Relation between diabetes mellitus and male fertility

Relação entre *diabetes mellitus* e fertilidade masculina

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ABSTRACT

Objective: The objective of the present study was to verify if there is any relation between *diabetes mellitus* and male infertility. **Methods:** the spermograms of 43 non-diabetic subjects and 12 diabetic patients (type 1 and 2) aged 20-60 years were compared. Spermiological findings in diabetic patients were compared with those of normal individuals of the same age. Serum testosterone, prolactin, follicle-stimulant hormone, luteinizing hormone, glucose and glycosilated hemoglobin were assayed in diabetic patients. **Results:** Six diabetic patients (four type 1 and two type 2) presented chronic complications attributed to neuropathy and vascular insufficiency. No difference was observed in the semen characteristics (odor, color, viscosity and pH) between the control group and the diabetic patients. There were no differences between seminal concentrations and percentage of motile spermatozoa during the first hour of observation in the two groups ($p < 0.05$). Impotence was reported by four diabetic patients (33.3%). Erectile failure was associated with diabetic microangiopathy and neuropathy. There were no controls with impotence. No significant hormonal changes were found in the diabetic patients. **Conclusions:** The present results suggest that neuropathy and vascular insufficiency may be implicated in sexual dysfunction in type 1 and 2 diabetic patients, without significantly affecting the hypothalamic-pituitary-gonadal axis.

Keywords: *Diabetes mellitus*/complications; Infertility, male; Impotence; Spermogram

RESUMO

Objetivo: O objetivo do presente estudo foi verificar se há relação entre *diabetes mellitus* e infertilidade masculina. **Métodos:** Foi estudado espermograma de 43 indivíduos não-diabéticos e 12 diabéticos (tipo I e tipo II) com idade variando entre 20 e 60 anos. Os diabéticos também foram submetidos à dosagem hormonal de testosterona, prolactina, hormônio folículo-estimulante e hormônio luteinizante, além da e glicemia de jejum e hemoglobina glicosilada. **Resultados:** Foram encontrados seis pacientes diabéticos (quatro tipo I e dois pacientes tipo II) com complicações crônicas decorrentes da vásculo- e neuropatia diabéticas. A análise do líquido seminal dos voluntários, não-diabéticos e diabéticos, não mostrou diferenças entre as características dos sêmens: odor, cor, viscosidade e pH. Também não houve diferença entre as concentrações seminais e a porcentagem de espermatozoides móveis durante a primeira hora de observação entre os dois grupos ($p > 0,05$). Foi relatada impotência por quatro diabéticos (33,3%) com complicações crônicas do diabetes, secundárias à neuropatia e à angiopatia diabética. Não foi encontrada impotência em nenhum paciente do grupo não-diabético. Não foram encontradas alterações hormonais significativas nos diabéticos. **Conclusões:** Os resultados sugerem que a neuropatia e insuficiência vascular podem estar relacionadas à disfunção sexual em pacientes diabéticos tipo I e II, sem, entretanto, comprometimento do eixo hipotálamo-hifofisário-gonadal.

Descritores: *Diabetes mellitus*/complicações; Infertilidade masculina; Impotência; Espermograma

INTRODUCTION

Diabetes mellitus, primary or idiopathic, is a chronic disorder of the carbohydrate, lipid and protein metabolism, characterized by insulin disorders, hyperglycemia and glycosuria. This condition may contribute to arteriosclerosis, microangiopathy, nephropathy and neuropathy[1]. Although most problems due to diabetes have been widely studied, the reproductive system affections are still little understood[2].

Diabetes mellitus has been associated to sexual dysfunction, both in men and women. It is believed that neuropathy, vascular insufficiency and psychological problems may be involved in the pathogenesis of some phenomena, such as impotence, ejaculation disorders

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and decreased libido, in addition to the reduced vaginal lubrication and orgasm dysfunctions[2-4].

Dinulovic et al. associated male infertility to inappropriate synthesis of testosterone, caused by molecular changes in the Leydig cells, secondary to diabetes[5]. The narrow relation between the function of Leydig and Sertoli cells could explain the changes found in the spermogram of diabetic patients. The involvement of the pituitary-gonadal system also interferes in these disorders[6].

On the other hand, Miralles-Garcia et al. found that insulin-dependent diabetes is associated to reduced ejaculated semen and decreased vitality and motility of the spermatozoa, with no change in sperm viscosity[7]. However, the relation between male infertility and altered plasma levels of testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) is still obscure[8]. In diabetic patients with organic impotence free testosterone is diminished. This is not found in the non-impotent diabetics and in individuals with psychological impotence, as well as in healthy men[6].

Insulin action in motility and in the metabolism of human spermatozoa is not defined. Defects in insulin secretion may change testicular and accessory sexual glands function. Usually, the concentration of seminal insulin is higher than that in the serum[9].

OBJECTIVE

Because of this gap in the literature, the objective of the present study was to verify the relation between *diabetes mellitus* and male fertility.

METHODS

This study was carried out according to the recommendations of the Helsinki Declaration and to the Resolution 196/96 of the Brazilian Ministry of Health, about research involving human beings. It was approved by the Research Ethics Committee of the Universidade Federal de Minas Gerais (UFMG). All patients agreed to participate in this study and signed the informed consent form[10].

Fifty-five male subjects, aged 20-40 years, were prospectively studied and classified as: Group 1 (n = 43): healthy individuals; Group 2 (n = 12): patients with *diabetes mellitus* – referred from the Endocrinology Outpatient Clinic, Hospital das Clínicas (UFMG).

All patients were asked about their history encompassing sexual history (frequency of sexual intercourse, presence of erectile or ejaculatory dysfunction, and previous paternity). Family history regarding infertility was also investigated. The diabetic patients were also asked about the use of insulin or glucose lowering agents, duration of disease, degree of diabetes control, and presence of chronic complications and associated diseases.

After five days of sexual abstinence, a spermogram was collected in a sterile vial, which was immediately sealed. The fluid analysis was conducted within the first hour after collection and consisted of evaluation of its physical and chemical characteristics (volume, aspect, odor, viscosity and pH) and of microscopic analysis to observe motility and morphology of the spermatozoa. After semen dilution at 1:20 (0.1 milliliters of semen in 1.9 milliliters of 0.9% saline solution), the spermatozoa were counted in a Neubauer chamber. They were counted in the five quadrants, the four lateral ones usually utilized for leukocyte count and the central one for erythrocyte count. The number obtained was multiplied by one million to determine the concentration of spermatozoa per milliliter. As to morphology, the spermatozoa were classified as normal (oval) and abnormal (spindle shaped, round, amorphous, immature, bicephalic, bicaudate, macrocephalic and microcephalic).

In diabetic patients, fasting glucose, glycosilated hemoglobin, testosterone, follicle stimulating hormone (FSH), luteinizing hormone (LH) and prolactin (PRL) were assayed. The reference values were: testosterone: 270 – 1070 ng%; prolactin: up to 20 ng/ml; follicle stimulating hormone: 1.8 – 9.0 mIU/ml; luteinizing hormone: 0.4 – 5.7 mIU/ml.

The fasting glucose and glycosilated hemoglobin were assayed on the same day, thirty minutes after blood was drawn; the diabetic patients fasted for eight hours prior to blood drawing. Glucose levels between 60 and 109 mg% and glycosilated hemoglobin up to 8.5 g% were considered normal.

For the hormone assays, after blood collection into Vacutainer tubes, the sample was centrifuged and stored at -8°C for thirty days, when all assays were analyzed. Kits for prolactin (IRMA) solid phase (IKPR 2) – DPC, a kit for follicle stimulating hormone (IRMA) solid phase (IKFS 2) – DPC, for luteinizing hormone (IRMA) solid phase (IKLH 2) – DPC and for testosterone (RIE) solid phase (TKTT 2) – DPC were used. Each serum sample was analyzed in duplicate.

For the statistical analysis the mean and the standard error for mean age of patients were calculated[11]. The results were compared using the Student's *t* test and the Fisher's exact test. The odds ratio for the likelihood of diabetes-related complication and its 95% confidence interval were also calculated. Significance was established at $p < 0.05$.

RESULTS

All patients agreed to participate in the study. The mean age of the controls was 28 ± 3 years and of the diabetic patients, 35 ± 4 years ($p = 0.34$).

All non-diabetic volunteers had negative sexual and family history for infertility and erectile disorders, as well as for affections that could be of risk for developing diabetes and previous urological disease. As to the use of insulin or oral glucose lowering drugs to control blood glucose, eight patients were using NPH insulin and four, glybenclamide. The duration of diabetes ranged from four to 18 years (8.3 ± 0.3 years), longer than ten years in 75% of patients. Six diabetic patients had vascular and neuropathic chronic complications of the disease.

The seminal fluid analysis of the controls (Group 1) and diabetics (Group 2) was not different regarding semen features: characteristic odor, clear gray colored, viscosity within normal limits and pH of 7. The volume of the ejaculated fluid ranged between 2.0 and 3.2 (2.5 ± 0.2) milliliters in controls and between 1.5 and 3.0 (2.4 ± 0.5) milliliters in diabetics (p = 0.56). There was no difference between the seminal concentration and the proportion of motile spermatozoa during the first hour of observation (p = 0.18) (Tables 1 and 2).

Table 1. Quantitative assessment of types of spermatozoa diabetic patients and non-diabetic (control) volunteers

Morphology	Group	
	Control (%)	Diabetics (%)
Oval	29	28
Spindle shaped	24	24
Round	23	23
Immature	7	8
Amorphous	9	8
Bicephalic	1	1
Bicaudate	1	1
Macrocephalic	3	3
Microcephalic	3	4

The percentage relates to the total number of spermatozoa; p = 0.89

Table 2. Mean concentration and percentage of motile forms found non-diabetic (control) volunteers and diabetic patients

Group	Concentration (M ± MSE) (number x 10^6/mL)	Mobile forms (%)
Control	80 ± 47	69.0
Diabetics	68 ± 06	64.0

M: mean; MSE: mean standard error; p = 0.18

The seminal fluid of diabetics was analyzed. One was altered, although not markedly, with lower volume of ejaculate semen, lower concentration and motility of the spermatozoa. In this patient there were hormone changes suggesting Leydig and Sertoli cell malfunction (Table 3).

Impotence was reported by four diabetic patients (33.3%) (three individuals were type 1 and one was type 2). These patients had chronic complications of diabetes secondary to neuropathy and angiopathy. No control subject complained of impotence (p = 0.0014) (OR = 1.50; 1.01 < OR < 2.24). Seventy-five percent of the impotent diabetic patients were using insulin NPH. No significant hormone changes were found in diabetic patients (Table 3).

DISCUSSION

Male impotence, which consists in difficulty in obtaining or maintaining full erection until the end of coitus, is a common sexual problem in diabetics[4,7]. The prevalence of this complaint ranges from 20 to 50%, increasing with patient age and duration of the disease[9], a fact that was also observed in the present study.

Boloña et al. stated that impotence is a multifactorial sexual disorder, secondary to endocrine, vascular, neurological and psychological disorders which act unfavorably on erection[12]. The findings of the present study point to vascular and neuronal anomalies as the

Table 3. Identification and characteristics related to the fertility of diabetic patients

Diabetics	Age (years)	Duration of diabetes (years)	Sexual potency	Insulin (U)	Chronic angiopathy and neuropathy	Seminal fluid	Glycosilated hemoglobin/ blood glucose	Hormones
1	21	8	N	50	-	↓	↑	↓
2	34	4	N	74	-	N	N	N
3	28	5	N	60	-	N	N	N
4	37	5	N	40	-	N	↑	N
5	58	7	N	-	P	N	N	↓
6	24	10	N	50	P	N	N	↓
7	60	6	↓	-	P	N	↑	↓
8	38	18	↓	40	P	N	N	N
9	37	6	N	72	-	N	N	↓
10	35	14	↓	50	P	N	N	N
11	46	3	N	-	-	N	↑	N
12	49	14	↓	50	P	N	N	↓

N: normal; ↓: reduced; ↑: increased; P: present

major causes of impotence in diabetic patients. On the other hand, hormones did not significantly affect this dysfunction.

The general seminal characteristics of color, odor and aspect were similar among all subjects. It could be argued that this occurred probably because of sample selection bias, due to exclusion of controls with signs of lower urinary tract infection, such as prostatitis or cystitis, even in the diabetic group.

Earlier studies on the hypothalamic-pituitary-gonadal axis dysfunction and impotence showed conflicting results[8,13]. In 2005, Pitteloud et al. observed that the Leydig cell population and testosterone metabolites were reduced, which was inversely related to the increase of insulin resistance[14]. However, other studies did not demonstrate altered serum testosterone levels among diabetics, regardless of their sexual performance[12,15]. Faerman did not find abnormalities in the number of Leydig cells, neither in testicular morphology in impotent diabetics[16].

According to Bansal et al., clinical reports prior to the insulin era suggested that insulin deficiency was the cause of impotence in diabetics, since they pointed to erectile dysfunction and testicular atrophy as the most common sexual disorders in poorly controlled diabetics. However, after insulin became available to treat diabetes, there was no change in this problem[17].

The relation between diabetes and male infertility is still being questioned[2,5]. Garcia-Diez et al. stated that type 1 *diabetes mellitus* (insulin-dependent) lowers seminal fluid volume. The concentration, motility, vitality and the proportion of normal shape spermatozoa is also lower[18]. On the other hand, Fairburn supported the idea that spermatogenic infertility was not common in diabetic men, but in those who had retrograde ejaculation[19]. In the present study, only one patient had seminal fluid changes associated to low serum testosterone and FSH levels, with normal LH, suggesting Leydig and Sertoli cell dysfunction.

The present study has limitations due to the small number of patients and to the need of performing new spermograms, which will be done in the follow-up study, looking at two different time points, one of them 12 months later.

CONCLUSIONS

The results of the present study suggest that neuropathy and vascular insufficiency may be related to sexual dysfunction in type 1 and type 2 diabetic patients, with no involvement of the hypothalamic-pituitary-gonadal axis.

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