Учебно-методические рекомендации для студентов
По дисциплине «Основы профессионального перевода»
К теме «ДИАБЕТ»

Составитель: ст.преп., к.п.н. И.А. Бибик

Благовещенск 2016
Данные методические рекомендации содержат 14 статей, взятых из оригинальных медицинских журналов. Каждая статья сопровождается упражнениями лексико-грамматического характера.

Цель - ознакомление студентов с необходимым лексическим минимумом по теме, развитие навыков устной речи, чтения и письма для профессионального общения.
1. THE HISTORY

1. Read the texts and answer the following questions.

1. To what should particular care be taken?
2. Will patients with type 1 diabetes mellitus complain of excessive thirst?
3. May other patients remain asymptomatic?

A thorough history may provide important clues to a more definitive diagnosis and the selection of appropriate therapy. In addition to the information contained in a good general history, the physician should elicit and record specific pertinent details from the patient's personal, family, and medical history, including a complete inventory of current medications.

PERSONAL HISTORY

The personal history should include notations regarding alcohol consumption, tobacco use, dietary habits and irregularities, weight changes, and exercise patterns.

FAMILY HISTORY

The record should include information regarding the family medical history, particularly any history of diabetes in siblings, parents, grandparents, or children.

MEDICAL HISTORY

The medical history should indicate whether the patient has had symptoms or signs of chronic complications. The following specific problems should be noted: heart disease, hepatitis, hypertension, kidney disease, thyroid disease (hypo-, hyperthyroidism), other endocrine disease, pain or numbness of the extremities, pancreatitis, peripheral vascular disease, sexual impotence, strokes, and urinary tract infections. The medical history should also include any previous history of allergies, particularly atopic reactions and drug allergies. Allergy to sulfonamides should be specifically elicited and noted in the record.

The patient should be questioned regarding any previous blood glucose elevation, glycosuria, or diagnosis of diabetes. If the patient has been previously diagnosed as diabetic, the record should indicate the age of onset, the presence of symptoms, the duration of symptoms, the treatment which was prescribed, and the level of control. In addition, a history of hypertension, hyperlipidemia, coronary artery disease, and insulin resistance (syndrome X) may be very important.

OBSTETRIC/ GYNECOLOGIC HISTORY

If the patient is female, a complete obstetric history should be obtained, including information regarding any history of stillbirths, miscarriages, or gestational diabetes (or abnormal glucose tolerance tests). The record should include a notation regarding the weight of all babies at birth. A complete gynecologic history should also be recorded, and the patient should be asked about any menstrual abnormalities and about frequent episodes of monilial vaginitis.

MEDICATION HISTORY

The physician should note all medications which the patient is currently taking. Particular care should be taken to identify medications which may influence the blood glucose level or affect the patient's response to treatment. A partial list of such drugs includes diuretics, beta blockers, corticosteroids, oral contraceptives, various psychoactive drugs (including tricyclic antidepressants, phenothiazines,
monoamine oxidase inhibitors, and lithium), sympathomimetics, analgesics, antipyretics, anti-inflammatory drugs, and nicotinic acid in high doses.

SYMPTOMS

The history should contain specific and detailed information regarding any symptoms which may have led to the patient's visit. Most commonly, patients with type I diabetes mellitus will complain of excessive thirst, urination, and hunger, also known as "the three Ps": polyuria, polydipsia, polyphagia. These symptoms may be associated with weight loss and fatigue. The patient may also report frequent infections, particularly of the skin and of the genital region, especially if the patient is female. Female patients may also report pruritus vulvae.

DIABETIC COMPLICATIONS

Other patients may remain asymptomatic, reporting no symptoms until complications develop. The most frequent signs and symptoms of diabetic complications include rapid changes or fluctuations in vision, numbness and/or tingling of the extremities, fatigue, anemia, and sexual impotence. Patients with visual problems will often perceive them as a problem with their eyeglasses and not as a problem with vision. Some patients present with severe periodontal disease, a complication which may be initially noted by the family dentist. Other symptoms which may be reported include constipation, cystitis, nocturnal, nocturnal diarrhea, and boils.

2. Найдите информацию, содержащуюся в тексте “History”.

History may provide, the selection of appropriate therapy;
should include, notations regarding dietary habit;
should include information regarding the family sport-history;
should indicate if the patient has had signs of bad temper;
should be questioned regarding any previous blood glucose elevation.

3. Вставьте пропущенные прилагательные, пользуясь текстом.

1) provide... clues
2) a... history
3) the family... history
4) signs of... complications
5) particularly... reactions
6) a complete ... history
7) any... abnormalities

4. Определите содержание четвертого абзаца.

1. The medical history should include previous history of allergies.
2. The medical history should be printed by the nurse.
3. The medical history should be kept in the clone.

5. Найдите значение выделенных слов.

1. A thorough history may provide important clues to a more definitive diagnosis.
   a) keys; b) things; c) treatment.
2. The personal history should include notations regarding alcohol consumption.
   a) symptoms; b) records; c) complications.
3. If the patient is female a complete obstetric history should be obtained.
   a) child; b) man; c) woman.

2. THE PHYSICAL EXAMINATION

1. Put questions to the text.

EXAM PROCEDURES

The physical examination should include measurement of the patient's height, weight, and vital signs; evaluation of the patient's general appearance; examination of the ocular fundi, with the pupils dilated; auscultation and palpation of the neck, chest, abdomen, and peripheral vascular system; evaluation of vascular status; examination of the neurologic system, including deep tendon reflexes, sensory reflexes, and cranial nerves; evaluation of skin changes; a pelvic examination and Papanicolaou smear if the patient is female; and examination of the feet.

DIABETIC COMPLICATIONS/SECONDARY DIABETES

Findings from the physical examination provide important clues to the presence of diabetic complications (retinopathy, nephropathy, neuropathy, vascular disease). In addition, in conjunction with laboratory findings, they provide a basis for determining whether the diabetes is primary or secondary to another disorder, such as cirrhosis of the liver, pancreatitis, hemochromatosis, Cushing's syndrome, acromegaly, pheochromocytoma, glucagonoma, or other endocrine abnormalities. Indications that the blood glucose elevation may be due to secondary diabetes or that diabetic complications may be present should be carefully investigated in the laboratory workup.

SKIN CHANGES

Skin changes can be a particularly valuable source of information regarding the patient's condition. Unusual skin conditions such as necrobiosis and xanthomas may warrant additional investigation and/or treatment.

3. DIFFERENTIAL DIAGNOSIS

1. Retell the text basing on the following phrases:

   - diagnosis of diabetes mellitus be restricted to those,
   - never progress to overt diabetes,
   - the data suggest that,
   - can be divided into 3 types,
   - urine test should be used,
   - to prevent the development of diabetic complications.

DIAGNOSTIC CRITERIA

The National Diabetes Data Group recommends that the diagnosis of diabetes mellitus be restricted to those persons in whom the blood glucose elevation is not due to drug use, endocrinopathies, severe liver or kidney disease, laboratory error, or other medical and non-medical causes, and who meet the following diagnostic criteria: (1) overt diabetic symptoms and unequivocal hyperglycemia; (2) FPG levels higher than 140 mg/dL on more than one occasion; or (3) normal FPG but plasma glucose levels during the OGTT greater than 200 mg/dL, both at 2 hours and at some point between time zero and 2 hours, on more than one occasion. The Data Group further recommends that the term "impaired
glucose tolerance" be used to designate persons who.5e FPG (or PG level during an OGTT) lies between normal Values and those required for a diagnosis of diabetes mellitus.

**IMPAIRED GLUCOSE TOLERANCE**

Although many individuals with impaired glucose tolerance never progress to overt diabetes, their health status should be checked periodically. Many of these individuals will return to normoglycemia; others may remain somewhat hyperglycemic with no additional complications. However, epidemiologic evidence indicates that one to five percent of these individuals annually progress to overt diabetes mellitus. In addition, the data suggest that these individuals run a higher than normal risk of atherosclerotic disease.

**CLASSIFICATION OF DIABETES MELLITUS**

Overt diabetes mellitus can be divided into three types: type I diabetes mellitus (insulin-dependent diabetes mellitus or IDDM, formerly called juvenile-onset diabetes); type II diabetes mellitus (non-insulin-dependent diabetes mellitus or NIDDM, formerly called maturity-onset diabetes); and gestational diabetes. The latter category is reserved for hyperglycemic pregnant females with no previous diagnosis of diabetes mellitus.

**TYPE I (IDDM)**

The fasting urine test should be used to distinguish between type I and type II diabetes. Type I diabetics will generally present with acetone in the urine. However, there may be pre-ketotic, non-insulin-dependent phases in the natural history of the disease. Individuals with IDDM generally present with average or below-average weight and, as suggested by the previous designation for this classification, they are generally diagnosed at an earlier age. Type I diabetes is now believed to be an autoimmune disorder.

**TYPE II (NIDDM)**

The term "non-insulin-dependent" may be confusing, especially since many patients may require insulin therapy as the disorder progresses. The major distinction between IDDM and NIDDM lies in the presence or absence of endogenous insulin. Except during the "remission" period evidenced by some patients with IDDM diabetes, patients who are "insulin-dependent" will require exogenous insulin to prevent life-threatening ketoacidosis. Patients with NIDDM may take insulin to control symptoms and, at least theoretically, to prevent the development of diabetic complications. However, they do not generally require insulin therapy to prevent ketosis. Individuals with NIDDM are not insulin-dependent or ketosis-prone. Although the majority (60-90 percent) of NIDDM subjects is obese, certain individuals in this category may present with normal or below-normal weight. Plasma insulin levels among members of this group range from below normal to significantly elevated; however, some endogenous insulin is generally measurable. Insulin resistance is thought to be the underlying disorder in type II diabetes, as well as in syndrome X (hypertension, hyperglycemia, and hyperglycemia).

**ADDITIONAL DATA**

In addition to the criteria described above, type I and type II diabetes may be differentiated by studies of the human leukocyte antigen (HLA) complex of the sixth chromosome, measurements of islet cell antibody titers, and assays of C-peptide levels after glucose stimulation studies. Such data may provide greater precision in distinguishing IDDM and NIDDM for the purpose of medical research. However, in ambulatory care settings, these studies are not generally warranted.
4. EXERCISE THERAPY

1. Look through the text. Arrange the following sentences in proper order to make a summary of the text.

1. To provide an adequate assessment of the patient's usual activity, the diary should be kept for at least 4 days.
2. In addition to an assessment of the patients' medical conditions, the physician may also find it helpful to assess the patient's attitude toward physical activity.
3. Most individuals with type 2 diabetes are also good candidates for adjunctive exercise therapy.
4. A careful medical evaluation is essential before any exercise recommendations are made.
5. In some patients exercise programs may increase the risk of complications.

EXERCISE BENEFITS

Most individuals with type II diabetes are also good candidates for adjunctive exercise therapy. For such individuals, a well-designed program of regular exercise may provide the following benefits: (1) improved insulin sensitivity and glucose tolerance; (2) promotion of weight loss and weight maintenance; (3) amelioration of cardiovascular risk factors; (4) reduction of drug dosages, or in some cases, elimination of the need for drug therapy; (5) enhanced work capacity; (6) enhanced quality of life and sense of well-being.

EXERCISE RISKS

Despite the potential benefits, in some patients exercise programs may increase the risk of complications such as exercise-induced hypoglycemia and deterioration of metabolic control, cardiovascular events, cerebrovascular events, and foot injuries. For this reason, a careful medical evaluation is essential before any exercise recommendations are made. The evaluation should include an assessment of the patient's metabolic control, cardiovascular status, and work capacity; it should also include a careful assessment for significant diabetic complications (i.e., proliferative retinopathy, micro- and macroangiopathy, and neuropathy).

ADDITIONAL DATA

In addition to an assessment of the patient's medical condition, the physician may also find it helpful to assess the patient's attitude toward physical activity; exercise interests—past, present, and future; access to exercise facilities; daily schedule, including home and work commitments; preference for individual or group activities; and personal support systems.

ACTIVITY LOG

It may also be helpful to ask the patient to keep an hour-by-hour diary of daily physical activity. To provide an adequate assessment of the patient's usual activity, the diary should be kept for at least 4 days and should include entries for both weekdays and weekends. Information collected in this diary should be discussed with the patient at the initiation of therapy so that the patient can see his or her current expenditure of energy. Table 6 lists the energy expenditure associated with common daily activities and athletic exercises.

2. Make up sentences of your own using the following words and phrases.

1. Most individuals, adjunctive exercise therapy, a well-designed program, promotion of weight loss, the need for drug therapy, cardiovascular events, an assessment of the patient's metabolic control,
home and work commitments current expenditure of energy, common daily activities.

5. ORAL AGENTS

1. Agree or disagree.

1. The sulfonylureas rarely produce side effects.
2. Patients who are being treated with oral agents shouldn't receive appropriate instruction.
3. Patients should be taught to monitor their urine or blood glucose levels.
4. By keeping accurate records of blood glucose measurements, patients can't become more involved in the control of their diabetes.
5. The patient should be encouraged to continue the tests.

SIDE EFFECTS

Although the sulfonylureas rarely produce side effects, the physician should be alert to the appearance of gastrointestinal problems, such as abdominal distress, heartburn, flatulence, or queasiness. Such symptoms may be relieved by switching to another agent, especially if the patient is taking chlorpropamide. More rarely, cholestatic hepatitis, allergic reactions, skin reactions, slight fever, the disulfiram reaction (a deep flush or cyanosis of the face and scalp after the consumption of alcohol), or fluid retention may occur. Hypoglycemia may also be seen, but it is usually mild. However, there are a small number of patients (particularly older patients with renal insufficiency who are taking chlorpropamide) who develop severe hypoglycemia, which should always be treated as a medical emergency. Recurrent hypoglycemic episodes may appear for several days in patients using drugs with a long duration of action.

DIET INSTRUCTION

Patients who are being treated with oral agents should receive appropriate instruction regarding the importance of continued dietary adherence. As patients respond to diet, it may be necessary to reduce the dosage of the oral agent to prevent hypoglycemia.

SELF-MONITORING OF BLOOD GLUCOSE

Patients should be taught to monitor their urine or blood glucose levels. Blood glucose monitoring is a more accurate measure of blood glucose fluctuation, and it allows for detection of both hyperglycemic and hypoglycemic episodes. At the present time, urine glucose monitoring is rarely recommended. By keeping accurate records of blood glucose measurements, patients can become more involved in the control of their diabetes and more motivated to continue the discipline necessary to stay in control. Initially, such tests should be performed daily before meals and at bedtime. As satisfactory control is achieved, however, the frequency can be reduced to 1 or 2 days per week. The patient should be encouraged to continue the tests as a way to monitor loss of control, which may result from illness, overeating, or the development of secondary failure (see page 40).

Table 8 lists products currently available for self-monitoring of blood glucose. Once patients have been instructed in self-glucose monitoring, skills and accuracy should be reassessed periodically, especially if reported values are inconsistent with hemoglobin A1c measurements.

2. Read the text.

PREVENTING HYPOGLYCEMIA

The patient should also receive appropriate instruction with regard to prevention of hypoglycemia,
including the importance of eating regularly spaced meals and the avoidance of prolonged fasting. This should include precautions regarding the use of other drugs while taking the oral agent. Specifically, the patient should be cautioned about the use of salicylates and alcohol, which may cause hypoglycemia, particularly with high doses of the oral agent.

CAUTIONS IN DRUG PRESCRIBING

The physician should also use caution when prescribing drugs which potentiate the effectiveness of the oral agent. Such drugs include phenylbutazone, oxyphenbutazone, clofibrate, sulfonamides, dicumarol, sulfinpyrazone, probenecid, monoamine oxidase inhibitors, anabolic steroids, and methotrexate. Caution should also be used with drugs which antagonize the hypoglycemic action of the oral agent. Such drugs include thiazide diuretics, furosemide, corticosteroids, estrogens, phenytoin, diazoxide, and, paradoxically, alcohol. Tricyclic antidepressants should also be used carefully, as they have been shown to have a variable effect on blood glucose levels and to increase the risk of hypoglycemia. Beta-adrenergic blockers should be prescribed with caution in patients taking either oral agents or insulin. Beta blockers may prevent the normal hepatic glycogenolytic response to the hypoglycemia induced by the oral agents or insulin. They may also inhibit the sympathetic signals of hypoglycemia, thereby masking the warning symptoms of a hypoglycemic episode.

FAILURE OF ORAL AGENTS

Primary failure of diet and sulfonylurea therapy occurs most commonly in patients who are at or near their ideal body weight at the time of diagnosis. In such patients the rate of primary failure averages between five and ten percent. Secondary failure may also occur in patients who have been previously well controlled by a sulfonylurea compound. Initially, the rate of failure is similar to that of primary failure, with five to ten percent of patients experiencing secondary failure during the first 2 years. After this time, the rate drops to approximately three to five percent per year. However, over the course of many years of treatment, a high percentage of these patients will eventually require insulin.

3. Change the following sentences so that a passive infinitive is used.

1. The patient should also receive appropriate instruction.
2. The physician should also use caution when prescribing drugs.
3. Beta blockers may prevent the normal hepatic glycogenolytic response to the hypoglycemia.
4. They may also inhibit the sympathetic signals of hypoglycemia.
5. However, over the course of many years of treatment a high percentage of these patients will eventually require insulin.

6. INSULIN THERAPY

1. Read the text.

LOCAL REACTIONS TO INSULIN INJECTIONS

Some patients will develop a skin reaction following the initiation of insulin therapy. This usually consists of mild discomfort, with itching and redness at the injection site. Such reactions do not require any special management, although an antihistamine given simultaneously with the insulin can be used to relieve the symptoms. The repeated use of insulin over a period of 6 weeks will result in desensitization. The patient should be reassured that the reaction will subside at that time.
SYSTEMIC REACTIONS/ INSULIN ALLERGY

More rarely, patients develop insulin allergy, a systemic reaction to insulin ranging from generalized urticaria to anaphylactic shock. Patients with atopic eczema or a previous history of allergy to penicillin or other drugs should be observed for such reactions. Intermittent insulin therapy particularly predisposes such patients to insulin allergy. To minimize the risk of developing insulin allergy, the use of human insulin is recommended for patients who may require only intermittent insulin therapy. Patients who develop systemic reactions can be desensitized with a specially designed kit. In most cases, the patient must be hospitalized briefly while undergoing desensitization.

LIPODYSTROPHY

Patients may also develop lipodystrophies, generally at the site of the injection, but this is also infrequent. Both lipoatrophy, which is more common in women, and lipohypertrophy, which occurs more often in men, can be alleviated somewhat by varying the injection site. If the reaction is significant, the patient should be switched to human insulin.

EMPHASIS ON DIET

Because insulin therapy frequently precipitates weight gain with resulting insulin resistance and loss of control, the physician should emphasize the importance of proper diet. Various studies have also shown that patients may reduce their insulin dosage through careful diet adherence and appropriate exercise, even if they are not obese.

COMBINATION THERAPY

Combination therapy with insulin and sulfonylurea agents has often been considered for patients who require large doses of insulin but still do not obtain good glucose control. A frequently used regimen combines bedtime insulin with daytime sulfonylurea agents. Combination therapy seems to be useful only when the patient has some residual capacity to secrete insulin. In addition, the physician should remember that combination therapy may increase the potential hazards for both medications. Some authorities believe that combination therapy should be reserved only for patients who require large doses of insulin and do not respond to other measures.

2. Составьте предложения из слов и словосочетаний.

1. Insulin therapy, of, some patients, a skin reaction following the initiation, develop, will.
2. Any, such reaction, require, do not any, special management.
3. At that time, the patient, that should/will subside, reassured.
4. Insulin allergy, more rarely, develop, patients.
5. To insulin allergy, intermittent, insulin therapy, predisposes, particularly, such patients.
6. Who, patients, can be desensitized, develop, reactions, systemic, with, designed kit, specially.
7. Insulin dosage, their, various, may reduce, studies, have, that patient, also, shown.

7. PATIENT AND FAMILY EDUCATION

1. Read the text and give summary of it using the following expressions:

The article is about...
The article deals with...(the problem of)
ACTIVE ROLE FOR PATIENT

Diabetes mellitus has been termed the "ultimate in patient management diseases," as the variables affecting the disease are all, ultimately, under the patient's control. For this reason, it is vital that patient education efforts be structured to help the patient see himself or herself as an active participant in the management of the disease. Referral to a specialized diabetes education center should be considered if office or hospital teaching does not meet the patient's educational needs.

BEGINNING PATIENT EDUCATION

Patient education efforts should begin with the first evidence of hyperglycemia or glycosuria. If the patient is asymptomatic and a routine examination reveals the presence of urinary glucose or elevated blood glucose, the physician should explain the significance of the elevation, the possible causes, and the reasons why remeasurement or evaluation will be required. However, the patient should not be unduly alarmed, particularly if the hyperglycemia or glycosuria has not been confirmed.

EXPLAINING THE DIAGNOSIS

Once the hyperglycemia is confirmed, the patient should be given a thorough explanation of the diagnosis. If the patient is asymptomatic, the physician should take special care to explain the importance of therapy. The patient should be cautioned about the potential dangers or complications of the disease.

The explanation of the diagnosis should be clear, concise, and complete. However, it should not receive disproportionate emphasis. Research on patient adherence indicates that inadequate knowledge of the diagnosis is seldom a critical factor in non-adherence. More important is time spent evaluating the patient's health beliefs regarding his or her condition.

ELICITING FEELINGS/ATTITUDES

The physician should try to assess the patient's understanding of the seriousness of the condition, and his or her personal susceptibility to it, as well as the patient's beliefs regarding the efficacy of treatment. Sensitive questioning, with ample time for the patient to discuss his or her feelings about the diagnosis, should provide the physician with important information regarding the patient's current attitudes. This information can, in turn, provide a good indicator of how much responsibility the patient is likely to assume for adhering to the regimen he or she is expected to follow.
Recent advances in understanding the biology of diabetes-associated bladder complications and novel therapy

NAOKI YOSHIMURA, MICHAEL B. CHANCELLOR*, KARL-ERIK ANDERSSON+ and GEORGE J. CHRIST*

Departments of Urology and Pharmacology, *Urology and McGowan Institute of Regenerative Medicine, University of Pittsburgh, Pittsburgh, PA, †Department of Clinical and Experimental Pharmacology, Lund University Hospital, Lund, Sweden, and ‡Department of Regenerative Medicine, Wake Forest University, Winston-Salem, NC, USA

Accepted for publication 12 October 2004

KEYWORDS

diabetes mellitus, detrusor, smooth muscle, nerve growth factor, urothelium

INTRODUCTION
Diabetes mellitus (DM) is at epidemic proportions and becoming a major problem in the USA. According to the Centers for Disease Control and Prevention, 18 million people in the USA have DM and the prevalence of DM increased from 4.9% in 1990 to 7.3% in 2000 [1]. Urological complications have increasingly become a concern in those affected by DM (both Type I and II). More than a quarter of diabetic patients will develop costly and debilitating urological complications, e.g. incontinence, infections, loss of sensation and retention of urine. The total annual cost of diabetes in 1997 has been estimated at more than $98 billion (http://www.diabetes.org).

In addition to diabetic bladder dysfunction, there is a greater incidence of asymptomatic and symptomatic bacteriuria, which can progress to kidney infection and kidney damage. This increase in infection has been attributed to numerous causes, from incomplete bladder emptying to changes in bladder wall components and immune dysfunction. A confounding factor for all basic studies on the bladder is the lack of published data on the urothelial cell, vascular, neurological and smooth muscle function, and interactions in bladder tissue from nondiabetic sources that can be used for comparison with the diabetic.

An important question is whether bladder dysfunction is secondary to an inherent neuropathology induced by diabetes, or caused by changes associated with bladder overdistension. Many animal models have been used to elucidate this and other questions associated with diabetic cystopathy. Streptozotocin (STZ)-induced diabetic rats and sucrose-drinking rats (sucrose induces a polyuria similar to that seen in diabetic patients) have generally been used. Paro et al. [2] noted that alloxan-induced diabetic rats had decreased and irregular contractions, while sucrose-fed rats had normal bladder contractions. This suggests that in alloxan-induced DM, contractile dysfunction is secondary to an inherent diabetic cystopathy, while bladder hypertrophy in sucrose-fed rats is an organ adaptation to polyuria. Other differences between STZ-induced diabetes and sucrose-induced bladder distension include a decrease in noradrenaline uptake and in choline acetyltransferase activity [3], and cystometrographic and supraspinal reflex latencies between the groups [4].

Clinically, the diagnosis of diabetic cystopathy is most readily made with urodynamic testing [5,6]. The most common urodynamic findings include elevated residual urine volume, impaired bladder sensation, involuntary detrusor contractions, increased cystometric capacity and decreased bladder contractility. Cystometry may show detrusor areflexia, which is usually found in patients with an impaired sensation of bladder filling [7-9]. Detrusor overactivity is also common in patients with DM [10]. Other aspects of the severity of DM, e.g. duration, glycaemic control and microvascular complications resulting in damage to innervation of the bladder, have been suggested as possible mechanisms for incontinence [11,12].

**PATHOPHYSIOLOGY**

The biology of DM-associated bladder complications is multifactorial and they can...
be a result of an alteration in the physiology of the detrusor smooth muscle cell, the innervation or function of the neuronal component, or urothelial dysfunction (Fig. 1). The experimental model most often used to assess bladder complications is the STZ rat model. As bladder smooth muscle contraction is mediated by acetylcholine released by the pelvic nerve acting on muscarinic receptors, a series of pharmacological studies have focused on the impact of STZ-DM on the responsiveness of bladder strips to externally applied muscarinic agonists. Neuronal dysfunction may reflect a deficiency of axonal transport of nerve growth factor (NGF) and be important in inducing diabetic neuropathy [13-15]. The urothelium undergoes changes in DM; thus, in the STZ-induced DM rat model, there are progressive increases in total bladder tissue, with hypertrophy of the bladder wall and dilatation of the bladder [16,17]. Both smooth muscle and urothelium have been shown to increase significantly with time. Thus there is strong evidence that DM adversely affects the bladder smooth muscle, nerves and the urothelium (Fig. 1).

DM AND DETRUSOR SMOOTH MUSCLE FUNCTION

DM has been shown to alter detrusor smooth muscle function in experimental animals, with the vast majority of these studies conducted on the STZ rat model. However, because there are no longitudinal studies conducted under similar experimental conditions, there is still uncertainty about the time course, magnitude and mechanism of DM-related changes in detrusor smooth muscle cell function.

STZ-DM: Pharmacological studies on isolated bladder strips have generated much confusion. While there is generally changes in isolated detrusor smooth muscle cell strips there is no agreement on either the phenomenon or the mechanism. For example, several studies documented an increase in responsiveness of DM bladder strips to externally applied muscarinic agonists [17,18] but others reported a decrease or no change in the muscarinic component [19]. There was an increase in muscarinic receptor density at both 2 and 8 weeks after STZ-induced DM [20]. A recent study found an increase in the P,-receptor-mediated relaxation response in isolated detrusor smooth muscle strips from 8-10 week STZ-DM rats [21]. Moreover, there was an increased contractile response to 5-hydroxytryptamine from 4-week STZ-DM rats.

One DM-related change that most experts agree on is an increased responsiveness of isolated rat bladder strips to electrical field stimulation (EFS) [22,23]. However, there is no consensus on the putative mechanism for this increased responsiveness to EFS. Theories include that the increased response to EFS is caused by DM-related changes in membrane lipid composition or other destabilizing membrane changes, or increased neurotransmitter release [24]. Belis et al. [25] suggested that the changes are related to increased calcium-channel activity, while Waring and Wendt [23] found no evidence for altered calcium regulation, and therefore suggested that the increased responsiveness may be a result of enhanced calcium sensitivity. Most recently, Bezuijen et al. [26] reported that decreased function was more notable in strips from diabetic rats with enlarged bladders. This does not elucidate the mechanism, but could...
explain some of the observed variability from previous studies. In addition, this same group recently showed that DM increases the rate of development of at least some aspects of bladder decompensation in rats with partial urethral outlet obstruction [27]. Such observations further highlight the multifactorial nature of diabetic cystopathy, and the potential array of causal mechanisms and clinical symptoms that might be apparent in an ageing population.

Hashitani and Suzuki [28] found increased depolarization of myocytes in STZ-DM rat bladder strips on applying acetylcholine, indicating enhanced muscarinic sensitivity in the diabetic bladder. They further noted decreased spontaneous electrical activity in the myocytes, presumably related to altered purinergic transmission. These observations are consistent with the effects generally associated with a decrease in neuronal transmitter release.

Poladia and Bauer [29] studied the changes in nitric oxide synthase (NOS) and reactive nitrogen species formation during DM-related bladder remodelling, using the STZ-DM rat model. They found early, time-dependent and cell-specific changes in the three isoforms of NOS, and region-specific increases in protein nitration. Endothelial NOS was significantly up-regulated in the lamina propria, neuronal NOS in the urothelium, lamina propria and in the smooth muscle layer, whereas inducible NOS was up-regulated only in the urothelium. They suggested that changes in NO production and impaired NO control are early events in diabetic cystopathy, and that mechanisms leading to increased oxidative stress and proteasomal activation may be key participants leading to organ dysfunction.

**BB/W rat:** There are only a few published studies with the BB/W rat diabetic model [14,22]. As with the STZ-rat model, the diabetic BB/W rat has the expected in vivo phenotypic characteristics, e.g. decreased overall body weight, and corresponding increases in voiding volumes and voiding frequency. From a mechanistic standpoint, Longhurst [30] reported an apparent absence of detectable effects of 6 months of DM in the BB/W rat on the pharmacology of isolated detrusor (i.e. bladder body) strip contractions. However, there were modest but statistically significant decreases in the sensitivity and magnitude of carbachol and ATP-induced contractions of detrusor strips when the data were normalized for tissue weight.

Given that motility disorders are an important component of diabetic cystopathy, it will be critical to more precisely determine the nature, time course, magnitude and mechanism for these changes (Fig. 2). Elucidating the contribution of detrusor myocytes to diabetic bladder disease will be important to the improved understanding, diagnosis and treatment of diabetic cystopathy. To do so will require multidisciplinary longitudinal studies in both man and experimental animals, in which the extent of DM is well characterized, and the effects of DM on bladder function in vivo documented.

**NEURONAL DYSFUNCTION IN DM**

Although the pathogenesis of diabetic neuropathy is not fully clarified, it is generally accepted that the cause of diabetic neuropathy is multifocal. Some of the
proposals for pathogenesis include altered metabolism of glucose, ischaemia, superoxide-induced free-radical formation and impaired axonal transport [31]. It is also known that the neuropathies of DM caused by the metabolic derangement of the Schwann cell result in segmental demyelination and impairment of nerve conduction. This gradual process of segmental demyelination has been confirmed histologically in the bladder and is consistent with the observed impairment of nerve conduction of the visceral afferent fibres within the bladder wall. Van Poppel et al. [32] reported that there was less acetylcholinesterase activity in bladder biopsy specimens from patients with severe insulin-dependent DM than in normal controls.

The deficiency of axonal transport of NGF may be important in inducing DM neuropathy, which contributes to DM cystopathy [2,13]. Sasaki et al. [33] recently reported, using STZ-DM rats, the relation between bladder function and NGF levels in the bladder and lumbosacral dorsal root ganglia (DRG), which contain afferent neurones innervating the bladder, and the feasibility of NGF gene therapy for treating DM cystopathy [34] (Fig. 3).

Using STZ-DM rats (65 mg/kg intraperitoneal) the effects of DM and gene therapy, using replication-defective herpes simplex virus (HSV) vectors encoding the NGF gene (HSV-NGF) injected into the bladder wall, were assessed on A8 afferent fibre-dependent conscious voiding and C-fibre-mediated bladder nociceptive responses. This was done using metabolic cage/awake cystometry and cystometry with intravesical instillation of 0.25% acetic acid under urethane anaesthesia, respectively. In addition, NGF levels in the bladder and L6-S1 DRG were measured by ELISA methods 3, 6, 9 and 12 weeks after STZ injection, and 4 weeks after the HSV-NGF treatment [33].

In DM rats, NGF levels in the bladder and L6-S1 DRG...
significantly decreased 12 weeks after STZ injection. In cystometry and metabolic-cage studies, bladder capacity and postvoid residual volume were significantly increased 12 weeks after STZ injection (Fig. 3). Bladder nociceptive responses, assessed by a reduction of intercontraction intervals after acetic acid instillation, were significantly decreased in a time-dependent manner during the 12 weeks after STZ injection.

Rat injected with HSV-NGF into the bladder wall 8 weeks after STZ injection had a significant increase in NGF levels in the bladder and L6 DRG 4 weeks after HSV-NGF treatment (i.e. 12 weeks after STZ injection). DM rats injected with HSV-NGF also had a significantly smaller bladder capacity and postvoid residual volume than DM rats injected with HSV encoding the LacZ gene (Fig. 3). However, HSV-NGF treated rats showed no significant bladder nociceptive responses after intravesical acetic acid infusion [34,35].

These results indicate that the reduced production of NGF in the bladder and/or impaired transport of NGF to L6-S1 DRG may be an important mechanism inducing DM cystopathy, which is attributable to defects in both AS-fibre and C-fibre bladder afferent pathways. NGF gene therapy using replication-defective HSV vectors, which
restores decreased NGF expression in the bladder afferent pathways, could be effective for treating DM cystopathy [13,35] (Fig. 4).

UROTHELIAL DYSFUNCTION IN DM

The location of the urothelium suggests that it is important for regulating permeability, transport and endocytosis. However, it has become increasingly clear that the urothelium is not only a passive barrier against urea and ion diffusion, but that it can also function as a sensor, controlling bladder function and dysfunction. The urothelium may have receptors and ion channels similar to those in bladder nerves, and injury or inflammation may alter the response of both urothelial cells and sensory afferents to nociceptive and other stimuli. Many mediators, e.g. ATP, NO and prostanoids, can be released from the urothelial cells [36,37]. Vanilloid receptors are expressed on urothelial cells [38], and it has been shown that ATP can potentiate the response to vanillooids by lowering the threshold for, e.g. protons and capsaicin [39]. This means that the large amounts of ATP released from damaged/sensitized cells in response to injury/inflammation may influence afferent nerves and contribute to the variety of abnormalities in DM-induced bladder dysfunction.

In the STZ-DM rat model there are progressive increases in total bladder tissue with hypertrophy of the bladder wall and dilatation of the bladder [15,16]. Both smooth muscle and urothelium (percentage of total tissue) increase significantly in a time-dependent manner. Pinna et al. [15] found that the epithelium from STZ-DM rat bladders was at least twice as thick and heavy as that from controls. In isolated urothelial layer preparations from bladders of STZ-DM rats, the absolute amount of endogenous prostaglandins E2 and F2α was higher than in corresponding preparations from control animals, but when prostaglandin F2α production was expressed as a fraction of tissue weight, it was reduced in the diabetic epithelium.

ATP and bradykinin significantly increased the endogenous release of both prostaglandins from the urothelium when compared with the release under basal conditions. This increase was time-dependent and was higher in diabetic than in control tissues. Bradykinin-induced release of prostaglandin E2 has also been reported in primary cultures of human urothelial cells [40]. Pinna et al. [15] showed that ATP evoked a phasic and tonic contraction in bladder strips from nondiabetic rats; in preparations from DM, but not from normal animals, the tonic contraction was abolished by removing the urothelium. Bradykinin evoked a long-lasting tonic contraction that was reduced significantly by removing the urothelium. Bradykinin thus seemed to depend on the generation and release of prostaglandins from the urothelium. This implies that both ATP (P2X) and bradykinin receptors might be present in the urothelium, and that these receptors may be important in, e.g. prostaglandin generation and release. In turn, prostaglandins may sensitize sensory nerves and increase the sensitivity of bladder smooth muscle to contractile stimuli, which may contribute to some of the bladder abnormalities, e.g. detrusor overactivity,
observed in DM.

The urothelium may also be important in DM-related UTI. It was reported that women with DM have bacteriuria more often than women without. Geerlings et al. [41] showed that Type 1 fimbriated Escherichia coli adhered twice as well to diabetic as to control epithelial cells. The receptors for these Type 1 fimbriae are glycoproteins (uroplakins), and it was proposed that diabetic uroepithelial cells have a different glycosylation of the receptor on their cells, resulting in higher adherence.

CONCLUSIONS

Although urological complications and major health problems in men and women with DM are common, data to define the expected prevalence, incidence and risk factors, and interventions to reduce the risk of developing these complications, are limited. New research initiatives are needed to further understand the basic disease mechanisms, to develop safe and effective prevention and treatment of the urological complications of DM. A better understanding of the biology of how DM affects the muscle, nerve and urothelium of the urinary bladder could lead to improved
FIG. 4. The relationship between bladder function and NGF: (i) In conditions of peripheral neuropathy such as DM, reduced NGF production in the bladder or deficiency in NGF transport to the bladder afferent pathway is an important factor in the pathogenesis of diabetic cystopathy that induces bladder hyporeflexia and decreased sensation. NGF supplement therapy may be useful to restore bladder function in these conditions. (ii) In conditions of bladder hypertrophy induced by BOO, spinal cord injury or bladder inflammation, there is increased NGF that can induce detrusor overactivity and bladder pain. Reducing NGF autonomic neuropathy.

CONFLICT OF INTEREST

None declared. Sources of Funding: NIH HD397658, DK55045, NIH DK57267, DK68557, NIH DK55076, DK60037 and DK60204 and Swedish Research Council, grant no. 6837.

REFERENCES

1 Mokdad AH, Bowman BA, Ford ES, Vinicor F, Marks JS, Koplan JP. The continuing epidemics of obesity and diabetes in the United States. JAMA 2001; 286: 1195-200


4 Steers WD, Mackway AM, Ciambotti J, de Groat WC. Effect of streptozotocin-induced diabetes on bladder function in the rat. JUrol 1990; 143: 1032-6
9 Ueda T, Yoshimura N, Yoshida O. Diabetic cystopathy: Relationship to autonomic neuropathy detected by


22Longhurst PA, Kauer J, Levin RM. The ability of insulin treatment to reverse or prevent the changes in urinary bladder function caused by streptozotocin-induced diabetes mellitus. *General Pharmacol* 1991; 22:305-11


27Longhurst PA, Levendusky MC, Bezuijen MW. Diabetes mellitus increases the rate of development of decompensation in rats with outlet obstruction. *J Urol* 2004; 171: 933-7

28Hashitani H, Suzuki H. Altered electrical properties of bladder smooth muscle in


36 Vlaskovsk M, Kasakov L, Rong W et al. P2X3 knock-out mice reveal a major sensory role for urotheliaically released ATP. *J/Neurosci* 2001; 21: 5670-7


40 Zenser TV, Thomasson DL, Davis BB. Characteristics of bradykinin and TPA increases in the PGE2 levels of human urothelial cells. *Carcinogenesis* 1988; 9: 1173-7


Correspondence: Michael B. Chancellor, 3471 Fifth Avenue, Suite 700, Pittsburgh, PA 15213, USA

e-mail: chancellormb@msx.upmc.edu

Abbreviations: DM, diabetes mellitus; STZ, streptozotocin; NGF, nerve growth factor; EFS, electrical field stimulation; NOS, nitric oxide synthase; DRG, dorsal root ganglia; HSV, herpes simplex virus.
SYMPTOMATIC BACTERIURIA IN PATIENTS WITH DIABETES — ENEMY OR INNOCENT VISITOR?

I "HE application of quantitative bacteriology to JL urine cultures almost five decades ago led to prospective scientific investigations of the epidemiology, pathogenesis, diagnosis, treatment, and prevention of urinary tract infections. Numerous studies have evaluated the frequency of asymptomatic and symptomatic bacteriuria in men and women with diabetes. The early studies showed no significant difference in the prevalence of bacteriuria between men with diabetes and men without diabetes. In contrast, the prevalence of asymptomatic bacteriuria is two to three times as high among women with diabetes as among women without diabetes, and the frequency of symptomatic urinary tract infections is higher among women with diabetes than among those without diabetes.

Furthermore, localization studies have shown that infection of the upper urinary tract at initial testing is more common among women with bacteriuria and diabetes (occurring in 63 percent) than among women with bacteriuria but no diabetes (43 percent). Eighty percent of women with diabetes and bacteriuria have been shown to have renal parenchymal infection by seven weeks after initial testing. An autopsy series documented a frequency of acute pyelonephritis among patients with diabetes that was four to five times as high as that among patients without diabetes. The urinary tract is also a more common source of bacteremia among patients with diabetes. Finally, among women with diabetes, complicated symptomatic urinary tract infections are associated with higher frequencies of acute pyelonephritis, urosepsis, and bilateral renal infection and a higher risk of hospitalization than they are among nondiabetic women with symptomatic bacteriuria. Other serious, although less common, complications of symptomatic bacteriuria associated with diabetes include renal and perirenal abscesses, emphysematous cystitis, emphysematous pyelonephritis, renal papillary necrosis, fungal urinary tract infections — most frequently caused by Candida species — and xanthogranulomatous pyelonephritis. Symptomatic bacteriuria in patients with diabetes mellitus is serious and warrants proper clinical attention for both diagnosis and treatment. Clinicians understand these facts well. Because of the frequency of upper urinary tract infection, potential upper tract complications, and frequent recurrent infections, most investigators recommend cultures for all urinary tract infections in patients with diabetes, whereas we no longer recommend initial urine cultures for nondiabetic women with uncomplicated cystitis. Follow-up urine culture after completion of antimicrobial therapy is also recommended for most women with diabetes in order to identify patients in whom bacteriologic cure has not been achieved.

Why do patients with diabetes mellitus have an increased frequency of urinary tract infections, and why do they have more serious complications? Despite numerous studies, the exact pathogenesis of this problem has not been clearly defined. Although risk factors such as age, degree of glycosuria, and instrumentation have been suspected, studies have not confirmed that these factors are major contributors. A variety of factors may contribute, of which bladder dysfunction as a result of diabetic neuropathy and cystopathy may be the most important. Impaired sensation in die bladder results in bladder distention and increased residual volume, which results in a physiological obstruction of the urinary tract, which, in turn, increases the susceptibility to infection and allows infection to be initiated by much smaller numbers of uropathogens. There is also a higher prevalence of genitourinary structural abnormalities (cystocele, cystourethrocele, and rectoccele) among women with diabetes who have recurrent urinary tract infections (30 percent) than among nondiabetic women with such infections (4 percent). Most agree that these factors and others contribute to die increased prevalence and severity of urinary tract infections in patients with diabetes.

What is the importance, if any, of asymptomatic bacteriuria in women with diabetes mellitus? Many investigators have recommended screening patients with diabetes to detect and treat asymptomatic bacteriuria because of the increased frequency and severity of upper urinary tract infections associated with symptomatic bacteriuria in such patients, even though there arc few data to support this
recommendation. Many of us have considered asymptomatic bacteriuria in patients with diabetes to be "die enemy at the gate." So why not attempt to eliminate the enemy before scri-
ous harm is done to our patients? This approach is definitely useful in pregnant patients to reduce their increased risk of acute pyelonephritis and the accompanying risks of prematur ity and low birth weight in their infants. This approach is also indicated in patients who are about to undergo urologic surgery, in order to reduce the risk of postoperative complications including bacteremia, and in recipients of renal transplants soon after transplantation. Since treatment of asymptomatic bacteriuria in these three groups of patients has been so successful, we suspected that it would also be effective in patients with diabetes mellitus and asymptomatic bacteriuria.

In this issue of the Journal, Harding et al. describe a detailed study of the effect of antimicrobial therapy on asymptomatic bacteriuria in women with diabetes mellitus. The study was a prospective, randomized trial comparing antimicrobial therapy with no antimicrobial therapy in women with diabetes and asymptomatic bacteriuria who were then followed for 36 months. For the first 6 weeks, the study was double-blinded and placebo-controlled, so that patients received either 14 days of antimicrobial treatment or placebo. Furthermore, patients were monitored meticulously, and there are data on duration and complications of diabetes, medications, ethnic background, sexual activity, previous urinary tract infections, genitourinary surgery, reproductive history, urinary symptoms, and quantitative urine cultures including sensitivity testing, urinalysis, and measurement of blood sugars, glycosylated hemoglobin, renal function, and urinary protein and glucose. All factors were analyzed statistically, and the results are unequivocal.

As compared with placebo, antimicrobial therapy effectively reduced the incidence of asymptomatic bacteriuria in treated women as assessed four weeks after therapy. However, the antimicrobial therapy did not alter the incidence of symptomatic bacteriuria (cystitis, pyelonephritis, and hospitalization) during the ensuing 17 months of follow-up, although there was a slight but nonsignificant trend in favor of the antimicrobial treatment. Treatment also did not alter the time to the first symptomatic episode of urinary tract infection. Most subjects in both treatment groups had no symptomatic episodes during the follow-up period. The treated patients did have significantly more new episodes of asymptomatic bacteriuria, and they had more adverse events from antimicrobial therapy for urinary tract infections. The metabolic status and diabetic complications (renal function, degree of proteinuria, and glycosylated hemoglobin level) remained similar in the treated and untreated groups. There was no association of symptomatic episodes with previous genitourinary surgery, ethnic background, type or duration of diabetes, presence or absence of retinopathy or nephropathy, blood glucose level, or pres-
ence or absence of pyuria, glycosuria, or proteinuria. Thus, the results of this complex but excellent study strongly suggest that there are no substantial benefits from screening women with diabetes mellitus for asymptomatic bacteriuria or from treating it. Although treatment resulted in the short-term clearance of bacteriuria, it failed to prevent symptomatic episodes and hospitalizations or even to delay the onset of symptomatic infections. These observations are consistent with earlier observations showing that treatment of asymptomatic bacteriuria was not beneficial in schoolgirls, patients with spinal cord injuries, or institutionalized elderly men and women.

The study by Harding and colleagues should lead to a change in our delivery of health care to women with diabetes mellitus. Resources now spent on screening and treatment in such patients should instead be used to identify the precursors that do lead to symptomatic urinary tract infections in patients with diabetes. Asymptomatic bacteriuria in women with diabetes mellitus may just be an innocent visitor; even if it is an enemy, a few weeks of antimicrobial therapy for asymptomatic infection is not beneficial. But we must fight back promptly and effectively when the enemy reveals itself and threatens the well-being of women with diabetes.

VINCENT T. ANDRIOLE, M.D.
Yale University School of Medicine
New Haven, CT 06520

REFERENCES
History of Diabetes Mellitus and Risk of Prostate Cancer in Physicians

K. Zhu, I-M. Lee, H. D. Sesso, J. E. Buring, R. S. Levine, and J. M. Gaziano

1 United States Military Cancer Institute, Washington, DC.
2 Division of Preventive Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA.
3 Department of Epidemiology, Harvard School of Public Health, Boston, MA.
4 Department of Internal Medicine, Meharry Medical College, Nashville, TN.

Received for publication August 14, 2003; accepted for publication March 2, 2004.

Some studies have suggested that diabetes mellitus may decrease the risk of prostate cancer because of lower insulin levels. To further investigate the relation between diabetes and prostate cancer, a nested case-control study was conducted within the US Physicians' Health Study. Cases (n = 1,110) had been diagnosed with prostate cancer, confirmed on medical record review, during follow-up in 1982-1995. Controls (n = 1,110) were selected randomly from men free of prostate cancer and were matched on age and date of randomization. Information on personal history of diabetes and other diseases, lifestyle habits, and body weight/height was self-reported. Logistic regression analysis showed that the odds ratio for prostate cancer was 0.64 (95% confidence interval (CI): 0.43,0.95) for men with diabetes, relative to those without the disease, after adjustment for potential confounders. Odds ratio estimates were 0.63 (95% CI: 0.35,1.14), 0.77 (95% CI: 0.35, 1.72), 0.59 (95% CI: 0.21, 1.66), and 0.59 (95% CI: 0.27, 1.27) for diabetes diagnosed 1-5, 6-10, 11-15, and >16 years prior to prostate cancer diagnosis (p for trend < 0.05). Adjusted odds ratios were 1.44 (95% CI: 0.34, 6.17) for stage A prostate cancer and 0.48 (95% CI: 0.28, 0.83) for stages B-D. Results suggest that history of diabetes may be associated with a decreased risk of prostate cancer, especially late-stage tumors.

case-control studies; diabetes mellitus; prostatic neoplasms

Abbreviations: BPH, benign prostatic hypertrophy; CI, confidence interval; IGF, insulin-like growth factor.

Animal studies have shown that induction of diabetes mellitus can reduce the weight of the prostate gland and decrease serum testosterone levels (1, 2). Conversely, such changes can be normalized by insulin administration (1, 3). In humans, men with diabetes mellitus are more likely to have reduced sexual function and impotence because of decreased testosterone levels (4, 5). Increased testosterone is a risk factor for prostate cancer (6). Therefore, it has been hypothesized that history of diabetes may be associated with reduced risk of prostate cancer because of decreased testosterone levels.

Previous epidemiologic studies of diabetes mellitus and prostate cancer have shown mixed results. Five studies showed an inverse association; odds ratios were 0.2 (95 percent CI: 0.59, 0.95) (9), 0.91 (95 percent CI: 0.87, 0.94) (10), and 0.7 (95 percent CI: 0.7, 0.9) (11) in three follow-up studies. An insignificant inverse association was found in another three studies including a community survey (12) and two case-control studies (13, 14). However, history of diabetes was not associated with risk of prostate cancer in four follow-up studies (15-18) and two case-control studies (19, 20).

To provide additional evidence on the hypothesized association, we conducted a nested case-control analysis by using data from the Physicians' Health Study. The purpose of this study was to investigate whether history of diabetes mellitus and
control studies and 0.75

thereafter. Information included self-reported age, race, height, weight, smoking, alcohol consumption, exercise, medical history (diabetes, myocardial infarction, stroke, cerebral ischemia, angina pectoris, hypertension, high cholesterol, gout, arthritis, vasectomy, benign prostatic disease, cancer, renal disease, and osteoporosis), and demographic factors. History of diabetes mellitus and other diseases was defined as onset before the diagnosis of prostate cancer (for cases) or the reference date (for controls). No information was obtained regarding whether diabetes was type 1 or type 2. Information at enrollment was used for other factors.

MATERIALS AND METHODS

Study subjects

Subjects were selected from the Physicians’ Health Study, a completed randomized trial of aspirin and beta-carotene among 22,071 US male physicians aged 40-84 years conducted from 1982 to 1995. Men were eligible for the study if they did not report a history of cancer (except nonmelanoma skin cancer), myocardial infarction, stroke, transient ischemic attacks, unstable angina, current renal or liver disease, peptic ulcer, or gout or current use of a vitamin A or beta-carotene supplement. Details of enrollment and follow-up have been reported previously (21, 22).

A nested case-control analysis was conducted for this project. Cases were 1,110 prostate cancer patients identified during a 13-year follow-up period. Prostate cancer was self-reported by subjects, then confirmed by medical record review conducted by an endpoints committee. More than 99 percent of self-reported malignant prostate tumors were subsequently confirmed by medical record review including confirmation of pathology reports (23). Unconfirmed cases were not considered in the analyses. Tumor stage at diagnosis was determined according to an A-D staging system, with A representing the earliest stage (24). Controls were 1,110 male physicians matched to cases on age at study enrollment (+2.5 years) and date of randomization. They were randomly selected from the cohort and did not have a history of prostate cancer at the time the case was diagnosed (reference date).

Data collection

Study participants completed questionnaires at enrollment, after the run-in period, every 6 months during the first year, and annually
TABLE 1. Characteristics of cases and controls, Physicians’ Health Study, United States, 1982-1995

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at reference date</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;54</td>
<td>21</td>
<td>21</td>
</tr>
<tr>
<td>55-59</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>60-64</td>
<td>179</td>
<td>181</td>
</tr>
<tr>
<td>65-69</td>
<td>274</td>
<td>273</td>
</tr>
<tr>
<td>70-74</td>
<td>264</td>
<td>263</td>
</tr>
<tr>
<td>75-79</td>
<td>187</td>
<td>187</td>
</tr>
<tr>
<td>&gt;80</td>
<td>102</td>
<td>102</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>890</td>
<td>976</td>
</tr>
<tr>
<td>Hispanic</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Black</td>
<td>7</td>
<td>4</td>
</tr>
<tr>
<td>Asian</td>
<td>8</td>
<td>21</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>186</td>
<td>97</td>
</tr>
<tr>
<td>Ever smoked</td>
<td>1.9</td>
<td>1.9</td>
</tr>
<tr>
<td>%</td>
<td>1.9</td>
<td>1.9</td>
</tr>
</tbody>
</table>

Statistical methods

Conditional logistic regression was used to analyze the relation between history of diabetes and prostate cancer while adjusting for potential confounding factors. Potential confounding factors included aspirin treatment assignment, beta-carotene treatment assignment, and race. Other factors were tested for their effects on the odds ratio estimate and were not included in the models since they did not change the odds ratio estimate for diabetes by 10 percent or more. We first examined whether cases and controls differed according to whether there was a history of diabetes. We then assessed the diabetes-prostate cancer relation in terms of number of years since diabetes diagnosis and of prostate cancer stage.

RESULTS

Table 1 displays the characteristics of cases and controls. The two comparison groups had the same age distribution because of matching. The distribution of racial background was similar. Cases and controls also did not differ regarding smoking, alcohol consumption, body mass index, exercise, and history of vasectomy. The prevalence of history of diabetes tended to be lower in cases than in controls.

TABLE 2. Odds ratios of prostate cancer associated with history of diabetes mellitus, Physicians’ Health Study, United States, 1982-1995

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases (no.)</th>
<th>Controls (no.)</th>
<th>Odds ratio</th>
<th>95% confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1,060</td>
<td>1,039</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>Yes</td>
<td>50</td>
<td>71</td>
<td>0.64</td>
<td>0.43, 0.95</td>
</tr>
<tr>
<td>No. of years from diabetes reference date</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No history of diabetes</td>
<td>1,060</td>
<td>1,039</td>
<td>1.00</td>
<td>Reference</td>
</tr>
<tr>
<td>1-5</td>
<td>20</td>
<td>30</td>
<td>0.63</td>
<td>0.35, 1.14</td>
</tr>
<tr>
<td>6-10</td>
<td>12</td>
<td>14</td>
<td>0.77</td>
<td>0.35, 1.72</td>
</tr>
<tr>
<td>11-15</td>
<td>6</td>
<td>10</td>
<td>0.59</td>
<td>0.21, 1.66</td>
</tr>
<tr>
<td>&gt;16</td>
<td>12</td>
<td>17</td>
<td>0.59</td>
<td>0.27, 1.27</td>
</tr>
<tr>
<td>P for trend &lt;0.05</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prostate cancer stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>A</td>
<td>1,110</td>
<td></td>
<td>1.44</td>
<td>0.34, 6.17</td>
</tr>
</tbody>
</table>

* Weight (kg)/height (m)
The relation between history of diabetes and prostate cancer is shown in table 2. Compared with controls, cases were less likely to have a history of diabetes (odds ratio = 0.64, 95 percent CI: 0.43, 0.95), after adjustment for randomized treatment assignment and race. Further adjustment for smoking, alcohol consumption, body mass index, exercise, height, weight, and history of myocardial infarction, stroke, cerebral ischemia, angina, hypertension, hypercholesterolemia, vasectomy, gout, arthritis, benign prostatic hyperplasia, renal disease, or osteoporosis did not change the odds ratio estimate.

When data were analyzed according to number of years from the diagnosis of diabetes to the reference date, the odds ratio estimates did not vary much by the time interval: 0.63 (95 percent CI: 0.35, 1.14), 0.77 (95 percent CI: 0.35, 1.72), 0.59 (95 percent CI: 0.21, 1.66), and 0.59 (95 percent CI: 0.27, 1.27) for 1-5, 6-10, 11-15, and >16 years, respectively, although the overall p value for trend was lower than 0.05. When the period of 1-5 years from the diagnosis of diabetes to the reference date was used as the baseline, the odds ratio estimates were around one and the 95 percent confidence interval included the null value for each of the time intervals of 6-10, 11-15, and >16 years. When data were analyzed by tumor stage at diagnosis, the odds ratio estimates appeared decreased for stage B-D tumors, while the corresponding estimate was 1.44 (95 percent CI: 0.34, 6.17) for stage A tumors. When stage B-D tumors were combined, the odds ratio estimate was 0.48 (95 percent CI: 0.28, 0.83).

DISCUSSION

Our results suggest that a history of diabetes mellitus may be related to a decreased risk of prostate cancer, especially late-stage tumors. With one known exception (8), previous studies have not examined the diabetes-prostate cancer relation according to tumor stage. In that study (8), prostate cancer cases were compared with controls having benign prostatic hypertrophy (BPH); it was observed that diabetics had a decreased risk of stage B-D prostate cancer but not stage A tumors. While the results of this study were suggestive, the authors did not exclude the possibility of bias due to use of BPH controls if men with BPH were more likely than men without to have diabetes, as has been suggested (26). The present study did not specifically choose men with BPH as controls, decreasing the likelihood of bias due to use of BPH controls. The odds ratio estimate for stage A was not significantly different from the null value in our study, although it appeared slightly increased. The slightly increased odds ratio for stage A tumors might have resulted from the possibility that men with a history of diabetes were more likely to be under medical surveillance and therefore more likely to have had earlier-stage prostate cancer detected.

This study also has several other strengths. First, there were a relatively large number of prostate cancer patients, compared with other studies. Second, subjects were physicians, who are able to report medical history more accurately than other populations. Third, history of diabetes was collected before the diagnosis of prostate cancer, making differential reports by cases and controls unlikely.

However, several limitations deserve discussion. First, we were unable to distinguish the two primary types of diabetes mellitus, insulin-dependent type 1 and non-insulin-dependent type 2 (27). The two types of diabetes differ metabolically; therefore, their effects on prostate cancer risk may also differ. Although type 2 diabetes is more prevalent among adults, type 1 also occurs in the population (27). Combining the two different types may dilute the association of a specific type of diabetes with prostate cancer. Second, misclassification of the exposure, history of diabetes, was possible for both cases and controls since diabetes tends to be underdiagnosed without laboratory tests. However, since the misclassification was unlikely to be differential by case-control status, its impact would likely dilute the true association. Third, residual confounding may
have affected our reported odds ratios. Obesity, dietary intake, and smoking are related to diabetes (28, 29) as well as prostate cancer (29, 30). Although we considered the potential confounding impacts by body mass index and smoking, which was minimal, we were unable to control for the potential effects of dietary factors; we did not collect detailed baseline dietary information, and limited dietary data were not available until 1996. Fourth, the study subjects might have been a selective group since they had a low frequency of diabetes and other diseases compared with those contacted but not ultimately randomly selected for the study for various reasons (31). However, this selectivity should not have influenced internal validity of the study.

Our results imply that late-stage prostate cancer may have a risk factor profile different from that of early-stage tumors because of the existence of factors that promote tumor growth. The similar prevalence rates of early-stage, latent prostate cancer in various countries, in contrast to the different incidence rates of late-stage, overt cancer (32, 33), suggest a multiple-step hypothesis for the occurrence of prostate cancer. That is, latent cancers may have undergone an initiating event(s), and the appearance of overt cancer may depend on exposure to promotion factors (34, 35). In this regard, history of diabetes may represent factors that suppress tumor promotion and thus inhibit progression of early-stage prostate cancer to clinical tumors. Therefore, history of diabetes would be less frequent in patients with late-stage cancer.

The mechanisms that underlie the suggested association are not known and may be complex. Reduced androgen levels in diabetics may restrain promotion of latent prostate cancer. In animal experiments (36, 37), androgens can cause invasive carcinoma in the lateral and anterior prostate in a dose-response fashion (36). The reduced promoting effects of testosterone may also extend to men, by making tumors less likely to progress to clinical stage in diabetics. Another possible mechanism relates to insulin-like growth factor (IGF)-1. It is known that insulin inhibits production of IGF binding protein-1 (38). The reduced IGF binding protein-1 causes increased levels of free IGF-1. Higher levels of IGF-1 can facilitate both initiation and progression of the disease (39, 40), leading to an increased risk of prostate cancer (41—43). In diabetics with reduced insulin secretion, circulating IGF-1 levels are reduced (44, 45) and therefore may be suppressing progression of prostate cancer to clinical stage.

Apart from the possible effects of testosterone and IGF-1, the observed association also may result from treatment for diabetes, rather than the endogenous changes associated with diabetes. However, Rosenberg et al. (8) showed that specific medications to treat diabetes were not independently associated with prostate cancer after adjustment for diabetes.

In summary, this study indicates that a history of diabetes mellitus may be associated with a decreased risk of prostate cancer, particularly late-stage tumors. The results contribute to the understanding of factors that may delay prostate cancer progression and are helpful for developing therapeutic and preventive interventions. Large studies with similar results will help to solidify the present findings.

ACKNOWLEDGMENTS

This study was supported by grants CA34944, CA40360, HL26490, and HL34595 from the National Institutes of Health.

The authors acknowledge the crucial contributions of the entire staff of the Physicians' Health Study, under the leadership of Charlene Belanger, as well as Mary Breen, Vadim Bubes, Jean MacFadyen, Geneva McNair, David Potter, Leslie Power, Harriet Samuelson, Dr. Miriam Schwartz, Mickie Sheehy, Joanne Smith, and Phyllis Johnson Wojciechowski.

REFERENCES


42. Moyad MA, Pienta KJ. Mind-body effect: insulin-like growth factor-I; clinical depression; and breast, prostate, and other cancer risk—an unmeasured and masked mediator of potential significance? Urology 2002;59:4-8.


Aspects of Type 2 Diabetes and Related Insulin-Resistant States
his is the fourth in a series of articles on presentations at the American Diabetes Association Annual Meeting, San Diego, California, 10–14 June 2005.

Exercise, diet, and lifestyle modification
Addressing the debate over aerobic versus anaerobic exercise, Sigal et al. (abstract 371) reported results of the Diabetes Aerobic and Resistance Exercise (DARE) clinical trial of 251 previously inactive persons with type 2 diabetes exercising at local YMCA s, supervised by personal trainers. Both aerobic and resistance training improved HbA1c (A1C) similarly over 6 months, with the combination of both forms of exercise improving A1C more than either type alone. Goh et al. (abstract 1089) reported a similar study from Singapore comparing 22 persons with type 2 diabetes randomized to either aerobic exercise, with a 10/10-mmHg decrease in blood pressure and a 0.3% decrease in A1C, or resistance training, with a 0.6% decrease in A1C. Morrato et al. (abstracts 1041 and 1063), analyzing the national Medical Expenditure Panel Survey (2000–2002) found that 55% of 97,422 adults 3:18 years of age, but 39% of those with self-reported diabetes, stated they participated in moderate/vigorous activity for at least 30 min at least three times weekly. Among those with BMI <25, 25–29.9, 30–39.9, and >40 kg/m², the likelihood of diabetes was 52, 59, 41, and 13% greater in inactive than in active persons, respectively, adjusting for age, sex, education level, race, ethnicity, and cigarette smoking.

Gail lard et al. (abstract 1086) reported a study of 46 African-American women without diabetes, showing that those with moderately good aerobic fit-
levels from —160 to 110 mg/dl following exercise, with glucose levels remaining —25 mg/dl below those on a sedentary day and with 48 vs. 28% having a blood glucose <60 mg/dl. Hypoglycemia occurred infrequently on the sedentary night if the prebedtime snack glucose exceeded 130 mg/dl, but this was not protective following exercise. There may, then, be sustained increase in glucose requiring following exercise in type 1 diabetes, increasing the risk of nocturnal hypoglycemia, suggesting the need to reduce insulin dosages and/or increase nutrient intake not only in the immediate postexercise period but for as long as 10 h thereafter.

In the Diabetes Prevention Program (DPP) (abstract 1037), diabetes incidence decreased from 11, 11, and 10 cases per 100 person-years at ages 25-44, 45-59, and >59 years with placebo to 6, 5, and 3 cases per 100 person-years with the lifestyle intervention, suggesting particular benefit with greater age. Weight loss with the lifestyle intervention in the three age-groups was 4, 5, and 6 kg, and the participants exercised 4, 6, and 19 metabolic-equivalent (MET) hours/week, respectively. Analysis of electrocardiograms performed in the DPP (abstract 1003) showed that estimates of sympathetic and of parasympathetic modulation of heart rate showed improvement only in the intensive lifestyle intervention. Higher heart rate was associated with greater risk of diabetes, and the heart rate declined 5 bpm in the lifestyle intervention versus 2 bpm with placebo and with metformin. Ramachandran et al. (abstract 366) randomized 531 Asian-Indian persons with impaired glucose tolerance (IGT) age 35-55 years to control, lifestyle, metformin, and lifestyle plus metformin for 30 months, with diabetes developing in 49.6, 35, 39.8, and 34.7%, respectively, suggesting that the benefit of lifestyle modification exceeds that of metformin and that there is no additive, effect of combining the two approaches.

A number of additional studies analyzed aspects of diet related to diabetes. Songetal. (abstract 1016) analyzed alcohol consumption among 38,018 women, age 45 years, without a history of coronary heart disease, stroke, cancer, or dia-

betes in the Women’s Health Study over 8.9 years of follow-up, showing decreases in risk of type 2 diabetes of 16, 28, 36, and 57% for women consuming 0-6.0, 6.1-12, 12.1-24, and >24 g/day, respectively, regardless of type of alcoholic beverage and controlling for age, Btvl, total calorie intake, smoking, physical activity, postmenopausal hormone use, family history of diabetes, and dietary factors, including glycemic load, total fat, fiber, magnesium, and caffeine intake. Pereira et al. (abstracts 1056 and 1057) followed 28,812 postmenopausal women without diabetes, heart disease, and cancer for 11 years. Compared with women not drinking coffee, those drinking more than five cups daily of decaffeinated and regular coffee had 34 and 17% lower likelihoods of developing diabetes, respectively, adjusting for age, baseline BMI, waist-to-hip ratio, estrogen use, education, cigarette smoking, physical activity level, and intake of alcohol, total calories, fatty acids, cereal fiber, tea, milk, and soda. Compared with women not drinking sugar-sweetened beverages, the study showed that those consuming at least seven such beverages weekly had a 1.7-fold increased risk of developing diabetes, while compared with those drinking no fruit juice, 3.5-6.5 servings, and 5 servings weekly—were associated with 24 and 38% increases in diabetes risk. Fowler et al. (abstract 1058) studied the relationship between soft drink consumption and weight gain, reporting that of those with baseline BMI <25 kg/m², drinking less than one-half can/day, one-half to less than can/day, one to less than two cans/day, and two or more cans/day of regular soda were associated with 26, 30, 33, and 47% likelihood of becoming overweight after 7-8 years. The respective risks associated with drinking diet soda were, however, even greater, at 37, 38, 55, and 57% increases in the risk of developing obesity, with risk increased 1.4-fold per can of diet soda consumed per day, suggesting that consumption of diet soda may not be a useful weight control strategy.

McMillan et al. (abstract 36) compared a low-fat/55% carbohydrate diet, a low-fat/55% carbohydrate low-glycemic index diet, a 25% protein/45% carbohydrate diet, and a 25% protein/45% carbo-

hydrate low—glycemic index diet in 129 overweight persons (116 completers) without diabetes. After 12 weeks, weight loss was greater with the second and third diets in women, but not in men, and reductions in glycemic index but not in carbohydrate in both men and women lowered LDL cholesterol. Atkinson et al.
(abstract 1766) fed 11 nondiabetic women on 4 different days a 25% protein/45% carbohydrate versus a low-fat/55% carbohydrate series of meals, with either low- or high-glycemic index carbohydrates, creating glycemic loads of 43, 84, 65, and 116. The respective incremental areas under the glucose curve were 196, 230, 523, and 315, suggesting physiologic validity to the concept of glycemic load. Furthermore, high-protein diets appeared to produce greater satiety. Manders et al. (abstract 7) administered a standard carbohydrate load with or without a casein protein hydrolysate containing additional leucine and phenylalanine to 10 patients with type 2 diabetes, showing tripling of insulin response and a 28% lowering of postload glycemia, associated with 43% greater glucose disposal based on labeled glucose turnover studies.

Heilbronn et al. (abstract 34) and Frisard et al. (abstract 35) compared 45 healthy overweight nonobese persons on a control diet with three dietary interventions, a 25% calorie restriction diet, a 12.5% calorie restriction with a 12.5% increase in energy expenditure by exercise, or a low-calorie diet until 15% weight reduction was achieved, followed by maintenance. Body weight decreased 10, 10, and 14% with the respective interventions; fasting insulin decreased 30, 17, and 11%; insulin sensitivity increased 40, 79, and 70%; intramuscular lipid was not affected; and intrahepatic lipid decreased 37, 28, and 40%, suggesting that it may be possible to specifically design interventions to optimize improvement in insulin sensitivity.

Maymadn et al. (abstract 1767) placed 30 children with BMI >95th per-centile on a low-glycemic load diet and exercise program, showing a 23% decrease in triglyceride-to-HDL ratio and a 19% decrease in CRP in those randomized to a 3-g daily long-chain to-3 fatty acid supplement. Winzell et al. (abstract 39) studied an insulin-resistant mouse model treated with linoleic acid for 8 weeks, showing that rather than being beneficial, insulin sensitivity and adiponectin levels decreased with these agents; they noted that the term "linoleic acid" actually refers to a group of polyunsaturated fatty acids, suggesting that various fatty acids may play different roles in insulin sensitivity. Vitamin D may be related to type 2 diabetes as well, with Piitas et al. (abstract 1772) reporting that of 81,680 women without history of diabetes, cardiovascular disease, or cancer followed for 20 years in the Nurses’ Health Study, adjusting for age, BMI, hypertension, family history of diabetes, smoking, physical activity, caffeine, and alcohol intake, those in the highest versus lowest quintiles of vitamin D intake had a 28% lower risk of developing type 2 diabetes. Pharmacologic approaches to weight loss were discussed in several presentations at the meeting. Aronne et al. (abstract 1,821) treated 148 persons with BMI 29-43 kg/m² with 10 mg sibutramine daily, with 95 achieving >5% weight loss (mean 8.3 kg) randomized to low-calorie diet using meal replacement therapy with versus without continued sibutramine, leading to 2.5-kg further weight loss vs. 2.8-kg weight gain. Long et al. (abstract 1822) and Fennoy et al. (abstract 1824) randomized 498 obese (mean BMI 36.1 kg/m²) adolescents ages 12-16 to 10 mg sibutramine daily versus placebo, showing 38, 23, and 39% vs. 82, 13, and 6% having respective weight loss <5, 5-10, and >10%, with expected improvement in blood pressure, triglyceride-ide, and HDL cholesterol levels. Yaturu and Bridges (abstract 1830) reported that 54 type 2 diabetic persons treated with orlistat and monthly nutritional counseling showed reduction in A1C with the treatment. Given the evidence that obesity may be a state of low growth hormone function, Kim et al. (abstract 1834) administered growth hormone versus placebo to 16 vs. 8 obese type 2 diabetic patients for 12 weeks, showing increased insulin sensitivity and decreased visceral fat, triglyceride, free fatty acid, fibrinogen, and plasminogen activator inhibitor-1 levels. Albert et al. (abstract 1823) randomized 40 obese persons to growth hormone versus placebo, showing decreased body fat assessed by dual-energy X-ray absorptiometry. Wittert et al. (abstract 1835) administered AOD9604, a modified growth hormone peptide fragment, or placebo, 1, 20 and 50 mg/day orally for 12 weeks, with
greatest weight loss at the 1-mg dose, at 2.6 vs. 0.8 kg with placebo. Kok et al. (abstract 1843) reported that administration of the dopamine 2 receptor agonist bromocryptine versus placebo to 18 healthy obese premenopausal women led to a 5% increase in resting energy expenditure, with reduction in fasting insulin suggesting improvement in insulin sensitivity. Addressing an important risk factor for weight gain, Ader et al. (abstract 1848) administered olanzapine, risperidone, or placebo to normal dogs for 6 weeks, showing increased food intake and fat mass with olanzapine. Fountaine et al. (abstract 1849) reported a 2.3% increase in food intake in 21 healthy persons receiving olanzapine 5 and then 10 mg daily versus placebo for 12 days. Rosenstock et al. (abstract 46) administered a controlled release formulation of topiramate to 111 persons with type 2 diabetes, showing that the mean BMI of 38 kg/m^2 decreased 5.8 vs. 2.3% with placebo, with a fall in A1C from baseline of 0.9 vs. 0.4%.

Andre Scheen (Liege, Belgium) gave the results of the Rimonabant In Obesity (RIO)-Diabetes study. Rimonabant is a selective CB1 receptor endocannabinoid blocker, having central action in decreasing food intake and showing evidence of action at the adipocyte in skeletal muscle, in the liver, and in the gastrointestinal tract, all further improving metabolic parameters. A total of 6,627 persons have been enrolled in four rimonabant phase II/III clinical development trials. RIO-Diabetes was a study of 5 vs. 20 mg rimonabant vs. placebo in 1,045 persons with diabetes who underwent a 2-week single-blind placebo period followed by 4 weeks of placebo versus 5 mg rimonabant, with the active treatment group then treated with 5 or 20 mg daily for a total of 52 weeks. Admission A1C was 6-10% (mean 7.3%), with the primary end point the change in body weight at 1 year and secondary end points A1C, lip-ids, waist circumference, metabolic syndrome, and safety. Totals of 348,358, and 339 subjects were treated with placebo, 5 mg, and 20 mg daily. Approximately 60% had hypertension and 55% dyslipidemia, 66% received metformin and 33% sulfonylureas, and 79% had metabolic syndrome. Body weight decreased 1.4, 2.3, and 5.3 kg, and waist circumference decreased 1.9,2.9, and 5.2 cm in the respective groups. Of patients, 14.5 vs. 21.7 vs. 49.4% lost >5% of initial weight and 2, 6.2, and 16.4% lost >10% of initial weight. At 1 year, the A1C was 7.3, 7.2, and 6.7%, with multivariate analysis suggesting that approximately half of the decrease in the 20-mg group was due to weight loss and half due to direct metabolic effect of CB1 receptor blockade at the level of the adipocyte, skeletal muscle, or liver. HDL cholesterol was 45 mg/dl at baseline and increased 7.1 vs. 9.2 vs. 15.4% at 1 year with 0, 5, and 20 mg. Their analysis suggested that more than half of the improvement was not attributable to weight loss. The triglyceride level increased 7.3 with placebo while decreasing 1.3 and 9.1% with active treatment. Compared with the placebo group, in which the prevalence of metabolic syndrome decreased 7.6%, the 20-mg group, metabolic syndrome decreased 18.9%. There were some safety issues, with nausea experienced by 5.7 vs. 12.1% of the placebo versus 20-mg groups, self-reported hypoglycemia occurring in ~1 vs. 5%, and anxiety in 2.8 vs. 5%. Of treated patients, 5.5, 7.8, and 15% discontinued the drug because of adverse events.

Oral agent treatment
Fan et al. (abstract 1000) reviewed diabetes treatment patterns in national samples of 1,215 persons with diabetes in 1988-1994 and of 758 such persons in 1999-2002. The frequencies of diet and insulin treatment alone decreased from 27 to 19% and from 24 to 14%, while the frequencies of oral agent treatment alone increased from 45 to 57% and that of oral agents in combination with insulin increased from 3 to 10%. Rates of achieving A1C <7% decreased from 44 to 40% in those age 565 years and increased from 40 to 44% in those age 45-64 years, while among those age <45 years, only 16% in either time period achieved A1C <7%. Koro et al. (abstract 999) analyzed phar-macotherapy change in response to elevated A1C in a dataset of 9,335 persons receiving oral antidiabetic monotherapy. Among patients with at least one A1C >7%, those with A1C 7-10% had phar-macotherapy change in a median of 372 days and those with A1C >10% had pharmacotherapy change in a median of 160 days. With two elevated A1C test results, median times from the second test were 275 and 70 days, respectively, suggesting considerable room for
improvement of diabetes treatment in the community. Sulfonylurea treatment. Several studies addressed aspects of metformin and sulfonylurea treatment. Holman et al. (abstract 596) examined P-cell function and insulin sensitivity using the homeostasis model assessment (HOMA)2 model in 1,741 U.K. Prospective Diabetes Study patients at the time of diagnosis of diabetes and after 1 year of therapy. ß3-Cell function increased 36% with sulfonylurea versus 11% with metformin, while insulin sensitivity decreased 4% versus increasing 10% with the respective therapies. Gottschalk et al. (abstract 264) compared glimepiride (mean 3.8 mg daily) versus metformin (mean 1,408 mg daily) in 263 children age 9-17 years with type 2 diabetes whose baseline A1C was 8.5%, showing 12-week A1C falls of 0.7 vs. 0.9%, with weight gain of 2.2 vs. 0.7 kg. Gerich et al. (abstract 266) randomized 428 type 2 diabetic persons with mean A1C 8.4%, not previously receiving pharmacologic treatment, to metformin plus either 120 mg nateglinide three times daily or 1.25-20 mg glyburide daily; both groups showed similar 2-year decreases in A1C of 1.5%, with 8 vs. 18% experiencing hypoglycemia. The A1C nadir occurred at 28 weeks, and A1C subsequently increased by ~0.3%/year in both groups. Girman et al. (abstract 994) reported the effect of adding a sulfonylurea to metformin in 2,220 persons with median age 63-years, A1C 8.8%, diabetes duration 3.8 years, and BMI 31.4 kg/m². A1C worsened before addition of the sulfonylurea, improved immediately after, and began worsening again 6 months after sulfonylurea initiation, particularly with higher initial A1C, younger age, and female sex. By 4 years, 85% of patients were predicted to have A1C ≥8.0%, although analysis of physician behavior suggested that only 34% would be given additional therapy. Nyback-Nakell et al. (abstract 454) studied 23 type 2 diabetic persons treated with insulin and sulfonylurea for 7-24 years, 13 of whom were also treated with metformin. To ascertain whether there was long-term benefit from sulfonylurea, the agents were discontinued, with glucose control worsening in 77%. The duration of diabetes and of sulfonylurea treatment correlated with ongoing sulfonylurea benefit, without predictive effect of weight, BMI, waist-to-hip ratio, insulin requirement, baseline A1C, fasting glucose, C-peptide, or serum triglycerides.

Metformin treatment. Eurich et al. (abstract 457) studied outcome of treatment of 1,833 persons who had developed heart failure among 12,272 new users of oral antidiabetic agents in the Saskatchewan Health database in 1991-1996, 208 of whom received metformin monotherapy, 773 sulfonylurea monotherapy, and 852 combination therapy. Over 2.5 years of follow-up, those receiving metformin monotherapy and combination therapy had 70 and 61% the mortality of those receiving sulfonylurea monotherapy, respectively, suggesting that it may be an ill-founded concept, that there is a contraindication to metformin use among patients with heart failure due to concerns over lactic acidosis. In another
analysis using the same database. Bowker et al. (abstract 521) studied 10,309 persons receiving metformin or sulfonylurea followed for a mean of 5.4 years, finding the latter to have a 30% increase in cancer-related mortality. Insulin use was associated with a 90% increase, suggesting either a protective effect of metformin or a deleterious effect of sulfonylurea and insulin. Aguiar et al. (abstract 607) reported improvement in weight, blood pressure, HDL cholesterol, and endothelial vascular reactivity in 31 nondiabetic relatives of persons with type 2 diabetes treated with 850 mg metformin twice daily for 90 days. Analysis of the effect of metformin in the DPP (abstract 1004) showed evidence of increase in insulin secretion along with weight loss, explaining the decrease in diabetes development in comparison to the placebo group.

New pharmacological approaches to type 2 diabetes
A number of additional approaches to treatment of type 2 diabetes were explored. Yo-shida et al. (abstract 472) studied CS-917, an orally administered inhibitor of fructose 1,6-bisphosphatase, a rate-limiting enzyme of gluconeogenesis, reporting a dose-dependent glucose lowering in overweight, fasted normal cynomolgus monkeys and in Goto-Kakizaki rats. Van Poelje et al. (abstract 503) reported reduction in glucose from 305 to 166 mg/dl with use of this agent over 30 days in a rat type 2 diabetes model. Kumeda et al. (abstract 473) and Yamamoto et al. (abstract 474) reported that SGL0010, an orally active inhibitor of proximal renal tubular sodium-dependent glucose cotransporters, results in dose-dependent glycosuria, which had glucose-lowering effect in type 1 and type 2 diabetic models, with less potential to cause hypoglycemia than glyburide. Fyfe et al. (abstract 522) reported that the glucokinase activators PSN105 and PSN010 lowered glucose levels in animal models of type 2 diabetes. Songetal. (abstract 526) performed a meta-analysis of treatment of persons with type 2 diabetes with oral magnesium, reporting nine randomized controlled trials lasting 4—24 weeks with 392 total participants, showing A1C reduced 0.3% and fasting glucose 5 mg/dl. Shankar et al. (abstract 535) administered acarbose versus placebo to 196 persons with early type 2 diabetes, characterized by glucose level fasting < 140 and at 2 h on glucose tolerance testing >200 mg/dl, reporting lowering of postprandial glucose and A1C but no reduction in progression from feting glycemia £140 to > 140 mg/dl or from £126 to >126 mg/dl, leading the authors to suggest that p-cell failure, as shown by fasting hyperglycemia, is not improved by lowering postprandial glucose levels. Satoh et al. (abstract 647) administered the t-glucosidase inhibitor voglibose versus placebo to 12 vs. 12 persons with type 2 diabetes, the former showing lowering of fasting glucose, C-peptide, HOMA of insulin resistance (HOMA-IR), apolipoprotein B, apolipoprotein E, and triglycerides, despite similar improvement of BMI and A1C. Voglibose also decreased soluble, intercellular adhesion molecule-1 and CRP, suggesting an anti-inflammatory effect.

Balkan et al. (abstract 618) administered PTP-3848, an inhibitor of the negative insulin signaling regulator protein tyrosine phosphatase IB, orally to C57 mice, which develop insulin resistance on a high-fat diet. Fatty acid synthase decreased with an increase in carnitine palmitoyltransferase 1 and circulating ke-tone levels. Weight gain was prevented, with no decline in adiponecin or increase in insulin levels. Sayo et al. (abstract 604) examined the effect of the antibody to tumor necrosis factor a infliximab in patients with rheumatoid arthritis, showing increase in insulin sensitivity and in adiponecin levels. Several studies suggested benefit of chromium picolinate. Martin et al. (abstract 1778) randomized 27 type 2 diabetic persons treated with 5 mg glipizide GITS daily to placebo versus chromium, 1 mg picolinate daily for 6 months, showing a decrease in A1C of 0.4 vs. 1.2% and weight gain of 2.2 vs. 0.9 kg with a 2.7-fold greater increase in abdominal fat and with evidence of insulin-sensitizing effect of chromium treatment. Albarracin et al. (abstract 1784) randomized 368 type 2 diabetic persons to 600 mg chromium picolinate plus 2 mg biotin daily versus placebo for 90 days, showing a 0.5, 0.7, 1.2, 1.8, and 2.0% lower A1C among those with baseline A1C 7—7.9, 8—8.9, 9—9.9, 10-10.9, and 2.11%.
tively. The decrease in LDL cholesterol among those with baseline cholesterol >200 mg/dl was 22 vs. 8 mg/dl.

**Gestational diabetes mellitus**

At a symposium addressing the use of metformin in pregnancy, Clifford Bailey (Birmingham, U.K.) discussed cellular and metabolic actions and pharmacology of metformin. Metformin is now the most used agent in the treatment of type 2 diabetes worldwide. In medieval Europe, Galega officinalis (French lilac, goatsrue, or professor-weed) was used as a treatment for diabetes, as well for increasing milk production by farm animals. In 1850, it was found to be rich in guani-dine. Guanidine was found in 1918 to lower glucose levels, with subsequent recognition that biguanides have glucose-lowering effects. In 1957, metformin and phenformin were introduced, with phenformin withdrawn in 1977 because of concern about risk of lactic acidosis, and metformin was introduced in the U.S. in 1995.

Metformin is composed chemically of two guanidine groups joined together by deamination, with phenformin and another biguanide, buformin, showing a similar basic structure. Absorption is rapid, and metformin circulates unbound with a 6-h half-life and little metabolism, with most elimination occurring by glomerular filtration and tubular secretion in the urine. Concentrations are high in the liver and intestinal wall, with the drug acting within the cytoplasm of target cells following cellular uptake via an organic cation transporter system. Metformin crosses the placenta with somewhat higher concentrations in fetal than maternal blood, but there are low concentrations in breast milk.

Metformin counters insulin resistance by insulin-dependent and -independent mechanisms, lowering basal insulin levels, and not causing hypoglycemia when administered alone. Its antihyperglycemic effect appears mainly to reflect hepatic action, although there also is a muscle effect. Interestingly, the agent increases anaerobic metabolism in the gastrointestinal tract, increasing lactate production. At the cellular level, metformin alters membrane surface electrical charges, affecting membrane fluidity and plasticity. It acts on the (3-subunit of the insulin receptor to increase tyrosine phosphorylation and increases glucose transporter movement to the cell membrane both via its effects at the insulin receptor and independently, may increase glucose metabolism mitochondrial effects, and may have effects on AMP kinase.

Clinically, metformin improves insulin resistance, reduces insulin levels, decreases the degree of abdominal obesity, decreases glucose levels, has modest triglyceride- and LDL cholesterol-lowering and HDL-raising effects, is antithrombotic, modestly decreasing plasminogen activator inhibitor-1 and lessening platelet aggregation, decreases advanced glycation endproduct levels, and increases endothelial and endothelium-indepen-
Pregnancy is an insulin-resistant state. Among pregnant women not developing gestational diabetes mellitus (GDM), insulin secretion increases. GDM is associated with particularly severe insulin resistance and with failure of insulin levels to increase appropriately, so that metformin might offer a logical approach to treatment. In toxicology studies in rats, at dosage levels equivalent to 20 times the upper dose in humans, adverse fetal outcomes were not found, with normal growth of neonatal rats and without teratogenic effect. If one does consider use of this agent during pregnancy, care should be taken to avoid patients at risk of renal insufficiency, so that caution is needed with preeclampsia, with liver disease, alcohol abuse, or cardiac, respiratory, or predisposition to hypoxia, with gastrointestinal pathology, or with impairment of vitamin B12 and folate absorption. Despite these caveats, however, the agent has intriguing potential as a therapy to prevent GDM in susceptible women. Furthermore, if the agent can be safely used during pregnancy, one might anticipate improvement in glycemic control with combined metformin-insulin treatment among women with GDM requiring insulin.

Gerald Briggs (Long Beach, CA) discussed approaches to determining whether metformin might have teratogenic actions. He reviewed potential causes of structural defects, noting that 40% of defects are of unknown cause, 8% are due to a monogenic abnormality, 6% to a chromosomal abnormality, as in Down's syndrome, and 8% environmental, with causes including infections, maternal illness (the vast majority diabetes), and chemicals including pharmaceutical agents. Approximately 40% of defects are left to reflect an interaction between multiple gene variants and environmental factors. Structural defects are seen at birth in 2-3% of infants and at 1 year in 5-6%, with rates increased four- to sevenfold among children of women having preexisting diabetes. In addition to structural defects, agents may cause developmental toxicity, leading to embryonic or fetal death, to growth retardation or restriction, or to functional or behavioral abnormality. As an example, atenolol causes severe intrauterine growth retardation during the second trimester, although it is not a teratogen. Angiotensin II—directed agents cause renal failure in the human fetus, with the consequent oligohydramnios reducing blood flow to the topmost portion of the skull during the third trimester, resulting in bone defects. Drugs may, then, exhibit a number of reproductive and developmental toxicities, including effects on fertility, parturition, lactation, and development. "We can't really say," Briggs explained, "that a drug is safe . . . We can say that it is low risk." Metformin has low molecular weight, negligible protein binding and is not metabolized. Although its plasma half-life is 6.2 h, the erythrocyte half-life exceeds 16 h, which Briggs characterized as "betting there for a long time."

Criteria for establishing human developmental toxicity include epidemiologic studies, assessing outcome of pregnancies with exposure during critical times of fetal development. Case reports are important, as rare exposures may lead to rare defects, as was seen in the unusual development defects associated with thalidomide use. For many drugs, the only data are from animal studies. Addressing the question of whether metformin causes developmental toxicity in animals, Briggs noted that in rabbits there is no evidence of structural defects at doses up to two- to sixfold maximal human dose (based on plasma levels or, less optimally, on dose per unit body surface area). Embryotoxicity has, however, been found in rats at doses somewhat over threefold the maximal human level, suggesting that there may be moderate risk, although there are many variables from one species to another, with characteristics of the human placenta possibly differing from those of experimental animals.

There is somewhat mixed human data. One study found more preeclampsia and increased
perinatal mortality with metformin, although without clear evidence that metformin was causally related (1). In analysis of studies comprising 152 women with PCOS, type 2 diabetes, and GDM, of whom 11 were treated only during the first trimester, and 141 received metformin throughout pregnancy, there were 21 spontaneous abortions, less than the number expected, and the only birth defect found was one case of chondrodysplasia (2-4). Biggs concluded that there is no evidence of growth retardation, fetal or perinatal mortality, or structural, functional, or behavioral deficits, which he contrasted with the strong evidence of toxicity from insufficient treatment of maternal diabetes. In women with GDM, then, there may be low risk with metformin. One must, of course, realize that the absence of evidence of risk is not evidence of the absence of risk, and given Bailey's warning of the potential for lactate accumulation with preeclampsia-induced renal insufficiency, the use of this agent will require extremely careful monitoring.

Charles Glueck (Cincinnati, OH) discussed the use of metformin in the first trimester and in the prevention of GDM, noting that the prevalence of GDM has greatly increased, over the past decade. More than half of women with GDM develop type 2 diabetes within 5 years, and perhaps 70% within 10 years, in association with birth defects and abnormal childhood growth and glucose regulation, leading to a "cross-generational cycle of GDM." Administration of metformin to women with PCOS reduces GDM and fetal macrosomia, promotes ovulation, protects against first trimester miscarriage, is not teratogenic, probably reduces preeclampsia and eclampsia, and promotes normal infant growth and development. In a study of women with PCOS who became pregnant without metformin treatment, only 32% had live births, while during a subsequent pregnancy with metformin treatment, 85% had live births. A similar study reported 58 vs. 11 % fetal loss, although both studies are limited by the use of historical controls (5). In a study comparing 97 pregnancies with 126 infants exposed to metformin throughout gestation for maternal PCOS treatment with 252 healthy control subjects, GDM occurred less often, in 7.6 vs. 15.9%, and preeclampsia occurred comparably in 5.3 vs. 3.6%. Birth weight and length were slightly decreased, perhaps related to the prevention of macrosomia, and at 3, 6, 9, 12, 18, and 36 months, there was no difference in growth or in motor or social development (6). Birth defects occurred in 1.4% of offspring of metformin-treated women, below the national average of —4.5%. Glueck inter-
metformin, 68 with sulfonylurea, and 42 with insulin during pregnancy, preeclampsia occurred in 32, 7, and 10% and stillbirths in 4, 0, and 1%, respectively, but weight was greater in the metformin-treated group at 31.23, and 25 kg/m². Rowan noted the implication that retrospective studies may be misleading, as "we're actually using the metformin in our highest risk women." She concluded that metformin appears to be a logical treatment for pregnancy-related diabetes and described the Metformin in GDM randomized controlled trial currently in progress of 750 women receiving insulin versus metformin, with results to be ready in 2006.

Research presentations at the ADA meeting addressed further aspects of GDM. Eriksson and Cederberg (abstract 152) studied whether oxidative stress plays a role in the teratogenicity of diabetic pregnancy by administering high doses of tocopherol and ascorbate to nondiabetic and streptozotocin-induced diabetic pregnant rats. Malformation rates were reduced from 29 to 19% and fetal resorption from 38 to 26%.

Zhang et al. (abstract 1912) assessed the relationship between prepregnancy physical activity and GDM among 19,462 participants in the Nurses' Health Study—without previous diabetes who reported at least one pregnancy from 1990 to 1998, 1,192 of whom developed GDM. Adjusting for BMI, women in the top 40th per-centile of physical activity had a GDM risk —20% lower than those reporting less activity. Climbing 10-14 and a 15 flights of stairs daily was 7% lower than those reporting less activity. Children had a 58% reductions in GDM rate. Hedderson et al. (abstract 1914) compared 114 women who had had GDM with 95 control subjects. Compared with women whose weight did not change, those with weight gain of 0.39-1.62 kg/year and 1.8-8.4 kg/year in the 6 years before pregnancy had 50 and 150% increases in likelihood of GDM, respectively. Di Gianni et al. (abstract 156) studied 166 women who had had GDM and 98 control women 16 months after delivery, with similar age and BMI, showing 61% higher HOMA-IR, correlating with CRP, with high fasting glucose in 8 vs. 0.7%, low HDL in 37 vs. 17%, hypertriglyceridemia in 10 vs. 2%, and abdominal obesity in 34 vs. 18%. Hypertension was not more prevalent, present in 5 vs. 7%, but metabolic syndrome prevalence was 9% vs. 1%. Montoro et al. (abstract 1913) found that HOMA-IR during the third trimester of pregnancy showed a significant, although only modestly strong (r = 0.47), correlation with insulin sensitivity directly measured with a euglycemic clamp. Finally, in an important warning of the need for improved glycemic control of women with pre-GDM, Al-Ahga et al. (abstract 154) analyzed 260 singleton pregnancies of type 1 diabetic women, finding week 1 30 J of C values of 6.3, 6.9, and 7.1% in

(7) Glueck showed further data that lactation appears to be more successful when metformin is used and that its presence in breast milk does not appear to be clinically significant, without effect on infant height, weight, or development at 3 and 6 months. He concluded that that gestational use of metformin, which he gave in doses up to 2.5 g daily, is beneficial for pregnancy and has no adverse effect on the infant.

Janet Rowan (Auckland, New Zealand) further addressed the use of metformin for type 2 diabetes during pregnancy and for GDM. Most of her patients are of Polynesian ethnicity and are severely obese. The number of women with GDM seen in her clinic in 2000, 2001, 2002, 2003, and 2004 was 169, 193, 294, 370, and 348, respectively, which she believes indicates a real change in incidence rather than a referral bias. More than 25% of her patients with GDM, she noted, have IGT or type 2 diabetes 6 weeks postpartum. Compliance with insulin is a problem in her clinic, and she noted a study finding cord insulin levels more than twice as great in offspring of women with GDM versus control subjects, suggesting that insulin treatment as typically employed may be ineffective, with increased fetal insulin associated with increased risk of childhood obesity and a 10-fold increase in risk of IGT at age 6 years. Of siblings born to women with GDM during only—one of two pregnancies, the second is more likely to be overweight and to develop diabetes (8). Thus, the use of metformin may be particularly appropriate during pregnancy, with potential benefit for offspring. In a retrospective study of 50 women treated with
women whose infants' birth weight was <4, 4.4-4.5, and >4.5 kg, respectively, suggesting the need to optimize glycemic control before the end of the first trimester.

Diabetes in specific disease states
Diabetes in HIV-infected patients.

Colleen M. Hadigan (Boston, MA) noted that HIV has an important overlap with insulin resistance and with diabetes. In a study of 1,278 HIV-infected men and control subjects in 1999, the prevalence of diabetes was 5% among control subjects and 6% among persons with HIV not receiving highly active antiretroviral therapy (HAART), but 14% among patients receiving HAART, a 4.6-fold increase in risk (9). In a follow-up study, the diabetes incidence based on lasting glucose ≥ 126 mg/dl increased 4.11-fold among persons with HIV receiving HAART and 1.64-fold among HIV-positive men not receiving this therapy, with particular risk for those treated with ritonavir and those whose CD4 count was <300/mm³. Among women, 2.8 vs. 1.2% of patients with HIV receiving versus not receiving antiretroviral treatment and 1.4% of control subjects had diabetes in one study, with BMI an additional strong diabetes predictor (10). Persons with HIV and hepatitis C virus (HCV) coinfection had a 3.7-fold increase in diabetes risk over those with HIV alone (11). There is increased risk of CVD with increasing duration of HAART, with diabetes a strong predictive factor; those with diabetes have a 2.38-fold increase in myocardial infarction risk (12).

There are a number of potential mechanisms of the association of HIV with insulin resistance and diabetes, with direct antiretroviral drug toxicity an important component. Insulin sensitivity is markedly reduced by a single dose of indinavir (13), and there are specific effects of protease inhibitors on the GLUT4 transporter (14) and of nucleoside reverse transcriptase inhibitors on mitochondrial function. Lipodystrophy is a crucial aspect of the association of HAART with insulin resistance, leading to relative preponderance of visceral fat, hepatic steatosis, and to fat deposition at other "ectopic" sites. In the fatless mouse animal model, diabetes and insulin resistance develop, responding to transplantation of subcutaneous fat (15). Using positron emission tomography imaging to assess muscle, liver, and subcutaneous fat, subcutaneous fat is almost completely absent and visceral fat increased in persons with HIV lipodystrophy, with decreased glucose disposal into muscle. Visceral adipose tissue area correlates inversely with whole-body glucose disposal in these persons. The protease inhibitor nevirapine increases adipocyte lipolysis in vitro (16). Persons with lipodystrophy have decreased insulin sensitivity and increased circulating tumor necrosis factor α levels (17). This and other inflammatory adipocyte secretory products can be shown to...
decrease lipid synthesis in cultured adipocytes (18). There is increased basal lipolyis in vivo in HIV-infected persons and particular increase in those receiving protease inhibitors (19). HIV-infected persons have decreased peroxisome proliferator-activated receptor 7, sterol regulator element-binding protein 1c, and other adipogenic markers (20), and Hadi-gan noted that patients treated with dideoxynosine/stavudine (d4T) for an 80-week period have decreased subcutaneous fat. In a study comparing glucose tolerance of 75 HIV-infected persons with age-, weight-, and sex-matched persons from the Framingham cohort, —35 vs. 5% had IGT and 7 vs. 0% diabetes, although among those with HIV without lipodystrophy, other than low HDL, there was no evidence of insulin resistance (21). Comparing HIV-infected persons with versus without lipodystrophy, the former have —50% reduction in plasma adiponectin and in adipose tissue adiponec-tin mRNA levels, correlating with insulin resistance and with increased cytokine levels (22). In persons manifesting insulin resistance with HAART, regimens limiting use of protease inhibitors and thymi-dine analogs improve lipoatrophy, with use of abacavir rather than d4T and aza-thioprine leading to increased limb fat, although such an approach has not been shown to improve insulin sensitivity (23). New antiretroviral agents may have better toxicity profiles. Certainly, use of diet and exercise are appropriate, and there is growing evidence that insulin sensitizers may be beneficial in these patients. A trial of metformin (500 mg twice daily) in 25 HIV-infected persons with waist-to-hip ratio >0.9 and fasting insulin > 15 uU/ml showed improved insulin response to oral glucose and decreased weight, waist circumference, and diastolic blood pressure, although no improvement was seen in lipid levels (24). Subcutaneous fat on cross-sectional computed tomography scanning increases with rosiglitazone, with increased adiponectin and "decreased free fatty acid levels (25), and a study of 108 persons with HIV and lipoatrophy treated with rosiglitazone versus placebo that failed to show a difference in limb fat, found that, concurrent d4T/azalhioprine use decreased limb fat and interfered with the effect of rosiglitazone (26). Thus, diabetes and insulin resistance are more prevalent in persons with HIV, direct and indirect effects of antiretroviral agents contribute, and a number of therapeutic strategies exist to improve insulin sensitivity and modify cardiovascular risk. Recognition and management of diabetes and insulin resistance in HIV is increasingly important. Diabetes and liver disease. James Lewis (Washington, DC) reviewed a number of diabetes-related issues encountered in the treatment of persons with liver disease. Cirrhosis may impact the treatment of diabetes, with sulfonyl-urea associated with greater likelihood of hypoglycemia, metformin with increased risk of lactic acidosis, difficulties in medication compliance among persons with encephalopathy, diarrhea leading to electrolyte abnormality associated with acar-bose, and issues of fluid retention with thiazolidinedione treatment. Contaminated glucose monitors have been associated with hepatitis B epidemics (27). Liver disease may be caused by medications for diabetes, notably that which was seen with troglitazone (and some hepatologists question the long-term safety of statins). Acute liver failure rates are increased in persons with diabetes, whose cumulative risk of acute liver failure is 2.31 per 10,000 person-years vs. 1.44 in nondiabetic persons (28). Another study reported acute liver failure rates of 0.15, 0.08, 0.12, and 0.10 per 1,000 person-years with insulin, sulfo-nylureas, metformin, and troglitazone, respectively (29). There is no evidence, however, that glycemic medications other than troglitazone cause chronic liver disease or cirrhosis, and exposure to other diabetes treatment without evidence of acute injury has not been found to lead to subsequent increased risk of liver disease. Diabetes may occur in the setting of liver disease treatment with steroids, inter-feron, lactulose, or calcineurin inhibitors such as tacrolimus or cyclosporine. It is difficult to determine the causal effect of specific agents in persons who may have coincident liver disease of other etiologies, including viral hepatitis, other drugs, such as statins, cholestatic
disorders, and underlying nonalcoholic steato-hepatitis (NASH)-related end-stage liver disease. An important association is that between diabetes and HCV. There is two-to fourfold increase in diabetes in persons with HCV, particularly among persons with cirrhosis, with some evidence that HCV can cause diabetes and that diabetes can increase the risk of contracting HCV. Genotype 2a HCV is disproportionately represented among persons with type 2 diabetes (30), and genotype 3 is associated with steatohepatitis and insulin resistance, while hepatitis B is not as strongly associated with diabetes (31). Among 9,841 adults in the National Health and Nutrition Examination Survey, 8.4% had type 2 diabetes and 2.1% HCV, with greater than a coincident finding of the two appearing together (32). HCV may cause [ ]-cell dysfunction, with evidence of HCV-positive islet cell staining (33) in infected persons, and insulin sensitivity may worsen with progression of hepatic fibrosis. Curing hepatitis C reduces the likelihood of developing diabetes and may improve glycemia in persons who have developed diabetes. Furthermore, markers of insulin resistance may be associated with HCV progression, with evidence that fatty infiltration and fibrosis correlate with leptin levels (34). Posttransplant diabetes is becoming more common, with — 16% of liver transplantation patients having preexisting diabetes, and with new-onset diabetes after transplantation seen in 7-28% of studies, averaging — 15%. The incidence of post-transplantation diabetes is tripled among persons with HCV, with tacrolimus, Cy-closporin, and steroids additional risk factors increasing the likelihood of diabetes. Implications for liver transplantation are of the need to minimize steroid dosages, with changing tacrolimus to cyclosporine, treating HCV, and striving for close glycemic control further considerations (35), although Lewis emphasized the need for perspective trials of these approaches. Certainly, persons with post-transplant diabetes have worse outcome (36). Hepatocellular carcinoma (HCC) is the leading cancer worldwide, with HCC risk tripling among persons with diabetes (37).

There is a complex relationship between the liver and metabolic syndrome, with NASH the most common liver disease in Lewis's population, and increasing appreciation that nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome (38). Eighty-five to 90% of persons with NAFLD have metabolic syndrome, while the risk of NAFLD triples among those who have metabolic syndrome (39). Diabetes or IGT develop in 23% of persons with NAFLD after 3 years of follow-up (40). Although there is thought to be a relationship between hemochromatosis and diabetes (41), Lewis noted that it is uncertain how often this is clinically relevant, with diabetes rarely resolving after treat-
decrease lipid synthesis in cultured adipocytes (18). There is increased basal lipolysis in vivo in HIV-infected persons and particular increase in those receiving protease inhibitors (19). HIV-infected persons have decreased peroxisome proliferator-activated receptor 7, sterol regulator element-binding protein 1c, and other adipogenic markers (20), and Hadi-gan noted that patients treated with dideoxyinosine/stavudine (d4T) for an 80-week period have decreased subcutaneous fat. In a study comparing glucose tolerance of 75 HIV-infected persons with age-, weight-, and sex-matched persons from the Framingham cohort, —35 vs. 5% had IGT and 7 vs. 0% diabetes, although among those with HIV without lipodystrophy, other than low HDL, there was no evidence of insulin resistance (21). Comparing HIV-infected persons with versus without lipodystrophy, the former have —50% reduction in plasma adiponectin and in adipose tissue adiponectin mRNA levels, correlating with insulin resistance and increased cytokine levels (22). In persons manifesting insulin resistance with HAART, regimens limiting use of protease inhibitors and thymi-dine analogs improve lipoatrophy, with use of abacavir rather than d4T and aza-thioprine leading to increased limb fat, although such an approach has not been shown to improve insulin sensitivity (23). New antiretroviral agents may have better toxicity profiles.

Certainly, use of diet and exercise are appropriate, and there is growing evidence that insulin sensitizers may be beneficial in these patients. A trial of metformin (500 mg twice daily) in 25 HIV-infected persons with waist-to-hip ratio >0.9 and fasting insulin >15 uU/ml showed improved insulin response to oral glucose and decreased weight, waist circumference, and diastolic blood pressure, although no improvement was seen in lipid levels (24). Subcutaneous fat on cross-sectional computed tomography scanning increases with rosiglitazone, with increased adiponectin and decreased free fatty acid levels (25), and a study of 108 persons with HIV and lipoatrophy treated with rosiglitazone versus placebo that failed to show a difference in limb fat found that, concurrent d4T/azathioprine use decreased limb fat and interfered with the effect of rosiglitazone (26). Thus, diabetes and insulin resistance are more prevalent in persons with HIV, direct and indirect effects of antiretroviral agents contribute, and a number of therapeutic strategies exist to improve insulin sensitivity and modify cardiovascular risk. Recognition and management of diabetes and insulin resistance in HIV is increasingly important.

Diabetes and liver disease. James Lewis (Washington, DC) reviewed a number of diabetes-related issues encountered in the treatment of persons with liver disease. Cirrhosis may impact the treatment of diabetes, with sulfonylurea associated with greater likelihood of hypoglycemia, metformin with increased risk of lactic acidosis, difficulties in medication compliance among persons with encephalopathy, diarrhea leading to electrolyte abnormality associated with acar-bose, and issues of fluid retention with thiazolidinedione treatment. Contaminated glucose monitors have been associated with hepatitis B epidemics (27).

Liver disease may be caused by medications for diabetes, notably that which was seen with troglitazone (and some hepatologists question the long-term safety of statins). Acute liver failure rates are increased in persons with diabetes, whose cumulative risk of acute liver failure is 2.31 per 10,000 person-years vs. 1.44 in nondiabetic persons (28). Another study reported acute liver failure rates of 0.15, 0.08, 0.12, and 0.10 per 1,000 person-years with insulin, sulfonylureas, metformin, and troglitazone, respectively (29). There is no evidence, however, that glycemic medications other than troglitazone cause chronic liver disease or cirrhosis, and exposure to other diabetes treatment without evidence of acute injury has not been found to lead to subsequent increased risk of liver disease. Diabetes may occur in the setting of liver disease treatment with steroids, interferon, lactulose, or calcineurin inhibitors such as tacrolimus or cyclosporine. It is difficult to determine the causal effect of specific agents in persons who may have coincident liver disease of other etiologies, including viral hepatitis, other drugs, such as statins, cholestatic disorders, and underlying
nonalcoholic steatohepatitis (NASH)-related end-stage liver disease. An important association is that between diabetes and HCV. There is two-to fourfold increase in diabetes in persons with HCV, particularly among persons with cirrhosis, with some evidence that HCV can cause diabetes and that diabetes can increase the risk of contracting HCV. Genotype 2a HCV is disproportionately represented among persons with type 2 diabetes (30), and genotype 3 is associated with steatohepatitis and insulin resistance, while hepatitis B is not as strongly-associated with diabetes (31). Among 9,841 adults in the National Health and Nutrition Examination Survey, 8.4% had type 2 diabetes and 2.1% HCV, with greater than a coincident finding of the two appearing together (32). HCV may cause β-cell dysfunction, with evidence of HCV-positive islet cell staining (33) in infected persons, and insulin sensitivity may worsen with progression of hepatic fibrosis. Curing hepatitis C reduces the likelihood of developing diabetes and may improve glycemia in persons who have developed diabetes. Furthermore, markers of insulin resistance may be associated with HCV progression, with evidence that fatty infiltration and fibrosis correlate with leptin levels (34). Posttransplant diabetes is becoming more common, with — 16% of liver transplantation patients having preexisting diabetes, and with new-onset diabetes after transplantation seen in 7-28% of studies, averaging — 15%. The incidence of post-transplantation diabetes is tripled among persons with HCV, with tacrolimus, cyclosporin, and steroids additional risk factors increasing the likelihood of diabetes. Implications for liver transplantation are of the need to minimize steroid dosages, with changing tacrolimus to cyclosporine, treating HCV, and striving for close glycemic control further considerations (35), although Lewis emphasized the need for prospective trials of these approaches. Certainly, persons with post-transplant diabetes have worse outcome (36). Hepatocellular carcinoma (HCC) is the leading cancer worldwide, with HCC risk tripling among persons with diabetes (37).

There is a complex relationship between the liver and metabolic syndrome, with NASH the most common liver disease in Lewis's population, and increasing appreciation that nonalcoholic fatty liver disease (NAFLD) is the hepatic manifestation of the metabolic syndrome (38). Eighty-five to 90% of persons with NAFLD have metabolic syndrome, while the risk of NAFLD triples among those who have metabolic syndrome. (39). Diabetes or IGT develop in 23% of persons with NAFLD after 3 years of follow-up (40).

Although there is thought to be a relationship between hemochromatosis and diabetes (41), Lewis noted that it is uncertain how often this is clinically relevant, with diabetes rarely resolving after treat-
27. Centers for Disease Control and Prevent


VASCULAR DAMAGE INDUCED BY TYPE 2 DIABETES MELLITUS AS A RISK FACTOR FOR BENIGN PROSTATIC HYPERPLASIA

A. P. Berger¹, M. Deibl², E. J. Halpern³, M. Lechleitner⁴, J. Bektic¹, W. Horninger¹, G. Fritsche³, H. Steiner¹, A. Pelzer¹, G. Bartsch¹ and F. Frauscher⁵

(1) Department of Urology, University of Innsbruck, Anichstrasse 35, 6020 Innsbruck, Austria
(2) Department of Statistics, University of Innsbruck, Innsbruck, Austria
(3) Department of Radiology, Thomas Jefferson University, Philadelphia, PA, USA
(4) Department of Internal Medicine, University of Innsbruck, Innsbruck, Austria
(5) Department of Radiology, University of Innsbruck, Innsbruck, Austria

Abstract

Aims/hypothesis The aim of this study was to evaluate the relationship between benign prostatic hyperplasia (BPH) and arteriosclerosis shown in a model of type 2 diabetes in a trans-sectional population study using contrast-enhanced colour Doppler ultrasound for exact assessment of prostatic blood flow.

Methods Contrast-enhanced transrectal colour Doppler ultrasound was performed using a microbubble-based ultrasound enhancer SonoVue for evaluating prostate vascularity (transitional zone [TZ] and peripheral zone [PZ]) in diabetic BPH patients, non-diabetic BPH patients and healthy subjects. Computer-assisted quantification of colour pixel intensity (CPI) was used to objectively evaluate the prostate vascularity. Resistive index measurements were obtained in the TZ and the PZ. Findings were compared between these three groups.

Results TZ-CPI was significantly lower in diabetic patients than in non-diabetic BPH men (p=0.001), whereas the CPI of the PZ showed no difference between these two groups (p=0.978). TZ-CPI of patients with diabetic and non-diabetic BPH were significantly lower than in controls (p<0.001), but no difference was found between diabetic and healthy patients in the PZ (p=0.022) and borderline significance was seen when comparing patients of the BPH group with the control patients (p=0.09). Resistive index values of the TZ in diabetic patients showed significantly higher values (p<0.001) than the BPH and control groups.

Conclusions/interpretation The significantly lower CPI and higher resistive index values of the TZ in diabetic patients compared with patients with non-diabetic BPH and healthy subjects indicate considerable vascular damage in the TZ of these patients. Diabetic vascular damage may cause hypoxia and may contribute to the pathogenesis of BPH.

Keywords Arteriosclerosis - Benign prostatic hyperplasia - Diabetes mellitus - Hypoxia - Transrectal colour Doppler ultrasound

Abbreviations BPH benign prostatic hyperplasia - CDUS colour Doppler ultrasound - CPI colour pixel intensity - ED erectile dysfunction - IIEF International Index of Erectile Dysfunction - PZ peripheral zone of prostate - RI resistive index - TZ transitional zone of prostate

Introduction

Dysregulation in the prostatic stromal cells is of decisive importance in the pathogenesis of
benign prostatic hyperplasia (BPH), the most common non-malignant proliferative disorder in the ageing male. In spite of evidence that androgens and oestrogens are involved in the growth of stromal and epithelial cells in the prostate and induction of fibromuscular overgrowth, the true aetiology of BPH remains unclear and seems to be multifactorial.

It has been postulated that a reawakening of the inductive properties of the prostatic stroma induces hyperplasia in the stromal and glandular compartment [1], and that abnormal blood flow patterns might contribute to hypoxia-stimulated prostate growth [2]. In a recently published study using a cell culture model of human prostatic stromal cells, it was shown that prostatic stromal cells respond to hypoxia by upregulation of secretion of several growth factors in vitro suggesting that hypoxia may trigger prostatic growth [3]. Hypoxia in the prostate may occur in patients who present with generalised or localised vascular damage, and indeed several studies have suggested an association between the presence of vascular disorders such as coronary heart disease or diabetes mellitus and prostatic disease [4-7]. The earliest report that discusses the association of diabetes mellitus with vascular degenerative complications goes back to the early 1950s [8]. A recent study clearly demonstrated the association between hypoxia and increased angiogenesis and growth in the rat bladder [9]. However, to date, no clear causative correlation has been found between vascular damage and BPH.

Colour Doppler ultrasound (CDUS) is a non-invasive method for the determination of blood flow, but subjective quantification of the CDUS data has shown limited efficacy [10]. In contrast, computer-assisted quantification of CDUS by calculation of the colour pixel intensity (CPI) has been shown to be an accurate technique that allows for exact assessment of organ and tissue perfusion [11, 12].

The resistive index (RI) obtained by pulsed-wave Doppler ultrasound is related to both blood flow and pressure and represents one of the most relevant indicators of vascular damage in the analysis of small vessels in the prostate [73].

This trans-sectional population study was performed to test the hypothesis of a causal relationship between BPH and type 2 diabetes mellitus by assessment of prostatic blood flow using contrast-enhanced CDUS.

Subjects and methods

From September 2003 to September 2004 a total of 64 men were enrolled to participate in the present study. The cohort was divided into three subgroups. The first subgroup included patients with manifest type 2 diabetes mellitus (defined as repeated fasting glucose levels 7.8 mmol/l) for a minimum duration of 5 years. The second group comprised men with BPH (International Prostate Symptom Score [IPSS] of 7) and a prostate volume of 30 cm$^3$ or higher. The control group consisted of healthy men with no signs of BPH (IPSS <7 and a prostate volume lower than 30 cm$^3$).

Patients with prostate cancer or who had undergone prostate surgery prior to the study were excluded, as well as men taking medication of 5-alpha reductase inhibitors or alpha blockers. Subjects with clinically evident prostatitis, acute urinary tract infection, or contraindication to the ultrasound contrast agent SonoVue (Bracco, Milano, Italy) including New York Heart Association stage IV heart failure were also excluded.

Twenty-eight diabetic patients were referred from the Department of Internal Medicine for routine urological check-up; 24 non-diabetic patients presented to our clinic with lower urinary tract symptoms due to BPH; and 12 healthy patients served as a control group. All patients provided informed consent, and the investigations were approved by the local ethics committee.
Information obtained by standardised interview at initial examination included history of type 2 diabetes mellitus, cigarette smoking and use of medications. Obesity was estimated using BMI (kg/m²). A patient with a BMI above 25 was considered obese. Blood pressure and pulse count were measured using a standard sphygmomanometer after the patient had been sitting for at least 5 min. Fasting lipid levels (total cholesterol, HDL and LDL cholesterol, triglycerides) as well as fasting glucose levels and the HbAiC value were determined in the hospital diagnostic laboratory.

Uroflowmetry and measurement of residual urine was performed in every patient, as well as determination of serum testosterone and prostate-specific antigen/free prostate-specific antigen. Patients with elevated prostate-specific antigen levels underwent ultrasound-guided prostate biopsy in order to rule out prostate cancer. Patients with biopsy-proven prostate cancer were excluded from the study.

For assessment of erectile function the International Index of Erectile Dysfunction (IIEF) [14] was used. Lower urinary tract symptoms were evaluated using the International Prostatic Symptom Score (IPSS).

All ultrasound investigations were carried out with one single experienced radiologist (F. Frauscher) performing contrast-enhanced CDUS with the high-frequency end-fire probe EC10C5 fitted to a Sequoia unit (Acuson, Mountain View, CA, USA). Patients were in the left lateral decubitus position. During imaging, care was taken to minimise probe pressure on the rectal wall. Patients underwent examination with an empty or nearly empty bladder so that compression of the bladder did not affect intraprostatic and bladder-neck vessels. Contrast-enhanced CDUS was used to visualise arteries of the transition zone (TZ) and peripheral zone (PZ) as well as the bladder neck, and to measure the RI. CDUS was performed in a transverse plane at the base, mid and apex of the prostate. Pulsed-wave spectral Doppler analysis for assessment of the RI was performed from arteries of the PZ and the TZ in each plane. The mean of each plane was calculated.

Doppler signal intensity in both zones (TZ and PZ) as well as for the bladder neck was evaluated using computer-assisted quantification of CPI. The region of interest was placed in areas with the highest detectable blood flow. To perform this, the red-green-blue output of the ultrasound unit was digitised using an IBM-compatible computer. The digitised images were post-processed using the NIH image software package (version 1.62, National Institutes of Health). For each subject, an area from the outer and inner gland underwent computer-assisted quantification of CPI. The digitised colour image was divided into its three colour components. Each colour channel consists of 256 brightness values according to the brightness of the colour. To minimise background noise, the threshold value for the blue and red colour channels was set to the middle of the brightness value dynamics range, namely at 128 for both colours. Within the defined region of interest, only colour pixels showing a brightness value greater than 64 were counted (Fig-1).
Fig. 1 Measurement of CPI: contrast-enhanced colour Doppler ultrasound images showing the defined rectangles around the regions of interest (20 mm²) in a non-diabetic patient with normal prostate (21 cm³, upper panel), a non-diabetic patient with BPH (74 cm³, middle panel) and a diabetic patient with BPH (81 cm³, lower panel).

Additionally, the RI and the acceleration time in penile vessels (corpora cavernosa) were evaluated. The acceleration time was measured by spectral wave Doppler ultrasound from the beginning of the systolic upstroke to the highest systolic peak in the waveform. Any break in the systolic upstroke before it reached its peak was ignored.

SPSS for Windows 12.0 software (Chicago, IL, USA) was used for all analyses. Data were expressed as medians and 25th and 75th percentiles. Differences between the three groups were analysed by Kruskal-Wallis tests. If these tests indicated statistical significance, Mann-Whitney tests were performed. Statistical significance was defined as p being less than 0.05. After Bonferroni's correction for three comparisons, p values of less than 0.017 were considered to indicate statistical significance.

Results

Sixty-four patients were evaluated in the present study among them 28 patients diagnosed with type 2 diabetes mellitus, 24 patients with non-diabetic BPH and 12 healthy patients who served as controls. Mean time interval after diagnosis of type 2 diabetes in the diabetic group was 8.4 years (range 5-14 years). Mean HbAic value in the diabetic group was 8.15% (range 5.8-12.7%). The clinical characteristics of the patients are presented in Table L.
Table 1 Clinical characteristics of the patients enrolled in the study
<table>
<thead>
<tr>
<th></th>
<th>Diabetic patients (n=28)</th>
<th>BPH patients (n=24)</th>
<th>Control group (n=12)</th>
<th>Kruskal–Wallis test value</th>
<th>Mann–Whitney U-test p</th>
<th>BPH vs diabetic</th>
<th>BPH vs control</th>
<th>Diabetic vs control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Testosterone (ng/ml)</td>
<td>3.35 (2.83/4.28)</td>
<td>4.55 (3.25/5.48)</td>
<td>4.5 (3.3/5.88)</td>
<td>0.05</td>
<td>0.03</td>
<td>0.804</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>Prostate-specific antigen (ng/ml)</td>
<td>1.05 (0.55/1.36)</td>
<td>1.78 (0.88/2.73)</td>
<td>0.39 (0.25/0.78)</td>
<td>&lt;0.001</td>
<td>0.046</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Prostate volume (cm^3)</td>
<td>44 (40/53.75)</td>
<td>43.5 (38.25/50.75)</td>
<td>19 (17/24)</td>
<td>&lt;0.001</td>
<td>0.607</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Maximum flow (ml/s)</td>
<td>16.5 (9.68/18)</td>
<td>16 (12.08/20.5)</td>
<td>29.6 (26.8/40.1)</td>
<td>&lt;0.001</td>
<td>0.526</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Average flow (ml/s)</td>
<td>7.95 (5.18/11)</td>
<td>8.45 (5.7/11.75)</td>
<td>17.7 (14.3/22.15)</td>
<td>&lt;0.001</td>
<td>0.7</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Residual urine (ml)</td>
<td>40 (21.25/87.5)</td>
<td>30 (0/67.5)</td>
<td>0 (0/0)</td>
<td>&lt;0.001</td>
<td>0.323</td>
<td>0.001</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Data are expressed as medians and 25th and 75th percentiles. Differences between the three groups were analysed by the Kruskal–Wallis test. If the Kruskal–Wallis test indicated statistical significance, Mann–Whitney U-tests were performed. Statistical significance was defined as p<0.05. After Bonferroni’s correction for three comparisons, p values of less than 0.017 were considered to indicate statistical significance.

CPI of the TZ was significantly lower in diabetic patients than in patients with non-diabetic BPH (median 183.5 [range 112–244] vs 217.0 [range 155–287]; p=0.001), whereas CPI of the PZ showed no difference between these two groups (mean 239.5 [range 165–341] vs 236.0 [range 176–312]; p=0.978). TZ-CPI in patients with both diabetic and non-diabetic BPH were significantly lower compared with the controls (p<0.001), but no difference was found between diabetic and healthy patients in the PZ (p=0.022), and a borderline significance was seen when comparing patients of the BPH group with the control patients (p=0.019).

RI values of the TZ in diabetic patients (mean 0.88 [range 0.74–0.92]) showed significantly higher values (p<0.001) compared with non-diabetic BPH patients (mean 0.80 [range 0.70–0.89]) and the control group (mean 0.63 [range 0.56–0.70]). RI measured in the PZ was not different between diabetic and non-diabetic BPH patients (mean 0.85 [range 0.77–0.92] vs 0.81 [range 0.68–0.91]; p=0.019), but was significantly different between the control group and the diabetic and non-diabetic BPH groups (p<0.001).

CPI and RI values measured at the bladder neck did not show any difference between diabetic and non-diabetic BPH patients (p=0.057 and p=0.305, respectively). There was a significant difference in CPI and RI between diabetic patients and the control group (p=0.002 and p=0.006, respectively), but no difference was observed in the CPI and RI values between the BPH patients and the control group (p=0.018 and p=0.019, respectively).
<table>
<thead>
<tr>
<th></th>
<th>Diabetic patients (n=28)</th>
<th>BPH patients (n=24)</th>
<th>Control group (n=12)</th>
<th>Kruskal–Wallis test value</th>
<th>Mann–Whitney U-test p</th>
<th>BPH vs diabetics</th>
<th>BPH vs control</th>
<th>Diabetic vs control</th>
</tr>
</thead>
<tbody>
<tr>
<td>RI (TZ)</td>
<td>0.88 (0.84/0.89)</td>
<td>0.8 (0.77/0.84)</td>
<td>0.63 (0.6/0.68)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RI (PZ)</td>
<td>0.85 (0.83/0.89)</td>
<td>0.81 (0.77/0.87)</td>
<td>0.72 (0.7/0.8)</td>
<td>&lt;0.001</td>
<td>0.019</td>
<td>0.015</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CPI (bladder-neck)</td>
<td>39.5 (28.5/51)</td>
<td>46.5 (39/57.25)</td>
<td>61.5 (49/71.5)</td>
<td>0.003</td>
<td>0.057</td>
<td>0.018</td>
<td>0.002</td>
<td>0.006</td>
</tr>
<tr>
<td>RI (bladder-neck)</td>
<td>0.96 (0.9/1)</td>
<td>0.92 (0.89/0.99)</td>
<td>0.84 (0.79/0.96)</td>
<td>0.01</td>
<td>0.305</td>
<td>0.019</td>
<td>0.018</td>
<td>0.286</td>
</tr>
<tr>
<td>RI (corpora cavernosa)</td>
<td>1 (1/1)</td>
<td>1 (0.95/1)</td>
<td>1 (1/1.08)</td>
<td>0.002</td>
<td>0.11</td>
<td>0.018</td>
<td>0.286</td>
<td></td>
</tr>
<tr>
<td>Acceleration time (corpora cavernosa/s)</td>
<td>0.11 (0.09/0.12)</td>
<td>0.05 (0.04/0.07)</td>
<td>0.02 (0.01/0.02)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IPSS</td>
<td>14 (11/21.75)</td>
<td>8 (6/15)</td>
<td>0 (0/2.75)</td>
<td>&lt;0.001</td>
<td>0.004</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quality of life score</td>
<td>3 (2/4)</td>
<td>2 (1/3)</td>
<td>0 (0/0)</td>
<td>&lt;0.001</td>
<td>0.011</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IIEF score</td>
<td>26 (18/32)</td>
<td>42 (34.25/52.75)</td>
<td>66 (60/68.75)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RR systolic BP (mm Hg)</td>
<td>140 (122.5/160)</td>
<td>140 (130/150)</td>
<td>130 (110/140)</td>
<td>0.149</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RR diastolic BP (mm Hg)</td>
<td>80 (71.25/90)</td>
<td>80 (71.25/80)</td>
<td>75 (70/80)</td>
<td>0.203</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulse rate (bpm)</td>
<td>74.5 (66.5/86)</td>
<td>72 (66.5/80)</td>
<td>70 (62.5/76)</td>
<td>0.222</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>4.89 (4.3/5.44)</td>
<td>4.80 (4.1/5.26)</td>
<td>4.77 (3.9/5.29)</td>
<td>0.798</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>2.40 (1.69/3.11)</td>
<td>1.52 (0.92/1.98)</td>
<td>1.36 (0.93/2.52)</td>
<td>0.004</td>
<td>0.001</td>
<td>0.96</td>
<td>0.049</td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>26.5 (24.25/29)</td>
<td>24.5 (22.25/27.5)</td>
<td>24 (22/25)</td>
<td>&lt;0.001</td>
<td>0.031</td>
<td>0.224</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Glucose (mmol/l)</td>
<td>9.73±2.94</td>
<td>5.59±0.56</td>
<td>5.03±0.48</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.15 (7.15/10.25)</td>
<td>5.5 (5.4/5.7)</td>
<td>5.35 (5.23/5.6)</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.379</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
RI measured in arteries of the corpus cavernosum did not show any difference between the three groups, but mean increase of arterial inflow was significantly slower in diabetic patients than in the BPH (p<0.001) and control (p<0.001) groups.

There was no significant difference between the three groups in terms of blood pressure, pulse count, fasting cholesterol levels (total, HDL and LDL), serum testosterone and cigarette use. Mean triglyceride levels were higher in diabetic patients compared with the BPH group (p=0.001) but not compared with the control group (p=0.049). Median BMI was lower in the control group than in diabetic patients (p=0.002), whereas there was no difference in BMI between the BPH group and the diabetic (p=0.031) and control groups (p=0.224).

Mean IPSS showed a significant difference between the diabetic and non-diabetic BPH men (p=0.004), and quality of life scores and IIEF scores were significantly worse in diabetic patients compared with non-diabetic BPH patients.

Mean prostate volume, maximum flow rate and residual urine volume did not show significant difference between diabetic and non-diabetic BPH patients (p=0.607, /7=0.526 and p=0.323, respectively), but all these parameters were better in the control group compared with in the diabetic group and patients with non-diabetic BPH.

Discussion

Previous studies have shown an association of arteriosclerotic disease manifestations such as type 2 diabetes mellitus, hypertension or dyslipidaemia and the development of BPH, indicating that BPH is a component of the metabolic syndrome and that the causal factor for BPH might be a systemic rather than a local factor. Recent studies demonstrated a significantly faster annual growth rate in diabetic patients compared with in other men presenting with lower urinary tract symptoms [75], and that diabetes is associated with greater BPH symptom severity even after age adjustment [6]. Long-lasting diabetes mellitus has repeatedly been shown to be an indicator disease for arteriosclerosis and to represent an independent predictor of significant arteriosclerosis [7j5, 17], as diabetes is significantly and positively associated with intima media thickness [18-20]. Up to now, however, the causal association of vascular damage and BPH remains unclear. There is an increasing recognition of the role of oxidative stress as an inducer of cell growth. Relevant to this are observations suggesting that there is a common pathogenetic mechanism for vascular smooth muscle cell growth and remodelling and prostate smooth muscle proliferation.

While in healthy prostatic vessels the RI is relatively low, in patients where BPH is advanced, arteries between the PZ and the TZ may be compressed, which has been found to lead to a marked increase in the RI of the capsular arteries [27]. The RI measurements in the symptomatic BPH patients as a group confirm the above-mentioned findings by showing higher RI values in the PZ than in the TZ (0.81 vs 0.80). In contrast, however, in the diabetic patients, higher RI values were measured in the TZ (0.88) than in the PZ (0.85), indicating significant vascular damage with increased vascular resistance particularly in the TZ of these patients. An important finding is the statistically significant increase of RI in the TZ of diabetic patients in contrast to non-diabetic BPH patients (p=0.019). CPI analysis as an objective analysis method for tissue perfusion confirmed these findings, showing almost identical results for the PZ (median 239.5 in the diabetic group vs 236.0 in the non-diabetic BPH group; />=0.978) but significantly different values for the TZ (median 183.5 in the diabetic group vs 217.0 in the group with BPH alone; p=0.001). While other studies investigating the vascular anatomy of the normal prostate RI measured in arteries of the corpus cavernosum did not show any difference between the three
groups, but mean increase of arterial inflow was significantly slower in diabetic patients than in the BPH (p<0.001) and control (p<0.001) groups.

There was no significant difference between the three groups in terms of blood pressure, pulse count, fasting cholesterol levels (total, HDL and LDL), serum testosterone and cigarette use. Mean triglyceride levels were higher in diabetic patients compared with the BPH group (p=0.001) but not compared with the control group (p=0.049). Median BMI was lower in the control group than in diabetic patients (p=0.002), whereas there was no difference in BMI between the BPH group and the diabetic (p=0.031) and control groups (p=0.224).

Mean IPSS showed a significant difference between the diabetic and non-diabetic BPH men (p=0.004), and quality of life scores and IIEF scores were significantly worse in diabetic patients compared with non-diabetic BPH patients.

Mean prostate volume, maximum flow rate and residual urine volume did not show significant difference between diabetic and non-diabetic BPH patients (p=0.607, /7=0.526 and p=0.323, respectively), but all these parameters were better in the control group compared with in the diabetic group and patients with non-diabetic BPH.

Discussion

Previous studies have shown an association of arteriosclerotic disease manifestations such as type 2 diabetes mellitus, hypertension or dyslipidaemia and the development of BPH, indicating that BPH is a component of the metabolic syndrome and that the causal factor for BPH might be a systemic rather than a local factor. Recent studies demonstrated a significantly faster annual growth rate in diabetic patients compared with in other men presenting with lower urinary tract symptoms [75], and that diabetes is associated with greater BPH symptom severity even after age adjustment [6]. Long-lasting diabetes mellitus has repeatedly been shown to be an indicator disease for arteriosclerosis and to represent an independent predictor of significant arteriosclerosis [7,5, 17], as diabetes is significantly and positively associated with intima media thickness [18-20]. Up to now, however, the causal association of vascular damage and BPH remains unclear. There is an increasing recognition of the role of oxidative stress as an inductor of cell growth. Relevant to this are observations suggesting that there is a common pathogenetic mechanism for vascular smooth muscle cell growth and remodelling and prostate smooth muscle proliferation.

While in healthy prostatic vessels the RI is relatively low, in patients where BPH is advanced, arteries between the PZ and the TZ may be compressed, which has been found to lead to a marked increase in the RI of the capsular arteries [27]. The RI measurements in the symptomatic BPH patients as a group confirm the above-mentioned findings by showing higher RI values in the PZ than in the TZ (0.81 vs 0.80). In contrast, however, in the diabetic patients, higher RI values were measured in the TZ (0.88) than in the PZ (0.85), indicating significant vascular damage with increased vascular resistance particularly in the TZ of these patients. An important finding is the statistically significant increase of RI in the TZ of diabetic patients in contrast to non-diabetic BPH patients (pO.OO1), whereas the RI of the PZ did not reveal any significant difference between these groups (p=0.019). CPI analysis as an objective analysis method for tissue perfusion confirmed these findings, showing almost identical results for the PZ (median 239.5 in the diabetic group vs 236.0 in the non-diabetic BPH group; />=0.978) but significantly different values for the TZ (median 183.5 in the diabetic group vs 217.0 in the group with BPH alone; p=0.001). While other studies investigating the vascular anatomy of the normal prostate found no significant difference between the RI values of the PZ and the TZ [22], in the present
study there was a clear difference between these two areas in the control group (0.72 in the PZ vs 0.63 in the TZ). Although the values are both significantly below the corresponding values measured in diabetic and non-diabetic BPH patients, in healthy subjects the vascular resistance seems to be higher in the outer gland (PZ) than in the inner gland (TZ).

TZ and PZ were defined according to the definition of McNeal [1_, 23]. Differentiation between the PZ and the TZ was adequately performed in all patients using the high-end ultrasound unit. No RI and CPI measurements were performed within a distance of 3 mm of the urethra to avoid any influence of urethral blood flow.

The mechanism behind the markedly increased RI and decreased CPI values in the TZ has not been clarified to date, but it has been suggested that mechanical obstruction by TZ might compress vessels of the TZ [24]. As the TZ is contained within a dense capsule, it seems reasonable that a high pressure is built up within the transition zone, which, in turn, will cause an increased compression of the vessels to the TZ in BPH and even more so in diabetic patients. However, the significantly higher RI values and the significantly lower CPI values of the TZ in diabetic patients compared with non-diabetic BPH patients indicate that in patients with vascular damage there might be additional reasons for these findings. Decreased pOj levels have been demonstrated in patients with arterial ischaemia using laser Doppler flowmetry [25], a method that has been shown to be comparable to CDUS in assessing blood flow [26]. The association between diabetes and the higher RI of the TZ clearly demonstrated a higher vascular resistance which seems to be related to diabetic vascular damage. Hypoxia induces not only expression of the transcription factor hypoxia inducible factor 1 (HIF1) but also expression of angiogenic growth factors such as vascular endothelial growth factor (VEGF), fibroblast growth factors 2 and 7 (FGF-2 and FGF-7) and TGF- as well as cytokines like IL8 [5, 27, 28]. Long-term exposure of the prostate stroma to increased growth factor levels as a result of chronic hypoxia may cause a stimulation over years and may contribute to the pathogenesis of BPH.

Although it is known that long-standing diabetes can cause lower urinary tract symptoms because of autonomic neuropathy, this has been shown to be due to functional parasympathetic, and to a lesser extent sympathetic, denervation of the detrusor muscle, so that diabetes primarily affects detrusor function [29, 30].

Interestingly, an inverse association between diabetes and prostatic cancer has been repeatedly described [4, 31]: this is compatible with a potential cancer-promoting role for endogenous testosterone, the level of which is lower in diabetic patients, which was also found in our patient cohort. However, the difference in testosterone levels between the diabetic and non-diabetic groups was not statistically significant (p=0.03). A risk-reducing effect of antidiabetic diet or hypoglycaemic agents may also contribute to the lower incidence of prostate cancer in diabetic men. On the contrary, others found hyperinsulinaemia to be a promotor of prostate cancer [32], and a significant association of coronary heart disease with the occurrence of prostate cancer has been described [5].

Erectile dysfunction (ED) is frequently of vascular origin, and an association between ED and ischaemia has been suggested as a consequence of endothelial disease of penile arteries. Thus, ED may also be considered to be the clinical manifestation of a disease affecting penile circulation as a part of a more general vascular disorder [33]. It is known that the increase of arterial inflow within the corpora cavernosa needed to obtain an erection is significant and minor abnormalities of this haemodynamic change are sufficient to cause ED [33]. Present data appear to support these findings. Although the RI values of arteries of corpora cavernosa did not


Литература: