Paradoxical glycaemic response to surgical treatment of ovarian hyperthecosis in a patient with type 2 diabetes

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Introduction

Ovarian stromal hyperthecosis in post-menopausal women is a rare disorder characterised by gradual virilisation and features of the metabolic syndrome similar to PCOS.[1] Improvement of diabetic control in hyperthecosis has been reported following oophorectomy, perhaps secondary to normalisation of the hyperandrogenaemia.[2] This is a report of worsening diabetes following oophorectomy. The case and possible explanations for the response are described.

Case report

A 56 year-old post-menopausal woman with type 2 diabetes was referred to the diabetes clinic in January 2002, the diabetes having been diagnosed in 2001 following an ischaemic stroke. Glycaemic control was poor with dyslipidaemia and elevated liver enzymes (Table 1). Hepatic steatosis was suggested on ultrasound in keeping with the lipid and liver function tests. Oral hypoglycaemic agents were converted to a basal bolus insulin regime on referral in 2002, resulting in a reduction of HbA_{1c} from 9.4% to 6.8%.

In 2005 the patient complained of gradual onset male pattern balding and excessive hair over the face, forearms, shoulders and legs that had been developing over two years. Results (reference range) showed that total and free testosterone concentrations were elevated at 6.7 nmol/L (<1.7) and 24.7 pmol/L (4.5–19.4) respectively, with SHBG low at 4.7 nmol/L

Abbreviations and acronyms

CT	computed tomography
DHEAS	dehydroepiandrosterone sulphate
FSH	follicle stimulating hormone
GGT	γ-glutamyl transferase
GnRH	gonadotropin releasing hormone
HbA_{1c}	haemoglobin A_{1c}
HPLC	high performance liquid chromatography
HDL-C	high density lipoprotein cholesterol
LDL-C	low density lipoprotein cholesterol
LH	luteinising hormone
PCOS	polycystic ovarian syndrome
PPAR	peroxisome proliferator activated receptor
SHBG	sex hormone binding globulin

(31.0–93.0). Androstenedione was marginally elevated at 13.1 nmol/L (1.7–12.9) and FSH and oestradiol were low at 13.7 IU/L (post-meonopausal: 26.7–133.4) and <73.4 pmol/L (post-menopausal: 37–1028) respectively. The rest of the results were within the normal reference ranges; LH 12.3 IU/L (post-meonopausal: 5.2–62.0), DHEAS 0.9 µmol/L (0.0–5.4), random cortisol 351 nmol/L and prolactin 544 mIU/L (98–784). Thyroid function tests and renal function were unremarkable.

Abdominal and pelvic CT scan did not reveal any pathology. A low dose dexamethasone suppression test demonstrated suppression of baseline values of cortisol and DHEAS from 437 to 36 nmol/L and 1.2 to <0.8 nmol/L, respectively, whereas testosterone did not suppress (6.3 to 5.7 nmol/L), suggesting that the elevated testosterone was mainly ovarian in origin. Trans-vaginal ultrasound showed bilateral solid heterogeneous adnexal masses. Treatment options were discussed with the patient and she elected for a bilateral oophorectomy (October 2006) as opposed to medical treatment with GnRH agonists. Following surgery the left (50×30×25 mm) and right (60×30×20 mm) ovaries were seen to contain subcapsular tan nodules, corpora albicans on the surface and the ovarian tissue had been replaced by a uniform ochre-coloured tissue, these findings consistent with stromal hyperthecosis.

The testosterone levels normalised post-operatively (within 2 weeks) and the patient reported improvements in both hirsutism and baldness at the six-week review. Subsequently the glycaemic control (Table 1, Figure 1) worsened despite no change in the patient's weight and lifestyle. Within 4 months an extra 100 units/day (124 to 224 units/day) of insulin were required, but

Table 1 Patient data (when available) before and after oophorectomy highlighting the change in glycaemic control and the increase in insulin requirement.

	Weight (kg)	Insulin (Units/day)	HbA$_{1c}$ (%/mmol/mol)	Total cholesterol (mmol/L)	Triglyceride (mmol/L)	HDL-C (mmol/L)	LDL-C (mmol/L)	γ-glutamyl transferase (IU/L)	Testosterone (nmol/L)	SHBG (nmol/L)
Jan-02			9.4/79.0	6.0	8.8			509		
Oct-03		138	6.8/50.8	4.9	2.2	1.0	2.9	193		
Oct-04	107.2	138	7.0/53.0	5.0	2.2	1.1	2.9	143		
Jan-05	106.2	138	6.5/47.5	4.6	2.1	1.0				
Aug-05	107.0	124	6.9/51.9	4.9	2.2	1.2	2.7	191	6.7	
Sep-05	106.9	124							9.7	14.7
Nov-05		124							6.3	
Dec-05	109.0	124	7.2/55.2	5.1	2.9	1.2	2.6	199	7.2	12.0
Feb-06	110.0	124							7.2	13.2
Jul-06	109.5	124	7.4/57.4					202	6.6	
				Oct-2006 - Surgery (oophorectomy)						
Nov-06	106.5	124	7.4/57.4	5.2	2.6	1.4	2.6	317	0.2	
Mar-07		224	8.5/69.4	5.4	3.7	1.4	2.3	509	0.4	
May-07	105.1	224	9.4/79.2	5.5	2.6	1.2	3.1	627		
Jul-07	107.8	224	8.9/73.8	5.6	2.2	1.3	3.3	583	0.2	
Sep-07		234	9.5/80.3	5.2	2.2	1.2	3	612		
Feb-08		268	8.9/73.8	5.5	2.4	1.3	3.1		0.3	
Mar-09	109.0	288	8.5/69.4					679	0.3	
May-09		292	7.8/61.7	5.9	2.3	1	3.8	546	0.6	23.5
Aug-09	105.0	292	7.4/57.4	6.3	1.9	1.1	4.3		0.7	24.3
Nov-10	108.0	302	7.3/56.3	5.8	1.8	1.1	3.9	447	0.5	
May-11	110.0	300	7.1/54.1	5.6	1.1	1.4	3.4	386	0.4	
Nov-11	108.0	300	7.1/54.1	6.7	2.4	1.4	4.2	433	0.3	
Sept-13	107.4	342	7.6/59.6	6.6	1.9	1.2	4.5	448	0.5	53

Figure 1. Change of insulin dose and testosterone levels over time (month/year).
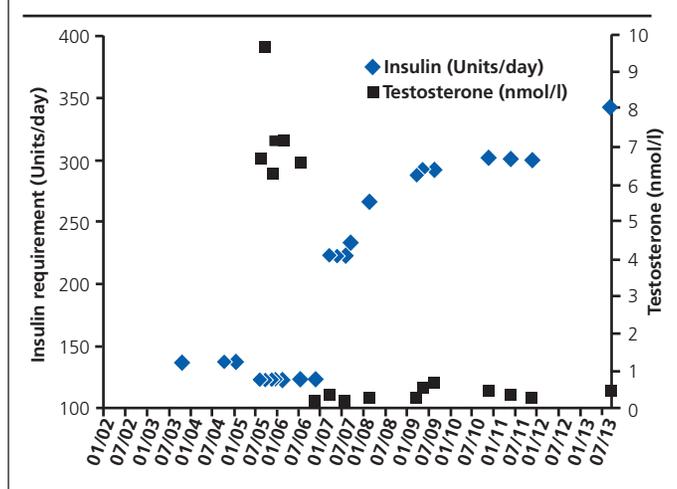
despite that, the HbA$_{1c}$ had risen from 7.4% (57.4 mmol/mol) to 9.4% (79.2 mmol/mol). A further 68 units/day were required to improve the HbA$_{1c}$ to pre-operative values (7.4% (57.4

mmol/mol)). There was also a deterioration in GGT levels which increased from pre-operative levels of approximately 200 to >500 IU/L (Table 1), mirrored to a lesser extent by ALT (from 35 to peak at 82 IU/L) which could be due to deteriorating hepatic steatosis. The cause of this cannot be elucidated but may be due to worsening of diabetes. Table 1 shows pre and post-operative details of weight, insulin requirement and biochemistry and Figure 1 graphically illustrates the change in glycaemic control coinciding with surgery.

All hormones were measured using Roche methodology (electrochemiluminescence, MODULAR® E170 analyser, Roche, Burgess Hill, UK) except androstenedione (chemiluminescence immunoassay, Immulite 2000, Diagnostic Products Corporation). HbA$_{1c}$ was measured by National Glycohemoglobin Standardis-ation Program certified HPLC (TOSOH Bioscience Ltd., Redditch, UK).

Discussion

This report describes a post-menopausal diabetic patient with greatly elevated testosterone who was diagnosed as having hyperthecosis. Contrary to our expectation, post-operatively her glycaemic control deteriorated significantly despite no change

in either weight or lifestyle. The GGT also increased, perhaps due to worsening fatty liver associated with the deteriorating glycaemic control, although this is speculation as liver biopsies were not carried out. There is no ready explanation for the change in glycaemic control.

There is a scarcity of data concerning the change in glycaemic control following an abrupt decrease in testosterone levels in post-menopausal patients. Barth *et al* described four cases (two had type 2 diabetes) of post-menopausal hyperthecosis. Treatment with GnRH agonists significantly reduced testosterone and hirsutism in three patients (the other patient died), but no data on hyperglycaemia were presented.[3] Another case of post-menopausal hyperthecosis with type 2 diabetes reported improvement of HbA$_{1c}$ following oophorectomy, from 10.1% to 8.2%, which required cessation of gliclazide due to hypoglycaemia.[2] More data are available in patients with PCOS, which is associated with increased androgens (albeit at lower levels), and insulin resistance. Studies of the treatment of PCOS with anti-androgen therapies are however contradictory, often depending on the exact agent used, demonstrating improvement, no change and worsening of hyperinsulinism.

It appears that a relationship is present between androgens and insulin resistance. A raised testosterone level in women has been associated with insulin resistance,[4] the opposite to men.[5] Androgens reduce SHBG levels and SHBG has been observed to be negatively correlated with insulin resistance.[5] Low SHBG levels have been associated with the onset of type 2 diabetes.[5] Insulin receptors present on the ovary and insulin-like growth factors enhance LH-dependent ovarian androgen synthesis and remain sensitive despite the presence of generalised insulin resistance.[6] Thus, a complex mechanism may exist where hyperandrogenism leads to insulin resistance and hyperinsulinism which in turn may result in the elevated insulin stimulating androgen release. It is tempting to speculate that an oophorectomy could disrupt this circular relationship. It is important to restate that, as the pre-operative testosterone concentration was greatly elevated, these associations may not apply.

This is the first case report of clinical resolution of the hyperthecosis with unexpected worsening of glycaemic control. The rapidity of the deterioration of glycaemic control without significant weight change may suggest that abrupt reduction in ovarian androgens has an aetiological role. Although we can but

Key messages

- Stromal hyperthecosis is a cause of hyperandrogenism presenting in post-menopausal women
- Hyperandrogenism is widely associated with insulin resistance and treatment of hyperandrogenism in women has improved insulin sensitivity in some reports
- The improvement in insulin resistance on treatment of hyperandrogenism in women is however not guaranteed and vigilance in regards to hypoglycaemic medications is urged, post treatment, to identify changes to glycaemic control

speculate on the reasons, it is possibly of benefit if glycaemic control is assessed in all patients where treatment leads to changes in androgen levels.

References

1. Chang RJ. A practical approach to the diagnosis of polycystic ovary syndrome. *Am J Obstet Gynecol* 2004;**191**:713-17. http://dx.doi.org/10.1016/j.ajog.2004.04.045
2. Leedman PJ, Bierre AR, Martin Fl. Virilizing nodular ovarian stomal hyperthecosis, diabetes mellitus and insulin resistance in a postmenopausal woman. Case report. *Br J Obstet Gynecol* 1989;**96**:1095-8. http://dx.doi.org/10.1111/j.1471-0528.1989.tb03388.x
3. Barth JH, Jenkins M, Belchetz PE. Ovarian hyperthecosis, diabetes and hirsuties in post-menopausal women. *Clin Endocrinol* 1997;**46**:123-8. http://dx.doi.org/10.1046/j.1365-2265.1997.1050916.x
4. Corbould A. Effects of androgens on insulin action in women: is androgen excess a component of female metabolic syndrome? *Diabetes Metab Res Rev* 2008;**24**:520-32. http://dx.doi.org/10.1002/dmrr.872
5. Ding EL, Song Y, Manson JE *et al*. Sex hormone-binding globulin and risk of type 2 diabetes in women and men. *N Engl J Med* 2009;**361**: 1152-63. http://dx.doi.org/10.1056/NEJMoa0804381
6. Nandi A, Poretsky L. Diabetes and the reproductive system. *Endocrinol Metab North Am* 2013;**42**:915-46. http://dx.doi.org/10.1016/j.ecl.2013.07.007