Hyperprolactinaemia in male diabetics

Arshag D. Mooradian, John E. Morley, Charles J. Billington, Michael F. Slag, Michael K. Elson and Rex B. Shafer

Neuroendocrine Research Laboratory & Department of Nuclear Medicine, VA Medical Center, Minneapolis, and Division of Endocrinology, Department of Medicine, University of Minnesota, Minneapolis, Minnesota, USA.

Summary: We recently investigated two patients with diabetes and elevated serum prolactin levels in whom no cause of hyperprolactinaemia could be found. For this reason we measured fasting serum prolactin levels in 72 diabetic males and compared the results with those of 63 healthy males and 90 non-diabetic males attending an Impotence Clinic. The diabetic group had significantly higher serum prolactin levels (13.1 ± 0.9 ng/ml) than the two control groups (9.9 ± 0.6 ng/ml for normal males and 7.7 ± 0.3 ng/ml for the non-diabetic impotent group). Eighteen percent of the diabetics studied had serum prolactin levels above the normal range for males (> 20 ng/ml). There was no correlation between serum prolactin levels and duration of diabetes, glycosylated haemoglobin level or presence of clinically apparent retinopathy. The correlation between serum prolactin level and fasting plasma glucose was weak though statistically significant ($r = 0.26$, $P < 0.05$).

Introduction

There have been several reports with conflicting conclusions on the diabetogenic effect of prolactin (Landgraf *et al.*, 1977; Barnett *et al.*, 1980; Katz *et al.*, 1981; Hagen *et al.*, 1979; Johnston *et al.*, 1980). In one study 3 of 10 male patients with pituitary prolactinomas were diabetic (Goodman *et al.*, 1980). On the other hand, high mean serum prolactin levels were reported in 10 diabetic patients without retinopathy, in contrast to 4 diabetics with retinopathy with normal prolactin levels (Hunter *et al.*, 1974). Subsequent work did not confirm these findings (Harter *et al.*, 1976; Froland *et al.*, 1977). A recent study found no difference in the mean serum prolactin concentration in insulin and non-insulin treated diabetic patients, but the mean serum prolactin levels were not compared to a control population (Lester *et al.*, 1981). Recently we studied two diabetic patients with elevated prolactin levels in whom no cause for the elevation could be found. For this reason, we prospectively studied prolactin levels in 72 diabetic patients and compared them to an age matched control group as well as 90 non-diabetic males attending the Impotence Clinic.

A.D. Mooradian, M.D.; J.E. Morley, M.B., Ch.B.; C.J. Billington, M.D.; M.F. Slag, M.D.; M.K. Elson, Ph.D.; R.B. Shafer, M.D.

Correspondence: Rex B. Shafer, Nuclear Medicine Service, VA Medical Center, Minneapolis, Minnesota 55417, USA.

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Index cases

Case 1

A 51 year old male with an eleven year history of diabetes mellitus treated with diet and oral hypoglycaemics, was evaluated in the Impotence Clinic for gradual decrease in erection and ejaculation capability over the past two years but with normal libido. He was married and had one son. He denied any change in facial or body hair or use of drugs known to cause impotence. His blood glucose levels were consistently greater than 200 mg/dl. He had lower extremity paraesthesias. Physical examination revealed blood pressure to be 140/80 mm Hg with no postural drop and a pulse of 76 beats/minute. He weighed 117 kg with a height of 2.03 m. He had a full beard and normal body and pubic hair. Fundoscopic examination was normal and there was no gynecomastia or galactorrhoea. Testes were firm but small (2×2 cm bilaterally). He had decreased sensation to light touch in both lower extremities and decreased deep tendon reflexes bilaterally.

Laboratory evaluation included normal blood count, electrolytes, liver function and creatinine clearance with no proteinuria. Prolactin levels on two separate occasions were 34 and 38 ng/ml (normal range for males 2.2–20 ng/ml), luteinizing hormone (LH) 24 mIU/ml (normal range 6–30 mIU/ml), folli-

cle stimulating hormone (FSH) 48 mIU/ml (normal range 5–25 mIU/ml and serum testosterone of 293 ng/dl (normal range 300–1000 ng/dl). Serum total thyroxine (T4) was 8.1 µg/dl (normal range 4–12.5 µg/dl), triiodothyronine (T3) uptake 24% (normal range 25–35%), and thyroid stimulating hormone (TSH) 1.9 µU/ml (normal range 0–6 µU/ml). The response of TSH, prolactin, FSH and LH to LH releasing hormone/thyrotropin releasing hormone (LHRH/TRH) stimulation test were normal. TSH increased from 1.9 to 8.3 µU/ml, prolactin increased from 26.5 to 47 ng/ml, LH increased from 17.7 to 79.7 mIU/ml and FSH increased from 36.8 to 69.3 mIU/ml. Serum cortisol at 08:00 h was 23.0 µg/dl with a serum ACTH of 21.6 pg/ml. After metapyrone, the serum compound S rose from 0.9 to 16.7 µg/dl. Computerized tomography of the pituitary was normal. The patient was diagnosed as having primary hypogonadism and discharged on depot testosterone 200 mg intramuscular injection every two weeks. On follow-up, his serum testosterone was 1757 mg/dl, with LH of 5.1 mIU/ml and FSH of 4.9 mIU/ml. Serum prolactin was persistently high at 45.1 ng/ml and there was a moderate improvement in his sexual potency.

Case 2

A 60 year old male complained of 15 years of impotence. He had diabetes mellitus treated with diet and oral hypoglycaemic agents for approximately the same length of time. Recent fasting blood glucose was 130 mg/dl and his haemoglobin A_{1c} was 6.8 mg/dl. Other chronic health problems included: Type IV familial hyperlipidaemia and hypertension treated with atenolol. His impotence was characterized by inability to provoke erection for 15 years. No changes in secondary sexual characteristics were noted, nor gynaecomastia or galactorrhoea. Physical examination was normal.

Laboratory evaluation showed normal renal func-

tion. Prolactin on two occasions was 60.4 and 67.2 ng/ml. Gonadotrophins were normal: LH 14.5 mIU/ml, FSH 19.3 mIU/ml, with serum testosterone 244 and 297 ng/dl on two occasions. Thyroid function was normal. High resolution computerized tomography failed to demonstrate any pituitary abnormality.

Materials and methods

Seventy-two consecutive male patients with diabetes mellitus were evaluated. The mean age was 53.5 ± 1.4 (range 26–74 y). Fourteen were on oral hypoglycaemics and a restricted diet, while the rest were on insulin therapy. Retinopathy was evaluated clinically. Sexual potency was evaluated by history. Impotence was defined as an inability to sustain an erection adequate for sexual intercourse. Hypothyroid and hypogonadal patients were excluded from the study as well as those with serum creatinine levels greater than 1.3 mg/dl, those taking drugs known to increase prolactin levels, and patients with liver disease. Sixty-seven healthy males with a mean age of 41.4 ± 1.5 y (range 19–63 y) and 90 non-diabetic impotent patients followed up in the Impotence Clinic with a mean age of 58.2 ± 0.8 y (range 31–79 y) served as the two control groups. All the samples of blood were drawn by venepuncture after an overnight fast. Serum glucose was measured with a Technicon Autoanalyzer, glycosylated haemoglobin was measured by microcolumns (Welch and Boucher, 1978) and serum prolactin was measured by radioimmunoassay (Sinha *et al.*, 1973). The intraassay coefficient of variation was 6.6% at 7.5 ng/ml and 4.2% at 35 ng/ml and the interassay coefficient of variation was 12.6% at 7.5 ng/ml and 7.8% at 35 ng/ml.

All results are expressed as mean $\pm$ SEM. Statistical analysis was done by two-tailed Student's *t*-test for unpaired variables and regression analysis where appropriate.

Table I Mean ages, duration of diabetes, glycosylated haemoglobin level and serum prolactin level in diabetics with or without retinopathy.

	Number	Age (y)	Duration of diabetes (y)	Glycosylated haemoglobin (%)	Prolactin (ng/ml)
Total	72	53.7 ± 1.4	13.3 ± 1.1	10.3 ± 0.3	13.1 ± 0.9
<i>Diabetics</i>					
With retinopathy	37	53.8 ± 1.8	18.8 ± 1.3	10.9 ± 0.5	12.2 ± 1.1
Without retinopathy	35	53.5 ± 2.1	7.4 ± 1.3	9.8 ± 0.3	13.7 ± 1.4
<i>Controls</i>					
Healthy	67	41.4 ± 1.5	—	—	9.9 ± 0.6
Impotent patients	90	58.2 ± 0.8	—	—	7.7 ± 0.3

Results

Table I shows the mean ages, duration of diabetes, mean glycosylated haemoglobin and mean serum prolactin levels of diabetics with or without retinopathy. The mean ages and serum prolactin of the two control groups are also shown. The diabetic group was older than the healthy control group and younger than the impotent control group. The mean fasting serum prolactin level (13.1 ± 0.9 ng/ml) was significantly higher than the mean serum prolactin level of the two control groups (9.9 ± 0.6 and 7.7 ± 0.3 ng/ml for the healthy and impotent controls, both $P < 0.01$). Thirteen of the 72 diabetics (18%) screened had serum prolactin levels above the upper limit of normal for males (> 20 ng/ml). Eight of those with serum prolactin levels above 20 ng/ml had impotence. The mean serum prolactin level of 52 impotent diabetics was not different from the level found in the diabetic subjects who were sexually potent (13.9 ± 1.1 ng/ml vs 13.4 ± 2.2 ng/ml, respectively). Serum prolactin levels of diabetics with retinopathy (12.2 ± 1.1 ng/ml) was not significantly different from those without retinopathy (13.7 ± 1.4 ng/ml). The mean glycosylated haemoglobin levels of the two subgroups was also not significantly different ($10.86 \pm 0.54\%$ for those with retinopathy vs $9.75 \pm 0.29\%$ for those without retinopathy) (Table I).

The mean serum prolactin level of the Type I diabetic subjects (12.4 ± 1.3 ng/ml) was not different from the level found in subjects with Type II diabetes (13.5 ± 1.1 ng/ml). There was no correlation between serum prolactin level and duration of diabetes ($r = 0.076$) or glycosylated haemoglobin level ($r = 0.202$). The correlation between serum prolactin level and concomitantly measured fasting plasma glucose was weak though statistically significant ($r = 0.26$, $P < 0.05$).

Discussion

Our results clearly indicate that diabetics as a group have higher fasting serum prolactin levels than normals. There was no difference between Type I and Type II diabetic subjects and there was no correlation between the serum prolactin level and sexual potency within the diabetic group. Previous studies on serum prolactin level in relation to retinopathy have been controversial and the number of patients studied was small (Hunter *et al.*, 1974; Harter *et al.*, 1976; Froland *et al.*, 1977). Hanssen and Torjesen (1977) reported mildly elevated serum prolactin levels in 8 patients with diabetic ketoacidosis, while serum prolactin levels were normal in patients with treated diabetes mellitus. Similarly Lester *et al.* (1981) found elevated serum prolactin levels in 3 of 83 male diabetics

screened but did not compare diabetics to controls. Two groups reported normal prolactin response to TRH testing in insulin dependent diabetics (Froland *et al.*, 1977; Morley *et al.*, 1978).

The cause of the elevated mean fasting serum prolactin level and occasionally observed hyperprolactinaemia in diabetics is not clear. Differences in dietary habits would be one possible explanation since diet is known to influence serum prolactin levels (Hill and Wynder, 1976; Hill, 1981; Quigley *et al.*, 1981). An alternative possibility would be abnormalities developing from microvascular infarcts of the pituitary stalk which interfere with the inhibitory stimuli of prolactin secretion. It is noteworthy in this regard that pituitary infarction has been associated with diabetes mellitus (Kovacs, 1969). Recently Saller and Chiodo (1980) reported that glucose administration in the rat suppresses the firing of central dopamine neurones; hence it is tempting to speculate that chronically elevated blood glucose in diabetics could raise serum prolactin level by suppressing dopaminergic neuronal activity, a known inhibitor of prolactin release (MacLeod, 1976). The correlation between serum prolactin and fasting plasma glucose found in this study is supportive of this speculation. Further studies are necessary to clarify the basic pathophysiology of the increased serum prolactin level in diabetics.

Hyperprolactinaemia is known to be associated with impotence (Franks *et al.*, 1978; Nagulesparen *et al.*, 1978). There is considerable evidence in the literature to suggest that excess prolactin can produce hypothalamic pituitary dysfunction and can suppress gonadal function directly (Kirby *et al.*, 1979). In our two index patients, the serum testosterone levels were modestly low without any elevation in serum luteinizing hormone (LH) levels. It is possible that the mild hyperprolactinaemia observed in our patients is at least partially responsible for these changes in serum testosterone levels. However, it is very unlikely that hyperprolactinaemia constitutes a significant cause of impotence in diabetic patients. In fact, in a study of 83 diabetic men, Lester *et al.* (1981) did not find any correlation between impotence and serum prolactin levels in their group of patients.

From the clinical standpoint it is important to recognize that elevated serum prolactin levels can be found in diabetics and may not be attributable to a specific cause of hyperprolactinaemia. We would suggest that the normal range for prolactin in diabetics be extended. In accordance with our study an upper level of 30 ng/ml would be appropriate.

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