Nail haemorrhage after high altitude; what is your diagnosis?

Hypocalcaemia of malignancy

Biochemical response and management of PBC

Quality of life, rehabilitation and mortality in a nursing home population

Reagent strips for spontaneous bacterial peritonitis

Risk stratification for healthcare planning in gestational diabetes
The Netherlands Journal of Medicine

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Primary biliary cholangitis, let’s try to keep the new nomenclature correct!

F. Harinck

Department of Gastroenterology and Liver Diseases, Erasmus MC, Rotterdam, the Netherlands, f.harinck@erasusmc.nl

It is only recently that the term primary biliary cirrhosis was changed into primary biliary cholangitis (PBC). One of the main reasons to do so was because the former name did not reflect the natural history of the disease in the vast majority of today’s patients. When the disease entity of PBC was established, advanced liver disease showing histological and clinical findings of cirrhosis was found in most of the patients. Since the introduction of antimitochondrial antibodies for the diagnosis of PBC, the majority of patients are diagnosed in the early stages, well before the cirrhosis stage. As most of these patients with early stage PBC respond well to medical therapy, it is in just a minority of patients that the disease will eventually progress to cirrhosis.

PBC is a chronic cholestatic disease of which the cause is still unknown. It is a slowly progressive autoimmune disease characterised by portal inflammation and necrosis of cholangiocytes in the small and medium-sized bile ducts. PBC has a strong female preference. The mean age at time of diagnosis is around 50 years.

Ursodeoxycholic acid (UDCA) is currently the only therapeutically effective agent for PBC. This drug does not cure but delays histological progression. After the introduction of UDCA in the 1990s the prognosis of PBC has dramatically improved. At present, two out of three patients diagnosed with PBC and treated with UDCA have an expected survival not different from the general population.

Ursodeoxycholic acid (UDCA) is currently the only therapeutically effective agent for PBC. This drug does not cure but delays histological progression. After the introduction of UDCA in the 1990s the prognosis of PBC has dramatically improved. At present, two out of three patients diagnosed with PBC and treated with UDCA have an expected survival not different from the general population. There is currently no consensus on how to treat patients with a suboptimal biochemical response to UDCA. Other drugs have been tested, but none have been found to be of benefit as single agent. The European guideline suggests a combination of UDCA and budesonide (6-9 mg/d) in non-cirrhotic patients (stages 1-3); however, the grade of evidence for this approach is low (grade III/Ca).

The biochemical response to UDCA after one year of treatment is an important indicator for the prognosis of PBC. Previous studies have shown that for patients fulfilling criteria for ‘good biochemical response’ the long-term outcome is significantly better than for non-responders. Non-responders remain at risk for requiring liver transplantation or premature death. Key papers with respect to the important prognostic information of biochemical response are those of Angulo et al. and of Pares et al.

This current issue contains a paper by Lammers et al. entitled ‘How the concept of biochemical response influenced the management of primary biliary cholangitis over time’. This is a retrospective study of a Dutch cohort of 851 PBC patients over a considerable period of time (1988-2011). The focus of this paper was to evaluate to what extent liver test results influenced patient management during a three-decade period, and whether this changed over time. In other words, if a patient was a non-responder on UDCA, was the therapeutic treatment modified in order to which this non-responder did respond effectively? For example, were other drugs added to UDCA? Unique to this cohort is that the study period includes both 1999 and 2006, the years in which the key papers with respect to the relevance of achieving good biochemical response were published. It could be expected that after these publications clinicians would be more aware of the importance of a good biochemical response and would adapt their clinical practice in the non-responders.

The authors found that management was modified in only a minority of the non-responders. They did not observe an increase of response-guided management over time. The most frequently seen modification was an increase in UDCA dose. Remarkably, budesonide was not added to UDCA in any of the non-responders.

I am not sure whether these somewhat ‘disappointing’ results are due to the lack of awareness among clinicians with respect to the concept of biochemical response. It seems logical to assume that this can mainly be explained due to the fact that we currently lack good second-line therapy. Fortunately, clinical trials are currently being...
conducted and will hopefully result in effective alternative treatment within a short time. In the meantime, we cannot do better than to follow the guidelines in order to hopefully prevent cirrhosis from developing for both responders and non-responders. In order to try to keep the new nomenclature ‘correct’ for all patients with PBC.

REFERENCES


Hypocalcaemia of malignancy

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ABSTRACT

Background: Hypercalcaemia of malignancy is well recognised, but hypocalcaemia in cancer patients is not, although it is increasingly encountered.

Methods: Analysis of an exemplary case and a narrative review of the literature based on the search terms cancer and hypocalcaemia.

Results: Hypocalcaemia may affect as many as 10% of hospitalised cancer patients. We identified 12 different potential mechanisms of hypocalcaemia of malignancy. Identifying the pathogenesis is essential for the correct treatment and can usually be performed at the bedside, based on serum parathyroid hormone (PTH) levels, creatinine, phosphate, magnesium, creatine kinase, liver enzymes and 25(OH)D. Essentially, decreased or normal PTH hypocalcaemia is seen after removal or destruction of its source, hypomagnesaemia, or cinacalcet treatment. In all other cancer-associated hypocalcaemia, PTH is elevated, including significant renal impairment, critically ill patients, extensive cell destruction (rhabdomyolysis, tumour lysis, haemolysis), acute pancreatitis, adverse drug reactions, cancer or cancer treatment-related malabsorption syndromes, vitamin D deficiency, or osteoblastic metastases. Different mechanisms may often operate in tandem. Pathogenesis determines treatment and affects prognosis. However, hypocalcaemia of malignancy as such did not imply a worse prognosis, in contrast with hypercalcaemia.

Conclusion: Hypocalcaemia in cancer patients is commonly encountered, particularly in hospitalised patients, may be mediated by diverse mechanisms and should be better recognised.

KEYWORDS

Hypocalcaemia, cancer, calcium metabolism, parathyroid hormone, critical care, rhabdomyolysis, tumour lysis syndrome, hypomagnesaemia, vitamin D, osteoblastic metastases.

INTRODUCTION

In patients with cancer, hypercalcaemia is common and may occur in up to 30%, often indicating advanced disease and poor prognosis.1 Lung, breast and haematological malignancies are involved in 84% of the cases but the mechanisms differ. Three major mechanisms have been identified: humoral hypercalcaemia due to secretion of parathyroid hormone (PTH)-related peptide by the tumour (for example, squamous cell carcinomas, renal, bladder, breast, or ovarian cancer), osteolytic bone lesions (for example, breast cancer or multiple myeloma), or production of 1,25-dihydroxyvitamin D (calcitriol) by the tumour (for example, lymphoma).2 In contrast, it is not well known that malignancy may also be associated with hypocalcaemia. A large variety of different and intriguing mechanisms may be involved and their full spectrum is not widely recognised.

Looking at these mechanisms, it might be conjectured that hypocalcaemia of malignancy will be increasingly encountered by clinicians in the future. We will present and discuss this entity in detail following the presentation of an exemplary patient. Our manuscript aims to draw attention to this potentially serious and relatively under-appreciated entity whose treatment is far from being uniform and must be adapted to its pathogenesis. It is based on a narrative review of the literature which covers incidence, pathogenetic mechanisms, aetiology-based diagnostic flowchart, prognosis, and treatment recommendations.

CASE REPORT

A community-dwelling 89-year-old man was admitted with a few days history of cough, dyspnoea and refusal to eat. His past medical history included dementia and prostatitis identified in a biopsy performed five years previously for nocturia and a prostate specific antigen (PSA) level of 20 ng/ml (N < 4 ng/ml). He was not on any
medications. On admission he was afebrile but hypoxaemic (saturation 91%), with bibasilar crepitations, elevated jugular venous pressure and leg oedema. A suprapubic prostatectomy scar was noted. ECG showed minor ST elevation in the precordial leads. Chest X-ray demonstrated pneumonia and pulmonary congestion. Blood test results are summarised in table 1. Six months before, the serum creatinine was 0.8 mg/dl, haemoglobin 10.8 g/dl and platelets 304 x 10^3/µl. Furosemide (80 mg), intravenous fluids (2.5 litres of saline), blood transfusions (2 units of packed cells) and antibiotics (ceftriaxone and azithromycin) were started. No hydronephrosis or masses were found on abdominal ultrasound. Urinalysis was unremarkable, sodium 10 mEq/l. The peripheral blood smear showed no fragmented erythrocytes. While the patient’s renal function improved to normal (creatinine 1.1 mg/dl) and the C-reactive protein significantly decreased, his hypocalcaemia unexpectedly worsened to 4.7 mg/dl with a serum albumin of 2 g/dl. Both were normal six months previously. The patient developed a positive Chvostek sign and prolonged QT interval. Serum phosphate, magnesium and creatine kinase were normal (table 1). The 25-hydroxyvitamin D level was 10.0 ng/ml (N > 50 ng/ml; < 8-10 identifies patients at high risk for osteomalacia). Intact parathyroid hormone (PTH) was increased to 319 pg/ml (N 15-68 pg/ml). Urinary 24-hour calcium level was 40 mg (N 100-300 mg). The prostatectomy pathology report arrived from another hospital, revealing that a markedly enlarged prostate (9 x 5.5 x 5 cm) resected four years ago had six foci of carcinoma involving the surgical margins, Gleason score 6. A bone scan was then normal and the patient declined treatment. A 99mTc bone scintigraphy now revealed symmetric homogenous increased uptake in the skeleton, so called ‘super scan’ (figure 1), consistent with extensive bone metastases of prostate cancer. The current PSA returned markedly

**Table 1. The patient’s blood tests on admission**

<table>
<thead>
<tr>
<th>Test</th>
<th>Admission Values</th>
</tr>
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<tbody>
<tr>
<td>Haemoglobin</td>
<td>7.1 g/dl (MCV 86)</td>
</tr>
<tr>
<td>WBC</td>
<td>8.0 x 10^3/µl (normal differential, lymphopenia)</td>
</tr>
<tr>
<td>Platelets</td>
<td>60 x 10^9/µl</td>
</tr>
<tr>
<td><em>Erythrocyte sedimentation rate</em></td>
<td>120 mm/h</td>
</tr>
<tr>
<td><em>C-reactive protein</em></td>
<td>293 mg/d (N &lt; 6)</td>
</tr>
<tr>
<td><em>Ferritin</em></td>
<td>&gt; 2000 ng/ml (N &lt; 320)</td>
</tr>
<tr>
<td>Glucose</td>
<td>98 mg/dl</td>
</tr>
<tr>
<td>Urea nitrogen</td>
<td>58 mg/dl, then 19</td>
</tr>
<tr>
<td>Creatinine</td>
<td>3.3 mg/dl, then 1.1</td>
</tr>
<tr>
<td>Sodium</td>
<td>153 mEq/l</td>
</tr>
<tr>
<td>Potassium</td>
<td>4.2 mEq/l</td>
</tr>
<tr>
<td>Calcium</td>
<td>6.8 mg/dl (corrected for serum albumin: 8.1) (N 8.5-10.5)</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>4.6 mg/dl</td>
</tr>
<tr>
<td>Magnesium</td>
<td>1.9 mg/dl</td>
</tr>
<tr>
<td><em>Albumin</em></td>
<td>2.4 g/dl, then 2.0</td>
</tr>
<tr>
<td>Globulin</td>
<td>3.6 g/dl</td>
</tr>
<tr>
<td>Aminotransferases</td>
<td>37/39 IU/l</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>910 IU/l</td>
</tr>
<tr>
<td>Alkaline phosphatase</td>
<td>860 IU/ (N &lt; 126)</td>
</tr>
<tr>
<td>Gamma-glutamyl transpeptidase</td>
<td>21 IU/l</td>
</tr>
<tr>
<td>Amylase</td>
<td>58 IU/l</td>
</tr>
<tr>
<td>Creatine kinase</td>
<td>140 IU/l, then 164 (N &lt; 200)</td>
</tr>
<tr>
<td>Troponin</td>
<td>0.06 mg/ml (N &lt; 0.03)</td>
</tr>
</tbody>
</table>

* Positive (ESR, CRP, ferritin) and negative (albumin) acute-phase reactants. WBC = white blood cell count; N = normal.

**Figure 1. The patient’s 99mTc bone scintigraphy showing a ‘super bone scan’. This pattern of uniform symmetric increased bone uptake of tracer relative to soft tissue is not pathognomonic to extensive osteoblastic skeletal metastases and can also be seen in hyperparathyroidism, osteomalacia and myelofibrosis**

Schattner et al. Hypocalcaemia of malignancy.
increased at 4.40 ng/ml. The hypocalcaemia was corrected by intravenous calcium gluconate (2 ampules of 10% solution equivalent to 180 mg elemental calcium in 50 ml 5% dextrose infused over 30 min and continued at 1.0 mg/kg/h) plus oral calcium and calcitriol (0.25 µg, twice daily), but the patient died before oncological treatment could be commenced.

**COMMENT**

The patient presented with symptoms of congestive heart failure due to an acute myocardial infarction associated with pneumonia. We suspected the acute kidney injury and cytopenias were due to ADAMTS13 deficiency and thrombotic thrombocytopenic purpura, which can be triggered by infectious agents but ruled it out. On admission, the hypocalcaemia (8.1 mg/dl, corrected for albumin) was considered incidental in an acutely ill geriatric patient with acute kidney injury. When he improved and the prerenal azotaemia resolved, his hypocalcaemia paradoxically worsened (6.3 mg/dl corrected for albumin). The differential diagnosis of hypocalcaemia in combination with elevated PTH and markedly increased alkaline phosphatase not related to the liver includes osteoblastic bone tumours and osteomalacia. Low urinary calcium excretion is common to both. Indeed, he had concomitant vitamin D deficiency – a common finding among cancer patients in correlation with disease stage and increasingly recognised in the general population. However, metabolic bone disease alone is unlikely to account for the extreme and escalating hypocalcaemia. Its unique pathogenesis in primarily osteoblastic metastases will be discussed below. Here, the presumptive diagnosis was supported by the associated marked cytopenias and confirmed by the pathology report, technetium bone scintigraphy and rising PSA levels.

**METHODS**

Most of the data on hypocalcaemia and cancer comes from case reports, case series or reviews of specific syndromes involving hypocalcaemia (e.g. tumour lysis syndrome, hypomagnesaemia, etc.). A narrative review methodology was therefore adopted. We searched PubMed using the terms cancer (or malignancy) and hypocalcaemia in adults, to capture and review all abstracted publications in the English language. Out of the abstracts (n = 777), more than 350 articles were reviewed. Any report of hypocalcaemia in the setting of cancer or its treatment was included, evaluated and classified according to the mechanism involved. A list comprising all the pathogenetic mechanisms identified was created. A few additional studies from the articles’ bibliographies were also included. Treatment recommendations were based on expert opinion and consensus statements, in the absence of more solid evidence.

**Incidence of hypocalcaemia in malignancy**

Only two studies have looked at the incidence of hypocalcaemia among cancer patients. Both are over 25 years old and their results are widely discrepant, probably due to differences in the patient populations studied. In Blomqvist’s study, 1.6% of 7625 ambulatory oncology patients were found to be hypocalcaemic, while D’Erasmo et al., who studied hospitalised patients, found an incidence of 10.8%. Since cancer treatment and survival has varied and several important aetiologies of hypocalcaemia in cancer may be more prevalent today, a current study is indicated, particularly among hospitalised patients. Thus, the entity seems to be far from rare. In patients with solid tumours and bone metastases, an incidence of 5-13% was reported by Riancho et al. and the difference depends on the formula used to correct total calcium for reduced serum albumin concentrations, which are common in cancer patients.

**Myriad of mechanisms of hypocalcaemia in malignancy**

Hypocalcaemia, a decrease in extracellular calcium defined as serum total calcium < 8.5 mg/dl corrected for serum albumin, triggers an increase in PTH secretion to restore homeostasis by enhancing tubular calcium reabsorption in the kidney, stimulating osteoclastic bone resorption and promoting active vitamin D synthesis in the kidney (1,25-(OH)2D3, calcitriol), which increases intestinal calcium absorption and enhances PTH effects. Thus, hypocalcaemia develops when the net efflux of calcium from the extracellular fluid exceeds its replacement, due to disruption of these defence mechanisms such as occurs in reduced PTH or PTH resistance, vitamin D deficiency, or hyperphosphataemia secondary to decreased phosphate excretion or increased load. Our literature review yielded altogether 12 potential mechanisms of hypocalcaemia in malignancy, excluding acute kidney injury/chronic kidney disease:

1. **Pseudohypocalcaemia**: in the context of hypoalbuminaemia (decreased binding) or recent MRI (gadolinium interference with assay). Ionised calcium remains unaffected but since hypoalbuminaemia is so common, its effect on serum total calcium must always be considered.

2. **Calcium chelators**: mild transient hypocalcaemia due to ionised calcium binding to citrate in patients receiving multiple transfusions.

3. **Hypocalcaemia** in the critically ill cancer patient (e.g., overwhelming infection, rapidly progressive disease):
multiple mechanisms mediate hypocalcaemia,\textsuperscript{7} which may affect up to 70\% of patients\textsuperscript{14} and be severe and ominous,\textsuperscript{9,13} possibly implicated in the development of critical illness polyneuromyopathy in ICU patients.\textsuperscript{20}

4. Acute pancreatitis (e.g. secondary to hypercalcaemia of malignancy, drug therapies or the disease itself). Several incompletely understood mechanisms operate, predominantly precipitation of calcium soaps in the abdominal cavity.\textsuperscript{11,22}

5. Acute hyperphosphataemia (leading to bone and extra-skeletal calcium-phosphate precipitation)

A. Endogenous: Tissue destruction

I. Tumour lysis syndrome: chemotherapy-induced (mostly) or spontaneous (rare), predominantly in haematological cancer but increasingly reported in solid tumours.\textsuperscript{43}

II. Rhabdomyolysis: Following grand mal seizures, electrolyte disorders, infections in susceptible hosts, immobilisation, drugs affecting the central nervous system or drugs used in anaesthesia, limb ischaemia following cancer hypercoagulability and atheroembolism, isolated limb perfusion for locally recurrent melanoma.\textsuperscript{24}

III. Acute severe haemolytic anaemia: Autoimmune haemolytic anaemia associated with malignancy (warm antibodies or cold agglutinin), drug-induced, etc.\textsuperscript{41}

B. Exogenous: Drug-induced phosphate load

Phosphate-based enemas for colon preparation, etc.\textsuperscript{26}

6. PTH deficiency: parathyroid gland destruction or removal: state after neck surgery for thyroid or laryngeal carcinoma (usually dissection, even minimally invasive), state after neck irradiation, rarely, parathyroid metastasis.\textsuperscript{11,27} Cinacalcet treatment (see below).

7. Magnesium depletion, causing PTH resistance (early) and decreased PTH secretion (late): chemotherapy-induced (e.g. cisplatin, cetuximab), antibiotic-induced (e.g. aminoglycosides, amphotericin), paraneoplastic renal magnesium losses (rare), post-obstructive diuresis, or protein-calorie malnutrition\textsuperscript{14} and poorly understood mechanisms (e.g. in cutaneous T-cell lymphoma).\textsuperscript{49}

8. Ectopic calcitonin secretion by the tumour: other than medullary carcinoma of the thyroid (hypocalcaemia not reported), breast and lung carcinomas and hepatomas may produce calcitonin. Hypocalcaemia was very rarely reported,\textsuperscript{39} possibly associated with concurrent hypomagnesaemia.

9. Oncological drugs (other than those mentioned in \#4, \#5, \#6, \#7 and \#10) often inhibiting osteoclastic bone resorption.\textsuperscript{31}

A. Chemotherapy: several medications implicated in hypocalcaemia include axitinib, nab-paclitaxel (hypocalcaemia estimated at \textasciitilde 33\%), estramustine (hypocalcaemia estimated at 20\%), high-dose interleukin 2, low-dose leucovorin/5FU, and octreotide (hypocalcaemia estimated at 22\%). The cause often remains unknown.\textsuperscript{16}

B. Treatment of neoplastic bone lesions, often with initial hypercalcaemia: parenteral bisphosphonates, denosumab,\textsuperscript{30} gallium nitrate or strontium 89. Raloxifene, a selective oestrogen receptor modulator which reduces the risk of hormone-receptor-positive breast cancer, inhibits bone resorption and may also cause hypocalcaemia when occult vitamin D deficiency coexists.\textsuperscript{34}

10. Vitamin D deficiency: this exceedingly common condition\textsuperscript{9} is associated with age, malnutrition, staying indoors, hospitalisation, malabsorption, drugs that metabolise vitamin D (e.g. anticonvulsants), all common among cancer patients.\textsuperscript{7,16}

11. Malabsorption: can occur in cancer patients either as a result of their specific disease (e.g. primary intestinal T cell lymphoma, enteropathy-associated or not; pancreatic exocrine insufficiency in pancreatic cancer)\textsuperscript{35} or develop in survivors, being related to their treatment (e.g. bacterial overgrowth after abdominal surgery, adverse effect of radiotherapy).\textsuperscript{15} In either case, hypocalcaemia is usually associated with low 25-hydroxyvitamin D and magnesium levels and malnutrition is a frequent contributing factor.

12. Osteoblastic metastases, with increased calcium uptake and utilisation:\textsuperscript{10} primarily carcinoma of the prostate or breast but also reported in gastrointestinal, lung, thyroid, salivary gland, and neuroendocrine cancer. In the rare osteosclerotic myeloma with or without POEMS syndrome, the same mechanism probably underlies hypocalcaemia.\textsuperscript{17}

Commonly, more than one mechanism is operative, highlighting the need for a comprehensive evaluation of all the key ‘players’ to ensure successful treatment.

Aetiology clarified and explained through a practical diagnostic workup

An informed use of a short set of clinical and laboratory data suffices for establishing the aetiological basis of hypocalcaemia in most cancer patients (\textit{figure} 2). Such an understanding is imperative for treatment decisions.

\textit{Phase 1. Confirm true hypocalcaemia.} Since about half of the circulating calcium is bound to serum proteins (mostly albumin), hypoalbuminaemia, which is prevalent in cancer patients, will be associated with decreased serum total calcium but the clinically important ionised calcium fraction ([iCa]) remains unaffected. So-called ‘pseudohypocalcaemia’ is present when albumin-adjusted calcium levels are within the normal range (a convenient, commonly used
Figure 2. Flow chart: diagnostic approach to the cancer patient with hypocalcaemia

Serum Total Calcium [STC] < 8.5 mg/dL (iCa < 4.7 mg/dl)

↓

Adjust for Serum Albumin*

↓

Normocalcaemia

STC < 8.5 mg/dl

(Pseudohypocalcaemia)

↓

Obtain serum PTH, creatinine, phosphate, magnesium, liver enzymes, amylase, CK, 25(OH)D and clinically assess the patient for cause**

↓

↓

PTH decreased or normal

(Hypoparathyroidism)

↓

• Removal or destruction of PTH source

• Hypomagnesaemia#

• Cinacalcet treatment

PTH elevated

• Renal dysfunction, advanced (CKD, AKI)

• Critically-ill patient (sepsis, surgery, etc.)

• Pancreatitis, acute

• Extensive cell destruction- ↑ phosphate

Rhabdomyolysis, Tumour lysis syndrome

Severe haemolytic anaemia

• Drug treatment, diverse

• Vitamin D deficiency (low phosphate)

• Osteoblastic metastases

*In critically ill patients obtain ionised calcium levels.
**Also determining acuteness, severity (STC<7.5) and symptoms /QT.
#In early hypomagnesaemia end organ resistance to PTH predominates and PTH levels may be elevated.

formula is to add 0.8 mg/dl calcium for every g/l albumin below 4.0 g/l). In critically ill or post-surgical patients, it is better to obtain direct ionised calcium levels since binding is pH dependent.

Phase 2. Consider acuteness, severity and symptoms. Hypocalcaemia in cancer patients usually develops acutely or sub-acutely. Severity is defined as serum total calcium levels of less than 7.5 mg/dl (iCa < 4.0 mg/dl) and symptoms to look for are related to neuromuscular irritability. They include paraesthesias (circumoral or distal) and tetany, which may be overt (e.g. muscle cramps) or latent (Chvostek or Trousseau’s signs). At the serious side of the spectrum, laryngospasm, seizures, cardiac

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arrhythmias associated with prolongation of the QT interval in the ECG or vascular collapse may occur.

**Phase 3. Assess prominent causes and obtain simple key tests.** Although the next step in understanding the pathogenesis of hypocalcaemia is dependent upon determination of PTH status (figure 2), this may take time whereas basic clinical evaluation will often yield the likely cause. For example, Hastbacka and Pettila found hypocalcaemia in up to 85% of critically ill patients, including cancer patients. Multiple mechanisms had been implicated and in this setting ionised calcium should be measured: severe reductions (iCa < 4.0 mg/dl) seem to be an independent predictor of mortality in patients with severe acute kidney injury. The estimated glomerular filtration rate (eGFR) can be readily determined and advanced kidney dysfunction (late stage 4 and over, eGFR < 22 ml/min/1.73m²) is a prominent cause of hypocalcaemia due to declining calcitriol levels and countering hyperphosphataemia by precipitation with calcium. Noticing a neck scar on examination or obtaining a history of neck surgery/irradiation suggests low PTH as the mechanism. Several ‘hypocalcaemic’ conditions can be readily diagnosed, such as acute pancreatitis whose hallmark is pain, hyperamylasemia and supportive imaging. Rhabdomyolysis with marked increases in serum creatine kinase levels, hyperkalaemia, hyperphosphataemia and early hypocalcaemia due to calcium-phosphate deposition in necrotic muscle. Drug and chemotherapy history are of the utmost importance and may indicate tumour lysis syndrome, hypomagnesaemia or a specific drug effect (see under Mechanisms) as the likely cause.

**Phase 4. Is PTH low (or normal, despite hypocalcaemia)?** PTH is essential for calcium homeostasis and for maintaining normocalcaemia. However, the parathyroid glands may have been surgically removed due to cancer in the region (e.g. near-total thyroidectomy, common), irradiated, or rarely involved by metastases - easily identifiable conditions. Infiltration by iron following multiple transfusions (secondary haemochromatosis) has also been reported in cancer patients. Hypomagnesaemia (usually magnesium < 1.2 mg/dl) is commonly drug-induced (e.g. cisplatin, cetuximab) but may have many other varied causes in patients with malignancy, including a rare paraneoplastic tubular effect. Severe magnesium depletion markedly impairs PTH release in response to hypocalcaemia causing functional hypoparathyroidism, thereby also interfering with renal calcitriol production. Concurrently, PTH resistance develops, causing skeletal resistance and impaired PTH-induced calcium release from bone. Hypomagnesaemia is frequent in hospitalised patients. A study from the Mayo Clinic found a prevalence of 20.2% among 288,120 patients. Low levels were particularly common in haematology/oncology patients and often unrecognised unless specifically tested for. It is an important precursor of hypocalcaemia, found in 23.3% of patients with hypocalcaemia not due to renal failure. This hypocalcaemia is refractory to calcium but responds to continuous magnesium supplementation. Cinacalcet, a calcimimetic drug used in treating parathyroid carcinoma (or secondary hyperparathyroidism), inhibits PTH release and is another potential cause of ‘low-PTH hypocalcaemia’ in malignancy, which is usually asymptomatic and transient.

**Phase 5. Hypocalcaemia associated with elevated PTH concentrations.** Otherwise, PTH is always increased in response to hypocalcaemia in an attempt at maintaining homeostasis. Malignant disease itself or its treatment can cause chronic kidney disease and acute kidney injury by a variety of prerenal, intrarenal (glomerular, tubulointerstitial, vascular) or postrenal mechanisms which often act concurrently and cause electrolyte abnormalities. With significant renal dysfunction and hyperphosphataemia, calcium-phosphate binding and precipitation cause hypocalcaemia. Thus, GFR and serum phosphate determinations are indispensable in evaluating hypocalcaemia. Exogenous administration of phosphate loads or extensive cell destruction releasing intracellular phosphate into the extracellular space during rhabdomyolysis, severe haemolysis or tumour lysis syndrome may also cause hypocalcaemia in cancer. With the emergence of new effective and targeted anticancer drugs, the incidence of tumour lysis syndrome is likely to rise. It is often associated with cytotoxic or monoclonal antibody treatment of haematological malignancies, but may also develop after radiation therapy, in treated solid tumours, and spontaneously. The greater the tumour burden and sensitivity to treatment, the greater the risk that massive tumour-cell lysis develops, releasing massive quantities of intracellular contents (potassium, phosphate, nucleic acids) into the systemic circulation and creating an oncological emergency. Acute kidney injury is central in tumour lysis syndrome and severe secondary hypocalcaemia to counter the phosphate load can be life-threatening and persistent. Rhabdomyolysis, when liberated phosphate from damaged muscle reaches critical levels in the serum, calcium-phosphate crystals form and are deposited in necrotic muscle. Hypocalcaemia in critically ill patients and in acute pancreatitis were discussed above. Importantly, hypocalcaemia is a recognised adverse reaction of multiple drugs used either in the treatment of cancer or its complications. Truly diverse mechanisms may be involved, as presented in

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While hypercalcaemia was associated with bone metastases, hypocalcaemia can and should be expected in many of the more potentially significant antecedent conditions. Avid calcium intake by extensive osteoblastic metastases (predominantly in prostate or breast cancer) is an intriguing cause of hypocalcaemia in cancer, which may rarely constitute its presenting feature. The mechanism of bone metastasis has been well studied: once within the bone microenvironment, prostate tumour cells proliferate, releasing multiple cytokines and growth factors which stimulate osteoblasts / stromal cells proliferation and production of further growth factors that also affect osteoclasts. A vicious cycle of tumour-cell growth and bone microenvironment, prostate tumour cells proliferate, releasing multiple cytokines and growth factors which stimulate osteoblasts / stromal cells proliferation and production of further growth factors that also affect osteoclasts. A vicious cycle of tumour-cell growth and calcium-consuming new (but fragile) bone formation is propagated. This syndrome involves very common diseases which often metastasise to bone and therefore even low percentages translate into large numbers of patients. Among 155 patients with solid tumours metastatic to bone, up to 13% had hypocalcaemia and their metastases were almost exclusively osteoblastic. In stage M1 prostate cancer (spread beyond the lymph nodes), the prevalence of hypocalcaemia was double (27%). Tucci et al. studied a consecutive case series of 192 patients and reported 51 cases of albumin-corrected hypocalcaemia (26.6%), 125 patients with normocalcaemia and 16 (8.3%) had hypercalcaemia. While hypercalcaemia was associated with a poor prognosis (increased adverse skeletal events or death), hypocalcaemia was not. This finding was unexpected, especially since hypocalcaemic cases had a higher bone tumour load, but it was confirmed by Riancho et al. and Berruti et al, who consecutively enrolled 112 patients and concluded that hypocalcaemia was usually mild and asymptomatic. Despite an osteoblastic appearance on radiography, these metastases are also associated with increased osteoclast activity, providing the rationale for treatment with osteoclast-targeted agents such as bisphosphonates or denosumab but also increasing the risk of significant hypocalcaemia.

Lastly, finding one operative mechanism does not exclude the common existence of additional contributing ones. For example, hypoalbuminaemia and acute kidney injury may be found together with severe hypocalcaemia due to osteoblastic metastases and significant nutritional vitamin D deficiency, as in our patient; or as Bergkamp et al. eloquently demonstrate, an associated cancer or chemotherapy-related obtunded PTH response.

**Prognosis**

Unlike hypercalcaemia of malignancy which is limited to three major mechanisms and its development is associated with poor prognosis, hypocalcaemia as a prognostic factor in cancer had never been studied systematically. However, its highly diverse mechanisms already suggest a more complex picture. Provided the patient is not critically ill, many cases of hypocalcaemia in cancer are relatively mild, asymptomatic and transient (e.g. most drug-related hypocalcaemia or hypovitaminosis D). The prognostic implications of hypocalcaemia in the setting of osteoblastic metastases have been discussed above and contrasted with hypercalcaemia. Hypocalcaemia can and should be anticipated in many of the more potentially significant and symptomatic syndromes (e.g. hypomagnesaemia, tumour lysis syndrome or bisphosphonate treatment) and can be reduced by monitoring before and during treatment and by the application of prophylactic measures as indicated (for example, among patients considered at risk of tumour lysis syndrome or magnesium depletion). Such measures may prevent some cases of hypocalcaemia or lead to their early detection and correction and to improvement in prognosis. However, symptomatic and even life-threatening hypocalcaemia in the context of cancer may still occur and mandate urgent treatment. Notwithstanding this variability, the underlying malignancy, its stage and amenability to treatment remain the cardinal prognostic factors in hypocalcaemia of malignancy.
Treatment

Treatment has also not been studied systematically, and recommendations are based on expert panel opinion, consensus statements and accepted practice or clinical experience, non-controlled trials or hard evidence. Generally, getting an early grasp on the pathogenesis (figure 2) is highly important, since calcium administration will hardly be effective unless essential deficiencies (for example, magnesium, vitamin D, or both) are attended to, and specific pathogenetic cascades mediating hypocalcaemia (for example, acute pancreatitis, tumour lysis syndrome or drug treatment) are targeted.36 Otherwise, treatment and monitoring does not differ from that of other settings of hypocalcaemia. The rate of decline, severity (usually serum total calcium < 7.5 mg/dl) and presence/severity of symptoms or QT prolongation (mild, severe, or life-threatening) determine treatment intensity. Several principles summarise the treatment of hypocalcaemia based on expert advice. First, the administration of calcium to severely hyperphosphataemic patients may result in widespread deleterious calcium-phosphate deposition. Combined serum phosphate > 8 mg/dl and symptomatic hypocalcaemia require dialysis to correct both. In asymptomatic patients, oral phosphate binders may improve hypocalcaemia too. Second, in symptomatic patients with associated hypomagnesaemia (< 1 mg/dl), intravenous magnesium sulphate (2 g in saline given over 30 min and followed by 4 g over 12 hrs) will allow correction of hypocalcaemia. Monitoring is required, particularly in patients with impaired renal function. Refractory unexplained hypocalcaemia in a susceptible patient may respond to magnesium even when normomagnesaemic.38 Third, in our experience, most patients will need concomitant vitamin D repletion (typically, 50,000 IU of vitamin D2 or D3 repeated as necessary). Finally, symptomatic / QT prolongation in hypocalcaemia patients (with neither hypomagnesaemia nor hyperphosphataemia) or patients with an acute decline < 7.5 mg/dl who will likely become symptomatic mandate intravenous calcium treatment. Calcium gluconate (1-2 g of 10% solution in 50 ml 5% dextrose given over 20 min, monitored and repeated) is an effective treatment.

CONCLUSIONS

With the advent of new potent drugs for the treatment of cancer and its skeletal complications, the increasing prevalence of vitamin D insufficiency and longer survival of patients with cancer, hypocalcaemia in malignancy is increasingly encountered in both hospitalised and ambulatory patients but nevertheless remains poorly recognised. A myriad of mechanisms may be involved, often concurrently, and they can often be evaluated almost instantaneously at the bedside. Their recognition and timely address may improve health outcomes and is of special importance in patients who may develop severe, even life-threatening symptoms.

DISCLOSURES

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How the concept of biochemical response influenced the management of primary biliary cholangitis over time


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ABSTRACT

Background: Criteria assessing biochemical response to ursodeoxycholic acid (UDCA) are established risk stratification tools in primary biliary cholangitis (PBC). We aimed to evaluate to what extent liver tests influenced patient management during a three decade period, and whether this changed over time.

Methods: 851 Dutch PBC patients diagnosed between 1988 and 2012 were reviewed to assess patient management in relation to liver test results during UDCA treatment. To do so, biochemical response at one year was analysed retrospectively according to Paris-1 criteria.

Results: Response was assessable for 687/851 (81%) patients; 157/687 non-responders. During a follow-up of 8.8 years (IQR 4.8-13.9), 141 died and 30 underwent liver transplantation. Transplant-free survival of non-responders (60%) was significantly worse compared with responders (87%) (p < 0.0001). Management was modified in 46/157 (29%) non-responders. The most frequent change observed, noted in 26/46 patients, was an increase in UDCA dosage. Subsequently, 9/26 (35%) non-responders became responders within the next two years. Steroid treatment was started in one patient; 19 patients were referred to a tertiary centre. No trend towards more frequent changes in management over time was observed (p = 0.10).

Conclusion: Changes in medical management occurred in a minority of non-responders. This can largely be explained by the lack of accepted response criteria and of established second-line treatments for PBC. Nevertheless, the observation that response-guided management did not increase over time suggests that awareness of the concept of biochemical response requires further attention,
particularly since new treatment options for PBC will soon become available.

**KEYWORDS**

Autoimmune liver disease, cholestasis, second-line therapy

**INTRODUCTION**

Primary biliary cholangitis (PBC) is a chronic cholestatic liver disease of autoimmune origin that mainly affects middle-aged women. To date, ursodeoxycholic acid (UDCA) at a recommended dosage of 13-15 mg/kg/day is the only approved therapy. An association between laboratory parameters and outcome during treatment with UDCA was first reported in 1999. Angulo and colleagues showed that patients with serum alkaline phosphatase levels < 2 times the upper limit of normal (ULN) following six months of UDCA treatment were less likely to have treatment failure. Subsequent studies found that not only levels of alkaline phosphatase, but also other biochemical variables including aspartate transaminase (AST), bilirubin and albumin values, following one or two years of UDCA treatment were predictive of liver transplant-free survival. Generally, patients fulfilling the criteria for biochemical response were shown to have a normal life expectancy, comparable with a matched general population, while non-responders remained at risk for requiring liver transplantation or premature death. Generally, Paris-1 criteria are considered to have the best predictability of transplant-free survival as validated in large studies, such as from the Global PBC Study Group and the UK PBC Consortium, and their usage has been recommended by an international PBC expert panel. Despite the clear relevance of biochemical response to UDCA, it has not been established whether biochemical response is considered an important objective in clinical practice and is used to guide further decision-making, in particular on possible additional second-line treatment. Therefore, we aimed to assess to what extent laboratory parameters during UDCA treatment, using Paris-1 biochemical response criteria, influenced management decisions in a large and nationwide cohort of PBC patients.

**MATERIALS AND METHODS**

**Patient population**

Patients were derived from a Dutch multicentre study and a large epidemiological study regarding primary sclerosing cholangitis and primary biliary cholangitis in the Netherlands. The protocol for this project was approved by the Central Committee for Research Ethics in Utrecht and the local ethics committees of participating hospitals (trialregister.nl no.: NTR2813). Patients were diagnosed according to established criteria, and included between November 1988 and December 2011 across 43 university and general hospitals. Patients with concomitant liver disorders at initial diagnosis of PBC, such as viral, alcoholic and autoimmune hepatitis, were excluded.

**Endpoints**

For the current study, entry (baseline) was defined as the date of starting UDCA therapy. Biochemical response to UDCA treatment was retrospectively assessed according to Paris-1 criteria; generally accepted as the criteria with the best performance in predicting outcome. Paris-1 was defined as alkaline phosphatase ≤ 3 times the ULN, AST < 2 times the ULN and bilirubin ≤ 1 mg/dl after one year of UDCA treatment, and Paris-2 criteria, defined as alkaline phosphatase ≤ 1.5 times the ULN, AST ≤ 1.5 times the ULN and bilirubin ≤ 1 mg/dl after one year of UDCA treatment. A composite of liver transplantation and death was used as clinical endpoint. Patients who did not reach a clinical endpoint were censored at their last follow-up visit.

**Data collection**

The original database comprised clinical and laboratory data at baseline and during follow-up. Clinical data included gender, age, details about the diagnosis of PBC, anti-mitochondrial antibody (AMA) status, liver histology obtained within one year of study entry, UDCA treatment (start date and dosage), and outcome (liver transplantation and death). Laboratory data (alkaline phosphatase, AST, alanine aminotransferase (ALT), gamma-glutamyl transpeptidase (GGT), bilirubin, albumin and platelets) were collected once a year. During site visits, additional follow-up information was gathered from medical charts for UDCA non-responders within the next two years following the retrospective assessment of biochemical response (figure 1). Data collected included changes in UDCA dosage, prescription of additional medication, and referral to tertiary centres.

**Statistical analyses**

Normally distributed data were expressed as mean ± standard deviation and skewed data were expressed as median and interquartile range (IQR). Differences between responders and non-responders were assessed by using the independent t-test and non-parametric Mann-Whitney U test, respectively. To assess differences between responders and non-responders concerning categorical variables, the
Pearson’s chi-squared test was used. The Kaplan-Meier method was applied for time-to-event analysis and survival difference was tested with log-rank test. Logistic regression modelling was performed to assess the association between baseline factors and UDCA response after one year of follow-up in univariate and multivariable approaches. A p < 0.05 was considered statistically significant. Analyses were performed using the statistical package of IBM SPSS Statistics 21.0 (SPSS Inc., Chicago IL, USA). The study started at initiation of ursodeoxycholic acid (UDCA).

RESULTS

Study cohort
The study cohort comprised 851 UDCA-treated PBC patients. The Paris-1 criteria could be assessed in 687 (81%) patients; 77% of patients were classified as responders and 23% as non-responders (figure 2). Non-responders were generally younger, at a more advanced disease stage, diagnosed in an earlier era and had higher serum bilirubin, alkaline phosphatase, AST and ALT values and lower albumin at baseline (table 1). The median follow-up period of the entire cohort was 8.8 years (IQR, 4.8-13.9) and follow-up for responders was significantly longer than for non-responders (9.2 vs. 7.8 years respectively, p = 0.047). During follow-up, 141 patients died and 30 underwent a liver transplantation (47 and 24 non-responders, respectively). Ten-year transplant-free survival for non-responders was significantly lower than for responders (60% vs. 87%, p < 0.0001) (figure 3).

Modification in management
Management was modified in 46/157 (29%) non-responders. The most frequently applied change was an increase in the UDCA dosage (26/46, 57%). Steroid therapy was started in only one non-responder. No other drugs were prescribed as second-line therapy. Nineteen patients were referred for a second opinion to a tertiary centre. For 6/157 (4%) non-responders management changes were not extractable from the medical charts.
Relation between publications on biochemical response and changes in patient management

In 1999, the first study was published addressing the significance of biochemical response. In our cohort, the therapeutic approach was modified in 33/104 (32%) of the non-responders before 1999 as compared with 13/53 (25%) after that year (p = 0.10). The key paper by Pares et al. on biochemical response was published in 2006. When comparing the proportion of management changes in non-responders before and after 2006, again no clear difference was found (p = 0.62).

Impact of increase in UDCA dosage

After one year of treatment with UDCA, the dosage was increased in a number of non-responders and responders within the following two years. Importantly, 9/26 (35%) of the non-responders became responders within the next two years following dosage increase. When applying the
more strict Paris-2 criteria for response,10 6/48 (13%) of non-responders became responders.
Eighteen of 26 (69%) non-responders in whom the UDCA dosage was increased were initially dosed inadequately (median daily dosage 9.60 mg/kg; IQR 8.80-11.16 mg/kg) according to current treatment guidelines. Further analysis showed that this mainly applied to patients diagnosed in 1999 or before (median dosage 9.33 mg/kg; IQR 8.21-9.93 mg/kg) and not for those diagnosed in 2000 or thereafter (median dosage 12.69 mg/kg; IQR 10.92-17.98 mg/kg).

**Baseline factors predictive of response**
Since biochemical response is of major importance in risk stratification, baseline factors were determined that were predictive of response (table 2). Higher serum albumin levels and higher UDCA dosage per kg were associated with increased response to UDCA treatment, whereas higher levels of bilirubin, alkaline phosphatase, AST, ALT and more advanced disease stage (defined as abnormal bilirubin and/or albumin15) were all associated with decreased response. On multivariable analysis more advanced disease stage, lower UDCA dosage per kg and higher serum alkaline phosphatase levels were independent factors predictive of poor response.

**DISCUSSION**
To our knowledge, this large nationwide multicentre cohort study in PBC is the first to assess potential changes in patient management prompted by the one-year response to UDCA treatment. We found that non-response to treatment did not result in management changes in nearly two-thirds of cases. In those patients in whom management was influenced, the most frequent change was an increase in the dosage of UDCA. Our data further showed that the proportion of UDCA non-responders in whom management was modified did not increase over time, suggesting that awareness of the concept of biochemical response in clinical practice may still be suboptimal.

Few data are available with respect to treatment policy based upon objective response criteria in PBC. Recently, preliminary data of an online survey among 200 gastroenterologists and hepatologists in the UK were presented:16 42% of gastroenterologists and 76% of hepatologists stated they used biochemical response criteria (e.g. Paris-1 criteria1 or Barcelona criteria17) to evaluate UDCA treatment. However, no information was provided about further treatment decisions based upon the observed response.

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**Table 2. Baseline factors predictive of response according to Paris-1 criteria**

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>Multivariable analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Odds ratio (95% CI)</td>
<td>P-value</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.03 (0.61-1.74)</td>
</tr>
<tr>
<td>AMA positivity</td>
<td>1.73 (0.90-3.42)</td>
</tr>
<tr>
<td>Advancing age at study entry</td>
<td>1.02 (1.01-1.04)</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td>1.06 (1.03-1.08)</td>
</tr>
<tr>
<td>UDCA dosage per kg</td>
<td>1.09 (1.02-1.16)</td>
</tr>
<tr>
<td>Disease stage*</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0.16 (0.10-0.26)</td>
</tr>
<tr>
<td>Advanced</td>
<td>0.02 (0.01-0.06)</td>
</tr>
<tr>
<td>Bilirubin (xULN) values</td>
<td>0.41 (0.32-0.54)</td>
</tr>
<tr>
<td>Alkaline phosphatase (xULN) values</td>
<td>0.65 (0.59-0.72)</td>
</tr>
<tr>
<td>AST (xULN) values</td>
<td>0.78 (0.69-0.89)</td>
</tr>
<tr>
<td>ALT (xULN) values</td>
<td>0.90 (0.82-0.99)</td>
</tr>
<tr>
<td>Albumin (xLLN) values</td>
<td>33.05 (7.86-138.93)</td>
</tr>
</tbody>
</table>

*Disease stage based on albumin and bilirubin according to biochemical disease classification of Ter Borg et al.15 AMA = anti-mitochondrial antibody; UDCA = ursodeoxycholic acid; ULN = upper limit of normal; AST = aspartate transaminase; ALT = alanine aminotransferase. LLN = Lower Limit of Normal.
Obviously, the results of our study should be interpreted with caution. In particular, it must be recognised that the majority of included patients were treated with UDCA well before emergence of the concept of biochemical response and that, in the context of this study, this response was assessed retrospectively. Therefore, by definition, decisions with respect to patient management could not have been influenced by assessing treatment response with one of the currently available tools. Irrespective of a formal response evaluation, however, our data suggest that management was modified in only a minority of cases despite persistently, occasionally markedly, abnormal biochemical liver tests. Moreover, our data demonstrate that during the last decade, despite increased awareness of the importance of sufficient biochemical improvement upon treatment with UDCA, this did not yet translate into an increase in response-guided management in general medical practice.

Another major factor that must be stressed when interpreting the results of the present study is the lack of evidence-based alternative treatments for PBC until now. This may largely explain why potentially effective drugs, including budesonide and fibrates, were rarely used. During recent years, evidence is accumulating that fibrates may have an additional, beneficial effect in UDCA-treated PBC. The same applies to budesonide and obeticholic acid, drugs that are currently undergoing randomised controlled trial evaluation. It seems likely that within a few years the therapeutic scenario in PBC will have changed considerably and an evidence-based approach of response-guided treatment in PBC will be a reality, potentially with a number of second-line treatment options available.

Our study emphasises the importance of adequate UDCA dosing. About 40% of UDCA non-responders in whom the dosage was increased became responders according to the criteria we used. Indeed, a multivariable analysis of factors predictive of response confirmed that higher UDCA dosage per kilogram was an independent predictor of response. These findings are in line with previous studies showing that UDCA doses in the range of 13-15 mg/kg/day are more effective than lower doses. Therefore, adequate dosing of UDCA remains of crucial importance.

A potential weakness of our study is its retrospective character, occasionally necessitating the retrieval of data from hand-written patient records more than 20 years old. Also, it may be very well possible that management changes did occur more frequently than documented in the present study, but that this was after more prolonged follow-up. On the other hand, we believe that this study of a large PBC population gives a unique and representative insight into general clinical practice since it was not restricted to high-volume university centres but also involved many smaller community hospitals.

In conclusion, in this long-term cohort study of PBC we found that changes in medical management occurred in a minority of patients who, retrospectively, responded insufficiently to UDCA treatment. During the last decade this did not change despite the emergence of established stratification tools. Now new therapeutic options for PBC are becoming available, awareness of the concept of biochemical response requires further attention.

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DISCLOSURES

The authors have no conflicts of interest to declare.

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Health-related quality of life, rehabilitation and mortality in a nursing home population

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ABSTRACT

Background: Health-related quality of life (HRQOL) in nursing home residents is generally low. The purpose of this study was to investigate the associations between HRQOL and two clinically relevant outcome measures, all-cause mortality and successful rehabilitation, in a nursing home population.

Methods: In an observational prospective cohort study in a nursing home population, HRQOL was assessed with the RAND-36. A total of 184 patients were included, 159 (86%) completed the RAND-36 and were included in the study. A Cox proportional hazard model was used to investigate the independent association between HRQOL, rehabilitation and mortality with adjustment for confounders. Risk prediction capabilities were assessed with Harrell’s C statistics and the proportion of explained variance ($R^2$).

Results: The median age (interquartile range) was 79 (75-85) years. The health dimensions vitality (HR 0.88 (95% CI 0.77-0.99)) and mental health (HR 0.86 (95% CI 0.75-0.98)) were inversely associated and role functioning-physical (HR 1.08 (95%CI 1.02-1.15)) was positively associated with mortality. The Harrell’s C value and the $R^2$ were ≤ 0.02 and ≤ 0.03 higher in the adjusted models with the dimensions role functioning-physical, mental health or vitality compared with the models without these dimensions. None of the health dimensions or summary scales were related to successful rehabilitation.

Conclusion: HRQOL was significantly associated with mortality for three dimensions, but partly in opposite directions. Additional value of HRQOL in mortality prediction is very limited. There were no independent associations between HRQOL and successful rehabilitation. Although HRQOL is an important outcome, this study did not provide evidence for an association between HRQOL and successful rehabilitation.

KEYWORDS

HRQOL, nursing home, rehabilitation, mortality, aged

INTRODUCTION

Comorbidities, depression, cognitive impairment and other geriatric problems are highly prevalent in old age and can greatly impact health-related quality of life (HRQOL).1-6 As a consequence, HRQOL is generally low in nursing home residents.1-6,7-9 Nursing homes in the Netherlands provide care and long-stay services for elderly patients with chronic mental or physical diseases, and the majority also provide rehabilitation services. Measuring HRQOL in nursing home patients could lead to an increased understanding of factors that negatively impact HRQOL, ultimately aiming to improve the HRQOL of this patient group, characterised by an overall very low HRQOL.

The evaluation of HRQOL in individual patients can be used to measure disease-related distress and overall perception of health. Next to the evaluation of HRQOL as a separate outcome measure, HRQOL also has prognostic value in non-nursing home settings. Furthermore, a lower HRQOL has been associated with increased mortality risk in non-nursing home settings, also in elderly patients. Besides, HRQOL is also used to evaluate therapeutic interventions. Therefore, HRQOL could have a variety of implications in decision-making processes regarding patients and medical interventions.
Increased understanding of HRQOL in nursing home patients could improve the HRQOL and outcome of these patients. As mortality risk is already very high in old age, other clinical outcomes, besides HRQOL itself, such as successful rehabilitation, may be more relevant. Several studies have reported a relationship between HRQOL and rehabilitation in, for example, stroke patients.\textsuperscript{16-18} Low HRQOL corresponds to substantial limitations in physical, emotional and social well-being due to a medical condition or its treatment.\textsuperscript{18} These aspects of HRQOL can negatively influence successful rehabilitation. The associations between HRQOL and rehabilitation may be bidirectional: on the one hand successful rehabilitation itself can improve HRQOL\textsuperscript{19-21} and on the other hand a higher HRQOL may improve motivation and increase the chance of successful rehabilitation. To our knowledge, there are no studies that have investigated the relationship between HRQOL and rehabilitation in a nursing home. Only one study investigated the relationship between HRQOL and mortality in a nursing home setting.\textsuperscript{22} Furthermore, no studies have reported whether measuring HRQOL had a discriminatory value, using for example the Harrell's C to assess the predictive capability of HRQOL in a nursing home population. The continuous growth of the elderly population in combination with the severely impaired HRQOL in our oldest old underlines the importance to gain more understanding of the implications of HRQOL in nursing home populations. The purpose of this study was to investigate the associations between HRQOL and two clinically relevant outcome measures, all-cause mortality and successful rehabilitation, in patients admitted to a nursing home.

**MATERIALS AND METHODS**

The study is reported according to the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) recommendations.\textsuperscript{17}

**Study sample**

The design and details of this prospective observational cohort study have been described previously.\textsuperscript{18} Only patients from rehabilitation and somatic departments were included. Patients admitted to a somatic department receive prolonged or permanent care whereas patients in the rehabilitation department are admitted with the intention to rehabilitate and return home. Recruitment and all study procedures, for example administering the HRQOL questionnaire, for patients in the somatic department took place between September 2010 and December 2011. Timing of inclusion was different for each somatic patient. For patients in the rehabilitation department, recruitment and all study procedures took place between September 2010 and December 2011, mostly within the first weeks of admission.

Patients admitted to the psychogeriatric department were excluded, because these patients are generally not able to complete HRQOL questionnaires.\textsuperscript{23} Other exclusion criteria were a life expectancy less than four weeks and an impending transfer to a hospice department.

**Data collection**

An elderly care physician collected all baseline data directly after inclusion. Baseline data included demographic characteristics, full medical histories (including cardiovascular disease (CVD), diabetes mellitus and hypertension), and medication use. Trained physicians or nurses administered the questionnaires at baseline. HRQOL was measured using the RAND-36 questionnaire.\textsuperscript{24,25} The RAND-36 is a generic instrument to measure aspects of health that are relevant to functional status and well-being.\textsuperscript{26-28} The RAND-36 consists of nine aspects of health status: physical functioning, role limitations due to physical problems (role functioning-physical), bodily pain, general health, vitality, social functioning, role limitations due to emotional problems (role functioning-emotional), mental health, and health change. Each dimension has a 100-point scale, where higher scores indicate better HRQOL. Of the nine scales two component summary scores can be calculated: a physical component summary (PCS) and a mental component summary (MCS). In 2015, vital status and cause of death were retrieved from the records maintained by the nursing home and general practitioners.

**Clinical outcome measures**

All-cause mortality and successful rehabilitation were the primary endpoints. Successful rehabilitation was defined as either discharge to the patient's own home or an adapted home for the elderly, where they were self-reliant. Successful rehabilitation was investigated in the subgroup of patients admitted to the rehabilitation department.

**Statistical analyses**

Continuous variables are presented as mean with the standard deviation for normally distributed variables, or as median with an interquartile range (IQR) for non-normally distributed variables. Cox proportional hazard modelling was used to investigate the relationship between HRQOL and: 1) all-cause mortality and 2) successful rehabilitation, with and without adjustment for the following confounders: age, gender, smoking, body mass index, a history of cardiovascular, or pulmonary disease, hypertension, psychiatric disease, length of stay before study inclusion, and the number of medications they were using. Collinearity was tested between each of the RAND-36 dimensions and the confounders.
hazard ratios refer to a ten-point higher score on the RAND-36 dimensions. In case of significant associations in the Cox regression models, risk prediction capabilities were assessed with Harrell’s C statistics and the proportion of explained variance ($R^2$).$^{22,23}$ The Schoenfeld residual plots were inspected for each predictor variable to check the assumption of proportional hazards; all assumptions were met unless stated otherwise. A two-sided p < 0.05 was considered significant. All statistical analyses were performed using SPSS software version 22 (IBM, Armonk, New York, USA) and STATA (version 13; StataCorp, College Station, Texas, USA).

**Ethical approval and clinical trial registration**

Before starting the study, the Central Committee of Research Involving Human Subjects (CCMO) in the Netherlands was contacted. The CCMO agreed that with the current design, no formal approval of an accredited medical ethics committee was needed. According to Dutch guidelines this research does not fall under the scope of the Medical Research Involving Human Subjects Act. This study was performed in accordance with the Declaration of Helsinki, the treating physicians and nurses obtained written informed consent from all patients and data were analysed anonymously. The study was registered on ClinicalTrials.gov (NCT01362751).

**RESULTS**

A total of 184 patients were included in this cohort. HRQOL data were completed for 159 (86%) patients. From the 159 included patients, 123 patients were admitted to the rehabilitation department and 36 to the somatic department. Baseline characteristics of the total study population are presented in table 1. The median age (IQR) was 79.2 (75.2-85.9) years. Median PCS and MCS (IQR) scores were 44 (34-57) and 59 (48-74), respectively.

Patients in the rehabilitation department were older, had a lower BMI, hypertension was seen more frequently, and psychiatric disease was seen less often compared with patients in the somatic department (Appendix table 1). No difference in mortality hazard was observed between the rehabilitation department and the somatic department (hazard ratio (HR) 0.90 (95% confidence interval (CI) 0.66-1.21). Patients with missing data had a higher history of dementia and CVD compared with patients without missing data (Appendix table 1). Missing data were not significantly associated with mortality or successful rehabilitation, HR 0.89 (95% CI 0.47-1.71) and HR 1.41 (95% CI 0.47-4.23), respectively.

**HRQOL and mortality**

During a median follow-up period of 3.4 years, 75 (47%) patients had died. Three out of nine health dimensions were independently associated with all-cause mortality (after adjusting for confounders). The health dimensions vitality and mental health were inversely associated with mortality: HR 0.88 (95% CI 0.77-0.99) and HR 0.86 (95% CI 0.75-0.98), respectively. The dimension role functioning-physical was positively associated with mortality: HR 1.08 (95% CI 1.02-1.15). PCS and MCS component scores were not significantly associated with all-cause mortality. In model 2, age was the only covariate besides the above-mentioned three health dimensions, which was significantly related to mortality (HR 1.08 (95% CI 1.04-1.12)). The results of the Cox regression analyses are presented in table 2.

Post-hoc analyses were performed according to type of department. Because of the small number of somatic long-term patients (n=36), we first adjusted for age and gender in both groups (Appendix table 2). The analyses with the fully adjusted model were only performed for the rehabilitation group (Appendix table 3). In additional analyses, stratified according to type of department, no significant associations were seen between HRQOL and mortality within the group of somatic patients. Within the rehabilitation group significant relations with mortality were observed for the dimensions mental health and general health perception: HR 0.80 (95% CI 0.69-0.94) and HR 0.85 (95% CI 0.74-0.99), respectively. After adjustment for all selected confounders, a significant relationship in the rehabilitation group was only seen between the dimension role functioning-physical and mortality (HR 1.08 (95% CI 1.00-1.18)).

The results of the analyses regarding the risk prediction capabilities are presented in table 3. The Harrell’s C values for the adjusted model of the dimensions role functioning-physical, mental health and vitality were 0.62 (95% CI 0.62-0.75), 0.69 (95% CI 0.63-0.75) and 0.68 (95% CI 0.62-0.74), respectively. The Harrell’s C values and the $R^2$ were ≤ 0.02 and ≤ 0.03 higher in the models with the HRQOL dimensions role functioning-physical, mental health or vitality compared with the models without these three dimensions.

**HRQOL and successful rehabilitation**

Data on HRQOL were missing for 5 (4%) out of 128 patients admitted to the rehabilitation department. During a median follow-up period of 36 days (IQR 7-88), 102 patients were successfully rehabilitated; 90 patients were discharged to their own home and 12 were discharged to an adapted home for the elderly. Patients who were successfully rehabilitated had higher scores on the subscales mental health, vitality and health change, while they scored lower on the subscale bodily pain. None of the health dimensions or summary scales were significantly associated to successful rehabilitation in the regression analyses (table 2).
DISCUSSION

HRQOL was significantly associated with mortality for three dimensions, but partly in opposite directions. We observed no independent association between HRQOL and successful rehabilitation.

HRQOL and mortality

During a median follow-up period of 3.4 years, 75 (47%) patients died. There is great variation in mortality rates in nursing home studies.16,24,25 Because nursing homes could provide care for patients with chronic mental or physical diseases or provide rehabilitation services or combined, mortality rates strongly depend on the type of nursing home. Taking this all together, it is difficult to make a reliable comparison of the mortality rates between the current and previous studies.

Higher scores on the dimensions vitality and mental health were related to a lower mortality risk, whereas a higher score on the dimension role functioning-physical was related to a higher mortality risk. The Harrell’s C values and the $R^2$ were ≤ 0.02 and ≤ 0.03 higher in the adjusted

Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total HRQOL N = 159</th>
<th>Deceased patients N = 75</th>
<th>Patients who survived N = 84</th>
<th>p-value</th>
<th>Successful rehabilitation N = 102</th>
<th>No successful rehabilitation N = 21</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>79 (75-85)</td>
<td>85 (79-88)</td>
<td>78 (72-84)</td>
<td>&lt; 0.005</td>
<td>81 (76-86)</td>
<td>85 (79-89)</td>
<td>0.04</td>
</tr>
<tr>
<td>Female gender</td>
<td>111 (70%)</td>
<td>49 (65%)</td>
<td>62 (74%)</td>
<td>0.25</td>
<td>74 (73%)</td>
<td>15 (71%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>27 (23-29)</td>
<td>25 (22-29)</td>
<td>26 (23-29)</td>
<td>0.73</td>
<td>25 (23-28)</td>
<td>24 (22-27)</td>
<td>0.38</td>
</tr>
<tr>
<td>Hypertension</td>
<td>124 (78%)</td>
<td>66 (88%)</td>
<td>58 (69%)</td>
<td>&lt; 0.005</td>
<td>81 (79%)</td>
<td>20 (35%)</td>
<td>0.09</td>
</tr>
<tr>
<td>History of CVD</td>
<td>67 (42%)</td>
<td>38 (51%)</td>
<td>29 (35%)</td>
<td>0.04</td>
<td>39 (38%)</td>
<td>8 (38%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>68 (43%)</td>
<td>36 (48%)</td>
<td>32 (38%)</td>
<td>0.21</td>
<td>45 (44%)</td>
<td>9 (43%)</td>
<td>0.92</td>
</tr>
<tr>
<td>Dementia</td>
<td>11 (7%)</td>
<td>7 (9%)</td>
<td>4 (5%)</td>
<td>0.26</td>
<td>4 (4%)</td>
<td>4 (19%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>54 (34%)</td>
<td>27 (36%)</td>
<td>27 (32%)</td>
<td>0.61</td>
<td>20 (20%)</td>
<td>12 (57%)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>40 (24%)</td>
<td>20 (27%)</td>
<td>20 (24%)</td>
<td>0.68</td>
<td>29 (28%)</td>
<td>4 (19%)</td>
<td>0.38</td>
</tr>
<tr>
<td>Current smoker</td>
<td>21 (13%)</td>
<td>8 (11%)</td>
<td>13 (16%)</td>
<td>0.37</td>
<td>12 (12%)</td>
<td>0 (0%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Number of medicines</td>
<td>9 (6-11)</td>
<td>9 (7-11)</td>
<td>8 (5-10)</td>
<td>0.06</td>
<td>9 (6-10)</td>
<td>8 (6-11)</td>
<td>0.70</td>
</tr>
<tr>
<td>Measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>10 (5-30)</td>
<td>10 (0-30)</td>
<td>13 (5-30)</td>
<td>0.36</td>
<td>15 (5-35)</td>
<td>10 (0-28)</td>
<td>0.10</td>
</tr>
<tr>
<td>Social functioning</td>
<td>50 (50-61)</td>
<td>63 (50-75)</td>
<td>50 (50-61)</td>
<td>0.19</td>
<td>50 (50-61)</td>
<td>50 (50-75)</td>
<td>0.76</td>
</tr>
<tr>
<td>Role functioning-physical</td>
<td>0 (0-50)</td>
<td>0 (0-75)</td>
<td>0 (0-44)</td>
<td>0.12</td>
<td>0 (0-25)</td>
<td>0 (0-38)</td>
<td>0.94</td>
</tr>
<tr>
<td>Role functioning-emotional</td>
<td>83 (0-100)</td>
<td>67 (0-100)</td>
<td>83 (0-100)</td>
<td>0.73</td>
<td>33 (0-100)</td>
<td>100 (0-100)</td>
<td>0.33</td>
</tr>
<tr>
<td>Mental health</td>
<td>68 (56-80)</td>
<td>64 (52-80)</td>
<td>72 (64-84)</td>
<td>0.02</td>
<td>72 (63-84)</td>
<td>56 (44-72)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>67 (22-80)</td>
<td>67 (33-88)</td>
<td>62 (21-86)</td>
<td>0.65</td>
<td>50 (20-78)</td>
<td>78 (47-90)</td>
<td>0.02</td>
</tr>
<tr>
<td>Vitality</td>
<td>65 (45-75)</td>
<td>60 (45-75)</td>
<td>65 (50-80)</td>
<td>0.08</td>
<td>65 (55-78)</td>
<td>50 (35-68)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>General health perception</td>
<td>55 (40-75)</td>
<td>50 (40-70)</td>
<td>60 (45-75)</td>
<td>0.06</td>
<td>58 (45-75)</td>
<td>55 (40-70)</td>
<td>0.33</td>
</tr>
<tr>
<td>Health change</td>
<td>50 (25-50)</td>
<td>50 (25-50)</td>
<td>50 (25-50)</td>
<td>0.14</td>
<td>50 (25-50)</td>
<td>25 (0-50)</td>
<td>0.03</td>
</tr>
<tr>
<td>PCS score</td>
<td>44 (34-57)</td>
<td>44 (34-57)</td>
<td>44 (34-56)</td>
<td>0.90</td>
<td>42 (33-54)</td>
<td>42 (34-54)</td>
<td>0.97</td>
</tr>
<tr>
<td>MCS score</td>
<td>69 (48-74)</td>
<td>58 (41-73)</td>
<td>61 (51-75)</td>
<td>0.32</td>
<td>58 (49-74)</td>
<td>59 (40-74)</td>
<td>0.38</td>
</tr>
</tbody>
</table>

Data are medians (interquartile range) or N (%). a Mann-Whitney U test was used to compare groups. b Chi square test was used to compare groups.

CVD = cardiovascular disease; PCS = physical component summary; MCS = mental component summary.
Health-related quality of life in a nursing home.

Hartog et al. (2016) investigated the relationship between health-related quality of life (HRQOL) and all-cause mortality, as well as successful rehabilitation in a nursing home setting. The study found that higher scores on the role functioning-physical dimension were associated with increased mortality risk, which is counterintuitive. This association could be due to the frailty of the patients, as they may be accustomed to living with substantial limitations in functioning. Additionally, the scale used for the role functioning-physical dimension may not be appropriate for nursing home residents, as it is composed of questions related to work or daily activities.

The study also performed Cox regression analyses to evaluate the predictive capability of HRQOL dimensions for all-cause mortality. The Harrell’s C statistic and the \( R^2 \) were used to assess the predictive power of adding HRQOL dimensions to the models. The results showed that the role functioning-physical, mental health, and vitality dimensions added significant predictive power to the models.
The mental health and vitality dimensions were inversely associated with mortality, which was as we had expected and confirmatory to results from prior studies in different populations. The mental health dimension is related to depression and anxiety and the vitality scale is related to fatigue and apathy. In a previous study in a nursing home setting, only physical functioning was significantly related to mortality. Despite the fact it was a nursing home population, the study population was very different compared with the present study. Mainly long-term residents were included and a high percentage (26%) of these residents had cancer, which may have resulted in different complaints and limitations, resulting in different HRQOL scores, but also in a different mortality risk. Within the rehabilitation department, the dimension role functioning-physical was positively related to mortality. Within the somatic department no relation with HRQOL and mortality was found. This difference in results between the somatic and rehabilitation department could be explained by the fact that patients rehabilitating in a nursing home are potentially physically more frail after a recent acute hospital admission. Patients in the somatic department are chronic patients and used to their physical status. Furthermore, patients admitted to the rehabilitation department were older compared with patients on the somatic ward. Because of the sample size, we cannot exclude that the stratified results concerning the somatic group were subject to a type 2 error.

Another study in community-dwelling elderly described a significant relationship between all subscales and mortality. In comparison with the present study, these community-dwelling elderly were not admitted patients but were selected by a demographic registration system, which probably explains the difference in HRQOL scores and may explain the other relationship with mortality.

In the present study the physical and mental component summary scores were not significantly related to all-cause mortality. This can be explained by the fact that the component summary scores are calculated from nine health dimensions, while only three health dimensions were significantly related to mortality. Besides, this could also be due to the sample size or the duration of follow-up.

A previous study in community-dwelling elderly patients with type 2 diabetes showed that MCS was only associated with mortality after an extended and long-term follow-up period. If HRQOL is indeed only related to mortality after a long follow-up period, using HRQOL for these prognostic capabilities will be irrelevant as a long follow-up is not feasible in an old and frail population.

Although our study showed that the dimensions role functioning-physical, vitality and mental health were an independent risk factor for mortality, based on a minimal increase in Harrell’s C values when adding role functioning-physical, vitality or mental health to the adjusted models, one may conclude that the additional value of these dimensions in mortality prediction is apparently very limited. It is important to realise that this study group is a group of frail patients with much comorbidity. Even in the fully adjusted models, the C value was lower than 0.70, indicating the poor predictive capability of the overall model.

**HRQOL and successful rehabilitation**

The results of the present study showed no significant association between HRQOL and successful rehabilitation. We hypothesised that higher HRQOL scores would be associated with successful rehabilitation. Due to better physical, emotional and social well-being, rehabilitation targets would be achieved sooner. Assessing changes in HRQOL could be used to measure improvements in relation to the rehabilitation process.

Although HRQOL was not significantly associated with successful rehabilitation, there was an inverse relationship between a history of psychiatric disease and successful rehabilitation (HR 0.41 [95% CI 0.24-0.69]). In previous studies the relationship between depressive symptoms and functional recovery has been described in post-stroke patients. Depression has a negative effect on recovery in functional status and treatment of depressive symptoms leads to enhanced rehabilitation.

Several previous studies showed improvements in HRQOL after different types of rehabilitation in diverse patient groups (stroke, COPD, cardiac problems, cancer), but the aims of these studies differed from the aim of the present study. In the present study we aimed to investigate the exact opposite, whether HRQOL could influence the rate of successful rehabilitation. To the best of our knowledge, there are no validation studies regarding the use of the RAND-36 in rehabilitation patients. Concerning its use in a nursing home population, a validation study has been performed. It can be questioned if the SF-36 or RAND-36 is a valid instrument in a nursing home population. Possibly, the SF-36 or RAND-36 could only be used for subgroups of rehabilitation patients, such as those with a higher cognitive and physical functioning.

Although we cannot exclude the possibility that rehabilitation itself may have positive consequences for HRQOL, the current study shows that baseline HRQOL is not related to an increased chance of successful rehabilitation.

**Strengths and limitations**

The main strengths of this study were the prospective design, the possibility to take into account the number of variables adjusted for in the multivariate model, and the representative group of nursing home patients. Representativeness was based on the fact that 86% of all admitted somatic or rehabilitation patients during the
study period participated in the present study. In addition, admission to a Dutch nursing home requires approval of a central indication committee and finally, the nursing home facility in the present study was a general nursing home, with somatic, psychogeriatric and rehabilitation departments, comparable with other Dutch nursing homes. There were also limitations. Firstly, due to the observational design it was not possible to establish a causal relation between HRQOL and mortality. Secondly, the RAND-36 questionnaires were not completed in 14% of the sample and this could have led to an uncertainty in the effect estimate. On the other hand, missing data were not significantly associated with mortality or successful rehabilitation: HR 0.89 (95% CI 0.47-1.71) and HR 1.41 (95% CI 0.47-4.23), respectively. The inability to complete questionnaires is a frequently observed problem in geriatric studies and indicative for severe morbidity. However, previous studies that investigated the RAND-36 had a lower response rate compared with present study.19,30,31

Thirdly, the adequacy of using the RAND-36 questionnaire within a nursing home population has been questioned in different studies.4,19 An important issue is that the RAND-36 entails several potentially inappropriate questions for this population.4,19 Due to the high heterogeneity in the nursing home population in general, the use of the RAND-36 could be more suitable for subgroups of rehabilitation patients, such as those with a higher cognitive and physical functioning.79

Fourthly, we did not investigate changes in HRQOL. A change in HRQOL could possibly have predicted mortality more accurately.37 Fifthly, successful rehabilitation was defined as discharge to home or a home for the elderly, where they remained self-reliant. As a consequence, patients with a worse outcome after rehabilitation but with a highly adapted home environment (e.g. stair lift, homecare, meal service) might have been discharged sooner. Finally, our study sample is rather small and therefore our results may be a matter of coincidence.

Confirmation of our results in other studies is necessary, preferably performed with HRQOL at several moments during rehabilitation.

CONCLUSIONS

HRQOL was significantly associated with mortality for three dimensions, but partly in opposite directions. The additional value of HRQOL in mortality prediction is very limited. There were no independent associations between HRQOL and successful rehabilitation. The evaluation of HRQOL is important as a goal on its own; however, this study did not provide evidence for an association between HRQOL and successful rehabilitation within a nursing home population.

DISCLOSURES

The authors declare no conflict of interest. No funding or financial support was received.

Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

REFERENCES


Hartog et al. Health-related quality of life in a nursing home.

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## Table 1. Baseline characteristics for somatic and rehabilitation department and patients with missing and without missing data

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Somatic patients N = 36</th>
<th>Rehabilitation patients N = 123</th>
<th>p-value</th>
<th>Missing data N = 25</th>
<th>Without missing data N = 159</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>80 (61-85)</td>
<td>82 (76-86)</td>
<td>0.01</td>
<td>82 (78-91)</td>
<td>79 (75-89)</td>
<td>0.16</td>
</tr>
<tr>
<td>Female gender</td>
<td>22 (61%)</td>
<td>89 (72%)</td>
<td>0.20</td>
<td>17 (68%)</td>
<td>111 (70%)</td>
<td>0.86</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28 (23-32)</td>
<td>25 (23-28)</td>
<td>0.02</td>
<td>26 (23-29)</td>
<td>27 (23-29)</td>
<td>0.64</td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (64%)</td>
<td>101 (84%)</td>
<td>0.02</td>
<td>23 (92%)</td>
<td>124 (78%)</td>
<td>0.10</td>
</tr>
<tr>
<td>History of CVD</td>
<td>20 (56%)</td>
<td>47 (18%)</td>
<td>0.06</td>
<td>16 (64%)</td>
<td>67 (42%)</td>
<td>0.04</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>14 (39%)</td>
<td>54 (44%)</td>
<td>0.39</td>
<td>6 (24%)</td>
<td>68 (43%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Dementia</td>
<td>3 (8%)</td>
<td>8 (7%)</td>
<td>0.70</td>
<td>10 (40%)</td>
<td>11 (7%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Psychiatric disease</td>
<td>22 (61%)</td>
<td>32 (26%)</td>
<td>&lt; 0.001</td>
<td>13 (52%)</td>
<td>54 (34%)</td>
<td>0.08</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>7 (19%)</td>
<td>33 (27%)</td>
<td>0.37</td>
<td>8 (32%)</td>
<td>40 (25%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Current smoker</td>
<td>9 (25%)</td>
<td>12 (8%)</td>
<td>0.02</td>
<td>3 (12%)</td>
<td>21 (13%)</td>
<td>0.87</td>
</tr>
<tr>
<td>Number of medicines</td>
<td>9 (7-12)</td>
<td>9 (6-10)</td>
<td>0.37</td>
<td>9 (8-13)</td>
<td>9 (6-11)</td>
<td>0.15</td>
</tr>
<tr>
<td>Measurements</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>5 (0-23)</td>
<td>15 (5-30)</td>
<td>0.02</td>
<td>-</td>
<td>10 (3-30)</td>
<td>-</td>
</tr>
<tr>
<td>Social functioning</td>
<td>50 (50-61)</td>
<td>50 (50-61)</td>
<td>0.99</td>
<td>-</td>
<td>50 (50-63)</td>
<td>-</td>
</tr>
<tr>
<td>Role functioning-physical</td>
<td>63 (0-100)</td>
<td>0 (0-25)</td>
<td>&lt; 0.001</td>
<td>-</td>
<td>0 (0-50)</td>
<td>-</td>
</tr>
<tr>
<td>Role functioning-emotional</td>
<td>100 (0-100)</td>
<td>67 (0-100)</td>
<td>0.12</td>
<td>-</td>
<td>83 (0-100)</td>
<td>-</td>
</tr>
<tr>
<td>Mental health</td>
<td>66 (48-84)</td>
<td>68 (60-80)</td>
<td>0.29</td>
<td>-</td>
<td>68 (36-80)</td>
<td>-</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>68 (45-100)</td>
<td>57 (22-78)</td>
<td>0.02</td>
<td>-</td>
<td>67 (22-80)</td>
<td>-</td>
</tr>
<tr>
<td>Vitality</td>
<td>55 (31-79)</td>
<td>65 (50-75)</td>
<td>0.19</td>
<td>-</td>
<td>65 (45-75)</td>
<td>-</td>
</tr>
<tr>
<td>General health perception</td>
<td>51 (40-79)</td>
<td>55 (45-75)</td>
<td>0.72</td>
<td>-</td>
<td>55 (40-75)</td>
<td>-</td>
</tr>
<tr>
<td>Health change</td>
<td>50 (25-50)</td>
<td>50 (25-50)</td>
<td>0.20</td>
<td>-</td>
<td>50 (25-50)</td>
<td>-</td>
</tr>
<tr>
<td>PCS score</td>
<td>51 (39-69)</td>
<td>42 (33-54)</td>
<td>0.03</td>
<td>-</td>
<td>44 (34-57)</td>
<td>-</td>
</tr>
<tr>
<td>MCS score</td>
<td>62 (46-76)</td>
<td>59 (48-74)</td>
<td>0.89</td>
<td>-</td>
<td>69 (48-74)</td>
<td>-</td>
</tr>
</tbody>
</table>

Data are medians (interquartile range) or N (%). 'Mann-Whitney U test was used to compare groups. 'Chi Square test was used to compare groups. CVD = cardiovascular disease; PCS = physical component summary; MCS = mental component summary.
### Table 2. Relationship between HRQOL and all-cause mortality stratified by type of department, only adjusted for age and gender

<table>
<thead>
<tr>
<th></th>
<th>Somatic department (N=36)</th>
<th>Rehabilitation department (N=123)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>0.90 (0.70-1.15)</td>
<td>1.01 (0.90-1.14)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>1.07 (0.79-1.47)</td>
<td>1.04 (0.90-1.20)</td>
</tr>
<tr>
<td>Role functioning-physical</td>
<td>1.05 (0.93-1.18)</td>
<td>1.05 (0.98-1.14)</td>
</tr>
<tr>
<td>Role functioning-emotional</td>
<td>1.01 (0.91-1.12)</td>
<td>1.00 (0.94-1.05)</td>
</tr>
<tr>
<td>Mental health</td>
<td>0.93 (0.76-1.14)</td>
<td>0.80 (0.69-0.94)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>0.94 (0.82-1.08)</td>
<td>1.03 (0.95-1.13)</td>
</tr>
<tr>
<td>Vitality</td>
<td>0.85 (0.70-1.02)</td>
<td>0.90 (0.77-1.04)</td>
</tr>
<tr>
<td>General health perception</td>
<td>0.93 (0.78-1.12)</td>
<td>0.85 (0.74-0.99)</td>
</tr>
<tr>
<td>Health change</td>
<td>0.85 (0.70-1.02)</td>
<td>0.96 (0.86-1.06)</td>
</tr>
<tr>
<td>PCS</td>
<td>0.91 (0.71-1.20)</td>
<td>1.01 (0.83-1.22)</td>
</tr>
<tr>
<td>MCS</td>
<td>0.93 (0.74-1.17)</td>
<td>0.87 (0.71-1.04)</td>
</tr>
</tbody>
</table>

The hazard ratios refer to a 10-point higher score on the RAND-36 dimensions. HR = hazard ratio; CI = confidence interval; PCS = physical component summary; MCS = mental component summary. Bold values correspond to a p-value of 0.05 or less.

### Table 3. Relationship between HRQOL and all-cause mortality stratified to rehabilitation department, adjusted for all selected confounders (the results for the total group are presented for comparison)

<table>
<thead>
<tr>
<th></th>
<th>Total group (N=159)</th>
<th>All-cause mortality (N=159)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95%CI)</td>
<td>HR (95%CI)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>0.99 (0.89-1.10)</td>
<td>1.02 (0.91-1.15)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>1.03 (0.91-1.17)</td>
<td>1.02 (0.88-1.18)</td>
</tr>
<tr>
<td>Role functioning-physical</td>
<td>1.08 (1.02-1.15)</td>
<td>1.08 (1.00-1.18)</td>
</tr>
<tr>
<td>Role functioning-emotional</td>
<td>1.01 (0.96-1.06)</td>
<td>1.00 (0.94-1.06)</td>
</tr>
<tr>
<td>Mental health</td>
<td>0.86 (0.75-0.98)</td>
<td>0.85 (0.72-1.01)</td>
</tr>
<tr>
<td>Bodily pain</td>
<td>1.01 (0.94-1.08)</td>
<td>1.04 (0.95-1.15)</td>
</tr>
<tr>
<td>Vitality</td>
<td>0.88 (0.77-0.99)</td>
<td>0.94 (0.80-1.10)</td>
</tr>
<tr>
<td>General health perception</td>
<td>0.91 (0.81-1.03)</td>
<td>0.90 (0.78-1.05)</td>
</tr>
<tr>
<td>Health change</td>
<td>0.93 (0.87-1.05)</td>
<td>1.00 (0.90-1.13)</td>
</tr>
<tr>
<td>PCS</td>
<td>1.02 (0.88-1.20)</td>
<td>1.05 (0.87-1.28)</td>
</tr>
<tr>
<td>MCS</td>
<td>0.91 (0.88-1.06)</td>
<td>0.91 (0.75-1.12)</td>
</tr>
</tbody>
</table>

Adjusted for age, gender, smoking, DM, history of CVD, hypertension, BMI, history of pulmonary disease, history of psychiatric disease, and the number of medications. The hazard ratios refer to a 10-point higher score on the RAND-36 dimensions. HR = hazard ratio; CI = confidence interval; PCS = physical component summary; MCS = mental component summary. Bold values correspond to a p-value of 0.05 or less.
Reagent strips are efficient to rule out spontaneous bacterial peritonitis in cirrhotics

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ABSTRACT

Background: The gold standard to diagnose spontaneous bacterial peritonitis (SBP) is a polymorphonuclear neutrophil count ≥ 250 cells/µl in ascitic fluid. This test is laborious and expensive. Urine reagent strips measuring leukocyte esterase activity have been proposed as a rapid and inexpensive alternative. The aim of this study was to assess the diagnostic accuracy of the Combur reagent strip for diagnosing SBP. Furthermore the possible advantage of a photospectrometer reading over visual reading of the strip was investigated.

Methods: This prospective study includes all ascitic fluid samples of cirrhotic patients undergoing diagnostic or therapeutic paracentesis over a 12-month period. The samples were collected for the standard diagnostic work-up and in addition tested with a bedside Combur reagent strip. The strip was read visually and with an automated spectrometer.

Results: A total of 157 samples were obtained from 53 patients, and spontaneous bacterial peritonitis was diagnosed in 12 patients based on the ascitic polymorphonuclear neutrophil count. The sensitivity, specificity, positive predictive value and negative predictive value of the reagent strip according to the photospectrometer were 100%, 93%, 55% and 100% respectively, and 75%, 99%, 82% and 98%, respectively, for visual interpretation. The diagnostic accuracy of the photospectrometer was found to be higher than visual interpretation (p = 0.007).

Conclusion: The diagnostic accuracy of leukocyte esterase reagent strips read out by a photospectrometer was comparable with the gold standard test and was excellent for excluding SBP. Our results support implementation of reagent strips in the diagnostic work-up of ascitic fluid.

KEYWORDS

Ascites, leukocyte count, liver cirrhosis, peritonitis, reagent strips

INTRODUCTION

Spontaneous bacterial peritonitis (SBP) is a life-threatening complication in cirrhotic patients with ascites.1 Late or misdiagnosed SBP can lead to increased mortality due to consequences such as gastrointestinal bleeding, development of hepatorenal syndrome and progressive liver failure. Therefore, the threshold for performing diagnostic paracentesis and ascitic analysis should be low.4 The reported prevalence of SBP in cirrhotic patients differs from 0-2.8% in outpatients to 10-30% in hospitalised patients.3-9 The gold standard test to diagnose SBP is a polymorphonuclear neutrophil count of ≥ 250/µl in ascites using a manual counting chamber, regardless of the outcome of the culture of ascitic fluid.2 This analysis is laborious, time-consuming and expensive. Automated cell counting has been proposed to be a reasonable alternative with a high diagnostic accuracy.10 In the past two decades several studies have examined the use of leukocyte esterase reagent strips for the bedside diagnosis of SBP.8,11-25 These strips are widely used for rapid urinary analysis and the principle is based on the detection of leukocyte esterase activity of granulocytes. Varying levels of diagnostic accuracy to diagnose SBP with reagent strips have been reported, with a sensitivity ranging from 45-100%, a specificity from 90-100%, a positive predictive value from 42-100% and a negative predictive value from 93-100%.8,9,11-31 These inconsistent results could be related to variability in reagent strips, patient populations, different cut-off values and the
subjective interpretation of the reagent strip result. However, the consistent high negative predictive value could make the reagent strips a very useful rule-out tool. This study was performed to 1) assess the diagnostic accuracy of reagent strips in comparison with the current gold standard test for diagnosing SBP in a mixed population of low-risk and high-risk patients, and 2) investigate the possible advantage of automated analysis of the reagent strips over visual non-automated reading.

**MATERIALS AND METHODS**

**Study design**

This prospective cohort study was carried out at the Department of Gastroenterology and Hepatology in a referral centre for liver disease in the Netherlands. The study was designed and carried out in accordance with the principles of the Helsinki Declaration and approval was given by the local medical ethics committee of the hospital.

**Patients**

Consecutive patients with cirrhosis undergoing diagnostic or therapeutic paracentesis were prospectively enrolled from July 2006 up to and including July 2007. The total study population was subdivided into a low-risk and high-risk population for the development of SBP. The low-risk population was defined as patients undergoing therapeutic, large volume paracentesis or outpatients undergoing diagnostic paracentesis. The high-risk population was defined as hospitalised patients undergoing a standard diagnostic paracentesis at admission or because of clinical deterioration. Patients with ascites secondary to causes other than liver disease were excluded.

**Methods**

Paracentesis was performed under strict sterile conditions. Ascitic fluid was routinely analysed in the central clinical laboratory with automated determination of the white blood cell count with differential. Ten millilitres of fluid was inoculated at the bedside in aerobic and anaerobic blood culture bottles (Bactec®). Fluid was collected in a sterile tube and assessed by two leukocyte esterase reagent strips (Combur® strips, Roche Diagnostics). Both strips were read out after 60 seconds, one strip visually and one with a photospectrometer (Urisys 1100®, Roche Diagnostics). The observer was unaware of the results of the spectrometer. The observer could differentiate between four different colour shades corresponding to 0, 25, 100 or 500 leukocytes/µl.

**Statistical analysis**

Data analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (Armonk, NY: IBM Corp.). A mean and standard deviation was computed for continuous variables and compared with the Student’s t-tests if normally distributed. A two-sided p-value < 0.05 was considered significant. Sensitivity, specificity, positive and negative predictive values with confidence intervals of 95% were calculated. Receiver operating characteristic (ROC) curves were computed and the optimal categorical cut-off point was analysed. Diagnostic performance between photospectrometer reading and visual interpretation was statistically compared using a McNemar test.

**RESULTS**

A total of 157 ascitic fluid samples were collected from 52 patients (range 1-14 samples per patient): 87 samples (55%) were obtained in the low-risk population and 70 (45%) in the high-risk population (table 1). The prevalence of SBP according to analysis of the polymorphonuclear neutrophil count was 4 (4.5%) in the low-risk group and 8 (11.6%) in the high-risk group (figure 1).

In the low-risk population, one culture (25%) was positive, identifying an *Enterococcus faecium*, whereas three cultures (37.5%) were positive in the high-risk population, identifying *Enterococcus coli, Haemophilus parainfluenzae* and *Pseudomonas aeruginosa* in one case each.

**Photospectrometer versus visual reading**

Of the total of 12 (25%) cases of SBP, three were not detected by optical reading of the strip but correctly diagnosed with the photospectrometer.

With visual reading, the sensitivity for diagnosing SBP was 75% (95% CI 41-93), the specificity 99% (95% CI 95-100), the positive predictive value 82% (95% CI 48-97) and the negative predictive value 98% (95% CI 94-100). The diagnostic accuracy for automated reading was slightly superior (p = 0.007 McNemar test): sensitivity 100% (95% CI 70-100), specificity 93% (95% CI 87-97), positive predictive value 55% (95% CI 33-75) and negative predictive value 100% (95% CI 97-100) (table 2). ROC curve analysis indicated that the diagnostic accuracy of the strips was optimal at a cut-off of 100 leukocytes/µl.

**Low- and high-risk group analysis**

The diagnostic performance of the strip with automated reading in the low- and high-risk populations was similar: the negative predictive value was 100% (95% CI 92-100%) and the specificity was 93% (95% CI 81-98%).

**DISCUSSION**

The results of the present study support the diagnosing value of leukocyte esterase reagent strips in ascitic fluid
Oey et al. Reagent strips to rule out spontaneous bacterial peritonitis. Analysis in patients with cirrhosis. In particular, this simple, quick and inexpensive method could reliably rule out SBP, with a 100% negative predictive value in populations at low- and high-risk for SBP. Automated reading of the reagent strip was superior to visual interpreting and prevented false-negative results. The diagnostic accuracy of the Combur 10 strip in ascitic fluid analysis has been studied previously by several groups. The results of these studies were comparable with our results in terms of a high negative predictive value of reagent strip testing. The cumulative data suggest that the sensitivity of strips for diagnosing SBP is variable and may not be optimal. A negative test result, however, strongly predicts absence of SBP. Thus, in patients undergoing diagnostic paracentesis, a negative reagent strip result may imply that further diagnostic studies — polymorphonuclear neutrophil count and bacterial cultures — are not useful and can be omitted. Obviously, preventing unnecessary diagnostic studies in a substantial proportion of patients presenting with ascites may lead to a marked reduction in costs.

Table 1. Baseline characteristics in 52 patients in the low-risk and high-risk group

<table>
<thead>
<tr>
<th></th>
<th>All (n = 52)</th>
<th>Low-risk group (n = 20)</th>
<th>High-risk group (n = 32)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%)</td>
<td>35 (67%)</td>
<td>17 (85%)</td>
<td>18 (56%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Age*, years</td>
<td>51 ± 10</td>
<td>51 ± 8</td>
<td>51 ± 11</td>
<td>0.981</td>
</tr>
<tr>
<td>Child-Pugh score*</td>
<td>10 ± 1.5</td>
<td>9 ± 1.4</td>
<td>10 ± 1.6</td>
<td>0.962</td>
</tr>
<tr>
<td>Aetiology of liver cirrhosis (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>18 (35%)</td>
<td>11 (55%)</td>
<td>7 (22%)</td>
<td>0.325</td>
</tr>
<tr>
<td>Cryptogenic</td>
<td>10 (19%)</td>
<td>3 (15%)</td>
<td>7 (22%)</td>
<td></td>
</tr>
<tr>
<td>Viral</td>
<td>7 (13%)</td>
<td>2 (10%)</td>
<td>5 (16%)</td>
<td></td>
</tr>
<tr>
<td>Viral + alcohol</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
<td>3 (9%)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>14 (27%)</td>
<td>4 (20%)</td>
<td>10 (31%)</td>
<td></td>
</tr>
</tbody>
</table>

*Mean ± standard deviation.

Table 2. Diagnostic accuracy of visual and automated reading of the leukocyte esterase reagent strip compared with the gold standard

<table>
<thead>
<tr>
<th></th>
<th>Visual reading</th>
<th>Photospectrometer reading</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>75% (95% CI 43-93%)</td>
<td>100% (95% CI 70-100%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>99% (95% CI 95-100%)</td>
<td>93% (95% CI 87-96%)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>82% (95% CI 48-97%)</td>
<td>55% (95% CI 33-75%)</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>98% (95% CI 94-99%)</td>
<td>100% (95% CI 97-100%)</td>
</tr>
</tbody>
</table>

Figure 1. Flowchart study participants and sample collection

157 Ascites samples from 52 patients

Samples from the low-risk group
87 (35%) SBP
4 (5%)

Samples from the high-risk group
70 (45%) SBP
8 (12%)
the gold standard for SBP. It has been suggested that protein could interfere with the test and has a negative effect on the accuracy. One study found a significantly higher mean ascitic protein content in patients with false-negative results than in patients with true-positive results.\(^\text{17}\) Furthermore, little is known regarding the effects of the different composition of ascites as compared with urine, for example with respect to bilirubin or pH level, on reagent strip diagnostic accuracy. Remarkable results – a 100% sensitivity and negative predictive value – have been reported with the Periscreen strip, a strip with specific characteristics for ascitic fluid analysis.\(^\text{18}\) These results await confirmation in a large cohort, which is currently being investigated in the Per-DRISLA study.\(^\text{18}\)

In conclusion, this study adds to already available data suggesting that Combur reagent strips are useful for ascitic fluid analysis in cirrhotic patients. Cumulative evidence clearly indicates that a negative test result reliably rules out SBP. We found reagent strips an inexpensive, time- and money-saving tool, which is available both during and after regular working hours. Reading the strips with a photospectrometer may be superior to visual reading.

ACKNOWLEDGEMENTS

We thank Roche Diagnostics (Almere, the Netherlands) for providing the Urisys 1100 analyser.

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Disclosures

The authors did not receive a grant support to conduct this study. The authors declare no conflict of interest.

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Oey et al. Reagent strips to rule out spontaneous bacterial peritonitis.
Oey et al. Reagent strips to rule out spontaneous bacterial peritonitis.


Risk stratification for healthcare planning in women with gestational diabetes mellitus

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ABSTRACT

Background: To identify relevant factors predicting the need for insulin therapy in women with gestational diabetes mellitus (GDM) and secondly to determine a potential ‘low-risk’ diet-treated group who are likely to have good pregnancy outcomes.

Methods: A retrospective analysis between 2011-2014. Multivariable backward stepwise logistic regression was used to identify the predictors of the need for insulin therapy. To identify a ‘low-risk’ diet-treated group, the group was stratified according to pregnancy complications. Diet-treated women with indications for induction in secondary care were excluded.

Results: A total of 820 GDM women were included, 360 (44%) women required additional insulin therapy. The factors predicting the need for insulin therapy were: previous GDM, family history of diabetes, a previous infant weighing ≥ 4500 gram, Middle-East/North-African descent, multiparity, pre-gestational BMI ≥ 30 kg/m², and an increased fasting glucose level ≥ 5.5 mmol/l (OR 6.03;CI 3.56-10.22) and two-hour glucose level ≥ 9.4 mmol/l after a 75-gram oral glucose tolerance test at GDM diagnosis.

In total 125 (54%) women treated with diet only had pregnancy complications. Primiparity and higher weight gain during pregnancy were the best predictors for complications (predictive probability 0.586 and 0.603).

Conclusion: In this GDM population we found various relevant factors predicting the need for insulin therapy. A fasting glucose level ≥ 5.5 mmol/l at GDM diagnosis was by far the strongest predictor. Women with GDM who had good glycaemic control on diet only with a higher parity and less weight gain had a lower risk for pregnancy complications.

KEYWORDS

Diet, gestational diabetes mellitus, insulin therapy, predictors, risk stratification

INTRODUCTION

Gestational diabetes mellitus (GDM) is one of the most common metabolic complications during pregnancy and occurs in 1-14% of all pregnancies, depending on the population demographics and the diagnostic criteria used.1 Given that obesity is a worldwide epidemic and the recent more stringent guidelines for screening and diagnosis, the prevalence of GDM is still increasing which burdens obstetric care systems.2-7

GDM is associated with an elevated risk of adverse obstetric and neonatal outcomes during pregnancy.8-11 However, studies demonstrated that GDM is a treatable condition and controlling blood glucose levels throughout pregnancy can reduce the risk of complications.12,13 Dietary advice is the first step and cornerstone in GDM treatment. When diet fails, insulin therapy is the second step in treatment, according to almost all the international guidelines.14

In our country, we have a special obstetric care system which is divided between primary and secondary care. The primary care is organised by independently practising

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midwives and general practitioners (GPs) who take care of normal pregnancy and childbirth, and secondary care is organised by in-hospital obstetricians and specialised clinical midwives caring for pathological pregnancy and childbirth or pregnancies accompanied by comorbidity.\textsuperscript{15} Since GDM pregnancies are at increased risk for adverse obstetric and neonatal outcomes, women with GDM are referred to hospitals for obstetric care and are advised to give birth in a hospital with good neonatal facilities. This is especially applicable for women with GDM who are treated with additional insulin therapy and who are considered to represent a more severe GDM group due to a greater difficulty to maintain glycaemic control.\textsuperscript{16}

However, there may be ‘low-risk’ women with GDM who do not need obstetric care in secondary care but can maintain care from their midwives or GPs. Women with GDM treated with diet only might be a potential ‘low-risk’ group who could be treated in a low-risk setting and even qualify for delivery at home. Such a policy demands the correct identification of women with GDM with a high-risk of adverse pregnancy outcomes.

In an earlier paper, we reported the neonatal and obstetric outcomes of pregnancies complicated with GDM after implementation of the 2010 Dutch Society of Obstetrics and Gynaecology GDM guideline on screening and treatment – diet only versus additional insulin therapy – and we compared these outcomes with the general obstetric population in the Northern region of the Netherlands.\textsuperscript{17} In the present study we aim to identify relevant factors predicting the need for insulin therapy in women with GDM and secondly to determine a potential ‘low-risk’ diet-treated group likely to have good obstetric and/or neonatal outcomes.

**MATERIALS AND METHODS**

**Study population and design**

The study population consisted of all women with singleton pregnancies who were diagnosed with GDM according to the Dutch national guidelines in the University Medical Center Groningen and in the Martini Hospital Groningen, between January 2011 and September 2014. As previously reported,\textsuperscript{17} pregnant women were recommended to undergo a 75-gram oral glucose tolerance test (OGTT) at week 24-28 of gestation if they had one or more risk factors for GDM according to the Dutch national guideline: previous GDM, first-degree relative with type 2 diabetes mellitus (DM), a previous neonate weighing ≥ 4500 gram, pre-pregnancy body mass index (BMI) ≥ 30 kg/m\textsuperscript{2}, some ethnic risk groups (South-Asian, Hindu, African-Caribbean, Middle Eastern, Morocco and Egypt), history of intrauterine foetal death (IUFD), and history of polycystic ovary syndrome (PCOS). Also women with signs suggestive of GDM (e.g. polyhydramnios and/or foetal macrosomia) were screened.\textsuperscript{18} Women with previous GDM were screened at week 16-18 of gestation and when the test was negative, it was repeated at week 24-28 of gestation. GDM was diagnosed if the fasting plasma glucose was ≥ 7.0 mmol/l and/or the two-hour plasma glucose ≥ 7.8 mmol/l. In addition, GDM was diagnosed if the fasting glucose was > 7.0 mmol/l or random glucose was > 11.1 mmol/l.\textsuperscript{19,18} The guideline uses these diagnostic criteria, based on the criteria of the World Health Organization (WHO) 1999.\textsuperscript{18}

Women with a twin pregnancy (n = 15) and women with missing data on neonatal complications (n = 4) were excluded. Women with pre-existing diabetes were not included in the study. This study has been exempted for approval according to the Medical Research Involving Human Subjects Act. This report is based on patient data acquired during care as usual, the data were analysed retrospectively and all the requirements for patient anonymity are in agreement with the regulations of the ethics committee of both hospitals. According to this and the Dutch law on Medical Research with Human Subjects, no approval from an ethics committee is necessary.

**GDM treatment regimens**

All women diagnosed with GDM received dietary advice by a trained dietician, which included education about carbohydrate intake and carbohydrate distribution. The women also received instructions regarding self-monitoring of blood glucose levels by a diabetes specialist nurse and were instructed to measure fasting and one-hour postprandial blood glucose levels every day for one week. After 1-2 weeks the blood glucose values were evaluated at the diabetes outpatient clinic. If the fasting plasma glucose level was ≥ 5.3 mmol/l and/or postprandial plasma glucose level ≥ 7.8 mmol/l additional insulin therapy was started. Insulin was commenced with two elevated blood glucose levels on two successive days and no expected benefits of further dietary intervention. There were three options for insulin therapy: once daily long-acting, prandial ultrashort-acting insulin or a combination of both (basal-bolus regimen), depending on the specific glycaemic profile. In both centres short-acting insulin analogues and NPH insulin were used in GDM treatment.

**Measures**

All data were assessed from medical and birth records. Ethnicity was classified into four categories: Caucasian, African-American, Middle-Eastern/North-African descents, and Asian (Indian or South-East Asian). Family history of diabetes was defined as having a first-degree relative with type 2 DM. Weight gain was calculated from pre-pregnancy weight to the first visit. HbA1c values were
measured by standardised HPLC method on a Tosoh G8 system (Tosoh, Tokyo, Japan), considering 22.42 mmol/mol (4.2-6.0%) as normal. The HbA1c values were measured at the time of GDM diagnosis within one week after the OGTT. Neonatal complications included: a composite outcome of perinatal complications (still-birth/neonatal death, birth trauma (shoulder dystocia, fracture of humerus or clavicle), hyperbilirubinaemia and neonatal hypoglycaemia), large for gestational age (defined as birth weight above the 90th percentile, adjusted for age, gender, parity, and ethnicity\(^\text{a}\)), small for gestational age (defined as birth weight below the 10th percentile, adjusted for age, gender, parity, and ethnicity\(^\text{a}\)), preterm delivery (defined as delivery < 37 weeks), Apgar score < 7 at 5 minutes, and admission to the neonatology department. The presence of neonatal hypoglycaemia was defined as a blood glucose level < 2.6 mmol/l or treatment with a glucose infusion. Obstetric complications included: instrumental delivery (forceps or vacuum extraction), planned caesarean section and secondary caesarean section.

**Statistical analyses**

Maternal characteristics are presented according to the GDM treatment regimen. Continuous data are presented as mean with standard deviation or as median and interquartile range [IQR] in case of skewed distribution. Categorical data are presented as number and percentage. For continuous data, the differences between the groups were tested using Student’s unpaired t-test or the Mann-Whitney U test in case of skewed distribution. Categorical variables were compared using the Chi-square test and Fisher’s exact test.

To examine the potential predictors of need for insulin therapy in GDM, analyses were performed using logistic regression models to calculate the odds ratios (ORs) and 95% confidence intervals (95% CIs). Factors considered in the model were: maternal age, smoking during pregnancy, parity, ethnicity, history of PCOS, history of IUFD, pre-gestational BMI, previous GDM, previous pregnancy, and ethnicity were observed between the groups. The frequency rates of previous GDM, a previous neonate weighing ≥ 4500 gram at birth, and first-degree relative with diabetes were higher in the insulin group. The median fasting glucose level and two-hour glucose level after a 75-gram OGTT at time of GDM diagnosis were higher in the insulin-group compared with the diet group.

The women in the insulin group were older, were more often multiparous, and had a higher pre-gestational BMI. No differences in earlier diagnosis of PCOS, hypertension, history of spontaneous abortion, smoking during pregnancy, and ethnicity were observed between the groups. The frequency rates of previous GDM, a previous neonate weighing ≥ 4500 gram at birth, and first-degree relative with diabetes were higher in the insulin group.

The median fasting glucose level and two-hour glucose level after a 75-gram OGTT at time of GDM diagnosis were higher in the insulin-group compared with the diet group.

### Predictors of need for insulin therapy

*Table 2* shows the significant predictors of need for insulin therapy. Previous GDM, family history of diabetes, a previous infant weighing ≥ 4500 gram, Middle-Eastern/North-African descent, multiparity, pre-gestational BMI ≥ 30 kg/m\(^2\), and an increased fasting glucose level and two-hour glucose after a 75-gram OGTT at GDM diagnosis were significant predictors of need for insulin therapy, with a fasting glucose level ≥ 5.5 mmol/l having the highest OR 6.03; CI 3.56-10.22.

### Stratification of diet-treated group

Of the 460 diet-treated women, 229 women (49.8%) were excluded because of other indications for induction. *Table 3* gives an overview of these indications. *Table 4*...
shows GDM pregnancies without (106 women (45.9%)) and with (125 women (54.1%)) obstetric and/or neonatal complications. Primiparity and higher weight gain during pregnancy were the best predictors for complications (predictive probability 0.586 and 0.603) respectively.

**DISCUSSION**

In this study we identified the following risk factors in GDM that predicted the need for additional insulin therapy: previous GDM, family history of diabetes, a previous infant weighing ≥ 4500 gram, Middle-Eastern/North-African descent, multiparity, pre-gestational BMI ≥ 30 kg/m², and a markedly increased fasting and two-hour glucose level after a 75-gram OGGT at time of GDM diagnosis. A fasting glucose level ≥ 5.5 mmol/l at time of GDM diagnosis was the strongest predictor of need for insulin therapy.

Moreover, the study showed that diet-treated primiparous women with GDM had more obstetric and/or neonatal complications compared with multiparous women. Also, a higher weight gain in diet-treated women with GDM was associated with more pregnancy complications.

**Predictors of need for insulin therapy**

Women who receive dietary advice but fail to maintain glycaemic control within 1-2 weeks generally receive additional insulin therapy. In several studies insulin therapy was required in ~20-30% of the women with GDM. In our study a higher percentage (44%) of women with GDM required additional insulin therapy. This is in line with two other studies which reported that 51-53% needed insulin therapy.

Possible explanations for the wide range in percentages for insulin need between studies are: differences in the study population, dietary compliance, criteria for diagnosis of GDM, and criteria to start insulin therapy.

A number of previous studies have addressed the possible predictors of the need for insulin therapy in women with GDM. In analogy to our study, three comparable studies with regard to sample size and ethnicity showed that...
Koning et al. Risk stratification in women with GDM.

Elevated fasting plasma glucose at time of GDM diagnosis was a potent predictor for additional insulin therapy. One study showed in a large cohort of 2365 women with GDM that women requiring insulin therapy were more likely to have a fasting blood glucose of > 5.3 mmol/l (> 95 mg/dl) before a 100-gram OGTT. Moreover, the study found that multiparity, obesity, history of GDM, diagnosis, a three-hour glucose tolerance test > 7.8 mmol/l (> 140 mg/dl), and HbA1c of ≥ 6.0% at GDM diagnosis were additional predictors of the need for insulin therapy. In a second study, BMI, gestational age when GDM was diagnosed, and fasting and two-hour glucose levels after a 75-gram OGTT were independent predictors of insulin therapy among 612 women with GDM. For each increase of 0.5 mmol/l to the level of the fasting glucose, they reported an OR for insulin therapy of 2.75. The last study identified a number of significant predictors for insulin including measures of glycaemia – fasting glucose level and two-hour glucose at time of GDM diagnosis. OGTT = oral glucose tolerance test; OR = odds ratio.

Table 2. Multivariable logistic regression analyses of predictors for additional insulin therapy

<table>
<thead>
<tr>
<th>Predictors</th>
<th>OR</th>
<th>95% CI</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Previous gestational diabetes</td>
<td>2.05</td>
<td>1.13-3.70</td>
<td>0.018</td>
</tr>
<tr>
<td>Family history of diabetes</td>
<td>1.90</td>
<td>1.36-2.66</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Previous infant weighing ≥ 4500 gram</td>
<td>1.68</td>
<td>0.98-2.89</td>
<td>0.061</td>
</tr>
<tr>
<td>Parity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1.00 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-2</td>
<td>1.83</td>
<td>1.27-2.66</td>
<td>0.001</td>
</tr>
<tr>
<td>&gt; 2</td>
<td>2.06</td>
<td>0.94-4.52</td>
<td>0.070</td>
</tr>
<tr>
<td>Ethnicity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1.00 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>0.98</td>
<td>0.39-2.47</td>
<td>0.973</td>
</tr>
<tr>
<td>Middle-East/North- African</td>
<td>2.45</td>
<td>1.29-4.65</td>
<td>0.006</td>
</tr>
<tr>
<td>Asian</td>
<td>0.98</td>
<td>0.48-1.99</td>
<td>0.944</td>
</tr>
<tr>
<td>Pre-gestational body mass index (kg/m²)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 25</td>
<td>1.00 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>25-30</td>
<td>1.37</td>
<td>0.90-2.09</td>
<td>0.141</td>
</tr>
<tr>
<td>≥ 30</td>
<td>1.63</td>
<td>1.08-2.45</td>
<td>0.020</td>
</tr>
<tr>
<td>Fasting glucose level (mmol/l)&lt;&gt;**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 4.6</td>
<td>1.00 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.6-5.0</td>
<td>1.47</td>
<td>0.90-2.41</td>
<td>0.121</td>
</tr>
<tr>
<td>5.0-5.5</td>
<td>2.54</td>
<td>1.02-2.67</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 5.5</td>
<td>6.03</td>
<td>3.56-10.22</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>2-hour glucose level after a 75-gram OGTT (mmol/l)&lt;&gt;**</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 8.1</td>
<td>1.00 (Ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8.1-8.6</td>
<td>1.13</td>
<td>0.71-1.81</td>
<td>0.609</td>
</tr>
<tr>
<td>8.6-9.4</td>
<td>1.65</td>
<td>1.02-2.67</td>
<td>0.040</td>
</tr>
<tr>
<td>≥ 9.4</td>
<td>1.93</td>
<td>1.20-3.11</td>
<td>0.007</td>
</tr>
</tbody>
</table>

ORs, 95% confidence intervals and p-values were derived from logistic regression models (backward-stepwise method). *P < 0.10 was considered statistically significant. **The fasting glucose level and two-hour glucose at time of GDM diagnosis. OGTT = oral glucose tolerance test; OR = odds ratio.
Finally, it has been shown that n = 229**. However,‡ 

The obstetric and/or neonatal complications in the diet group, weight gain during pregnancy were risk factors to develop can be treated with diet alone, and who could possibly other hand a potential ‘low-risk’ group of women who group of insulin-treated women with GDM, but on the This study allowed the recognition of a more complex-care on obstetric healthcare worldwide due to higher costs. diagnostic threshold strongly increases the number of diagnosis of GDM were performed. Stratifiation of diet-treated group type 2 DM.

Plasma glucose are already in an advanced stage to develop elevated glucose levels during pregnancy also predict the need for insulin. why the fasting glucose level is a strong predictor for insulin secretion; this might be a plausible explanation diagnostic OGTT is more associated with a defect in basal production and therefore the abnormality might only be seen in the postprandial blood glucose values. However, it has been demonstrated that GDM women not only have defects in insulin sensitivity but also in insulin secretion. Studies also suggest that the fasting glucose level on diagnostic OGTT is more associated with a defect in basal insulin secretion; this might be a plausible explanation why the fasting glucose level is a strong predictor for the need of insulin. Finally, it has been shown that elevated glucose levels during pregnancy also predict the development of type 2 DM after pregnancy. So it may be that women with more pronounced increased fasting plasma glucose are already in an advanced stage to develop type 2 DM.

**Stratifiation of diet-treated group**

After the findings on the benefits of GDM treatment, worldwide revisions of the guidelines for screening and diagnosis of GDM were performed. Lowering the diagnostic threshold strongly increases the number of women referred for treatment, which imposes a large burden on obstetric healthcare worldwide due to higher costs. This study allowed the recognition of a more complex-care group of insulin-treated women with GDM, but on the other hand a potential ‘low-risk’ group of women who can be treated with diet alone, and who could possibly be referred back to primary care. Only primiparity and weight gain during pregnancy were risk factors to develop obstetric and/or neonatal complications in the diet group, but these risk factors had a very low predictive probability. The rather large proportion of 54% of the diet-treated women who suffered pregnancy-related complications could not validly be identified beforehand. Therefore, it is not possible to identify a circumscribed ‘low-risk’ diet-treated group from our data based on pregnancy outcomes. As some authors suggest that diet-treated women – who are likely to maintain good glycaemic control throughout pregnancy with diet only – can be referred back to midwives in primary care, there remains uncertainty regarding the possible development of pregnancy-related complications. To be able to refer women back to primary care, a healthcare system with optimal interaction and communication between primary and secondary care is required. However, such shared-care models require further evaluation for GDM care. There is more need for prospective studies investigating the safety of treating diet-only women with GDM in primary care.

The strengths of the study are the large cohort of women with GDM and the large database with the collection of commonly used measures. A limitation of the study is the retrospective nature of the analyses and the fact that this GDM cohort is based on the ‘old’ WHO 1999 diagnostic criteria for GDM in our national guideline, which differ greatly from the new WHO 2013 criteria, while for

![Table 3. Indications for the diet group for surveillance of pregnancy and delivery in secondary care](image)

| Table 3. Indications for the diet group for surveillance of pregnancy and delivery in secondary care |
|-----------------------------------------------|-----------|
| **Indication** | **n = 229** |
| Pre-existing diseases |
| Crohn’s disease | 2 |
| Hyperthyroidism with medication | 1 |
| Chronic hypertension | 15 |
| Asthma with medication | 4 |
| Obstetric history |
| IUFD/perinatal death | 9 |
| Preterm birth < 33 weeks | 3 |
| Caesarean section | 18 |
| Pre-eclampsia | 6 |
| Complications during pregnancy |
| Pregnancy-induced hypertension | 43 |
| Pre-eclampsia | 16 |
| Polyhydramnios/foetal macrosomia | 165 |
| Post-term pregnancy | 8 |

*aIndications are based on the List of Obstetric Indications used by midwives in the Netherlands. **Some women had more than one indication for treatment in secondary care. †Chronic hypertension was defined as a pre-gestational systolic blood pressure ≥ 140 mmHg and/or a diastolic blood pressure ≥ 90 mmHg on two occasions or the use of blood-pressure lowering drugs. ‡Preeclampsia was defined as a combination of gestational hypertension and proteinuria (≥ 300 mg/24 h) and included eclampsia and the haemolysis elevated liver enzymes and low platelets (HELLP) syndrome. §Post-term pregnancy was defined as being pregnant for 42 weeks. IUFD = intrauterine foetal death
In summary, in this GDM population we found various relevant factors predicting the need for additional insulin therapy in GDM. Especially, a fasting glucose level ≥ 5.5 mmol/l at GDM diagnosis was the strongest predictor of need for insulin therapy. These predictors might be helpful to recognize a complex-care group of insulin-treated women within the GDM population. Women with GDM who had good glycaemic control on diet only with a higher parity and less weight gain, had a lower risk for obstetric and/or neonatal complications. However, from our data a risk-stratification approach for the diet group based on neonatal and obstetric complications alone did not have predictive utility.

**Acknowledgements**

The authors wish to thank the diabetes specialist nurses, and dietitians of the University Medical Center and Martini Hospital Groningen. Further we want to thank: B.J. Schering and M.G. Baas for assistance with the data collection.

**Disclosures**

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The authors declare no conflicts of interest.
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2. JNVE: The Young Dutch Society for Endocrinology; JNVE meeting; October 30;Holiday Inn Hotel, Leiden, The Netherlands. Title: Predictors of need for insulin therapy in gestational diabetes mellitus.
PHOTO QUIZ

Abdominal pain with a remarkable origin

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CASE REPORT

A 72-year-old man presented to the Emergency Department with generalised abdominal pain, anorexia and vomiting for the last two days. His medical history revealed diabetes mellitus type 2, hypertension and a haemorrhagic cerebrovascular accident. For a few years, he had been complaining about pain in the right upper abdomen and episodes of diarrhoea once every six months which lasted for several days. His stools and urination were normal. He had no fever, but in the last few weeks he complained about dyspnoea and a non-productive cough.

At physical examination an adipose, hemiplegic man was seen. On auscultation, peristalsis was normal, but at palpation a painless, pulsating tumour was found. In the groin strong pulsations were palpable on both sides (left < right). Other physical examination did not reveal any abnormalities. Laboratory examination was normal apart from a C-reactive protein of 28 mg/l and leukocyte count 11.6 x 10⁹/l. An X-ray of the abdomen showed a large mass in the centre of the abdomen (figure 1).

WHAT IS YOUR DIAGNOSIS?

See page 271 for the answer to this photo quiz.
DIAGNOSIS

Our suspected diagnosis was confirmed by a CT scan of the abdomen, showing an infrarenal aneurysm of the abdominal aorta (AAA) with a diameter of 17 cm, causing a mechanical ileus (Figure 2).

AAAs are relatively common and potentially life-threatening. They are defined as a focal dilatation of an artery with at least a 50% increase over the vessel’s normal diameter. Therefore, an infrarenal aorta that is 3 cm or more is considered an AAA. An AAA of 17 cm is an exceptional finding, because the risk of rupture increases strongly with increasing diameter. AAAs with a diameter > 8 cm are associated with a yearly chance of rupture of 30-50%. AAAs generally affect elderly Caucasian men. Risk factors include smoking, chronic obstructive pulmonary disease, and increased body mass index. In addition, individuals with first-degree relatives with AAAs are at increased risk.

Most AAAs are asymptomatic until they expand (or rupture) and many are detected as an incidental finding. However, patients may experience a wide range of complaints such as pain in the back, abdomen or groin. Other symptoms originate from local compression such as nausea, vomiting, or urinary symptoms. Mechanical ileus, as in our patient, has been described before, and occurs in < 1%.

AAAs are treated surgically. The primary methods are by an open or endovascular approach. Our patient was treated with an aortobifemoral prosthesis through the classic open approach by laparotomy. The list of potential complications is long. Open elective repair is accompanied by a mortality rate of 1.5-8% (endovascular repair < 1%).

Our patient had suffered from abdominal symptoms for a number of years. We suspect that recent enlargement of an AAA caused the recent increase in his complaints. The post-surgical admission to the intensive care unit was uncomplicated, after three days the mechanical ileus dissolved. He was discharged in a good clinical condition.


DISCLOSURES

The authors report no conflicts of interest. No funding or financial support was received.

REFERENCES

PHOTO QUIZ

Spontaneous, painful nail haemorrhages and onycholysis in a patient at high altitude

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CASE REPORT

A 23-year-old female patient presented with spontaneous appearance of nail haemorrhages on both hands after a tracking holiday in Peru and Bolivia. At altitudes above 3000 meters, she initially developed painful splinter haemorrhages (figure 1), followed by subungual haematoma (figure 2) and eventually distal onycholysis at all fingernails on both hands (figure 3). Remarkably, her toenails were spared. Her previous medical history included acne conglobata, for which she was recently treated with doxycycline 100 mg once daily for three months by her dermatologist. Other medication included malarone prophylaxis and ethynylestradiol/levonorgestrel. The remaining physical examination and blood analysis were within normal ranges.

WHAT IS YOUR DIAGNOSIS?

See page 273 for the answer to this photo quiz.
DIAGNOSIS

This patient developed spontaneous nail changes due to doxycycline-induced photo-onycholysis. Doxycycline in combination with prolonged and intense exposure to the sun (UVA/UVB) causes a phototoxic reaction in which the nail plate detaches from the nail bed with superimposed nail haemorrhaging. Her toenails were spared, because she wore hiking boots with subsequently no exposure to sunlight. Doxycycline-induced photo-onycholysis without other skin photosensitivity is a rare phenomenon, medical practitioners should be aware of. The nail abnormalities disappeared spontaneously after she stopped taking doxycycline. The prognosis is good with usually complete nail recovery in three to six months.

DISCLOSURES

The authors report no conflicts of interest. No funding or financial support was received.

REFERENCES

PHOTO QUIZ

A case of bilious pleuritis after radiofrequency ablation

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CASE REPORT

A 76-year-old man was referred to the hospital with progressive dyspnoea and abdominal pain in the right upper quadrant of the abdomen. Medical history showed colon carcinoma with metastasis of the liver, for which radiofrequency ablation had been performed several times, most recently three weeks prior to presentation. Physical examination showed a temperature of 38.6 °C and respiratory rate of 32 breaths/min with diminished breath sounds at the right basal area with fine rales and abdominal tenderness of the right upper quadrant. Blood analysis showed a C-reactive protein level of 92 mg/l (normal value 0-10 mg/l) and a leukocyte count of 14.2 x 10^9/l (normal value 3.5-10.0 x 10^9/l). Chest X-ray showed consolidation of the right lower lobe and ligula, right-sided pleural fluid and thickening of the minor fissure (figure 1). Computed tomography, performed after drainage of the pleural fluid, showed a lesion in the liver with air and a perforation of the right hemi-diaphragm with a small ventral pneumothorax (figure 2).

WHAT IS YOUR DIAGNOSIS?

See page 275 for the answer to this photo quiz

Figure 1. Chest x-ray showing a consolidation of the right lower lobe and ligula, right-sided pleural fluid and thickening of the minor fissure

Figure 2. Chest CT showing a RFA lesion with disruption of the right hemi-diaphragm and small ventral pneumothorax on the right side
**DIAGNOSIS**

To differentiate bilious pleuritis (with or without empyema) from carcinomatous pleuritis a transthoracic needle aspiration was performed which yielded a clear brown fluid. Analysis of the pleural fluid showed a low leukocyte count, a high bilirubin level of 137 µmol/l (normal value 0-20 µmol/l) without malignant cells or bacterial growth. This strongly suggests a disruption of the hepatobiliary system and the presence of a thoraco-biliary fistula.

Radiofrequency ablation of liver tumours has been widely practised around the world in the treatment of early and late stages of cancer. It is generally performed for unresectable primary or metastatic liver, lung and kidney tumours and can be conducted in a minimally invasive manner through a percutaneous route or using a laparoscopic or thoracoscopic approach. It is less invasive than surgical resection and preserves maximal normal parenchyma. Mulier et al. described the most common complications of radiofrequency ablation which were re-bleeding, intra-abdominal infection and damage to the biliary tract resulting in the formation of a biloma. Pulmonary complications were found in 0.6% of patients. Symptomatic pleural effusions were found in 6.1% of patients. Diaphragmatic injury was described in five (0.1%) patients. Since bile is a very good nesting ground for a bacterial superinfection, bilious pleuritis poses a therapeutic challenge for clinicians.

A fibrotic thorax has also been described, as bile is a fibrogenic agent; hence a delay in drainage of the pleural fluid can rapidly progress to a permanent state of compromised lung function. In our case the patient was transferred to an academic centre with the thorax drain in situ. He underwent endoscopic retrograde cholangiopancreatography where bile leakage was seen for which two endoprostheses were placed. Bile was adequately drained and the chest drain stopped producing bilious fluid. In conclusion, it is important for clinicians to recognise bilious pleuritis as a potential complication of radiofrequency ablation. The symptoms may occur days to weeks after the treatment. It is a rare complication that should be considered, as it is treatable if recognised.

**DISCLOSURES**

The authors report no conflicts of interest. No funding or financial support was received.

**REFERENCES**

LETTER TO THE EDITOR

4-Aminopyridine as a life-saving treatment in calcium channel antagonist intoxication

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To the Editor,

With interest we read the article written by Rietjens et al. concerning practical recommendations for calcium channel antagonist poisoning. The authors give a nice overview of the pathophysiology and the treatment options. However, one potential life-saving option was not mentioned. In 2007 we published a case report on the use of 4-aminopyridine (fampridine) treatment in case of calcium channel poisoning. We described a case of amlodipine intoxication but this substance has also been used in verapamil intoxication. 4-Aminopyridine inhibits different types of potassium channels (G-protein coupled potassium channels, ATP-sensitive potassium channel, Na+ -activated potassium channel). This blocking action causes a slight depolarisation, thereby opening Na+ and subsequently calcium channels. In particular, the Na+ influx can elicit a rise in cytosolic Ca2+ concentration by inhibiting the Na+/Ca2+ exchanger, which under physiological conditions removes Ca2+ out of the cell driven by the Na+ gradient. 4-Aminopyridine-mediated Na+ influx will decrease the Na+ gradient and thereby decrease the driving force for this Ca2+-extruding Na+/Ca2+ exchanger. Therefore, in calcium entry blocker overdose, 4-aminopyridine can increase the cytosolic Ca2+ concentration very efficiently independent of the calcium channels.

In addition, variability exists between calcium entry blockers as intoxication with diltiazem can usually be treated with calcium infusion and we do not advise 4-aminopyridine in this type of intoxication. Any differentiation in the type of calcium entry blocker is lacking in the paper by Rietjens et al. In conclusion, we think that the 4-aminopyridine-treatment option deserves a place in a review concerning this topic.

DISCLOSURES

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LETTER TO THE EDITOR

Could extracorporeal albumin dialysis be considered as an adjunct therapy in calcium channel blocker overdose?

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To the Editor,

Recently, Rietjens et al. presented an up-to-date stepwise strategy to manage calcium channel blocker (CCB) overdose including supportive care (mechanical ventilation, vasopressors and inotropic drugs), gastrointestinal decontamination and evidenced antidotes (calcium salts and high-dose insulin). In life-threatening CCB poisoning, refractory to standard therapies, they advised to consider lipid emulsion and extracorporeal life support.1 We agree with this strategy and would like to clarify the role of extracorporeal albumin dialysis mentioned by the authors.

All CCBs have some similar pharmacokinetic properties including high protein binding rates (up to 80%), octanol-water partition coefficients (logP > 2.8) and distribution volumes (up to 5 l/kg), making them non-removable by dialysis. The rationale for extracorporeal albumin dialysis is based on the ability of albumin contained in the circuit to enhance the elimination of the toxicant released from the proteins by physicochemical interactions with the membrane and cleared from the blood by diffusion.2 Four refractory CCB poisonings (diltiazem [n = 2], verapamil [n = 1] and amlodipine [n = 1]) were treated with the Molecular Adsorbent Recirculating System (MARS).3,4 Significant tapering of the catecholamine infusion rate was reported and attributed to the faster drop in blood CCB concentrations during MARS.5 However, in the case of amlodipine poisoning, the fraction of amlodipine removed by MARS (< 1%) was negligible,6 questioning the exact mechanisms involved in MARS-attributed improvement of CCB-poisoned patients. Interestingly, extraction of diltiazem, verapamil and their respective active metabolites by MARS has not been investigated.7 Several hypotheses can explain how MARS contributes to improvement in CCB poisoning. CCBs induce vasodilatation by stimulating endothelial nitric oxide (NO) synthase and increasing the production of cyclic guanosine monophosphate, a potent vasodilator. In acute and decompensated chronic liver failure patients, MARS was shown to remove NO from plasma by binding NO to the albumin contained in the circuit as S-nitrosothiol-albumin.5 MARS may thus act in CCB-poisoned patients by scavenging the overproduced NO. Additionally, as in liver failure patients, removal of pro-inflammatory cytokines by MARS may explain the observed improvement in haemodynamics.2 Finally, although elevation of liver enzymes and decrease in prothrombin time were not reported in the CCB-poisoned patients treated by MARS,3,4 significant alteration in liver function due to cardiovascular failure cannot be ruled out. Since all involved CCBs are strongly metabolised by the liver, liver function support using MARS may explain the reported clinical benefit by maintaining CCB metabolic clearance. However, since its usefulness is still low-evidenced, the routine use of extracorporeal albumin dialysis cannot be recommended to manage CCB poisoning.

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RESPONSE TO THE LETTERS TO THE EDITOR FROM VAN DER VOORT ET AL. AND VODOVAR AND MÉGARBANE

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To the Editor,

We thank our colleagues Van der Voort et al. for proposing 4-aminopyridine as an alternative treatment for calcium channel antagonist (CCA) intoxication.² Our manuscript focused on the most practical treatments.³ However, apart from the treatments that we discussed, several other treatments have been suggested for CCA overdose, e.g. phosphodiesterase III inhibitors, levosimendan, methylene blue, L-carnitine and 4-aminopyridine.⁴ The clinical evidence for these treatments is mostly based upon animal studies and anecdotal human reports. In our opinion, further research is needed to establish the efficacy and safety of these therapies before they can be routinely implemented in the treatment of CCA overdose.

4-Aminopyridine is a mechanistically appealing treatment candidate for CCA overdose. It blocks potassium channels on the cytoplasmic side of the membrane, resulting in depolarisation and opening of voltage-gated calcium channels. Several animal models have shown haemodynamic improvement after 4-aminopyridine administration,⁴⁹ although severe side effects, such as muscle fasciculation and seizures, were also noted.⁶-⁸ Only few human data are published on the use of 4-aminopyridine in CCA overdose.¹⁰-¹³ Wilffert et al. describe a patient with amlodipine/lorazepam overdose who haemodynamically improved after administration of a three-hour intravenous infusion with 4-aminopyridine.¹³ In a patient with verapamil overdose it was unclear whether the haemodynamic improvement could be attributed to 4-aminopyridine or other treatments.¹⁴ In addition, as Wilffert et al. already mentioned in their manuscript, intravenous preparations of 4-aminopyridine are only sparsely available in Dutch hospital pharmacies.

Phosphodiesterase III inhibitors inhibit the breakdown of cyclic adenosine monophosphate, resulting in increased intracellular calcium concentrations, and improved inotropy.¹⁴ Levosimendan is a calcium sensitisier, showing direct interaction with troponin C in the myofilaments of cardiomyocytes.¹⁵ However, both phosphodiesterase III inhibitors and levosimendan can cause significant vasodilatation, worsening CCA-induced hypotension. Methylene blue inhibits nitric oxide synthase and guanylcyklase activity, decreasing the production of cyclic guanosine monophosphate (cGMP). Elevated intracellular cGMP concentrations lead to relaxation of myocardium and vascular smooth muscle. Methylene blue can possibly counteract CCA-induced toxicity by inhibition of excessive production of cGMP.¹⁶ In CCA overdose, the metabolism of cardiac myocytes is switched from free fatty acids to glucose. L-carnitine could positively influence cardiac metabolism, by reversing the metabolism back to free fatty acids.¹⁷-¹⁸ The effectiveness of these alternative treatments, including evaluation of adverse effects, should be further explored in order to draw more definite conclusions about their therapeutic value in CCA overdose.

Furthermore, we would also like to thank Vodovar and Mégarbane for proposing and clarifying the role of extracorporeal albumin dialysis (Molecular Adsorbent Recirculating System (MARS)) in CCA overdose.¹⁹ Interestingly, the improvement in haemodynamics is not always accompanied by a substantial removal of toxin by MARS. Several hypotheses are provided that could explain the beneficial effects of MARS in CCA overdose.¹⁹ However, the limited availability of MARS will obstruct general application of this technique. In the Netherlands, only a few university hospitals perform this treatment. An alternative but promising treatment is the use of extracorporeal life support,²⁰-²¹ which should be used as a rescue therapy when conventional pharmacological interventions are not sufficiently effective.

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REFERENCES


