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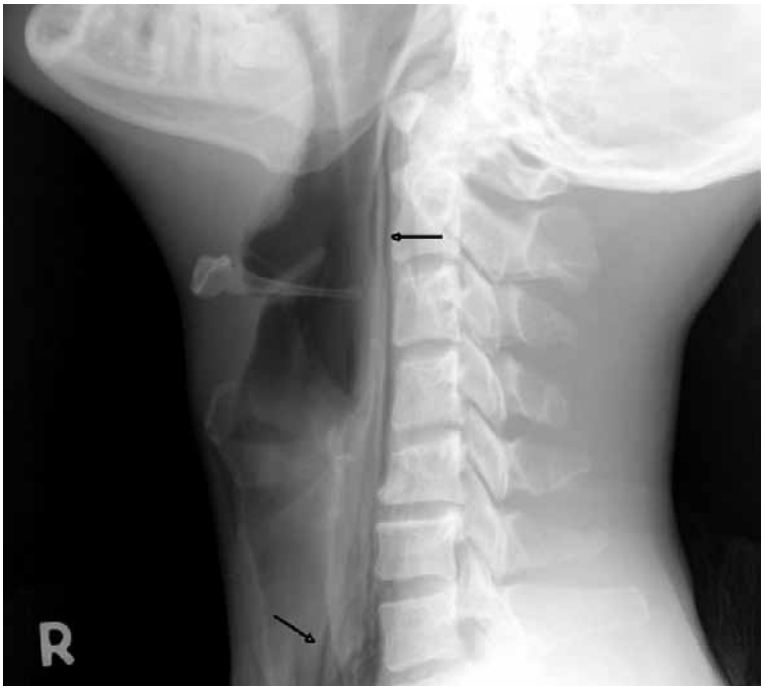

Sore throat after dumbbell exercise: What is your diagnosis?

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EDITORIAL

Quicker, faster, better?

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It may happen any day in a hectic department of emergency care. Critically ill patients with, for example, sepsis, respiratory insufficiency, heart failure and gastrointestinal bleeding present simultaneously to the residents and staff of the Department of Internal Medicine. The nurses on the emergency department are busy arranging diagnostic procedures and the initial care of these patients. Suddenly, the trauma alarm rings, announcing the arrival of a traffic accident victim in ten minutes. All the nurses and staff on the emergency department immediately drop whatever they were doing and start preparing for the arrival of the unfortunate victim of the car collision, correctly according to preset protocols that precisely dictate the immediate and highly organised management of trauma patients, since it has been well established that early and immediate intervention leads to a better outcome in these patients. When the traffic accident patient arrives, it appears that she is totally stable and although being unfortunate enough to present with a humerus fracture as a consequence of the car collision, there are no other injuries. In the mean time, the patients who had presented with sepsis, respiratory insufficiency, heart failure, and gastrointestinal bleeding had been left unattended.

Obviously, this anecdote does not serve to disqualify the adequate and immediate attention that is given to trauma patients. However, it is rather strange that we have not implemented similar protocols for medical patients who present with potentially life-threatening conditions. In fact, it is time that we as internists intensify our work on better systems for rapid identification and more immediate treatment of patients with severe medical conditions who arrive in our departments of emergency care. Patients with severe medical conditions, with (potentially) threatened vital parameters, need the best medical care they can get and initial treatment without any delay. In fact, the traditional medical work-up of history-taking, physical examination, (differential) diagnosis and laboratory testing and/or imaging may not be appropriate for the acutely ill medical patient. Immediate safeguarding of vital signs and initiation of important treatment of the most probable diagnoses, even before they are confirmed by traditional means, may require a shift in our current thinking and our usual way of working with these patients. This paradigm has long been recognised by traumatologists, leading to the uniform and successful implementation of advanced life support protocols (ATLS). However, this has only recently been adopted by some major medical institutions for medical patients, for example by practising and teaching the 'MedicALS' for acutely ill medical patients.

Immediate management of critically ill patients means that we should be able to recognise these patients, which requires adequate training of our residents.[1] There are many strategies available that are helpful in identifying these patients, as has also been published in this Journal,[2,3] and we should consider implementing these measures in our daily practice. In addition, we should be willing to start treatment even before we have definitively established the diagnosis. Some people will argue that this may lead to 'overtreatment' and, for example, administration of pharmaceutical agents to patients who turn out not to need them. However, the potential 'risk' of this strategy is not always very high and should be balanced against the risk of delaying treatment to patients who really need it. There is sufficient evidence from various areas in acute medicine that supports the idea of immediate treatment ameliorating the eventual clinical outcome. The concept of door-to-needle time (or recently door-to-balloon time) directly comes from the treatment of patients with acute myocardial infarction and has repeatedly been shown to significantly improve the outcome in individual patients.[4] Similarly, and to the surprise of many hospital doctors, we now also see neurologists running through the corridors of the hospital to administer thrombolytics to stroke patients as rapidly as they can.[5]

Also for patients with infections, it has repeatedly been shown that the sooner the first dose of antibiotics is administered, the better the outcome, for example in terms of morbidity and duration of hospital stay. In addition, rapid onset of antibiotic treatment was shown to independently reduce in-hospital and 30-day mortality

in three very large retrospective Medicare studies in 297 US hospitals, 14,069 hospitalised pneumonia patients and 18,209 in-patients aged ≥65 years, respectively, even after correction for disease severity and comorbidity.[6] The advantage of early administration of antibiotics has been shown in numerous studies regardless of the type of infection and was confirmed in patients with sepsis, pneumonia, meningitis, or urinary tract infections.[7-10] Also Dutch studies have shown the appropriateness of rapid antibiotic treatment in patients who present in the emergency department and ways to implement this practice.[11]

In this issue of the *Netherlands Journal of Medicine*, van Tuijn *et al*. present the evaluation of various implementation strategies to improve the door-to-needle time (i.e. the time between arrival to the emergency department and the first dose of antibiotics) in patients with various types of severe infections.[12] Having sufficient doctors present in the emergency department at peak hours, not waiting for extensive laboratory analyses before initiating treatment, and administration of the first dose of antibiotics in the emergency department and not on the ward all shortened the door-to-needle time in their patients. The authors were also able to show that their combined interventions significantly reduced the duration of hospital stay by 17%.

Although intuitively logical, it is not totally clear why rapid administration of the first dose of antibiotics is so important. Hypothetically, each patient with an infection has a unique point in their disease course after which the potential of antibiotics to rapidly and advantageously change the course and outcome of the infection and even prevent death is lost. It is estimated that on average four to eight hours after arrival would represent the average of those points over thousands of cases.[6]

Rapid initiation of antibiotic treatment is just one example of appropriate caring for critically ill medical patients who present at the emergency department. For integral improvement of the care in these patients, adequate education of residents and staff is required and up-to-date and practical protocols are needed as well. In the Netherlands, all teaching hospitals have contributed to national guidelines for the emergency treatment of patients with more than 100 medical conditions, which have now been published by the Netherlands Association of Internal Medicine (NIV) in the form of a small booklet and will soon be available for hospital websites and personal digital assistants. We will have to work very hard to improve the care of acutely presenting patients with severe medical illness and follow the example of traumatologists, cardiologists and other specialists who have developed systems to appropriately deliver immediate care to their patients and thereby improve their outcome. The broadness of internal medicine and the complexity of the presentation of some patients with acute medical illness should thereby not be viewed as an impediment but rather as a challenge for our profession and as a great opportunity to further improve the quality of our care.

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REVIEW

Update in prolactinomas

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ABSTRACT

Prolactinomas are a frequent cause of gonadal dysfunction and infertility, especially in women. Dopamine agonists are first-line therapy and their efficacy in the treatment of prolactinomas is well established. Current challenges related to the management of prolactinomas remain in the recurrence of the disease after withdrawal of dopamine agonists, the potential of increased risk of cardiac valvulopathy, which is observed in patients treated with high-dose cabergoline for Parkinson's disease, the effects of pregnancy, and impaired quality of life associated with pituitary adenomas in general, and prolactinomas in particular. Although most prolactinomas are biochemically well controlled by pharmaceutical treatment, long-term follow-up is required.

KEYWORDS

Prolactinomas, dopamine agonist, valvulopathy

PROLACTIN AND CAUSES OF HYPERPROLACTINAEMIA

Prolactinomas are adenomas derived from lactotroph cells in the pituitary gland, and are characterised by hypersecretion of prolactin. Unlike the other anterior pituitary hormones, the hypothalamic control of prolactin production and release is mediated by tonic inhibition by dopamine.[1] Normal prolactin concentrations in women and men are, depending of the assay used, below 25 µg/l and 20 µg/l, respectively.[2] Prolactin is not exclusively produced by the lactotroph cells in the pituitary gland. The largest portion of prolactin is produced outside the pituitary gland (extrapituitary prolactin), including hair follicles, adipose tissue and immune cells. Prolactin may act as a hormone, by the classic endocrine pathway, and as a growth factor, neurotransmitter, or immunoregulator, by autocrine or paracrine mechanisms. The primary action of prolactin is stimulation of lactation after delivery.

Hyperprolactinaemia can be caused by physiological processes, pharmacological effects, and pathological effects. Physiological causes of hyperprolactinaemia include pregnancy, physical or psychological stress, and breast stimulation. Drugs that stimulate dopamine receptors on lactotroph cells (e.g. metoclopramide, phenothiazides) or those that inhibit dopamine release from the hypothalamus (e.g. monoamine oxidase inhibitors, tricyclic antidepressants, serotonin re-uptake inhibitors), induce hyperprolactinaemia. In general, drug-induced hyperprolactinaemia is relatively mild with plasma prolactin concentrations up to 100 µg/l.[3] Hyperprolactinaemia can be caused by prolactinomas. Compression of the pituitary stalk due to suprasellar extension of craniopharyngioma, meningeoma, nonfunctioning macroadenomas, or severe head trauma can disrupt dopamine transport to the pituitary, and result in hyperprolactinaemia. Furthermore, primary hypothyroidism can cause hyperprolactinaemia due to increased synthesis of thyrotropin-releasing hormone, stimulating prolactin secretion. Other conditions associated with increased circulating prolactin concentrations are chronic renal failure and liver cirrhosis.

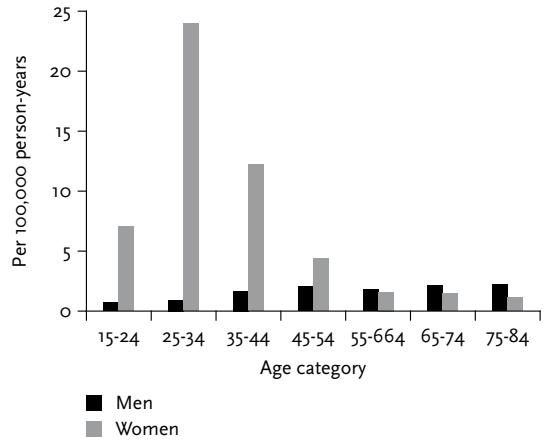
High concentrations of prolactin can also be explained by macroprolactinaemia. This refers to the presence of elevated concentrations of prolactin of high molecular mass, mostly due to complexes of monomeric prolactin with immunoglobulins (prolactin-autoantibody complexes). These larger molecules have no bioactivity and prolonged clearance

rate similar to that of immunoglobulins. Depending on the immunoassay used, macroprolactinaemia accounts for up to 25% of biochemically documented hyperprolactinaemia.[4] This indicates that macroprolactinaemia represents a common diagnostic pitfall. Consequently, in the initial diagnostic phase of hyperprolactinaemia, especially in the absence of symptoms (e.g. in the presence of normal menstrual cycles), sera should routinely be treated with polyethylene glycerol (PEG) to exclude the presence of macroprolactinaemia. In case of macroprolactinaemia, the prolactin concentrations will decrease to normal after PEG precipitation.

EPIDEMIOLOGY OF PROLACTINOMAS

Prolactinomas are the most frequent pituitary adenomas, and account for approximately 40% of all pituitary adenomas, with an estimated prevalence of 60 to 100 per million inhabitants.[5] Recently, higher prevalence rates of 44 to 62 per 100,000 inhabitants have been reported.[6,7] We recently estimated the gender-specific prevalence in a large population-based Dutch cohort.[8] The prevalence of dopamine agonist-treated prolactinomas in female patients was almost five times higher (94 per 100,000) compared with male patients (20 per 100,000). Estimated incidence rate of dopamine agonist-treated prolactinoma was 8.7 per 100,000 person-years for women and 1.4 per 100,000 for men. The highest incidence rate was found in women between 25 and 34 years of age: 23.9 per 100,000 person-years (*figure 1*). A possible explanation for this higher prevalence of prolactinomas in premenopausal women is the higher likelihood of diagnosing hyperprolactinaemia in women of reproductive age because it presents with symptoms such as oligo/amenorrhoea and infertility. In contrast, in men symptoms are more subtle and/or even nonexistent, except when the tumour size causes signs of pituitary gland enlargement, such as headache and visual field defects. Whereas women present with microprolactinomas in the majority of cases, most men present with macroprolactinomas. This difference is probably caused by the subtle clinical symptoms in men in the early course of the disease.

Figure 1. *Incidence of patients with dopamine agonist (DA)-treated hyperprolactinaemia per 10 year age category for men and women from 1996 until 2006*



***Adapted from Kars M. et al. Estimated Age- and Sex-Specific Incidence and Prevalence of Dopamine Agonist-Treated Hyperprolactinemia. J Clin Endocrinol Metabol. 2009 Aug; 94(8):2729-34. Copyright 2009, The Endocrine Society.**

PATHOGENESIS OF PROLACTINOMAS

Hypotheses concerning the pathogenesis of prolactinomas include decreased stimulation by dopamine (dopaminergic receptor or postreceptor dysregulation) and clonal somatic mutations.[1] There are several arguments against the first hypothesis. First, decreased dopamine delivery to the pituitary due to long-term use of neuroleptic drugs or pituitary stalk compression does not induce prolactinomas. Second, most adenomas are only confined to a certain portion of the pituitary gland rather than characterised by widespread hyperplasia of prolactin producing pituitary cells. Third, after initial cure of the adenoma, e.g. by surgery, there is a low recurrence rate of adenoma. The local mutation hypothesis is based on X-chromosomal inactivation analysis, showing that almost all human pituitary adenomas are monoclonal.[1] However, specific mutations underlying prolactinomas remain to be established, with the exception of genetic syndromes such as MEN 1 syndrome, which is also associated with an increased prevalence of prolactinomas.

CLINICAL PRESENTATION OF PROLACTINOMAS

Prolactinomas cause gonadal and sexual dysfunction related to hyperprolactinaemia, and symptoms related to tumour expansion. Hyperprolactinaemia causes hypogonadotropic hypogonadism in both men and women due to inhibitory effect of increased prolactin concentrations on hypothalamic gonadotropin-releasing hormone (GnRH) release. Consequently, the most common symptoms of hyperprolactinaemia in premenopausal women are amenorrhoea and galactorrhoea. Amenorrhoea is often detected after discontinuation of the use of oral contraceptives (post-pill amenorrhea) or after pregnancy. In men, the symptoms are impotence, decreased libido and decreased beard growth. Unlike in women, gynaecomastia and galactorrhoea are uncommon in men. In some cases, prolactinomas are found as incidentalomas.[9,10]

Prolactinomas are classified according to their diameter in microprolactinomas (<10 mm in diameter), macroprolactinomas (≥10 mm in diameter), and giant prolactinomas (>40 mm in diameter).

Macroprolactinomas typically present with prolactin concentrations that exceed 200 µg/l and symptoms related to tumour expansion, such as headache, visual disturbances, and/or cranial nerve dysfunction. A discrepancy between a large pituitary adenoma and only mildly elevated prolactin concentrations may be due to either pituitary stalk compression by suprasellar extension of a nonfunctioning macroadenoma or a 'high-dose hook effect' of the assay for prolactin. This analytical artefact causes falsely low prolactin determination due to insufficient antibody-prolactin binding in the immunoassay. The correct prolactin concentration will be obtained after appropriate dilution of the serum. Underestimation of actual prolactin concentrations may lead to the erroneous diagnosis of a nonfunctioning macroadenoma instead of a macroprolactinoma. This distinction is of major clinical relevance because a nonfunctioning macroadenoma with visual field defects requires transsphenoidal surgery, whereas the primary treatment of a macroprolactinoma is a dopamine agonist. Therefore, in case of a macroadenoma with only mildly elevated prolactin concentrations, serial dilution of the serum samples should be performed to exclude the presence of this high-dose hook effect of the prolactin assay.

At presentation, patients with microprolactinomas do not have pituitary deficiencies, except for suppressed gonadotrophin concentrations, or visual field defects.[11,12] In patients with macroprolactinomas, hypopituitarism, other than hypogonadism, is present in ~45% of the patients.[11-14] Suprasellar extension of the adenoma often compresses the optic chiasm and classically results in bitemporal hemianopia and diminished visual acuity. Visual field defects are present in ~35% of the patients with macroprolactinomas.[11-13,15,16] In accordance with the higher prevalence of hypopituitarism in men, visual field defects are slightly more prevalent in men compared with women.[11]

TREATMENT OF PROLACTINOMAS

The therapy of prolactinomas is aimed at: 1) reduction of prolactin concentrations and its clinical consequences, such as gonadal dysfunction, infertility, and osteoporosis; 2) reduction of tumour mass, thereby relieving visual field defects and hypopituitarism; 3) preservation of residual pituitary function; 4) prevention of continuing growth of tumour mass, and 5) improvement of quality of life. Treatment goals are similar for micro- and macroprolactinomas, although in the case of macroprolactinomas more emphasis of the therapy is focussed on control of tumour size.

Medical treatment of prolactinomas

Medical therapy with dopamine agonists is the initial treatment of choice in all prolactinomas. These drugs inhibit prolactin secretion and reduce tumour volume. The most commonly used dopamine agonists are the ergot-derived dopamine agonists bromocriptine and cabergoline, and the non-ergot derived dopamine agonist quinagolide. Dopamine agonists have a wide spectrum of pharmacological actions at different receptor sites.[17] Therefore, it is not surprising that these drugs display a number of side effects. Dopamine inhibits prolactin secretion through D2 dopamine receptors, expressed by both normal and tumorus pituitary lactotrophs.

Almost 35 years ago, bromocriptine was introduced into clinical practice as the first medical treatment for prolactinomas.[18] It has a relatively short elimination half-life and dosages range from 2.5 to 15 mg, three times daily. For microprolactinomas, bromocriptine normalises prolactin concentrations, restores gonadal function, and induces tumour shrinkage in 60 to 80% of the patients.[13,19,20] For macroprolactinomas, bromocriptine is effective in only 50 to 70% of patients.[13,21,22] Disadvantages of bromocriptine treatment are the frequent occurrence of side effects, leading to interruption of therapy in 12% of the patients.[19,23] Tumour regrowth after discontinuation has been reported, although data on this issue are scarce.[24]

The non-ergot-derived dopamine agonist quinagolide has a longer half-life and is taken only once daily. It is effective in normalisation of prolactin concentrations (in 70 to 100% of the patients with microprolactinomas, and in 67 to 88% of the patients with macroprolactinomas), fertility, and to induce tumour shrinkage (in 55% of the patients with microprolactinomas, and in 75% of the patients with macroprolactinomas).[25-31] Therefore, quinagolide seems to be slightly more effective than bromocriptine, and it is associated with less side effects than bromocriptine.[25,27]

At present, cabergoline is the preferred dopamine agonist in the treatment of prolactinomas. Cabergoline is a potent agonist of the D2 dopamine receptor, and, in general, the mean starting dose is 0.25 to 0.5 mg twice a week. In microprolactinomas, the average dose is 0.5 mg/week, and in macroprolactinomas 1 mg/week. Several studies have demonstrated the efficacy of cabergoline in normalising prolactin concentrations, and in inducing tumour shrinkage, especially in microprolactinomas. Normalisation of prolactin concentrations are achieved in 75 to 90% of the patients with micro- or macroprolactinomas, and an average decrease in tumour volume of 72 to 92% is reported.[12,15,16,19,32,33] Even in patients with resistance to other dopamine agonists, cabergoline has proven to be effective.[15] Furthermore,

cabergoline seems to induce much fewer and less severe side effects than other dopamine agonists, since only 4% of the patients had to discontinue treatment.[16,19]

Surgical treatment of prolactinomas

In some patients medical treatment does not result in adequate control of micro- and macroprolactinomas. This is mostly due to intolerance to dopamine agonists. In some patients, there may be resistance to the effects of dopamine agonists. In these patients, surgery is mandatory.

Success rates of transsphenoidal surgery differ between micro- and macroprolactinomas. Furthermore, surgical success rates are highly dependent upon the experience of the neurosurgeon.[34] For microprolactinomas, surgery initially restores prolactin concentrations in 85 to 90%.[35-39] For macroprolactinomas, initial surgical remission rates, i.e. normoprolactinaemia, vary between 18 and 80%.[36,38-40] Especially in those macroprolactinomas with parasellar extension, transsphenoidal surgery alone is not curative. A review by Gillam *et al.*, which combined the data from 45 series (n=2137) of microprolactinomas, and 39 series (n=2226) of macroprolactinomas, initially reported remission rates of 75% and of only 34%, respectively.[24] From the same series, long-term recurrence rates were reported of 18% for microprolactinomas, and 23% for macroprolactinomas. Prolactin concentrations, measured one day after surgery, predicted long-term cure.[41]

An adverse effect of transsphenoidal surgery is the induction of hypopituitarism which is more likely to occur after surgery for macroprolactinomas compared with microprolactinomas. The overall mortality rate following transsphenoidal surgery is less than 0.5%.[38,39]

Postoperative radiotherapy of prolactinomas

The role of radiotherapy is limited in the treatment of prolactinomas. In most cases, radiotherapy is applied after unsuccessful transsphenoidal surgery or, rarely, after medical therapy alone. Therefore, in general it is considered a third-line therapy after failure of medical and surgical treatment. In series of patients with unsuccessful transsphenoidal surgery, conventional, fractionated radiotherapy normalised prolactin concentrations in ~34%.[24] Hypopituitarism can be induced by both surgery and radiotherapy, with a cumulative risk after postoperative radiotherapy of ~50% at 10 to 20 years.[42,43]

In conclusion, the efficacy of medical therapy, especially of cabergoline, has limited the indication for surgery. Surgery is reserved for patients with intolerance and/or resistance to dopamine agonists. Multimodal therapy containing pretreatment with dopamine agonists, surgical debulking, and subsequent adjuvant radiotherapy may be necessary for giant or invasive prolactinomas.

LONG-TERM OUTCOME OF TREATMENT OF PROLACTINOMAS

Remission after withdrawal of dopamine agonists

Withdrawal of bromocriptine or quinagolide results in recurrence of hyperprolactinaemia in almost all patients.[25,44-46] In the past 10 to 15 years, wide variations in remission rates have been reported after withdrawal of cabergoline, with a range of 10 to 70%.[14,25.32,46-48] Colao *et al.* evaluated withdrawal of cabergoline (median duration of therapy 36 to 48 months) in 200 patients with nontumoural hyperprolactinaemia (n=25), microprolactinomas (n=105), and macroprolactinomas (n=70).[14] Recurrence rates of hyperprolactinaemia after a median follow-up of 12 to 18 months were 24% in nontumoural hyperprolactinaemia, 30% in microprolactinomas, and 36% in patients with macroprolactinomas. In this prospective study, normal prolactin concentrations and tumour shrinkage of 50% or more on MRI were stringent conditions before cabergoline withdrawal, indicating that, at least in a subset of patients, dopamine agonists can be withdrawn successfully. This has led to novel guidelines for the treatment and withdrawal of dopamine agonists in patients with prolactinoma.[49] A recent study in a limited number of patients that followed these guidelines reported a recurrence of over ~60% by 18 months.[50] Recently, we performed a meta-analysis on the effects of withdrawal of dopamine agonists in prolactinomas, which included 19 studies with a total of 743 patients. This meta-analysis showed that only 21% of the patients had persisting normopolactinaemia after dopamine agonist withdrawal.[51] Only treatment duration was correlated with treatment success.

In conclusion, withdrawal of cabergoline after duration of therapy of three to five years can be attempted, especially if imaging has demonstrated tumour shrinkage of 50% or more. Although remission is reported in ~60% of patients with prolactinomas, periodic assessment of prolactin concentrations, for example every three months in the first year, would be advisable. In macroprolactinomas, dopamine agonist therapy should be reinstituted whenever hyperprolactinaemia occurs, whereas in microprolactinomas an expectant approach can be followed.

Safety of dopamine agonists

Adverse effects of dopamine agonists can be grouped into three categories: gastrointestinal, neurological, and cardiovascular side effects. Symptoms tend to occur after the first dose and after increases of the dose, but can be minimised by introducing the drug in a low dose at bedtime. The most common gastrointestinal effects are nausea and vomiting. The most frequent neurological adverse effects are headache and drowsiness. Psychiatric adverse effects, such as psychosis or

exacerbation of pre-existing psychosis, are infrequent and entirely reversible when the drug is discontinued.[24] Mood alterations, such as anxiety and depression, occur frequently during treatment with dopamine agonists. These psychological side effects are often subtle and therefore difficult to detect.

The dopamine agonists pergolide, bromocriptine, and recently cabergoline, have been associated with increased risk of cardiac valve regurgitation in patients with Parkinson's disease and to induce retroperitoneal and pulmonary fibrosis.[52-63] However, these adverse effects appear to be dose-dependent, and the dose used for the treatment of prolactinomas is approximately ten times lower compared with the dose used for the treatment of Parkinson's disease. At present, eight observational studies on the relationship between cabergoline and cardiac valve regurgitation in prolactinoma patients have been published so far and are summarised in *table 1*.[64-71] Overall, five of these eight studies did not report a significant association between treatment with cabergoline and prevalence of cardiac valve regurgitation, whereas two studies reported an increased prevalence of mild, but not clinically relevant, tricuspid regurgitation and only one study showed an increased prevalence of moderate tricuspid regurgitation (*table 1*). Furthermore, only one study demonstrated a correlation between clinically significant moderate tricuspid regurgitation and the cumulative dose of cabergoline.[68] Single studies reported increased prevalence of morphological changes of cardiac valves, including thickening and calcification,[66] or increased mitral tenting area.[64] Recently, a meta-analysis including six of the above-mentioned studies with a total of 393 patients treated with cabergoline for hyperprolactinaemia showed a significant increased risk of mild plus moderate tricuspid valve regurgitation.[72]

In conclusion, it seems that the risk for valvulopathy in patients treated with dopamine agonists for prolactinoma is low. An increased risk of cardiac valvulopathy should be considered in patients requiring higher doses or long duration of therapy with dopamine agonists. Hence, none of the patients with clinically significant regurgitation had symptoms of cardiac valve disease and the regurgitation was revealed only by systematic echocardiographic evaluation. Therefore, echocardiography should be performed on a regular basis in patients treated with ergot-derived dopamine agonists for prolactinoma until long-term follow-up studies have shown that there is no increased risk after longer duration of treatment than that has been evaluated at present.

Resistance to dopamine agonists

Varying definitions of dopamine agonist resistance are used. Molitch has proposed to use a uniform definition, defining dopamine agonist resistance related to prolactin concentrations as the failure to achieve normoprolactinaemia, and with respect to tumour size as the failure to achieve tumour size reduction of 50%.[73] The prevalence of resistance of prolactinomas to dopamine agonists differs between specific dopamine agonists, macro- or microprolactinomas, and between naive and previously treated prolactinomas. Overall, resistance with respect to normalisation of prolactin concentration and tumour shrinkage can be expected in 25 to 50% of patients taking bromocriptine, and in 5 to 15% taking cabergoline.[73]

Table 1. *Cabergoline and cardiac valve disease in patients treated for prolactinoma*

Author, year of publication (ref.)	No. of patients	No. of controls	Gender (F/M)	Mean age (yr)	Mean cumulative cabergoline dose (mg)	Mean cabergoline duration (months)	Clinically relevant regurgitation	Valvular thickening/ calcification	Mitral tenting area
Lancellotti, 2008[64]	102	51	73/29	51	204*	79*	NS	NS	Sign. increased
Vallette, 2008[65]	70	70	37/33	44	282	55	NS	NS	NA
Kars, 2008[66]	47	78	34/13	46	363	62	NS	Significantly more MV and AV calcification Significantly more TV thickening	NA
Wakil, 2008[67]	44	566	32/12	42	311	45	NS	NS	NA
Colao, 2008[68]	50	50	44/6	37	414	NA	Significantly more moderate TR	NS	NA
Bogazzi, 2008[69]	100	100	79/21	41	279	67	NS	NA	NA
Herring, 2009[70]	50	50	20/30	51	443	792	NS	NS	NS
Nachtigall, 2009[71]	100	100	52/48	44	253	48	NS	NA	NA

NA = not available; NS = non significant; TR = tricuspid regurgitation; MV = mitral valve; AV = aortic valve; TV = tricuspid valve. * Median.

Possible treatment options for patients with dopamine agonist resistance are to increase the dosage or to switch to another dopamine agonist, or transsphenoidal surgery.

Pregnancy

Two major issues arise in the treatment of prolactinomas and pregnancy: 1) effect of pregnancy on prolactinomas, and the possibility of growth of prolactinomas; 2) effect of dopamine agonists on foetal development.

During normal pregnancy, oestrogens stimulate prolactin synthesis and secretion, and promote lactotroph cell hyperplasia. Throughout normal pregnancies, there is an increase in pituitary volume up to 136%, beginning in the second month of gestation.[74] After delivery, the pituitary rapidly involutes and returns to its normal size by six months postpartum. According to data collected by Gillam *et al.*, five studies have reported data on the risk of symptomatic tumour enlargement in pregnant women with prolactinomas.[24] These data indicate that the risk of detectable tumour enlargement is only 3% (12 of 457 pregnancies) for microprolactinomas, but as high as 32% (45 of 142 pregnancies) for macroprolactinomas not previously operated. Surgical intervention was necessary in 12 of these 142 cases (8%). In five patients with microprolactinomas and 17 patients with macroprolactinomas, dopamine agonist bromocriptine was reinstituted.

Most women diagnosed with prolactinomas will require treatment of hyperprolactinaemia for restoration of fertility. Therefore, it is likely that the foetus will be exposed to dopamine agonists, at least for the initial three to four weeks of gestation. Moreover, all dopamine agonists have been shown to cross the placenta in humans. The use of bromocriptine, however, taken in the first weeks of gestation, has not been associated with an increase of spontaneous abortions, premature delivery, or congenital malformations in a very large number of pregnancies (n=6239).[24] Childhood development was analysed in 64 of these children, without adverse effects.

Considerably fewer data are available on the effects of bromocriptine used throughout the whole gestation. Although data on the safety of quinagolide during pregnancy are scarce, in a review of 176 pregnancies, spontaneous abortions occurred in 14%, and there was one ectopic pregnancy, one stillbirth (at 31 weeks of gestation), and nine cases of malformations.[23] Therefore, quinagolide should not be used if pregnancy is desired. Experience with the use of cabergoline in the first weeks of pregnancy is accumulating, and data of exposure to 350 cases have been reported without an increased incidence of spontaneous abortion, premature delivery, or congenital malformations.[24] Recently, Colao *et al.* reported data of 329 pregnancies in women during the use of cabergoline.[75] Spontaneous abortions occurred in 9%, and there were eight cases of stillbirths (3%), and 23 cases of neonatal major and minor abnormalities (7%). The incidence of spontaneous abortion in the general European population is approximately 11%.[76] Major neonatal abnormalities are estimated at 6% worldwide.[75]

The follow-up of women with microprolactinomas during pregnancy includes withdrawal of dopamine agonists at the moment pregnancy is established. Periodic assessment of prolactin concentrations is not useful, due to the physiological rise during pregnancy. Routine periodic visual field testing and/or MRI are not cost-effective, considering the low incidence of tumour enlargement. Therefore, visual field testing and/or MRI should be assessed when symptoms of mass effects, such as headache or visual disturbances, occur. If tumour enlargement is confirmed, reinstitution of the dopamine agonist bromocriptine is often sufficient to reduce size. However, persistent visual field defects may necessitate transsphenoidal surgery. In women with macroprolactinomas, the decision to continue or withdraw dopamine agonist treatment should be made on an individual basis, taking into consideration the extent of para-/suprasellar extension of the macroprolactinoma and its relation with optic chiasm/nerves. Furthermore, careful follow-up with visual field testing is advisable. MR imaging is reserved for those patients with symptoms of tumour enlargement and/or progressive or new visual field defects. Again, if tumour enlargement is confirmed, reinstitution of the dopamine agonist bromocriptine is preferred to surgery, and transsphenoidal surgery is reserved for women who do not respond to bromocriptine and in whom progressive deterioration of visual fields is documented despite bromocriptine therapy.

In conclusion, growth of prolactinomas during pregnancy is due to the withdrawal of dopamine agonists and stimulatory effects of high oestrogen concentrations. Bromocriptine is the therapy of choice to treat hyperprolactinaemia in order to restore fertility, and can be safely withdrawn in women with microprolactinomas when pregnancy is confirmed. Careful monitoring is warranted for women with macroprolactinomas during pregnancy. For women who are intolerant to bromocriptine, cabergoline is a reasonable second choice.

Bone mineral density

Patients with prolactinomas are susceptible to develop osteopenia and osteoporosis. Prolactinoma-related bone loss is related to the duration of secondary hypogonadism before the diagnosis of prolactinoma is established and treatment is instituted. Prolactinomas are more prevalent at young age, and, therefore, peak bone mass may be affected in young patients with prolactinomas. In a cross-sectional study of 45 women with prolactinomas, 22% had Z scores of bone mineral density (measured using dual energy X-ray

absorptiometry) below the expected range for age at one or more sites.[77] Furthermore, in 15% of men with prolactinomas osteoporosis of the lumbar spine was present.[78] In most men and women with hyperprolactinaemia, bone loss is reversed, or at least interrupted, once prolactin concentrations and gonadotropins are normalised. This indicates the importance of adequate disease control, i.e. normoprolactinaemia, to prevent long-term complications.

Quality of life

Endocrine diseases have clear psychological implications.[79] Furthermore, despite normalisation of excessive endogenous hormone production or optimal hormone-replacement strategies in hypopituitarism, persistent imperfections in endocrine homeostasis most likely result in subtle physiological and psychological derangements and impaired quality of life.[80] Assessment of functional and mental well-being has become an important outcome of long-term follow-up in pituitary adenomas. Quality of life, measured with self-reported health parameters, is decreased in patients with pituitary adenomas.[81-90] In women treated for microprolactinomas, quality of life is impaired, especially due to increased anxiety and depression.[91,92]

Malignant prolactinoma

The incidence of pituitary carcinomas is extremely low.[93] Until recently, only ~140 cases with pituitary carcinomas have been reported, one-third of these being malignant prolactinomas.[94,95] Unless (distant) metastases have developed, it is very difficult to distinguish benign (invasive) prolactinomas from malignant prolactinomas. Overall, malignant prolactinomas present with atypical clinical symptoms, such as progressive symptoms of headache or cranial nerve compression, and resistance to dopamine agonists, expressed by increasing prolactin concentrations. Furthermore, histological parameters, such as proliferative Ki-67 index and p53 immunoreactivity, are correlated with biological behaviour of pituitary adenomas.[93,96] It is postulated that pituitary carcinomas arise from the transformation of initially large, but benign adenomas.[93] This argument is based on observations that the initial presentation is not different from other macroadenomas, the long duration needed for the transformation into carcinomas, and the increasing accumulation of genetic aberrations.[96] Once metastatic disease is established, treatment modalities are surgery, radiotherapy, and chemotherapy. In some patients, treatment with octreotide is an option. If tolerated, dopamine agonists should be continued.

CONCLUSION

Prolactinomas are the most prevalent pituitary adenomas. Dopamine agonists are the first-line of treatment for prolactinoma, capable of effectively relieving symptoms, normalising prolactin concentrations and reducing tumour size in most cases. Recurrence of the disease after withdrawal of dopamine agonists occurs in a considerable proportion of patients, and therefore follow-up after withdrawal is necessary. The probability of persisting normoprolactinaemia after withdrawal is highest when tumour volume has reduced by 50% or more, and normoprolactinaemia has remained stable even after tapering the dose. Follow-up of prolactinomas also requires assessment of bone mineral density and attention to quality of life. Although dopamine agonist treatment appears safe in most patients treated for prolactinoma, evaluation of cardiac valvulopathy should be considered in patients treated with ergot-derived dopamine agonists, with repetitive echocardiography in those treated with a relative high dose and/or long duration of bromocriptine or cabergoline. Additional treatment with transsphenoidal pituitary surgery and/or radiotherapy should be reserved for patients with intolerance or resistance to dopamine agonists, since these secondary therapies have a high risk of developing hypopituitarism.

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REVIEW

Role of vitamin D in cardiovascular disease

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ABSTRACT

There is increasing evidence for health benefits accomplished by activated vitamin D through interaction with the vitamin D receptor (VDR) that go beyond calcium and bone homeostasis and regulation of parathyroid hormone (PTH) secretion. Treatment with vitamin D receptor agonists (VDRAs) is associated with reduced mortality in (pre)dialysis patients. Interestingly, these relations are independent of PTH levels and calcium x phosphorus product. This suggests the presence of biological functions of vitamin D that are independent of its interaction with the parathyroid glands. Because chronic kidney disease leads to increased cardiovascular mortality, mechanisms in which VDRAs can influence cardiovascular disease are discussed. These mechanisms comprise the potential ameliorating effects of VDRAs on atherosclerosis, arterial media calcification, cardiac hypertrophy, the renin-angiotensin system and thrombosis. Moreover, treatment strategies with VDRAs are discussed together with several recent observational studies. Treatment advice consists of correction of 25(OH) vitamin D deficiency, low-dose calcitriol in patients with secondary hyperparathyroidism, and activated vitamin D analogues may be indicated when higher doses are needed to suppress PTH secretion. New insights into biological and clinical effects of VDRAs may broaden the patient group that may benefit from VDRA treatment to patients with creatinine clearances in the 30 to 60 ml/min range.

KEYWORDS

Vitamin D receptor activation, cardiovascular disease, kidney disease

INTRODUCTION

Vitamin D is known for its primary role in calcium and bone homeostasis and regulation of parathyroid hormone (PTH) secretion. There is increasing evidence for health benefits accomplished by activated vitamin D through interaction with the vitamin D receptor (VDR) that go beyond these classical functions. The VDR is expressed by many tissues and is present in, for instance, arteries, heart, the immune system and endocrine organs (*table 1*).[1] As kidney function deteriorates, activated vitamin D levels decline.[2] Therefore patients with renal dysfunction are a suitable population to study the effects of vitamin D treatment. Low serum 1,25$(OH)_2$D levels cause an increase in PTH secretion and the development of secondary hyperparathyroidism (SHPT). High serum PTH and hyperphosphataemia are known risk factors for increased mortality among patients on dialysis. Therefore, recent guidelines have formulated new, stricter, target ranges for serum calcium, phosphorus and PTH levels.[3,4]

In recent years, it has become clear that there is increased mortality among vitamin D deficient patients on dialysis.[5] Moreover, treatment with vitamin D receptor activators (VDRAs) is associated with reduced mortality in (pre) dialysis patients.[6-8] Interestingly, these relations are

Table 1. *Tissue distribution of the vitamin D receptor*

System	Tissue
Endocrine	Parathyroid, pancreatic B cells, thyroid C cells
Cardiovascular	Arterial smooth muscle cells, cardiac myocytes
Musculoskeletal	Osteoblasts, chondrocytes, striated muscle
Gastrointestinal	Oesophagus, stomach, intestine
Hepatic	Liver parenchymal cells
Renal	Tubules, juxtaglomerular apparatus, podocytes
Reproductive	Testis, ovary, uterus
Immune	T and B cells, bone marrow, thymus
Respiratory	Lung alveolar cells
Epidermis	Keratinocytes, hair follicles
Central nervous system	Brain neurons

independent of PTH levels and calcium x phosphorus product. This suggests the presence of biological functions of vitamin D that are independent of its interaction with the parathyroid glands. What these theoretical mechanisms comprise and what the effects are of VDRA use will be discussed.

CARDIOVASCULAR DISEASE

Below an estimated glomerular filtration rate (eGFR) of 60 ml/min, chronic kidney disease (CKD) leads to increased cardiovascular mortality in nondialysed patients.[9] In patients on dialysis this risk further increases: half of the mortality rate is caused by cardiovascular events.[10]

The two most important arterial complications leading to cardiovascular events are intimal and medial calcification. Arterial intima calcification is associated with atherosclerosis and leads to plaque formation and rupture with subsequent blood vessel occlusion. Arterial media calcification is associated with proliferation of vascular smooth muscle cells and leads to calcification and stiffening of the vessel wall.[11] The magnitude of coronary artery calcification, assessed by electron beam computed tomography and ultrasound, is correlated with clinical cardiac events.[12] Studies evaluating patients with stage 3 to 5 CKD (*table 2*) have demonstrated excessive coronary artery calcification,[13] even in young adults,[14] and suggest that coronary artery calcification is an independent predictor of death in patients on dialysis.[15] Whether this excessive calcification is primarily due to intimal or medial calcification is subject of debate. There is evidence that in patients with CKD increased arterial media calcification, more than arterial intima calcification, is responsible for the high cardiovascular mortality rate. This was demonstrated histologically through staining of inferior epigastric arteries from patients on dialysis that showed 'pure' medial calcification.[16] In another study among patients on dialysis ultrasonography of carotid arteries showed arterial intima calcification in older patients with a clinical history of atherosclerosis. Arterial media calcification was observed mainly in the younger group without conventional atherosclerotic risk factors.[11] Vitamin D can inhibit various aspects of inflammation leading to intimal and medial calcification. Further on we will explain how.

Table 2. *Stages of kidney disease*

Stage	GFR	Description
1	>90	Normal kidney function but urine findings or structural abnormalities or genetic trait point to kidney disease
2	60 - 89	Mildly reduced kidney function, and other findings (as for stage 1) point to kidney disease
3	30 - 59	Moderately reduced kidney function
4	15 - 29	Severely reduced kidney function
5	<15 or on dialysis	Very severe, or end-stage kidney failure

GFR = glomerular filtration rate.

VDRA DIRECTED CYTOKINES: EFFECTS ON ATHEROSCLEROSIS

T lymphocytes and macrophages are known stimulators of intimal thickening and plaque formation in arteries susceptible of atherosclerosis. Th1 lymphocytes secrete interferon-gamma (IFN-γ), which is a potent macrophage activator and a Th2 lymphocyte suppressor. Th2 lymphocytes, in their turn, are antiatherogenic through production of Il-10, which inhibits macrophage activation.[17] The development of CD4+ T cells into either Th1 or Th2 cells determines the outcome of an immune response, and is primarily directed by cytokines; Th1 cells develop in response to IL-12 and IFN-γ, whereas IL-4 induces the development of Th2 cells. VDRA have potential ameliorating effects on the development of atherosclerosis by several mechanisms. Firstly, they have a direct effect on naive CD4+ T cells by enhancing the development of Th 2 lymphocytes (through Il-4 production).[18] Furthermore treatment with VDRA inhibits the transcription of IFN-γ that is either required for Th1 development or is a product of Th1 cells.[18,19] Moreover, human and mouse naive CD4+ cells differentiated into IL-10 producing T cells, after treatment with VDRAs and dexamethasone.[20] Through these mechanisms VDRAs may change the Th1/Th2 balance and influence the production of (anti) inflammatory mediators.

VASCULAR CALCIFICATION

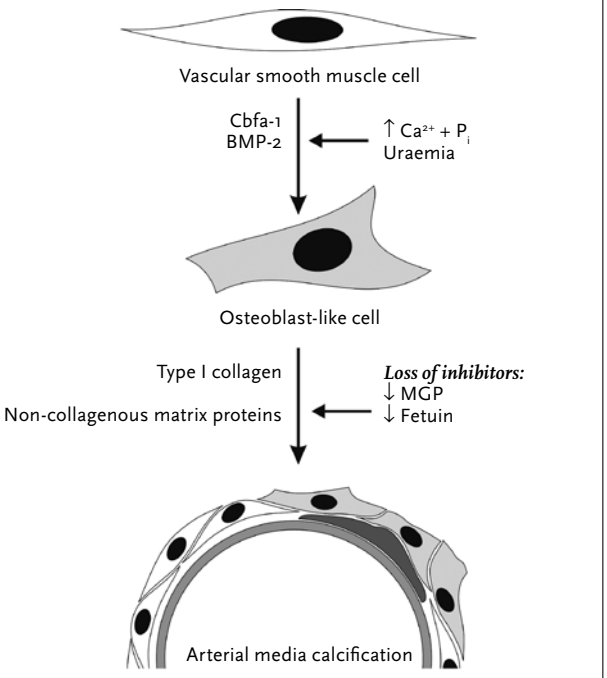
Vascular smooth muscle cells (VSMCs) and osteoblasts derive from a similar mesenchymal precursor cell. Core binding alpha-1 (Cbfa1) is thought to be the switch that turns this mesenchymal cell into an osteoblast. Moe and Chen observed expression of Cbfa1 in inferior epigastric arteries of renal transplant patients while only minimal expression was found in noncalcified arteries.[21] Uraemic toxins present in serum from dialysis patients and the expression of osteogenic markers, such as bone morphogenetic protein-2 (BMP-2), also lead to accelerated transformation of VSMCs into osteoblast-like cells.[16] These cells are capable of producing bone matrix proteins (type1 collagen, osteopontin, bone sialoprotein), which may subsequently regulate mineralisation.[22]

Once mineralisation is initiated, an increased calcium x phosphorus product, as occurs in patients with renal insufficiency, may accelerate the process of calcification which leads to stiffening of the vessel.[23] In the past accelerated calcification in patients on dialysis has been interpreted to be caused by the presence of potentiators of calcification. An alternative interpretation is that uraemic serum lacks calcification inhibitors.

Recently several inhibitors of vascular calcification have been identified. Matrix gla protein (MGP) inhibits vascular calcification in several possible ways. Muscle phenotype transition was tested *in vivo* using MGP -/- mice that spontaneously develop calcification in all major arteries. The calcified arteries showed an upregulation of osteopontin and induction of Cbfa1 protein expression.[24] Furthermore MGP is an inhibitor of BMP-2.[25] A number of circulating proteins may inhibit the vascular calcification process, including fetuin-A,[26] PTH-related-peptide and C-natriuretic protein.[27]

These mechanisms demonstrate that vascular calcification is a highly regulated process resulting from an imbalance between the loss of inhibitory factors and the increase of inducing factors present both in vessels and in the circulation (*figure 1*). Knowledge of the role of VDRAs in this new paradigm is evolving.

Figure 1. *Development of vascular calcification*



Cbfa-1 = core binding alpha-1; BMP-2 = bone morphogenetic protein-2; MGP = Matrix gla protein.

ROLE OF VDRAS IN VASCULAR CALCIFICATION

The survival benefit of the use of VDRAs seems contradictory to the perception that VDRAs, due to their potential impact of increasing serum phosphorus and calcium, may cause vascular calcification.[28] Yet there is evidence for an inhibitory role of VDRAs in vascular calcification. For a start, VDRs are present in VSMCs and treatment with VDRAs inhibits the synthesis of type 1 collagen.[22] More importantly, VDRA treatment reduces cbfa-1 synthesis,[29] stimulates the synthesis of MGP and inhibits BMP-2 production in cultured osteoblastic cells.[30,31]

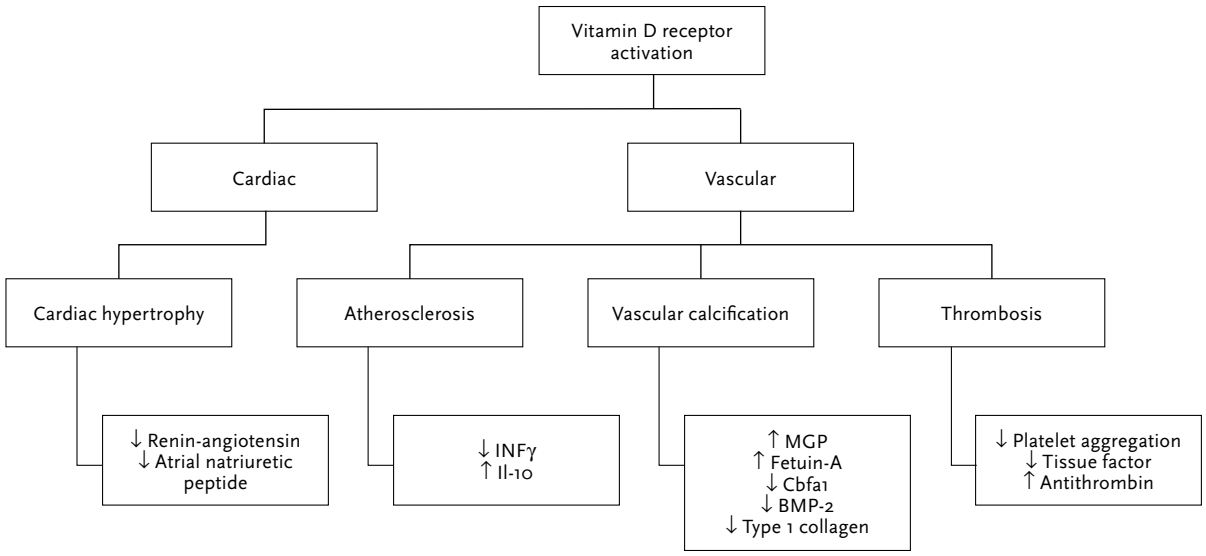
OTHER MECHANISMS

Decreased vitamin D activity increases renin expression, renin levels, atrial natriuretic peptide and angiotensin II levels and causes hypertension and cardiac myocyte hypertrophy in mouse models.[32-34] Recently it was found that VDR activation has ameliorating effects on cardiac hypertrophy and inhibits several renin-angiotensin system (RAS) components. Intravenous treatment with calcitriol in patients on haemodialysis has been demonstrated to be strongly associated with regression of myocardial hypertrophy.[35] Treatment of nephrectomised rats with paricalcitol was associated with suppression of renin, renin receptor, angiotensinogen and angiotensin II type 1 receptor. Hypertension and the deterioration of renal function were significantly improved with VDRA treatment.[34] Furthermore VDR activation probably has impact on the cardiovascular system by preventing thrombosis. In vitamin D knockout mice platelet aggregation was enhanced, tissue factor expression was upregulated and thrombomodulin/antithrombin were downregulated,[36] which are all prothrombotic conditions (*figure 2*).

TREATMENT STRATEGIES

Recently it has become clear that very low levels of 25(OH) vitamin D (<17.8 ng/ml or 44.5 nmol/l) are associated with increased all-cause mortality in patients with and without kidney disease.[37,38] Studies examining replacement of 25(OH) vitamin D in patients without kidney disease support a small but beneficial effect on survival.[39] Moreover, treatment with 25(OH) vitamin D results in significant reduction in PTH levels in patients with 25(OH) vitamin D levels <75 nmol/l, irrespective of their kidney function.[40,41] Therefore patients with 25(OH) vitamin D levels below 75 nmol/l should receive replacement therapy with native vitamin D/ergocalciferol.

Figure 2. *Inhibitors of cardiac hypertrophy and vascular damage through vitamin D receptor activation*



Usually this treatment is not sufficient to achieve suppression of SHPT in advanced chronic kidney disease and VDRAs are needed. VDRA therapy in patients with CKD has been associated with improved survival. Intravenous calcitriol or paracalcitriol treatment of patients on haemodialysis offered a significant survival advantage of 20 to 25% over patients who did not receive parental vitamin D.[6] This has prompted some other observational studies examining outcomes associated with the use of VDRAs by patients on dialysis and predialysis patients.[7,8] These studies consistently showed that patients treated with any kind of VDRA experienced significantly lower all-cause and cardiovascular mortality rates compared with patients not receiving any treatment. Subgroup analyses indicated that virtually all patients benefited from VDRA therapy, including patients with lower PTH or higher calcium or phosphorus levels. These findings emphasise a physiological effect of VDRAs that is PTH independent. Despite these convincing data we have to be cautious in using observational data as a final proof of a beneficial effect and randomised trials are warranted.

WHICH VDRA, DOES IT MATTER?

Several studies using oral calcitriol in predialysis and dialysis patients have shown a reduced overall mortality risk ranging from -26 to -45%.[8,42,43] The advantage included patients with the highest levels of serum calcium, phosphorus and PTH. In predialysis patients high pharmacological doses of calcitriol may hasten loss of kidney function,[44] but this effect is not seen with lower doses of calcitriol. On the contrary: low-dose calcitriol (<0.25 µg/day) has been associated with a trend towards slower progression of kidney disease and lower mortality risk.[8] For reasons of convenience, in haemodialysis patients active vitamin D is often administered parenterally after dialysis. Oral treatment with calcitriol is presumably equally effective in reducing SHPT and mortality risk and is far less expensive.

Clinical guidelines suggest stringent control of PTH, calcium and phosphate in an attempt to lower the risk of vascular calcification and bone disease.[3] Very recently KDIGO (Kidney Disease: Improving Global Outcome) guidelines stated that in patients with CKD stage 3 to 5 not on dialysis, in whom serum PTH is rising above the upper limit of normal, despite modifiable factors, VDRAs are warranted.[4] Implicit in these recommendations is the avoidance of the native VDR activator calcitriol if the calcium and phosphate levels exceed their upper limits. This has advocated the use of several VDRAs that can suppress PTH production with less induction of concomitant hypercalcaemic and hyperphosphataemic effects.[45] One could question the importance of this favourable side-effect profile since the benefit of calcitriol extends to patient groups with high calcium and phosphorus levels. On the other hand long-term positive calcium balance may contribute to vascular calcification. Moreover, observational data suggest a decreased rate of progression of established vascular calcification with non-calcium containing phosphate binders.[46]

Examples of activated vitamin D analogues with this favourable side-effect profile are doxercalciferol, paricalcitol, and alfacalcidol. Animal models show a potential advantage for paricalcitol; it induces less vascular calcification compared with calcitriol.[47] Earlier we mentioned the historical cohort study by Teng *et al.*, where 67,339 patients on haemodialysis were examined. In this

study paricalcitol was associated with a 16% lower all-cause mortality compared with treatment with calcitriol.[6] In another study these findings were not confirmed. Tentori *et al*. compared outcomes in patients receiving calcitriol, paricalcitol and doxercalciferol and found lower mortality in patients on paricalcitol and doxercalciferol in unadjusted models. But in adjusted models this difference was not statistically significant.[7] Obviously, more studies are needed to prove the benefit of activated vitamin D analogues on survival.

TREATMENT ADVICE

Treatment of SHPT is the generally accepted and approved indication for treatment with vitamin D. It seems reasonable to correct 25(OH) vitamin D deficiency as a first step in the treatment of SHPT. New insights into biological and clinical effects of VDR activation may broaden the patient group that may benefit from VDRA treatment to patients with creatinine clearances in the 30 to 60 ml/min range. Low-dose calcitriol is indicated for patients with early SHPT. A switch to activated vitamin D analogues is indicated when higher doses are needed to suppress PTH secretion and treatment goals concerning calcium x phosphorus levels have to be met.

ACKNOWLEDGEMENTS

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REVIEW

Optimal nutrition and its potential effect on survival in critically ill patients

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ABSTRACT

Optimal nutrition serves to maintain normal organ function and to preserve body energy stores to guarantee survival during times of shortage of food. Especially total body protein content is an important determinant of survival. However, recommendations about nutrition refer mostly to total energy intake with either no emphasis on total protein content or protein intake only considered as a fixed percentage of caloric intake.

This paper focuses on the role of total body protein mass or lean body mass (= mass of organs and muscle) (LBM) on survival of healthy humans and critically ill patients. Recommendations on the amount of protein per kg bodyweight are made based on the scarce evidence available in humans.

KEYWORDS

Lean body mass, protein content, diet, critical illness, mortality

OPTIMAL NUTRITION

Nutrition is often referred to as the adequate amount of energy intake with a fixed composition of macronutrients (35% fat, 50% carbohydrates and 15% protein). The optimal goal of nutrition is survival during times of shortage of food with fat mass and total body protein mass being the most important determinants, but for short-term survival replenishment of carbohydrates is sufficient. This demonstrates that optimal nutrition depends on the actual circumstances and therefore cannot always be simplified in a standard menu. However, recommendations about nutrition refer mostly to energy intake with either no emphasis on protein content or protein intake only considered as a fixed percentage of caloric intake (usually 15%).

This review focuses on protein mass or lean body mass (= mass of organs and muscle) (LBM). Lower body mass index (BMI) values have been related to low LBM, a condition associated with increased mortality.[1] This is easily understandable because proteins are involved in almost all metabolic processes. Although this seems a reasonable statement, its proof is less certain. Data on this issue are scarce for obvious reasons. Observations on the relation between protein mass and mortality are biased by comorbidity which can/will influence time of death. Observations on the relation between protein mass and mortality in otherwise healthy subjects are extremely rare.

LOSS OF LEAN BODY MASS DURING STARVATION

Observations in Irish and Turkish hunger strikers have shown that they die ~60 days after a complete fast without water restriction, while having lost 40 to 50% of their bodyweight. Observations in famine victims report a minimum BMI of 10 kg/m^2 to be required for survival.[2,3] Detailed body composition studies have not been done, but from the rate of loss of each body compartment during semi-starvation reasonable assumptions can be made. The most comprehensive studies have been done by Keys, in his classical 'Minnesota Experiment', which documented on body composition during weight loss in healthy young men on a six-month hypocaloric diet of 40% of their daily energy need. After three months, the subjects had lost around 50% of their body fat and 20%

of their LBM. After six months, the losses were 70% and 28% respectively.[4] Studies with (very) low calorie diets confirm this observation.[2]
Calculations from data obtained in various studies in hunger strikers show that on the third day and thereafter ~20% of the energy loss was derived from protein catabolism, resulting at death in the virtual absence of fat depots, whereas the loss in LBM was less than 50%.[2] The fraction of LBM lost when the fat stores reach total depletion represents the dispensable component of the protein compartment that is compatible with life. This corresponds with a BMI of ≈10 kg/m^2.[2] These observations suggest maintenance of protein mass above a critical minimum to be more important for survival than maintenance of fat mass.
In conclusion, a critical amount of LBM is essential for the body to function in a vital manner. Data from hunger strikers show that a loss of total body protein of more than 40%, corresponding with a BMI of approximately 10 kg/m^2, is not compatible with life.

PROTEIN MASS AND MORTALITY IN CRITICAL ILLNESS

The questions arises whether a comparable relation between protein mass and mortality exists in critically ill patients. Studies on this issue are by definition observational, as intervention studies are unethical. Studies on the exact relation between total body protein mass and mortality in critically ill patients do not exist, as *accurate* measurement of protein mass (only via *in vivo* neutron activation analysis) in critically ill patients is extremely difficult. In addition, this research tool is available at only very few centres worldwide. It provides a noninvasive analysis of the total body content of major molecules (calcium, nitrogen, sodium, oxygen, hydrogen, and carbon). It is based on the principle that each atom is capable of undergoing nuclear reactions when exposed to neutrons. The excited atom releases energy in the form of gamma rays which is specific for each atom and can be detected and counted with a gamma counter. Because there is a fixed relation between nitrogen and protein [protein (g)=6.25 x nitrogen (g)], total body protein can be calculated from measured total body nitrogen. This is considered the gold standard for estimating total body protein.[5]
This problem is due to the fact that protein content and LBM are not completely interchangeable concepts. The constant relation between lean body mass and protein content, found in healthy subjects, is disturbed in critically ill patients due to changes in intracellular water content.
BMI is sometimes used as a surrogate marker of LBM, although it is well known that the correlation between BMI and LBM is not very tight, in the higher ranges especially.[6] However, in general a low BMI approximates to low weight, fat mass and fat-free mass.[7] Observations in large groups of critically ill patients indicate that a low BMI is an independent risk factor for mortality. It increased as a continuous variable down to a BMI of 15 kg/m^2 in 1488 mechanically ventilated adults with acute lung injury.[8] These data are not in contradiction to a study in over 40,000 critically ill patients, showing excess mortality only in patients with a BMI <20 kg/m^2.[9]

In conclusion, data from critically ill subjects suggest that the size of the dispensable part of the protein component is not different from that in healthy subjects. In other words, loss of a significant amount of body protein has the same influence on mortality in critical illness as it has in otherwise healthy subjects during starvation.

MAXIMAL STIMULATION OF WHOLE BODY PROTEIN SYNTHESIS AND MAINTENANCE OF PROTEIN MASS

The size of total protein mass is determined by the balance between protein synthesis and protein breakdown. Under normal circumstances in healthy volunteers, whole body protein breakdown after an overnight fast is greater than protein synthesis, resulting in a negative protein balance. After a meal protein synthesis is stimulated and nitrogen balance becomes positive. This situation will remain for a few hours after the meal. After that period, the balance gradually becomes negative again, until a new meal is consumed. The net effect of these fluctuations in fasting and feeding during the day is a zero-balance.[10,11]
The capacity to synthesise protein from meal-derived amino acids is limited. The maximum capacity of protein synthesis on whole body level is reached with a protein intake of 1.5 g/kg/day in healthy volunteers as well as in critically ill patients.[12-14] Insulin slows down the rate of protein breakdown and augments the effects of amino acid delivery on the synthesis of protein,[15] suggesting that its combination with sufficient amino acids in an anabolic state provides the best basis for optimal nutrition. However, before implementing this viewpoint, the following question is relevant: Is 1.5 g protein/kg/day really the amount that best maintains whole body protein mass in patients? In such a study, whole body protein content should be determined in a reliable way. The gold standard is the *in vivo* neutron activation analysis (see above). At this moment, we are aware of only two studies that have used this technique in critically ill patients. One study was carried out in surgical patients after major abdominal surgery, which reported that a mean provision of 0.9 g protein/kg preoperative body weight/day proved to be insufficient to preserve muscle mass and prevent nitrogen loss, whereas

body protein mass was conserved when 1.6 g protein/kg preoperative bodyweight/day was given.[16] The other study was a retrospective analysis carried out in critically ill sepsis and trauma patients. Due to overhydration of most patients, the protein amount was indexed to normally hydrated corrected fat free mass which resulted in a protein amount of either 1.1, 1.5 and 1.9 g of protein/kg fat free mass during 14 days.[17] Provision of 1.5 g protein/kg fat free mass proved the optimal amount to preserve protein mass. This amount corresponded with 1 g protein/kg actual total body weight/day. The authors conclude that for critically ill patients the optimal nutrition is 1 g protein/kg actual bodyweight or 1.2 g protein/kg pre-admission bodyweight/day. This difference in recommendation relates to overhydration of most critically ill patients. Whether 1.2 g protein/kg/day would have been as effective as 1.6 g protein/kg/day in the surgical patients has not been studied, but a difference between mechanically ventilated and immobilised ICU patients and mobile patients on a surgical ward can be expected. Muscle contractions are essential for sustaining muscular mass. For instance, in healthy volunteers subjected to full immobilisation for four to five weeks, the nitrogen balance becomes negative despite an intake of 90 g protein and 2700 kcal.[18]

In conclusion, to maintain total body protein mass 1.5 g protein/kg preadmission bodyweight/day in patients in general and 1.2 g protein/kg preadmission bodyweight/day in ICU patients could be used as a target for providing adequate nutritional therapy.

EFFECT OF ADMINISTRATION OF OPTIMAL PROTEIN ON MORTALITY IN CRITICAL ILLNESS

Guidelines have proposed optimal nutrition for patients admitted to the intensive care to be the provision of energy as determined by indirect calorimetry, and a protein content of at least 1.2 g/kg preadmission weight per day.[19] In one of the scarce prospective studies evaluating this approach in 283 medical-surgical ICU patients, women who reached their nutritional goals had a significantly lower hazard ratio of dying on the ICU as well as lower 28-day mortality. This benefit on mortality was not present in women reaching their energy target whilst not reaching the protein target. In men, no statistically significant effects of nutrition on outcome could be detected. This difference was ascribed to a gender-related difference in body composition with larger absolute protein stores in men.[20] No studies have been published on gender-related minimal protein mass decisive for survival. When this mass is an absolute one and not related to bodyweight, males have an advantage in nutritional reserve, because of larger absolute protein stores. This will protect them longer from reaching the absolute threshold of minimal body protein needed to guarantee normal organ function. Another explanation could be related to the calculation of protein per kg bodyweight instead of per kg fat free mass. Women have a lower percentage of fat free mass per kg bodyweight and therefore in that study received a higher amount of protein per kg fat free mass which may be beneficial for survival.

This manuscript focuses on optimal protein content in nutrition of critically ill patients. Caloric need was defined in a national guideline on perioperative nutrition.[21] This guideline defined energy need as the amount of energy calculated with the Harris and Benedict 1984 formula + 30%. For long-term patients in the intensive care unit, the guideline advocated tailoring energy provision towards resting energy expenditure determined by indirect calorimetry + 10%. Caloric need and required macronutrients differ between healthy subjects and critically ill patients as shown in *table 1*. Recently it has been shown that implementation of guidelines and evidence on nutrition can be ameliorated by using an algorithm with an advice module available on-line.[22]

Table 1. *Recommendation for required macronutrients for healthy subjects[23] and critically ill subjects not admitted to ICU, based on a caloric need of 1800 kcal/day in a 70 kg subject, expressed in absolute amounts and as percentage of energy expenditure. Caloric need was estimated as equal for both groups, as in general the increase in oxygen consumption induced by critical illness is equalised by its lack of physical exercise*

	Healthy subjects	Critically ill subjects
Energy expenditure (kcal/day)	1800	1800
Protein (g/day)	56	105
Carbohydrate (g/day)	250	250
Fat (g/day)	65	40
Energy expenditure (kcal/day)	1800	1800
Protein (kcal/day)	225	420
Carbohydrate (kcal/day)	1000	1000
Fat (kcal/day)	575	380

CONCLUSION

Maintenance of protein mass in critically ill patients above an (absolute?) value is mandatory for influencing survival. The optimal amount of protein is 1.2 g/kg preadmission bodyweight/day in critically ill septic and trauma patients. For surgical non-ICU patients, it has been shown that 1.6 g protein/kg preadmission bodyweight/day was able to prevent nitrogen loss and preserve muscle mass. In combination with

earlier studies showing that whole body protein synthesis is maximally stimulated during intake of 1.5 protein/kg body weight/day, we recommend 1.5 protein/kg body weight/day as optimal for non-critically ill patients. More evidence is needed to study the effect of some of these nutrition goals on outcome.

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ORIGINAL ARTICLE

Reduction of the door-to-needle time for administration of antibiotics in patients with a severe infection: a tailored intervention project

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ABSTRACT

Background: Door-to-needle time (DNT), defined as the time between arrival at the emergency department (ED) and intravenous (iv) antibiotic administration is of crucial importance in the treatment of patients suffering from serious infections. The aim of this project was to reduce the DNT for patients with a serious infection as primary outcome parameter.

Methods: All adult patients arriving at the ED with a suspected infection for whom admission and iv antibiotics were indicated were included.

Results: Firstly, baseline DNT was measured and potential delaying factors were identified. Subsequently, five tailored interventions were implemented at regular intervals and their effects on the DNT were analysed. The interventions were: 1) additional resident attendance during peak hours, 2) immediate examination by residents prior to laboratory results, 3) chest X-ray at the ED instead of the external radiology department, 4) iv antibiotic administration at the ED instead of the ward and finally, 5) primary dipstick urine analysis at the ED.

A total of 295 patients were included (53.9% men), median age was 59 years (IQR 46 to 73). Median baseline DNT was 183 min (IQR 122 to 296). Implementation of the first three interventions did not reduce the DNT; however, after implementation of the fourth (administer all antibiotics at the ED) and finally all five interventions the DNT was reduced by 15.3% (p=0.040) to a final median DNT of 155 min (IQR 95 to 221).

Conclusion: Identification of delaying factors and implementation of tailored interventions reduces the DNT.

KEYWORDS

Door-to-needle time, hospital stay, infection, antibiotics

INTRODUCTION

A suspected severe infection is the main reason for admission to the Department of Internal Medicine in our hospital in nearly 40% of the patients. Almost all of these patients are admitted through the emergency department (ED). The optimal treatment of a patient with a severe infection encompasses many aspects. Besides proper supportive treatment and empirical therapy, the time between the arrival of the patient and administration of antimicrobial agents is a very important variable and correlates with better outcome. This so-called 'door-to-needle time' (DNT), defined as the time between arrival at the ED and administration of intravenous (iv) antibiotics, has been widely studied considering outcomes such as morbidity and mortality.[1,2] The majority of studies focus on patients treated for the most common infection, i.e. pneumonia.[3-5] Retrospective studies showed positive associations between antibiotic administration within four to eight hours,[3,5,6] and a decreased mortality and an almost half day shorter length of stay in the hospital,[1,3] compared with a longer DNT. For example, in patients with meningitis (n=119) a similar association has been described between the effect of reduction of DNT and mortality. In this study a DNT over six hours was associated with an 8.4 times greater risk of mortality.[2] Hood *et al*. (1998) retrospectively studied patients with a urinary tract infection. They also concluded

that timely (within four hours) antibiotic administration was associated with a shorter length of hospital stay.[7]

Based on these studies we presumed that DNT is an important denominator for treatment outcome and therefore should be a standard component of quality of care for patients with a severe infection. However, a reduction in the DNT has not yet been prospectively studied in a large population who presented to the ED with different kinds of infections. In this article, we describe the results of a health care improvement project, in which we tried to reduce the DNT (primary outcome) for all patients with a serious infection arriving at the ED of our hospital. Furthermore, we measured the result of these interventions on the duration of hospital stay (HS) and whether a shorter DNT was associated with presentation during office-hours (secondary outcome parameters).

METHODS

Project group and interventions

A prospective survey of medical records and prescription charts was performed at the Department of Internal Medicine of a tertiary teaching hospital in the Netherlands. Between March 2006 and December 2006 all adults presenting to the ED with a suspected infection, according to the ED physician and the attending internist, for whom admission and iv antibiotics were indicated, were considered to have a severe infection and included in the survey. No exclusion criteria were present, all patients were included. Several patient characteristics concerning vital signs, concomitant diseases, medication use, laboratory results (at least white blood counts and creatinine level) and readmissions within 30 days were noted on case record forms.

An expert group of all participating professionals: the project coordinator (C.T.), two ED nurses, two ED residents (M.V., S.W.), one logistic expert (R.R.), the head of the ED (J.L.), and the project leader (S.G.) analysed the results every month. Possible slowing factors and appropriate interventions to decrease the DNT were discussed. All interventions were sequentially introduced on the first day of the next month. Continuous measurements were obtained during this period.

Implementation

Interventions were strategically implemented by the contingency model.[8] A questionnaire about the characteristics of the ED and the innovation (reducing the DNT) was sent to all residents of the Department of Internal Medicine and ED nurses. Firstly, we presented the results of the questionnaires, because we wanted the staff members to be aware of their basic assumptions. Hidden and unconscious opinions about this innovation among staff members could be brought out into the open by discussing the results of these questionnaires. Secondly, presentations were given at the beginning, half way through and at the end of the project. The aim of these presentations was to support and to start a decentralised management of the project. Thirdly, by stressing innovations or a particular result, we stimulated a 'we-feeling', which represents and promotes a team-oriented configuration.

Statistics

This project was a health innovation project rather than a conventional study. Therefore, we did not perform a sample size calculation, but included all consecutive patients with the suspicion of a severe infection during a pre-specified period. Distribution of the DNT and HS was expressed as median with corresponding inter-quartile range (IQR) unless stated otherwise. Differences in DNT and HS between intervention groups were tested with the Mann-Whitney U test. Differences in categorical data between groups were tested with the χ^2 test. P values ≤ 0.05 were considered statistically significant. Statistical analysis was performed by using SPSS 12.0.2 (SPSS Inc, Chicago, IL).

RESULTS

Baseline characteristics

Patient characteristics are summarised in *table 1*. A total of 295 patients were included (46.1% female). Median age was 59.0 years (inter quartile range (IQR) 46 to 73). Diagnoses were reported when patients were dismissed from hospital. Consequently, 13.4% of the patients suspected of having an infection in the ED did not have a discharge diagnosis of infection. During the project period, DNT and HS were measured in 60 patients before

Table 1. *Baseline characteristics*

Characteristics	
N	295
Female (%)	46.1
Age*	59.0 (46-73)
Infection diagnoses (%):	
• Respiratory tract infection	18.5
• Urinary tract infection	17.1
• Liver and biliary tract infection	9.2
• Skin/soft tissue infection	3.7
• Septicaemia	1.7
• Intravenous catheter infection	2.7
• Fever of unknown focus	9.8
• Neutropenic fever	3.4
• Bone and joint infection	0.7
• Other infections	15.1
• None	13.4

***Median (IQR)**
Age is given in median with inter quartile range (IQR). All other numbers are percentages (%) of the total number of patients. None means that at the moment of discharge from the hospital it was clear that the patient did not have an infection, but had an alternative diagnosis.

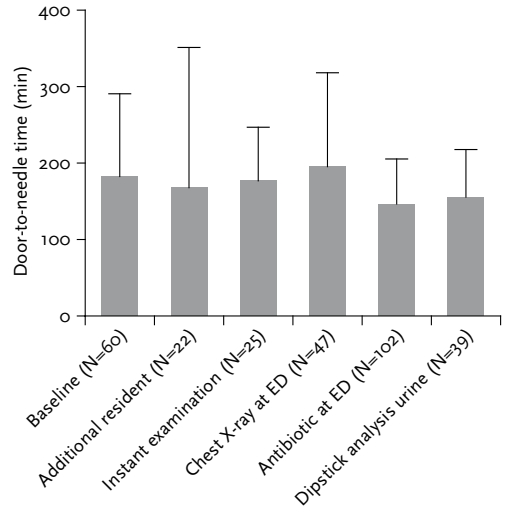
implementation of the intervention, and in 22, 25, 47, 102 and 39 patients, respectively, after implementation of each of the five subsequent interventions. Different variables were studied (age, the percentage of patients who had concomitant chronic diseases such as diabetes, admission to the intensive care unit, positive blood cultures or death). No differences between the groups were noted.

INTERVENTIONS AND DNT

Baseline DNT was measured and potential delaying factors were identified. Sixty patients were included in this period. *Figure 1* shows the effects of implemented interventions on DNT during the project period. Median DNT at baseline was 183 minutes (IQR 122 to 296).

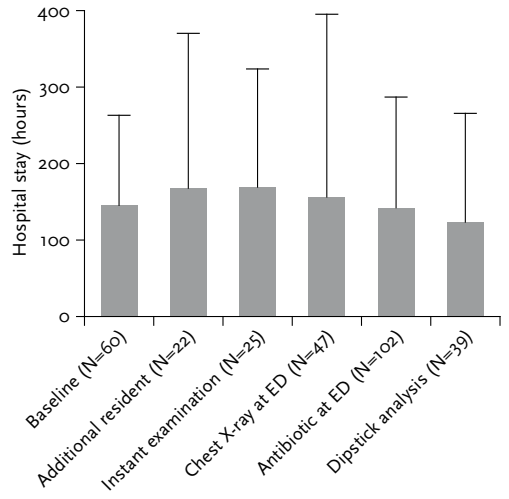
1. The first intervention consisted of two parts. Firstly, the attendance of an additional resident during peak hours. Earlier research at the ED of our hospital showed a peak of patients' visits between 18.00 and 21.00 hours. Unfortunately, during this period the residents changed shifts. Therefore, the first intervention was to add an extra resident at the ED during these peak hours. Secondly, a planning board was installed to enable ED staff to coordinate the care of patients at the ED better. Both interventions reduced DNT slightly to 169 (IQR 120-348) minutes.
2. During discussion meetings it became clear that most residents waited for the laboratory results before examining the patient, which is likely to result in a delay in antibiotic administration. Therefore, the second intervention required residents to immediately examine patients after arrival at the ED. This intervention resulted in a small increase in DNT to 176 (IQR 101 to 250) minutes compared with the DNT after implementation of the first intervention, but still a decrease compared with baseline measurements.
3. Prior analyses of the chest X-ray process showed a 45-minute delay in taking and assessing a chest X-ray at the (external) Radiology Department. So, the third intervention consisted of taking chest X-rays immediately at the ED instead of the Radiology Department. The combined effect of the first three interventions increased DNT to 196 (IQR 138 to 319) minutes.
4. An interim analysis showed a delay in iv antibiotic administration, when administration took place on the ward instead of the ED (*figure 3*). Therefore, the fourth intervention was to administer all iv antibiotics at the ED instead of the ward. The cumulative effect of the first four interventions resulted in a substantial DNT decrease to 147 (IQR 93 to 207) minutes (p=0.014) when compared with the baseline DNT.
5. The results of the project were discussed with the residents and their supervisors. It became clear that in patients with the suspicion of a severe infection a positive result from a urine analysis was enough to start antimicrobial treatment. Because results of urine analysis done at the ED were available faster than results of blood tests, it was decided to introduce a final intervention: to perform a primary dipstick urine analysis at the ED. By adding this fifth intervention, the DNT showed a slight increase to a median DNT of 155 (IQR 95 to 221) minutes. Finally after all five interventions were implemented the DNT was reduced by 15.3% (p=0.040) when compared with baseline DNT.

Figure 1. *Effect of the interventions on the door-to-needle time in minutes*



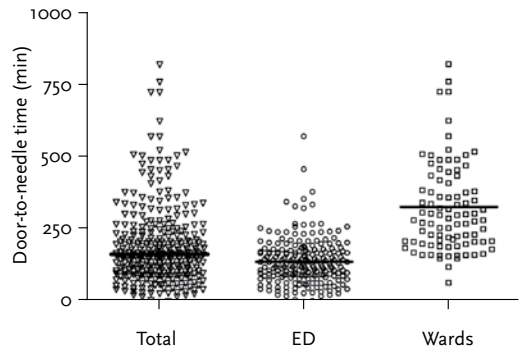
Absolute numbers (median, IQR) of all included patients after each new intervention are given. *p=0.14 compared with baseline.

Figure 2. *Effect of the interventions on the hospital stay in hours*



Absolute numbers (median, IQR) of all included patients after each new intervention are given.

Figure 3. *Effect of the location of antibiotic administration on the door-to-needle time in minutes*



All dots are individual patients. ED=Emergency Department.

Additional assessment was carried out one year later at the ED to study whether the interventions still had an effect on the DNT. During a one-month period, we included 35 patients with the same criteria as all the other patients in this project. We found a comparable median DNT of 153 minutes (IQR 109 to 194).

HOSPITAL STAY AND PRESENTATION TIME

Figure 2 shows the effects of the five implemented interventions on hospital stay (HS). Median baseline HS was 144 hours (IQR 96 to 264) (6 days). After the first, second and third intervention the HS increased to 168 (IQR 96 to 354) hours (7 days), 168 (IQR 108 to 324) and 156 hours (IQR 72 to 402) (6.5 days), respectively. After the fourth intervention HS returned to baseline, namely 144 (IQR 96-288) hours (6.0 days). Finally, after implementation of the fifth intervention the combined effect of all interventions reduced HS to 120 hours (IQR 72-264) (5 days), when compared with baseline HS, leading to a trend towards a significant reduction of HS from 16.7%. Median DNT appeared to be shorter (145 minutes, IQR 95-201) in patients who arrived at the ED at night (between 17.30 and 20.30 hr) than in patients who arrived during office hours (173 minutes, IQR 118 to 258) (p=0.006).

DISCUSSION

The aim of this project was to decrease the door-to-needle time (DNT) and hospital stay (HS) in patients with a severe infection by using tailored interventions. After five tailored interventions, the DNT and HS were reduced by 15.3 and 16.7%, respectively.

Despite availability of treatment guidelines for the most serious infections, the efficiency of the process depends on many factors. Patients arriving at the ED are seen by a multidisciplinary team of professionals in an often busy and chaotic setting. We studied the effect of a reduction in the DNT in patients with a severe infection, not only pneumonia. Previously, it was shown in several studies that a reduction in DNT is possible in patients with pneumonia by using specific interventions. Examples of interventions in these studies are educational interventions.[9,10] Investigators educated the ED staff about the importance of rapid antibiotic delivery and confronted the staff with long DNT in their hospital. Another example is a multifaceted strategy, in which a steering committee designed a care pathway,[11] based on existing guidelines. The interventions in those studies were implemented using a combination of information packs, interactive group educational sessions, using posters and electronic reminders.

In a comparable project in another Dutch university hospital,[12] Natsch *et al*. used interventions such as newsletters and lectures to inform the medical staff about the delay in administration of antibiotics and distributed guidelines on managing patients and obtaining cultures. In addition, they improved the availability of antibiotics at the ED and removed financial restraints. These interventions are comparable with the interventions we implemented in our project. As expected, they also found a shorter DNT when the patient was admitted during the night, which is comparable with the results of our project. Concerning the DNT, Natsch *et al*. reduced the DNT by 1.8 hours (p=0.04), but started with a longer baseline DNT of 5.0 hours. However, we started with a shorter baseline DNT of 3.0 hours and reduced DNT by 0.47 hours to 155 minutes. Even though our reduction is less spectacular, the final DNT in our project is shorter than reported in earlier research. The literature generally uses a cut-off point of a maximum of four hours concerning DNT. The question remains what minimum DNT is necessary and achievable. It has been shown that each hour of delay in antimicrobial administration was associated with an average decrease in survival of 7.6%,[13] in patients with a septic shock. However, the number of patients in the present project was too small to do a subanalysis for this specific patient population.

After implementation of four out of five interventions, a reduction in DNT was observed in the present project. This fourth intervention stated that all antibiotics had to be given in the ED. This is in concordance with the recently developed guideline for the treatment of community acquired pneumonia in which it is mentioned: the first antibiotic dose has to be administrated while the patient is still at the ED.[14] In our project we noted that not all antibiotic agents were present at the ED and in addition, as a result of our intervention, antibiotics were used in larger doses, which initially resulted in supply problems.

We conclude that only the fourth intervention (antibiotics at the ED) resulted in a clear effect compared with other interventions. The pitfall of DNT reduction, on the other hand, may be that patients at the ED receive doses of antibiotics that are too high, as has been reported for patients with community acquired pneumonia.[15]

Unfortunately, implementing the first three interventions did not really decrease our DNT. This is not due to differences in patients characteristics, since we demonstrated that characteristics of the patients were comparable between the groups. A cumulative effect might have resulted in the decrease after the implementation of the last two interventions. However, our project was not designed to demonstrate the separate effect on the DNT for each intervention. With respect to the secondary outcome parameter HS, it is important to notice that HS is more likely to be influenced by external factors than DNT. For example, difficulties with discharging to nursing homes, because of waiting lists and Christmas holidays. However, implementation of tailored interventions as mentioned can result in a reduction in the DNT and might improve the survival of patients presenting with infections at the ED.

This study was part of a health care innovation project. We included all patients arriving at the ED for a period of nine months. The total number of patients included in this study as well as the distribution between the groups are therefore based on daily practice.

In conclusion, cumulative implementation of tailored interventions, especially administrating antibiotics at the ED, results in a reduction of the DNT.

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PHOTO QUIZ

Sore throat after dumbbell exercises

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CASE REPORT

A 26-year-old man presented to our emergency department (ED) with a progressively sore throat and dysphagia. At bedtime the day before arrival to the ED, he had performed dumbbell exercises. He did not experience abdominal pain, nausea, or vomiting. In addition, the patient denied a history of trauma or systemic disease, nor did he have a habit of smoking. The vital signs revealed a body temperature of 36.7 °C, blood pressure of 137/72 mm/Hg, heart rate of 64 beats/min and a respiratory rate 18 breaths/min. On physical examination, the neck showed swelling and crepitus on palpitation. Chest examination revealed clear and symmetrical breathing sounds. Laboratory examination was within normal limits.

WHAT IS YOUR DIAGNOSIS?

See page 131 for the answer to this photo quiz.

Netherlands
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PHOTO QUIZ

A dysfunctional central venous line

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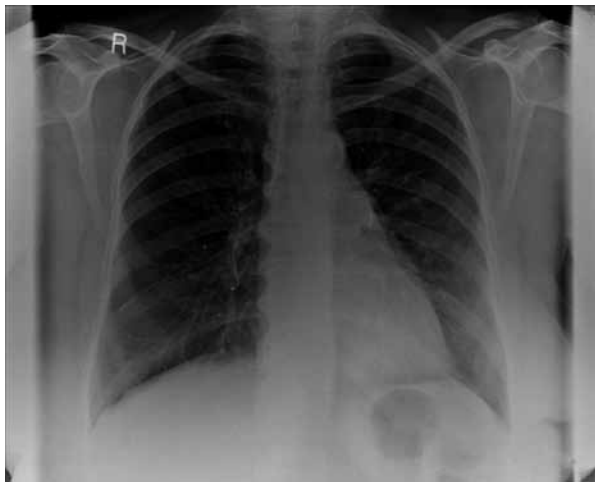
CASE REPORT

A 62-year-old lady with breast cancer had a peripherally inserted central catheter (PICC) line inserted four months ago to receive adjuvant Herceptin therapy. At the time, the chest radiograph confirmed the tip of the line in the superior vena cava. She received three weekly Herceptin with no problems for four months. She attended the chemotherapy day unit to receive the next cycle of treatment, having recently returned from a week's holiday abroad. The chemotherapy nurse was unable to aspirate blood from the line. On examination she could not feel the part of the catheter distal to the external connector. The patient had not noticed any leakage or other changes at the insertion site since her last treatment three weeks ago and was well without any symptoms. She was haemodynamically stable and no abnormality was found on her systemic examination. The line was initially thought to be blocked and a chest radiograph was arranged before urokinase injection.

Figure 1



WHAT DOES THE CHEST RADIOGRAPH SHOW?

See page 133 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

An X-ray that helps to solve the puzzle

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CASE REPORT

A 70-year-old man, who used to be a metalworker, was admitted for analysis of pleural effusion. His medical history revealed longstanding hypertension, atrial fibrillation, transurethral resection of the bladder, heart failure and renal failure for which he was treated with haemodialysis. He did not mention any complaints besides some migrating pain of the knee and the wrist after activity. He did not have morning stiffness and could sleep well. On physical examination a raised right lung border was found. No lymph nodes were palpable. The left knee showed minimal hydrops without other signs of arthritis. Laboratory investigations showed a raised erythrocyte sedimentation rate (83 mm/h), leucocytes of 9.4/mm^2, a monocytopenia (0.09/mm^2), a lactate dehydrogenase of 352 U/l and a C-reactive protein of 1.45 mg/dl. Serology was negative for anti-CCP, complement factors, antinuclear antibodies, antineutrophil cytoplasmic antibodies and rheumatic factor. A puncture of the pleural fluid showed an exsudate. The culture of the pleural fluid showed no growth of bacteria and interferon gamma release assay testing was negative. A PET-CT scan showed the radiological picture of pleural thickening with pleuritis and perirenal inflammation. A pleural biopsy was performed which showed focal accumulation of histiocytes with positive staining for CD68 and negative staining for S100, CD1a and markers for a mesothelial origin. A bone marrow puncture showed no abnormalities. Bone radiographs of the legs and arms were taken, which confirmed the suspected diagnosis (*figures 1* and *2*).

WHAT IS YOUR DIAGNOSIS?

See page 134 for the answer to this photo quiz.

Figure 1.

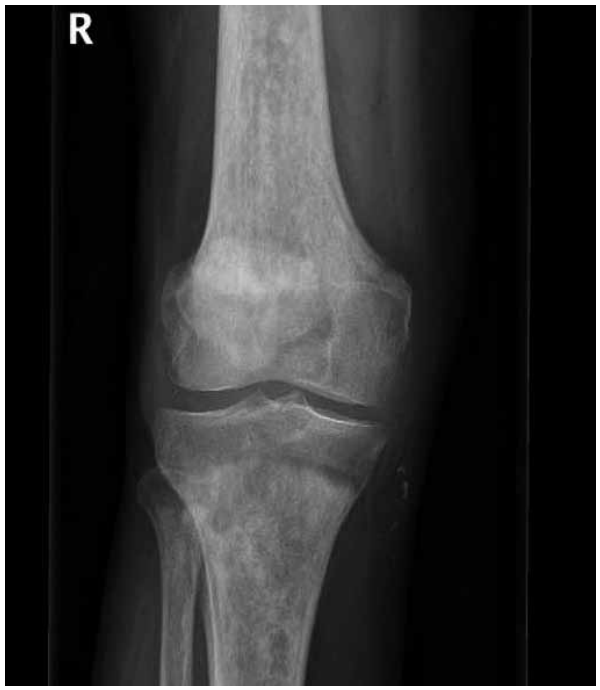
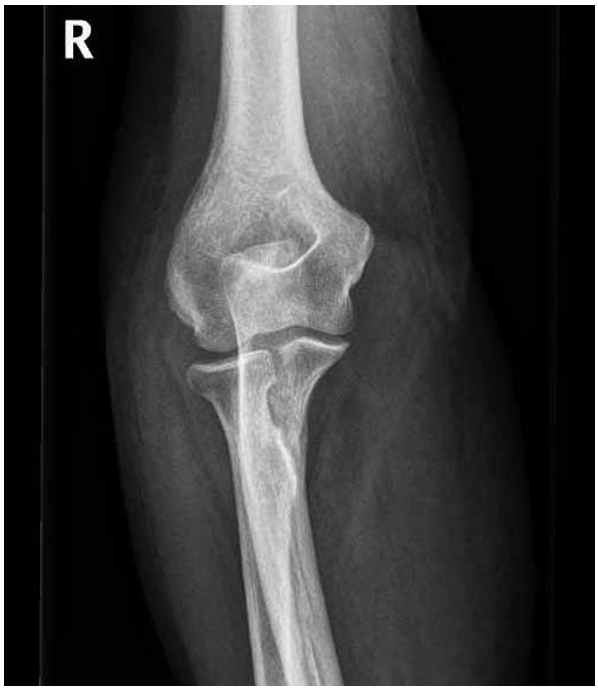


Figure 2.



ANSWER TO PHOTO QUIZ (PAGE 128)

SORE THROAT AFTER DUMBBELL EXERCISES

DIAGNOSIS

Conventional radiological imaging revealed retropharyngeal free air (*figure 1*). Coronal computerised tomography (CT) of the chest illustrated subcutaneous emphysema of the neck and pneumomediastinum. Axial CT of the chest illustrated free air acuminated along with the vessel of bronchioles (*figure 2*). He was treated with oxygen via nasal cannula with rate 3 l/min and analgesics. After treatment for two days, his symptoms improved and after one week the subcutaneous emphysema had disappeared on plain radiograph and the patient had made an uneventful recovery.

Spontaneous pneumomediastinum (SPM) is an uncommon entity, characterised by the presence of free air in the mediastinum, developing in the absence of traumatic or iatrogenic causes or preceding pulmonary pathology such as emphysema, chronic bronchitis or lung cancer.[1] It generally affects young adults, especially tall thin males. Young patients with SPM typically present with a history of asthma or recent inhalation of cocaine, methamphetamine, ecstasy, marijuana or hydrocarbons.[2] Other causes include rapid ascent in scuba divers, Valsalva manoeuvres, vomiting, infections, and extreme effort when the glottis is kept closed. The rise in pressure inside distal alveoli, usually up to values greater than 40 mmHg, produces a pressure gradient between them and the adjacent vessels; this results in alveoli rupture.[3] In our case, the patient held his breath inappropriately during dumbbell exercises resulting in elevated pressure inside distal alveoli causing their rupture. The most common presentation of SPM is nonspecific pleuritic chest pain with dyspnoea. Potential life-threatening consequences

Figure 1. *Conventional radiological imaging shows retropharyngeal free air (horizontal arrow) and subcutaneous emphysema (oblique arrow)*

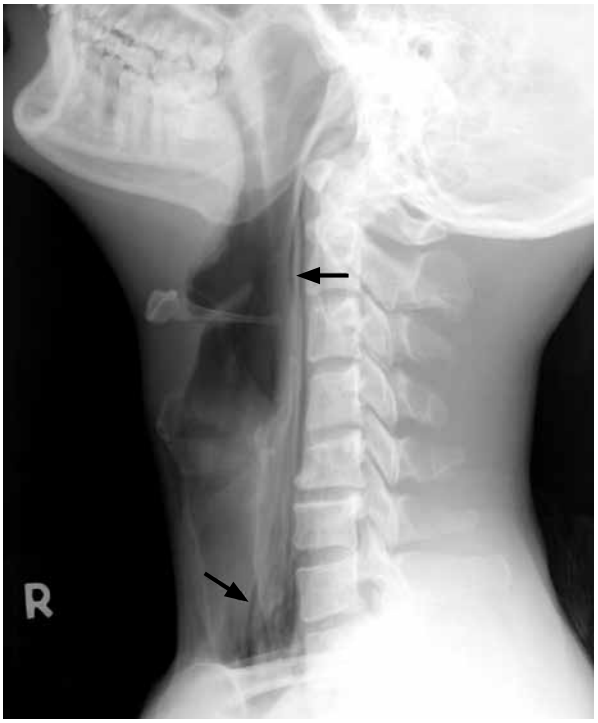
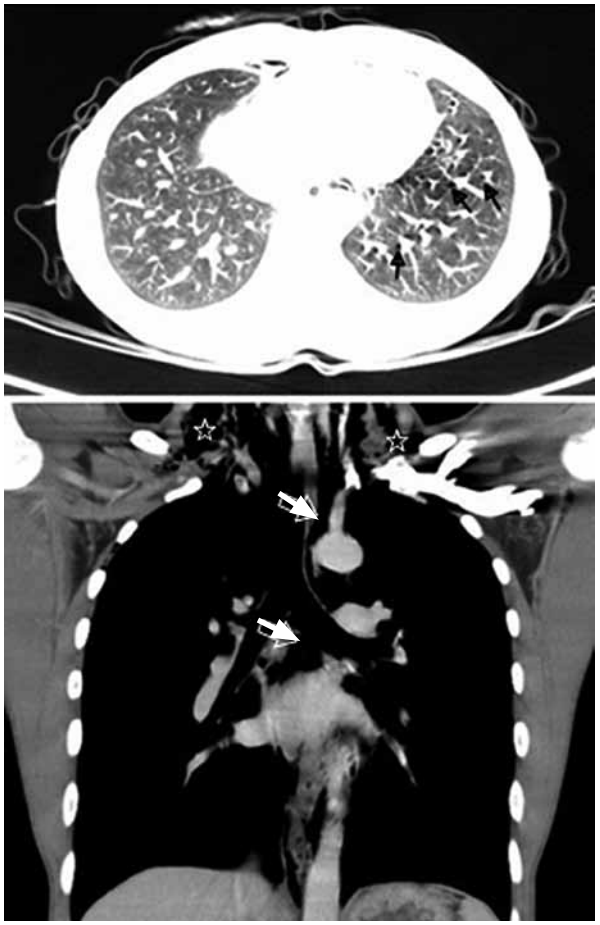


Figure 2. *Axial CT of the chest illustrates free air acuminated along with the vessel of bronchioles (black arrows). Coronal CT of the chest illustrates subcutaneous emphysema (asterisks) of the neck and pneumomediastinum (white arrows)*



include oesophageal rupture and tension pneumothorax, mediastinitis, deep neck infection and pneumothorax, which may require urgent treatment. Neck or chest radiology and CT are the basic diagnostic tools for the diagnosis of SPM. However, an extensive workup might be necessary in potentially life-threatening conditions. Treatment is generally limited to observation with the air typically reabsorbing over a period of one to two weeks without intervention and only rare recurrence.[4]

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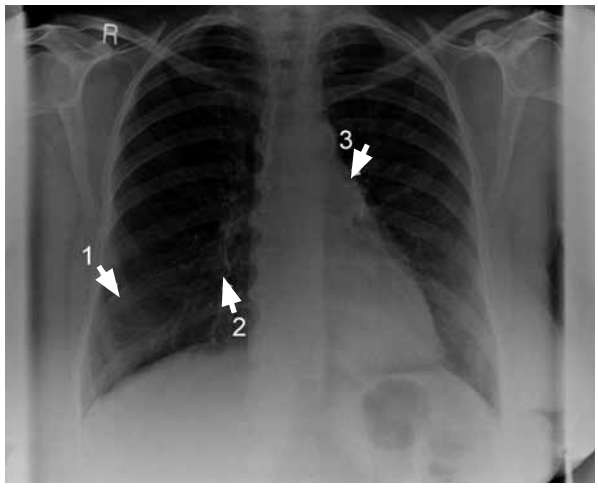
ANSWER TO PHOTO QUIZ (PAGE 129)

A DYSFUNCTIONAL CENTRAL VENOUS LINE

DISCUSSION

The chest radiograph revealed the entire piece of PICC line lying in the right main pulmonary artery (arrows 1, 2, and 3) with both ends in the medial and lateral basal segment branches in the right lower lobe (arrows 1 and 2). It was later removed successfully by endovascular snaring. PICC lines are widely used to administer intravenous therapy in patients with cancer. They have the advantage of providing easier venous access, especially in situations where prolonged intravenous treatment is required and are associated with fewer complications compared with centrally placed tunnelled lines. Fracture and embolisation of PICC lines are very rare, but can cause potentially serious complications such as pulmonary embolism, cardiac arrhythmias, cardiac perforation and sepsis.[1] Patients may present with symptoms such as pain or dyspnoea. Alternatively, they may be asymptomatic and present simply with a PICC line that cannot be flushed, as in this case. The treatment of choice is endovascular snaring.[2] The incidence of this complication is likely to rise as PICC lines are increasingly used in patients undergoing intravenous outpatient therapy.[3] Physicians and nurses therefore need to be more aware of this potential complication and a chest radiograph should be requested if unable to aspirate.

Figure 2.



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ANSWER TO PHOTO QUIZ (PAGE 130)

AN X-RAY THAT HELPS TO SOLVE THE PUZZLE

DIAGNOSIS

The radiographs showed sclerosis of the diaphyseal and metaphyseal regions. The combination of the radiological signs, histological abnormalities, the pleural thickening, pleural effusion and perirenal inflammation confirmed the diagnosis of Erdheim-Chester disease. Erdheim-Chester disease is a non-Langerhans cell histiocytosis of unknown aetiology with a broad clinical spectrum. The diagnosis is based on the typical radiographic signs of symmetrical sclerotic or mixed sclerotic and lytic lesions of the metaphyseal and diaphysial regions combined with specific histological features of histiocytic infiltration with positive staining for CD68 and negative staining for S-100 and CD1a.[1] Bone pain is a typical complaint but approximately half of the patients exhibit extraskeletal manifestations as well.[2] These manifestations can be present in multiple organs such as the lung and kidney, as illustrated in this report. In total, 20 to 35% of the patients exhibit pulmonary disease, which can consist of interlobular septal thickening, centrilobular nodular opacities, fissural thickening, pleural thickening and pleural effusions.[3] Renal involvement of Erdheim-Chester disease is described as well. Perirenal involvement in Erdheim-Chester disease is characteristically manifested as a rindlike soft-tissue (inflammation) surrounding the kidneys and ureters.[4]

The prognosis of the disease depends on the extent and distribution of the extraskeletal manifestations. In general, one third of the patients with pulmonary involvement die within six months. Treatment is still controversial. Corticosteroids, interferon alpha, cyclophosphamide and surgery all have been described, but there is no consensus concerning the optimal treatment modality and the influence on the prognosis.

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Netherlands
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CASE REPORT

Hyperthyroidism caused by excessive consumption of sausages

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ABSTRACT

Hyperthyroidism results from excessive production of thyroid hormones. This is usually caused by Graves disease, but exogenous thyroid hormones can lead to similar symptoms. Recognition of the latter is difficult as excessive intake of thyroid hormone is not usually admitted nor recognised. To our knowledge, exogenous hyperthyroidism caused by thyroid-contaminated food has been described twice, but not in the Netherlands.

A 77-year-old man presented at the Outpatient Department of Internal Medicine with lab values revealing hyperthyroidism. There were no abnormal findings at the physical examination. Antibodies against the thyroid-stimulating hormone (TSH) receptor were not detectable. Thyroid scintigraphy with ^{123}I showed an uptake of less than 1%. Silent thyroiditis was diagnosed and the natural course was awaited, but with no improvement in the thyroid values. The thyroglobulin was very low. Further anamnesis revealed an excessive daily consumption of sausages. Thyroid hormones were detectable in these sausages. After the patient stopped eating them, he became and remained euthyroid. The case stipulates the importance of a thorough anamnesis.

KEYWORDS

Exogenous hyperthyroidism, sausages, thyroid hormone

INTRODUCTION

Hyperthyroidism usually has an endogenous cause such as Graves disease, toxic multinodular struma or silent thyroiditis. A less frequently recognised cause is exogenous hyperthyroidism, in which the hyperthyroidism is the result of an excessive intake of thyroid hormone. This is either done deliberately or by accident. We describe a patient with an exogenous hyperthyroidism caused by excessive intake of sausages contaminated with thyroid hormone.

PATIENT HISTORY

Patient A, a 77-year-old male, was referred to our Outpatient Department of Internal Medicine by the general practitioner because of abnormal lab values revealing hyperthyroidism. His medical history included hypertension, myocardial infarction and a coronary bypass surgery. His medication consisted of carbasalate calcium, quinapril and pravastatin; there was no history of amiodarone use. He complained of involuntary weight loss, 12 kilos in one year. He noted no diarrhoea, sweating, palpitations or neck pain. On examination he was not ill-looking, he was slightly overweight (BMI 25.5 kg/m^2), with a blood pressure of 110/60 mmHg and a pulse of 80 beats/min. Examination of heart, lungs, abdomen and extremities showed no abnormalities, the thyroid was not enlarged and had a normal consistence. Laboratory results

What was known about this topic?
Hyperthyroidism can be caused by exogenous intake, and it is not always recognised. Food in itself is not often considered a cause.

What does this add?
This article stresses the importance of a thorough anamnesis and search for a causative agent for hyperthyroidism, and not to diagnose a silent thyroiditis too easily.

showed a hyperthyroidism (reference values between brackets); thyroid-stimulating hormone (TSH) of 0.01 (0.44 to 4.22) mU/l and a free T_4 of 21.9 (7.0 to 17.1) pmol/l. Total T_3 and total T_4 were also elevated at 3.6 (1.0 to 3.0) and 178 (72 to 161) nmol/l, respectively. Antibodies against the TSH receptor were not detectable. Other lab values were in the normal range.

Thyroid scintigraphy with ^{123}I showed an uptake of less than 1%. We made the diagnosis of silent thyroiditis in this patient and awaited the natural course. After six months the patient's TSH/free T4 values had not improved. A control thyroid scintigraphy again showed a very low uptake: 3%. Thyroglobulin was tested to exclude exogenous hyperthyroidism; it was very low at 0.7 pmol/l (2.5 to 50.0). The patient had not had any contact with potential thyroid-containing food supplements or iodide-containing roentgen contrast. He did eat a large amount of sausages (300 g/day) bought at a budget supermarket. We tested two sausages for thyroid hormone. The sausages indeed contained T_4 (26 and 71 ng/g) and T_3 (7 and 3 ng/g) (no reference values, no confidence interval known). So, the patient was consuming between 7.8 and 21.3 µg T_4 and between 2.1 and 1 µg T_3 a day. We advised the patient to stop eating sausages of this specific brand after which he became and remained euthyroid. The thyroid scintigraphy after five months showed an uptake of 13%. We concluded that this patient had an exogenous hyperthyroidism caused by excessive intake of thyroid-containing sausages. We reported the case to the Dutch food authority.

Table 1. *Causes of thyreotoxicosis*

Frequent	Rare
Graves disease	Silent thyroiditis
Toxic multinodular struma	Thyroiditis post partum
	Hashimoto toxicosis (patients eventually become hypothyroid)
	Choriocarcinoma, germ cell tumours (direct stimulation TSH receptor by HCG)
	Radiation thyroiditis
Iatrogenic (excessive thyroxin suppletion in hypothyroidism)	Medication-induced thyroiditis (amiodarone, interferon-α, interleukin-2)
Knowingly suppressing TSH with exogenic thyroxin suppletion for control of struma or thyroid carcinoma	Ectopic thyroid tissue (struma ovarii)
	Pregnancy
	Functional metastatic follicular carcinoma
	TSH-producing pituitary adenoma
	Thyreotoxicosis factitia

TSH = thyroid-stimulating hormone; HCG = human chorionic gonadotropin.

DISCUSSION

Epidemiology

There is little known about the incidence and prevalence of thyreotoxicosis factitia. In the literature we found reports on outbreaks of hyperthyroidism caused by eating hamburgers containing ground beef thyroid (Nebraska 1984,[1] Minnesota 1986[2]). In 2001 a Canadian case report described hyperthyroidism caused by eating grounded beef.[3]

Causes

Excessive intake of thyroid hormone is usually accidental: patients are prescribed the wrong dose of levothyroxin by their doctor or children take a parent's medicine. Patients trying to lose weight can take thyroid hormone on purpose, or consume it accidentally (diet pills).[4] Beef containing ground thyroid is found incidentally as described above.[1-3] In *table 1*, we list the most frequent causes.

Symptoms

The symptoms depend on the amount and sort of thyroid hormone ingested. T_3 will cause symptoms earlier due to a greater absorption and a higher activity. Age is an important factor, younger and healthier patients experience fewer symptoms. Presentation of a patient with an exogenous hyperthyroidism resembles other causes such as Graves disease or toxic multinodular struma. Tachycardia and elevated systolic blood pressure are often present in patients with exogenous hyperthyroidism. Struma and exophthalmia are usually not present.[3,4]

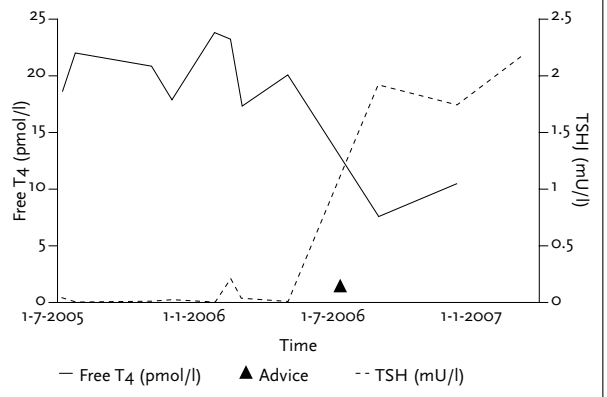
Diagnosis

Exogenous hyperthyroidism must be considered when a patient has hyperthyroidism, no struma, a low uptake in thyroid scintigraphy and a low serum thyroglobulin. A low uptake in a thyroid scintigraphy, due to suppression of TSH secretion, is present in exogenous hyperthyroidism, thyroiditis or in iodide-induced hyperthyroidism. The final diagnosis can be made by testing thyroglobulin as thyroglobulin is low in exogenous hyperthyroidism and elevated in the other causes of hyperthyroidism.[3-5] One study evaluated faecal T_4 measurements to diagnose exogenous hyperthyroidism. Faecal T_4 was increased twofold (normal subjects 1 nmol/g) in patients with Graves disease and 12 to 24-fold increased in patients with exogenous hyperthyroidism.[6] Serum concentrations of T_4 and T_3 can be useful to diagnose which kind of thyroid hormone is ingested.

Treatment

Treatment is symptomatic and consists of discontinuation of the intake of thyroid hormone and, if necessary, β-blockade for relief of symptoms.[4,5] Acute intoxication

Figure 1. *Thyroid function in time. Arrow: moment at which the patient was instructed to quit eating the sausages*



after excessive intake can be treated with a gastric lavage. When the intoxication is life-threatening, plasmapheresis can be considered, but is only partially effective as 25 to 30% of the total ingested dose is removed.[4]

CONCLUSION

Hyperthyroidism is rarely caused by excessive intake of thyroid hormone. As mentioned above, there have been published cases of hyperthyroidism due to intake of beef with ground thyroid. In 1933, hyperthyroidism caused by iodised kitchen salt was described by Pinkhof.[7] As far as we know, this is the first case of hyperthyroidism caused by ground beef in the Netherlands. We do not know how the sausages where contaminated with thyroid tissue and how long they had been contaminated. Perhaps there are more cases which have not been recognised (yet), and we ask colleagues to be aware of this possibility.

ACKNOWLEDGEMENT

The authors wish to thank Dr. J. ten Kate, clinical chemist, for the analyses of the thyroid hormones in the sausages.

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Netherlands
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CASE REPORT

Human recombinant insulin and amyloidosis: an unexpected association

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ABSTRACT

A 48-year-old patient with diabetes mellitus was treated with human (recombinant) insulin. He developed cutaneous amyloidosis twice at different locations where subcutaneous insulin had been injected. There were no signs of systemic amyloidosis. Additional pathological-anatomical investigations demonstrated insulin in one (the most recent) amyloid tumour. A limited number of similar cases have been reported in the literature, although mostly associated with porcine insulin. Cutaneous amyloidosis may be associated with local injections of human (recombinant) insulin. One should therefore also consider this diagnosis when finding tumours at sites where insulin has been injected.

KEYWORDS

Diabetes mellitus, amyloidosis, insulin

INTRODUCTION

Diabetes mellitus is a disease with a high incidence and prevalence. A large number of diabetes patients are being treated with subcutaneously injected insulin. Local complications include infections and the development of lipoatrophic and lipohypertrophic areas. Cutaneous amyloidosis is not a frequent complication. In this manuscript we describe a patient who repeatedly developed amyloid tumours at insulin injections sites.

CASE REPORT

A 48-year-old man had been visiting our outpatient clinic since 1995 for treatment of his type 2 diabetes mellitus. His medical history included Horton's neuralgia (1982), an epileptic seizure during an episode of hypoglycaemia (1998) and essential hypertension (2003). The patient was initially treated with oral antidiabetic agents, but started insulin therapy in 1995 (Mixtard 30/70, twice a day). After 2000, the treatment was intensified to a regime of human recombinant insulin four times a day (Actrapid, Insulatard). His diabetes was generally well managed and no secondary complications had developed. In 2006, an abdominal tumour of 1 x 2 cm (left side, para-umbilical) was discovered. After excision, pathological-anatomical evaluation revealed an unexpected diagnosis: an amyloid tumour (although it was not clear whether it was an AA-amyloidosis or AL-amyloidosis. Extensive additional tests and examinations were performed, including computerised tomography (CT) scans of his thorax and abdomen, a PET scan, a bone marrow aspiration was obtained and a serum protein electrophoresis. No indications for a systemic amyloidosis were found and the final diagnosis was, therefore, a cutaneous amyloid tumour. The patient remained an outpatient and was checked

What was known on this topic?
Insulin injections may be associated with (local) amyloidosis. Only few findings have been reported in the literature and these were generally associated with porcine insulin.

What does this add?
This case report draws attention to amyloidosis as a rare side effect of – also human recombinant – insulin injections. This case report may also serve to remind physicians to consider this potentially serious side effect when finding a tumour at an insulin injection site.

frequently. In 2008 he complained of a tumour on his left arm. A core biopsy was taken. Again an amyloid tumour (nodular type) was diagnosed. The patient was treated surgically. The pathologist's conclusion (amyloid tumour, compatible with AL light chain) confirmed the diagnosis: microscopic evaluation showed local, poorly demarcated, areas consisting of dense collagenous tissue (*figure 1A*). After staining for amyloid (Congo red), these areas clearly showed apple-green bi-refringence using polarised light (*figure 1B*). This was confirmed in fluorescence after thioflavine staining. Immunohistochemical staining for insulin showed dark deposits in the same areas, which tested positive for the amyloid stains (*figure 1C*). The patient had developed a similar tumour twice in two years, which was remarkable in itself. Retrospectively, it was conspicuous that both amyloid tumours arose at insulin injection sites.

DISCUSSION

Amyloidosis in general

Amyloidosis is a disease characterised by extracellular deposition of fibrils. These are non-dissolvable polymers constructed out of subunits with a low-molecular weight, originating from a large diversity of proteins. Several types of amyloidosis exist; one can generally classify a primary form of amyloidosis (AL) and a secondary form (AA). AL amyloidosis is caused by deposition of immunoglobulin light chains. AA amyloidosis occurs with chronic diseases, especially those involving some form of an inflammatory process. Amyloidosis may affect various organs, but can also be limited to a single organ system. Signs and symptoms are, of course, highly dependent on the organ system involved.

Cutaneous amyloidosis

The skin may also be affected by amyloidosis. Several types of primary cutaneous amyloidosis have been described. The three main forms of primary cutaneous amyloidosis are lichen (or papular) amyloidosis, macular amyloidosis and nodular amyloidosis.[1] In the first two forms amyloid fibrils are deposited in the papillary dermis. Nodular cutaneous amyloidosis is much rarer and may affect dermis, subcutis, but also vascular walls, and it may be attributed to some form of a localised plasma cell dyscrasia. Furthermore, the nodular type has a higher recurrence rate than the other forms. Progression from a local cutaneous form to systemic disease is rare, but in nodular cutaneous amyloidosis progression to a systemic disease has been reported in 7 to 50%.[2,3] Although there is no unanimous form of treatment, cutaneous amyloidosis is often treated by surgical excision. In case of nodular cutaneous amyloidosis, testing for systemic disease and extended follow-up appears appropriate, given the relatively high rate of progression to systemic amyloidosis.

Cutaneous amyloidosis and insulin

In our case it was remarkable that the location of both cutaneous amyloid tumours coincided with the sites at which our patient administered his insulin subcutaneously. The differential diagnosis of a tumour at such a location may include lipohypertrophy, a dermoid cyst or a lipoma, but should also include amyloidosis. As early as in 1983 the occurrence of amyloidosis at insulin injection sites was described in rats.[4] Although numbers are limited, a few diabetes patients have been described in literature, with cutaneous amyloidosis arising at the site of (repeated) subcutaneously administered insulin.[4-11] In several cases insulin (fragments) could be demonstrated in the amyloid tumours, as was the case in our patient. However, most case reports describe cutaneous amyloidosis in relation to non-human, i.e. porcine, insulin. The association with human (recombinant) insulin has, to our knowledge, been reported in even fewer case reports.[6,9] The mechanism of insulin-induced amyloidosis

Figure 1A. *Haematoxylin and eosin staining of the tumour. In the cutis distinct homogeneous eosinophilic areas with low cell density are present*

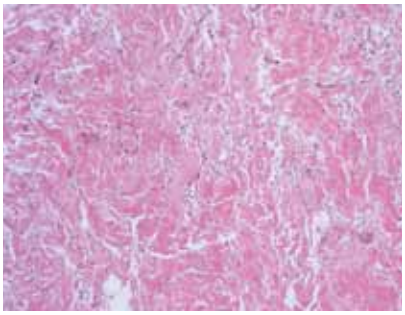


Figure 1B. *Area from figure 1A after staining with Congo red and using polarised light; the homogeneous areas are apple green, which is quite characteristic for amyloid*

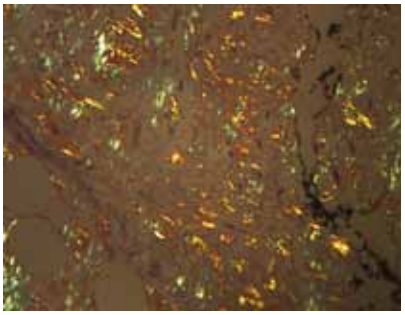
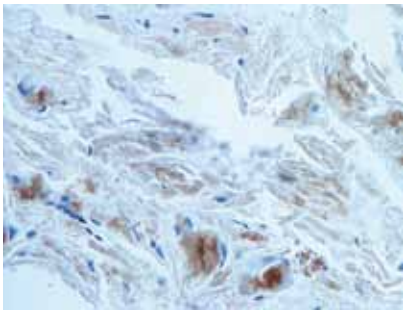


Figure 1C. *Same area as in figure 1B after immunohistochemical staining with an insulin marker. The patchy brown areas are considered to be positive for insulin*



is still unknown; it may be related to local accumulation of insulin, but further study is needed to clarify the pathophysiology of the association.[9]

CONCLUSION

Cutaneous amyloidosis may be associated with local subcutaneous injections of insulin. Although initially only reported in patients using porcine insulin, the association also appears to apply to human (recombinant) insulin. Given the high prevalence of diabetes mellitus and insulin treatment, it is therefore advisable to also consider this diagnosis when finding tumours at sites of insulin injection.

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Netherlands
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LETTER TO THE EDITOR

Tamsulosin and hyperglycaemia in patients with diabetes

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ABSTRACT

Three patients developed hyperglycaemia during tamsulosin use. All patients had diabetes and recovered after withdrawal. A pharmacological mechanism for this adverse drug reaction is suggested: stimulation of the α_1-receptor is one of the insulin-independent pathways for glucose uptake, hence inhibition might increase plasma glucose concentrations. Physicians should be aware of hyperglycaemia as possible adverse drug reaction in patients with diabetes using tamsulosin.

KEYWORDS

Adverse drug reaction, hyperglycaemia, tamsulosin, α_1-receptor antagonist, diabetes

INTRODUCTION

Achieving glycaemic control is one of the key elements in disease management of patients with type 1 or type 2 diabetes.[1] Maintaining glucose levels has proved to have a positive effect on diabetic complications.[2,3] Hyperglycaemia is defined as an increased level of plasma glucose. The following cut-off levels for concentrations in venous plasma are used: ≥11.1 mmol/l in non-fasting and ≥7.0 mmol/l in fasting conditions.[4]

Tamsulosin is an α_1-receptor antagonist that binds selectively and competitively to α_1-receptors. It is indicated for the treatment of urinary tract symptoms related to benign prostate hyperplasia.[5] Common adverse drug reactions are dizziness, headache, palpitations and nausea.[5] In this paper we present three reports on hyperglycaemia in association with tamsulosin use in patients with type 2 diabetes and discuss a possible pharmacological explanation.

METHODS AND RESULTS

Case reports

The Netherlands Pharmacovigilance Centre Lareb received three reports of hyperglycaemia in association with the use of tamsulosin. The reporters were contacted to obtain clinical information according to the guidelines for publications about adverse drug reactions.[6] These reports are summarised in *table 1*.

All patients used insulin for diabetes. Patient A was a 61-year-old male with type 2 diabetes, who used oral antidiabetic drugs (metformin and glimepiride) and insulin. He was prescribed tamsulosin for benign prostatic hyperplasia. On the first day of treatment his glucose levels – normal 8 to 9 mmol/l – increased to 18 to 20 mmol/l. After withdrawal his glucose levels returned to normal. The patient was taking metoprolol, quinapril, atorvastatin, acetylsalicylic acid and sildenafil (as needed) as concomitant medication.

What was known on this topic?

- Tamsulosin is an α1-receptor antagonist that can act peripherally
- Hyperglycaemia has not been associated with tamsulosin use in patients with diabetes

What does this add?

- Hyperglycaemia was associated with the use of tamsulosin in three patients with diabetes in the Netherlands.
- The adverse drug reaction is pharmacologically plausible by inhibition of an alternative, insulin independent, α_1-receptor mediated route of glucose uptake.

Table 1. *Reports of increase of blood glucose concentration associated with tamsulosin use*

Patient, sex, age	Suspect drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to first symptoms, outcome
A (75483) M, 61	Tamsulosin 0.4 mg for benign prostatic hyperplasia	Metformin Glimepiride Insulin Metoprolol Atorvastatin Acupril Acetylsalicylic acid Sildenafil	Blood glucose increased (normal level: 8-9 mmol/l; increased to 18-20 mmol/l)	1 day, recovered after discontinuation of tamsulosin
B (61032) M, 67	Tamsulosin 0.4 mg for miction problems	Metformin Insulin Enalapril Atorvastatin Telmisartan Sildenafil	Blood glucose increase (normal 7.5 mmol/l; increase to 18.8 mmol/l) Drug interaction between insulin and tamsulosin	2 days, recovering after discontinuation of tamsulosin
C (53015) M, 71	Tamsulosin 0.4 mg for benign prostatic hyperplasia Insulin for diabetes	Enalapril Simvastatin	Blood glucose increased Drug interaction between insulin and tamsulosin	1 day, discontinuation of tamsulosin, recovered

Patient B was a 67-year-old male who was diagnosed with type 2 diabetes 11 years prior to the adverse drug reaction. Initially he was treated with oral antidiabetic drugs, and after three years insulin was added. The patient experienced few complications from his diabetes and was adherent. The patient visited his GP with micturition problems. He had normal plasma glucose levels of 7.5 mmol/ml, and the GP initiated tamsulosin treatment. Two days later, his plasma glucose had increased to 17.8 mmol/l. Tamsulosin was withdrawn, and the GP now suspected that a urinary tract infection had caused the micturition problems. The patient was treated with antibiotics: first one day of sulphamethoxazole/trimethoprim (discontinued due to hypersensitivity) and subsequently ciprofloxacin. The patient had no fever or other objective symptoms that supported the diagnosis of the urinary tract infection. Glucose levels returned to normal two to three days after withdrawal of tamsulosin. Concomitant chronic medication consisted of insulin, atorvastatin, metformin, enalapril, telmisartan, and sildenafil (as needed).

Patient C was a 71-year-old male who had been diagnosed with type 2 diabetes eight years ago. His diabetes was well controlled, although the patient had complications. The patient was on enalapril for hypertension and simvastatin for hypercholesterolaemia, as concomitant medication. Insulin had been added five years ago; the patient was not taking oral antidiabetic drugs. Glucose levels increased to 10 to 11 mmol/l at one day after tamsulosin was started to treat benign prostatic hyperplasia compared with normal fasting levels of 3 to 4 mmol/l. Within two weeks after withdrawal of tamsulosin, the glucose levels returned to normal. The reporter mentioned that no other explanations for hyperglycaemia were present.

DISCUSSION

In our cases, all patients were diabetic, and this association might be related to patients in whom insulin-dependent glucose uptake is limited. We suggest a potential mechanism that could explain limited glucose uptake by blockade of the α_1-receptor that might be relevant if insulin-dependent pathways are impaired. The Lareb database does not contain any other reports of α_1-receptor antagonists associated with hyperglycaemia.

The major pathway for glucose uptake is insulin-dependent. Glucose is transported into the cell by the GLUT4 glucose transporter.[7] After binding to the insulin receptor, diverse intracellular signalling pathways result in translocation of the GLUT4 glucose transporter, and glucose uptake is initiated.[7]

However, in diabetic patients non-insulin dependent pathways may also contribute to glucose uptake.[8] One of these is regulated by the α_1-receptor.[8-10] Several studies have demonstrated that α_1-receptors mediate increase in glucose uptake in rat muscle cells and adipocytes. Stimulation of the α_1-receptor leads to phospholipase C activation initiating hydrolysis of phosphatidylinositol biphosphonate. This leads to activation of protein kinase C (PKC) by release of intracellular calcium and diacylglycerol.[11] Lipids in the phosphatidylinositol biphosphonate pathway can be substrates for phosphatidylinositol 3-kinase (PI3K), which is an important kinase for glucose uptake.[9] The stimulatory effect of α1-antagonist on glucose uptake was inhibited by the α_1-receptor antagonist prazosin.[8]

The role of the α_1-receptor in glucose uptake in humans was also shown. In two studies, one in healthy[12] and the other in obese subjects,[13] interstitial glucose concentrations were measured using microdialysis. Stimulation with

an α_1-agonist resulted in a decrease of interstitial glucose concentrations.[12,13] The α_1-antagonist uradipil was able to inhibit α_1-agonist induced glucose decrease.[13] Also, α_1-receptor stimulation increased glucose intake in human adipose tissue.[12;13]

The described studies illustrate a potential clinical role for the α_1-receptor in glucose metabolism, especially in diabetic patients in whom insulin-stimulated glucose uptake is impaired.[8] These pathways might be more prominent in obese persons who have relatively more adipose tissue.[13] Inhibition of the α_1-receptor pathway can result in a decreased glucose uptake, and hence an increased glucose plasma concentration.

In patients with diabetes, several other causes might explain hyperglycaemia, such as intake of glucose/carbohydrates, non-adherence to antidiabetic drugs or (infectious) diseases.[14] In our reports, patient B reported a concomitant urinary tract infection which could have contributed to increased glucose levels. However, no objective support for an infection was found. In the patients we have presented, further alternative causes for hyperglycaemia were reported to be unlikely.

This adverse drug reaction and the proposed mechanism need to be further proven. The mechanism might offer a clue for studies in diabetes management: as inhibition of the α_1-receptor can result in decreased glucose uptake, stimulation might lead to increased uptake, which might be relevant, for example, for patients who develop insulin resistance.

In conclusion, we present three cases relating hyperglycaemia to the use of tamsulosin, and propose a plausible pharmacological mechanism. Health care professionals should be aware of hyperglycaemia as possible adverse drug reaction in patients with diabetes using tamsulosin.

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LETTER TO THE EDITOR

Tryps after adventurous trips

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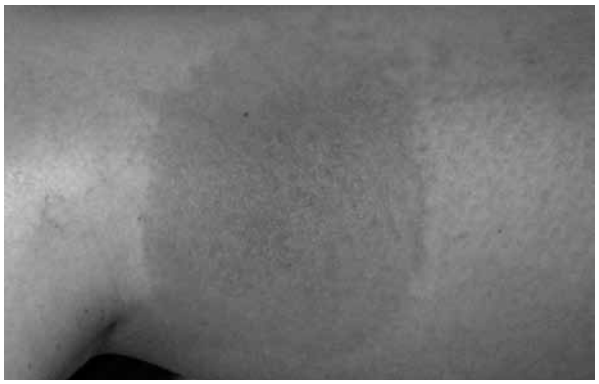
A 30-year-old previously healthy woman was admitted to the general medical ward because of a one-day history of high fever. Six to ten days before, she had visited Tanzania on her honeymoon and went on safari tours in open jeeps in Tarangire, Lake Manyara, Serengeti and Ngorongoro Crater National Parks, successively. She recalled multiple tsetse fly bites. Four days before admission she felt ill and noticed a chancre on her leg (*figure 1*). She was taking atovaquone/proguanil for malaria prophylaxis and had been vaccinated against yellow fever, hepatitis A and B and typhoid fever. On presentation, she looked ill and was jaundiced, not obtunded, with a temperature of 40°C, blood pressure 125/70 mmHg and pulse 120 beats/min. There was no nuchal rigidity and on auscultation discrete crackles were heard over the left chest. A thick smear revealed no malaria parasites but trypomastigotes of *Trypanosoma brucei* spp. Her laboratory results revealed pancytopenia (haemoglobin 6.6 mmol/l, leucocytes 2.2 x 10^9/l, thrombocytes 37 x 10^9/l), diffuse intravascular coagulation, metabolic acidosis, elevated bilirubin (212 µmol/l, conjugated fraction 0.66), ASAT (594 U/l) and ALAT (416 U/l), serum creatinine 55 µmol/l and a mild proteinuria.

Figure 1. *Chancre on the left calf 4 days after its first appearance due to infection with Trypanosoma cruzei rhodesiense after a bite by an infected tsetse fly*



To exclude central nervous system infestation, a lumbar puncture was performed. Cerebrospinal fluid analysis was normal with no trypomastigotes. The electrocardiogram showed repolarisation abnormalities and her chest X-ray was normal. She was treated with suramine intravenously, first with a test dose of 200 mg and then 1000 mg on days 1, 3, 10, 17, 24 and 31. The following day, she developed progressive dyspnoea. Now the chest X-ray showed diffuse changes compatible with acute respiratory distress syndrome (ARDS) and she was transferred to the intensive care unit, where hydrocortisone was given from day 2 to 4 and supportive care. No intubation or vasoactive medication were required.

Clinical improvement started on day 3. On day 4 the blood smear was negative for trypomastigotes. The proteinuria disappeared during treatment. However, her serum creatinine gradually increased to 110 µmol/l three months after the start of the treatment, with a creatinine clearance of 79 ml/min. No other side effects of the suramine were noticed (adrenal insufficiency, polyneuropathy). After six months she has fully recovered and the serum creatinine has normalised.

This patient presented with acute sleeping sickness or human African trypanosomiasis (HAT) with severe disease and multi-organ involvement four to five days after the first symptoms and after a remarkably short incubation time of less than seven days following visits to game parks in Tanzania.

In 2002, Jelinek *et al.*[1] reported nine cases of sleeping sickness among tourists travelling to the Tarangire and Serengeti National Parks in Tanzania. Three of them had multiple organ failure and one died. In travellers to endemic areas, blood smears for malaria should also be examined for trypomastigotes. Not all textbooks mention icterus as an early sign of HAT as we observed in this patient. A lumbar puncture in the diagnostic workup is controversial: meningo-encephalitis is unlikely in the first week of illness and false-positive results may occur, which could prompt unnecessary treatment with the toxic

melarsoprol. Theoretically, accidental contamination of the cerebrospinal fluid after a traumatic lumbar puncture is possible, although proven cases have not been described. HAT is caused by protozoa of the *Trypanosoma* genus. Transmission to humans occurs by the bite of a tsetse fly (*Glossina* genus), infected with either *T. brucei gambiense* or *T. brucei rhodesiense*. Less than 10% of cases are caused by *T. brucei rhodesiense* and can be found in Eastern and Southern Africa.[2] Since the year 2000, when the World Health Organisation reinforced surveillance and disease control measures, the number of reported cases of East African sleeping sickness has stabilised: 669 in 2000 and 486 in 2006.[3,4]

Tourists travelling to endemic areas are at risk, although the risk of acquiring trypanosomiasis is much lower than malaria. The number of tourists returning to Europe yearly with HAT is not known, but presumably very low. Travellers to endemic areas should be made aware of the risk of acquiring trypanosomiasis and minimise exposure to the bite of the vector.

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

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