) before or at the time of CFRD onset. Indeed, many research groups have found that hyperglycemia at OGTT earlier time points (30, 60 or even 90 minutes) correlates better with CF clinical status decline than the standard 2-h diagnosis value. Interestingly because most CF patients present a specific glucose excursion pattern characterized by normal fasting glucose followed by abrupt glucose excursion followed by a rapid decrease, a lot of these patients with frankly high glucose at intermediate time points are classified as normal glucose tolerant. In cross sectional studies these CF patients with high 1h-OGGT glucose value (G60) or low plasma insulin value (I60) present reduced pulmonary function and/or weight as observed in patients with *de novo* CFRD diagnosis [12-15] but one longitudinal study showed no relationship between 1-h glucose values and pulmonary function evolution over a three-year follow-up period [16].

Prospective studies on large cohorts are still needed to confirm the clinical relevance of early time OGTT values to predict clinical decline over time.

The objective of this study is to describe the course of BMI and lung function evolution associated with hyperglycemia and hypoinsulinemia at 60 minutes of an OGTT test over a 4-year period in two large Canadian and French cohorts of adult patients with CF.

Methods

- *Study popualtion : GLYCONE database*

Data from patients were obtained from two large prospective cohorts of CF patients (Montreal, Canada and Rhône-Alpes region, France) previously described [17]. Briefly, main inclusion criteria were: patients over 18 of age with confirmed CF diagnosis, pancreatic insufficient with pancreatic enzyme supplementation, without known diabetes at inclusion and clinically stable for at least one month before the OGTT visit. Main exclusion criteria were previous diagnosis of diabetes, pregnancy, CF exacerbations in the past month or conditions that could interfere with glucose metabolism such as intravenous antibiotic, steroids (oral or intravenous) or growth hormone treatment. Patients diagnose with confirmed *de novo* CFRD diagnosis during follow-up were excluded from further protocol visit and referred to an endocrinologist. The combined database includes 371 patients, 42 were excluded because of lacking FEV1, G60 and/or I60 data during follow-up leaving 329 available patients: 210 Canadian patients and 119 French patients for the present analysis. The follow-up period was four years as the maximal follow-up of the French patients was 4 years.

- *OGTT*

Patients in both cohorts performed an annual OGTT (between 12 and 18 months between visits depending on clinical status). When not clinically stable (e.g. pulmonary infections, intravenous antibiotic, etc.), OGTT testing was postponed upon 2 months of clinical stability. After an 8-hours fast, patients consume a glucose beverage (1.75g/kg of body weight up to a maximum of 75g, 300 mL) in less than 5 minutes. Plasma glucose (glucose

oxydase) and insulin (centralized dosage in Québec by BI-INS-IRMA; Cisbio Bioassays, France) values were measured before OGTT and then again at 60 (G60 for glucose & I60 for insulin) and 120 minutes. OGTT were then performed annually for at least 4 years.

- *Clinical data*

On the day of the OGTT, patients performed a lung function test to assess pulmonary function by spirometry using the forced expiratory volume in 1 second in L (FEV1) using Hankinson 1999 formula for FEV1(%)[18]. Weight and height were measured. BMI was calculated using weight in kilograms divided by height in square meter (kg/m^2). These values of FEV1 and BMI were then obtained annually on the day of OGTT testing. Bacterial colonization with *P. aeruginosa* and *S. aureus* in the year preceding the OGTT was also collected from medical files as well as data relating to hospitalization and intravenous antibiotic treatment.

- *Statistical analysis*

Descriptive statistics were used to summarize characteristics of patients at the year of entry into the cohort. Continuous data were presented as means and standard deviations, categorical data were presented as frequencies and percentage.

A linear mixed regression model with random intercept and random slope was fitted to assess the effect of G60 and I60 at inclusion in the cohort on the mean FEV1 at baseline and on the mean slope of FEV1 change over time. Baseline G60 and I60 were considered as categorical variables based on widely used threshold for G60 ($\geq$ or $<$ 11.1 mmol/L) (10) and median value for I60 ($\geq$ or $<$ 24 mU/l^3). Effects of G60 and I60 were controlled for the cohort, age, sex, Pseudomonas aeruginosa colonization, year of inclusion into the cohort (as medical care might have changed) and BMI at inclusion. Interaction between covariates (cohort, G60 and I60) and time were tested to characterize differences in longitudinal rates of change. After checking for linearity assumption, continuous variables were mean-centered (25 years old for inclusion age and 21 kg/m^2 for BMI at inclusion). Nonsignificant covariates ($p>0.05$) were removed by backward elimination.

A similar approach was used to assess the association between G60 and I60 at inclusion in the cohort and change BMI over time. Interaction between covariates cohort, time and gender were tested to control for

difference between males and females. Age at inclusion was included as categorical variable (<20 yrs, 20 to 29 yrs, 30 to 34 yrs and ≥35 yrs) to account for the nonlinear relationship between BMI and age.

Results were interpreted with a 5% threshold for statistical significance. Statistical analyses were performed with SAS version 9.4 software (SAS Institute Inc.).

Results

- *Inclusion*

A total of 329 patients are included: 210 Canadian CF patients and 119 French patients. Patients' characteristics are described in Table 1. Mean age of participants at inclusion in the cohorts is 24.7 ± 6.3, 141 (43%) are women and 183 (56%) are F508del homozygous. At inclusion mean FEV1% is 68.7 ± 19.9 and mean BMI is 21.0 ± 2.6 kg/m2. 213 (70%) of patients have chronic colonisation with pseudomonas at inclusion in the cohort. Mean plasma glucose (G60) at inclusion is 10.9 ± 3.0. 138 (42%) patients present a G60 value above ≥ 11.1 mmol/L. Conversely mean insulin (I60) at inclusion is 29.2 ± 19.3 mU/L. 160 patients (49%) have a value above the median (≥ 24mU/L).

- *Glycemia at 60 minutes (G60) and pulmonary function over time*

FEV1 measurements over a 4-year follow-up period were obtained in the 329 patients, with a mean of 2.9 observations for each subject (range: 1-7), for a total of 981 observations. The overall mean decreased in FEV1 is 0.9% per year (95% CI: -1.3 to -0.4; $p < 10^{-3}$). As previously reported, mean FEV1 at inclusion is significantly higher in Canadian patients than in French patients (+5.6%, 95% CI: [1.4; 9.8]; p < 0.001) (17). Patients with G60 values above 11.0 mmol/L tend to have a lower mean inclusion FEV1 than patients with G60 values below this threshold (-3.4%; 95% CI: -7.4 to 0.6; p<0.10). A similar non-significant trend is observed in patients with I60 values above the median (≥ 24mU/L) when compared with patients below this threshold (-2.8%; 95% CI: -6.8 to 1.3; p = 0.179). The relationship between the FEV1 decline and baseline G60 for Canadian and French patients is represented graphically in Figure 1. No significant interaction involving baseline G60 and FEV1 values over time is observed regardless the cohort of belonging, indicating that the longitudinal changes in FEV1 over follow-up are not different between cohorts and not influenced by the baseline G60. The only factors significantly influencing mean FEV1 are age and BMI at baseline. Details are given in Table 2.

- *Insulin at 60 minutes (I60) and BMI over time*

BMI measurements over the 4-year follow-up period was obtained in 328 patients, with a mean of 2.9 observations for each subject (range: 1-7), for a total of 981 observations. As presented in Table 2, the linear mixed model depicts a significant gender differences in both the baseline mean BMI and the rate of change over the 4-year follow-up. Mean BMI is lower in females than males (- 0.2 kg/m², 95% CI: 0.1 to 0.3; $p < 10^{-3}$). The average rate of increase is + 0.2 kg/m²/year for males (95% CI: 0.1 to 0.3; $p < 10^{-3}$) and + 0.1 kg/m²/year for females (95% CI: 0.0 to 0.2, p=0.203). A cohort difference is found ($p <10^{-3}$) and the effect is different between gender (p=0.018). Canadian male patients have a significant higher mean BMI compared to French male patients (+1.7 kg/m², 95% CI: 0.9 o 2.4, $p<10^{-3}$). For females, the mean BMI is not different between Canadian and French patients (+0.4 kg/m², 95% CI: -0.4 to 1.2, p= 0.328). There is no statistically significant association between BMI and G60 values at baseline above the threshold (p=0.782). Patients with I60 values above 24mU/L tended to have a higher mean BMI than patients below this threshold (+0.5 kg/m²; 95% CI: 0.0 to 1.1, p=0.05). In both cohorts, no interaction between time and I60 is observed indicating that rate of change of BMI was similar in patients with above and below the I60 threshold. The relationship between the BMI change and baseline I60 for Canadian and French patients is represented graphically in Figure 2.

Discussion

Our study does not support an association with baseline hyperglycemia at one hour with lung function decline neither in French nor in Canadian cohort. Low insulinemia at baseline tend to be associated with lower BMI at baseline but is not associated with decline of BMI over time. Despite a significant number of reports for significant associations between 1h-OGTT high glucose and/or low insulin values with lower pulmonary function and/or lower BMI [13-15], such relationship has not been tested prospectively. Only one longitudinal study showed no link between 1-h glucose values evolution over time and FEV1 evolution in adult patients over three year [16]. We used two large international CF cohort to test longitudinally this hypothesis. We observed that 1) 1-h OGTT glucose values (G60) does not appear to influence FEV1% at cohort inclusion and during

follow-up, 2) 1-h OGTT insulin values (I60) tends to significantly influence BMI at inclusion but not for evolution over time. As previously described with the same database [17], these data show that Canadians patients, for a similar age and similar genotype, have better weight and lung function at inclusion than French patients at inclusion. However, regardless of G60, lung function decreased similarly over 4 years and weight increased in a similarly way irrespectively of the French or Canadian origin.

The current 2h glucose-OGTT threshold (≥ 11.1 mmol/L) to diagnosed CFRD is the one that have been established for type 2 diabetes diagnosis based on retinopathy risk [19]. Several groups have hypothesized that in patients with CF, the potential impact of hyperglycemia on lung function could occur at lower values implying that current diagnosis may be made too late at a time at which the possible negative impact of hyperglycemia might be difficult to reverse [20, 21]. Though most studies are reporting fasting and 2h OGTT glucose values, current mandatory values to establish glucose tolerance diagnosis, a lot of attention have been recently given to OGTT glucose intermediate times. In non CF patients, intermediate points and especially 1-h glucose values, have been associated stronger and independently of 2-h glucose values to a wide variety of adverse outcomes [22]. Patients with CF present a specific post-meal or post challenge glucose excursions characterized by frequent normal fasting glucose followed by early abrupt hyperglycemia and then rapid glucose values normalization [23, 24], indeed a specific glucose category exist for these patients (Indeterminate glucose tolerance; INDET) [12, 13]. Most studies showing that lower weight and lung function is associated with HG60 have been cross-sectional or sometimes retrospective [13-15]. Follow-ups over time following clinical parameters and 1-h glycemia are rare [15]. Several CGM studies exploring patients with CF have found that G60 was a better marker of clinical deterioration than the classical 2-h value [11]. Hameed et al. showed that the maximal blood glucose observed during continuous glucose monitoring (CGM) or OGTT was associated with worse weight and pulmonary function in children and adolescents, while the 2-h OGTT value was not [13]. Others have also shown that the INDET status is associated with reduced lung function and weight, to a comparable level to what is observed in CFRD patients [12]. The INDET status is a good illustration of some patients who can still normalize their 2-h glucose value but with early significant hyperglycemia which could affect clinical status [11, 20].

However, the current study does not agree with previous observations and does not confirm the deleterious effect of 1-h OGTT hyperglycemia (G60≥11.1 mmol/L) in adults with CF. At least in adult patients without known CFRD, this study may lead to reconsider the usefulness of G60 to detect the risk of future FEV1 decline. Still at baseline a trend exists between a higher G60 value and a lower FEV1. It is thus possible that at a younger age before adulthood hyperglycemia could have a more significant impact. This hypothesis was not confirmed in the study by Reynaud et al. [16], which included children with a three-year follow-up. Although we found that lung function may be lower at baseline when G60 is high, over a 4-year period the decline is not faster than for patient with normal G60, and weight may even increase over time. Since these patients are all adults, which is different from most of previously published studies, it is possible that the consequences of hyperglycemia are mainly important during childhood and adolescence but then have less impact in adults.

In patients with CF lower insulin values are associated and proportional to lower weight [14, 25]. This can be explained by the anabolic role of insulin [26]. The progressive loss of insulin secretion can lead to muscle and fat mass loss [5, 6]. Importantly this process can be reversed by insulin therapy [7, 27]. However regardless of the I60 value, patients included in this study gained weight over a 4-year period. One possible explanation is that, since all patients are adults without CFRD at inclusion thus these patients could still have sufficient insulin secretion to protect against protein catabolism [28]. It is possible that sickest patients with low insulin secretion category have developed CFRD before adult age and thus have not been included in this cohort.

Interestingly both cohorts gained weight with time, a factor usually associated with better lung function [29, 30]. This weight gain was observed regardless the baseline weight and insulin secretion category. This positive weight trend could be related to intensive nutritional therapy in our cohorts with high caloric intake, enzyme replacement therapy and nutritional follow-up which in the context of reduced but sufficient insulin secretion. We observed a sex dysmorphism for weight gain which over time was more pronounced in men than in women. Lower weight have already been reported in women leaving with CF^2 but this might not be related to insulin secretion as surprisingly in a previous report form the Canadian cohort, adult women presented higher insulin secretion than adult men at a comparable level with what is observed in healthy individuals [31].

This study has several limitations. Inclusion criteria are strict since patients must be adults without CFRD at inclusion and without pulmonary transplantation. Thus, sickest patients diagnosed with CFRD or transplanted

before adulthood are not included in this analysis. However, the investigated group represent a large proportion of adults followed in CF centers. Despite good phenotyping of our cohort, additional unmeasured parameters could influence FEV1 and BMI (e.g. nutritional intake, physical activity, modifiers genes, etc.). Despite these limitations, both cohorts are well characterized with harmonized data allowing the prospective analysis of the impact of hyperglycemia and hypoinsulinemia on pulmonary function on weight evolution over time. Despite some baseline differences already reported[17], overall results are similar in the two cohorts. This analysis does not preclude a positive role for early insulin therapy on BMI and/or lung function.

In conclusion, hyperglycemia at one hour of an oral glucose tolerance test is not associated with a significant lower lung function at inclusion and then decline over subsequent 4-year challenging its adverse effect on lung function in adult patients with CF. Low insulin value at one hour of an oral glucose tolerance test tends to be associated with lower BMI at baseline but then patients increase their BMI over time regardless their baseline insulin secretion.

Declaration of interest:

None.

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Tables and figure legends

Table 1. Patient characteristics at entry in each cohort

Abbreviations : SD : Standard Deviation, FEV1 : Forced expiratory volume in 1 second, PG60 : OGTT 1-h glycemia value, IG60 : OGTT 1-h insulinemia value, BMI : Body Mass Index.

Table 2 : Effect of PG60 at baseline on the change in FEV1 over time

[a] Mean FEV1 at entry in the cohort for a French patient aged 25 years, with BMI equals to 25 kg/m², with no colonisation with *P. Aeruginosa*, with a baseline PG60 < 11.1 mmol/l and with baseline IG60 < 24 mU/l[3]

[b] Baseline age centered at 25 years

[c] Baseline BMI centered at 21 kg/m²

[d] Mean BMI at entry in the cohort for a French males aged 18 to 20 years with no colonisation with *P. Aeruginosa*, with a baseline PG60 < 11.1 mmol/l and with baseline IG60 < 24 mU/l[3]

Abbreviations : CI : Confidence Interval, FEV1 : Forced expiratory volume in 1 second, BMI : Body Mass Index, PG60 : OGTT 1-h glycemia value, IG60 : OGTT 1-h insulinemia value

FIGURE 1 : PROTOTYPICAL FEV1 TRAJECTORIES FOR CANADIAN AND FRENCH PATIENTS ACCORDING HIGH PG60 VALUES (≥11.1 MMOL/L) AT ENTRY IN EACH COHORT

FIGURE 2 : PROTOTYPICAL BMI TRAJECTORIES FOR CANADIAN AND FRENCH PATIENTS ACCORDING HIGH IG60 VALUES (≥ 24 MU/L[3]) AT ENTRY IN EACH COHORT

Table 1. Patient characteristics at entry in each cohort

	Total	Canada	France
Number of patients Number of observations	329 978	210 572	119 413
Women, n(%)	141 (43)	90 (43)	51 (43)
Mean age (SD), yrs	24.7 (6.3)	24.5 (6.0)	24.9 (6.8)
F508del homozygous, n (%)	183 (56)	121 (58)	62 (52)
Colonisation with *P. Aeruginosa*, n (%)	213 (70)	152 (72)	79 (66)
Colonisation with *S. Aureus*, n (%)	199 (61)	115 (55)	84 (71)
FEV1, %, mean (SD)	68.7 (19.9)	71.4 (18.9)	63.9 (20.8)
BMI, kg/m^2, mean (SD)	21.0 (2.6)	21.4 (2.8)	20.3 (2.2)
Courses of IV antibiotic per year, mean (SD)	0.7 (1.1)	0.6 (1.1)	0.8 (1.2)
PG60 ≥ 11.1 mmol/l, n (%)	138 (42)	104 (50)	34 (29)
IG60 ≥ 24 mU/l^3, n (%)	160 (49)	112 (64)°	48 (40)

Abbreviations : SD : Standard Deviation, FEV1 : Forced expiratory volume in 1 second, PG60 : OGTT 1-h glycemia value, IG60 : OGTT 1-h insulinemia value, BMI : Body Mass Index.

Table 2 Effect of PG60 at baseline on the change in FEV1 over time and Effect of IG60 at baseline on the change in BMI over time

Factor	Coefficient [95% CI]	p-value
PG60 on FEV1		
Intercept[a]	70.8 [65.9;75.7]	<.0001
Time (year)	-0.9 [-1.3;-0.4]	0.0001
Canadian	5.6 [1.4;9.8]	0.0098
Baseline PG60 ≥11.1 mmol/l	-3.4 [-7.4;0.6]	0.0995
Baseline IG60 ≥24 mU/l[3]	-2.8 [-6.8;1.3]	0.1792
Baseline age (years) [b]	-1.1 [-1.5;-0.8]	<.0001
Baseline BMI (kg/m²) [c]	2.8 [2.0;3.6]	<.0001
Colonisation with *P. Aeruginosa*	-4.1 [-8.5;0.2]	0.0643
IG60 on BMI		
Intercept[d]	20.4 [19.5;21.3]	<.0001
Time (years)	0.2 [0.1;0.3]	<.0001
Canadian	1.7 [0.9;2.4]	<.0001
Women	-0.2 [-1.0;0.7]	0.0040
Women*Canadian	-1.3 [-2.3;-0.2]	0.0182
Time*Women	-0.1 [-0.3;0.0]	0.0446
Colonisation with *P. Aeruginosa*	-0.7 [-1.3;-0.1]	0.0147
Age group		
20-29 yrs	-0.4 [-1.0;0.3]	0.3009
30-34 yrs	1.9 [0.9;2.9]	0.0002
≥35 yrs	1.5 [0.5;2.5]	0.0029
Baseline PG60 ≥11.1 mmol/l	-0.1 [-0.6;0.5]	0.7824
Baseline IG60 ≥24 mU/l[3]	0.5 [0.0;1.1]	0.0521

[a] Mean FEV1 at entry in the cohort for a French patient aged 25 years, with BMI equals to 25 kg/m², with no colonisation with *P. Aeruginosa*, with a baseline PG60 < 11.1 mmol/l and with baseline IG60 < 24 mU/l[3]

[b] Baseline age centered at 25 years

[c] Baseline BMI centered at 21 kg/m²

[d] Mean BMI at entry in the cohort for a French males aged 18 to 20 years with no colonisation with *P. Aeruginosa*, with a baseline PG60 < 11.1 mmol/l and with baseline IG60 < 24 mU/l[3]

Abbreviations : CI : Confidence Interval, FEV1 : Forced expiratory volume in 1 second, BMI : Body Mass Index, PG60 : OGTT 1-h glycemia value, IG60 : OGTT 1-h insulinemia value

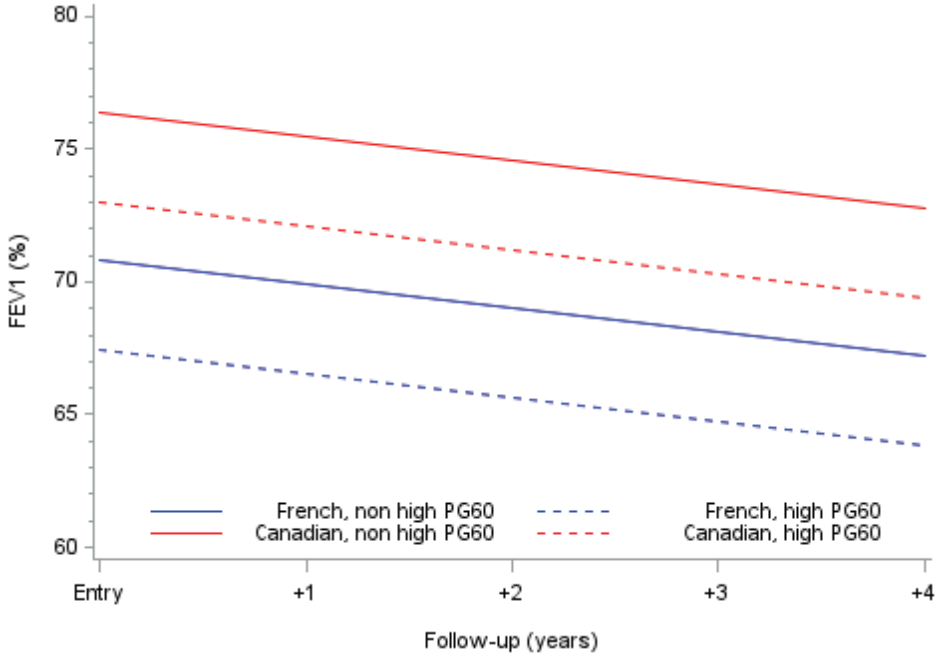

FIGURE 3 : PROTOTYPICAL FEV1 TRAJECTORIES FOR CANADIAN AND FRENCH PATIENTS ACCORDING HIGH PG60 VALUES (≥11.1 MMOL/L) AT ENTRY IN EACH COHORT

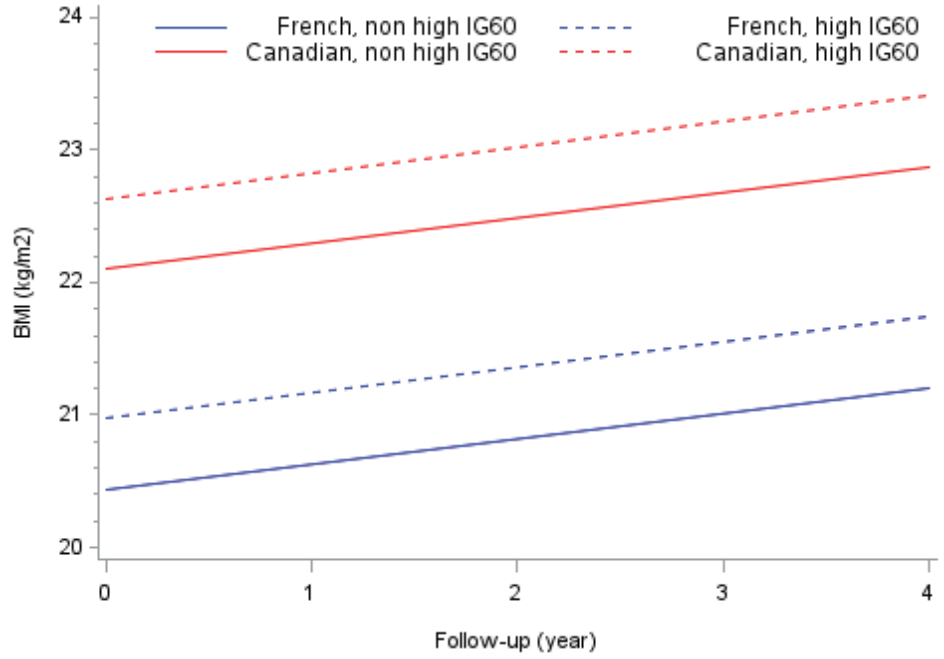

FIGURE 4 : PROTOTYPICAL BMI TRAJECTORIES FOR CANADIAN AND FRENCH PATIENTS ACCORDING HIGH IG60 VALUES (≥ 24 MU/L^3) AT ENTRY IN EACH COHORT

D. Etude GLYCONE : points clés

L'étude GLYCONE a permis de comparer 2 cohortes de patients adultes avec un accès aux soins comparable. Malgré une prévalence de DAM plus importante dans la cohorte canadienne, l'état clinique (fonction respiratoire et IMC) est meilleur dans ce groupe en comparaison du groupe français. La dégradation clinique du groupe canadien est moindre que celle du groupe français mais il n'est pas mis en évidence de différence entre les groupes normo-tolérants et intolérants.

L'étude de l'impact clinique des valeurs intermédiaires à une heure du test HGPO, confirme les résultats de DIAMUCO, c'est-à-dire l'absence d'impact clinique péjoratif de valeurs de glycémie élevées à 1 heure. Une valeur d'insulinémie basse à 1 heure tend à être associée à un IMC bas mais les patients prennent du poids au cours du suivi. Les résultats nuancent ceux de la plupart des études publiées dans la littérature qui décrivent l'effet délétère de l'hyperglycémie à 1 heure sur la fonction respiratoire. Une des hypothèses pourrait être que la dégradation clinique a lieu précocement dans l'enfance, et ce d'autant plus que les populations testées dans ces études sont majoritairement pédiatriques contrairement à GLYCONE.

Une étude de cohorte incluant une population pédiatrique avec un suivi plus long permettrait peut-être de mieux comprendre les mécanismes et l'impact clinique des troubles précoces du métabolisme glucidique.

Impact pronostique du diabète de la mucoviscidose dans certains contextes cliniques spécifiques de l'adulte : la grossesse et la transplantation pulmonaire

1. Impact pronostique du diabète sur la grossesse au cours de la mucoviscidose

Etude MUCOG : contexte

En raison de l'amélioration de l'espérance de vie des patientes atteintes de mucoviscidose et de l'amélioration globale de leur état de santé, de plus en plus de femmes ont un désir de grossesse. Le nombre de grossesses recensées dans les Registres nationaux de la mucoviscidose en Europe est en nette augmentation (3). La grossesse n'est actuellement plus considérée comme un facteur pronostic négatif pour l'évolution de la maladie, mais elle doit malgré tout rester très encadrée avec une prise en charge spécifique et très rapprochée (98).

L'avancée en âge des patientes atteintes de mucoviscidose les expose au risque de DAM. Le DAM est considéré comme un facteur de risque de dégradation dans la mucoviscidose, notamment sur plan nutritionnel ce qui peut bien sûr être problématique en cas de grossesse.

La plupart des études évaluant le risque associé aux grossesses dans la mucoviscidose, ont comparé des femmes atteintes de mucoviscidose avec et sans grossesse, sans prendre en compte les comorbidités spécifiques de la maladie comme le DAM (99,100).

L'étude MUCOG est une étude multicentrique observationnelle réalisée à partir des données du Registre français de la mucoviscidose. Il a été mis en place en 2002 par l'équipe du Registre Français, l'équipe INED (Gil Bellis) et le Pr Durieu à l'occasion de l'enquête ayant donné lieu à la première publication sur le sujet des grossesses en France (101). La quasi-totalité des grossesses des femmes atteintes de mucoviscidose suivies dans l'un des 49 CRCM français y est enregistrée.

Objectif

L'objectif de l'étude est de comparer l'évolution clinique de deux groupes de femmes avec une première grossesse menant à une naissance, identifiées diabétiques ou non avant le début de la grossesse dans le Registre français de la mucoviscidose entre 2001 et 2012. Les deux groupes sont suivis pendant quatre années consécutives à partir de l'année précédant la grossesse, jusqu'à deux années après la grossesse.

Résultat

Les femmes atteintes de DAM avant leur grossesse accouchent plus fréquemment par césarienne que les non diabétiques, mais le DAM n'impacte pas le poids de naissance des enfants, ou le caractère prématuré de la naissance. Les femmes diabétiques avant la grossesse ont une fonction pulmonaire plus basse que les non diabétiques mais l'évolution clinique (fonction respiratoire et IMC) au cours du suivi des deux groupes ne semble pas significativement différente.

Les résultats de l'étude sont produits dans l'article intitulé "**Pregnancy outcome in women with cystic fibrosis-related diabetes"**, publié en 2017 dans la revue Acta Obstetrica et Gynecologica Scandinavia.

Discussion

L'absence de différence significative sur l'évolution clinique au cours du suivi pourrait être expliquée par différents facteurs. L'encadrement du projet de grossesse et sa préparation est un élément majeur pour en limiter l'impact clinique. La prise en charge nutritionnelle rapprochée et une prise en charge agressive du diabète en cas de projet de grossesse peut aussi contribuer à l'absence de différence.

AOGS
Acta Obstetricia et Gynecologica Scandinavica

AOGS ORIGINAL RESEARCH ARTICLE

Pregnancy outcome in women with cystic fibrosis-related diabetes

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Key words
Cystic fibrosis, cystic fibrosis-related diabetes, diabetes, pre-gestational diabetes, pregnancy

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Conflict of interest
The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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Abstract

Introduction. With increasing life expectancy, more women with cystic fibrosis and diabetes mellitus become pregnant. We investigated how pre-gestational diabetes (cystic fibrosis-related diabetes) influenced pregnancy outcome and the clinical status of these women. *Material and methods.* We analyzed all pregnancies reported to the French cystic fibrosis registry between 2001 and 2012, and compared forced expiratory volume (FEV_1) and body mass index before and after pregnancy in women with and without pre-gestational diabetes having a first delivery. *Results.* A total 249 women delivered 314 infants. Among these, 189 women had a first delivery and 29 of these had pre-gestational diabetes. There was a trend towards a higher rate of assisted conception among diabetic women (53.8%) than non-diabetic women (34.5%, $p = 0.06$), and the rate of cesarean section was significantly higher in diabetic women (48% vs. 21.4%, $p = 0.005$). The rate of preterm birth and mean infant birthweight did not differ significantly between diabetic and non-diabetic women. Forced expiratory volume before pregnancy was significantly lower in the diabetic group. The decline in forced expiratory volume and body mass index following pregnancy did not differ between the women with and those without pre-gestational diabetes. *Conclusion.* Pre-gestational diabetes in women with cystic fibrosis is associated with a higher rate of cesarean section but does not seem to have a clinically significant impact on fetal growth or preterm delivery. The changes in maternal pulmonary and nutritional status following pregnancy in women with cystic fibrosis were not influenced by pre-gestational diabetes.

Abbreviations: BMI, body mass index; CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; FEV_1, forced expiratory volume in one-second.

Introduction

There have been substantial advances in care for individuals with cystic fibrosis (CF). Women with CF are now likely to survive into adulthood [the median predicted survival is around 40 years in Europe (1)] and therefore young women with CF have typical expectations for their reproductive health. The number of pregnancies in these women has consequently increased in most countries (2),

and pregnancy is no longer considered to have a negative impact on survival of CF women (3–6). Increased life expectancy has, however, also led to diabetes becoming a common complication in CF, affecting up to half of those aged 30 years and older (7). Diabetes in CF is considered a risk factor for clinical degradation and it is associated with more severe pulmonary disease, more frequent pulmonary exacerbations, and poorer nutritional status (7).

Most authors who have investigated pregnancies in CF have done so by comparing pregnant and non-pregnant CF women without taking into account known risk factors for poorer outcomes in such patients (3–6,8–11). It is also of note that CF women have an increased likelihood of receiving treatment for diabetes both during and after pregnancy (12), which could be related to the overall improvement in survival of young CF women. However, the specific risk to pregnancies and maternal health status associated with pre-pregnancy cystic fibrosis-related diabetes (CFRD) has not been established. The aim of the present study was therefore to compare pregnancy outcome and clinical decline in CF women having a first pregnancy leading to birth included in the French CF registry according to their diabetic status before pregnancy.

Material and methods

Study population and setting

A multicenter observational study was conducted using data from the French CF registry in which pregnancies in CF women attending one of the 49 French CF care centers are recorded.

We included all pregnancies registered between 1 January 2001 and 31 December 2012 irrespective of pregnancy outcome (miscarriages, induced abortion for medical reasons, voluntary interruption). Pregnancies in women who had received a pulmonary transplantation before pregnancy were excluded.

For comparison between diabetic and non-diabetic women, we analyzed only those with a first pregnancy leading to birth between 1 January 2001 and 31 December 2012, and with a two-year follow up after delivery without a second pregnancy. We considered for each woman a study period of four consecutive years starting the year before pregnancy until two years after pregnancy; the maximum observational study period was therefore the years 2000–014.

Collected data from the French CF registry

Data in the French CF registry is completed annually for each patient. Data extracted for the present study included forced expiratory volume in one-second (FEV_1) (best value of the year) and body mass index (BMI; value measured at the time of best FEV_1), assisted conception, mode of delivery (vaginal or cesarean section), and prematurity, as well as newborn birthweight and CF status. The outcome of pregnancy was defined as preterm birth in case of birth before 37 weeks' gestational age.

Outcome measures

Cystic fibrosis women were categorized according to their diabetic status before pregnancy. The outcome measures were rate of FEV_1 and BMI decline during the follow-up period. The FEV_1 and BMI values used were those annually collected in the registry. Analyses compared CF women with pre-pregnancy diabetes to CF women without pre-pregnancy diabetes.

Statistical analyses

Descriptive data are presented as median with range and number of available data. For comparisons between groups, the Chi-square or Fisher's test was used, including Wilcoxon's test for quantitative variables. Variations in the FEV_1 and BMI observed during follow up in each group were also compared. To assess the potential effect of diabetes on FEV_1 and BMI, a linear regression was used to estimate the rate of change in FEV_1 and BMI decline during the four-year period of follow up. The Wilcoxon test was used to compare the median rate of FEV1 and BMI decline. All analyses were performed using SAS software version 9.3 (SAS Institute; Cary, NC, USA). All *p*-values reported are two-tailed; values <0.05 were considered statistically significant.

Ethical approval

According to the current French legislation, demographic and clinical data were extracted from the French CF registry with permission from the institutional review board (CCTIRS, registration number 10536, 3 December 2015) and from the national data protection commission (Commission Nationale de l'Informatique et des Libertés. DR number 1202233/February 2016).

Key Message

Pre-pregnancy diabetes in women with cystic fibrosis is not associated with an increased risk of deterioration of maternal pulmonary or nutritional status.

Results

Pregnancies in the CF French registry between 2001 and 2012

Between 2001 and 2012, 294 pregnancies in 232 women were reported in the French CF Registry. There were 180 women who had one pregnancy, 42 women had two, and 10 who had three; 234 births in all. Median (range) age at pregnancy was 27 years (15–42) and 37.3% of women were homozygous for the F508del mutation, 79.8% had pancreatic insufficiency, and 3.6% received chronic enteral feeding. At initiation of the follow-up period, median (range) FEV_1 was 65.0% (18.9–131.5) and the median (range) BMI was 20.2 kg/m^2 (14.9–34.2). Of the 234 births, 62.6% of pregnancies were spontaneous, 70.3% of pregnancies ended in a term-delivery, and delivery was by cesarean section in 26.7% of cases. None of the newborns died. Median (range) weight at birth was 3000 g (650–3990). CF was diagnosed in three children. There were 16 cases of therapeutic termination, 13 cases of voluntary abortion, 29 miscarriages, and two cases for which data were not available.

Comparative analysis according to diabetic status before first pregnancy

Considering only the first pregnancies leading to birth and with a two-year follow up after delivery without a second pregnancy, 189 pregnancies were analyzed: 29 (15%) pregnancies occurred in diabetic women and 160 (85%) in non-diabetic women. Nine women received transplantation more than two years after pregnancy; among them, two were diabetic the year before pregnancy.

The main characteristics of diabetic and non-diabetic groups the year of pregnancy are described in Table 1. There was a non-significant trend towards a higher rate of assisted conception in diabetic women than non-diabetic women ($p = 0.06$). The rate of cesarean section was significantly higher in diabetic women ($p = 0.005$). There was no significant difference in the rate of premature births between the groups. Diabetic women were older ($p = 0.05$). The median FEV_1 was significantly lower in diabetic women ($p = 0.03$), and the median BMI of diabetic and non-diabetic women was not significantly different ($p = 0.55$).

FEV_1 and BMI rate of decline

There was no significant difference in the rate of FEV_1 decline over the four-year study period between diabetic women [median (range): −6.0 (−23.3 to 4.9)] and non-diabetic women [−2.03 (−61.2 to 31.0)] ($p = 0.07$; Figure 1). Median (range) FEV1 of diabetic and non-diabetic women at Y−1 was 55.0% (36.7–113.6) and 65.0% (29.3–117.3); the year of pregnancy it was 49.9% (25.6–111.1) and 66.9% (24.3–119.4), at Y+1 it was 49.3% (32.0–111.2) and 63.5 (22.1–131.4), and at Y+2 it was 45.9 (22.1–111.6) and 64.4 (13.7–128.4), respectively.

Table 1. Characteristics in the year of pregnancy for those analyzed.

	Diabetic women	Non-diabetic women	*p*
Pregnancy characteristics ($n = 189$)			
	$n = 29$	$n = 160$	
Medically assisted conception	14 (53.8%)	51 (34.5%)	0.06
Cesarean section delivery	12 (48.0%)	31 (21.4%)	0.005
Newborn characteristics ($n = 189$)			
	$n = 29$	$n = 160$	
Premature birth	10 (38.5%)	41 (28.5%)	0.31
Birthweight (g)	2950 (650–3510)	3000 (860–3990)	0.32
Dead newborns	0	0	
Characteristics of women the year of pregnancy ($n = 189$)			
	$n = 29$	$n = 160$	
Age	29.0 (19.0–41.0)	26.0 (17.0–41.0)	0.05
FEV^1	49.9 (25.6–111.1)	66.9 (24.3–119.4)	0.03
BMI	19.9 (17.0–26.7)	21.1 (13.0–37.0)	0.55

BMI, body mass index; FEV_1, forced expiratory volume in one-second (%); *p*-value, Wilcoxon, all continuous variables were expressed as median (min–max).

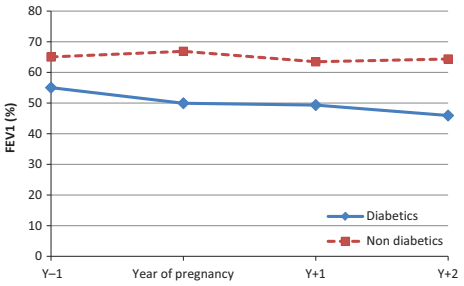

Figure 1. Median forced expiratory volume in one-second (FEV_1) according to diabetic status. Y−1: one year before pregnancy; Y+1: one year after pregnancy; Y+2: two years after pregnancy. The median (range) rate of FEV_1 decline in diabetic women was −6.03 (−23.31 to 4.94) and in non-diabetic women −2.03 (−61.18 to 30.98) ($p = 0.07$). [Color figure can be viewed at wileyonlinelibrary.com].

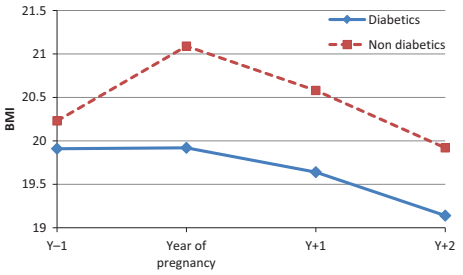

Figure 2. Median body mass index (BMI) according to diabetic status. Y−1: one year before pregnancy; Y+1: one year after pregnancy; Y+2: two years after pregnancy. The median (range) rate of BMI decline in diabetic women was −0.37 (−3.32 to 0.67) and in non–diabetic women it was 0.30 (−4.17 to 5.98) (p = 0.62). [Color figure can be viewed at wileyonlinelibrary.com].

There was also no significant difference in the change in BMI between groups over the same period [−0.37 (−3.32 to 2.67) and 0.30 (−4.17 to 5.98)] (p = 0.62; Figure 2). Median (range) BMI of diabetic and non-diabetic women at Y−1 was 19.9 (16.9–25.9) and 20.2 (15.1–34.1), the year of pregnancy it was 19.9 (17.0–26.7) and 21.1 (13.0–37.0), at Y+1 it was 19.6 (16.9–26.6) and 20.6 (14.2–34.4), and at Y+2 it was 19.1 (14.9–25.7) and 19.9 (14.2–34.4), respectively.

Discussion

The present study found that CFRD in pregnant French women was associated with higher risk of cesarean section rate and a trend in more frequent use of assisted conception techniques. There was no significant deleterious effect of CFRD on FEV_1 or BMI decline over the study period.

Herein, cesarean section delivery was more frequent among those with diabetes than those without diabetes, as has been described in diabetic women among the general population (13,14). Diabetic women had a significantly lower FEV_1 in the year of pregnancy, which might be explained by older age, but their lower FEV_1 did not seem to have a negative impact on lung function after pregnancy, although CFRD has been reported to be associated with this in the general population (7). Diabetic women did not have a poorer nutritional status, as reflected by BMI, possibly because of high treatment burden and surveillance in the case of diabetes. The absence of a higher gestational weight gain in pregnancy in the pregnant women with CFRD than in those without CFRD [19.9 (17.0–26.7) and 21.1 (13.0–37.0), p = 0.36] may be explained by higher energy expenditure related to low FEV1 in diabetic women.

More generally, the absence of a more rapid decline of pulmonary and nutritional status in diabetic women could, at least in part, be related to the early identification and aggressive treatment of diabetes, which has reduced the negative impact of CFRD on CF clinical status (15). Another explanation could be that pregnancy is now well prepared for by CF women and care providers, leading to optimal preconception care and close monitoring of pulmonary exacerbations and nutritional status according to published guidelines (16). However, as highlighted by recent studies, reproductive decision making is complex for both young women with CF and care providers, particularly concerning CF women with complicated clinical conditions such as CFRD (17,18); the data reported in the present study provide some information to help the decision making.

The study has some limitations. The most important one is that the size of the diabetic group is small, and even modest differences between the groups may have been missed, as suggested by the data on FEV_1 decline. However, the analysis considered a fairly long follow up for adult women, which was sufficient to observe a clinical impact. Inherent differences in patients who became pregnant and those who did not are likely to exist, and women with a better health status are more inclined to initiate and successfully complete a pregnancy, as demonstrated in a previous study (8). Registration of diabetes diagnosis in the French registry may have induced bias, as it included both treated and non-treated diabetes. Furthermore, the screening rate for diabetes in CF has also improved since 2001. No specific data regarding diabetes treatment or monitoring during the study period were available. It was also not possible to evaluate the medical and psychological events prior to the pregnancy that may influence patients to choose to become pregnant.

The number of CF women of childbearing age with a good health status is increasing owing to the consistent use of symptomatic CF therapies, and this number will increase further with the arrival of CFTR modulators. Much remains to be done to clarify the impact of diabetes on pregnancies in CF, but this study emphasizes the good prognosis of pregnancies in diabetic CF women. In conclusion, pre-pregnancy diabetes in CF women does not seem to be associated with an increased risk of a decline in maternal clinical status.

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2. Impact pronostique du diabète au cours de la transplantation pulmonaire

Etude MUCOTRANSPLAN : contexte

La transplantation pulmonaire est le traitement de référence de l'insuffisance respiratoire terminale chez les patients atteints de mucoviscidose (102). Le nombre annuel de transplantations pulmonaires en France pour mucoviscidose est d'environ 90. Dans le rapport annuel du Registre français de la mucoviscidose portant sur l'année 2017, 600 patients étaient porteurs d'un transplant (3). L'âge moyen au moment de la greffe est de 28,5 ans contre 58 ans environ pour les patients greffés toutes pathologies confondues. Les greffes pédiatriques sont actuellement très rares. La médiane de survie après transplantation pulmonaire dans la mucoviscidose est actuellement de 8,5 ans. Les comorbidités non respiratoires associées à la transplantation, toutes pathologies sous-jacentes confondues, et référencées dans le Registre ISHLT (Registry of the International Society for Heart and Lung Transplantation) sont : l'hypertension artérielle, le diabète, l'insuffisance rénale, la dyslipidémie, les cancers (103). Leur fréquence augmente avec la durée de survie des patients transplantés. La mucoviscidose est elle-même associée à des comorbidités non respiratoires dont la fréquence augmente avec l'âge (diabète, ostéoporose, insuffisance rénale, pathologies néoplasiques), et susceptibles de s'aggraver après transplantation (1,61,62).

Les données sur l'évolution du DAM après transplantation pulmonaire sont discordantes. En effet, certaines données suggèrent que la mucoviscidose est un facteur de risque de développement d'un diabète après la transplantation (104). D'autres données rapportent que la réduction de l'inflammation pulmonaire chronique permet l'amélioration du diabète (105).

Nous avons étudié la cohorte de patients atteint de mucoviscidose et ayant reçu une transplantation bi-pulmonaire entre 2004 et 2014 dans les centres de transplantation de Lyon et Grenoble, et suivi dans l'un des quatre CRCM de la région Rhône-Alpes.

Objectif

L'objectif de cette étude était d'estimer l'incidence du DAM après la transplantation pulmonaire chez les patients greffés, et de décrire l'évolution du DAM préexistant à la transplantation. L'impact pronostique du DAM avant la transplantation était évalué en comparant la survie après transplantation des patients diabétiques et non diabétiques avant la greffe. Compte tenu de l'impact du diabète sur la fonction rénale en population générale, nous avons également analysé son impact sur la fonction rénale post-transplantation.

Résultat

La présence d'un DAM avant la greffe semble associée à une moins bonne survie après transplantation. Les patients diabétiques avant la transplantation peuvent voir leur besoin en insuline diminuer après la transplantation et quelques patients diabétiques voient leurs statuts glycémiques se modifier en post-greffe et ne sont plus considérés comme diabétiques. Nous n'avons pas identifié d'impact du diabète sur l'évolution de la fonction rénale après la transplantation.

Les résultats de l'étude sont produits dans l'article intitulé "**Cystic fibrosis-related diabetes before lung transplantation is associated with lower survival but does not affect long-term renal function"**, publié en 2019 dans la revue Pediatric Pulmonology.

Discussion

Le diabète semble avoir un impact négatif sur la survie après la transplantation comme cela a été observé dans d'autres études auparavant, mais pas sur l'évolution de la fonction rénale en post transplantation. Cela suggère l'importance du contrôle du diabète le plus optimal possible avant et après la transplantation. La transplantation pulmonaire permet de diminuer les besoins en insuline pour la

majorité des patients, impact principalement expliquer par le meilleur contrôle de l'inflammation chronique.

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ORIGINAL ARTICLE: CYSTIC FIBROSIS—PEDIATRIC & ADULT

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Cystic fibrosis-related diabetes before lung transplantation is associated with lower survival but does not affect long-term renal function

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Abstract

Objective: To describe the prevalence of cystic fibrosis-related diabetes (CFRD) before and after lung transplantation (LT); to analyse the survival and renal function after LT according to the CFRD status before LT.

Methods: Sixty cystic fibrosis (CF) patients transplanted at the Lyon University Hospital between 2004 and 2014 were included. Genotype, pancreatic status, age at LT, survival were recorded. Glucose tolerance status, daily insulin dose requirement, glomerular filtration rate (GFR), and daily glucocorticoid (GC) dose were recorded before LT and until December 2016.

Results: The median follow-up was 5.6 (3.8-8.2) years, and nine patients died. Survival was poorest for patients with CFRD before LT compared with those without CFRD ($P = 0.03$) but was not correlated with the GFR before LT, with sex, age at LT, or CF genotype. The prevalence of CFRD was 68% at 2 years and 54% at 5 years. For persistent insulin-treated CFRD, the insulin requirement decreased (−2.1 IU/d/y; $P < 0.01$) and was correlated with the daily GC dose (+0.4 IU/d for one additional milligram, $P = 0.012$). Seven (11%) patients who had insulin-treated CFRD before LT became nondiabetic after LT, with a median time of 2 (1-4) years. After LT, the GFR decreased (−5.3 ml/min/1.73 m^2/y; $P < 0.001$) and was not correlated with the CFRD status before LT.

Conclusions: CFRD before LT is associated with poor survival after LT, which should lead to better management of diabetes. Some patients with pre-LT CFRD became nondiabetic after LT. CFRD is not associated with renal insufficiency after LT.

KEYWORDS
cystic fibrosis, cystic fibrosis-related diabetes, lung transplantation, renal function

1 | INTRODUCTION

Lung transplantation (LT) is the only option for patients with end-stage lung disease in cystic fibrosis (CF).[1] CF accounts for approximately 23% of bilateral LT recipients, and CF patients have better survival than patients receiving LT for other indications.[2] The mean age at transplantation for CF patients was 31.5 years in France in 2016,[3] and the young age of CF patients at the time of transplantation is specific to the disease. In addition to the comorbidities associated with LT, CF patients remain exposed to CF comorbidities, such as cystic fibrosis-related diabetes (CFRD).[1,4] LT may modify the natural history of CF comorbidities, but the data are lacking. For example, CF and transplantation are both associated with a risk of CFRD; however, the evolution or the development of CFRD following LT remains incompletely understood.

The main objective of our study is to describe the prevalence of CFRD before and after LT and to analyse the survival and renal function after LT according to the CFRD status before LT.

2 | PATIENTS AND METHODS

2.1 | Patients

CF patients transplanted at the Louis Pradel Hospital (Bron, France) between 2004 and 2014 were retrospectively included in the study. All CF transplanted patients were seen at least yearly by a CF physician in the Center Hospitalier Lyon Sud CF-reference center during follow-up.

Baseline characteristics before transplantation were examined in each individual: sex, CF genotype, pancreatic status, chronic *Pseudomonas aeruginosa* colonization status using the criteria proposed by Pressler et al,[5] and treatment with aminoglycoside within 5 years before LT (defined by the number of courses and the cumulative dose). All the patients were treated with once-daily intravenous infusion of aminoglycoside and sample monitoring of residual concentration after 2 days of treatment. The age at LT and the date of LT were also recorded.

The following criteria were recorded at the pretransplantation period (in the 3 months before LT), in the postoperative period (between 3 and 6 months after LT), and yearly during follow-up (closer to the anniversary date of LT), until December 2016:

- respiratory function measured by the forced expiratory volume in the first second (FEV1), expressed as the percentage of the predicted value (FEV1%)[6];
- body mass index (BMI) in kg/m^2;
- glucose tolerance status, classified in CFRD or others, defined according to international guidelines, including World Health Organization and American Medical Association criteria,[7] and determined with an annual oral glucose tolerance test (OGTT) and daily insulin dose requirement (in IU/d);
- renal function, defined by the estimated glomerular filtration rate (GFR), which was calculated with the Modification of Diet in Renal Disease (MDRD) formula.[8] Chronic kidney disease was divided into five types according to the international criteria[9];
- CF-associated liver disease (CFLD) status: cholestasis parameters (γ-glutamyl transpeptidase [GT]), liver cell parameters (aspartate aminotransferase [ASAT] and alanine aminotransferase [ALAT]), liver ultrasonography results (classified into normal or abnormal) were collected. CFLD was defined according to the criteria proposed by Colombo et al.[10]

The survival (years) and the cause of death were recorded for all patients.

2.2 | Transplantation and immunosuppression

The protocol for preoperative immunosuppression was 10 mg/kg methylprednisolone at the beginning of the surgery and two doses of basiliximab 20 mg (patients transplanted before November 2006 received methylprednisolone alone). In the immediate postoperative period, all the patients were treated with a triple drug combination of glucocorticoids, tacrolimus, and mycophenolate mofetil. The immunosuppressive regimen was recorded each year (tacrolimus and mycophenolate mofetil [MMF], tacrolimus and other immunosuppressive drug, other than tacrolimus). The daily glucocorticoid (GC) dose was also recorded.

2.3 | Legislation

All patients received oral and written information informing them of their unrestricted rights to ask for the deletion of their data. A dispensation for the consent obtained was asked for deceased patients. This study was conducted according to the legislation in place at the time of the study and in compliance with the protocol of Good Clinical Practices and principles of the Declaration of Helsinki.

2.4 | Statistical analysis

2.4.1 | Patient characteristics

Baseline characteristics were assessed by descriptive statistics. The normality assumption was verified, and continuous variables were compared using *t* tests. Categorical variables were compared using the χ^2 statistic or Fisher's exact test.

2.4.2 | Survival analysis

Survival time was calculated from the date of LT to the date of censoring or death. Overall survival was estimated using the Kaplan-Meier method. Survival curves were compared with the log-rank test. A Cox model was performed and adjusted for age, sex, CF genotype, and CFRD status before LT.

2.4.3 | Long-term analysis of comorbidities

The prevalence of each comorbidity was calculated before LT as well as 2 and 5 years after LT. The analysis of the repeated measures data (FEV1%, BMI, daily dose of insulin, and calculated GFR) was conducted by using multivariable linear mixed-effect regression models that included both fixed and random effects. The time of follow-up (annual discrete taking values from 6 months to 10 years after LT) was considered an explanatory variable for each model, which included FEV1%, BMI, daily dose of insulin, or calculated GFR as responses of interest.

Confidence intervals (CI) were calculated at 95%. For all statistical analyses, $P < 0.05$ was considered significant. Analyses were performed with R v3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) with packages "survival", "nlme", and "ggplot2" available at http//www.R-project.org.

3 | RESULTS

3.1 | Pretransplantation characteristics

Between 2004 and 2014, 63 adult CF patients were transplanted. Three of sixty-three patients (5%) died in the first 3 postoperative months; two of them were diabetic before LT. The details of the pretransplantation characteristics of the 60 patients alive 3 months after LT according to their CFRD status before LT are described in Table 1. Using the Colombo et al criteria, two patients presented with CFLD before LT. One patient had both liver and lung transplants; the other died within the first month.

3.2 | Immunosuppressive regimen

During the follow-up, 43 of 60 (72%) patients were on GC, tacrolimus, and MMF. The median (interquartile range [IQR]) daily dose of GC at 6 months was 20 (20-25) mg/d, after 1 year was 7.5 (7.5-10) mg/d, and thereafter was 5 (5-60) mg/d. MMF was switched to other immunosuppressive drugs in 16 patients: azathioprine (n = 7), everolimus (n = 5) or sirolimus (n = 4); tacrolimus was switched to cyclosporine in one patient.

3.3 | Changes in renal function

Before LT, the mean ± SD calculated GFR was 109 ± 47 ml/min/1.73 m^2 and was not significantly different according to the CFRD status ($P = 0.68$). There was no correlation between the calculated GFR before LT and the cumulative dose of aminoglycoside (tobramycin: $P = 0.57$, amikacin: $P = 0.92$, and gentamycin: $P = 0.10$) or the number of aminoglycoside courses ($P = 0.83$). After LT, the calculated GFR decreased over time, with an estimated slope of −5.3 ± 5.3 ml/min/1.73 m^2/y ($P < 0.001$; Figure 1).

The evolution of the calculated GFR over time was not significantly associated with the CFRD status before LT ($P = 0.10$),

TABLE 1 Pretransplantation characteristics of the 60 CF adult patients with long-term follow-up according to their CFRD status before LT

	Total (N = 60)	CFRD+ (N = 42)	CFRD− (N = 18)
Male, n (%)	26 (58)	17 (41)	9 (50)
Genotype, n (%)			
Homozygote F508 del	32 (53)	23 (55)	9 (50)
F508 del + other	21 (35)	14 (33)	7 (39)
Other + other	7 (11)	5 (12)	2 (11)
Age at LT, y, mean ± SD	27.6 ± 8.4	27.9 ± 7.9	26.9 ± 9.6
Date of LT, n (%)			
2004-2010	24 (40)	14 (33.3)	10 (55.6)
2010-2014	36 (60)	28 (66.7)	8 (44.4)
Pancreatic insufficiency, n (%)	60 (100)	42 (100)	18 (100)
Body mass index, kg/m^2, mean ± SD	18.2 ± 2.2	18.1 ± 2.3	18.2 ± 1.8
CFRD with insulin requirement, n (%)	36 (60)	36 (85.7)	NA
Chronic *Pseudomonas aeruginosa* colonization, n (%)	53 (88)	36 (85.7)	17 (94.4)
Minimum of GFR, ml/min/1.73 m^2, mean ± SD	109 ± 47	111 ± 52	106 ± 36
Cumulative dose of aminoglycoside			
Tobramycin, mg, mean ± SD[a]	69 260 ± 39 950	68 280 ± 42 520	72 120 ± 32 920
Gentamycin, mg, mean ± SD[a]	4760 ± 3550	3590 ± 4120	7100 (one patient)
Amikacin, mg, mean ± SD[a]	45 980 ± 43 740	54 660 ± 44 990	11 250 ± 5870
Number of aminoglycoside cure, n, mean ± SD[a]	14.7 ± 6.7	14.4 ± 6.7	15.6 ± 7.1

Abbreviations: CF, cystic fibrosis; CFRD, cystic fibrosis-related diabetes; GFR, glomerular filtration rate estimated with the Modification of Diet in Renal Disease (MDRD) formula; F508del, delta F 508 deletion; LT, lung transplantation.
[a]Within 5 years of LT.

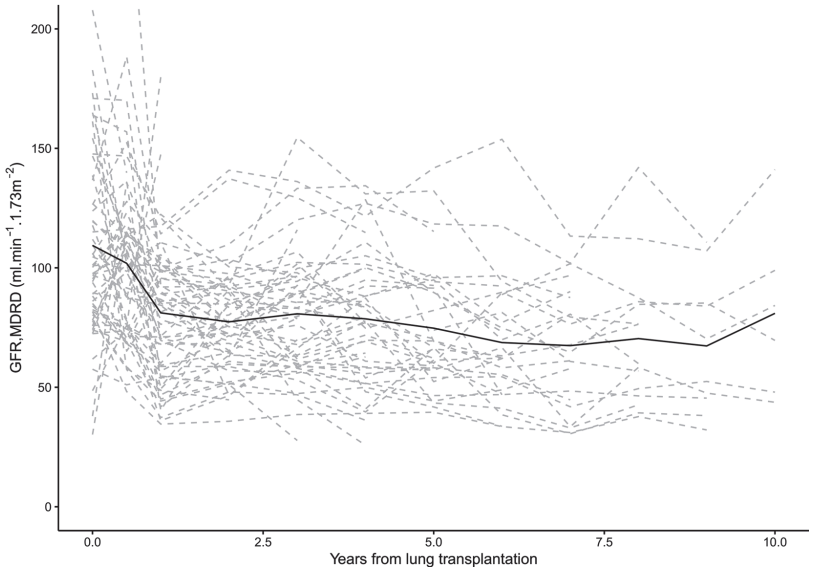

FIGURE 1 Evolution of the glomerular filtration rate (GFR) estimated with the Modification of Diet in Renal Disease (MDRD) formula (ml/min/1.73 m^2) over time after lung transplantation in adult cystic fibrosis patients. Dashed gray lines indicate individual trajectories; the solid black line indicates the mean of the considered values

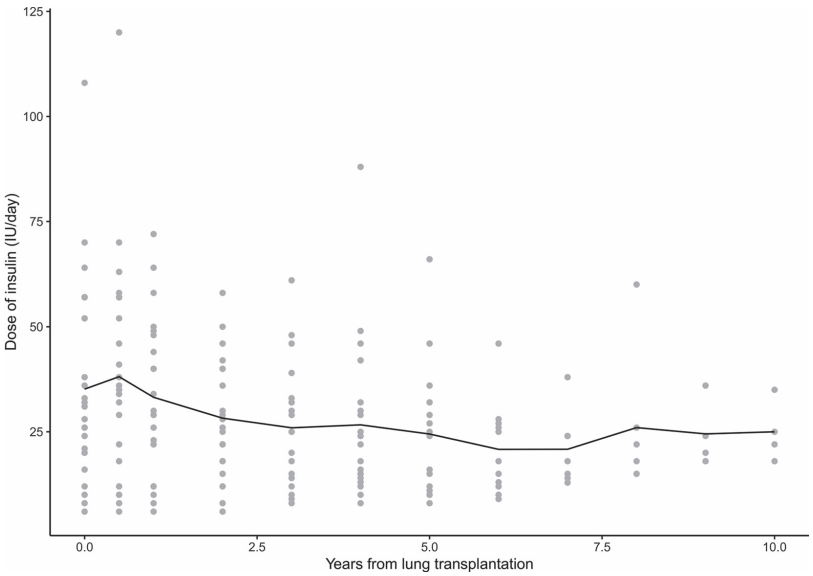

FIGURE 2 Evolution of the daily dose of insulin (IU/d) over time after lung transplantation in adult cystic fibrosis patients who had insulin-treated cystic fibrosis-related diabetes before lung transplantation (LT), which was persistent over time after LT. Gray points indicate the individual dose recorded at each year of follow-up; the black line indicates the mean daily dose of insulin

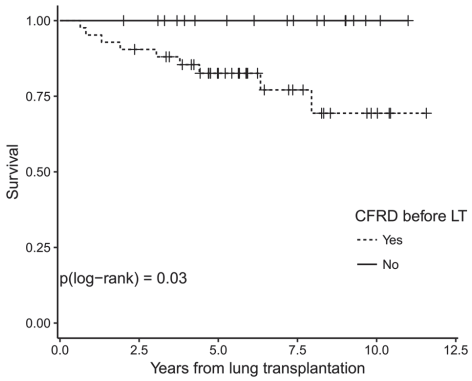

FIGURE 3 Survival of cystic fibrosis adult patients after lung transplantation represented by Kaplan-Meier curves according to their cystic fibrosis-related diabetes (CFRD) status before lung transplantation (LT)

the cumulative dose of aminoglycoside regardless of the molecule, the number of aminoglycoside courses ($P = 0.24$), or the immunosuppressive regimen categories (compared with tacrolimus and MMF, tacrolimus and other: $P = 0.88$, other: $P = 0.59$). Chronic kidney disease was diagnosed in 22 of 60 (37%) patients, and, among them, renal insufficiency was considered stage 5 in medical charts for 18 of 60 patients (30%), including one patient on a waiting list for kidney transplantation but none requiring dialysis. No patients with end-stage renal insufficiency had a calculated MDRD below 15 ml/min/1.73 m^2 during the follow-up.

3.4 | Glucose tolerance status

All patients were pancreatic insufficient. Forty-two of the sixty patients (70%) with survival greater than 3 months after LT had CFRD before LT. The prevalence of CFRD significantly decreased over time and was 68% (41 of 60) 2 years after LT and 54% (20 of 37) 5 years after LT ($P = 0.016$).

3.4.1 | Patients with insulin-treated CFRD before LT

Thirty-six of sixty patients (60%) were treated with insulin before LT (mean ± SD dose before LT = 33.3 ± 21.6 IU/d). For 27 of these patients (27 of 60, 45%), insulin treatment was maintained over time after LT. Insulin requirement transiently increased in the postoperative period and then decreased over time, with an estimated slope of −2.1 ± 2.9 IU/d/y (Figure 2, $P < 0.01$). In this group, the daily dose of insulin was positively associated with the daily GC dose (+0.4 IU/d for one additional GC milligram, $P = 0.012$). The nine of sixty (15%) other patients stopped insulin after LT at a median time of 2 (1-4) years; seven patients no longer had CFRD during follow-up (controlled by annual OGTT), one had CFRD without treatment, and one required insulin again later.

3.4.2 | Patients with nontreated CFRD before LT

Six of sixty (10%) patients had CFRD without insulin treatment before LT. Four of sixty patients (7%) needed insulin in the postoperative period (in the 6th months following LT). CFRD was persistent over time for two patients and was transient for the two patients. The fifth patient needed insulin later during the follow-up. The last patient no longer had CFRD 6 months after LT.

3.4.3 | Patients without CFRD before LT

Eighteen of sixty patients (30%) did not have CFRD before LT: 14 of 60 (23%) never developed CFRD, 2 of 60 (3%) developed insulin-treated CFRD (one in the postoperative period and one 6 years after LT), and 2 of 60 (3%) needed transient insulin therapy (one patient was treated during the first year following the LT, and one patient was treated 1 year after LT for 1 year).

3.5 | Survival and cause of death

The median (IQR) time of follow-up of the 63 patients was 5.6 (3.8-8.2) years. Six (10%) patients were followed-up at 10 years. Twelve (20%) patients died during the follow-up. Among the three patients who died in the early postoperative period, two patients died from transplantation surgery complications and one from unexplained

TABLE 2 Evolution of the characteristics after lung transplantation

	2 y (n = 57)	5 y (n = 37)	10 y (n = 6)
Estimated survival, % (95% CI)	88.9 (81.5-97.0)	83.4 (74.4-93.4)	75.6 (63.2-90.4)
FEV1%, percentage of theoretical value, mean ± SD	80.9 ± 22.0	81.4 ± 22.9	71.6 ± 30.5
Body mass index, kg/m^2, mean ± SD	20.4 ± 2.5	20.6 ± 3.2	19.4 ± 2.9
CFRD, n (%)	34 (60)	20 (54)	4 (67)
Daily dose of insulin, IU/d, mean ± SD	28.2 ± 13.9	24.5 ± 16.0	25.0 ± 7.3
GFR, ml/min/1.73 m^2, mean ± SD	77.4 ± 21.1	74.7 ± 25.6	80.9 ± 36.2

Abbreviations: CFRD, cystic fibrosis-related diabetes; CI, confidence interval; FEV1, forced expiratory volume in the first second; GFR, glomerular filtration rate.

circumstances, although an autopsy proved acute rejection 2 weeks after LT. The nine other deaths (3.4 ± 2.5 years after LT) were the result of chronic lung allograft dysfunction in six patients, malignancies (pulmonary lymphoma and non-small–cell lung carcinoma) and an unexplained respiratory failure. Four patients were retransplanted at 2 weeks as well as 1, 4, and 8 years after their first LT.

The estimated survival after LT is summarized in Table 2.

3.6 | Analysis of survival according to patient characteristics before LT

Among the 60 patients followed more than 3 months, the estimated Kaplan-Meier survival of patients with CFRD before LT was lower than that of those without CFRD ($P = 0.03$; Figures 1-3). All the patients who died during the follow-up had CFRD before LT. It was thus not possible to calculate the Cox hazard ratio (HR) of the CFRD status before LT because no deaths were reported in the group of patients without CFR D before LT. In the univariate Cox model, survival was not associated with the calculated GFR before LT ($P = 0.12$), sex ($P = 0.62$), age at LT ($P = 0.98$), or the CF genotype ($P = 0.42$ and $P = 0.60$), and the multivariate analysis was not performed.

4 | DISCUSSION

This study reports the long-term evolution of both CFRD and renal function after LT as well as survival according to pretransplantation CFRD and renal status in a cohort of French adult CF transplanted patients, with a 5-year median time of follow-up.

The 10-year survival of these patients, which was estimated to be approximately 76%, is in accordance or slightly higher than that described in registries encompassing such a long period.[2,11]

We observed a lower survival after LT in CFRD patients. Two out of the three patients who died within the first 3 months after transplantation (mostly due to surgical complications) had CFRD before LT. All the other deaths during the follow-up (nine patients) concerned CFRD patients. The negative impact of CFRD status before LT on survival has been previously described in CF, with a threefold increase in the mortality risk for patients with pre- and post-LT CFRD, which also includes those who developed CFRD after LT.[12] This finding may be explained by a high rate of pre-LT pulmonary infections in diabetic patients, which is associated with a higher rate of postoperative complications.[13] In our cohort, all the patients were pancreatic insufficient, suggesting a severe genotype for all patients and a comparable phenotype.

Most of the surviving patients experienced an improvement in CFRD symptoms with a reduction or sometimes a withdrawal of insulin, as previously described in a French multicentric retrospective study.[14] One of the key factors of decrease in insulin requirement after LT for pre-LT CFRD patients may be the improvement of insulin sensitivity related to the control of pulmonary infection and lower inflammation,[14,15] and also to the reduction of corticosteroids dosage over time. Although some studies have reported an increase in the prevalence of CFRD in the first year following LT,[16] we demonstrated an improvement in CFRD which mostly occurred after the first year in our study. In fact, we observed a decrease in the prevalence of CFRD over time after LT that has not been reported before. It may be explained by the combination of (i) a CFRD reversibility in 15% of the all patients leading to the cessation of insulin at a median time of 2 years of follow-up; and (ii) a poorer survival for CFRD patients, since all the observed deaths during follow-up concerned patients with CFRD. Nevertheless, CFRD worsened in some patients, and it is important to improve our knowledge of the predictive factors associated with CFRD progression, for example, the duration of diabetes before LT. Therefore, a combined pancreatic or pancreatic islet-LT may be an option for CFRD treatment.[17,18]

We observed an important decrease in renal function over time, as previously reported.[2,19] At the date of LT, renal function was not associated with the cumulative dose of aminoglycoside, as previously demonstrated using measured GFR[20]. Controversial results have been previously published; Al-Aloul et al[21] found a strong correlation between aminoglycoside use and the decrease in renal function, while Quon et al[22] reported no correlation between renal insufficiency and antibiotic use but between renal insufficiency and CFRD. According to our results, the decrease in renal function was not correlated with the survival, CFRD status or immunosuppressive regimen, as suggested by recently published data.[23] Therefore, several other factors may explain the decline of the renal function after LT. First, hypotension, hypoperfusion, nephrotoxic agents such as radiocontrast, sepsis, and aggressive diuresis in the perioperative period may explain this result[24] by precipitating acute kidney injury, which was associated with a fivefold increased risk for chronic renal failure in LT.[19] Second, the use of other nephrotoxic agents before LT, like vancomycin or amphotericin, may also explain the decline of renal function. It is worth noting that vancomycin, used to treat methicillin-resistant *Staphylococcus aureus* (MRSA), is an additional nephrotoxic agent especially when combined to aminoglycoside, as well as additional agents, that is, antifungals. The microbiological status about MRSA and the use of other agents than aminoglycosides were not collected for this study because their use is very infrequent in our center; further works concerning the deleterious impact of MRSA need to be considered even though it does not appear as a studied predictor of posttransplant mortality in a recent meta-analysis.[25]

It is noteworthy that the estimation of renal function using the MDRD formula was not satisfactory, and renal insufficiency was not correlated with the estimated GFR in our study. This formula led to a frequent overestimation of the GFR, as previously described.[20,26,27] The measure of the iohexol or inulin clearance should be systematic before and regularly after LT.

Our study has some limitations. The exclusion of patients who died in the early postoperative period could induce a bias in the survival analysis, but our objective was to determine the specific mortality associated with extrarespiratory comorbidities. We included a restricted number of patients who were followed in one single center, which limits the power of some statistical analyses and the ability to identify some significant associations. Nevertheless, our single-center study led to homogenous treatment and follow-up before and after LT as well as a high quality of recorded data.

In conclusion, CFRD before LT was associated with poor survival after LT in CF patients, which highlights the importance of better CFRD control in the perioperative and postoperative period after LT. Nevertheless, some patients with pre-LT CFRD were free of CFRD after LT. CFRD before LT was not associated with the onset of renal insufficiency before or after LT.

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CONFLICT OF INTERESTS

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SYNTHESE

Les travaux conduits et la discussion des résultats dans les publications ont permis d'aborder certains points.

Les troubles du métabolisme glucidique sont fluctuants au cours du temps avec une variabilité intra-individuelle importante.

Les résultats de l'étude DIAMUCO confirment la grande variabilité intra-individuelle des troubles du métabolisme glucidique au cours du temps. La prise en compte de cette variabilité permet d'identifier des trajectoires de glycémie pour chaque patient en fonction du temps. Envisager les troubles glucidiques comme un profil ou trajectoire plutôt que comme une mesure transversale peut permettre de mieux appréhender les situations associées à une dégradation clinique, afin d'être capable d'identifier des profils de patient à risque pour pouvoir adapter leur prise en charge nutritionnelle et discuter de l'introduction précoce d'un traitement. Cette variabilité remet en question le fait que le diabète soit un processus continu depuis l'état de normo-tolérant, à intolérant puis diabétique et interroge sur les multiples mécanismes responsables des troubles du métabolisme glucidique.

Les résultats de nos études sur l'impact du diabète de la mucoviscidose nuancent les résultats de la littérature.

Dans plusieurs publications, le DAM est décrit comme un facteur de mauvais pronostique responsable de la dégradation de la fonction respiratoire (47,50,106), avec même une dégradation qui précède l'identification des troubles du métabolisme glucidique (53). Le DAM est associé à de plus mauvais résultats cliniques chez les patients, se traduisant par des exacerbations pulmonaires plus fréquentes, un statut nutritionnel plus médiocre et une survie réduite (6,50,106,107). Le statut pré-diabétique avec intolérance au glucose est également décrit dans la littérature comme associé à une détérioration clinique majeure (50,108–110). L'étude DIAMUCO nuance ces résultats car les différents groupes de statut glycémique n'évoluent pas différemment sur le plan respiratoire. Le modèle statistique original de l'étude DIAMUCO avec des trajectoires de glycémie confirme ces résultats chez

l'enfant et pour la glycémie à 1 heure chez l'adulte. La seule dégradation significative de la fonction respiratoire chez l'adulte est dans le groupe de patients avec glycémie élevée et persistante à 2 heures. Dans l'étude GLYCONE, malgré une prévalence du DAM plus élevée chez les canadiens, leurs statuts cliniques respiratoires et nutritionnels étaient meilleurs que ceux des patients français. Le déclin respiratoire des patients normo-tolérants ou intolérants n'était pas différent, quel que soit le pays d'origine. La dégradation de la fonction respiratoire des canadiens au cours du suivi était moins importante que celle des français, alors qu'il y avait plus de patients diabétiques dans le groupe canadien.

Plusieurs hypothèses pourraient expliquer l'impact moins délétère du DAM observé dans nos études. Les patients adultes incluent dans les études plus anciennes, avaient un profil clinique de patients sévères, alors que les patients de notre étude plus récente pourraient avoir un profil clinique global moins sévère. Cela était déjà décrit par Moran et al à propos de la mortalité du DAM (106). Une équipe Danoise rapporte l'absence de dégradation clinique chez des patients diabétiques par rapport à des patients non diabétiques sur une cohorte suivi jusqu'en 2011 (111). Malgré l'amélioration globale de l'état nutritionnel des patients certaines différences peuvent persister : un apport calorique élevé chronique et / ou des différences d'activité physique peuvent influencer l'IMC par exemple. De plus, les différences de population de fond en matière de diabète et d'obésité, qui sont toutes deux plus importantes au Canada comparativement à la population française, pourraient également expliquer des disparités indépendamment du statut de mucoviscidose. Ces facteurs associés pourraient influés sur l'impact pronostic du DAM et sur le poids respectif des mécanismes d'insulino-résistance et d'insulinopénie.

Les valeurs de glycémie et d'insulinémie du test d'HGPO à une heure sont-elles corrélées à une dégradation clinique ?

La prise en compte isolée de la glycémie à 2 heures au cours de l'HGPO est remise en question, d'autant plus que certains patients ont des anomalies importantes des valeurs de glycémie au cours des temps précoces de l'HGPO, mais ont des valeurs à 2 heures normales et sont cependant considérés comme normo-tolérants. L'hyperglycémie à 1 heure est décrite par de nombreux auteurs comme associée à

une dégradation clinique plus importante (60,77,91,109). Les résultats de nos études nuancent cette association. L'étude DIAMUCO ne montre pas d'association entre les valeurs de glycémie à 1 heure et l'évolution de la fonction respiratoire chez des patients enfants et adultes sur trois ans. Dans l'étude GLYCONE, on ne retrouve pas d'interaction entre les valeurs de glycémie à 1 heure et la fonction respiratoire à l'inclusion à l'inclusion et pendant le suivi de quatre ans, quel que soit la fonction respiratoire de départ et le pays d'origine. Les valeurs d'insulinémie à 1 heure influencent l'IMC à l'inclusion dans la cohorte mais n'interagissent pas avec l'évolution de l'IMC au cours du suivi de quatre ans. Ces résultats remettent en question l'intérêt d'utiliser ces marqueurs (glycémie et insulinémie à 1 heure) comme prédictifs de la survenue d'un DAM et/ou d'une dégradation clinique. Malgré tout, l'étude GLYCONE retrouve à l'inclusion une tendance à avoir une fonction pulmonaire plus basse si la glycémie à 1 heure est élevée. Il est donc possible que l'impact de l'hyperglycémie à 1 heure se fasse au préalable dans l'enfance (112), mais cette possibilité n'est pas confirmée par l'étude DIAMUCO où la population pédiatrique a été étudiée.

Doit-on modifier la stratégie de dépistage du diabète en utilisant d'autres critères que le test HGPO ?

Le test HGPO est actuellement le test de référence de dépistage du diabète de la mucoviscidose mais il pose plusieurs difficultés. Les valeurs utilisées à 2 heures pour le diagnostic de DAM sont discutables, comme expliqué plus avant. D'après nos résultats, la glycémie à 1 heure n'est pas associée à une dégradation clinique et son intérêt est donc remis en cause. Il existe un besoin important de trouver une autre méthode qui permettrait non seulement d'identifier le DAM, mais également le risque d'accélération de la perte de poids et de la détérioration de la fonction pulmonaire, tout en étant plus acceptable pour les patients et les équipes de soins en comparaison de l'HGPO. Ces méthodes de dépistage alternatives doivent être validées de manière prospective par rapport au standard clinique actuel (HGPO) ainsi que par les résultats cliniques pertinents pour la mucoviscidose.

Mainguy et al. proposent un processus en deux étapes utilisant l'indice HOMA-% β (indice de fonction des cellules β du pancréas) pour identifier les patients devant être

dépistés par HGPO (84). En comparant ces indices à la CGM, les auteurs ont obtenu une sensibilité de 91% pour identifier les patients diabétiques de novo avec un indice HOMA-β% réduit. L'équipe de Montréal a observé une sensibilité de 69% de l'indice HOMA-β% (80). Pour HOMA-IR, représentant la résistance à l'insuline, la sensibilité testée dans l'équipe canadienne est intéressante (75%), mais en utilisant cette approche, la spécificité est faible, ce qui rendrait probablement cette approche inacceptable en pratique clinique (75). De plus, l'absence de standardisation de la posologie de l'insuline plasmatique empêchera l'établissement d'un seuil ayant une validité externe. Un projet est en cours sur la cohorte DIAMUCO pour évaluer les paramètres HOMA et leur intérêt dans le dépistage, en comparaison de l'HGPO.

Pour les patients atteints de mucoviscidose, plusieurs groupes de recherche ont comparé le profil glycémique de la CGM avec des excursions glycémiques au test HGPO standard (85,86,113–115). Des études prospectives sont nécessaires pour confirmer l'association entre les excursions glycémiques sur la CGM et la détérioration clinique. L'établissement de critères plus précis fondés sur la CGM pour diagnostiquer le DAM et / ou le risque de détérioration clinique accélérée nécessitera des cohortes nombreuses avec un suivi prospectif évaluant les résultats cliniquement pertinents. Un projet collaboratif avec l'équipe du Pr Rabasa-Lhoret est en réflexion sur ce sujet. Récemment, Burgess *et al*. (116) ont proposé qu'un seuil d'HbA1c plus bas (≥ 5,8%) permettrait de détecter efficacement (sensibilité de 93,8% et spécificité de 53%) les patients nécessitant une HGPO. Ces résultats contrastent avec ceux de Boudreau *et al*., (80) qui retrouvent avec une valeur seuil d'HbA1C ≥ 5,9% une sensibilité de 68,2% et une spécificité de 81,2%, considérées comme inacceptables par rapport à test HGPO classique (120 min) ou raccourci (90 min) (81). Pour avoir une sensibilité acceptable d'environ 95%, le seuil d'HbA1c devrait être réduit à 5,5%. L'utilisation d'un seuil d'HbA1c aussi faible pour le dépistage du DAM pourrait ne présenter aucun avantage pratique, car très peu d'individus pourraient être épargnés par la nécessité d'une HGPO (81).

PERSPECTIVES

A court terme

Cohorte GLYCONE

L'objectif est de poursuivre l'implémentation de la cohorte GLYCONE, pour obtenir un suivi plus long et un effectif plus important. Nous souhaitons continuer à travailler sur l'impact clinique des anomalies glucidiques, l'impact des anomalies de la glycémie et l'insulinémie à 1 heure du test HGPO en comprenant mieux les enjeux d'insulinopénie et insulino-résistance. La stratégie de dépistage du DAM doit être améliorée. Le test optimal devrait être acceptable et facile d'utilisation pour les patients et les équipes de soins mais surtout efficient c'est-à-dire capable d'identifier les situations de trouble du métabolisme glucidique associées à un risque de dégradation clinique. A partir de l'étude GLYCONE nous pourrons évaluer différentes méthodes de dépistage, notamment la CGM et les critères HOMA, en y intégrant des données d'impact clinique. Un travail sur les critères HOMA est en cours et un autre projet sur l'apport de la CGM dans le dépistage est en cours d'élaboration.

Etude MONA

Le maintien d'un état nutritionnel satisfaisant est toujours un élément clé de la prise en charge compte tenu du lien existant entre statut nutritionnel et état clinique. La plupart des publications rendent compte des données nutritionnelles chez les enfants et peu de rapports concernent le statut nutritionnel des patients adultes. Aucune étude n'a évalué l'association entre le profil nutritionnel et le statut glucidique chez des patients adultes atteints de mucoviscidose, en intégrant les données de consommation (profil nutritionnel détaillé en quantité et qualité) et de dépense énergétique (dépense énergétique de repos, composition corporelle, et activité physique). Compte tenu des modifications épidémiologiques dans la mucoviscidose et à l'interaction potentielle entre statut nutritionnel et troubles du métabolisme glucidique, l'association entre ces facteurs reste à étudier. Nous avons pour objectif de mener une étude (« MONA »), centrée sur les liens entre nutrition et trouble du métabolisme glucidique dans la mucoviscidose, qui permettra de répondre à ces questions grâce à l'utilisation de questionnaires alimentaires type FFQ et d'analyses

nutritionnelles, des paramètres cliniques et biologiques de l'HGPO, des questionnaires d'activité physique, des mesures de calorimétrie et d'impédancemétrie.

Etudier l'évolution des tests HGPO des patients traités par modulateurs de CFTR (lumacaftor + ivacaftor)

Les premiers résultats de la cohorte de patients français traités par l'association lumacaftor + ivacaftor viennent d'être publiés (117). Dans cette première publication, seule l'évolution des valeurs de l'HbA1C des patients diabétiques a été suivie, ne montrant pas d'évolution significative après l'instauration du traitement, mais les valeurs initiales étaient peu élevées. Un travail réalisé pour évaluer l'impact des modulateurs de CFTR sur les troubles du métabolisme glucidique a montré chez 40 patients au stade d'intolérance, après un an de traitement, une amélioration de leur résultat d'HGPO (Misgault B et al, en révision, Journal of Cystic Fibrosis). Un élément intéressant pour évaluer l'impact des modulateurs de CFTR sur les troubles du métabolisme glucidique serait d'étudier l'évolution des HGPO après un an de traitement par modulateur pour ceux qui ont bénéficié d'un test HGPO juste avant l'introduction du traitement et à un an du début du traitement.

A moyen terme

Implémentation de la décision médicale partagée pour le traitement par insuline dans le diabète

La compréhension de l'impact clinique des troubles du métabolisme glucidique est primordiale pour juger de la nécessité d'instaurer un traitement par insuline qui représente une charge supplémentaire de soins très lourde. Compte tenu de l'incertitude de l'impact délétère des troubles du métabolisme glucidique chez certains profils de patients, de la charge en soins déjà très lourde pour les patients, et du fardeau que représente l'initiation d'un traitement par insuline, il nous parait utile de proposer une décision médicale partagée pour le traitement par insuline, dans la situation spécifique d'un patient stable. Nous avons construit un outil d'aide à la décision spécifique au diabète selon la méthode décrite dans le Guide personnel

d'aide à la décision d'Ottawa (118). Il a été testé au sein de quatre CRCM français. Nous envisageons son déploiement et son évaluation dans les centres volontaires.

Base SNDS (Système National de Données de Santé) : consommation de soins et coût de prise en charge des patients diabétiques

Le chainage du Registre français de la mucoviscidose et de la base SNDS de l'assurance maladie que nous avons pu réaliser va permettre : d'évaluer les données renseignées dans le Registre en comparant les données concernant le diabète issues du Registre et observées dans la base SNDS, d'évaluer les coûts de prise en charge globaux des patients diabétiques non transplantés et transplantés.

A plus long terme

Changements épidémiologiques induits par les modulateurs du CFTR sur la prévalence, l'âge d'apparition du diabète, et son pronostic

Les avancées thérapeutiques récentes avec l'introduction progressive des traitements modulateurs de CFTR, vont peut-être encore modifier la prévalence et l'impact des troubles du métabolisme glucidique, comme cela semble être le cas pour l'ivacaftor (119). La possibilité d'un traitement précoce des enfants va probablement aussi encore nettement modifier l'épidémiologie et l'impact du DAM. Quelques études montrent que la restauration de la fonction CFTR permet d'améliorer les troubles du métabolisme glucidique. La compréhension des différents mécanismes de réversibilité ou de prévention de l'apparition des troubles du métabolisme glucidique est incomplète car la physiopathologie du DAM lui-même est incertaine. La question à laquelle il va falloir répondre est de savoir si l'augmentation de sécrétion d'insuline favorisée par les modulateurs du CFTR, sera suffisante pour prévenir ou traiter le DAM, ou au moins réduire les besoins en insuline des patients diabétiques (120).

Les études de suivi des essais princeps de ces nouvelles molécules permettront de répondre en partie à ces questions. L'étude des Registres nationaux qui renseignent les critères de diabète et les traitements reçus par les patients, notamment la cohorte

française ayant bénéficié du traitement associant modulateur et correcteur du CFTR sera également un moyen de répondre à ces questions dans un cadre plus proche de la réalité de terrain.

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