Optimal glycaemic control and a low rate of micro and macrovascular complications in patients with HNF1A-MODY treated in a dedicated tertiary referral centre.

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Introduction:

MODY refers to Maturity Onset Diabetes of the Young, an autosomal dominant form of diabetes affecting beta-cell function. Mutations in multiple genes are known to cause MODY. The most common MODY subtype in European countries, including Ireland, is HNF1A-MODY, caused by heterozygous mutations in the *HNF1A* gene encoding the transcription factor hepatocyte nuclear factor 1 alpha [1-3]. There are a limited number of studies in the literature determining the response to sulphonylureas in individuals with HNF1A-MODY [4,5]. There is also very limited literature available as to both the micro-and macrovascular complications associated with HNF1A-MODY [6-8].

Aims:

A principal aim of the study was to determine the success of sulphonylurea therapy in this group. A further aim was to assess the prevalence and severity of micro-and macrovascular complications in this cohort over an extended period compared to a cohort of participants with Type 1 DM.

Methods:

A total of 60 participants from 19 families with a confirmed genetic diagnosis of a *HNF1A* mutation were identified as part of the MODY screening study in the Mater Misericordiae University Hospital. All participants in the type 1 DM cohort (recruited from the same centre), were Caucasian and matched for BMI, duration of diabetes and age to the HNF1A-MODY cohort. All subjects were phenotyped, additional samples were drawn for the cardiovascular biomarkers sCD36/hs CRP. Retinal screening occurred on an annual basis. Detailed clinical follow up of the HNF1A-MODY cohort occurred on a bi-annual basis for 84 months.

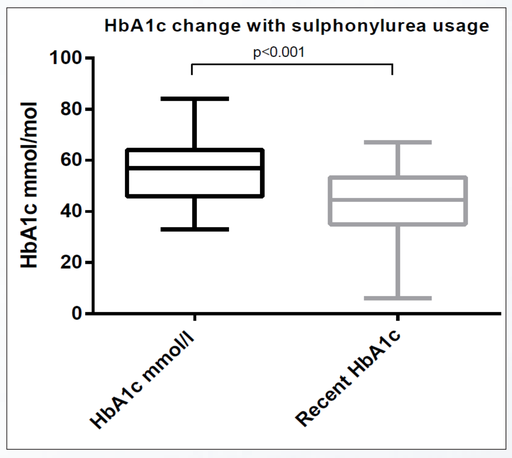
Results:

Table 1 demonstrates the clinical characteristics, micro and macrovascular complication rates associated with HNF1A-MODY and a cohort of Type 1 DM participants. Following a genetic diagnosis of MODY the majority remained insulin independent at 84 month follow up (80%). Successful treatment (i.e. not requiring an additional agent) with a sulphonylurea resulted in a significant improvement in HbA_{1c} over a duration of 84 months; (49mmol/mol (44-63)/6.6% (6.2-7.9) vs. 41mmol/mol (31-50)/5.9% (5-6.7), p=0.003) (see figure 1). The median dose of Gliclazide required to maintain optimal control in this group was 80mg (40-80mg) per day. There was no reported incidence of severe hypoglycaemia in participants treated with sulphonylurea therapy. Those that required an additional agent to sulphonylurea therapy had a longer duration of diabetes (20 yrs. [12-28] vs.9 yrs. [8-21], p=0.01) and had a higher HbA_{1c} at initial presentation to the MODY clinic (60mmol/mol [50-73]/ vs. 49mmol/mol [44-63]/, p=0.04) when compared to the successful sulphonylurea transfer group. In addition, the cohort that required an additional agent to sulphonylurea therapy gained an average of 7kg weight during follow up. The rate of retinopathy was significantly lower than that noted in the Type 1 DM group (18.3% vs. 50%, p=0.0001). There was also a lower rate of microalbuminuria, neuropthy and cardiovascular disease in the HNF1A-MODY group than that noted in the Type 1 DM group.

Table 1: Clinical Characteristics and complication rate in HNF1A-MODY vs. Type 1 DM study population.

	HNF1A-MODY [median [IQR]] N=60	T1DM [median [IQR]] N=60	P value
Sex (M:F)	24:36	30:30	na
Smoker	14	18	0.6
Age (yrs.)	39[21-52]	36 [23-48.5]	0.8
Duration of Diabetes (yrs.)	11[6-25]	19 [3.5-28]	0.2
BMI (kg/m^2)	24.1[21-26]	25.3 [22-28]	0.08
HbA_{1c} (mmol/mol)/%	45[38-58]/6.3[5.6-7.5]	64[57-76]/8[7.4-9.1]	<0.0001
Total Cholesterol (mmol/l)	4.4[3.7-4.9]	4.3[3.8-4.8]	0.6
Retinopathy (%)	9 (18.3)	30 (50)	0.0001
Proliferative Retinopathy (%)	2 (3.3)	10 (16)	0.01
Microalbuminuria (%)	3(5)	5(8.3)	0.2
Nephropathy(%)	3(5)	4(6)	0.4
Coronary Heart Disease (%)	4(6.6)	5(8.3)	0.4

Figure 1: Improvement in Hba1c in sulphonylurea treated group.



Conclusions:

- We report on the successful switch and maintenance of patients with HNF1A-MODY to sulphonylurea therapy in the long term. 80% of HNF1A-MODY patients remain insulin independent.
- Prevention of excessive weight gain appears to determine the success of sulphonylurea therapy in the HNF1A-MODY cohort.
- We report a lower incidence of both micro- and macro-vascular complications amongst the HNF1A-MODY study population compared to that previously reported in the literature.
- Early genetic confirmation of HNF1A-MODY appears to significantly influence the incidence of complications amongst this unique cohort.
- This study re-emphasises the importance of the genetic characterisation of HNF1A-MODY.

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Diabetes (to include obesity, pathophysiology & epidemiology)

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