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Cross-sectional analysis of glucose metabolism in Friedreich Ataxia

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ABSTRACT

Objectives: To evaluate the relationship between disease features in Friedreich ataxia and aberrant glucose metabolism.
Methods: Fasting glucose, fasting insulin and random HbA1C were obtained in 158 patients with Friedreich ataxia. Regression analysis evaluated glucose, insulin, and homeostatic model assessment (HOMA) of insulin resistance (IR) and beta-cell function (ß) in relation to age, BMI, sex, and genetic severity. Categorical glucose values were analyzed in relation to other FRDA-associated disease characteristics.
Results: In the FRDA cohort, age and GAA repeat length predicted fasting glucose and HbA1c levels (accounting for sex and BMI), while insulin and HOMA-IR were not predicted by these parameters. Within the cohort, average BMI was consistently lower than the national average by age and was marginally associated with insulin levels and HOMA-IR. Within juvenile subjects, insulin and HOMA-IR were predicted by age. Controlling for age and genetic severity, diabetes-related measures were not independent predictors of any quantitative measure of disease severity in FRDA. Glucose handling properties were also predicted by the presence of a point mutation, with 40% of individuals heterozygous for point mutations having diabetes, compared to 4.3% of subjects who carried two expanded GAA repeats.
Interpretation: In FRDA, aberrant glucose metabolism is linked to increasing age, longer GAA repeat length on the shorter allele, frataxin point mutations, and increasing BMI. The effect of age to some degree may be mediated through changes in BMI, with increasing age associated with increases in BMI, and with HOMA-IR and insulin increases in children.

1. Introduction

Friedreich ataxia (FRDA) is a neurodegenerative disorder caused by autosomal recessive mutations in the *FXN* gene [21]. The majority of patients (95–97%) have pathologic GAA triplet repeat expansions in intron 1 of this gene, while the remaining 3–5% are compound heterozygotes carrying an expanded GAA repeat on one allele and a point mutation on the other [4,6,7,23]. Rare individuals with partial to complete deletions of *FXN* have also been identified [2,11]. GAA expansions are thought to cause pathology by decreasing frataxin protein levels due to decreased mRNA transcription. Loss of frataxin protein function may impair iron homeostasis within the mitochondria, enhance free radical generation, and cause mitochondrial dysfunction [26]. The length of the GAA repeat on the shorter allele correlates with age of onset and disease severity. Clinically, FRDA is characterized by gait disturbances, loss of sensory reception, and areflexia. Some individuals also develop cardiomyopathy, scoliosis, loss of visual acuity, and pes cavus [10,17,20,21,26,27].

An increased risk of diabetes (DM) or impaired fasting glucose is also a feature of FRDA. The incidence of DM is between 10–40% of patients with FRDA, though its type and mechanism have been debated [18,30,33]. Oral or intravenous (IV) glucose tolerance testing reveals that insulin resistance is a prominent feature in some patients [8,15,19,31], but the diabetes observed in individuals with FRDA also reflects pancreatic beta-cell failure [8,15,31]. The exact role of frataxin in the development of a diabetic phenotype in FRDA is not well understood although mitochondrial dysfunction may play a pivotal role.

While longer GAA repeat lengths in the *FXN* gene appear to increase the incidence of diabetes in FRDA [14], the relationship between

Abbreviations: FRDA, Friedreich ataxia; HOMA, Homeostatic Model Assessment; BMI, Body mass index; GAA, Guanine–adenine–adenine; FARS, Friedreich ataxia rating scale; CHOP, Children's Hospital of Philadelphia.

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diabetes and other features of FRDA has not been determined. The current study explores the relationship between age, sex, frataxin levels, body mass index (BMI) and the presence of point mutations to the level of glucose handling abnormalities, either insulin deficiency or insulin resistance, in patients with FRDA. In addition we sought to ascertain whether diabetes or insulin resistance alters the severity of FRDA or its manifestations.

2. Methods

2.1. Subjects

The study was approved by the Institutional Review Board at the Children's Hospital of Philadelphia (CHOP), and informed consent was obtained prior to participation. Clinical data from 158 patients (109 adults, 49 children) were accumulated from an ongoing natural history study and from a subcohort (n = 45) who were screened for a clinical trial [20].

2.2. Laboratory testing

Fasting glucose, insulin, and HbA1c values were measured in the Clinical and Translational Research Center at CHOP (n = 91). Glucose measurements were taken from whole blood using the Stat Strip Xpress Glucose Hospital Meter (Nova Biomedical, UK), and insulin was measured from plasma using the ALPCO Diagnostics (Salem, NH) human insulin ELISA kit (# 80-INSHU-E10.1). In a second group of subjects, fasting glucose, insulin, and HbA1c values were obtained from clinical studies performed in outside labs (n = 69). In addition, individuals with FRDA and overt treated diabetes from an ongoing natural history study were included to provide a perspective on diabetes in FRDA and a sample of the continuum of the phenotype from normal to impaired fasting glucose to diabetes. These diabetic individuals were not included in the analysis of insulin, glucose, HOMA-IR, or HbA1C, but only in the analysis of relationships between glucose handling properties and disease severity.

Frataxin levels were measured in whole blood as described previously [11]. Visual acuity (scored out of 70 points) was measured binocularly using retro-illuminated high contrast vision charts at a distance of 3.2 m (Precision Vision, La Salle, IL). Height and weight were obtained clinically during the patient visits or from recent medical records when data from research visits were unavailable. Similarly, ejection fraction measurements were taken from patient-supplied cardiology records or records obtained through an ongoing, retrospective observational study on the contribution of cardiomyopathy to progression of FRDA. The Friedreich Ataxia Rating Scale (FARS), a quantifiable neurological measure used to assess progression of FRDA, was used as described previously [22,32]. Genetic testing results were confirmed, and GAA repeat lengths were available on all subjects.

2.3. Statistics

Statistical analyses including summary statistics, correlations, and linear or logistic regressions were performed using STATA 11.2 (StataCorp LP, College Station, TX). Two tailed tests were used. Linear regressions involving the predictive value of BMI, frataxin levels, visual acuity, ejection fraction, and FARS score on fasting glucose values were performed accounting for age, sex and GAA repeat length. For all calculations involving GAA repeat length, the length of the shorter allele was used [20];[14]. In some tests, to allow inclusion of treated diabetic individuals, categorical delineations between normal and abnormal glucose values were used: normal (<100 mg/dL), impaired fasting glucose (100–126 mg/dL) and diabetic (>126 mg/dL) which was divided into two subcategories: untreated and treated. Treatments included dietary in combination with sulfonylurea-based medications, or insulin injections. This categorization eliminates spurious findings driven by variations of glucose values within the normal range, although HOMA-IR and HOMA-β still take these into account. For summary statistics, data were untransformed. However, glucose, insulin, HOMA-IR, and Hba1c values were logarithmically transformed for parametric statistics and linear regressions to account for the skewed nature of these variables. After transformation, insulin and HOMA-IR fit a normal distribution with skewness values of 0.40 and 0.38, respectively. Transformation of glucose and HbA1c significantly reduced the skewness of these variables but did not allow them to fit a normal distribution. Population norms were used from previous large scale reports on glucose and insulin [24], body mass index [3,25], and HOMA-IR [9]. Data are presented as mean ± standard deviation.

3. Results

3.1. Demographic and metabolic features of the cohort

The mean age of the cohort was 25 ± 15 years (range 5–69); the average GAA repeat length was 604 ± 222 on the shorter allele, and mean age of symptom onset was 13.2 ± 8.5 years old. Ten percent (n = 16) of subjects were compound heterozygotes, and an additional 2 subjects had a large deletion in the frataxin gene on one allele. The cohort was 51% male and the average body mass index (BMI) was 21.7 ± 5.2 (range 12.4–41.8) with 20% of juvenile subjects at or below the 5th percentile (underweight by the guidelines outlined by the Centers for Disease Control). Only 5% of adult subjects were considered underweight (BMI less than 18.5). The average FARS score was 63.5 ± 20.5, a score which reflects an individual having significant difficulty ambulating independently. The mean level of frataxin in the blood was 29.2 ± 17.5% of frataxin levels in control blood (range 6% to 76%). Ten (6.3%) subjects were overtly diabetic and 26% of the cohort had fasting glucose levels above normal (greater than 99 mg/dL) (range 68–264).

Table 1
Correlation analysis of disease features.

	Glucose	Insulin	HOMA-IR	HbA1c	Frataxin	BMI
Sex	0.036	0.029	0.061	−0.20	0.086	0.090
Age	0.19*	0.18*	0.19*	0.089	0.50***	0.46***
AOO	−0.034	0.024	0.017	−0.17	0.67***	0.34***
GAA	0.15	−0.085	−0.075	0.15	−0.66***	−0.24*
BMI	0.35***	0.37***	0.37***	−0.075	0.34**	–
Disease duration	0.25**	0.14	0.15	0.34**	0.14	0.35***

Data represented as Pearson's correlation coefficient with associated p-value. Glucose, insulin, HOMA-IR, and HbA1c values were logarithmically transformed prior to analysis. Blood frataxin levels correlate well with age, age of onset (AOO), short GAA length (GAA), and body mass index (BMI). Glucose, insulin, and HOMA-IR correlate moderately with age and BMI. BMI correlates well with age, AOO and disease duration, and moderately with GAA.

* $P < 0.05$.
** $P < 0.01$.
*** $P < 0.001$.

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