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Supplementary appendix

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Physiological Tests Repeated After 10 Years (n=6 patients)*Oral Glucose Tolerance Test*

Following an overnight fast and basal sampling, 1.75 g per kg oral glucose (maximum 75 g) was ingested over 2 minutes at time 0 and plasma was collected at 0, 30, 60, 90, and 120 minutes for assay of glucose, insulin, and C-peptide. Sulfonylurea was taken as normal in the morning the day of the plasma collection.

Intravenous Glucose Tolerance Test

Following an overnight fast and basal sampling, 0.3 g per kg glucose was given over 1 minute and plasma was collected at -10, -4, 0, 1, 3, 5, 7, 10, 20, and 60 minutes for glucose, insulin and C-peptide assay. Sulfonylurea was taken as normal in the morning the day of the plasma collection. Increment was calculated as a delta value for each timepoint.

Laboratory Assays

Venous blood was obtained for centralised assays. Serum glucose and insulin were obtained before and after the glucose load. The Laboratory Clinic at Haukeland University Hospital, Norway, performed assays for HbA_{1c} with values aligned with those in the Diabetes Control and Complications Trial (DCCT) according to its standard procedures.

Link To Online Study Protocol

<https://www.clinicaltrials.gov/ct2/show/NCT02624817?term=NCT02624817&rank=1>

| Table S1. Characteristics of Whole Cohort vs. Patients Eligible but Not Followed Up. | | | |
|---|--|--|----------------------------|
| Characteristic | All Patients (N=65-81)* | Patients Eligible but Not Included (N=3-8)* | P Value[§] |
| KCNJ11 mutation | 35 ArgR201His, 19 Val59Met, 11 ArgR201Cys, 2 Gly53AspD, 2 His46TyrY, 2 LysK170ArgR, GluE51Ala, PheF33Ile, PheF35Val, Gly53ArgR, Gly53Ser, LysK170AsnN, LysK170Thr, ArgR201Leu, ArgR50Pro, Val59Ala | 2 ArgR201His, 2 unknown, GluE22LysK, Gly53AspD, RArg201Cys, RArg50GlnQ | N/A |
| Age at initiation of sulfonylurea treatment (years), median(IQR) | 4.8 (1.7-11.4) (n=81) | 15.0 (7.0-18.0) (n=8) | 0.04 |
| Age at diagnosis (weeks), median(IQR) | 8.0 (4.0-12.0) (n=74) | 0 (0-4.5) (n=8) | 0.002 |
| Male sex - % (number) | 57 (46/81) | 50 (4/8) | 0.70 |
| Birthweight (g) | 2715 (2480 – 3050) (n=78) | 2638 (2315-2875) (n=8) | 0.36 |
| Pre-sulfonylurea BMI SDS | 0.18 (-0.28 – 0.84) (n=65) | 0.51 (-0.83-1.91) (n=6) | 0.63 |
| Pre-sulfonylurea HbA1c (%), median(IQR) | 8.2 (7.2-9.2) (n=76) | 8.1 (7.4-8.3) (n=6) | 0.70 |
| Pre-sulfonylurea HbA1c (mmol/mol), median (IQR) | 66.1 (55.2-77) (n=76) | 65 (57.4-67.2) (n=6) | 0.70 |
| Year 1 HbA1c (%), median(IQR) | 5.9 (5.5-6.5) (n=71) | 6.2 (6.2-7.3) (n=5) | 0.07 |
| Year 1 HbA1c (mmol/mol), median (IQR) | 41 (36.6-47.5) (n=71) | 44.3 (44.3-56.3) (n=5) | 0.07 |
| Pre-sulfonylurea insulin dose (units/kg), median(IQR) | 0.69 (0.59-0.94) (n=71) | 0.68 (0.52-0.78) (n=8) | 0.63 |
| Year 1 sulfonylurea dose (mg/kg/day) | 0.30 (0.14-0.53) (n=73) | 0.53 (0.10-0.59) (n=5) | 0.96 |

*N is different for each variable due to missing data. Year 1 values are those closest to the anniversary of the sulfonylurea transfer and had to fall between 3 months and 2 years for inclusion.

[§]Mann-Whitney test was used for numerical data, and 2 sample test of proportions for categorical data.

Abbreviations: BMI, body mass index; IQR, interquartile range; N/A, not applicable; SDS, standard deviation score.

| Case | 1 | 2 | 3 | 4 | 5 | 6 | Median |
|---|------------|------------|---------------------|------------|----------|------------|---------------|
| Current age | 21 | 13 | 21 | 26 | 16 | 17 | 19 |
| Age at sulfonylurea transfer (years) | 10 | 3.2 | 10.5 | 14.3 | 4.7 | 4.8 | 7.4 |
| Age at which insulin re-introduced (years) | 15.3 | 12.6 | 18.3 | 22.5 | n/a | 12 | 15.3 |
| Birth weight (g) | 2551 | 2750 | 2450 | 3160 | 2710 | 3120 | 2730 |
| Mutation | ArgR201Cys | RArg201His | ArgR201His | ArgR201His | Val59Met | ArgR201His | N/A |
| Duration of follow-up (years) | 7.3 | 9.7 | 10.6 | 11.2 | 10.8 | 11.7 | 10.7 |
| Duration when insulin re-introduced (years) | 5.3 | 9.4 | 7.9 | 8.2 | n/a | 7.2 | 7.9 |
| Most recent sulfonylurea dose (mg/kg/day) | 0.43 | 0.42 | 0.23 | 0.31 | 0.21 | 0.19 | 0.27 |
| HbA1c when insulin re-introduced (%) | 9.2 | 8.1 | 11.4 | 7.7 | n/a | n/a | 8.7 |
| HbA1c when insulin re-introduced (mmol/mol) | 77 | 65 | 101.1 | 60.7 | n/a | n/a | 71.6 |
| Most recent HbA1c on insulin (%) | 8.8 | n/a | 12.9 | 8.2 | 10.2 | 7.7 | 8.5 |
| Most recent HbA1c on insulin (mmol/mol) | 72.7 | n/a | 117.5 | 66.1 | 88 | 60.7 | 69.4 |
| Insulin name | Detemir | Glargine | Lispro and Glargine | Detemir | Detemir | Glargine | N/A |
| Most recent insulin dose (units/day) | 26 | 31 | 21 | 8 | 91 | 12 | 23.5 |
| Most recent insulin dose (units/kg/day) | 0.45 | 0.75 | 0.32 | 0.13 | 1.89 | 0.22 | 0.38 |
| Adherence* issues noted by clinician | No | Yes | Yes | No | No | No | N/A |

*Adherence was not formally measured as part of the study, however 2 clinicians specifically reported poor adherence at some point during the follow up period. Abbreviations: N/A, not applicable; n/a, not available.

| Table S3. Characteristics of Patients With and Without Microvascular Complications. | | | |
|--|---|--|----------------------------|
| Clinical Characteristic | Without Complications (N=59-74)* | With Complications (N=6-7)* | P Value[§] |
| Age at sulfonylurea transfer (years) | 4.1 (1.3-10.2) (n=74) | 20.5(10.5-24.0) (n=7) | 5x10 ⁻⁴ |
| Pre-sulfonylurea insulin dose (units/kg/day) | 0.68 (0.57-0.94) (n=64) | 0.82 (0.60-1.16) (n=7) | 0.52 |
| Pre-sulfonylurea HbA1c (%) | 8.0(7.1-9.1) (n=69) | 8.7(7.4-9.6) (n=7) | 0.28 |
| Pre-sulfonylurea HbA1c (mmol/mol) | 63.9(54.1-76) (n=69) | 71.6(57.4-81.4) (n=7) | 0.28 |
| Most recent HbA1c (%) | 6.3(5.9-7.3) (n=73) | 6.5(6.3-8.5) (n=7) | 0.16 |
| Most recent HbA1c (mmol/mol) | 45.4(41-56.3) (n=73) | 47.5(45.4-69.4) (n=7) | 0.16 |
| Pre-sulfonylurea BMI SDS | 0.25(-0.32-0.89) (n=59) | 0.17(0.02-0.24) (n=6) | 0.63 |
| Most recent BMI SDS | -0.24(-1.1-0.42) (n=71) | -0.24(-0.75-1.63) (n=7) | 0.45 |

*N is different for each variable due to missing data. Complications were retinopathy (5 of 7), microalbuminuria (2 of 7), proteinuria (1 of 7), and neuropathy (1 of 7).

[§]Mann-Whitney test was used for numerical data

Abbreviations: BMI, body mass index; SDS, standard deviation score.

| Characteristic | Neurological features identified before transfer to sulfonylureas (n=38) | | Neurological features identified after transfer to sulfonylureas (n=15) | No neurological features identified (n=28) |
|---|--|-----------------------------|---|--|
| Mutation in <i>KCNJ11</i> gene | 19 Val59Met, 7 RArg201His, 3 RArg201Cys, 2 Gly53AspD, 2 RArg50Pro, Gly53ArgR, Gly53Ser, GluE51Ala, His46TyrY, Val59Ala | | 6 ArgR201His, 4 RArg201Cys, Phe33Ile, PheE35Val, His46TyrY, LysK170NAsn, RArg201Leu | 21 ArgR201His, 4 RArg201Cys, 2 KLys170ArgR, KLys170Thr |
| Age at sulfonylurea initiation (years), median(IQR) | 6.1 (1.3-12.1) | | 2.1 (0.4-8.9) | 6.1 (2.8-12.5) |
| Current age (years), median(IQR) | 18.0 (14.0-23.0) | | 14.0 (12.0-20.0) | 19.0 (15.0-24.5) |
| Male sex - % (number) | 55 (21/38) | | 60 (9/15) | 57 (16/28) |
| Most recent sulfonylurea dose (mg/kg/day), median(IQR) | 0.27 (0.12-0.50) | | 0.26 (0.14-0.36) | 0.20 (0.13-0.38) |
| <i>KCNJ11</i> associated neurological features | Pre SU transfer (n) | Post SU transfer (n) | Post transfer only (n) | N/A |
| Developmental delay (delayed developmental milestones) | 29 | 26 | 0 | |
| Epilepsy | 10 | 11 | 1 | |
| Muscle weakness | 10 | 10 | 0 | |
| Other* | 12 | 7 | 0 | |
| <i>KCNJ11</i> associated psychiatric/neuropsychological features | | | | N/A |
| Learning difficulties | 18 | 30 | 14 | |
| ADHD | 4 | 12 | 5 | |
| Autism | 2 | 6 | 1 | |
| Anxiety | 2 | 10 | 4 | |
| Sleep problems | 2 | 3 | 2 | |
| Other** | 5 | 2 | 0 | |
| Ketoacidosis related cerebral oedema associated CNS features | | | | N/A |
| Spastic tetraplegia | 3 | 3 | 0 | |
| Spastic hemiplegia | 1 | 1 | 0 | |

* Other features reported pre-transfer were hypotonia (5), cerebellar signs (5), gross/fine motor problems (2), myoclonic jerks (2), ptosis (1), tics (Tourette's) (1). Other features reported post transfer were hypotonia (1), cerebellar signs (2), gross/fine motor problems (2), ptosis (1), tics (Tourette's) (1).

**Other features reported pre-transfer attention or concentration deficits/hyperkinesia (5). Other features reported post-transfer attention or concentration deficits/hyperkinesia (2).

Abbreviations: ADHD, attention, deficit hyperactivity disorder; CNS, cerebral nervous system; IQR, interquartile range; N/A, not applicable; SU, sulfonylurea

