

Retinopathy Predicts Future Cardiovascular Events Among Type 2 Diabetic Patients

The Valpolicella Heart Diabetes Study

We read with interest the recent article by van Hecke et al. (1) showing that diabetic retinopathy is associated with an increased risk of mortality and cardiovascular disease (CVD) incidence among type 1 diabetic patients.

Because the available data on associations between retinopathy and incident CVD in large population samples of type 2 diabetic patients are limited and conflicting (2–4), we would like to offer recent findings from our large observational study. We carried out a prospective, nested, case-control study in 2,103 type 2 diabetic outpatients, who were free of diagnosed CVD at baseline. More details of study design and methods have been published elsewhere (5).

During 5 years of follow-up, 248 participants (62% men; age 66 ± 4 years; diabetes duration 14 ± 3 years) subsequently developed nonfatal coronary heart disease (myocardial infarction and coronary revascularization procedures), ischemic stroke, or cardiovascular death. Using risk-set sampling, 496 control subjects, among those who remained free of diagnosed CVD during follow-up, were randomly selected in a 2:1 ratio, matched for age and sex to the case patients. At baseline, a single ophthalmologist diagnosed retinopathy after pupillary dilation, according to a clinical disease severity scale (6). Overall, 364 (48.9%) participants had retinopathy, 285 of whom had nonproliferative retinopathy and 79 proliferative retinopathy (as also confirmed by fluorescein angiography). After adjustment for age, sex, BMI, smoking history, plasma lipids, HbA_{1c}, and diabetes duration and treatment, those with nonproliferative (odds ratio 1.7 [95% CI 1.2–2.3]; $P < 0.001$) or proliferative (4.1 [2.0–8.9]; $P < 0.001$) retinopathy had a higher risk of incident CVD than those without retinopathy. Additional adjustment for hypertension (defined as blood pressure $\geq 130/85$ mmHg or treatment) and macroalbuminuria (defined as urinary albu-

min-to-creatinine ratio ≥ 25 mg/mmol) considerably attenuated these associations, particularly among those with nonproliferative retinopathy (1.1 [0.7–1.5]; $P = \text{NS}$); the risk of incident CVD remained twofold greater, but statistically nonsignificant, among those with proliferative retinopathy (2.04 [0.9–5.8]; $P = 0.08$).

These results show that retinopathy is associated with a moderately increased risk of incident CVD among type 2 diabetic individuals, thus suggesting that retinopathy and CVD may have similar pathophysiological backgrounds. However, this association seems to be largely explained by occurrence of classical risk factors, especially hypertension and nephropathy. Thus, our data emphasize the importance of evaluating the CVD risk among diabetic patients with retinopathy; these patients could be candidates not only for aggressive treatment of their eye disease but also for blood pressure lowering, as well as aggressive treatment of underlying CVD risk factors.

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Prostatic Cancer, Hypogonadism, and Insulin Resistance

A case report

A 47-year-old Greek diabetic man presented with erectile dysfunction and a decrease in sexual desire. The patient had type 2 diabetes for the previous 8 years and was on treatment with rosiglitazone and metformin with strict glycemic control (HbA_{1c} 5.8%). No symptoms or signs of neuropathy were present. Hypogonadotrophic hypogonadism was found.

His plasma testosterone level was very low (100 ng/dl [reference range 300–1,000]) and there was no luteinizing hormone response to luteinizing hormone–releasing hormone (LHRH) test. Further work-up with a magnetic resonance imaging scan and hypophyseal function tests did not reveal any space-occupying lesions of the hypothalamic pituitary site.

The process led to the diagnosis of idiopathic hypogonadotropic hypogonadism. On further work-up, the patient was found to have a prostatic carcinoma. There was no evidence of metastatic disease (his plasma prostate specific antigen [PSA] level was 1.9 ng/ml).

Six years earlier, the patient was treated with finasteride for benign prostatic hypertrophy. A radical prostatectomy was performed and a poorly differentiated adenocarcinoma was found (Gleason grade 10, T3N1Mx).

Postoperatively his plasma testosterone rose to normal levels (530 ng/dl), and there was no need for diabetes medica-

tion, given that his fasting plasma glucose values never exceeded 6 mmol/l while only on diet.

His homeostasis model assessment of insulin resistance (HOMA-IR) (fasting serum insulin [$\mu\text{U/ml}$] \times fasting plasma glucose [$\text{mol} \cdot \text{l}^{-1}/22.5$]) was 1.8, and an oral glucose tolerance test performed with 75 g glucose was absolutely normal. His PSA value was 0.3 ng/ml.

After surgery there was very little change in body weight. His BMI before the operation was 26.6 kg/m^2 and after the operation 26.5 kg/m^2 . This minimal change in body weight could not account for the observed euglycemia, nor could his diet given that it was virtually unchanged.

Combined androgen blockade therapy was initiated with goserelin acetate and bicalutimide. Three weeks later his plasma testosterone level fell well in the hypogonadotropic range (80 ng/ml) with a simultaneous, abrupt worsening of his glycemic control. Fasting plasma glucose ranged from 10 to 15 mmol/l and HOMA-IR rose to 15, indicating an insulin-resistant state. Again there was no significant change in his body weight; his BMI was 26.5 kg/m^2 .

Treatment with metformin and rosiglitazone was reinstituted with a significant euglycemic response (fasting plasma glucose 5.5 mmol/l).

The presence of diabetes in the preoperative hypogonadal state, the remission of it in the immediate postoperative eugonadal phase, and the reappearance of insulin resistance after the institution of androgen deprivation treatment indicate that in this patient, the effect of testosterone was insulin sensitizing.

Marked hyperglycemia in prostatic cancer patients, after initiation of androgen deprivation therapy, has been reported in the literature with good response to pioglitazone (1). In the present case, prostatic carcinoma presented as hypogonadotropic hypogonadism. Schaeffer and Walsh (2) eloquently suggested that adenocarcinoma of the prostate should be considered in the differential diagnosis of hypogonadism based on the suppression of the hypothalamic-pituitary-testicular axis occasionally caused by this carcinoma. Undifferentiated prostatic carcinomas may yield normal PSA values, and this should be kept in mind when considering testosterone replacement therapy in men with hypogonadism. Another point of significance is that our patient was receiving rosiglitazone and peroxisome

proliferator-activated receptor- γ ligands, which may modify PSA levels (3).

Based on the above information, it is clear that in diabetic patients presenting with sexual dysfunction, prostatic carcinoma should be considered in the differential diagnosis, regardless of the PSA level. Further research is needed to examine the possible relationship between testosterone and insulin resistance and the possible role of hyperinsulinemia in the course of prostatic carcinoma disease, given that in recent years it has become clear that there are multiple androgen-independent routes.

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A Case of Type 1 Diabetes Followed by Methimazole-Induced Hypersensitivity Syndrome

Viruses have generally been considered to be a major environmental factor in the etiology of type 1 diabetes. Drug-induced hypersensitivity

syndrome (DIHS) is characterized by a severe drug eruption and multiorgan involvement, and reactivation of human herpesvirus-6 (HHV-6) may contribute to its pathology (1). This is the first reported case of type 1 diabetes followed by DIHS.

Recently, we have reported a case of DIHS induced by methimazole for Graves' disease (2). This patient developed type 1 diabetes during treatment of DIHS. Briefly, a 50-year-old Japanese male subject was diagnosed as having DIHS caused by methimazole in November 2003, based on the physical manifestations and laboratory findings including elevated anti-HHV-6 IgG titer. The administration of glucocorticoids gradually improved his clinical manifestations.

In December 2003, fasting plasma glucose was 4.9 mmol/l. His glycemic control, thereafter, gradually worsened despite treatment with nateglinide (270 mg/day). In March 2004, laboratory studies showed fasting plasma glucose to be 14.4 mmol/l; HbA_{1c} , 12.1%; fasting serum C-peptide, 0.35 ng/ml (normal range 0.5–2.73); and urinary excretion of C-peptide (which means integrated intrinsic insulin secretion), 17.24 mg/day (normal range 40–120). Basal level of serum C-peptide was finally undetectable. Anti-GAD antibody was 24.1 unit/ml (normal range <1.5). Response of serum C-peptide to glucagon was blunted. Thus, we diagnosed the patient as having type 1 diabetes. He started insulin injections immediately. His glycemic control gradually improved.

The coexistence of type 1 diabetes and Graves' disease is not infrequent. The onset age of type 1 diabetes in this case is fairly later, and anti-GAD antibody titer is relatively low, although type 1 diabetes with autoimmune thyroid disease was reported to be clinically characterized as high titer (609 ± 166 units/ml) of anti-GAD antibody and later-onset age (~ 30 years) compared with the general type 1 diabetic population (3). Therefore, these findings cannot exclude the possibility that the coexistence of type 1 diabetes and Graves' disease may be not incidental.

It is possible that viral infections such as coxsackie B4 virus and cytomegalovirus can trigger autoimmune reactions against pancreatic β -cells, which leads to type 1 diabetes. Molecular mimicry has been considered as a pathogenetic mechanism for autoimmune disease (4).