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Pancreatic beta-cell function dynamics in youth with *GCK*, *HNF1A*, and *KCNJ11* genes mutations during mixed meal tolerance test

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Abstract

Objective: The aims were (1) to assess beta-cell function in *GCK* diabetes patients over 2-year period; (2) to evaluate the dynamics of beta-cell function in *HNF1A* and *KCNJ11* patients after treatment optimization; using mixed meal tolerance test (MMTT) as a gold standard for non-invasive beta-cell function assessment.

Research Design and Methods: Twenty-two *GCK* diabetes patients, 22 healthy subjects, 4 patients with *HNF1A* and 2 with *KCNJ11* were recruited. Firstly, beta-cell function was compared between *GCK* patients versus controls; the dynamics of beta-cell function were assessed in *GCK* patients with two MMTTs in 2-year period. Secondly, the change of beta-cell function was evaluated in *HNF1A* and *KCNJ11* patients after successful treatment optimization in 2-year period.

Results: *GCK* diabetes patients had lower area under the curve (AUC) of C-peptide (CP), average CP and peak CP compared to controls. Also, higher levels of fasting, average, peak and AUC of glycemia during MMTT were found in *GCK* patients compared to healthy controls. No significant changes in either CP or glycemia dynamics were observed in *GCK* diabetes group comparing 1st and 2nd MMTTs. Patients with *HNF1A* and *KCNJ11* diabetes had significantly improved diabetes control 2 years after the treatment was optimized (HbA1c 7.1% vs. 5.9% [54 mmol/mol vs. 41 mmol/mol], respectively, $p = 0.028$). Higher peak CP and lower HbA1c were found during 2nd MMTT in patients with targeted treatment compared to the 1st MMTT before the treatment change.

Conclusion: In short-term perspective, *GCK* diabetes group revealed no deterioration of beta-cell function. Individualized treatment in monogenic diabetes showed improved beta-cell function.

KEYWORDS
beta-cell function, C-peptide, mixed meal tolerance test, monogenic diabetes, targeted treatment

1 | INTRODUCTION

Monogenic diabetes (MD) is a very heterogenous group of disorders from relatively benign hyperglycaemia caused by mutations in glucokinase (*GCK*) gene to syndromic diabetes with severe clinical presentation.[1–3] The most common types of MD are subtypes of maturity onset diabetes of the young (MODY) that results of pathogenic variants in the genes encoding transcription factors *HNF1A*, *HNF4A*, and *HNF1B*. Even this relatively small group of disorders can manifest in different phenotypes.[1,4] The precise molecular diagnosis could lead to targeted individualized treatment, well demonstrated in patients with neonatal *KCNJ11* diabetes successfully treated with high-dose sulfonylureas.[5]

Improved HbA1c and quality of life after successful switch from multiple daily insulin injections to oral agents in MD patients are well described by various authors.[6–8] However, there is a lack of specific data on the dynamics of their pancreatic beta-cell function after the change of treatment. Moreover, *GCK* diabetes is usually described as stable hyperglycaemia requiring no specific treatment without substantial deterioration,[9,10] but little evidence exists about the dynamics of actual beta-cell function in these patients.

The aims of this study were to evaluate pancreatic beta-cell function in patients with *GCK* diabetes within 2-year period and to assess the change of beta-cell function after treatment optimization in patients with *HNF1A* and *KCNJ11* diabetes. To accomplish these goals, we applied the mixed meal tolerance test (MMTT) as a gold standard for non-invasive assessment of pancreatic beta-cell function.

2 | RESEARCH DESIGN AND METHODS

2.1 | Design and study cohort

This study enrolled 22 patients with diagnosis of *GCK* diabetes, and their beta-cell function was compared with that of 22 healthy controls. About 63.6% ($n = 14$) of *GCK* patients agreed to undergo a second MMTT 2 years after the first one, for the evaluation of dynamics of beta-cell function.

Two MMTTs were also performed in *HNF1A* ($n = 4$) and *KCNJ11* ($n = 2$) diabetes patients before and 2 years after successful treatment optimization (switch to oral sulfonylurea agents).

Detailed research design is presented in Figure 1. This particular study group is a part of binational Lithuanian-Swiss project "Genetic Diabetes in Lithuania". The entire cohort ($n = 1209$) was represented previously.[11,12] In general, the cohort comprised of young (under the age of 25) diabetes patients. At the 1st step, 153 patients were selected for genetic analysis, after exclusion of the diagnosis of autoimmune type 1 diabetes. Forty-one patients (22 *GCK*, 8 *HNF1A*, 3 *HNF4A*, 4 *KCNJ11*, 2 *ABBC8*, 1 *INS*, and 1 *KLF11*) were confirmed with a diagnosis of genetic diabetes due to a pathogenic variant in one of known MD genes, they were in depth described previously.[11]

The control group consisted of healthy volunteers with no documented chronic disease. Volunteers were young adults aged 18–25 years (median age 21.75 years), as well as participants in the entire cohort; for bioethical reasons, subjects under the age of 18 were not included in the study as volunteers.

2.2 | Mixed meal tolerance test

MMTT was performed after a night of fasting, between 7 and 10 AM. Patients with diabetes were admitted to the in-patient Department of Endocrinology to ensure optimal glycemia (3.9–11.1 mmol/L) before the investigation, and healthy controls underwent the MMTT in the out-patient clinic. Fasting glycemia was tested before the MMTT and it did not exceed 5.6 mmol/L in any of the healthy subjects.

The portion of standard liquid meal (1 kcal/ml) was calculated based on participants' weight 6 ml/kg (maximum 360 ml). Commercially available drink BOOST® (Mead-Johnson) was used for this test. Blood samples for CP levels and glycemia were taken at nine time points: 10 min prior to the meal (t_{-10}), at the mealtime (t_0), and at 15 (t_{15}), 30 (t_{30}), 60 (t_{60}), 90 (t_{90}), 120 (t_{120}), 150 (t_{150}), and 180 min (t_{180}) after the meal. The full MMTT protocol was described previously.[12]

2.3 | Laboratory assays

Detailed methods for measuring C-peptide (CP) and plasma glucose levels have been described previously.[12] Briefly, CP levels were measured by immunoradiometric assay (IRMA), and glycemia levels were measured using the oxygen coefficient method.

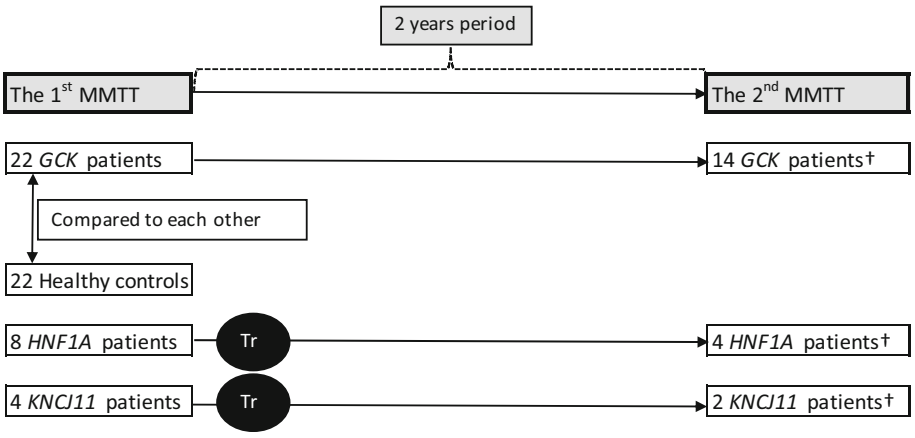


FIGURE 1 Flowchart of study design. †Number of patients who agreed to undergo the 2nd MMTT. MMTT, mixed meal tolerance test; Tr, treatment optimization attempt

2.4 | Analysis of pancreatic beta-cell function dynamics

Kinetic indices of CP: area under the curve of CP (AUC_{CP}), fasting baseline CP (CP_{Base}), peak CP level (CP_{max}), average CP concentration (CP_{Ave}), and glycemia dynamics during MMTT were evaluated in all subjects.

The parameters were compared between the *GCK* diabetes group and the control group. The dynamics of beta-cell function were assessed in 14 *GCK* diabetes patients, who agreed to undergo both MMTTs over a 2-years break.

A treatment optimization trial was performed for all patients with *HNF1A* ($n = 8$), *HNF4A* ($n = 3$), *KCNJ11* ($n = 4$), and *ABCC8* ($n = 2$) after the first MMTT across the entire project cohort. Six patients with *HNF1A* and three patients with *KCNJ11* were successfully switched from insulin injections to oral sulfonylureas, described previously.[12] Of these, four patients with *HNF1A* and two with *KCNJ11* diabetes agreed to undergo a second MMTT and were included in this analysis. None of the patients from "unsuccessful" switch agreed to undergo the 2nd MMTT.

2.5 | Statistical analysis

Statistical analysis was performed using SPSS software version 23.0. The median with lowest and the highest values in parentheses are used to represent the data, unless stated otherwise. The Mann–Whitney *U* test was used to compare *GCK* diabetes and control groups, and the Wilcoxon Signed Rank test was used to compare dynamics of beta-cell function during both MMTTs in the same MD group. A *p*-value <0.05 was considered statistically significant, all tests were two-tailed, unless stated otherwise.

2.6 | Bioethics

The research project received regional and national ethical approvals (No. BE-2-5). All patients were included in the study after they and/or their parents or official guardians gave an informed consent. The study was conducted in accordance with the Declaration of Helsinki.

TABLE 1 General characteristics of *GCK* diabetes group and healthy controls

		GCK ($n = 22$)	Controls ($n = 22$)	*p*-value
Females, % (*n*)		59.1 (13)	72.7 (16)	0.34
BMI, % (*n*)	Normal	77.3 (17)	86.4 (19)	0.35
	Overweight	13.6 (3)	13.6 (3)	
	Underweight	9.1 (2)	0	
Age at MMTT, months		164 (35; 291)	261 (231; 279)	<0.01
Duration of diabetes, months		44 (9; 146)	NA	NA
HbA1c, %		6.2 (5.4; 6.7)	NA	NA
HbA1c, mmol/mol		44.3 (35.5; 49.7)		

Note: Data presented as median (min; max), unless stated otherwise.
Abbreviations: BMI, body mass index; HbA1c, glycosylated hemoglobin; MMTT, mixed meal tolerance test; NA, not appropriate.

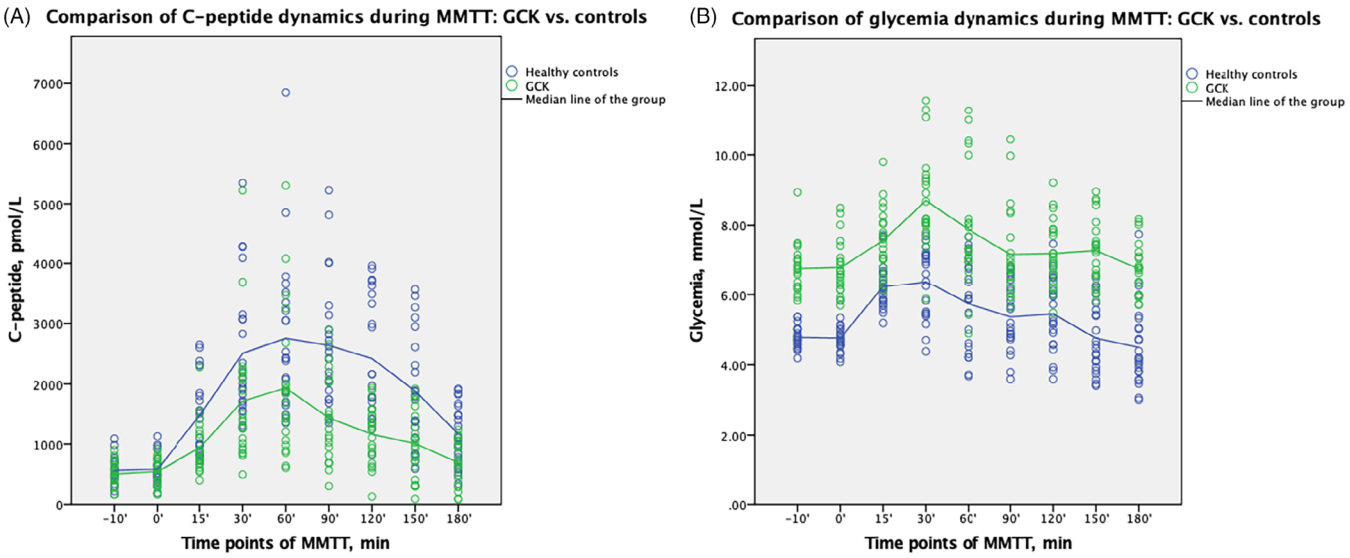


FIGURE 2 Comparison of (A) C-peptide dynamics and (B) glycemia dynamics during MMTT: *GCK* (green) versus controls (blue)

3 | RESULTS

3.1 | General characteristics of GCK patients and control group

All clinical characteristics comparing *GCK* diabetes group and healthy controls are presented in Table 1. Patients in *GCK* diabetes group were significantly younger, therefore, all subsequent comparisons between *GCK* diabetes and control groups were age-adjusted. No specific treatment was given to any of the patients with *GCK* diabetes. There were no other identified conditions that could influence glucose metabolism in the control group.

3.2 | Beta-cell function in GCK patients versus control group

The dynamics of CP and glycemia during MMTT in *GCK* group versus control group are presented in Figure 2. The Mann–Whitney *U* test showed significantly lower CP indices in *GCK* group versus controls, comparing median of AUC_{CP} 246435 versus 343,475 pmol/L/180 min, $p < 0.001$; CP_{max} 1963 (162; 913) versus 2935 (1430; 6850) pmol/L, $p = 0.012$, and CP_{Ave} 1102 (352; 2250) versus 1554 (1082; 3202) pmol/L, $p = 0.001$, and significant differences comparing glycemia indices, all data are provided in Table 2.

3.3 | Dynamics of beta-cell function in GCK patients

The median age at the 1st MMTT was 164 (35; 219) months, at the 2nd MMTT—187 (58; 245) months in *GCK* diabetes group ($n = 14$) with both MMTTs. The median of time interval between MMTTs was 24 (22; 26) months. No difference in HbA1c before the 1st and 2nd MMTTs was found, 6.2% (5.4; 6.7) versus 6.3% (5.6; 6.5), respectively, $p = 0.723$. The Wilcoxon test revealed that there were no statistically significant changes either in CP or in glycemia kinetics, the data is presented in Supplementary Table 1.

TABLE 2 Comparison of C-peptide and glycemia kinetics between *GCK* diabetes and control groups

	GCK ($n = 22$)	Controls ($n = 22$)	*p*-value*
AUC_{CP}, pmol/L/180 min	246,435 (69,615; 470,240)	343,475 (234,225; 729,925)	<0.001
CP_{Base}, pmol/L	601 (162; 913)	510 (190; 1130)	0.851
CP_{max}, pmol/L	1963 (854; 5307)	2935 (1430; 6850)	0.012
CP_{Ave}, pmol/L	1102 (352; 2250)	1554 (1082; 3202)	0.001
$AUC_{Glycemia}$, mmol/L/180 min	1345 (1209; 1718)	1002 (793; 1375)	<0.001
Fasting glycemia, mmol/L	6.6 (5.7; 8.5)	4.7 (4.1; 5.5)	<0.001
Max glycemia, mmol/L	8.2 (7.6; 11.6)	6.9 (5.5; 7.7)	<0.001

Note: Data presented as median (min; max).
Abbreviations: AUC, area under the curve; CP, C-peptide; CP_{Base}, the baseline C-peptide; CP_{max}, the highest value of C-peptide; CP_{Ave}, the average level of C-peptide.
*Data was age-adjusted.

TABLE 3 General characteristics of *HNF1A* and *KCNJ11* patients

Affected gene	Subject ID and mutation	Gender	Age at diabetes diagnosis (months)	Age at molecular diabetes diagnosis and 1st MMTT (months)	Treatment at the time of 1st MMTT	Dose (U/kg/d)	Age at 2nd MMTT (months)	Targeted treatment (Dose, mg/d)
HNF1A	Subject A (c.814C>T (p.Arg272Cys))	M	178	182	Insulin	0.24	206	Gliclazide (60)
	Subject B (c.347C>T (p.Ala116Val))	F	234	246	Insulin	0.6	274	Gliclazide (60)
	Subject C (c.872 dup (Gly292Argfs*25))	F	186	285	Insulin	0.6	309	Gliclazide (30)
	Subject D (c.872 dup (Gly292Argfs*25)	M	210	235	Diet	–	264	Gliclazide (30)
KCNJ11	Subject E (c.149G>A (p.Arg50Gln))	M	5	183	Insulin	1.1	211	Glibenclamide (30)
	Subject F (c.602G>A (p.Arg201His))	F	5	288	Insulin	1.1	305	Gliclazide (180)

Note: Data presented as median (min; max).
Abbreviations: F, female; M, male; MMTT, mixed meal tolerance test.

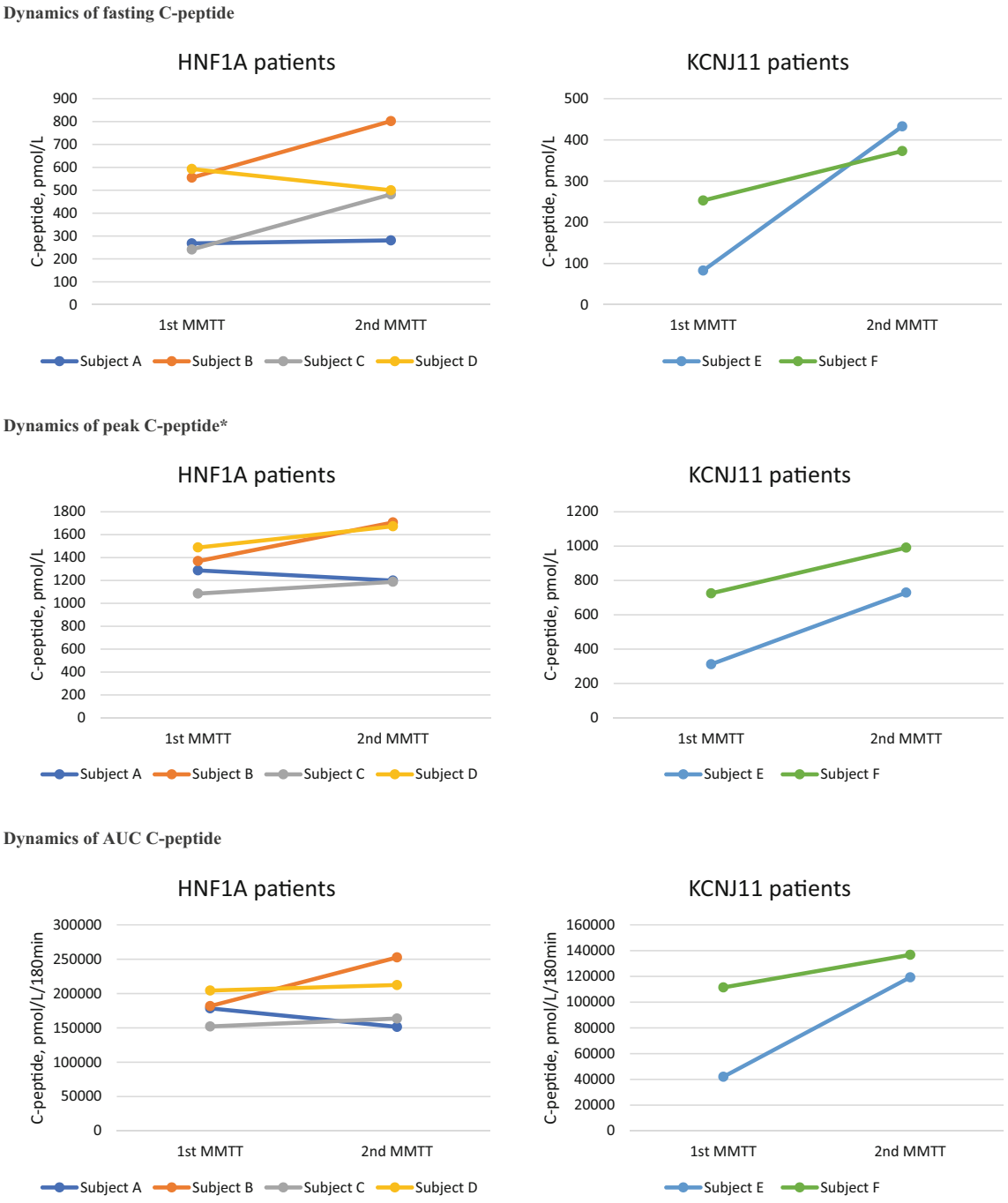


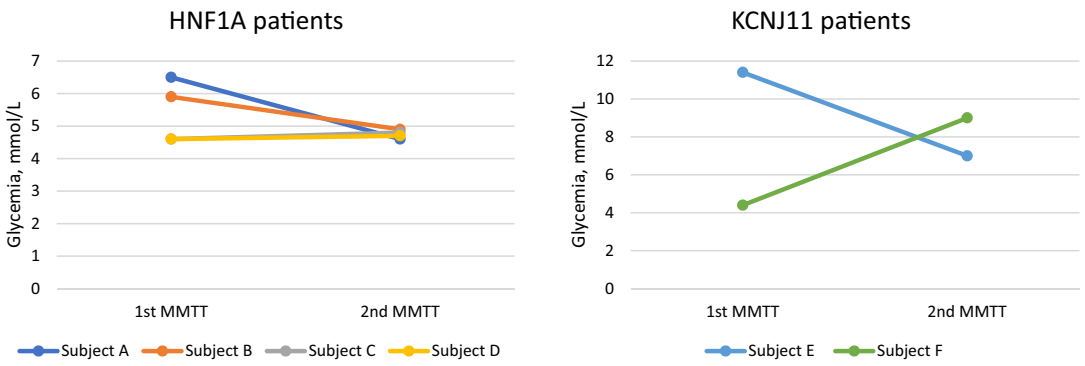
FIGURE 3 Dynamics of C-peptide and glycemia indices in MD patients with successful treatment optimization. *Significant difference in the treatment switch groups using Wilcoxon Signed Rank test for repeated measurements ($p < 0.05$). AUC, area under the curve; HbA1c, glycosylated hemoglobin; MMTT, mixed meal tolerance test.

3.4 | Dynamics of beta-cell function in MD patients with treatment switch

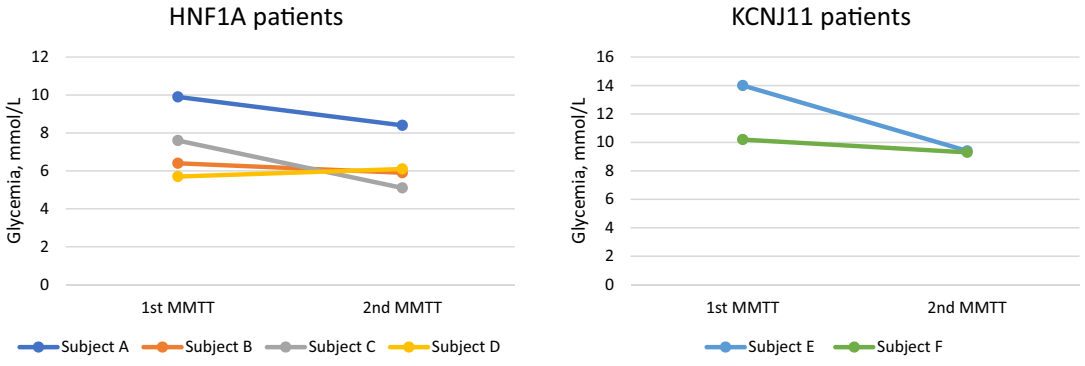
General characteristics of four *HNF1A* and two *KCNJ11* patients are presented in Table 3, none of the patients were related.

Wilcoxon Signed Rank test for repeated measurements before and after the treatment switch (in 4 *HNF1A* and 2 *KCNJ11* patients) showed that the average glycemia was lower 7.3 mmol/L versus 8.8 mmol/L ($p = 0.046$), HbA1c was better 5.9% (41 mmol/mol) versus 7.1% (54.1 mmol/mol) ($p = 0.028$), and CP_{max} was slightly higher 1193 (729; 1707) versus 1186 (312; 1488) pmol/L, $p = 0.046$, after successful optimization of treatment. Comparisons of the data from the 1st and 2nd MMTTs for each subject, separately for *HNF1A* and *KCNJ11* patients, are presented in Figure 3 with Spagetti plots.

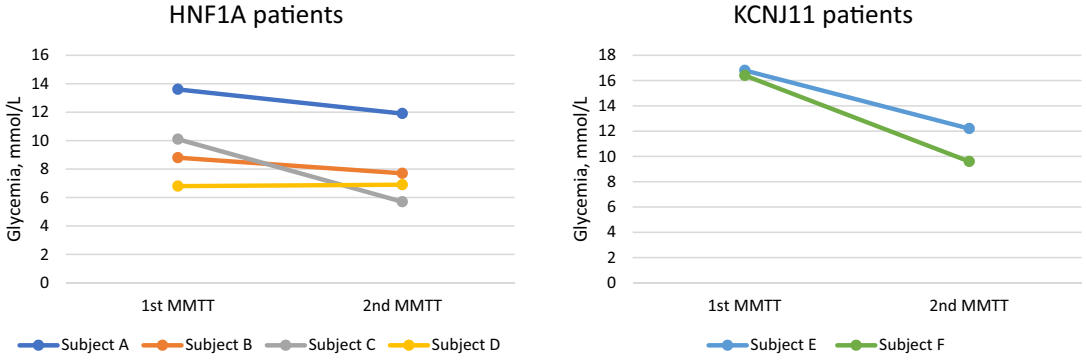
Dynamics of fasting glycemia



Dynamics of average glycemia*



Dynamics of peak glycemia



Dynamics of HbA1c*

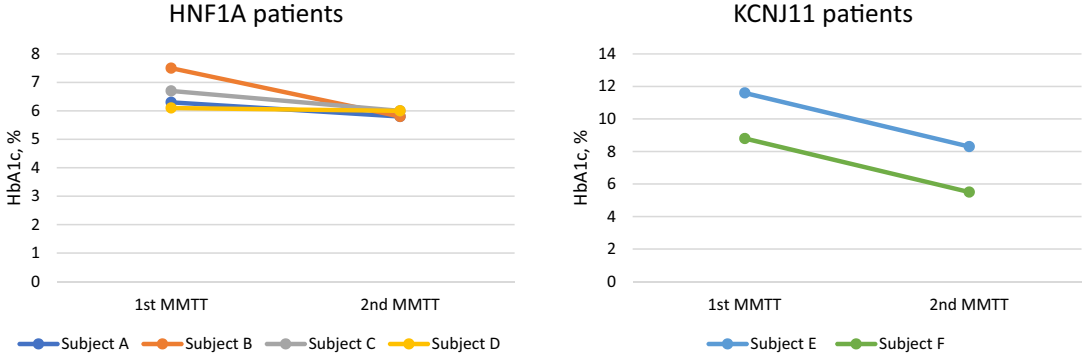


FIGURE 3 (Continued)

4 | DISCUSSION

This study presents relevant data about pancreatic beta-cell function in patients with *GCK* diabetes and patients with *HNF1A* and *KCNJ11* diabetes after successful treatment optimization. *GCK* diabetes is considered to be a distinct type of genetically caused beta-cell disorders, as it presents with stable hyperglycaemia throughout life, the prevalence of vascular complications being similar to general population, and most importantly it does not need any treatment, except specific cases in pregnancy, depending on the fetal status.[9,13–15] However, *HNF1A* and *KCNJ11* manifest with different clinical presentations from biochemical hyperglycaemia to severe diabetic ketoacidosis especially in neonates with *KCNJ11* mutations.[6,13] Right molecular diagnosis guides to targeted individualized treatment in these patients, which not only improves the quality of life, but also diabetes control and HbA1c[16,17]; however, there is still a gap in evidence about the real dynamics of pancreatic-beta cell function after treatment switch.

MMTT as a gold standard for non-invasive beta-cell function assessment revealed the kinetics of CP and glycemia in *GCK* patients; it confirmed the common phenotype: mild hyperglycaemia, often reported up to maximum of 8–9 mmol/L, with an increase up to 3 mmol/L after 2-h glucose load.[2,8,9] However, our study showed not only glycemia dynamics, but also CP dynamics during MMTT which is superior to oral glucose tolerance test as stimulation of insulin secretion is closer to the physiological process of real-life nutrition.[10,18] Our analysis showed significant differences between *GCK* diabetic patients and healthy subjects, particularly in AUC_{CP}, CP_{max}, CP_{Ave}, fasting, peak, and average glycemia indices. Overall, healthy control group showed better pancreatic beta-cell response during MMTT than *GCK* patients, suggesting a possible rationale for further follow-up of these patients regardless of the absence of significant glycemic fluctuations and necessity of immediate treatment.

Our study did not demonstrate any significant deterioration of beta-cell function in relatively short period of time in *GCK* patients. However, cross-sectional study of 99 patients with *GCK* diabetes in the United Kingdom (UK) showed slight increase in glycemia with age, with a slope of 0.17% per year, although it was concluded by glycemia and HbA1c changes without performing MMTT. We believe that these results differ from ours because of relatively young cohort (median age 13.7 years) in our study versus older UK's cohort with median age of 48.6 years.[19] Although HbA1c was slightly higher in their cohort versus ours (6.9% vs. 6.2%, respectively), the fasting glycemia levels were very similar 6.5 mmol/L (7; 7.5) versus 6.6 mmol/L (5.7; 8.5), respectively. These findings prove that stable hyperglycaemia is one of the major characteristics of *GCK* diabetes throughout the life.

Various authors have presented improved diabetes control in *HNF1A* and *KCNJ11* patients after successful transfer to sulfonylureas,[6,7,17] this analysis confirms previous findings. Our patients reached HbA1c 5.9% after switch to sulfonylureas versus 7.1% while on insulin injections. *HNF1A* diabetes is described as progressive beta-cell dysfunction[20] and successful treatment switch in *KCNJ11* patients mainly depends on mutation and duration of diabetes.[17] Some of our patients had long standing diabetes and were treated with multiple insulin injections until molecular diabetes diagnosis and treatment switch, for example, Subject C more than 8 years with *HNF1A* mutation (c.872 dup (Gly292Argfs*25)), Subject E almost 15 years and Subject F more than 23 years with *KCNJ11* neonatal diabetes. Nevertheless, our MMTT analysis in 2 years after treatment switch showed better CP_{max}, lower average glycemia, decreased glycemia variations and tendencies to have higher fasting CP and average CP, emphasizing the advantages of genetic analysis and targeted treatment plan for these patients.

The main limitation of this study is small sample size, especially in *HNF1A* and *KCNJ11* group. The main strength of the study is the assessment of beta-cell function with MMTT which is considered as the gold standard. However, MMTT procedure requires a lot of time and energy from medical staff and patients determination to perform MMTT more than once. Therefore, we believe that international cooperation would be important to increase the sample size and achieve more reliable results in the future.

To conclude, this study showed that, compared to healthy subjects, patients with *GCK* diabetes have decreased beta-cell function, with no deterioration in the short-term perspective. Patients with *HNF1A* and *KCNJ11* benefit from treatment switch from multiple insulin injections to targeted treatment with oral sulfonylureas, as shown by improved beta-cell function during MMTT after the change of treatment.

AUTHOR CONTRIBUTIONS

Ingrida Stankute participated in subjects' enrolment, data collection, database creation, carried out statistical analyses and wrote the manuscript, takes responsibility for the integrity of the data and the accuracy of the data analysis. Rimante Dobrovolskiene coordinated pediatric patient's data collection. Evalda Danyte coordinated adult patients' enrolment and data collection. Rasa Steponaviciute performed C-peptide and glycemia lab analysis. Valerie M. Schwitzgebel participated in the conception and design of the study, edited and revised the manuscript. Rasa Verkauskiene participated in the conception, design and coordination of the study, reviewed the manuscript.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

PRIOR PRESENTATION

Abstract "Evaluation of β-cell Function in Young MODY Patients Using a Mixed Meal Tolerance Test" was presented at 58th Annual European Society for Pediatric Endocrinology (ESPE) Meeting: 19–21 September, 2019, Vienna, Austria.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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