



Lower fasting blood glucose in neurofibromatosis type 1

Aline Stangherlin Martins¹, Ann Kristine Jansen², Luiz Oswaldo Carneiro Rodrigues¹, Camila Maria Matos¹, Marcio Leandro Ribeiro Souza¹, Juliana Ferreira de Souza¹, Maria de Fátima Haueisen Sander Diniz³, Sandhi Maria Barreto⁴, Leonardo Mauricio Diniz³, Nilton Alves de Rezende^{1,5} and Vincent Michael Riccardi⁶

¹Neurofibromatosis Outpatient Reference Center, Federal University of Minas Gerais, Alameda Álvaro Celso 55, Belo Horizonte, Minas Gerais, Brazil

²Department of Nutrition, Federal University of Minas Gerais, Professor Alfredo Balena Avenue, 190, Santa Efigênia, Belo Horizonte, Minas Gerais, Brazil

³Department of Medical Clinic, Federal University of Minas Gerais, Professor Alfredo Balena Avenue, 190, Santa Efigênia, Belo Horizonte, Minas Gerais, Brazil

⁴Department of Preventive and Social Medicine, Federal University of Minas Gerais, Professor Alfredo Balena Avenue, 190, Santa Efigênia, Belo Horizonte, Minas Gerais, Brazil

⁵Department of Internal Medicine, Federal University of Minas Gerais, Professor Alfredo Balena Avenue, 190, Santa Efigênia, Belo Horizonte, Minas Gerais, Brazil

⁶The Neurofibromatosis Institute, 5415 Briggs Avenue, La Crescenta, CA, USA

Correspondence should be addressed to N A de Rezende
Email
 narezende@terra.com.br

Abstract

Studies indicate a lower occurrence of diabetes mellitus (DM) in patients with neurofibromatosis type 1 (NF1). Fasting blood glucose (FBG) level is the main criterion used to diagnose DM and glucose intolerance. Therefore, this study compared FBG level between adults with NF1 and non-NF1 controls. We selected clinical records of 57 out of 701 individuals attending the Neurofibromatosis Outpatient Reference Center of the Clinics Hospital of the Federal University of Minas Gerais in Brazil. The selected patients with NF1 were matched to non-NF1 controls selected from the Brazilian Longitudinal Study of Adult Health according to sex, age (range, 35–74 years) and BMI at a ratio of 1:3. In both groups, individuals with DM were excluded. Median FBG level in the NF1 group (86 mg/dl (range, 56–127 mg/dl)) was lower than that in the non-NF1 control group (102 mg/dl (range, 85–146 mg/dl)) ($P < 0.001$). Prevalence of FBG level ≥ 100 mg/dl in the NF1 group (16%) was lower than that in the non-NF1 control group (63%) ($P < 0.05$). The chance of a high FBG level was 89% lower in the NF1 group (odds ratio, 0.112; 95% CI, 0.067–0.188) ($P < 0.05$). In conclusion, adults with NF1 showed a lower FBG level and a lower prevalence of high FBG level compared with non-NF1 controls.

Key Words

- ▶ fasting blood glucose
- ▶ neurofibromatosis type 1
- ▶ type 2 diabetes mellitus
- ▶ insulin resistance
- ▶ nutritional status

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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant genetic disease caused by an inherited or new mutation at the NF1 locus on the long arm of chromosome 17. This intragenic or whole-gene-deletion mutation results in dysfunction of the protein neurofibromin, which is

involved in controlling growth and/or behavior of various tissues (1). NF1 is the most common human monogenetic disease, with a prevalence of approximately 1:3500 (2).

Clinical characteristics of NF1 include café au lait spots; cutaneous, subcutaneous, and plexiform



neurofibromas; axillary and/or inguinal freckling; Lisch nodules; intracranial gliomas; malignant peripheral nerve sheath tumors; and vascular and bone dysplasia (3, 4, 5). The longevity of patients with NF1 is shorter than that of the general population (6). A 12-year study of 70 adult patients with NF1 found a decrease in life expectancy of approximately 15 years (7).

Although malignant tumors are the main cause of death in individuals with NF1 (7), the higher mortality rate also has been associated with other diseases, including atherosclerotic cardiovascular disease (ASCVD). Rasmussen *et al.* (6) evaluated the death certificates of 3770 individuals with NF1 in the USA from 1983 to 1997 and found that 658 deaths (17.4%) were related to vascular disease (VD), whereas only 64 (1.7%) were related to type 1 or type 2 diabetes mellitus (DM). Similarly, Masocco *et al.* (8) reviewed the death certificates of 632 individuals with NF1 in the USA from 1995 to 2006 and found that 101 deaths (16%) were associated with VD, but only 2 (0.3%) were related to DM. Madubata *et al.* (9) also reported a low frequency of DM-related medical claims among patients with NF1. In two studies of general population death certificates, Belfort and Oliveira (10) found that the DM-related mortality rate was from 3.97 to 4.41% in Brazil, while Rampatige *et al.* (11) found that such mortality rate was 10% in Sri Lanka.

VD refers to arterial and/or venous disorders in general, including developmental vascular dysplasia, ASCVD, and aneurysm. However, the specific type of VD in individuals with NF1 and its correlation with fasting blood glucose (FBG) level has not been investigated in previous studies (6, 8).

Both type 1 and type 2 DM contribute to development of VD (12). Type 1 DM is associated with an inadequate availability of insulin and usually manifests in childhood, whereas type 2 DM is related to insulin resistance and usually manifests in adulthood (13). The low incidence of DM-associated mortality in patients with NF1 (0.3%) seems paradoxical because DM is one of the main risk factors for ASCVD and associated death in the general population (14).

The Neurofibromatosis Outpatient Reference Center (CRNF) of the Clinics Hospital of the Federal University of Minas Gerais has managed over 800 patients with NF1, among whom there has been no reported case of type 2 DM and only two cases of type 1 DM. Moreover, to our knowledge, there has been no study on the prevalence of DM or increased FBG level in individuals with NF1.

Riccardi, in the first two editions of his book on neurofibromatosis (15, 16), to some degree focused on

body habitus, DM, and FBG. In the 1986 edition, there were several noteworthy observations: i) in 147 patients with NF1, the age- and sex-corrected average weight centile was 45.4 ± 32.1 (i.e., there was an inclination toward leanness); and ii) in 233 patients with NF1 (of all ages), FBG level was normal, except for equivocal elevation in seven cases (3%). In the 1992 edition, they reported having seen very few cases of DM among patients with NF1.

According to the American Diabetes Association (ADA), FBG level is the main criterion used to diagnose DM (17). Therefore, the present study aimed to compare FBG level between adults with NF1 and non-NF1 controls.

Methods

This retrospective, observational, cross-sectional study was based on medical record review of all patients with NF1 attending CRNF from January 1, 2005, to December 31, 2013. Inclusion criteria were age between 35 and 74 years; recorded data on FBG, sex, weight, and height; and at least three positive diagnostic criteria for NF1 according to the National Institutes of Health guidelines (18). All records with a diagnosis of DM were excluded from analysis. The age cut-off points were chosen to match the non-NF1 controls available from the Longitudinal Study of Adult Health (ELSA) in Brazil.

The newest FBG data in the medical record were used. Patients were instructed to fast for at least 8 h based on NF1 subject written information, and FBG level was measured using a colorimetric method (VITROS equipment and Ortho-Clinical Diagnostics reagent; Ortho Clinical Diagnostics, Raritan, NJ, USA).

The NF1 group was compared with a non-NF1 control group selected from the ELSA study – a cohort of 15 000 active and retired employees from six federal Brazilian research institutions (19). As in the NF1 group, all ELSA participants with a diagnosis of type 1 or type 2 DM were excluded. Three non-NF1 individuals from ELSA were selected to match each NF1 patient (three controls for each case) according to sex, age, and BMI by a person who was blinded to the FBG levels. Similarity was expressed by a distance measure; in this case, we used the Mahalanobis distance. Pairing was performed using the matching package for R (20).

To stratify FBG level, cut-off points were established according to the ADA guidelines (21) and were designated as normal (≤ 99 mg/dl) or high (≥ 100 mg/dl). BMI was calculated by the equation 'weight (kg) divided by height (m) squared,' and was classified according to the World Health Organization scale for adults (22). Stature was

Table 1 Characteristics of the NF1 and non-NF1 control groups.

Characteristic	NF1 group (n=57)	Non-NF1 control group (n=171)
Age, mean ± s.d. (years)	48.9 ± 10.7	48.7 ± 10.3
Sex, n (%)		
Female	32 (56.1)	96 (56.1)
Male	25 (43.9)	75 (43.9)
BMI, mean ± s.d. (kg/m ²)*	25.6 ± 5.5	25.61 ± 5.3
BMI classification, n (%)*		
Normal	32 (56.0)	98 (56.0)
Overweight	25 (44.0)	73 (44.0)
Height, mean ± s.d. (m)**	1.58 ± 0.08	1.65 ± 0.09

* $P > 0.05$, ** $P < 0.001$.

evaluated based on the Centers for Disease Control and Prevention/National Center for Health Statistics parameters for adults (2007–2010) (23). Low height was defined as less than the percentile five.

Ethical aspect

The Ethics Committee of the Federal University of Minas Gerais approved the present study (No 258.325) and ELSA–Brazil (No 186/06).

Statistical analyses

Categorical variables included absolute and relative frequencies. The normality of the distribution of variables was tested by using the Kolmogorov–Smirnov test. Normally distributed variables were described as mean ± s.d., while non-normally distributed variables were described as median, minimum and maximum values. The Wilcoxon signed-rank test was used to compare median FBG level between the two groups, while the McNemar test was used to compare proportions of normal and altered

FBG levels between the two groups. The Mann–Whitney *U* test was used to compare median FBG level according to BMI and height, while the chi-square test was used to compare proportions of normal and altered FBG levels according to BMI and height. Stepwise multivariate logistic regression was used to evaluate the associations between independent variables and high FBG level (≥ 100 mg/dl). Covariates with a *P* value of ≤ 0.25 in bivariate analysis and biologic plausibility were considered as candidates for the final model. Independent variables were entered into the model one by one in order of decreasing statistical significance, and those that lost this characteristic were excluded. The strength of the association was assessed by calculating the odds ratio (OR) with a CI of 95%. The OR was calculated by using logistic regression to estimate the magnitude of the likelihood of a patient with NF1 having a high FBG level compared with a non-NF1 control, with a CI of 95%. Statistical significance was established when *P* was < 0.05 . Analyses were performed using SPSS version 13.0 (SPSS, Inc.).

Results

We evaluated 701 medical records from CRNF: 175 were excluded because they had less than three diagnostic criteria for NF1 or had other diagnoses (such as neurofibromatosis type 2, Schwannomatosis, or Legius syndrome); two (0.3%) were excluded due to diagnosis of type 1 DM; and 20 were excluded due to absence of exact birth date. Within the 701 records, 504 had at least three diagnostic criteria for NF1, and 184 had data on FBG, weight and height. Of these, 57 patients were aged 35–74 years and were included in this study.

The average age was 48.9 ± 10.7 years in the NF1 group and 48.7 ± 10.3 years in the non-NF1 control group.

Table 2 Median FBG concentration and prevalence of normal and high FBG concentrations in the NF1 and non-NF1 control groups according to sex.

Variable	NF1 group			Non-NF1 control group		
	All (n=57)	Female (n=32)	Male (n=25)	All (n=171)	Female (n=96)	Male (n=75)
FBG level, median (range), mg/dl	86.0 (56–127)*	85.4 (76–126)**	87.0 (56–127)***	102.0 (85–146)*	100.0 (85–128)**	105.0 (90–146)***
Normal FBG concentration, n (%)	48 (84) ^a	28 (87) ^b	20 (80) ^c	64 (37) ^a	44 (46) ^b	20 (27) ^c
High FBG concentration, n (%)	9 (16)*	4 (13)**	5 (20)*	107 (63)*	52 (54)**	55 (73)***

*NF1 < non-NF1 ($P < 0.001$), **Female NF1 < female non-NF1 ($P < 0.001$), ***Male NF1 < male non-NF1 ($P < 0.001$).

^aNF1 > non-NF1 ($P < 0.001$).

^bFemale NF1 > female non-NF1 ($P < 0.001$).

^cMale NF1 > male non-NF1 ($P < 0.001$).

Table 3 Median FBG concentration and prevalence of normal and high FBG concentrations in the NF1 and non-NF1 control groups according to BMI and height.

Variable	NF1 group				Non-NF1 control group			
	Normal BMI (n = 32)	Overweight (n = 25)	Normal height (n = 30)	Low height (n = 27)	Normal BMI (n = 98)	Overweight (n = 73)	Normal height (n = 131)	Low height (n = 40)
FBG level, median (range), mg/dl	83.5 (56-127)	90.0 (73-116)	86.0 (73-127)	84.0 (56-116)	100.0 (85-146)*	105.0 (88-131)*	101.0 (85-146)	105.0 (90-123)
Normal FBG level, n (%)	29 (90)	19 (76)	27 (90)	23 (85)	46 (47)**	18 (25)**	50 (38)	14 (35)
High FBG level, n (%)	3 (10)	6 (24)	3 (10)	4 (15)	52 (53)**	55 (75)**	81 (62)	26 (65)

* $P=0.001$, ** $P<0.05$.

Women comprised 56.1% of the participants, and normal BMI was observed in 56% of both groups. Average height was significantly lower in the NF1 group (1.58 ± 0.08 m) than in the non-NF1 control group (1.65 ± 0.09 m) ($P < 0.001$) (Table 1).

Median FBG level in the NF1 group (86 mg/dl (range, 56–127 mg/dl)) was significantly lower than that in the non-NF1 control group (102 mg/dl (range, 5–146 mg/dl)) for both sexes ($P < 0.001$). Prevalence of normal FBG level was significantly higher in the NF1 group (84%) than in the non-NF1 control group (64%) ($P < 0.001$) (Table 2).

Table 3 shows the median FBG level and prevalence of normal and high FBG levels according to anthropometric measurements in both groups. In the NF1 group, median FBG level was not affected by overweight status (90 mg/dl (range, 73–116 mg/dl)) or normal BMI (83.50 mg/dl (range, 56–127 mg/dl)). In the non-NF1 control group, median FBG level was significantly higher in overweight individuals (105 mg/dl (range, 88–131 mg/dl)) than in those with a normal BMI (100 mg/dl (range, 85–146 mg/dl)) ($P < 0.001$). In both the NF1 and non-NF1 control groups, median FBG level was not affected by height.

The chance of a high FBG level was 89% lower in the NF1 group than in the non-NF1 control group (OR, 0.112; 95% CI, 0.067–0.188). Table 4 shows the final logistic regression model for the factors that influence the FBG levels in the NF1 and non-NF1 control groups. In the NF1 group, age and BMI significantly influenced FBG level. The chance of a patient with NF1 having a high FBG level increased by 5% for every increase of one year in age and by 12.5% for every increase of one unit in BMI. In the non-NF1 control group, male patient's sex, age, and BMI significantly influenced FBG level. The chance of a non-NF1 control having a high FBG level increased by 5% for every increase of one year in age and by 17% for every increase of one unit in BMI. Men had a 2.3 times greater chance of having a high FBG level compared with women.

Discussion

In this study, adults with NF1 showed a lower median FBG level and a lower prevalence of high FBG level compared with non-NF1 controls matched by sex, age, and BMI. A literature review found no previous studies assessing the prevalence of abnormal FBG level in patients with NF1 of any age other than the notations by Riccardi cited above. In a recent study, Souza *et al.* (24) evaluated 60 adults with NF1 and found a similar median FBG level (82 mg/dl) in a younger population (mean age, 34 years) than that reported here.

Table 4 Final logistic regression model for the factors that influence the FBG levels in NF1 and non-NF1 control groups.

	OR (95% CI)	P value
NF1 group		
BMI	1.12 (1.04–1.20)	0.001
Age	1.05 (1.01–1.09)	0.009
Non-NF1 control group		
Male sex	2.34 (1.17–4.48)	0.016
BMI	1.17 (1.073–1.28)	<0.001
Age	1.05 (1.01–1.1)	0.007

In the present study, 44% of patients with NF1 were overweight, but FBG levels were similar between overweight individuals and those with a normal BMI. Average height of patients with NF1 was significantly lower than that of non-NF1 controls, which has been reported previously (25, 26). Nevertheless, median FBG levels were similar regardless of height in both groups.

In logistic regression analysis, BMI influenced FBG level more significantly in the NF1 group than in the non-NF1 control group. In the general population, the relationships between high BMI, age, and impaired FBG level and type 2 DM are well established (27). However, in adults with NF1, the relationship between high BMI and high FBG level has not been established. According to our data, patients with NF1 had a lower chance of having a high FBG level compared with non-NF1 controls. Although data from animal studies have indicated that neurofibromin plays a role in regulating functions of the hypothalamus and pituitary gland (28), which are involved in body energy balance (29), it is unclear whether neurofibromin deficiency could be responsible for the reduced FBG level in individuals with NF1.

A second hypothesis is that adults with NF1 may have higher insulin sensitivity and lower insulin resistance mediated by adipocytokines (leptin, visfatin, resistin, and adiponectin). Adipocytokines are bioactive proteins secreted by adipose tissue (30, 31), which influence such physiologic processes as control of food intake, energy homeostasis, angiogenesis, vascular protection, regulation of blood pressure, blood clotting, and insulin sensitivity (30). Several studies have shown the relationships between insulin resistance and type 2 DM and increased plasma concentrations of leptin (32), visfatin (33), and resistin (34), as well as decreased concentration of adiponectin (35). Individuals with NF1 could have lower levels of leptin, resistin, and visfatin, and a higher level of adiponectin, leading to lower insulin resistance, which favors maintenance of lower FBG level and reduced chance of type 2 DM.

Another hypothesis to explain the lower FBG level in patients with NF1 considers production of insulin-like growth factor 2 (IGF2) by neurofibromas (3, 5). IGF2 increases peripheral glucose consumption and decreases glucose production in the liver, leading to hypoglycemia (36). However, further studies are required to verify whether IGF2 produced by neurofibromas could affect FBG level.

The present results suggest the need for further studies to assess glucose metabolism in terms of the glucose tolerance test and 2-h postprandial measurement of serum insulin, glucagon, and glucose.

The sample size could be seen as a limitation of the present study; however, the final number of patients with NF1 (57) is considered high enough for a rare disease study. Finally, another possible limitation of the present study is that the non-NF1 controls were selected from ELSA data without systematic exclusion of conditions, other than DM, that could alter FBG level.

Conclusions

In conclusion, adults with NF1 showed a lower FBG level and a lower prevalence of high FBG level compared with non-NF1 controls matched by age, sex, and BMI.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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