ORIGINAL ARTICLE

Macroprolactinaemia in diabetic patients

Nese Ersoz Gulcelik, Aydan Usman

Department of Endocrinology and Metabolism, Faculty of Medicine, Hacettepe University, Ankara, Turkey

Correspondence to: Nese Ersoz Gulcelik, MD.
Hacettepe University Medical School, Department of Endocrinology,
06100 Sihhiye, Ankara, Turkey.
FAX: +90 312 305 17 07; E-MAIL: nersoz@hacettepe.edu.tr

Submitted: 2009-03-27 Accepted: 2009-11-12 Published online: 2010-04-28

Key words: **prolactin; diabetes; macroprolactin**

Neuroendocrinol Lett 2010; **31**(2):270–274 **PMID:** 20424586 NEL310210A07

Abstract

OBJECTIVE: Prolactin levels have been shown to be reduced in poorly controlled diabetes mellitus; however, diabetic patients with high prolactin levels may be seen in clinical practice. The aim of this study was to evaluate diabetic patients with hyperprolactinemia, and to determine the role of macroprolactinaemia in these patients.

MATERIALS AND METHODS: The study included 174 patients (153 women and 21 men) with hyperprolactinemia, retrospectively reviewed over a 2 years period. Data on presenting symptoms, the presence of diabetes mellitus, prolactin levels, macroprolactin levels, pituitary magnetic resonance imaging were collected in all patients. In addition; HbA1c, fasting blood glucose levels and postprandial glucose levels were collected in diabetic patients.

RESULTS: Of the 174 patients, 27 were diagnosed with diabetes mellitus (15.5%). Eighteen of the diabetic patients with hyperprolactinaemia had macroprolactinaemia (66.6%). The prevalence of macroprolactinaemia in diabetic patients is higher than the non-diabetic population (66.6% vs. 39.5%, p=0.009). In diabetic patients with macroprolactinaemia, HbA1c levels were higher than the diabetic patients without macroprolactinaemia.

CONCLUSION: The prevalence of macroprolactinaemia in diabetic patients was higher than the non-diabetic population. It seems necessary to determine macroprolactin levels in diabetic patients with hyperprolactinaemia; and in this case, further diagnostic evaluation is not warranted.

INTRODUCTION

Molecular weight variants of prolactin other than monomeric prolactin can be demonstrated in serum (Suh & Frantz 1974; Fraser & Zhuang 1990). These molecular variants include big prolactin, which has a molecular mass of 50–60 kDa and accounts for approximately 10–15% of prolactin. Furthermore, big big prolactin, or macroprolactin, which has a molecular mass of more than 150 kDa, usually contributes a small, variable amount to circulating levels (Suh & Frantz 1974; Smith & Norman 1990). The clinical importance of these forms is that they are not bioactive and have little or no pathological significance, but have a long half-life in serum, resulting in the development of hyperprolactinaemia. This pseudo-hyperprolactinaemia associated with macroprolactin may not

be causally associated with any symptoms, but may be associated with co-incidental symptoms (Suliman *et al.* 2003; Gibney *et al.* 2005).

Macroprolactin seems to be heterogeneous in its etiologies; however, the most frequently observed form of macroprolactin is a complex proposed to consist of immunoglobulin G (IgG) and monomeric prolactin (Leite *et al.* 1992; Hattori *et al.* 1992a, Hattori *et al.* 1992b). In patients with hyperprolactinaemia, the prevalence of macroprolactinaemia varies from 10% to 46% (Hauche *et al.* 2002; Donadio *et al.* 2007; Vallette-Kasic *et al.* 2002). All commercial assays for prolactin that have been examined to date react with macroprolactin. The degree of interference of each assay is variable and depends on the formulation of the immunoassay and the nature of the macroprolactin species (Gibney *et al.* 2005; Fahie-Wilson, 2000; Smith *et al.* 2002; Fahie-Wilson, 2005). Failure to recognize macroprolactinaemia may result in unnecessary investigations, inaccurate or delayed diagnosis, and inappropriate treatment (Suliman *et al.* 2003; Gibney *et al.* 2005, Olukoga *et al.* 1999).

Prolactin levels have been shown to be reduced in poorly controlled diabetes mellitus, which may result in reduced lactation in women (Ikawa *et al.* 1992, Montelengo *et al.* 1992; Ostrom & Ferris, 1993; Valimaki *et al.* 1991). However, although it is not very common, diabetic patients with high prolactin levels may be seen in clinical practice. In this study, we aimed to evaluate diabetic patients with hyperprolactinemia and to determine the role of macroprolactinaemia in these patients.

MATERIALS AND METHODS

The study included 174 patients (153 women and 21 men) with hyperprolactinemia retrospectively reviewed over a 2-year period. Data on presenting symptoms, the presence of diabetes mellitus, prolactin levels, macroprolactin levels, pituitary magnetic resonance imaging (MRI) were collected in addition to HbA1c, fasting blood glucose levels, and postprandial glucose levels in diabetic patients. Serum prolactin levels higher than 29.5 ng/ml in women and higher than 18.5 ng/ml in men were defined as hyperprolactinemia. We excluded the patients taking mediacations which may affect serum prolactin levels, patients with hypothyroidism, renal failure and polycystic ovary syndrome, patients that were operated on for pituitary adenoma, and patients with pituitary adenoma secreting growth hormones or other pituitary hormones. Prolactin levels were measured by 7K76 Architec Prolactin Reagent KİT (Abbott, Ireland); macroprolactin was detected by PEG precipitation. Recoveries ≤40 were classified as macroprolactinaemia and recoveries ≥50 were classified as monomeric prolactin. Patients with recovery between 40% and 50% were excluded from the study.

Descriptive statistics were expressed as mean ± standard deviation. The differences between two groups were examined by an independent samples t-test. The chi-square test or Fisher's exact test was used for the analysis of categorical variables. Associations between variables were assessed by Pearson correlation coefficients. Data analysis was performed by SPSS 10.0 (Statistical Package for Social Sciences) software package. A $p<0.05$ was accepted as statistically significant.

RESULTS

Macroprolactinemia was detected in 76 of 174 patients (43.7%) with a mean prolactin level of 79.1±51.6 ng/ml. These prolactin levels were not statistically different ($p=0.683$) from those observed in the remaining 98 patients with monomeric hyperprolactinaemia (75.3±65.9 ng/ml). Of women, 69 out of 153 (45.1%) and 7 out of 21 men (33.3%) had recoveries below 40%. The characteristics of the patients are given in Table 1. Among the symptoms that prompt prolactin

Tab. 1. Characteristics of the patients with and without macroprolactinaemia

Characteristics	Macroprolactin + (n=76)	Macroprolactin – (n=98)	*p*-value
Female/Male	69/7	84/14	NS
Age (years)	39.1±11.0	39.6±12.0	NS
Prolactin (ng/ml)	79.1±51.6	75.3±65.9	NS
Post PEG Prolactin (ng/ml)	13.3±8.1	59.01±58.0	<0.001
Diabetes Mellitus (n)	18 (23.7%)	9 (9.2%)	0.008
pituitary MRI			
Normal	62(81.6%)	30 (32.6%)	<0.01
Microadenoma	13 (17.1%)	51 (52.0%)	<0.01
Macroadenoma	0 (0%)	14 (14.3%)	<0.01
Empty sella	1 (1.3%)	3 (3.1%)	<0.01
Clinical features (in women)*			
Oligo/amenorrhoea	68.4%	60.2%	NS
Galactorrhoea	15.8%	54.1%	<0.001
Infertility	10.5%	11.2%	NS
Headache	7.9%	6.1%	NS
Clinical features (in men)			
Decreased libido	2 (28.6%)	1 (7.1%)	NS
Erectile dysfunction	3 (42.9%)	7 (50%)	NS
Headache	2 (28.6%)	3 (42.9%)	NS

Data are presented as mean ± SD. NS: not significant.
*30 patients with monomeric prolactineamia and 2 patients with macroprolactinaemia had both galactorrhoea and oligo/amenorrhoea.

Tab. 2. Characteristics of the diabetic patients with macroprolactinaemia and without macroprolactinaemia

Characteristics	Macroprolactin + (n=18)	Macroprolactin – (n=9)	*p*-value
Female/Male	15/3	9/0	NS
Age (years)	47.1±10.3	46.7±4.7	NS
Prolactin (ng/ml)	51.3±23.5	45.1±14.6	NS
Post PEG Prolactin (ng/ml)	11.5±7.1	32.1±6.5	0.001
HbA1c (%)	7.0±0.7	6.0±0.4	0.001
FBG (mg/dl)	121.1±24.8	111.8±12.2	NS
PPG (mg/dl)	159.4±27.6	154.8±34.8	NS
Diabetes duration (years)	4.1±1.3	3.2±1.9	NS

Data are presented as mean ±SD. NS: not significant. FBG: fasting blood glucose, PPG: postprandial blood glucose.

measurement, only galactorrhoea was more frequent in monomeric hyperprolactiaemic patients than the macroprolactinaemic patients (Table 1). Thirty-one patients with monomeric prolactinaemia and two patients with macroprolactinaemia had both galactorrhoea and oligo/amenorrhoea. In men, erectile dysfunction, decreased libido, and headache were in similar proportion in monomeric hyperprolactinaemic and macroprolactinaemic patients. Sixty-two patients with macroprolactinaemia had normal pituitary imaging (81.6%), thirteen had microadenoma (17.1%), and one had empty sella (1.3%) (Table 1).

Of the 174 patients, 27 were diagnosed with diabetes mellitus (15.5%). Diabetic patients had lower prolactin levels before and after PEG precipitation than the non-diabetic patients (49.2±20.9 ng/ml vs. 82.07±63.3 ng/ml, $p<0.001$ and 18.4±12.0 ng/ml vs. 42.8±52.5 ng/ml, $p<0.001$, respectively). Eighteen of the diabetic patients had macroprolactinaemia (66.6%). The prevalence of macroprolactinaemia in diabetic patients was higher than the non-diabetic population (66.6% vs. 39.5%, $p=0.009$) (Figure 1). Duration of diabetes did not differ between the patients with macroprolactinaemia and the patients without macroprolactinaemia (4.1±1.3 years vs. 3.2±1.9 years, respectively, $p=0.636$). In diabetic patients with macroprolactinaemia, HbA1c levels were higher than the diabetic patients without macroprolactinaemia (7.0±0.74% vs. 6.1±0.37%, respectively, $p=0.001$). There was no correlation between HbA1c levels and prolactin levels in diabetic patients (r=0.325, $p=0.098$), but HbA1c levels were negatively correlated with prolactin levels after PEG precipitation (r=–0.520, $p=0.005$). Fasting blood glucose levels and postprandial glucose levels did not differ between each group (Table 2).

In diabetic women with macroprolactinaemia, four had galactorrhoea (26.7%) and eleven had oligo/amenorrhoea (73.3%). In all three diabetic men with macroprolactinaemia, they each had erectile dysfunction. In diabetic women with monomeric prolactinaemia, three had galactorrhoea (33.3%), three had oligo/amenorrhoea (33.3%), and three had both oligo/amenorrhoea and galactorrhoea (33.3%). In diabetic patients with macroprolactinaemia, pituitary imaging revealed that 16 (88.9%) had normal pituitary imaging and two had microadenoma (11.1%). In diabetic patients with monomeric hyperprolactinaemia, one had normal pituitary imaging (11.1%), six had microadenoma (66.7%), and two had empty sella (22.2%).

DISCUSSION

After the introduction of macroprolactin, we were aware of the fact that some patients we treated as idiopathic hyperprolactinaemia were those with pseudo-hyperprolactinaemia as a result of the detection of macroprolactin in commercial assays.

Pseudo-hyperprolactinaemia leads to misdiagnosis and overtreatment of hyperprolactinaemia; it even delayed diagnosis of underlying diseases. In patients with hyperprolactinaemia, the prevalence of macroprolactinaemia varies from 10% to 46% (Hauche *et al.* 2002; Donadio *et al.* 2007). In our study, the prevalence of macroprolactinaemia is 43.7%. This value is in line with Donadio *et al.* (2007) and Hauache *et al.* (2002). In fact, all commercial assays for prolactin that have been examined to date react with macroprolactin. The degree of interference of each assay is variable and depends on the formulation of the immunoassay and the nature of the macroprolactin species (Gibney *et al.* 2005; Fahie-Wilson 2000; Smith *et al.* 2002; Olukoga *et al.* 1999). Among the prolactin assays, Architect (Abbott) found to be among those exhibiting higher reactivity toward macroprolactin. Therefore, it is conceivable that this high prevalence of macroprolactinaemia may be due to methodological bias.

As far as the symptoms of hyperprolactinaemia are concerned, galactorrhoea was more frequently observed in women with monomeric hyperprolactinameia than in women with pseudo-hyperprolactinaemia. Symptoms such as oligo/amenorrhea, infertility and headaches in women as well as erectile dysfunction and decreased libido in men were present in patients with macroprolactinaemia in similar proportion to that found in patients with true hyperprolactinaemia. The clinical features are not distinguishable to detect macroprolactineamia in hyperprolactinemic patients as indicated previously (Donadio *et al.* 2007). This may be because these patients are subject to prolactin level determination as a result of these symptoms, but the diagnosis is not always monomeric hyperprolac-

tinaemia. In this case, failure to recognize macroprolactinaemia may result in unnecessary investigations, inaccurate or delayed diagnosis, and inappropriate treatment (Suliman *et al.* 2003; Gibney *et al.* 2005; Ikawa *et al.* 1992). The prevalence of abnormal pituitary imaging was 17.1% in macroprolactinaemic patients, which is similar to that in the general population undertaken CT or MRI imaging for reasons other than the pituitary reasons (Molitch & Russel 1990). In patients with macroprolactinaemia, 81.6% had normal pituitary imaging in accordance with the previous studies (Suliman *et al.* 2003; Gibney *et al.* 2005).

Poorly controlled diabetes mellitus can result in decreased prolactin production and thus can result in problems with lactation, reproduction, and other physiological processes (Ikawa *et al.* 1992, Montelengo *et al.* 1992; Ostrom & Ferris 1993; Valimaki *et al.* 1991). In diabetic rats, cell death in the anterior pituitary begins 4 weeks after the onset of diabetes, involving the activation of caspase-8. However, increased death of lactotrophs in poorly controlled diabetic rats is followed by increased proliferation of this cell type after 8 weeks, even when no treatment is given. Hence, between 4 and 8 weeks of diabetes evolution lactotrophs are highly affected and are the underlying cause of these changes; and, whether insulin treatment can prevent or reverse it remains unknown (Arroba *et al.* 2006). However, whether the proliferation in lactotrophs after 8 weeks seen in diabetic rats occurs in humans is suspicious, as there is sufficient disparity in the control of the production, distribution, and physiological functions of prolactin among rats and mice to warrant careful and judicial extrapolation to humans (Ben-Jonathan *et al.* 2008) and if occurs the clinical relevance of this proliferation is unknown. A few human studies about the prolactin levels during and after the gestation were conducted; it was found that diabetics have lower levels of prolactin than the control group (Ikawa *et al.* 1992; Ostrom & Ferris 1993). Low prolactin levels lead to diminished or decreased lactation and reproduction. In our study, 15.5% of the patients with hyperprolactinaemia were diabetic. However, 18 of the 27 diabetic patients had macroprolactinaemia (66.6%). This indicates that two-thirds of the hyperprolactinaemic patients had pseudo-hyperprolactinaemia associated with macroprolactinaemia. Only 9 diabetic patients had monomeric hyperprolactinaemia. We can speculate that these patients' lactotrophs may not be subject to atrophy or delayed proliferation of the lactotrophs which may occur in these patients. The prevalence of macroprolactinaemia in diabetic patients is higher than the non-diabetic population. In our study, diabetic patients with macroprolactinaemia had significantly higher HbA1c levels than the ones without macroprolactinaemia. Poor glycemic control may have a role in the formation of macroprolactin in diabetic patients. The etiology of macroprolactin in diabetic patients and the effect of poor glycemic control are unknown. Further studies by gel filtration electrophoresis and affinity chromatography on Concanavalin-A-sepharose electrophoresis may reveal this issue.

Galactorrhoea was more frequently observed in diabetic women with monomeric hyperprolactinameia than women with macroprolactinaemia, but it was also seen in macroprolactinaemic patients. The other symptoms that prompt the prolactin measurement did not differ in diabetic patients with or without macroprolactinaemia. The clinical features do not help to distinguish the diabetic patients with macroprolactinaemia, and monomeric hyperprolactinaemia, and determination of macroprolactin levels is needed. Furthermore, diagnostic evaluation of these patients revealed that 88.9% of macroprolactinaemic patients had normal pituitary imaging. Further diagnostic evaluation seems unnecessary in diabetic patients with macroprolactinaemia.

In conclusion, 15.5% of the hyperprolactinaemic patients had diabetes. The diabetic patients had lower levels of prolactin than the non-diabetic patients. In diabetic patients, the cause is mostly macroprolactinaemia. Moreover, diabetic patients with hyperprolactinaemia needed to be evaluated for the presence of macroprolactin, which may help to overcome misdiagnosis, unnecessary investigations, and inappropriate treatment.

REFERENCES

1 Arroba AI, Lechuga-Sancho AM, Frago LM, Argente J, Chowen JA. (2006). Increased apoptosis of lactotrophs in streptozotocin-induced diabetic rats is followed by increased proliferation**.** J Endocrinol. **191**: 55–63.

2 Ben-Jonathan N, Lapensee CR, Lapensee EW. (2008). "What Can We Learn from Rodents about Prolactin in Humans? Endocr Rev. **29**(1): 1–41.

3 Donadio F, Barbieri A, Angioini R, Mantovani G, Beck-Peccoz P, Spada A, Lania AG. (2007). Patients with macroprolactinaemia: clinical and radiological features. Eur J Clin Invest. **37**(7): 552–557.

4 Fahie-Wilson MN. (2000). Detection of macroprolactin causing hyperprolactinemia in commercial assays for prolactin. Clin Chem. **46**: 2022–2023.

5 Fahie-Wilson M, John R, Ellis AR. (2005). Macroprolactin; high molecular mass forms of circulating prolactin: Ann Clin Biochem. **42**: 175–192.

6 Fraser IS, Zhuang GL. (1990). Polymers of prolactin and their clinical significance. Obstet and Gynecol Surv. **45**: 515–520.

7 Gibney J, Smith TP, McKenna TJ. (2005). The impact on clinical practice of routine screening for macroprolactin. J Clin Endocrinol Metab. **90**(7): 3927–3932.

8 Hattori N, Ikekubo K, Ishihara T, Moridera K, Hino M, Kurahachi H. (1992a). A normal ovulatory woman with hyperprolactinemia: presence of anti- prolactin autoantibody and the regulation of prolactin secretion. Acta Endocrinol. **126**(6): 497–500.

9 Hattori N, Ishihara T, Ikekubo K, Moridera K, Hino M, Kurahachi H. (1992b). Autoantibody to human prolactin in patients with idiopathic hyperprolactinemia. J Clin Endocrinol Metab. **75**(5): 1226–1229.

10 Hauche OM, Rocha AJ, Maia AC, Maciel RM, Vieira JG. (2002). Screening for macroprolactinaemia and pituitary imaging studies. Clin Endocrinol. **57**: 327–31.

11 Ikawa H, Irahara M, Matsuzaki T, Saito S, Sano T, Aono T. (1992). Impaired induction of prolactin secretion from the anterior pituitary by suckling in streptozotocin-induced diabetic rat. Acta Endocrinologica. **126**: 167–17.

12 Leite V, Cosby H, Sobrinho LG, Fresnoza MA, Santos MA, Friesen HG. (1992). Characterization of big, big prolactin in patients with hyperprolactinaemia. Clin Endocrinol. **37**(4): 365–372.
13 Molitch ME, Russel EJ. (1990). The pituitary 'incidentaloma'. Ann Intern Med. **112**: 925–931.
14 Montelongo A, Lasuncion MA, Pallardo LF, Herrera E. (1992). Longitudinal study of plasma lipoproteins and hormones during pregnancy in normal and diabetic women. Diabetes. **41**: 1651–1659.
15 Olukoga AO, Dornan TL, Kane JW. (1999). Three cases of macroprolactinaemia. J R Soc Med. **92**(7): 342–344.
16 Ostrom KM, Ferris AM. (1993). Prolactin concentrations in serum and milk of mothers with and without insulin-dependent diabetes mellitus. Am J Clin Nutr. **58**: 49–53.
17 Smith CR, Norman MR. (1990). Prolactin and growth hormone: molecular heterogeneity and measurement in serum. Ann of Clin Biochem. **27**: 542–550.
18 Smith TP, Suliman AM, Fahie-Wilson MN, McKenna TJ. (2002). Gross variability in the detection of prolactin in sera containing big big prolactin (macroprolactin) by commercial immunoassays. J Clin Endocrinol Metab. **87**: 5410–5415.
19 Suh HK, Frantz G. (1974). Size heterogeneity of human prolactin in plasma and pituitary extracts. J Clin Endocrinol Metab. **39**: 928–935.
20 Suliman AM, Smith TP, Gibney J, McKenna TJ. (2003). Frequent misdiagnosis and mismanagement of hyperprolactinemic patients before the introduction of macroprolactin screening: application of a new strict laboratory definition of macroprolactinemia. Cli Chem. **49**(9): 1504–1509.
21 Valimaki M, Liewendahl K, Nikkanen P, Pelkonen R. (1991). Hormonal changes in severely uncontrolled type 1 (insulin-dependent) diabetes mellitus Scand J Clin Lab Invest. **51**: 385–393.
22 Vallette-Kasic S, Morange-Ramos I, Selim A, Gunz G, Morange S, Enjalbert A. (2002). Macroprolactinemia revisited: a study on 106 patients. J Clin Endocrinol Metab. **87**: 581–588.