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EDITORIAL INFORMATION

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EDITORIAL

Metformin: evidence-based versus rational pharmacotherapy

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INTRODUCTION

In this issue, Wulffelé *et al.* report on the efficacy of metformin in insulin-treated type 2 diabetes by showing a 36% increase in the daily insulin requirement after stopping metformin.[1] In patients who discontinued metformin treatment, the HbA1$_c$ percentage did not change as a result of the adjustments in insulin dose. In contrast, HbA1$_c$ decreased by almost 1% in the control group, probably as a result of the slight increase in the insulin dose required to reach the predefined targets of metabolic control. The study by Wulffelé *et al.* confirms the efficacy of metformin in the treatment of type 2 diabetes mellitus, and in particular confirms the fact that the drug increases insulin sensitivity. Previous studies have already shown that addition of metformin to insulin therapy improves metabolic control and/or reduces daily insulin requirements.[2] Furthermore, the efficacy of metformin has been documented in a variety of combination therapies, including the combination of metformin with α-glycosidase inhibitors,[3] sulphonylurea derivatives[4] and thiazolidinedione derivatives.[5] Finally, the drug has proven its efficacy in monotherapy strategies,[6] and can even reduce the risk of developing diabetes as shown in the Diabetes Prevention Programme.[7] As such, metformin may currently be the most valuable oral blood glucose lowering drug for the treatment of type 2 diabetes mellitus.

RATIONAL VERSUS EVIDENCE-BASED PHARMACOTHERAPY

It is interesting to note that metformin is a drug whose efficacy has been widely documented, even at the level of evidence-based medicine,[6] whereas its mechanism of action at cellular level is not known. Nowadays, new drugs are developed with a specific molecular or cellular target, followed by documentation of their therapeutic efficacy. In the final post-marketing phase, large studies are initiated to find positive observations at the level of evidence-based medicine. In the case of metformin, the sequence is the other way around. The drug is widely used, evidence of treatment efficacy is even documented at the level of hard endpoints,[6] but the molecular target of the drug is still not known. Should this have consequences for the use of this drug? In other words, do clinicians need to know the mechanism of action of drugs or is it enough to know that the drug is efficacious? This question raises the apparent differences between the concepts of *evidence-based pharmacotherapy* versus *rational pharmacotherapy*.

The concept of rational pharmacotherapy is based on a fundamental understanding of the interaction between the drug and the patient. On the one hand, this understanding concerns the mechanism of action of the drug, preferably ranging from the molecular and cellular level to the level of the cell, the tissue and the integrative organism. On the other hand, the concept of rational pharmacotherapy is based on a comprehensive knowledge of the pathophysiology of the patient. Ideally, the rational base for the choice of a certain drug is a perfect match between the pharmacological mechanisms of the drug and the pathophysiology of the patient (pharmacodynamics). Subsequently, the pharmacokinetics will reveal the optimal pattern of dosing of the drug. Within this concept of rational pharmacotherapy, the individual approach with the possibility of changing the drug or its dose based on pharmacodynamic, pharmacokinetic or pathophysiological grounds is central.

In the concept of evidence-based pharmacotherapy, positive results of double-blind randomised therapeutic trials are

central. This concept focuses on the fact that the drug saves lives or works preventively and not on how the drug acts. Moreover, the concept is based on observations in populations rather than in individuals. The individual response to the drug is thought to be more or less the same as the mean response in a population. Most importantly, the response concerns hard endpoints, whereas surrogate endpoints are frequently used in the concept of rational pharmacotherapy. Based on these two concepts, the use of drugs can be classified as being compatible with one of the concepts, both concepts, or neither. *Table 1* shows that four different classes can be distinguished in this approach. The HMG-coA-reductase inhibitor *simvastatin* is a good example of a drug that scores positively in both the rational and the evidence-based pharmacotherapy concept. The mechanism of action of the drug is well described and fits perfectly with the pathophysiology of lipid disorders in particular.

Table 1
Rational versus evidence-based pharmacotherapy

Rational pharmacotherapy	Yes	Yes	No	No
Evidence-based pharmacotherapy	Yes	No	Yes	No
Example:				
- Indication	High LDL	Heart failure	Diabetes mellitus type 2	Viral respiratory tract infection
- Pharmacotherapy	Simvastatin	Ibopamine	Metformin	Feneticillin

Furthermore, large population studies have shown that the drug reduces hard endpoints. This ideal combination offers clinicians the opportunity to develop protocols and guidelines on the one hand, and tools to individualise treatment based on pharmacodynamic, pharmacokinetic or pathophysiological arguments on the other. The drug *ibopamine* is a good example of the second group. The rational concept of a so-called inodilator drug in the treatment of heart failure is well described. However, large clinical trials have shown increased mortality after the use of ibopamine, and as such the two concepts do not match. For many drugs, there are no data at the level of evidence-based medicine and therefore that particular cell of the table contains no 'Yes' or 'No' but simply a question mark. As discussed above, the biguanide *metformin* is an example of the third group. The lack of an appropriate rational concept may limit the clinician's ability to individualise treatment. Finally, the use of *feneticillin* in the treatment of viral infections of the upper respiratory tract is an example of the fourth group.

The key message of the table is that the concepts do not exclude each other, but should be considered to be complimentary. In the ideal situation, drugs should be prescribed when both concepts are applicable. In the case of metformin, it may be difficult to individualise the data from population studies, simply because the molecular and cellular mechanisms are not known. This means that the clinician may encounter difficulties in using pharmacodynamic, pharmacokinetic or pathophysiological arguments to predict whether an individual patient will respond well, poorly, or even negatively.

POTENTIAL MECHANISMS OF ACTION OF METFORMIN

The blood glucose lowering effects of metformin have been shown to be predominantly based on the inhibition of hepatic glucose production. Furthermore, a slight increase in peripheral glucose uptake contributes to its effect.[4,5] Although metformin's mechanism of action is roughly known at the tissue and organ level, its molecular and cellular targets have not been elucidated. However, two new potential mechanisms have been identified in the past few months. Two recent publications suggest that metformin inhibits the mitochondrial electron transporting enzyme complex I of the respiratory chain.[8,9] According to thermodynamic principles, metformin is thought to accumulate in the mitochondrial maxtrix. This implies that with the daily dosing of metformin, concentrations can be reached at which complex I inhibition will occur. Subsequently, inhibition of complex I may be responsible for the inhibition of gluconeogenesis, modest inhibition of fatty acid oxidation, increased production of lactate and may even explain the increase of glucose uptake in muscle and fat. These findings suggest that the spectrum of metabolic effects observed during metformin treatment may well be explained by a slight inhibition of the respiratory chain complex I.

The second potential molecular target for metformin is the enzyme AMP-activated protein kinase (AMPK).[10,11] AMPK is an important intracellular regulator which acts by phosphorylating and inactivating a variety of key enzymes in lipid and glucose metabolism. Recent data strongly suggest that AMPK has a role in fatty acid oxidation and muscle glucose uptake, and in particular in the expression of hexokinase and glut-4 transporters. Recently, Zhou *et al.* convincingly showed that metformin activates AMPK in hepatocytes. A specific AMPK inhibitor was able to prevent the observed effects of metformin, whereas metformin effects were mimicked by AICAR (5-aminoimidazole-4-carboxamide ribonucleoside), a well-documented AMPK activator. Surprisingly, the thiazolidinedione-derivative rosiglitazone was capable of stimulating AMPK in the model of Zhou *et al.*, albeit by a mechanism distinct from that of

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metformin. Interestingly, one of the endogenous pathways to stimulate AMPK is the increase in the intracellular concentration ratio of AMP over ATP. Since inhibition of the respiratory chain may ultimately lead to a fall in ATP, the two potential mechanisms mentioned here may theoretically interfere with each other (see *figure 1*).
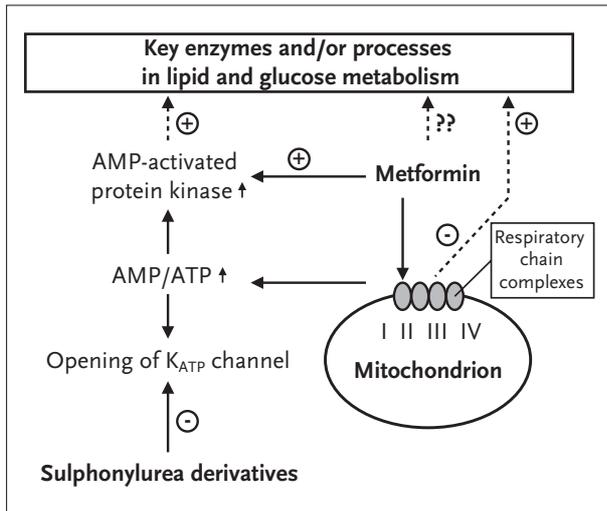
Figure 1

Potential molecular targets of the biguanide-derivative metformin

Recent publications point towards two cellular targets: 1) inhibition of complex I of the mitochondrial respiratory chain, and 2) stimulation of AMP-activated protein kinase. The two pathways may be interrelated because complex I inhibition may reduce the production of ATP, and an increase in the intracellular AMP/ATP ratio is a well-known stimulus for AMP-activated protein kinase. The increase in the AMP/ATP ratio is also a trigger to open K$_{ATP}$ channels. Opening of K$_{ATP}$ channels contributes to the restoration of the AMP/ATP ratio by reducing the calcium influx through voltage dependent calcium channels, and thereby reducing the use of ATP. Sulphonylurea derivatives like glibenclamide are potent K$_{ATP}$-channel blockers and may therefore enhance the rise in the AMP/ATP ratio induced by metformin.

A fall in the intracellular ATP level also triggers the opening of so-called ATP-sensitive potassium channels. Opening these channels will hyperpolarise the cell membrane and will subsequently close voltage-dependent calcium channels. This mechanism will reduce calcium influx and consequently the intracellular calcium concentration, thereby reducing the energy expenditure/ATP breakdown of the cell. So, opening the K$_{ATP}$ channel is an endogenous mechanism, which will contribute to a restoration of the intracellular ATP levels. Sulphonylurea derivatives such as glibenclamide are potent K$_{ATP}$-channel blockers and may therefore interfere with the endogenous protective mechanisms. From this perspective, the combination of metformin and glibenclamide may be a serious assault

on the metabolic state of cells. Although this may be a rather speculative view, it should be noted that several epidemiological data point towards a negative effect on the specific combination of metformin and glibenclamide in the treatment of type 2 diabetes.[6,12]

In summary, metformin is a drug that has been used successfully for decades in the treatment of type 2 diabetes mellitus. Recent insights into the molecular mechanism of action of metformin may enable clinicians to use the concept of rational pharmacotherapy besides that of evidence-based pharmacotherapy with respect to this particular drug. Furthermore, new insights into the mechanisms of action of metformin define new molecular targets for the development of drugs in the treatment of insulin resistance.

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Retroperitoneal fibrosis

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ABSTRACT

Retroperitoneal fibrosis (RPF) is an uncommon collagen vascular disease of unclear aetiology. It is characterised by a chronic non-specific inflammation of the retroperitoneum, which can entrap and obstruct retroperitoneal structures, notably the ureters. Because of the protean manifestations of RPF, awareness of the disease is important. It is still not uncommon to detect RPF only after severe renal failure is present. This comprehensive review deals with the various aspects of RPF and tries to provide a framework for the diagnosis, treatment and follow-up of this intriguing condition. Although it may have various causes, chronic periaortitis appears to be an increasingly encountered form of secondary RPF in patients with advanced atherosclerosis. Irrespective of its cause, most cases of non-malignant RPF – if in the active 'cellular' stage – will respond to treatment with corticosteroids, thereby obviating the need for surgical treatment. The clinical and radiographic improvement seen after starting steroid therapy is often impressive and reassuring as to the diagnosis. Treatment with corticosteroids may also make aneurysmectomy, if indicated, feasible in the patient who presents with peri-aneurysmal fibrosis and renal failure. Accumulating data suggest alternative treatment strategies for steroid-resistant cases (i.e. intensive immunosuppression) or when steroids are not feasible (i.e. other forms of immunosuppression or hormonal treatment, particularly tamoxifen). Although early diagnosis and treatment provide excellent renal and patient outcome, long-term follow-up is mandatory in all cases.

INTRODUCTION

Retroperitoneal fibrosis (RPF) is an uncommon disorder of unclear aetiology. It is characterised by a chronic non-specific inflammation of the retroperitoneum, which can entrap and obstruct retroperitoneal structures, notably the ureters.[1] Because of the protean manifestations of RPF, the condition is frequently detected during evaluation of newly diagnosed renal failure or hypertension.[2,3] Its true incidence is unknown and estimates vary from 1:200,000 to 1:500,000 per year.[4,5] Although more than 500 papers devoted to the various aspects of RPF can be found in the literature, there is still no accepted diagnostic or therapeutic strategy.

However, the routine use of sophisticated imaging techniques has now refined the diagnostic process.[4,6] In addition, an increasing number of authors propound the view that the non-surgical approach of RPF should have more support.[2,6-8] This comprehensive review deals with recent advances in our understanding of this intriguing condition and current diagnostic and therapeutic procedures are discussed in an attempt to assess the present role of non-surgical treatment, particularly corticosteroids, in the treatment of RPF.

CLINICAL MANIFESTATIONS

Retroperitoneal fibrosis occurs predominantly in men in the fifth and sixth decade of life, the male-to-female ratio approximating 3:1.[6-8] To date, however, at least 33 cases of this condition have been reported in children under 18 years of age.[9-19] The early symptoms are non-specific and the correct diagnosis is often made only when obstructive uropathy or renal failure occurs.[2,8,20] Duration of symptoms prior to diagnosis is usually four to six months and

sometimes more than one year.[2,3,6] Symptoms result from entrapment of the ureters, the great vessels and their branches, and the surrounding nerves. In the majority of patients, the presenting symptom is pain in the lower back, flank and/or abdomen. Insidious in onset, the pain is dull and non-colicky and, as the disease progresses, becomes (more) severe.[2,3,6] Other frequent symptoms are loss of weight, malaise, anorexia, and non-specific gastrointestinal symptoms. Less frequently, urinary symptoms are present: frequent micturition, oliguria or anuria.[2,3,8,20] Rare symptoms include fever, testicular pain, abdominal angina, intermittent claudication, oedema or gross haematuria.[6,8,20,21] Physical examination is usually unremarkable except for the presence of hypertension, probably of renal origin.[2,6,22] Urinary tract obstruction may lead to acute hypertension in some patients, possibly by a rise in renin release; volume-dependent hypertension can occur as a result of obstructive nephropathy.[23] Reversibility of hypertension depends on the history and success of ureterolysis. In rare cases,[9,20,24] hypertension resulted from entrapment of the renal artery. Of note, patients presenting with malignant hypertension and hypertensive encephalopathy have been described.[25] Occasionally, an abdominal or pelvic mass is present.[26,27] Rare physical findings include peripheral oedema and/or thrombosis, ascites, hydrocele, jaundice, small bowel or colonic obstruction, spinal cord compression and scoliosis.[6,8,12,20,28,29]

Laboratory investigation primarily reflects the systemic response to inflammatory disease and/or impairment of renal function. An elevated erythrocyte sedimentation rate (ESR) is almost invariably present; commonly with a normochromic, normocytic anaemia and to a lesser extent polyclonal gammopathy or mild thrombocytosis.[1,3,6] Although azotaemia was present in 50 to 75% of patients in most early reviews, this is less common today as more patients are diagnosed before renal insufficiency develops.[3] However, raised serum creatinine levels of varying degrees are still frequent findings, typically with normal findings on routine urinalysis.[6,30]

DIAGNOSIS

The provisional diagnosis is usually only made after radiographic evaluation. Several diagnostic approaches are available for the evaluation of RPF (*table 1*). Before the advent of sonography (*figure 1*), CT (*figure 2*) and MR imaging (*figure 3*), the initial radiological indication of RPF was usually provided by excretory and/or retrograde pyelography (*figure 4*).[1,3,5,6] CT is, at present, the preferred imaging method[5,6,31-35] as it may provide a virtually characteristic picture (*figure 2*). On occasions, differentiating RPF from malignant lymphoma or retroperitoneal adenopathy may be difficult.[4] Although MR imaging (*figure 3*) may have

Table 1

*Diagnostic procedures in the evaluation of retroperitoneal fibrosis**

RADIOLOGICAL PROCEDURE	TYPICAL FINDINGS	COMMENT
Excretory/retrograde pyelography	Extrinsic ureteric compression at the level of L4L5; hydroureteronephrosis; during retrograde studies, a 5F or 6F catheter can usually be passed easily through the strictured area	Medial deviation of the ureter, long considered a classic sign of RPF, has been shown to be a normal variant; no information about the actual fibrosis
Ultrasonography	Hypo/anechoic, well-demarcated and irregularly contoured retroperitoneal mass; hydronephrosis	Examination of the retroperitoneum may be precluded by abdominal bowel gas or obesity; RPF may be missed unless its presence is sought along the entire length of the prevertebral and paravertebral areas
Computed tomography	Paraspinal, well-demarcated retroperitoneal mass, isodense with the surrounding muscles; no displacement of psoas muscles or great vessels; degree of contrast enhancement correlates with activity of disease, being less in advanced fibrotic stage and greater in an active, inflammatory stage	May demonstrate possible causes of RPF (severe atherosclerosis or aortic aneurysm, adjacent inflammatory process, etc); differentiating RPF from lymphoma, sarcoma or retroperitoneal adenopathy may occasionally be difficult
Magnetic resonance imaging	Low or medium intensity retroperitoneal mass similar to adjacent psoas muscle on T_1-weighted images; vascular structure and patency well defined; high signal intensity or inhomogeneity of the plaque on T_2-weight images may suggest malignancy	Avoids the risk of contrast medium related nephrotoxicity; benign RPF may also exhibit high signal intensity on T_2-weight images; limited experience
[67]Gallium-scintigraphy	Avid uptake of [67]gallium in early, cellular stage of RPF; no uptake in late, fibrotic stage	May suggest potential beneficial effect of steroids; no information about actual fibrosis

* = other procedures, not considered in the primary work-up of RPF but possibly providing additional information, include colour Doppler ultrasound (delineation vascular involvement; differentiation vascular/non-vascular structures); cavography (smooth, tapered narrowing of inferior vena cava?), arteriography (narrowing of aorta, common iliac arteries or other major arteries?) and 123I-MIGB scintigraphy (carcinoid-related RPF?).
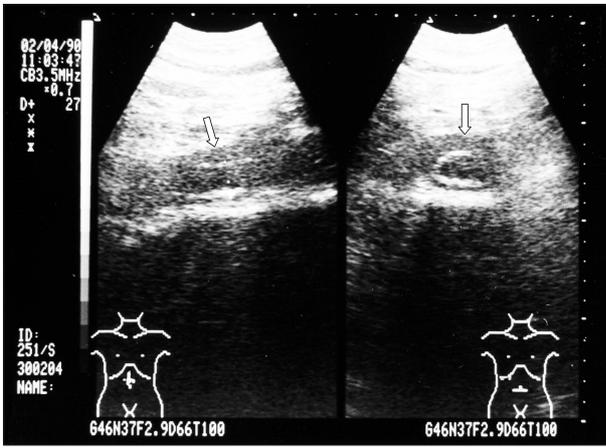
Figure 1

Longitudinal and transverse ultrasonography

Revealing a smooth-bordered, hypo/anechogenic mass surrounding the aorta.

Figure 2a

Contrast-enhanced abdominal computed tomography

Demonstrating a well-delineated soft tissue mass, enveloping but not displacing the great vessels and not displacing the psoas muscles.

Figure 2b
Repeat CT scan

Six months after initiating steroid therapy, showing almost complete disappearance of the retroperitoneal mass.

Figure 3

T₁-weighted MR imaging

Showing a well-demarcated periaortic mass with low-signal intensity similar to adjacent psoas muscles.

Figure 4

Excretory pyelography

Showing medial deviation of the right ureter at the level of L4/L5/S1 with dilated pelvis and calyces and only a faint nephrogram on the left. On both sides, a 6-French catheter was passed with ease to the level of the renal pelvis.

Van Bommel. Retroperitoneal fibrosis.

several theoretical advantages to CT (*table 1*), its superiority has not yet been shown.[5,36-39] Additional measures, such as nuclear medicine (*figure 5*), may provide useful information regarding the stage of disease, thus indicating a potential response to medical treatment.[40]

Several authors have stressed the importance of laparoscopic or open biopsies to establish a definite diagnosis and rule out malignancy.[3,5,30,39,41] However, relatively few cases of malignant RPF have been reported, most of them with a previous history of malignancy.[8,42-45] Moreover, both laparoscopic and open biopsy are potentially fallible in that malignant areas may be missed.[42] Therefore, a careful search for (occult) malignancy and intelligent use of CT will provide an accurate diagnosis in nearly every case.[6,7,42] Recently, it was suggested that fine-needle aspiration (FNA) of the retroperitoneal mass may provide additional cytological information.[43,44] However, because of limited experience with FNA, CT or sonographic-guided percutaneous needle biopsy should be performed in each case of diagnostic doubt.[6,43,46]

PATHOLOGY

The macroscopic appearance of RPF is of a plaque-like fibrotic mass along the posterior aspect of the retroperitoneal cavity. It surrounds the lower abdominal aorta and commonly follows the course of the aorta beyond the common iliac bifurcation.[47] Many intra-abdominal structures may be compromised but the urinary tract is most susceptible.[2,6,25,47] Of gynaecological interest, fibrosis has been reported to involve the ovary, ovarian vessels, fallopian tube, uterus, cervix, and vagina.[27]

The histological appearance of RPF is of a non-specific inflammatory process and varies according to stage and activity of the disease.[47,48] Early on, the affected tissue consists mainly of collagen bundles with capillary proliferation and abundant inflammatory cells, predominantly lymphocytes, plasma cells and fibroblasts. Small numbers of eosinophils are usually present (active 'cellular' stage, *figure 6a*). In advanced cases, the entire retroperitoneal tissue becomes matted within a mass of relatively acellular and avascular, dense connective tissue (chronic 'fibrotic' stage, *figure 6b*). Signs of venulitis, perivasculitis and vasculitis (*figure 6c*) may be present.[1,3,47,49]

Histologically, RPF secondary to malignancy (malignant RPF) is indistinguishable from idiopathic RPF.[20] Only the demonstration of the small islands of tumour cells within the fibrotic mass can indicate malignancy as the probable cause of RPF. The demonstration of lymphoid and plasma cell polyclonality by immunohistological studies may differentiate between RPF and malignant lymphoma.[50]
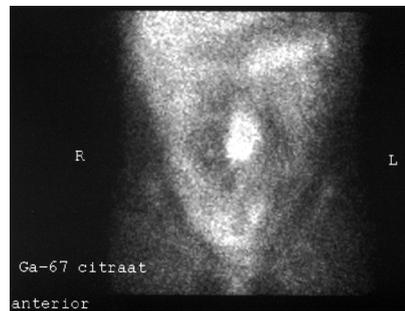
Figure 5
[67]Gallium-citrate imaging at 48 hours

Showing a focal area of abnormally increased activity in the paravertebral midline. Activity within the bowel and liver are normal.
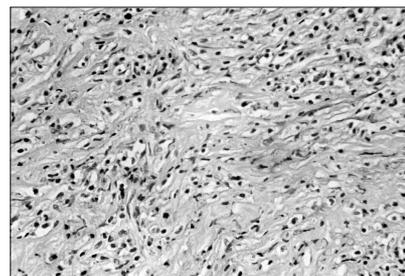
Figure 6a
Biopsy specimen of a retroperitoneal mass

Demonstrating a marked inflammatory infiltrate, predominantly consisting of lymphocytes, plasma cells and fibroblasts, in areas of collagen bundles with capillary proliferation, indicating the active 'cellular' stage of retroperitoneal fibrosis (HE x 250).
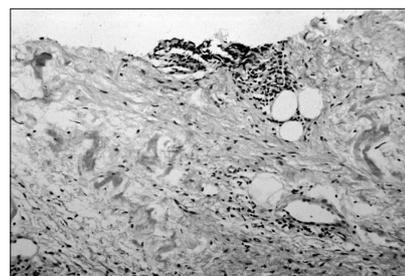
Figure 6b
Biopsy specimen of a retroperitoneal mass

Showing relatively acellular and avascular, dense connective tissue, indicating the chronic, 'fibrotic' stage of retroperitoneal fibrosis (HE x 250).
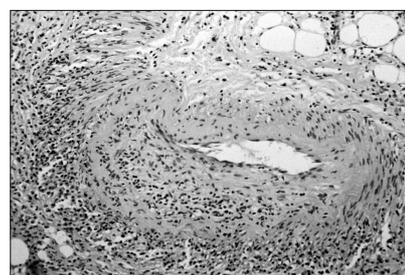
Figure 6c
Bands of collagen and extensive perivascular and intramural infiltration of inflammatory cells involving a medium-sized artery (HE x 250)

AETIOLOGY

A wide variety of conditions have been implicated as a possible cause of RPF but 60 to 70% of cases are idiopathic.[3,6,9,20] However, before labelling a condition as idiopathic RPF, all identifiable causes should be excluded (*table 2*).

Injury or inflammation of the retroperitoneal space can be induced by previous abdominal, pelvic or retroperitoneal surgery; extension of adjacent intra-abdominal processes (e.g. diverticulitis, appendicitis, ulcerative colitis) or specific infection or injury of the retroperitoneal space (e.g. pancreatitis, retroperitoneal haematoma, radiation therapy, urinary tract infections, urine or contrast material extravasation).[3,8,20,39,51]

The occurrence of RPF in patients with connective tissue diseases or autoimmune phenomena (*table 3*) is noted frequently, both in children and adults.[6,52-60] The incidence of co-existing RPF and aortic aneurysm (perianeurysmal fibrosis, 'inflammatory' aneurysm) ranges from 4 to 12%.[61-63] However, it is now clear that *not* aneurysmal formation but the presence of severe atherosclerosis is the prerequisite to develop RPF in such patients (see *pathogenesis*). Much attention has focused on drug-related RPF,[3,6,42,64-76] but convincing evidence exists only for the long-term use of methysergide, an ergot-alkaloid used as prophylaxis for migrainous headaches (*table 4*). To date, at least 40 cases of methysergide-induced RPF have been reported.[66] Several case reports have also linked the long-term use of other ergot-alkaloids, notably bromocriptine, to RPF.[65,67-69] Several β-blocking agents have been implicated as a possible cause of RPF.[70-73] However, there is now doubt whether β-adrenergic blocking agents or other antihypertensive drugs cause RPF; it seems more likely that they were used to treat hypertension caused by unrecognised RPF.[76] Likewise, analgesics may have been used to treat the early symptoms of unrecognised RPF.[42] Only anecdotal data are available for other drugs and the association is probably coincidental rather than causal (*table 4*).

Approximately 8% is associated with malignancy, mostly metastatic disease from lung, breast, prostate or digestive tract, and malignant lymphoma or sarcoma.[8,20] Therefore, although malignant RPF may be indistinguishable (both radiographically and histologically) from non-malignant RPF, the presence of the primary tumour is usually already known or otherwise readily apparent. RFP has been associated with both benign and malignant carcinoid[8,20,77] and in rare cases with cervix carcinoma[78] and tumours of the urinary system.[79]

Table 2
Aetiology of retroperitoneal fibrosis[*]

Idiopathic[#]
Severe atherosclerosis (periaortitis; 'inflammatory' aortic aneurysm)[#]
Chronic inflammation/trauma retroperitoneal space
Autoimmune diseases
Drug-induced
Malignancy

[*] = aetiological factors depicted in decreasing frequency, [#] = in many earlier cases, chronic periaortitis was classified as RPF of unknown cause, thus overestimating the incidence of idiopathic RPF (see aetiology/pathogenesis).

Table 3
Autoimmune diseases/phenomena in retroperitoneal fibrosis

Systemic lupus erythematosus
Rheumatoid arthritis
Scleroderma
Systemic vasculitis: - Takayasu's disease - Henoch-Schonlein purpura - Wegener's granulomatosis - Polyarteritis nodosa
Recurrent polychondritis
Immune-complex glomerulonephritis
Immune thrombocytopenia
Autoimmune phenomena[*]: - Positive direct Coombs; ANA positivity - Hypocomplementaemia C3, C4 - ANCA positivity (c-ANCA, anti-Pr3; p-ANCA, anti-MPO)

[*] = autoimmune phenomena detectable but no definite systemic disease.

Table 4
Suspected drug-related retroperitoneal fibrosis

Ergot-alkaloids: methysergide[*], bromocriptine, (dihydro-)ergotamine, pergolide, lysergic acid diethylamide
β-adrenergic blocking agents: timolol, propranolol, sotalol, metoprolol, pindolol, oxprenolol, acebutolol
Analgesics: aspirin, phenacetin, codeine, paracetamol
Antihypertensive agents: hydralazine, α-methyldopa, hydrochlorothiazide, reserpine
Miscellaneous: amphetamines, haloperidol, sulpha-derivatives, anticonvulsants, antihistamines, ampicillin, glibenclamide

[*] = firm data only exist for methysergide-induced RPF with more then 40 reported cases in the literature.

PATHOGENESIS

Apart from direct causes, autoimmune mechanisms are probably of prime importance in inducing the chronic inflammatory reaction.[80] The reported familial occurrence[13,81,82] and the presence of HLA-B27[82-85] in several patients with idiopathic RPF suggest that the liability to develop this disorder may sometimes be governed by genetic factors. However, no abnormal loci have been demonstrated by karyotyping.[13]

An important issue in the pathogenesis of idiopathic RPF is whether it in fact represents a localised disease process or is just the most prominent manifestation of a systemic disease. Co-existing autoimmune diseases/autoimmune phenomena (*table 3*), biopsy specimens revealing systemic vasculitis (*figure 6c*) and additional fibrosis elsewhere (e.g. Riedels thyroiditis, orbital pseudotumour, sclerosing cholangitis, periarticular fibrosis) in some patients[1,3,6,8,86-88] suggest systemic rather than local mechanisms in its pathogenesis. Moreover, of the 33 reviewed childhood cases, nine were associated with immune-mediated diseases while multisite fibrosis was present in another five cases. However, in a subset of patients with *presumed* idiopathic RPF it may be a local complication of advanced atherosclerosis.[89] The presence at necropsy of severe atheromathous plaques in arteries adjacent to areas of idiopathic RPF has led to the hypothesis that insoluble lipid leaks into the perivascular tissue causing an autoallergic inflammatory reaction mediated largely by IgG.[90,91] The allergen is believed to be ceroid, an oxidative lipoprotein by-product, elaborated in the human atheroma.[91] This so-called 'chronic periaortitis'[89] also provides an explanation for the association of RPF with aortic aneurysm and mediastinal involvement of systemic fibrosis.[89-91] So it seems that a significant number of patients with presumed idiopathic RPF are in fact suffering from chronic periaortitis, which should be considered a secondary form of RPF, found in patients with severe atherosclerosis. Indeed, the increased incidence of RPF in men may well be explained by the higher incidence of symptomatic atherosclerotic disease in men.

An immune phenomenon may also play a role in the pathogenesis of malignant RPF, involving both tumour antigens and antigens associated with tumour growth but unrelated to tumour cells.[79] The fibrous reaction associated with the carcinoid tumour is believed to be the result of circulating serotonin or its metabolic products.[77]

The mechanism by which drugs cause RPF is unknown. Methysergide acts as a strong serotonin-antagonist. By analogy to the carcinoid tumour, 'rebound' release of serotonin following a prolonged intake of this drug might be responsible.[42,70] However, this does not explain the association of RPF with another ergot-alkaloid, bromocryptine, which is not a serotonin-antagonist.[65-69] Possibly, it consists in some haptenic role of these drugs.

For most other drugs, it is also suggested that they serve as haptens, thereby inducing a hypersensitivity or autoimmune reaction.[42,74,92]

The factor(s) that determine the degree of fibrosis produced during the course of the chronic inflammation and its regulation are as yet unknown. Cells of the immune system are known to be sources of mediators regulating fibroblast proliferation.[79,88] As in other fibrotic disorders (e.g. scleroderma, idiopathic pulmonary fibrosis, chronic graft-versus-host disease),[88,93] the dramatic proliferative response of fibroblasts may be mediated by abnormal secretion or response to growth factors released at sites of chronic inflammation.[79,88] Ewald *et al.* reported elevated serum levels of a platelet-derived growth factor, i.e. connective tissue activating peptide III, in a patient with extensive retroperitoneal and periarticular fibrosis.[88] Eosinophil-derived products, shown to be present in idiopathic RPF as well as in related disorders (sclerosing cholangitis, sclerosing mediastinitis and idiopathic pulmonary fibrosis), may also stimulate fibroblast proliferation.[94]

MANAGEMENT

The therapeutic approach to RPF includes the removal of any identifiable inciting agents, preservation of renal function and suppression of the inflammatory process. No controlled therapeutic trials have been performed and, because of the rarity of the disease, are unlikely to be initiated. In addition, although rare, spontaneous regression of RPF may occur.[95]

The initial management of all patients depends on the level of renal impairment. In cases of severe renal failure, emergency decompression can be accomplished with retrograde ureteral catheterisation or percutaneous nephrostomy.[7,18,96-98] Although retrograde insertion of catheters is usually easy to achieve,[96,99] great care should be taken to prevent retrograde infection in such cases.[96,97] Percutaneous nephrostomy may be the preferred method as this technique is associated with less risk of infection and because evaluation of response to treatment is easily achieved by descending ureterography through the nephrostomy tube or subsequent clamping of the tube, which can be removed as soon as the ureter is found to be patent.[7,96] External compression of the ureter may also be managed by endoluminal balloon dilatation or permanent indwelling self-expending stents.[97,98]

Surgery

The standard approach for RPF has conventionally consisted of open biopsy, ureterolysis and transpositioning (either laterally or, preferably, intraperitoneally) or omental wrapping of the involved ureter(s).[3,30,99-101] More recently, several authors report successful laparoscopic ureterolysis and

intraperitonialisation of the ureter.[16,102] In case of irreparable damage of the ureter due to difficult surgical dissection, autotransplantation,[103] use of spermatic vein patch graft,[99] ileal interposition,[80] ureteroneocystotomy[24] or psoas hitch ureteral reimplatantantion[104] has been described. Surgical treatment is not without hazard. Ureteral devascularisation, tears and strictures due to difficult surgical dissection of the ureter, ureteric leakage or urinary fistula are frequent complications.[7,96,100,105]

Some authors reported a high incidence of postoperative complications related to hypertension and thromboembolism.[22,106] Several other authors have noted a significant morbidity and mortality associated with surgery[6,107-109] as well as a high incidence of ipsilateral or contralateral recurrences.[96,107,108]

In recent years, the use of steroids to treat recurrences after surgery or to prevent recurrences after surgery has gained general acceptance. In a large multi-institutional retrospective study, surgery alone was followed by recurrence in 48% (38 of 79 cases), whereas in combination with steroids in only 10% (8 of 77 cases).[80] Other authors have also reported good results with combined treatment.[3,24,30,100] One exception is a retrospective study by Cerfolio *et al.*, who found no significant difference in recurrence rate between patients treated with surgery plus steroids and patients treated with surgery alone (5/12 *versus* 2/19 patients).[110]

Non-surgical approach

Although evidence that exists as to the pathogenesis of RPF would logically suggest the use of corticosteroids, their use as the sole treatment is still controversial. Some authors are reluctant to use corticosteroids as the primary form of treatment, as they consider laparoscopic or open biopsies the only way to establish a definite diagnosis and to exclude malignancy.[5,30,41,101,110] Different views as to the initial treatment of RPF probably also depend on the different physicians involved in the management of this disease (internist, urologist, surgeon or rheumatologist) as well as on the level of expertise of the specific physician (i.e. incidental or repeated exposure to the disease).
However, malignant RPF is rare and most of these patients have a history of previous malignancy.[7,8,42] As stated previously, a thorough search for occult malignancy and careful application of CT will allow a correct diagnosis in nearly every case.[6,7,42] Moreover, as the prognosis of malignant RPF is poor, a short delay in the diagnosis of malignancies of this nature will make little difference to in the outcome.[7]

Several authors have emphasised that support for the use of steroids as the primary form of treatment depends on anecdotal data only.[3,39,41,70] However, excluding isolated case reports in both children and adults (because of positive publication bias), a total of 147 patients treated primarily with steroids could be retrieved from the literature of reported case series of non-malignant RPF.[2,12,14-18,105,111-132] Clinical presentation varied from severe hydro-ureteronephrosis to less advanced disease in these patients. Good results were reported in 122 of these 147 patients (83%). Recurrences were reported in nine of 55 patients (16%), most of these occurring within one year after starting treatment, of whom eight responded to re-institution of steroids. The other was treated with ureterolysis and steroids. Lack of data precluded a further analysis of these data, for instance a comparison of response between idiopathic and secondary RPF.

My personal experience now includes 21 patients with non-malignant RPF treated primarily with steroids, of whom 19 (89%) had a good response. Two of these 19 patients suffered a recurrence within one year. One of them responded to reintroduction of steroids. The other patient was treated successfully with a combination of azathioprine (2 mg/kg) and prednisone and, as documented on repeat CT scanning after four months, showed almost complete disappearance of the retroperitoneal mass.
So it seems that, irrespective of its cause, steroids will prove to be of value in most cases of non-malignant RPF. Steroids have been shown to be effective in perianeurysmal fibrosis, not only in reversing ureteral obstruction but also in making resection of the aneurysm, if indicated, feasible.[61-63,133] Dose and duration of steroid treatment varied considerably in the literature (30-75 mg/day for four weeks to 19 months), but most patients were treated for >6 months. Follow-up varied from one to nine years. Our policy is to start with a high initial dose (40-60 mg/day) for six weeks, than gradually reduce to a maintenance dose (5-10 mg/day) which is continued for at least six months and, depending on severity (i.e. extension of the retroperitoneal mass), frequently up to one year. Steroids act through reduction of inflammation and oedema, inhibition of fibroblastic proliferation, and immunosuppression.[70,80,120,121] Although steroids do not reverse established fibrosis, further fibroblastic proliferation may be slowed and symptomatology reversed. The degree of contrast enhancement on CT correlates with activity of the disease (*table 1*) and may indicate a potential benefit of steroid therapy.[34,120,121,124]

An important feature not previously emphasised seems to be the almost characteristic response to steroid treatment. Pain and constitutional symptoms often disappear within a few days and a rapid fall of ESR is seen.[50,112,113,115,121] Recovery of diuresis can be observed within seven to ten days and frequently as early as 24 to 48 hsours after starting treatment.[7,113,116] Several authors have described CT-documented regression of the retroperitoneal mass within a

few weeks after starting treatment.[120,124,125] Some authors favouring medical treatment suggest that surgery may still be indicated in cases of radiographic non-functioning kidneys or in the presence of severe renal failure.[116,117] However, radiographic follow-up studies have documented a (partial) recovery of renal function in several of these cases following steroid treatment.[9,116,117] In addition, longstanding ureteral obstruction will lead to irreversible obstructive nephropathy and this will not benefit from surgical treatment.[7]

So it seems that a trial of medical treatment may be indicated in all cases, when needed with urgent renal drainage, surgery being reserved for steroid-resistant cases or those not tolerating steroids. Frequent clinical and radiographic (e.g. descending ureterography through the nephrostomy tube, ultrasound) follow-up should be conducted to detect a beneficial response to treatment (*figure 7*). Absence of the typical clinical or radiographic response within a few weeks should be considered an indication for repeat CT scan or biopsy.[6,7,120] In steroid-resistant cases, when there is no doubt as to the initial diagnosis, other forms of immunosuppression, either alone or in combination with steroids, may be useful (*table 5*).[80,119,134-139]

In addition, an increasing number of case reports describe the successful use of medroxyprogesterone acetate, progesterone, and particularly tamoxifen as an alternative treatment for RPF.[19,140-152] Pelvic desmoid tumours, sharing similar

Table 5
Reported medical treatment of non-malignant retroperitoneal fibrosis

Immunosuppression:
Corticosteroids
Azathioprine/corticosteroids
Cyclophosphamide/corticosteroids*
Mycophenolate-mofetil/corticosteroids*
Cyclosporin*
Hormonal:
Medroxyprogesteronacetate*
Progesterone*
Tamoxifen

* = only anecdotal experience available.

pathological features with RPF, have been treated successfully with tamoxifen, which prompted these case trials with tamoxifen for the treatment of RPF. Of interest, successful treatment of Riedel's thyroiditis, an RPF-associated fibrotic disorder, with tamoxifen has also been reported.[153] *In vitro*, medroxy(progesterone) acetate is a strong inhibitor of fibroblastic proliferation.[151] Tamoxifen is thought to transduce growth-promoting signals of some growth factors, such as transforming growth factor β (TGFβ), epidermal growth factor (EGF) and growth-stimulating histamines, among others, thereby inhibiting growth of both epithelial and mesenchymal cells.[146,147] Thus, it may involve an altered balance of growth factors such that fibroblast proliferation is inhibited.[152] Oestrogen receptor levels were very low or undetectable nor were oestrogen, progesterone or androgen receptors found upon immunocytochemical studies of biopsy material, underlining the potential hormonal-independent actions of these drugs.[140,144,147]

To date, successful treatment with tamoxifen has been documented in 12 cases, (six female, six male subjects) including my own experience with a 56-year-old male patient with no reported significant side effects, except for a decrease in libido.[19,140-153] Dose and duration varied widely (10-40 mg for six months to three years). Tamoxifen was successful in treating RPF unresponsive to high-dose steroids in a prepubertal child.[19] In the other 11 cases, however, tamoxifen was used as the primary treatment. Therefore, it is not yet clear whether it may serve as an alternative for (all) steroid-resistant cases. In addition, although it may be an attractive alternative to the long-term use of corticosteroids, limited experience (efficacy, dose and duration, side effects) precludes that definite conclusions can be made.

Figure 7
Descending ureterography through nephrostomy tubes in a previously anuric patient with severe bilateral hydroureteronephrosis due to RPF, after one week of prednisone treatment

There is return of contrast passage to the bladder but still apparent marked medial deviation and tapered narrowing of both ureters at the level of L5/S1.

FOLLOW-UP

As noted, recurrences usually occur within the first year after diagnosis. However, in more extensive disease,

recurrences are more unpredictable and may occur at any time from three months to more than ten years. Therefore, long-term follow-up is mandatory.[2,6,30] At presentation, serial CT is indicated for documentation of the extent of the retroperitoneal mass as well as to assess the response to medical treatment (*figures 2a* and *2b*).[6,121,154] It should be realised that a residual CT plaque may persist in some cases following treatment and is not necessarily indicative of treatment failure.[123]

For routine follow-up, regular measurement of ESR and serum creatinine, and serial sonography to exclude hydronephrosis will suffice.[7,30] CT is indicated when the ESR or serum creatinine begins to rise, typical symptoms reappear or hydronephrosis is suspected.[121,154,155] Some authors suggest that CT scanning at 6 to 12 month intervals is indicated in patients not receiving steroids.[155] Excluding cases associated with malignancy, the prognosis is good.[3,6,8] In a large retrospective study, cumulative mortality was only 9%.[19]

CONCLUSION

Although RPF is considered rare, it is occasionally encountered in clinical practice. Nowadays, through awareness of its presentation and routine application of CT or MR imaging, the diagnosis should become more common and can be made at an earlier stage than in the past. RPF may have various causes, but the majority of cases remain classified as idiopathic. However, a significant number of patients with presumed idiopathic RPF are probably suffering from chronic periaortitis. Indeed, this so-called chronic periaortitis, found in patients with severe atherosclerosis, appears to be an increasingly recognised form of secondary RPF. Evidence to date suggests that the pathogenesis of the inflammatory component in RPF may be multifactorial in nature with some, as yet unknown, mechanism acting upon the resultant inflammatory tissue to produce striking fibrosis. Prompt recognition and treatment with corticosteroids can provide good prospects for recovery, notably preservation of renal function, and will obviate the need for surgical treatment. The clinical and radiographic improvement seen after commencing corticosteroid therapy is often impressive and reassuring as to the diagnosis. In addition, a growing body of literature is providing alternative treatment strategies for steroid-resistant cases or when steroids are not feasible. Long-term follow-up, however, is mandatory in all patients. Some important points to consider when suspecting or treating RPF are outlined in *table 6*.

Table 6
Points to consider when suspecting or treating retroperitoneal fibrosis

Identify and discontinue suspected drug
Exclude (treatable) metastatic cancer or malignant lymphoma
In case of doubt, perform CT-guided biopsy
Identify stage of disease (active 'cellular' *versus* late 'fibrotic' stage)
If non-malignant 'active' RPF, start steroids as primary treatment, with urgent renal drainage when needed
If aneurysmectomy is mandatory, consider prior steroid treatment
In steroid-resistant cases or contraindications for steroids, consider alternative treatment
Long-term follow-up is indicated in all cases

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Factors associated with switching from oral hypoglycaemic agents to insulin therapy

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ABSTRACT

Background: The aim of our study was to determine which factors are associated with switching from oral hypoglycaemic agents to insulin therapy in patients with type 2 diabetes mellitus in general practice.

Methods: Longitudinal, observational study in a Dutch general healthcare centre. All pharmacologically treated patients with type 2 diabetes mellitus were included (n=152). Comorbidity, laboratory results and medication use were obtained from the general practitioners' files.

Results: A total of 31 (20.4%) patients switched from oral hypoglycaemic agents to insulin therapy; they were significantly younger at the onset of diabetes, 50.5 *versus* 57.7 years. Fasting blood glucose levels and HbA_{1c} values were significantly higher after the switch compared with patients on oral treatment, 10.0 mmol/l *versus* 8.4 mmol/l and 8.8% *versus* 7.9%, respectively. Concerning comorbidity, they suffered more frequently from acute myocardial infarction, lipid disorders, depression, retinopathy and atrial fibrillation. Cardiovascular disease in general was more often present in patients who switched over to insulin, 77.4% *versus* 52.9% (OR 3.1; CI 1.2-7.6).

Conclusions: Patients who switch over to insulin therapy are younger at diagnosis, suffer from more health problems besides diabetes, especially cardiovascular disease, and have worse metabolic control, compared with users of oral hypoglycaemic agents.

INTRODUCTION

As type 2 diabetes mellitus (DM) advances, secondary failure of oral hypoglycaemic therapy develops as a consequence of progressive loss of β-cell function and worsening of insulin resistance caused by persistent hyperglycaemia and possible development of drug resistance.[1]
The yearly failure rate of this therapy following an optimal initial response is approximately 5 to 10% and increases with the duration of diabetes.[2] If oral treatment initially works but later fails (secondary failure), patients are switched over to insulin therapy.[3-6] The increasing number of patients with type 2 DM and recent insights regarding the importance of strict glycaemic control are expected to result in a larger number of type 2 diabetic patients receiving insulin treatment.[3]

Although the results of the United Kingdom Prospective Diabetes Study (UKPDS) underline the importance of good glycaemic control,[7] many general practitioners (GPs) appear hesitant to switch patients over to insulin therapy.[8] The recently updated diabetes mellitus guidelines of the Dutch College of General Practitioners ('NHG-Standaard') provide no clear indication when insulin should be given or when the patient should be referred to a specialist.[9,10] Only a limited number of studies have investigated which factors are associated with the decision whether or not to convert type 2 DM patients to insulin therapy and none of these were performed in general practice.[11-14] Nevertheless, GPs possess a wealth of information on the health of their patients, and on many aspects of their medical treatment. Therefore, we compared 'switchers' and 'non-switchers' with respect to patient characteristics, course of the disease, metabolic control and comorbidity, using a GP database.

MATERIALS AND METHODS

Population

This study was carried out among people who were registered in a general healthcare centre in Almere, the Netherlands (n=6800). This healthcare centre offers all aspects of primary care and is staffed by six GPs. Their practices were of similar size, between 1010 and 1145 patients, and similar in age and sex distribution. All patient information is stored in one database (Medicom®). To guarantee privacy, all analyses were performed using anonymous records.

Study design

The study population consisted of all prevalent cases of type 2 DM and all patients diagnosed during the study period, from January 1995 until June 1999. In the Netherlands, most patients with type 2 DM visit their GPs for regular check-ups. They were identified from the register by the use of oral hypoglycaemic agents or *International Classification of Primary Care* (ICPC) codes T90 or T90.2, and/or the description 'diabetes mellitus type 2' in their medical records. Subsequently diet-treated patients were excluded (n=46).

Medical treatment starts with a first-generation sulphonyl-urea (tolbutamide), followed by second-generation sulphonylureas and/or additional biguanide or α-glucosidase inhibitors (in obese patients). Diabetic patients are treated according to a locally developed treatment protocol ('Diabetes Care Almere'). Patients should be switched over to insulin therapy if they are on maximised oral medication and still have HbA_{1c} values greater than 8%.
Following the diabetes care protocol, maximum daily dosages of oral agents are: glibenclamide 15 mg, gliclazide 240 mg, glipizide 20 mg, glimepiride 6 mg and metformin 3000 mg. The protocol included three steps of insulin treatment:
1) a single dose of bedtime (long-acting) insulin plus daytime sulphonylurea therapy;
2) two injections of intermediate-acting insulin;
3) multiple daily injections, combination of short-acting and intermediate-acting insulin.

We defined 'switchers' as subjects who switched to insulin therapy (ATC code A10A) with or without continuation of oral hypoglycaemic medication. Some of the initial patients were already being treated with insulin. The following data were obtained from the anonymous patient records: all medication prescriptions, demographic data, comorbidity (defined according to ICPC classification), diabetic complications, doctor in attendance (specialist, GP), referrals to specialists, and the medical journal (a database file containing free text, as written down by the GP).
Regarding medication prescriptions, all drugs were coded according to the Anatomical Therapeutic Chemical (ATC) Classification.[15]
Microalbuminuria was defined as having at least one measurement of urinary albumin concentration higher than 20 mg/l. For other continuous variables (glycosylated haemoglobin (HbA_{1c}), fasting plasma glucose, total serum cholesterol, body mass index, et cetera) we calculated a mean yearly value per patient and subsequently a mean value per patient over the whole study period. As we expect measurements to be carried out more frequently in poorly controlled patients, this approach gives equal weight to each subject.

Data analysis

For the comparison of continuous variables and categorical variables between switchers and non-switchers, we used the Student's *t*-test and chi-square test, respectively. Odds ratios (ORs) and 95% confidence intervals (95% CI) were calculated to compare risks of other diseases and disorders, and drug use for those patients on insulin therapy *versus* those using oral medication. P values less than 0.05 were considered statistically significant. We divided the follow-up period of patients who were switched over to insulin therapy into two phases, *before* and *after* the changeover to insulin therapy.
The Kaplan-Meier method was used to calculate the cumulative incidence of switching over to insulin among the cases present in 1995. Survival time was defined as months on oral hypoglycaemic treatment. So, the cumulative incidence of switching was calculated as: 1 - cumulative survival probability. All analyses were carried out using the statistical package SPSS.
For descriptive variables without further statistical testing, for instance to determine reasons for not switching despite secondary failure of oral treatment, the medical journal as registered by the GP was used.

RESULTS

Figure 1 shows the number of type 2 DM patients, excluding those on dietary treatment only, during the study period. Between 1995 and 1999 there was an increase in the total number of patients diagnosed with type 2 DM; 72 patients in 1995 increasing to 136 patients in 1999. Two of the initial patients enrolled were already on insulin therapy. The estimated prevalence of type 2 DM on 30 June 1999 was 2.1% (136/6510; 95% CI 1.7%-2.4%).
In the study 79 men and 73 women, aged between 32 and 94 years (mean age 62.8 years), with type 2 DM were enrolled. Their clinical and demographic characteristics are given in *table 1*. During the study period 14 patients died, three in the insulin-requiring group. Two patients moved out of the country in 1997.

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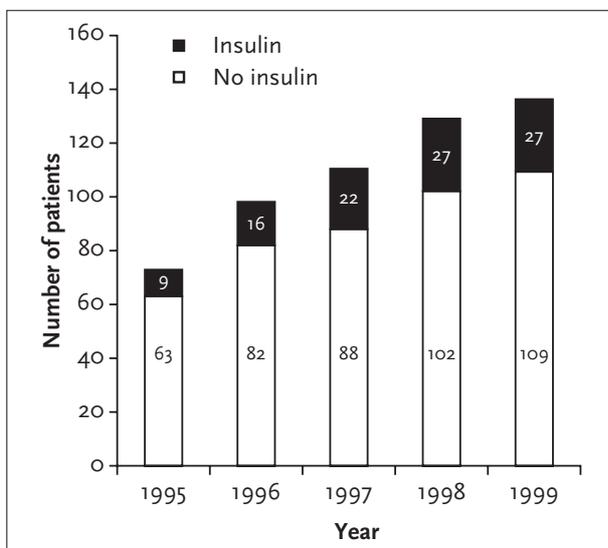
Figure 1

Insulin treatment over time in a healthcare centre in Almere

Table 1

Characteristics of type 2 diabetic patients

VARIABLE	n=152
Age at onset (years)	56.3 ± 1.2
Male (%)	52.0 ± 4.1
Duration of disease (years)	5.8 ± 0.5
Fasting blood glucose (mmol/l)	8.7 ± 0.2
HbA$_{1c}$ (%)	8.0 ± 0.2
Systolic blood pressure (mmHg)	149.3 ± 1.9
Diastolic blood pressure (mmHg)	85.2 ± 0.8
Total serum cholesterol (mmol/l)	5.8 ± 0.1
HDL cholesterol (mmol/l)	0.7 ± 0.1
Triglycerides (mmol/l)	1.2 ± 0.1
Body mass index (kg/m²)	31.6 ± 0.7
Weight (kg)	85.4 ± 1.5

Values are proportions or means ± standard error of the mean (SEM)
HDL = high-density lipoprotein.

Conversion to insulin therapy

Of 152 patients, 31 (20.4%) switched from oral hypoglycaemic agents to insulin therapy. The cumulative incidence of switching to insulin treatment among prevalent cases in 1995, who had been diabetic patients for a mean of 5.9 years, was 36% (95% CI 23%-48%) in June 1999. Before switching, 16 patients (62%) were on the maximum dosage of a sulphonylurea derivative (SU), while 12 patients (46%) were treated with an SU in combination with metformin. Four patients (15%) had an obvious or plausible reason for switching over to insulin without maximising oral medication in accordance with the guidelines; two had a myocardial infarction, one wished to become pregnant and another

patient had no adequate response to oral hypoglycaemic agents within six weeks. In total 22 patients (75%) were referred to diabetiologist or were hospitalised at the moment they switched to insulin therapy. After stabilisation of their metabolic state, in 18 patients (85%) diabetes care was continued by their GP.

Reasons for not switching

Within the study population ten patients did not switch to insulin therapy despite secondary failure of oral hypoglycaemic agents, defined by latest HbA$_{1c}$ equal to or greater than 8.0%, and maximal treatment with oral hypoglycaemic agents. Subsequently, we identified reasons for not switching, according to the GP, by examining the medical journal. The main reasons for not switching were: resistance (n=6), hesitation or unwillingness to undergo insulin therapy (n=1), non-compliance with appointments (n=2), and medication regimen (n=5). Two of these patients were already self-monitoring their blood glucose levels. The reasons for not switching remained unclear in two patients.

Switchers compared with non-switchers

The differences between type 2 diabetic patients treated with insulin and patients on oral hypoglycaemic agents are listed in *table 2*, on the next page. Patients switching over to insulin therapy were significantly younger at the onset of the disease, and had a shorter duration of diabetes (4.0 *versus* 4.8 years). At the end of the study period, there was no significant difference in age between the two groups; the mean age for switchers was 60.7 (± 13.1) years, compared with 63.4 (± 14.3) years in the patients who did not switch over to insulin. The fasting blood glucose and HbA$_{1c}$ values of insulin-treated patients compared with those on oral hypoglycaemic agents were significantly higher after the switch (p=0.01 and p=0.02, respectively). Before these patients were converted to insulin therapy they had significantly higher total serum cholesterol levels, 6.4 mmol/l *versus* 5.7 mmol/l (p=0.04). Microalbuminuria was present in patients on oral hypoglycaemic agents (OHA) about as frequently as in those treated with insulin. But we also found that the urinary albumin concentration was less tested in insulin-treated patients than in those on OHA, 41.9% *versus* 61.2% (OR 0.5; 95% CI 0.2-1.0). Retinopathy and neuropathy were more frequent in insulin-treated patients, although the difference in prevalence of neuropathy was of borderline significance; odds ratios were 3.4 (95% CI 1.1-10.6) and 3.1 (95% CI 0.9-10.7) respectively.

Comorbidity

Comorbidity, defined as a health problem besides diabetes in the GP list, was present in 31 (100%) of the switchers and in 106 (87.6%) of the subjects that were not converted to insulin therapy (p=0.04).

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Table 2

Insulin-treated patients compared with those on oral hypoglycaemic agents

MEASURE	INSULIN THERAPY (n=31)		NO INSULIN THERAPY (n=121)
	Before switch	After switch	
Age at onset (years)[*]	50.5 ± 2.2	57.7 ± 1.3	
Duration of disease (years)[*]6.6 ± 1.3	2.6 ± 0.2	4.8 ± 0.5	
Cigarette smokers (%)	50.0	64.0	
Fasting blood glucose (mmol/l)[†]	8.8 ± 0.6	10.0 ± 0.6	8.4 ± 0.2
HbA$_{1c}$ (%)[†]	8.5 ± 0.3	8.8 ± 0.4	7.9 ± 0.2
Total serum cholesterol (mmol/l)[‡]	6.4 ± 0.2	5.8 ± 0.2	5.7 ± 0.1
Systolic blood pressure (mmHg)	156.3 ± 6.1	155.8 ± 4.9	148.1 ± 2.0
Diastolic blood pressure (mmHg)	86.0 ± 3.1	85.5 ± 2.3	85.0 ± 0.9
Body mass index (kg/m²)[§]	32.8 ± 2.5	31.3 ± 1.6	31.8 ± 0.9
Weight (male)[§]	82.3 ± 6.2	91.3 ± 3.9	88.3 ± 2.3
Weight (female)[§]	95.0 ± 6.3	84.1 ± 6.3	80.8 ± 2.4
Diabetic complications:			
- Microalbuminuria[‖]	53.8		37.8
- Retinopathy[*]	19.4	6.6	
- Neuropathy	16.1	5.8	
Other medical disorders (number)[*]	7.0 ± 0.9	4.5 ± 0.3	

Values are proportions or means ± SEM, [*] = p value <0.05, insulin-treated patients compared with those on oral hypoglycaemic agents, [†] = p value <0.05, insulin-treated patients after switch, compared with those on oral hypoglycaemic agents, [‡] = p value <0.05, insulin-treated patients before switch, compared with those on oral hypoglycaemic agents, [§] = sparse data about BMI and weight before switch (2 and 11 respectively), [‖] = urinary albumin concentration ≥20 mg/l.

Patients who were converted to insulin therapy had more comorbidity, notably acute myocardial infarction (OR *versus* non-switchers 3.5; 95% CI 1.3-9.6), depression (OR 14.3; 95% CI 2.7-74.9), disorders in lipid metabolism (OR 2.9; 95% CI 1.1-7.8), and atrial fibrillation (OR 8.8; 95% CI 1.5-50.6). Of borderline significance were the higher frequencies of benign prostate hypertrophy (OR 6.4; 95% CI 1.0-40.0) and chronic obstructive pulmonary disease (OR 4.3; 95% CI 1.0-18.4) in patients on insulin. Cardiovascular disease in general was more often present in patients that were switched over to insulin therapy; the prevalence was 77.4% *versus* 52.9% (OR 3.1; 95% CI 1.2-7.6). All diseases mentioned usually occurred *before* patients converted to insulin therapy; these percentages varied between 63.6% (acute myocardial infarction) and 100% (benign prostate hypertrophy).

Co-medication

Drugs most frequently prescribed besides the hypoglycaemic medications were analgesics, non-steroid anti-inflammatory drugs, psycholeptics, antibiotics, and antimycotic drugs. Of the patients on insulin treatment, 83.9% were taking one or more cardiovascular drug(s), identified as groups B01, C01-C03 and C07-C10 following the ATC classification, *versus* 62.8% in subjects on oral treatment only (OR 3.1; 95% CI 1.1-8.6). When we inspected the cardiovascular medication further, patients on insulin were taking cardiac drugs, angiotensin-converting enzyme inhibitors, lipid-lowering medication and antithrombotic agents about twice as often as those not on insulin, ORs were 2.9, 3.0, 3.2 and 2.5, respectively (*table 3*).

Table 3

Medication use in insulin treated versus non-insulin-treated patients

GENERIC NAME	ATC[*]	% USE	ODDS RATIO	[95% CI]
Cardiacs	C01	45.2 *vs.* 22.3	2.87	[1.25-6.55]
Diuretics	C03	41.9 *vs.* 28.9	1.78	[0.79-4.01]
Beta-blocking agents	C07	35.5 *vs.* 28.1	1.41	[0.61-3.25]
Calcium channel blockers	C08	29.0 *vs.* 20.7	1.57	[0.64-3.83]
ACE inhibitors[†]	C09	58.1 *vs.* 31.4	3.02	[1.35-6.80]
Other antihypertensive drugs[‡]	C02	12.9 *vs.* 1.7	8.82	[1.53-50.63]
Lipid-lowering medication	C10	38.7 *vs.* 16.5	3.19	[1.34-7.59]
Antithrombotic agents	B01	54.8 *vs.* 33.1	2.46	[1.10-5.49]
Antidepressants	N06A	12.9 *vs.* 7.4	1.84	[0.53-6.44]
Antiasthmatics	R03	35.5 *vs.* 25.6	1.60	[0.69-3.70]

[*] *ATC = Anatomical Therapeutic Chemical classification,* [†] *ACE = angiotensin-converting enzyme,* [‡] *= including for instance antiadrenergic agents (doxazosin), agents acting on arteriolar smooth muscle (hydralazine), serotonin antagonists (ketanserin).*

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DISCUSSION

This study describes patients with type 2 diabetes mellitus who switched from oral hypoglycaemic agents to insulin therapy in a primary care setting. Several factors potentially associated with the decision to convert to insulin therapy were found, notably: younger age at diagnosis, more comorbidity, worse metabolic control, and use of more cardiovascular medication.

General practice networks provide databases that may fruitfully be used for research. The use of computerised databases permits analysis of diagnostic, treatment and prescribing patterns in different patient groups within the general population. These databases enhance access to health-related information of large groups of patients over a long period of time.[16,17] The sensitivity of general practice registers in identifying patients with diagnosed diabetes exceeds 90%.[18] The prevalence of 2% which we found in this GP population closely approximates the estimated prevalence in the Netherlands.[19,20] Also, the increase in diabetes is in agreement with the trend reported for the Netherlands. The increase is based on both the ageing of the population and increased awareness of diabetes among GPs.[21]

One advantage of using data derived from a healthcare centre is the uniform approach to the treatment. GPs and district nurses cooperate closely, following to a locally developed treatment protocol. However, the individual physicians all make their own decisions. Because of the strict protocol, the effect of variability will be limited. Data on body mass index and smoking were very incomplete (available in 27.6% and 43.4% of the patients, respectively). Given the high mean values (*tables 1* and *2*) it seems that GPs only record these characteristics in obese and smoking patients. Although most patients are weighed regularly, body height was seldom measured. Our main results did not derive from these variables, so there was no influence on the associations we found.

Secondary failure of treatment with oral hypoglycaemic agents is defined as an inadequate glucose-lowering effect of oral drugs after an initial good response.[11-13] Failure implies that the whole treatment strategy failed, not simply the drug treatment.[12]

The causes of failure include non-compliance, weight gain, declining β-cell function, infection and the use of diabetogenic drugs, such as glucocorticoids, thiazides, and β-blockers.[11] In our study, the cumulative incidence of switching to insulin therapy was 36% over a 4.5 year period, which is comparable with other studies.[22-24] After nine years of follow-up in the United Kingdom Prospective Diabetes Study (UKPDS), 30% of the patients had switched over to insulin treatment.[23]

Groop and colleagues concluded that secondary failure of treatment with oral hypoglycaemic agents is determined by the disease itself rather than by patient-related factors.[11] The presence of islet cell and thyrogastric antibodies can unmask a distinct group of type 2 diabetic patients with a high risk of secondary drug failure and subsequent insulin dependency.[12] However, this is probably only a small proportion of the patients who become insulin users. Although experimental studies show that insulin therapy can be safe and efficacious in improving glycaemic control in type 2 diabetes,[7,25,26] little is known about factors determining the decision to use insulin in type 2 DM. In a randomised controlled trial (UKPDS 26), higher failure rates were found in patients with higher glucose concentrations than in those who were younger, those with lower β-cell reserve and those randomised to glibenclamide compared with chlorpropamide.[27] In the literature we did not find any studies that described determinants in type 2 diabetic patients associated with switching over from oral hypoglycaemic agents to insulin therapy in *primary care*. Goddijn studied prospectively a cohort of type 2 diabetic patients referred by GPs to an outpatient department for consideration of insulin therapy. As in our study, she found that switchers had a higher HbA_{1c}. However, in contrast to our findings, her patients had a lower body mass index and had been taking oral hypoglycaemic agents longer.[13] These differences might indicate that GPs wait longer to refer patients for insulin than switching the patients themselves. In addition, Goddijn's study was performed a few years ago. Since then GPs seem more likely to switch to insulin therapy, probably because of increased awareness of the importance of strict glycaemic control.

It is well known that diabetic patients suffer from more (cardiovascular) morbidity than subjects without diabetes.[28,29] In addition, we found that insulin users suffered more frequently from other diseases besides diabetes. Also the higher frequency of depressive disorders has been described elsewhere. Among other things, depression is associated with poorer medication regimen adherence.[30] Furthermore, 64 to 100% of these disorders developed or occurred in the period before patients converted to insulin, suggesting that the course of the disease in diabetic patients who eventually switch over to insulin therapy is more severe. The younger age of onset and shorter duration of diabetes in these patients further support their increased severity.

The United Kingdom Prospective Diabetes Study (UKPDS) has shown that more intensive management aiming for near-normal glucose levels reduces the risk of diabetes-related complications, particularly microvascular disease.[7] This suggests that physicians should be on the alert for patients with secondary failure who should be converted to insulin therapy in time.

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Our results suggest that insulin therapy is started after the development of diabetic complications and other comorbidity; in other words, 'one locks the stable after the horse has bolted'.

In conclusion, we found that patients who switch over to insulin therapy due to secondary failure are younger at diagnosis, more frequently suffer from depression, acute myocardial infarction, lipid disorder, atrial fibrillation, and retinopathy and have higher HbA_{1c} and total serum cholesterol values.

ACKNOWLEDGEMENT

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ORIGINAL ARTICLE

Discontinuation of metformin in type 2 diabetes patients treated with insulin

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ABSTRACT

Background: Metformin added to insulin therapy in type 2 diabetic patients improves glycaemic control and decreases the required daily dose of insulin (DDI). Metformin should be discontinued if cardiac, hepatic or renal failure develops. We examined whether glycaemic control can be maintained after metformin cessation.

Methods: We included 45 type 2 diabetic patients treated with insulin plus metformin, and 45 matched controls treated with insulin only. After discontinuation of metformin in the first group, we aimed for tight fasting and postprandial blood glucose levels, 4-7 and 4-10 mmol/l, respectively, in both groups. During 12 weeks we assessed glycaemic control every two weeks and, if necessary, adjusted the insulin dosage.

Results: In the group in which metformin was discontinued, DDI increased from 67.9 ± 22.9 to 92.2 ± 29.4 IU (p<0.001) leaving glycaemic control unchanged. In the controls, glycated haemoglobin (GHb) decreased by 0.93% (p<0.001), while DDI increased slightly from 62.4 ± 22.9 to 72.3 ± 27.3 IU (p<0.001). The increase in DDI was larger in patients in whom metformin was discontinued than in the controls (p<0.001).

Conclusions: In type 2 diabetic patients treated with insulin plus metformin, glycaemic control can be maintained after discontinuation of metformin by increasing the DDI substantially (20 to 36%) during application of an intensified treatment protocol.

INTRODUCTION

Metformin is a widely used antihyperglycaemic drug in the treatment of type 2 diabetes mellitus (DM), not just as monotherapy, but also in combination with sulphonylureas.[1,2] Several trials have shown favourable effects of metformin on glycaemic control and diabetes-related angiopathy in patients treated with insulin.[3-5] Therefore, metformin might be considered the drug of choice in the treatment of type 2 DM patients.[6]

Metformin has been associated with a small risk of developing a life-threatening lactic acidosis in patients with cardiac, hepatic and/or renal failure.[7-10]

However, if these at-risk patients are excluded from metformin usage, the risk of lactic acidosis is negligible. The cessation of metformin will in general result in impaired glycaemic control. This poses problems in certain groups of patients, for example in patients developing renal failure due to diabetic microangiopathy, who would especially benefit from tight glycaemic control.[11].

In view of these considerations, we studied whether, in patients with type 2 DM treated with insulin plus metformin, glycaemic control can be maintained after stopping metformin by increasing the daily dose of insulin.

MATERIALS AND METHODS

Patients
The patients included had consented to participate in a randomised clinical trial comparing insulin plus placebo with insulin plus metformin.[12] During the prerandomisation

period of this trial, 45 consecutive subjects with type 2 DM, who had been treated with insulin and metformin for at least three months (group M), had consented to stop taking metformin and were treated with insulin only. All these metformin-stoppers were included in the present study without selection. These subjects were matched with 45 others (group C), who were treated with only insulin before and after inclusion. The criteria for inclusion are shown in *table 1*. Both groups were matched for age, gender and glycated haemoglobin (GHb) at baseline. After collection of data at baseline, metformin was discontinued in group M. Thereafter, all patients from both groups were asked to adhere to intensified glucose monitoring and extra support by a nurse specialised in diabetes care (*figure 1*). All patients gave written informed consent. The medical ethical committees of all the participating hospitals had approved the study protocol.

Table 1
Inclusion and exclusion criteria

INCLUSION CRITERIA
Type 2 diabetes mellitus diagnosed after the age of 25 or previously treated with oral drugs
Age between 30 and 80

EXCLUSION CRITERIA
Ketoacidosis in the medical history
Metformin-induced lactic acidosis
Cockroft-Gault estimated creatinine clearance <50 ml/min
Pregnancy or the wish to become pregnant
Cardiac failure NYHA class III and IV
Hepatic failure, defined as a cholinesterase <3.5 U/l

| Insulin plus metformin (M)	Only insulin
Only insulin (C)	Only insulin
	Intensive treatment protocol
-12 weeks	0 weeks 12 weeks
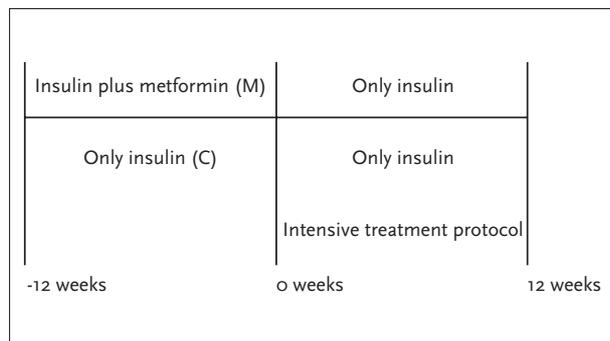
Figure 1
Study outline

All patients were treated with either insulin plus metformin (M) or with insulin alone (C) for at least 12 weeks prior to the study. Baseline measurements were taken at 0 weeks and follow-up measurements after 12 weeks. During these 12 weeks each patient monitored blood glucose levels carefully every two weeks and discussed them with a nurse specialised in diabetes care. If necessary the insulin dose was adjusted to fulfil the criteria mentioned in the text.

Glucose monitoring and assessment of the DDI
All subjects monitored their blood glucose levels with the same home-monitoring device (Glucotouch, Johnson and Johnson). Measurements were taken seven times on a single day every two weeks, i.e. just before and one and a half hours after each meal and just before going to sleep. The next day, the results were telephoned to a nurse specialised in diabetes care. If necessary, she adjusted the insulin dosage aiming for a fasting blood glucose between 4 and 7 mmol/l, and postprandial blood glucose between 4 and 10 mmol/l. At baseline and after 12 weeks, GHb was measured and the daily dose of insulin was assessed in both groups.

Laboratory measurements
Methods used for the GHb assay (normal value 4.0 to 6.0%) were Roche Unimate and HPLC using an Amersham Pharmacia Mono-S HR5/2 column. Method comparison according to Passing & Bablok[13,14] showed no significant deviation between these two methods. At baseline and at follow-up the same method was used for each subject.

Statistical analyses
We used two-tailed, paired T-tests to compare means and the Pearson correlation to calculate the relation between the previous dose of metformin and the resulting increment of insulin dose. A p value less then 0.05 was considered to be significant and all data are expressed as mean (SD) or mean difference (95% confidence interval (CI)).

RESULTS

All patients
The mean age in group M was 61.8 (7.6) years compared with 61.7 (11.5) years in the control group; both groups consisted of 30 women and 15 men. Mean bodyweight was 92 (16) kg in the metformin group and 89 (14) kg in the control group (p=0.34).
The results of 12 weeks of insulin treatment for both groups are shown in *table 2*. The mean GHb in group M was 8.78% (1.44) at baseline and changed to 8.85% (1.02; p=0.69) 12 weeks after discontinuation of metformin. However, to maintain this level of glycaemic control a substantial increment of insulin dose was required. The daily dose of insulin increased from 67.9 ± 22.9 IU/day at baseline to 92.2 ± 29.4 IU/day at 12 weeks (p<0.0001, increment 24.3 IU/day (95% CI 20.2-28.5) or 36% (95% CI 30-42).
In group C, GHb dropped from 8.86 ± 1.50% at baseline to 7.92 ± 1.16% after 12 weeks (decrease 0.93%; 95% CI 0.69-1.22). The mean increase in the daily dose of insulin was 9.9 IU/day (95% CI 6.9-13.0) or 16% (95% CI 11-20).

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Table 2
Baseline values and the results after 12 weeks of intensive insulin therapy

	SUBJECTS	GHB (%)	DDI (IU)
Baseline	M	8.78 (1.44)	67.9 (22.9)
	C	8.86 (1.50)	62.4 (22.9)
	Difference	0.09 (-0.37 to 0.54)	5.6 (-4.4 to 15.5)
	P value (M *vs.* C)	0.701	0.266
12 weeks	M	8.85 (1.02)	92.2 (29.4)
	C	7.92 (1.16)	72.3 (27.3)
	Difference	-0.93 (-1.26 to -0.59)	-19.9 (-31.9 to -7.9)
	P value (M *vs.* C)	<0.0001	0.002
	Difference M *vs.* baseline	0.07 (-0.41 to 0.27)	24.3 (20.2 to 28.5)
	P value	0.687	<0.0001
	Difference C *vs.* baseline	-0.95 (-1.2 to -0.7)	9.9 (6.9 to 13.0)
	P value	<0.0001	<0.0001

M = previous metformin users, C = control subjects, GHb = glycated haemoglobin, DDI = daily dose of insulin, numbers = mean (SD) or mean (95% confidence interval).

These changes in GHb and the daily dose of insulin were significantly different between the two groups (*table 2*).

Different metformin dosages
Before the discontinuation of metformin, the daily dose of metformin varied from 500 mg (3), 850 mg (6), 1000 mg (14), 1500 mg (6), 1700 mg (11) to 2550 mg (5). As shown in *figure 2*, the daily dose of metformin correlated significantly with the later increment of the daily dose of insulin
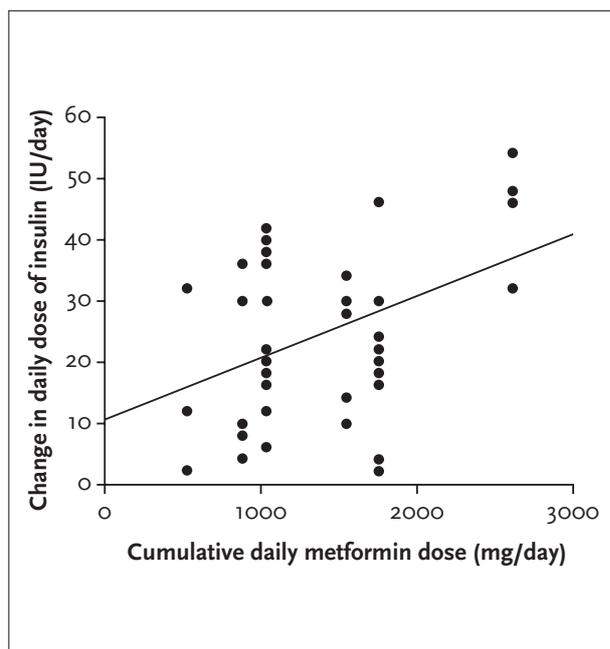
Figure 2
Correlation between the previous daily dose of metformin and the change in daily dose of insulin after 12 weeks of intensive treatment with insulin only (Pearson correlation = 0.399, p=0.007)

necessary to maintain glycaemic control after stopping metformin (r=0.399, p=0.007).

DISCUSSION

In a routine practice of internists in three regional hospitals, stopping metformin in type 2 DM patients treated with insulin plus metformin required a 36% increment in the insulin dose during application of an intensified treatment protocol to maintain glycaemic control for 12 weeks. In matched controls, this intensified treatment protocol improved glycaemic control, but the DDI increased by only 16%.
These results, however, are somewhat hard to interpret quantitatively. We included a control group to estimate the effects of intensifying glycaemic control on the DDI. This was associated with an increase in the DDI of 16%. The increase in DDI associated with stopping metformin may therefore be estimated to be about 36-16=20%. However, glycated haemoglobin decreased in the control group but not in the metformin group, and the 20% increase in DDI associated with stopping metformin is therefore likely to be somewhat of an underestimate.
We did not find any previous studies that reported the effects of metformin cessation on glycaemic control and insulin requirements. Several trials, however, have studied the effect of metformin addition to insulin therapy in type 2 diabetic patients.[3-5] All report an evident improvement of glycaemic control with less insulin in the patients treated with insulin and metformin, as compared with patients treated with insulin alone. These studies found reductions in daily insulin requirements of about 25% after addition of metformin

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to insulin therapy, i.e. of about the same magnitude as the increment we report after stopping metformin in patients receiving combination therapy with insulin and metformin.

In the light of the earlier reports mentioned above, one might expect that glycaemic control would deteriorate after metformin cessation in insulin therapy. We show that with intensified insulin therapy such impairment can be prevented. The result of the application of our intensive treatment protocol is displayed by the rise in the daily dose of insulin in both groups and the improved glycaemic control of the control group. However, we were only able to maintain a moderate level of glycaemic control, at least during 12 weeks, in the patients who had previously taken metformin. It is not known by how much the daily dose of insulin has to be increased to improve glycaemic control until a treatment goal of GHb <7% can be achieved, or whether that goal will be achievable at all with insulin alone.

Because impaired renal and cardiac function are typical diabetes-related complications, and because the use of metformin is increasing, physicians will more often face the decision to discontinue metformin. We have shown that, by closely monitoring plasma glucose values and instant adjustment of the insulin dose using an intensified treatment protocol, glycaemic control can be maintained at the cost of an increase of the daily dose of insulin by 20 to 36%. This depends, albeit weakly, on the previously used dose of metformin.

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CASE REPORT

Endoscopic resection of a large Brunner's gland adenoma

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ABSTRACT

Brunner's gland adenoma is a rare benign tumour of the duodenum. Less than 150 cases have been reported in English literature. We report a 73-year-old woman presenting with upper gastrointestinal obstructive symptoms and melaena. Duodenoscopy revealed a large pedunculated tumour in the bulbus duodeni. Endoscopic snare polypectomy was successfully performed. Histological examination revealed a Brunner's gland adenoma. The literature on Brunner's gland adenoma is reviewed.

INTRODUCTION

Brunner's gland adenoma (also referred to as Brunneroma or Brunner's gland hamartoma) is a rare benign tumour of the duodenum. The first to report this condition was Cruveilhier in 1835, describing a Brunner's adenoma causing intussusception with lethal outcome. Since then approximately 150 cases of Brunner's adenoma have been reported in the English literature.[2] We present a 73-year-old female evaluated for microcytic anaemia and melaena. Endoscopy and barium studies revealed a large pedunculated polyp in the duodenum, which was endoscopically resected and proven to be a Brunner's adenoma on histology. The literature on Brunner's adenoma is reviewed. Aetiology, clinical picture, radiographic appearances, differential diagnosis and treatment of this rare syndrome are discussed.

CASE REPORT

A 73-year-old woman presented to the outpatient clinic with cardiac chest pain during exercise, dyspnoea and fatigue. She had difficulty in eating for the last six weeks with nausea and vomiting. Her stools were black coloured. The medical history showed diabetes mellitus type 2, cardiac surgery (CABG) and a cerebral vascular accident. Her medication included acetylsalicylic acid 38 mg once daily. On physical examination the patient was dyspnoeic, respiratory frequency 30 per minute, blood pressure 100/55 mmHg. and pulse 84 beats per minute. Physical examination was otherwise unremarkable. Apart from a microcytic anaemia, Hb 3.9 mmol/l (normal 7.5-9.0 mmol/l) and MCV 67 (normal 80-95) routine laboratory tests showed normal results. She was admitted to hospital for evaluation of her microcytic anaemia. On admission she received blood transfusions.

On upper endoscopy a large pedunculated tumour was seen in the first part of the duodenum and biopsies were taken. On pathology these showed signs of active chronic inflammation with erosion, no adenomatous changes, dysplasia or malignancy. An enteroclysis was performed; this revealed a polypoid-filling defect in the duodenum (*figure 1*). Endoscopic resection was performed in the operating room so that if complications occurred, the surgeon could take over and convert the procedure into laparotomy. Endoscopic polypectomy was successfully performed and a tumour measuring 4.5 x 2.8 x 2.4 cm was excised (*figure 2*). Histological examination indicated a Brunner's gland adenoma.
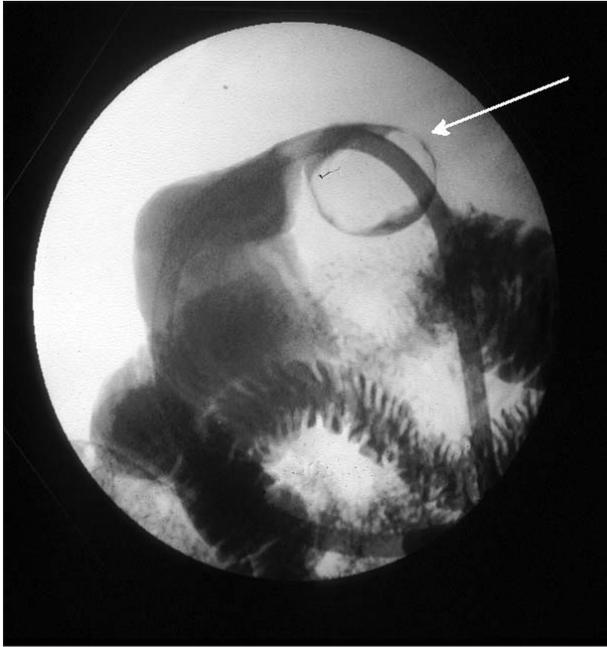
Figure 1
Barium contrast study revealing a polypoid-filling defect (arrow) in the duodenum

Figure 2
Resection specimen measuring 4.5 x 2.8 x 2.4 cm

DISCUSSION

Benign tumours of the duodenum are rare. They are reported in 0.008% of the patients at autopsy; Brunner's gland adenoma comprises 10.6% of these lesions.[3]
In the English literature approximately 150 cases have been reported since the first description by Cruveilhier in 1835.[2]
Brunner's glands are branched acinotubular structures located in the submucosa and deeper parts of the duodenum wall. They are most numerous in the proximal part of the duodenum, immediately distal to the pylorus and diminish more distally in the duodenum. Very seldom they extend beyond the papilla of Vater. Laarman *et al.*[4] reported a Brunner's gland adenoma located in the proximal jejunum and Henken and Forouhar describe a patient with a Brunner's gland adenoma situated in the proximal ileum.[5]

The function of Brunner's glands is secretion of alkaline mucoid fluid, which contains glycoproteins forming an adherent layer on the duodenal mucosa, protecting it from the acid chyme of the stomach.[6] In addition, Brunner's glands produce urogastrone, an inhibitor of gastric acid secretion.[7]

Feyrter[8] classified three types of Brunner's gland hyperplasia: diffuse nodular hyperplasia, occupying most of the duodenum; circumscript nodular hyperplasia, the most common type mainly present in the duodenal bulb; and adenomatous hyperplasia, which may be sessile or pedunculated. This last-mentioned type corresponds with the Brunner's gland adenoma found in our patient. Hyperplasia refers to multiple lesions (usually less than 1 cm) and adenoma refers to a lesion larger than 1 cm. Brunner's gland adenomas are considered to be benign but malignant degeneration has been reported in two cases, including one patient with microcarcinoid tumours.[9,10]

The aetiology of Brunner's gland hyperplasia is not perfectly understood, but associations with peptic ulcer disease, chronic pancreatitis and chronic renal insufficiency have been described.[11] Brunner's gland hyperplasia is believed to act as a mechanism which serves the protection of the duodenal mucosa.

Brunner's gland adenoma is mostly present in middle age without sex predominance.[12] Levine *et al.*[12] studied the characteristics of a group of 27 patients with a Brunner's gland adenoma. He defined three types of clinical picture. The first group were symptomatic patients in whom the Brunner's gland adenoma was an incidental finding. The second group consisted of patients presenting with bleeding complications. The last group comprised patients complaining of prolonged obstructive upper gastrointestinal symptoms. Of the patients with a Brunner's gland adenoma, 11% are asymptomatic. Bleeding complications occur in 40 to 50% of patients. These patients present with melaena, fatigue, malaise and anaemia.[13,14] Although blood loss is commonly occult, massive and even fatal haemorrhage has been described.[15] Obstruction is present in about 50% of patients, giving rise to epigastric pain, nausea, vomiting and postprandial discomfort.[13,14] Our patient presented initially with anaemia and appeared to have had obstructive symptoms for some time as well.

Diagnostic radiographic studies include ultrasonography, barium contrast studies and endoscopy. Large adenomas may be detected by ultrasonography.[16] Upper gastrointes-

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tinal barium studies may reveal multiple small filling defects ('Swiss cheese' appearance) in Brunner's gland hyperplasia or in the case of an adenoma, a smooth surfaced polypoid lesion may be seen.[5,13] Upper intestinal endoscopy with biopsies is essential in making the diagnosis. Biopsies must be sufficiently deep for diagnosis, because of the submucosal location.[17] Furthermore endoscopy may be used to resect the tumour in a less invasive and more cost-effective way than laparotomic surgery. In our patient the Brunner's gland adenoma was first seen on upper gastrointestinal endoscopy: biopsies, however, showed normal tissue with only slight changes of inflammation. Endoscopic resection was therefore performed and histology of the resection specimen revealed a Brunner's gland adenoma.

The differential diagnosis of a Brunner's adenoma includes benign tumours of the small intestine such as adenoma of the Islet cells, polypoid adenoma, leiomyoma, lipoma, angioma, aberrant pancreatic tissue, prolapsed pyloric mucosa, duodenal duplication cyst and malignant tumours as adenocarcinoma, lymphoma, carcinoids tumour and leiomyosarcoma.[4,18]

Treatment can be conservative as long as a Brunner's gland adenoma remains asymptomatic. Brunner's gland adenomas are considered a benign disorder. Malignant degeneration has only been described twice in literature.[9,10] No recurrence of a resected Brunner's gland adenoma has been described in literature. Surgical or endoscopic resection is indicated when a patient becomes symptomatic. Endoscopic resection has proven to be a safe and efficacious technique when tumours are pedunculated and still relatively small.[19] In our patient endoscopic snare polypectomy was performed without complications.

CONCLUSION

Brunner's gland adenomas are rare benign tumours of the duodenum. Patients may present with symptoms of bleeding or obstruction. This disorder should be considered when a polypoid duodenal mass is seen. Diagnosis should be confirmed histologically. Endoscopic or surgical resection is indicated for symptomatic patients. When technically possible, endoscopic resection is the treatment of choice.

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CASE REPORT

Intraspinal extramedullary haematopoiesis in a patient with myelofibrosis

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ABSTRACT

A 54-year-old patient with myelofibrosis developed paresis of the legs, and bladder dysfunction due to extramedullary haematopoiesis in the spinal channel. He was given palliative radiotherapy but died shortly afterwards. Although rare, the possibility of extramedullary haematopoiesis in the central nervous system should be considered when neurological symptoms appear in a patient with myelofibrosis, because good palliation is possible with timely radiotherapy.

INTRODUCTION

Myelofibrosis is a chronic myeloproliferative disorder, characterised by a leuco-erythroblastic blood picture and extramedullary haematopoiesis (EMH). EMH rarely involves the central nervous system (CNS). We report a case of myelofibrosis with an intraspinal infiltrate, which resulted in clinically symptomatic spinal cord compression.

CASE REPORT

A 54-year-old man with a ten-year history of myelofibrosis or agnogenic myeloid metaplasia (AMM) presented at the neurology department because of headache, pain in the neck, drowsiness, nausea, vomiting and diarrhoea. Seven years before, he underwent splenectomy because of gastrointestinal complaints and progressive anaemia; however, this had no effect on transfusion requirements. As a consequence of multiple blood transfusions (443 units of

packed cells between August 1993 and April 2000), he developed haemochromatosis with involvement of the liver, skin and CNS. However, he had no diabetes mellitus and no clinical signs of cardiomyopathy. As he was considered ineligible for parenteral desferrioxamine therapy because of his poor condition and severe thrombocytopenia, he was treated with deferiprone (L1), an oral iron chelator.

On admission, physical examination showed stigmata of haemochromatosis such as increased skin pigmentation, testicular atrophy and hepatomegaly. He also had a slight proximal paresis of both legs superimposed on a long-standing hereditary type of distal polyneuropathy. Tendon reflexes were absent and there was marked radiculopathy. The treating clinicians at that time judged that he had end-stage haematological disease and made a clinical diagnosis of subarachnoid haemorrhage caused by thrombocytopenia (5 x 10^9/l). Only palliative measures were taken, they did not even perform a lumbar puncture.

One month later he was readmitted, this time to the medical ward, because of vomiting and impaired bladder emptying. He was icteric, bedridden and slightly disoriented. There was marked hepatomegaly and progression of pre-existing paresis of the left and to a lesser extent the right leg; the left patella reflex was absent. Lymph nodes were not enlarged. Laboratory examination revealed thrombocytopenia (8 x 10^9/l) with a normal leucocyte count (8.9 x 10^9/l) and liver function abnormalities: alkaline phosphatase 66 U/l, LDH 665 U/l, ASAT 176 U/l, ALAT 144 U/l, total bilirubin 39 μmol/l, direct bilirubin 28 μmol/l, and gamma-GT 70 U/l. In the leucocyte

differential cell count, immature myeloid and erythroid elements were found. The ferritin level was strongly increased (7816 µg/l). An ultrasound of the kidneys, bladder and prostate disclosed no abnormalities. Sagittal MRI examination with contrast (Gadolinium) showed three extradural foci of decreased signal intensity at the level of the thoracic spine from Th3 to Th12 (*figure 1*), compatible with EMH.[1] The spinal marrow was compromised from Th5 to Th8 which could well explain the paresis of the legs and the bladder dysfunction. In retrospect, the presumed subarachnoid haemorrhage one month before was probably a manifestation of EMH.

Radiation therapy of the spinal cord from Th2 to Th9 was started in a dose of 8 Gy in two fractions. Three days later, some improvement of strength and motility in the legs occurred and the patient was discharged. He was readmitted again some weeks later because of generalised seizures. CT scan showed hydrocephalus possibly due to intracranial EMH. The patient died shortly afterwards.

At autopsy the liver showed micronodular cirrhosis due to haemochromatosis, with an iron deposition level of 275 mmol/kg (normal <30 mmol/kg). Medullary and extramedullary haematopoiesis were found, with EMH mainly in the meninges at thoracic, cervical and cranial level. Haemosiderin was found in the EMH lesions, indicating intralesional bleedings. This caused a communicating hydrocephalus with ultimately fatal consequences.

DISCUSSION

Primary or idiopathic myelofibrosis is a haematological disorder with an estimated incidence of 0.5-1.5 per 100,000 inhabitants.[2] It is mainly seen from the age of 50 onwards, without preference of sexes, and with a higher incidence in Caucasians. AMM is characterised by clonal proliferation of myeloid precursor cells in bone marrow and extramedullary sites. Fibrosis of the bone marrow is reactive, since the fibroblasts are shown to be polyclonal. The term 'idiopathic'

Figure 1
MRI picture
The figure on the right is a simplified reproduction of the MRI picture on the left. Location of the spinal cord and extramedullary haematopoiesis at the thoracic level is indicated. The spinal cord is clearly compromised at the thoracic level.

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thus seems inaccurate.[3] The production of transforming growth factor β (TGFβ) is increased in AMM, which possibly plays a role in the increase of fibrosing tissue.[4] Fibrosis of bone marrow, however, is also seen in other myeloproliferative diseases as polycythaemia vera and granulomatous infections.[5]

While fibrosis occurs in the bone marrow, EMH can appear in several organs, especially the spleen (80 to 100% at diagnosis) and, particularly after splenectomy, the liver. At the time of diagnosis about 25% of the patients are asymptomatic.[6] Besides poor general condition, patients usually have anaemic symptoms and complaints caused by an enlarged spleen. Characteristic is a leuco-erythroblastic blood picture, teardrop cells, poikilocytosis and prominent megakaryocytic hyperplasia in the bone marrow.

Without treatment a large proportion of the asymptomatic patients remain stable for many years. The mean survival is estimated at 3.5 to 5.5 years (range 1-15 years).[2,6,7] Poor general condition, anaemia, severe cytopenia, circulating blasts, increased amount of granulocytic precursors and cytogenetic abnormalities are associated with short survival. The mean survival in the absence of these symptoms is about ten years, whilst in the presence of two or more of them it decreases to less than three years.[2,7,8] Mortality is mostly caused by infection, bleeding, cardiac failure, post-splenectomy mortality, or progression to acute leukaemia.

Treatment is symptomatic and consists of transfusion of red blood cells and platelets. Hydroxyurea is used when the disease is progressive, as manifested by progressive leucocytosis, thrombocytosis, or organomegaly. Splenectomy can improve symptoms in selected patients with transfusion-dependant anaemia.[2] For patients younger than 55 years with an HLA-identical sibling, allogeneic stem cell transplantation can be considered. Despite the fibrosis, re-population of the marrow and complete haematological remission is possible in 70% of the patients; five-year survival rate is 47%.[9] Because of the high morbidity and mortality, it is difficult to decide when transplantation should be performed.

Extramedullary haematopoiesis
Any of the foetal blood-forming organs may be activated as a compensatory phenomenon in order to combat long-standing anaemia of variable cause, leading to EMH. Compression of the spinal cord due to intraspinal EMH was first described in 1954. Case studies are mostly associated with thalassaemia, while the association with other chronic haemolytic anaemias and rarely myelofibrosis has been described.[5,10-14] A few cases present with rapid progression, as described here. MRI shows a preference for localisation in the middle and lower portion of the thoracic

spine. Some authors related this to the narrow spinal diameter at this level.[15]

MRI is the preferred diagnostic procedure in patients suspected of spinal compression by EMH. Diagnosis can be confirmed by histological or cytological evidence of EMH, but often this can not be performed because of thrombocytopenia. In those cases, a radionuclide scan can be used to detect abnormally localised haematopoietic tissue.[16,17]

Management of spinal marrow compression by EMH is controversial. Usually, low doses of radiotherapy are recommended, with possible significant clinical response.[2,14] Surgical decompression, followed by radiotherapy can result in a complete cure.[12,18,19] Blood transfusions are also given in order to suppress erythropoiesis, with the hope that the EMH mass declines and symptoms diminish. However, its effect is often incomplete and temporary.[12,20]

If the possibility of EMH had been considered when this patient with a longstanding haematological disease presented for the first time with neurological symptoms, more significant palliation could have been attained with timely radiotherapy. Unfortunately, the real origin of his complaints was not initially recognised and precious time was lost.

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CASE REPORT

Diffuse diabetic glomerulosclerosis in a patient with impaired glucose tolerance: report on a patient who later develops diabetes mellitus

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ABSTRACT

Diabetic glomerulosclerosis might be seen in diabetics but its presence in patients with impaired glucose tolerance is quite rare. A 31-year-old woman who was admitted to our department was diagnosed with hypertension, nephrotic syndrome and impaired glucose tolerance. Her renal biopsy was compatible with diabetic glomerulosclerosis. She developed overt diabetes mellitus (DM) after one year of impaired glucose tolerance. Hypertension might have accelerated the progression of diabetic nephropathy.

INTRODUCTION

Diabetic nephropathy can occur during the course of both type 1 and type 2 diabetes mellitus (DM). The characteristic lesions are diffuse or nodular diabetic glomerulosclerosis.[1] However, a few cases of diabetic nephropathy causing nephrotic syndrome have been reported in patients with impaired glucose tolerance (IGT).[2,3] We describe a patient who presented with nephrotic syndrome when her fasting blood glucose level was normal. She was found to have impaired glucose tolerance and her renal biopsy revealed diffuse diabetic glomerulosclerosis. One year later, she developed overt DM and insulin therapy was started.

CASE REPORT

A 31-year-old woman came to our department one year ago with fatigue, swelling of the face and feet, and weight gain. She was a housewife with two previous pregnancies and there had been no abnormalities of the glucose metabolism during the pregnancies. Her medical history was otherwise non-contributory. Her mother was on a chronic haemodialysis programme three times a week but she did not know the cause. The patient neither smoked nor drank alcohol. She denied the usage of any drugs. On admission, her blood pressure was 160/100 mmHg, and pulse rate was 80 beats per minute. Her face was swollen and she had oedema of the lower extremities. Fundoscopy revealed grade I hypertensive retinopathy. Her body mass index was 27.5 kg/m². The physical examination was otherwise normal. The urine was 3+ for protein, and the sediment revealed 2-3 leucocytes and granular cylinders. Creatinine clearance and the protein excretion in 24 hours were 104 ml/min and 5.6 g/day, respectively. Other laboratory data were as follows: glucose, 93 mg/dl; urea, 32 mg/dl; creatinine, 0.8 mg/dl; uric acid, 6.5 mg/dl; total protein, 7.1 g/dl; albumin, 4.4 g/dl; total cholesterol, 246 mg/dl; and triglyceride, 313 mg/dl. Whole blood count, erythrocyte sedimentation rate, C-reactive protein and HbA_{1c} were normal. Serum protein and immunoelectrophoresis as well as immunoglobulin quantitations were also normal. HBsAg, anti-HBs (total), anti-HCV, anti-HIV, VDRL, p-ANCA, c-ANCA and cryoglobulins were negative. C3 and C4 complement, RF, FANA, and anti-dsDNA were all in normal ranges. The patient's chest X-ray and electrocardiography were normal. Renal ultrasound demonstrated kidneys with normal sizes and echogenicity.

The patient was diagnosed as having hypertension and nephrotic syndrome and she underwent a renal biopsy. Light microscopic examination demonstrated thickening of the glomerular capillary basement membranes with expan-

sion of the mesangial area and hyalinosis of some afferent and efferent arterioles (*figure 1*). No amyloid accumulation was seen with Congo red staining. Immunofluorescence did not show anything significant. Electron microscopy was not performed. The renal biopsy findings were compatible with diffuse diabetic glomerulosclerosis and a 75-gram oral glucose tolerance test was performed. It revealed a fasting plasma glucose concentration of 91 mg/dl; the first and the second hour plasma glucose concentrations were 205 mg/dl and 177 mg/dl, respectively. These results indicated IGT in the patient. Insulin and C-peptide levels were normal. Islet-cell antibody (ICA), insulin autoantibody (IAA) and antiglutamate decarboxylase (GAD) were negative. She was prescribed a diet and an ACE inhibitor plus diuretic combination and was discharged from hospital. The patient was followed up every two months, and all her laboratory values were within normal limits. On her sixth follow-up visit, the fasting glucose was 187 mg/dl; urea 35 mg/dl; creatinine 1.1 mg/dl; HbA_{1c} 7.2%; creatinine clearance 80 ml/min; and protein excretion in 24 hours 1.5 g/day. The repeated fasting glucose measurement was 216 mg/dl. The patient was accepted as having overt type 2 DM after a period of IGT and she was put on insulin therapy.
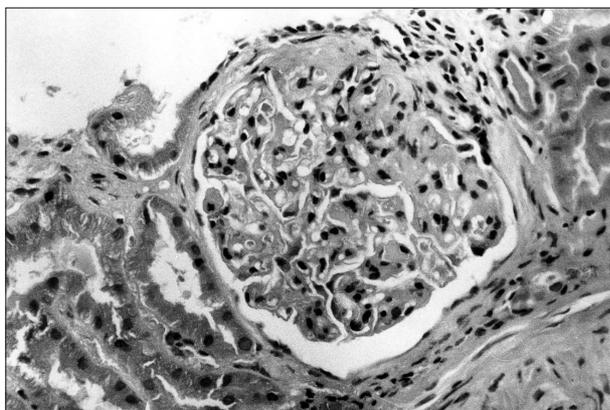

Figure 1
One glomerulus with mildly thickened capillary basal membrane, minimally increased cellularity, segmentally increased mesangial matrix, focal hyalinisation and adherence to the Bowman capsule (HE x 400)

DISCUSSION

The characteristic renal lesion in DM is nodular or diffuse glomerulosclerosis. Diffuse lesions and thickening of the glomerular basement membrane are almost always seen in diabetics with more than 15 years of disease.[1] Our patient did not have a prior diagnosis of DM or any other systemic disease which could be responsible for the nephropathy. Her mother had chronic renal failure of an unknown aetiology and this might raise the question of whether the patient had any kind of hereditary nephropathy, which might be responsible for the impaired glucose metabolism. However, her renal biopsy revealed diffuse glomerulosclerosis, which might indicate an association with DM. Also, the IGT diagnosed soon after renal biopsy made us consider a causal relationship between IGT and nephropathy. In addition, the normal creatinine clearance helped us to exclude any derangement in glucose metabolism secondary to impairment of renal function.

Until now, only two cases of diabetic glomerulosclerosis secondary to IGT have been reported in the literature.[2,3] Only one of them had retinopathy.[2] Our patient had no retinopathy nor any signs of nephropathy on ultrasonography suggestive of longstanding DM. Also, Chan *et al.*[4] reported on a patient with normal oral glucose tolerance who had proliferative retinopathy and hypertension, and whose renal biopsy revealed nodular and diffuse glomerulosclerosis. However, according to current criteria, that patient would be classified as having IGT.

There are studies which say that microalbuminuria and macroalbuminuria are increased in patients with IGT in the way as in diabetics.[5-7] Hotta *et al.*[6] found an increased excretion of urinary albumin in both IGT and DM patients. Collins *et al.*[5] reported a statistically significant increased number of IGT patients with microalbuminuria (33.1%) compared with non-diabetic controls (20.9%). The percentages for macroalbuminuria were 9.7% *versus* 5.4%, respectively, which was not significantly different. Likewise, in the study by Fujimoto *et al.*[8] urinary protein excretion was found to be increased in diabetics, but the urinary protein excretion in IGT patients was similar to controls.

In the study conducted by Collins *et al.*[5] in the population of Nauru, fasting blood glucose and hypertension were found to be the factors most closely associated with urinary albumin excretion. It has been reported that subjects with IGT have significantly higher blood pressure measurements than normal individuals.[9] Both IGT and elevated systolic blood pressure might increase glomerular haemodynamics, leading to glomerular hyperperfusion. This will impair autoregulation and increase urinary albumin excretion.[6,10] In this case, the patient had obviously had hypertension for some years before coming to our attention. So, in addition to IGT, which was responsible for the development of diabetic nephropathy, uncontrolled hypertension might have accelerated the progression of nephropathy in this case. Furthermore, GH and IGF-1, which have been shown to play important roles in the pathogenesis of early diabetic nephropathy, might have been associated with the renal abnormalities in our case.[11,12]

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There is evidence based on follow-up of patients and familial studies that some diabetic subjects have a genetic tendency to both the development and progression of diabetic nephropathy.[13,14] The young age of the patient rises the question whether she had one of the genetically determined diabetic subtypes (formerly MODY types), which might increase the tendency to develop nephropathy earlier. MODY has autosomal dominant inheritance and is linked to some genes, the most important of which are the glucokinase gene and the adenosine deaminase gene.[15,16] Unfortunately, we did not have the chance to search for these genetic abnormalities in our patient.

We are reporting this case because it is exceptionally rare. Even in patients with normal blood glucose levels and microalbuminuria or macroalbuminuria, a 75-gram oral glucose test must be undertaken. Patients with IGT or DM should be advised about an appropriate diet, physical exercise and medical therapy. Additionally, hypertension should be treated effectively and monitored closely, especially in patients with IGT or DM, because well-controlled arterial pressure might inhibit the progression of nephropathy.

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LETTER TO THE EDITOR

Tumour lysis syndrome in myeloma

With interest I read the article by J.J. van de Kerkhof, W.G. Peters, J. Visser and G.J. Creemers entitled 'acute tumor lysis syndrome in a patient with multiple myeloma treated with dexamethasone monotherapy', which was published in The Netherlands Journal of Medicine 2001;59:83-5. The authors draw attention to the clinical risk of acute tumour lysis syndrome in patients with multiple myeloma who are treated with steroids.

While the authors mention the rare occurrence of acute tumour lysis syndrome in multiple myeloma, they do not provide an explanation why this patient developed this serious clinical complication. Based on the described pathology, it appears that the diagnosis in this patient was not multiple myeloma. The presence of plasmablasts, organ infiltration, loss of the M protein and a high serum LDH suggests a transformation to an immature plasmablastic phenotype.
Acute tumour lysis syndrome is rarely observed in multiple myeloma. The incidence is probably less than 1% of patients treated with intermediate or high-dose chemotherapy. It is only occasionally observed with dexamethasone or prednisone treatment, which is often included in various treatment regimens for multiple myeloma.
This is in sharp contrast with the high incidence of acute tumour lysis syndrome in malignant lymphomas and acute lymphoblastic leukaemia. A possible explanation for this difference is the fact that multiple myeloma cells reside in the bone marrow and are dependent on the microenvironment for their proliferation and growth. In multiple myeloma, the interaction between tumour cells and bone marrow stromal cells triggers the production of cytokines, such as interleukin 6, mediating autocrine and paracrine growth and survival of multiple myeloma cells. Dexamethasone induces apoptosis of B cells, including monoclonal lymphoma cells and acute lymphoblastic leukaemia cells. However, in multiple myeloma the dexamethasone-induced apoptosis is abrogated by interleukin 6. Thus, in multiple myeloma the malignant plasma cells are restricted to the bone marrow and depend for their growth on interleukin 6 and adhesion molecules, which bind them to the bone marrow stroma. Consequently, the dexamethasone-induced response will be of short duration because of the antagonistic effect of interleukin 6 and therefore extensive tumour lysis rarely occurs. This situation may change when de-differentiation of multiple myeloma occurs as is occasionally seen at relapse or rapid progression of the disease. In such cases, the plasmablastic nature of the malignant cells is associated with a dramatic loss of adhesion molecules such as syndecan, VLA-4 and VLA-5. This de-differentiation results in an abrogation of the bone marrow microenvironment and of the interleukin 6 mediated antiapoptotic effect. The plasmablasts are no longer restricted to the bone marrow microenvironment and they disseminate in the body. In such patients, dexamethasone treatment will induce extensive cell loss and eventually result in acute tumour lysis syndrome. It is important to realise that dexamethasone-induced tumour lysis syndrome will not be routinely observed in multiple myeloma patients, unless the de-differentiation and plasmablastic appearance outside the bone marrow microenvironment imposes a higher risk of this grave clinical complication. Since dexamethasone treatment is a highly effective and often the only possible palliative therapy in patients with refractory multiple myeloma, its use should not be prohibited by the low risk of a tumour lysis syndrome. Recently, thalidomide has become available for the treatment of refractory patients and this agent has a synergistic effect with dexamethasone in approximately 30% of the patients. This development creates new opportunities for the use of dexamethasone in refractory myeloma patients.

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The author of the article, J.J. van de Kerkhof, preferred not to respond.
The editors
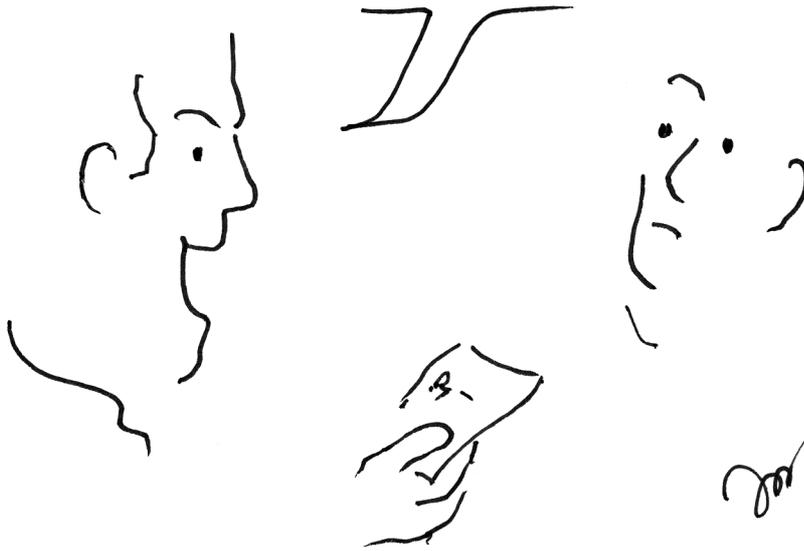
Primary and secondary preventive nutrition

Edited by: A. Bendlich and R.J. Deckelbaum
Publisher: Humana Press Inc. Totowa, New Jersey, USA

Primary and secondary preventive nutrition is the last of seven volumes in a series on Nutrition and Health that has already included three volumes on primary prevention. The present volume, however, not only considers the role of diet, dietary factors and nutrients in primordial and primary prevention to optimise health and reduce the risks of food-related and preventable diseases, but also deals with nutritional strategies to improve and treat pre-existing conditions.

The main topics are cancer, cardiovascular disease, type 2 diabetes mellitus, obesity, and bone disease. Especially the chapters on cancer (3), artherosclerosis and diabetes (4), and bone disease (2) are well designed, addressing the role of nutrients in primary and subsequently in secondary prevention. The five chapters on obesity are a hotchpotch. The pathophysiology is restricted to a discussion focusing mainly on genetics and environmental influences, without referring to diseases contributing to overweight, the complex network of gastrointestinal and brain hormones, neurotransmitters and their role in satiety, satiation and food intake, and psychological and behavioural factors. Data on cardiovascular disease and diabetes related to children are not discussed in the respective chapters but in the chapter on obesity and childhood. Many facts are out of date and most of the references go back to 1998-1999.

The second part of the book is a mix of very divergent and incoherent themes. A chapter on growth, immunity and infection discusses infant growth and the importance of long polyunsaturated fatty acids, vitamin A-related blindness and autoimmune diseases such as rheumatoid arthritis and psoriasis, but also IgA nephropathy, Crohn's disease and ulcerative colitis.

The last part deals with critical issues for the 21st century such as preventive nutrition in different ethnic and socioeconomic groups, touching on the typically American situation without giving a global view. It also contains chapters on micronutrient deficiencies, alcohol consumption and preventive nutrition through the lifecycle. Health claims and ways to improve the incorporation of preventive nutrition in the medical school curriculum together with a list of nutrition-related books and websites conclude the volume.

Inherent to the concept, some chapters are really outstanding, for instance the epidemiological research on vitamin supplements and cancer risk with a summary of all the literature up till 1999, including a clear graphic presentation of odds ratios and their 95% confidence intervals for each vitamin. Impossible to read is the chapter on antioxidant vitamins and atherosclerosis, mainly because of a summing up of figures without any graphic presentation. Even worse is the use of many abbreviations in this as well as in many other chapters that detracts most from the value of the book. It makes the chapter hard to read as no uniform way is used to abbreviate words and a list of abbreviations is not given. Moreover, if one looks up a word in the Index, the relevant passage in the text is incomprehensible with abbreviations, such as ME (Medical Education), M&M (mortality and morbidity) and athsc (atherosclerosis). Also, many of the references to previous or following chapters are incorrect.
All in all, this is not an easily accessible reference book and not to be recommended.

E.M.H. Mathus-Vliegen
Amsterdam, the Netherlands

Lithographic art

Karin Elfrink

This month's cover shows lithographic art by Karin Elfrink. Karin works in Nijmegen, the Netherlands. She has been exhibiting her work at numerous individual and group exhibitions in the Netherlands (such as the Municipal Museum in Arnhem, BV Staal in Venlo, Aemstelle Museum in Amstelveen, Arti et industriae and 'Vliegers' in The Hague, Kunsthuis 13 and Klas Vijf in Velp, Huntenkunst Art Exhibition in Doetinchem and Galerie de Pol in Pannerden) and abroad (including International Art Forum in Barcelona/Spain and Kunstpreis 1999 in Moers/Germany).

Urban architecture is an important theme in her paintings and graphic art.
Her work is about the experience of space created by people, so space in cities, space for living, space that is transient. Such space has ever-present boundaries that kindle curiosity. Human beings are invisibly present here.
A limited edition of originals prints (size 28.5 x 37 cm) of this month's cover is available at a price of € 200. You can order the print at Galerie Unita, Rijksstraatweg 109, 6573CK Beek-Ubbergen, the Netherlands or by e-mail: galerie-unita@planet.nl.

Aims and scope

The Netherlands Journal of Medicine publishes papers in all relevant fields of internal medicine. In addition to reports of original clinical and experimental studies, reviews on topics of interest or importance, case reports, book reviews and letters to the Editor are welcomed.

Manuscripts

Manuscripts submitted to the Journal should report original research not previously published or being considered for publication elsewhere. Submission of a manuscript to this Journal gives the publisher the right to publish the paper if it is accepted. Manuscripts may be edited to improve clarity and expression.

Language

The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

Preparation of manuscripts

Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process number the pages; also we would appreciate seeing the line numbers in the margin (Word: page set-up - margins - layout - line numbers). Divide the manuscript into the following sections: Title page, Abstract, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

A *Covering letter* should accompany the manuscript, identifying the person (with the address, telephone and telex numbers, and e-mail address) responsible for negotiations concerning the manuscript: the letter should make it clear that the final manuscript has been seen and approved by all authors. Conflicts of interest, any commercial affiliations, consultations, stock or equity interests should be specified. In the letter 1-3 sentences should be dedicated to what this study adds. All authors should sign the letter.

The *Title page* should include authors' names, degrees, academic addresses, address for correspondence including telephone, fax and e-mail, and grant support. Also the contribution of each author should be specified.
The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than

50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

Abbreviations: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for proprietary names of substances and materials. At first mention of a chemical substance, use the correct chemical designation as well as the generic name.

The *Abstract*, not exceeding 200 words, should be written in a structured manner and with particular care, since this will be the only part of the article studied by some readers. In original articles, the abstract should consist of four paragraphs, labelled Background, Methods, Results, and Conclusions. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

The *Introduction* should be brief and set out the purposes for which the study has been performed.

The *Materials and methods* should be sufficiently detailed so that readers and reviewers can understand precisely what has been done without studying the references directly. The description may be abbreviated when well-accepted techniques are used.

The *Results* should be presented precisely without discussion.

The *Discussion* should directly relate to the study being reported. Do not include a general review of the topic, but discuss the pertinent literature.

Acknowledgement: All finding sources should be credited here. Also a statement of conflicts of interest should be put here.

References should be numbered consecutively (in square brackets) as they appear in the text. Type the reference list with double spacing on a separate sheet. References should accord with the system used in Uniform requirements for manuscripts submitted to biomedical journals (N Engl J Med 1991;324:424-8).

Examples:

[1.] Smilde TJ, Wissen S van, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184-95.

[2.] Kaplan NM. Clinical Hypertension. 7th Edition. Baltimore: Williams & Wilkins; 1998.

[3.] Powell LW, Isselbacher KJ. Hemochromatosis. In: Harrison's Principles of Internal Medicine, 15th Edition, Braunwald E, Fauci AS, Kasper DL, et al. (eds). New York: McGraw-Hill; 2001. p. 2257-61.

Please note that the first six authors should be listed; when seven or more, list only the first three and add *et al.* Do not include references to personal communications, unpublished data or manuscripts either 'in preparation' or 'submitted for publication'. If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against reference list after your manuscript has been revised.

Tables should be typed with double spacing each on a separate sheet, numbered consecutively with Arabic numerals, and should contain only horizontal lines. Provide a short descriptive heading above each table with footnotes and/or explanation underneath.

Figures must be suitable for high-quality reproduction. Submit line drawings made in Word or other computer programmes but not in a PowerPoint file. India ink drawings or sharp, strongly contrasting photographic prints on glossy paper are also acceptable. Lettering should be complete, of professional quality, and of a size appropriate to that of the illustration of drawing, with the necessary reduction in size taken into account. Figures should be no larger than 12.5 x 18 cm. Submit half-tone illustrations as black-and-white prints on glossy paper, with as much contrast as possible. Identify each figure on the back with a typed label, which shows the number of the figure, the name of the leading author, the title of the manuscript and the topside of the figure. Colour figures are occasionally possible and will be charged to the authors.
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Brief reports containing concise reports on original work will be considered for publication. Case reports which are relevant for understanding the pathophysiology or clinical presentation of disease may also be accepted under this heading. Articles published in this section should be no longer than 1000 words, and be supplied with a summary of about 60 words, preferably no more than two figures and/or tables, and no more than 15 references.

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Letters to the editor referring to articles previously published in the journal will be considered by the editors; letters should be no more than 500 words and sent both on disk or e-mail and in hard copy.

Submission

Manuscripts should be sent to the Editor in chief, Prof. J.W.M. van der Meer, University Medical Centre St Radboud, Department of General Internal Medicine, PO Box 9101, 6500 HB Nijmegen, the Netherlands, tel.: +31 (0)24-361 04 59, e-mail: g.derksen@aig.azn.nl. They should be submitted in four complete copies, which include four sets of the figures; authors should retain one copy of the manuscript. Rejected manuscripts will not be returned to the author unless specially requested at the time of submission.

Reviewing process

After external and editorial review of the manuscript, the authors will be informed about acceptance, rejections or revision. Unless stated otherwise in our letter, we require revision within three months.

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After acceptance we prefer electronic submission of text and figures, either by e-mail to g.derksen@aig.azn.nl or on floppy disk. A disk plus two final and exactly matching printed versions should be submitted together. It is important that the file saved is in the native format of 'Word' or any other computer programme used. Label the disk with the name of computer programme used, your name, and the name of the file on the disk.

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