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BRIEF COMMUNICATION

OGTT is recommended for glucose homeostasis assessments in Friedreich ataxia

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Abstract

Diabetes is a common complication of Friedreich ataxia, requiring sensitive diagnostic methods. Here, we compared the performance of different tests that assess glucose tolerance, insulin sensitivity, and β-cell function in Friedreich ataxia patients, heterozygous *FXN* mutation carriers and controls. We find that diabetes is underdiagnosed with fasting glucose alone. The oral glucose tolerance test (OGTT) provides 1.2- to 3.5-fold more diagnoses of impaired glucose homeostasis and diabetes, and adequately measures insulin sensitivity, insulin secretion, and β-cell function. Clinicians in charge of Friedreich ataxia patients and researchers should incorporate the OGTT as an accurate diagnostic and research tool.

Introduction

Friedreich ataxia (FRDA) is a progressive autosomal recessive neurodegenerative disease caused by homozygous GAA expansions in the *FXN* gene, affecting 1 in 29,000 Caucasians.[1] It is the most common of inherited ataxias,[1] presenting at an average age of 10 years. The clinical presentation combines progressive gait disturbances, spasticity, loss of sensory perception, and areflexia. It is caused by decreased production of the mitochondrial protein frataxin, which leads to mitochondrial dysfunction. Extraneurological features such as cardiomyopathy further characterize the disorder. FRDA also increases risk of impaired glucose tolerance (IGT) and diabetes mellitus, with diabetes prevalence rates varying between 8 and 32%.[2–13] The variability in reported diabetes prevalence may be explained by the choice of the diagnostic test. Diabetes is diagnosed by fasting glycemia ≥126 mg/dL (normal <100 mg/dL) on two separate days, or plasma glucose ≥200 mg/dL (normal <140 mg/dl) two hours after a 75-g oral glucose load. Impaired fasting glucose (IFG) and IGT are states of intermediate results, associated with increased risk for diabetes. HbA1c reflects chronic glucose exposure, and can be used in the general population to diagnose diabetes if ≥6.5% (normal <5.7%); again, intermediate values indicate increased diabetes risk.

In FRDA patients, insufficient insulin secretion – due to pancreatic β-cell dysfunction and death – is the key driver of diabetes development.[3] Glucose homeostasis is further negatively impacted by insulin resistance. The current recommendations for diagnosis (and treatment) of

Table 1. Characteristics of study participants.

	Controls	Carriers	FRDA patients
n	53	26	40
Age (years)	36 ± 13	46 ± 13[1]	36 ± 12[2]
BMI (kg/m²)	24.9 ± 5.4	25.9 ± 5.1	23.0 ± 3.9[2]
F/M (n (%F))	36/17 (65%)	17/9 (68%)	21/19 (53%)
NGT (n (%))	35 (66%)	13 (50%)	15 (38%)
IFG ± IGT (*n* (%))	17 (32%)	12 (46%)	20 (50%)
Diabetes (*n* (%))	1 (2%)	1 (4%)	5 (12%)

Age and BMI are shown as mean ± standard deviation. F female, M male, NGT normal glucose tolerance, IFG ± IGT impaired fasting glucose and/or impaired glucose tolerance. A Mann-Whitney U test was used for group comparisons of age and BMI as they were not normally distributed in the subgroups. A Chi-square test to compare the F/M ratio showed no statistical difference between the three groups. [1]$P < 0.05$ carriers versus controls, [2]$P < 0.05$ FRDA versus carriers.

FRDA diabetes are consensus based, as limited evidence is available to develop guidelines.[14] The oral glucose tolerance test (OGTT) is the preferred diagnostic tool as it has a better sensitivity than fasting plasma glucose. Because HbA1c changes slowly over time and diabetes onset can be abrupt and ketoacidotic in FRDA, a normal HbA1c value does not allow to exclude diabetes in these patients. HbA1c does have an important place in the follow-up of diabetic FRDA patients to monitor glucose control in response to treatment.[14] For research purposes, no studies have addressed the optimal way of assessing glucose tolerance and measuring insulin secretion and sensitivity in FRDA. Papers have used anything from the simplest approach of measuring fasting glycemia to labor-intense and expertise-requiring intravenous glucose tolerance tests (IVGTTs).

The aim of this study was to assess the validity of the OGTT as a diagnostic and research tool in the setting of FRDA, and make recommendations for future clinical studies on diabetes in FRDA.

Methods

We analyzed a dataset from a previous study in which FRDA patients, first-degree relatives and healthy volunteers were recruited to study diabetes pathogenesis in FRDA.[3] Forty-one FRDA patients (not clinically known to have diabetes), 26 first-degree relatives carrying a heterozygous GAA repeat expansion in *FXN* and 53 healthy volunteers underwent OGTT and IVGTT, as described.[3] One FRDA patient was excluded from the present analysis because she had very high (outlier) insulin secretion during the OGTT. Gender, age, and body mass index (BMI) of the three groups are shown in Table 1. From the IVGTT, the insulin sensitivity index (S_I) was calculated using the minimal model[15] and insulin secretion was defined as the acute insulin response to glucose (AIR_g). The disposition index was calculated as AIR_g x S_I and represents β-cell function adjusted for the person's insulin sensitivity.[15] Insulin sensitivity and insulin secretion were estimated with fasting glucose and insulin using the homeostatic model assessment (HOMA-ISI 22.5 x 18/insulin [μU/mL] x glucose [mg/dL] and HOMA-β 360 x insulin [μU/mL]/glucose [mg/dL] – 63).[16] The Matsuda index and the oral glucose insulin sensitivity (OGIS) were calculated to evaluate insulin sensitivity with OGTT data.[17,18] The insulinogenic or C-peptidogenic index, determined as (insulin or C-peptide at 30 min – fasting insulin or C-peptide)/(glucose at 30 min – fasting glucose), represents a measure of insulin secretion. To evaluate β-cell function with OGTT data, different oral disposition indices were calculated by multiplying the insulinogenic and C-peptidogenic indices by HOMA-ISI, Matsuda or OGIS. Categorical discrimination between normal and abnormal glycemia was defined by American Diabetes Association criteria: fasting glycemia <100 mg/dL normal, 100–125 mg/dL IFG and ≥126 mg/dL diabetes, or two-hour glycemia <140 mg/dL normal, 140–199 mg/dL IGT and ≥200 mg/dL diabetes. From the OGTT, the total and incremental (above fasting glycemia) areas under the curve (AUC) for glucose were calculated.

Statistical correlations, linear regressions and the calculation of Pearson's correlation coefficients with associated two-tailed p-values were performed using GraphPad Prism (La Jolla California USA). Calculation of confidence intervals, comparisons between correlations and group characteristics were done using SPSS version 25 (Chicago Illinois USA). The correlations were compared within groups using William's t-test for two non-independent parameters with SPSS, using syntax codes built by Weaver and Wuensch.[19] A value of $p < 0.05$ was considered significant.

Figure 1. Measures of glucose tolerance, insulin sensitivity, insulin secretion and β-cell function. (A and B) Correlation between fasting glucose (A) and 2 h glucose (B) values and the total AUC of glycemia during the OGTT. (C) Numbers and percentage of individuals with normal glycemia (white bars), IFG and/or IGT (grey bars) and diabetes (black bars) in controls, carriers and FRDA patients. In each subgroup the left bar represents the diagnosis based on fasting plasma glucose and the right bar on plasma glucose 2 h after a 75 g oral glucose load. (D) Correlation between the Matsuda index and the insulin sensitivity index S_I. (E) Correlation between the insulinogenic index and AIR_g. (F) Correlation between the Matsuda-corrected insulinogenic index and disposition index. The linear regression analysis was performed on the complete data set. Different subgroups are indicated by different symbols (+ controls; ○ carriers; ▲ patients).

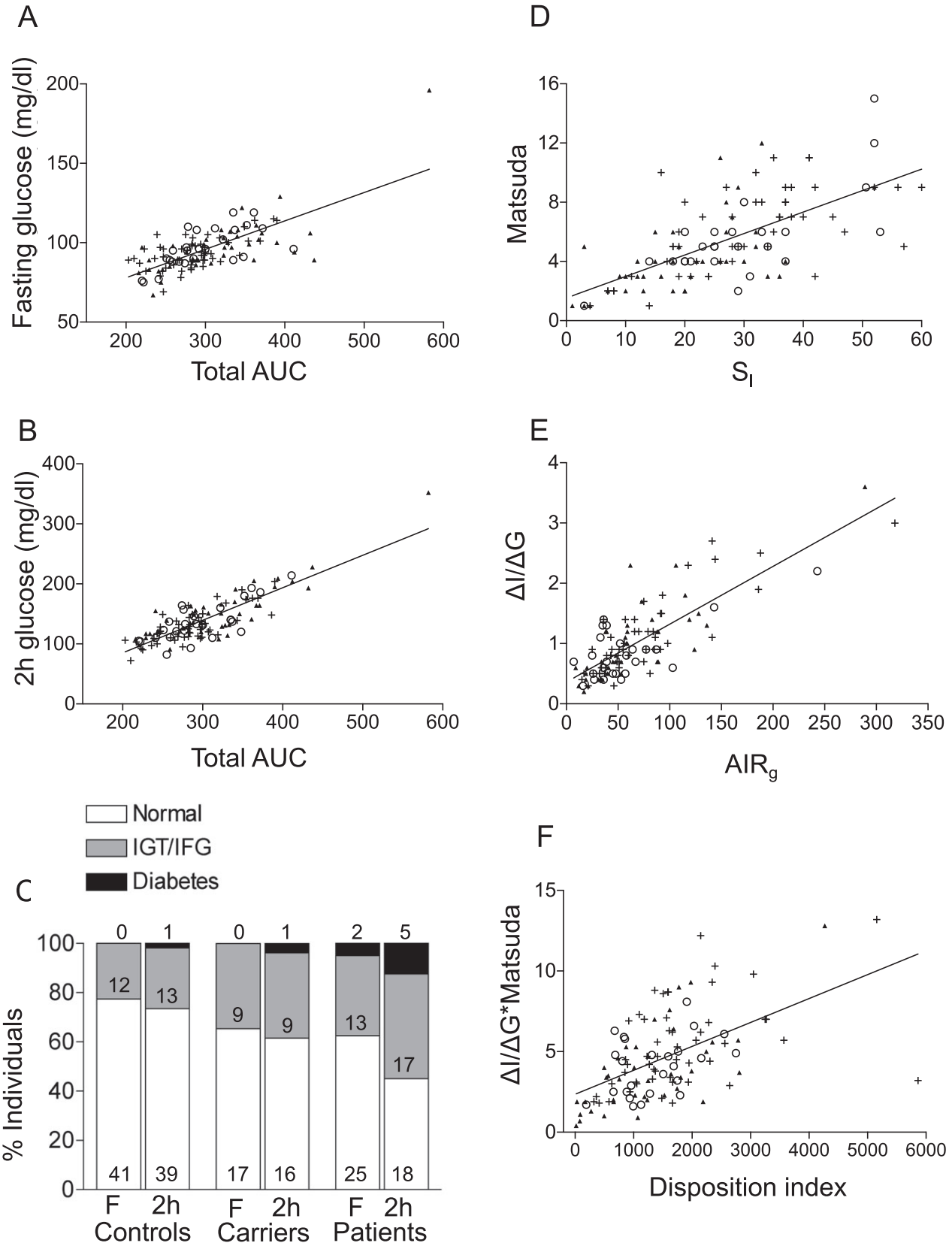
A
Fasting glucose (mg/dl)
Total AUC
B
2h glucose (mg/dl)
Total AUC
C
Normal
IGT/IFG
Diabetes
% Individuals
F Controls
2h Controls
F Carriers
2h Carriers
F Patients
2h Patients
D
Matsuda
S_I
E
ΔI/ΔG
AIR_g
F
ΔI/ΔG*Matsuda
Disposition index

Table 2. Comparison between glucose homeostasis parameters.

Total AUC glucose	All		Controls		Carriers		Patients	
Fasting glucose	0.71^{3a}	[0.61 to 0.79]	0.59^{3a}	[0.38 to 0.74]	0.66^{3a}	[0.36 to 0.83]	0.76^{3a}	[0.58 to 0.86]
120′ glucose	0.84^{3b}	[0.78 to 0.89]	0.77^{3b}	[0.63 to 0.86]	0.74^{3a}	[0.49 to 0.87]	0.87^{3a}	[0.76 to 0.93]
Incremental AUC glucose	All		Controls		Carriers		FRDA	
Fasting glucose	0.28^{2c}	[0.10 to 0.44]	0.18^{c}	[−0.09 to 0.43]	0.20^{b}	[−0.20 to 0.54]	0.32^{1b}	[0.01 to 0.57]
120′ glucose	0.70^{3d}	[0.59 to 0.78]	0.68^{3d}	[0.50 to 0.80]	0.63^{3c}	[0.32 to 0.81]	0.70^{3c}	[0.49 to 0.83]
S_I	All		Controls		Carriers		FRDA	
Matsuda	0.67^{3e}	[0.55 to 0.76]	0.64^{3e}	[0.44 to 0.78]	0.74^{3d}	[0.48 to 0.87]	0.58^{3d}	[0.32 to 0.75]
OGIS	0.57^{3f}	[0.43 to 0.68]	$0.60^{3e,f}$	[0.39 to 0.75]	0.62^{3d}	[0.29 to 0.81]	0.49^{2d}	[0.20 to 0.69]
HOMA-ISI	$0.53^{3f,g}$	[0.38 to 0.65]	0.44^{2f}	[0.19 to 0.63]	0.69^{3d}	[0.40 to 0.85]	0.50^{3d}	[0.22 to 0.70]
AIR_g	All		Controls		Carriers		FRDA	
ΔI/ΔG	0.80^{3h}	[0.72 to 0.86]	0.83^{3g}	[0.72 to 0.90]	0.70^{3e}	[0.41 to 0.85]	0.81^{3e}	[0.66 to 0.89]
ΔCpep/ΔG	0.72^{3i}	[0.62 to 0.80]	0.74^{3h}	[0.58 to 0.84]	$0.68^{3e,f}$	[0.38 to 0.84]	0.73^{3e}	[0.53 to 0.85]
HOMA-β	0.44^{3j}	[0.28 to 0.57]	$0.77^{3g,h}$	[0.62 to 0.86]	0.44^{1f}	[0.05 to 0.70]	0.14^{f}	[−0.18 to 0.43]
Disposition index	All		Controls		Carriers		FRDA	
ΔI/ΔG*Matsuda	0.55^{3k}	[0.41 to 0.66]	$0.43^{2i,k}$	[0.17 to 0.63]	$0.39^{g,i}$	[−0.01 to 0.67]	$0.68^{3g,h}$	[0.46 to 0.82]
ΔI/ΔG*OGIS	$0.49^{3k,l}$	[0.34 to 0.62]	$0.45^{3i,l}$	[0.20 to 0.64]	$0.06^{h,j}$	[−0.34 to 0.44]	$0.65^{3g,h}$	[0.42 to 0.80]
ΔI/ΔG*HOMA	0.38^{3l}	[0.21 to 052]	$0.17^{j,l}$	[−0.11 to 042]	0.50^{1g}	[0.13 to 0.74]	0.65^{3g}	[0.42 to 0.80]
ΔCpep/ΔG*Matsuda	0.49^{2k}	[0.34 to 0.62]	0.37^{2i}	[0.10 to 0.58]	0.48^{1g}	[0.10 to 0.73]	$0.57^{3g,h}$	[0.31 to 0.75]
ΔCpep/ΔG*OGIS	0.55^{3k}	[0.41 to 0.66]	0.51^{3i}	[0.27 to 0.69]	$0.13^{i,j}$	[−0.27 to 0.49]	$0.65^{3g,h}$	[0.42 to 0.80]
ΔCpep/ΔG*HOMA	0.32^{3l}	[0.14 to 0.47]	0.10^{j}	[−0.18 to 0.36]	0.55^{2g}	[0.19 to 0.77]	0.54^{3h}	[0.27 to 0.73]

Data are Pearson's correlation coefficients with 95% confidence intervals shown in square brackets and associated p values for all study participants combined or in the different subgroups. $^1P < 0.05$, $^2P < 0.01$, $^3P < 0.001$. Correlations were compared for each parameter within each subgroup (columns). Correlations with a common superscript letter are not statistically different, while those with different superscript letters are statistically different with $P < 0.05$ (e.g., in controls, for total AUC glucose, the correlation coefficient for fasting glucose (a) is statistically different from the correlation coefficient for 120′ glucose (b)).

Results

We first compared different methods to assess glucose tolerance and diagnose dysglycemia or diabetes. We previously reported that fasting glucose was not different in FRDA patients matched to controls for age, sex, and BMI (Table 1), but patients had significantly higher glycemia 2 h after the 75-g oral glucose load.[3] 2 h glycemia was well correlated with total and incremental AUC of the OGTT, while fasting glycemia was less well correlated with incremental AUC (Fig. 1A and B, Table 2). The Pearson's correlation coefficients were significantly higher for 2 h glucose than for fasting glucose, when all study participants were pooled (Table 2), pointing to differential regulation of fasting and postprandial glycemia. Fasting glycemia is regulated by hepatic insulin sensitivity and insulin and glucagon levels that determine endogenous glucose production rates, while postprandial glycemia is controlled by insulin and glucagon and glucose uptake in insulin-sensitive tissues, including muscle that may be particularly affected in FRDA. From a clinical diagnostic point of view, the 75-g OGTT with 2 h glucose measurements allows to identify more cases of IGT or diabetes, compared to fasting glycemia alone (Fig. 1C). In FRDA patients, 10 cases (eight IGT and two diabetes) were detected by OGTT but not with fasting glycemia, meaning that 40% of all glucose homeostasis abnormalities would have been missed without an OGTT. The overlap in abnormal fasting (≥100 mg/dL) and abnormal 2 h glucose (≥140 mg/dL) is rather limited: 15% for controls, 23% for carriers and 30% for FRDA patients.

The gold standard to measure insulin sensitivity is the hyperinsulinemic euglycemic clamp. This technique is not applicable in a clinical setting, and even in research environments it is little used because of the specialized skills needed to properly conduct the clamp. We used the IVGTT-derived S_I as an alternative gold standard, and compared the simpler HOMA-ISI, Matsuda, and OGIS indices to it (Fig. 1D, Table 2). The Matsuda index was more strongly correlated with S_I than OGIS or HOMA-ISI when all subjects were pooled, but the indices performed similarly in FRDA patients.

We then compared the measures of insulin secretion insulinogenic index ΔI/ΔG, C-peptidogenic index ΔCpep/ΔG and HOMA-β. The correlation to the gold standard measure AIR_g was the highest for the insulinogenic index (Fig. 1E, Table 2). HOMA-β performed poorly, with a low correlation coefficient in patients.

Lastly, we assessed β-cell function using the gold standard IVGTT-derived disposition index.[15] This measure adjusts the insulin secretory response to the person's insulin sensitivity: as in all endocrine systems, hormone secretion is influenced by hormone action. We therefore adjusted the insulinogenic and C-peptidogenic indices by

Matsuda, OGIS or HOMA-ISI. All oral indices correlated well with the disposition index in FRDA patients (Fig. 1F, Table 2).

Discussion

Diabetes is a very common metabolic complication of FRDA. In our earlier study of FRDA patients, we excluded people with a prior clinical diagnosis of diabetes; 49% had IFG and/or IGT, and 12% were newly diagnosed as diabetic.[3] These numbers justify the need for an accurate and timely diagnosis. Moreover, it is a relevant outcome in clinical and therapeutic FRDA research. Our study shows that diabetes is underdiagnosed by assessing fasting glycemia alone, as is commonly done in clinical settings; the OGTT unveils more cases of IGT and diabetes.

The pathogenic mechanism underlying most if not all cases of diabetes is insufficient insulin secretion by pancreatic β-cells. The consequences of relative insulin deficiency are accentuated in the presence of insulin resistance. This is also true for FRDA diabetes: β-cell failure is the key driver of loss of glucose tolerance, but the patients' metabolic situation is probably compounded by insulin resistance.[3] Here, we provide a comparison between different methods to assess these variables.

The gold standards to assess insulin sensitivity are clamps and IVGTTs. Both have limited clinical use because they are complex, non-physiological, time-consuming, and costly tests.[20,21] Obligate fluid administration during glucose infusion in the clamp should be considered in FRDA patients, many of whom have cardiomyopathy. Whole body insulin sensitivity can be measured by the Matsuda index and OGIS, both of which rely on OGTT and are highly correlated with glucose disposal during the euglycemic insulin clamp.[17,18] In our data in controls, carriers and FRDA patients, the Matsuda index was more strongly correlated with S_I than OGIS and HOMA-ISI.

HOMA-β is the simplest tool to evaluate β-cell function, based on fasting glycemia and insulin or C-peptide levels.[16] In keeping with studies in different patient populations, HOMA-β performed poorly. Fasting levels do not assess dynamic β-cell secretory responses, while OGTT and IVGTT perform much better since these are nutrient-stimulated assessments of insulin secretion.

For the interpretation of insulin secretion, it is essential to adjust for the prevailing insulin sensitivity, as under normal conditions the development of insulin resistance will induce a compensatory increase in insulin secretion; this has led to the concept of the disposition index. Here, we observed good correlations with the IVGTT-based disposition index for the insulinogenic or C-peptidogenic indices adjusted for Matsuda or OGIS measures of insulin sensitivity, for the whole cohort as well as the FRDA patients separately. In another study, significant correlations were found among fasting, oral, and intravenous measures of insulin sensitivity and secretion, but not for disposition indices.[22] This may be due to the smaller sample size (31 FRDA patients and 10 controls).

Collectively, our data show that the OGTT provides accurate measures of key variables controlling glycemia, as well as a sensitive assessment of glucose tolerance. The OGTT can be done in clinical routine and in clinical research settings, without the need for specialized personnel. Our study was limited to adult patients and volunteers, but the OGTT can also be used in children, at an oral glucose load of 1.75 g/kg and a maximum of 75 g. In conclusion, we encourage clinicians and researchers to use the OGTT in FRDA patients, and not limit themselves to fasting measures only.

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Conflict of Interest

None declared.

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