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EDITORIAL

Red blood cell transfusion and furosemide in cardiac surgery: friend or foe?

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Acute kidney injury (AKI) is one of the most common complications of cardiac surgery and even when the injury is relatively modest it is independently associated with both a high morbidity and mortality.[1,2] The pathogenesis of AKI in cardiac surgery (CS-AKI) is complex and incompletely understood with aetiological features that are both common to other types of AKI as well as some specific features.[3] The mechanisms include action of exogenous and endogenous toxins, metabolic factors, ischaemia-reperfusion injury, neurohormonal activation, inflammation and oxidative stress.[3] Each may play a role in the pathogenesis of CS-AKI throughout the process but are not necessarily temporally related. Numerous therapies for the prevention of AKI have been tested but none have been proven particularly effective.[4] This lack of effective therapies prompted Dr Vellinga and colleagues to try and identify modifiable risk factors for reducing AKI after cardiac surgery as published in this issue of *The Netherlands Journal of Medicine*.[5] The authors performed a single-centre retrospective analysis in 565 adult patients who underwent coronary artery bypass grafting (CABG) with cardiopulmonary bypass (CPB). Serum creatinine (SCr) was determined at admission and at 24-hour intervals for a minimum of 48 hours and a maximum of seven days. Unfortunately urine output and fluid balance were not recorded. AKI was determined by the modified AKIN criteria employing only the serum creatinine criteria. Eighty-three patients were diagnosed with AKI, of which 74 (89%) were classified as AKIN I, 4 (5%) patients AKIN II, 3 (4%) patients AKIN III with 2 (2%) patients receiving renal replacement therapy (RRT). Despite the impressively low rate of CS-AKI both mortality rate and length of hospital stay were not reported. Based on their multivariate analysis findings the authors concluded that intraoperative and postoperative red blood cell (RBC) transfusion as well as administration of furosemide played a significant role in the development of AKI.

These findings are in keeping with some other studies and as such are not unique. Numerous studies have reported renal risk factors derived in a multivariate fashion from larger cohorts of patients undergoing cardiac surgical procedures. For example, in 2009 Karkouti *et al*. performed a large multicentre study in 3500 patients who underwent cardiac surgery with CPB using the modified RIFLE criteria (GFR criteria only) to define AKI.[6] Although the most predictive risk factors were CPB duration and intra-aortic balloon pump before surgery, three potentially modifiable and interrelated risk factors (preoperative anaemia, perioperative RBC transfusions, and the need for reexploration) were strongly associated with the development of AKI. Very recently, Parolari *et al*. performed a large single-centre study in 3669 patients who underwent on-pump cardiac surgery, using the modified AKIN (SCr only) to define AKI.[7] This demonstrated that as well as conventional preoperative risk factors for AKI such as increasing age, preoperative SCr, and diabetes, drug administration (especially inotropes, vasoconstrictors, diuretics), RBC transfusion, and perfusion or cross-clamp times were significantly associated with AKI.[7] However, an obvious limitation of all these retrospective studies is the potential for confounding effects, particularly when the trigger for intervention is not clearly defined. Thus, RBC transfusion during cardiac surgery *may* contribute to AKI but is itself often consequent to significant blood loss, the cause of which may also contribute to the development of AKI. Likewise, furosemide *may* contribute directly to AKI, but again, it may be that the administration of the diuretic was initiated by a response to oliguria heralding AKI. Therefore, despite the fact that this study implies that transfusion and diuretic administration are independent risk factors for the development of CS-AKI we are left wondering whether this is the chicken or the egg.

However, this study does raise some interesting points. Transfusion of RBCs may cause AKI through interaction

between donor RBCs and transfusion recipients as a consequence of receiving RBCs altered by processing and storage (the so-called 'storage lesion').[8] The storage lesion has effects on overlapping pathways of oxygen delivery, RBC rheology as well as effects on immune modulation.[8] It has been suggested that transfusion of 'younger' blood results in less morbidity/mortality; however, it is not currently known if clinical outcomes are affected by the age of transfused blood and uncertainty remains regarding the clinical importance of RBC storage duration as well as when 'new' blood can be viewed as 'old' blood.[9] Of note, in an experimental pig model RBC transfusion during CPB protected against AKI.[10] Another approach was recently suggested by Karkouti *et al*. in a small unblinded randomised pilot clinical trial in cardiac surgery patients showing that prophylactic transfusion one to two days before surgery limits the deleterious effects of blood transfusions compared with standard of care (transfusion as indicated).[11] The rationale for this approach was that RBC transfusion may increase the amount of circulating free iron, which could exacerbate the oxidative stress injury during surgery. Preoperative transfusion may allow time for iron metabolism to stabilise and/or chelation to occur before the effects of surgery come into play, thus keeping free iron levels at more acceptable, less damaging, levels.[11] The study, however, was not powered to detect differences in AKI. Notably, in a very recent pilot study by Haase *et al*. low preoperative levels of the iron regulatory hormone hepcidin were found to be a risk factor for mortality after cardiac surgery, adding to the evidence that altered metabolism may contribute to organ dysfunction after major surgery.[12]

Loop diuretics such as furosemide have been extensively studied because of their main pharmacokinetic actions: reduction of vascular resistance and inhibition of active transport in the thick ascending limb of the loop of Henle. This latter effect has been proposed as 'protective' with reduction in the energy requirements under ischaemic conditions. In experimental trials the administration of furosemide protected the chronically hypoxic juxtamedullary regions during ischaemic events.[13] In contrast, clinical trials were unable to reproduce this beneficial effect in humans, and it was even suggested that the use of furosemide was detrimental.[14] Nevertheless, very recently Gandhi *et al*. constructed a best evidence topic according to a structured protocol. The question addressed was 'Does perioperative furosemide usage reduce the need for renal RRT in cardiac surgery patients?'[15] Based on ten studies which represented the best evidence to answer this clinical question the authors concluded that the evidence supporting the benefit of this strategy in terms of reducing the need for RRT is weak. At the same time, current best available evidence, albeit from small RCTs, suggests that the timely introduction of continuous furosemide infusion does not increase the incidence of renal impairment after cardiac surgery.

So, where does this study leave us? Although the results are of interest, no firm conclusions can be drawn as to potential interventions to limit CS-AKI. As pointed out the need for intervention is almost certainly as relevant as the intervention itself. Clearly, when faced with a surgical patient with significant haemorrhage, for whatever reason, transfusion cannot be withheld and one may argue that not reacting to volume loss is probably a greater risk factor. Similarly, unchecked positive volume balance is also associated with increased morbidity and mortality and hence may necessitate intervention. Vaara *et al*. recently performed a prospective multicentre observational cohort study in 283 RRT-treated critically ill patients and showed that patients with fluid overload at RRT initiation had twice as high crude mortality compared with those without.[16] In another recent observational single-centre study in 502 post-cardiac surgery patients, both fluid overload and changes in SCr correlated with mortality.[17] Of note, fluid overload was the variable most related to length of stay in intensive care.[17] Perhaps the best way to limit CS-AKI is in terms of technique employed. Early observational studies comparing off-pump CABG with on-pump CABG showed a significant reduction in CS-AKI and a subsequent meta-analysis confirmed these observations.[18,19] By meta-analysis, off-pump CABG was associated with a 40% lower odds of CS-AKI although interestingly there was little effect on overall mortality. Perhaps what we should bear in mind is that all our interventions have an effect on our patients and some carry greater risks than others!

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REVIEW

The combination of insulin and GLP-1 analogues in the treatment of type 2 diabetes

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ABSTRACT

GLP-1 analogues have been proven to be effective in the treatment of type 2 diabetes mellitus. They stimulate insulin production and secretion, and suppress glucagon secretion, depending on the blood glucose level. They also have an effect on the brain, enhancing satiety, and on the gut, where they delay gastric emptying. Theoretically, in type 2 diabetes mellitus patients, the combination of a GLP-1 analogue with insulin seems attractive, because of the weight loss perceived in users of GLP-1 analogues in contrast to the weight gain seen in most patients starting insulin therapy, leading to even more insulin resistance. There are only a few randomised controlled trials which have studied this combination and several uncontrolled studies, which will be reviewed here.

KEYWORDS

GLP-1 analogue, review, diabetes mellitus, insulin, combination

INTRODUCTION

GLP-1 analogues have been proven to be effective in the treatment of type 2 diabetes mellitus.[1] They stimulate insulin production and secretion, and suppress glucagon secretion, depending on the blood glucose level. They also have an effect on the brain, enhancing satiety, and on the gut, where they delay gastric emptying. In Europe, these drugs are being reimbursed for use in patients with a body mass index (BMI) of 35 kg/m^2 or higher, in combination with a sulphonylurea or metformin or a thiazolidinedione, or in triple therapy, in combination with metformin and a sulphonylurea, or with metformin and a thiazolidinedione. Before starting the GLP-1 analogue, it is mandatory that the combination of metformin and a sulphonylurea has been proven ineffective in the maximum tolerable dose. The combination of a GLP-1 analogue and insulin is not reimbursed in the Netherlands, although the combination of insulin glargine and exenatide has been approved by both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA). In practice, this leads to frustration in patients who have type 2 diabetes mellitus, use insulin and are obese, and would like to use a GLP-1 analogue in combination with insulin, or even substitute insulin for a GLP-1 analogue, because they hope to lose weight when using these drugs and reduce their insulin dose. The question is whether the combination of insulin and GLP-1 analogues is effective and does have an effect on weight, and whether this combination leads to other side effects than use of a GLP-1 analogue alone.

Recently, several studies were published concerning the use of GLP-1 analogues and insulin in type 2 diabetes. There are only three randomised controlled trials and several retrospective case series. We will discuss them here.

EFFECT OF GLP-1 ANALOGUES

GLP-1 or glucagon-like peptide 1 is an incretin secreted from enteroglucagon-producing cells in the lower gut. It is a gastrointestinal hormone that regulates insulin and glucagon secretion in response to ingested nutrients. GLP-1 stimulates insulin production and secretion, and suppresses glucagon secretion, both in a glucose-dependent manner. Furthermore, it has an effect on the brain, enhancing satiety, and on the gut, where it delays gastric emptying. GLP-1 analogues mimic the endogenous GLP-1. They were shown to normalise blood glucose

concentrations in the fasting state in patients with poorly controlled type 2 diabetes with secondary failure after sulphonylurea treatment by elevating insulin and reducing glucagon concentrations.[2] Furthermore, after glucose levels had normalised, insulin levels decreased and glucagon levels increased despite ongoing infusion of the GLP-1 analogue.

A recent Cochrane review discussed the effects of GLP-1 analogues in patients with type 2 diabetes.[1] Studies had to be randomised controlled trials of a minimum duration of eight weeks. Comparisons that were included were GLP-1 analogue as a third-line agent *vs* placebo or another antihyperglycaemic agent, GLP-1 analogue as a second-line agent *vs* placebo or another antihyperglycaemic agent, or GLP-1 analogue *vs* another GLP-1 analogue. In total, 17 randomised controlled trials with relevant data on 6899 participants were included. Conclusions were that GLP-1 analogues significantly improve glycaemic control when added to dual treatment with oral antihyperglycaemic drugs, and can be an alternative to starting insulin. There was an improvement of 1% in HbA1c, and in the percentage of patients reaching the target HbA1c. The majority of clinical trials reported a significantly larger reduction of body weight compared with placebo. Most commonly reported adverse events were nausea, vomiting and diarrhoea, but these complaints were mainly present during the initial weeks of treatment. Hypoglycaemia was more often seen in patients on exenatide and concomitant sulphonylurea and on 1.8 mg liraglutide than on placebo. Beta cell function improved with GLP-1 analogues, as was estimated by a variety of measures such as HOMA-B, HOMA2-%B, proinsulin-to-insulin ratio or proinsulin-to-C-peptide ratio. Exenatide in its once weekly formulation and liraglutide were superior to insulin glargine with regards to HbA1c improvement, weight loss, and hypoglycaemia incidence. There were no trials available comparing GLP-1 analogues with neutral protamine Hagedorn (NPH) insulin. The authors said that there were concerns regarding side effects as pancreatitis and renal failure with exenatide, and pancreatitis and thyroid carcinoma with liraglutide, but the studies were not long enough to prove or dispute these concerns.

The effect of GLP-1 analogues on weight loss was reviewed in another paper.[3] Vilsboll *et al.* included 25 trials of adult patients with or without type 2 diabetes, with a BMI of 25 kg/m^2 or more. Patients used exenatide twice daily (bid) or once weekly or liraglutide once daily. Controls were placebo, no intervention, or blood glucose lowering drugs (including another GLP-1 analogue). The duration of the trial had to be at least 20 weeks. All trials reported weight loss, more in the GLP-1 analogue group than in the control group. A random effects meta-analysis was performed including 3395 participants randomly assigned to GLP-1 analogue and 3016 to the control group. Overall change in body weight was expressed in a weighted mean difference between the GLP-1 analogue and the control group and amounted to -2.9 kg (95% CI -3.59 to -2.22). Weight loss occurred in participants with and participants without diabetes. There was no difference between liraglutide and exenatide. Also, there was a reduction in systolic and diastolic blood pressure and total cholesterol in participants treated with a GLP-1 analogue. Again, the most frequent adverse events were nausea, vomiting, and diarrhoea.

COMBINATION WITH INSULIN: RATIONALE

The start of insulin therapy generally leads to an increase in body weight. Several mechanisms underlie this effect. First of all, there will be reduction of glucosuria, hence the number of calories wasted by this is reduced. Secondly, insulin has been reported to increase appetite, and thirdly, patients need to take extra amounts of carbohydrates when hypoglycaemia occurs. This weight gain leads to further insulin resistance, and ultimately leads to a new equilibrium in which a higher dose of insulin is required for adequate glucose control. As a consequence, in daily clinical practice many patients with type 2 diabetes need a large amount of insulin to control their diabetes. In this situation, very low calorie diets have been tried with short-term success, but limited data are available about their long-term effects.[4] By addition of a GLP-1 analogue to existing insulin therapy, patients may benefit from the combined effects on endogenous insulin secretion, on reduction of increased appetite, and on slowing of gastric emptying. Taken together, on theoretical grounds, it could be expected that there would be a reduction of caloric intake, less pronounced postprandial blood glucose increase, and possibly also a lower need for exogenous insulin.[5]

PROSPECTIVE STUDIES

Unfortunately, there are only a few randomised controlled clinical trials in patients with type 2 diabetes mellitus, in whom a GLP-1 analogue was added to existing insulin therapy. A first short-term, small-scale, randomised controlled clinical trial was performed by Kolterman *et al.*[6] This was a proof-of-concept study for the study later published by Buse *et al.*[7] They showed a reduction in postprandial glycaemic excursion when adding exenatide bid in 24 participants, of whom only six were using insulin.

Three randomised controlled trials have subsequently been reported. The study by Arnolds *et al.* was a single-centre, randomised, open-label, active comparator-controlled study

with a three-arm parallel group design.[8] They studied 48 subjects with type 2 diabetes treated with insulin glargine and metformin. These subjects were randomised to receive additional exenatide 5 µg bid for the first two weeks, and 10 µg bid for the second two weeks, or sitagliptin 100 mg once daily, or no additional drug. After four weeks, a standardised breakfast meal challenge was performed. The addition of exenatide or sitagliptin led to a significantly smaller unadjusted 6-hour postprandial blood glucose excursion (17% reduction for exenatide, and 20% for sitagliptin), and lowered HbA1c. Baseline HbA1c was 8.1 ± 0.7% overall, 7.9% in the sitagliptin and control group, and 8.4% in the exenatide group, and dropped for exenatide by -1.8 ± 0.7, and for sitagliptin by -1.5 ± 0.7 *vs* -1.2 ± 0.5% points in the control group. The decrease of HbA1c in the exenatide group was significantly larger than in the control group. Addition of exenatide led, however, to the highest number of adverse events (47 *vs* 12 and 10 in the sitagliptin and control group respectively), mostly gastrointestinal (56%), and one subject stopped the study because of loss of appetite. There was no difference in hypoglycaemia rates, which were low. Body weight decreased in the exenatide group (-0.9 ± 1.7 kg) and was stable in the sitagliptin (0.1 ± 1.6 kg) and the control group (0.4 ± 1.5 kg). As was discussed by the authors in their article, the number of patients was relatively small, and the mean duration of diabetes was only six years. Also, in addition to the between-group difference in baseline HbA1c, the duration of the study was too short to see the full effect on HbA1c, and the open-label design represents a limitation.

The study by Buse *et al.* was a parallel, randomised, placebo-controlled trial, blocked and stratified by HbA1c level at site.[7] The trial was performed in 59 centres in five countries in 261 participants with type 2 diabetes who used insulin glargine alone or in combination with metformin or pioglitazone, or both. Participants were randomised to exenatide 10 µg bid (138 participants) or placebo injections (123 participants). The trial lasted 30 weeks. HbA1c level decreased by 1.74% in the exenatide group and 1.04% in the placebo group (between-group difference -0.69%, p<0.001). The proportion of participants reaching the target HbA1c of 7.0% or less was 60% in the exenatide group and 35% in the placebo group (between-group difference 25%, p<0.001), and the target HbA1c of 6.5% or less was 40% in the exenatide group and 12% in the placebo group (between-group difference 28%, p<0.001). The authors did not observe a reduction in insulin dose, not even in the exenatide group. The insulin dose increased by 13 units per day in the exenatide group and 20 units per day in the placebo group (between-group difference -6.5, p=0.030). There was no difference in fasting plasma glucose levels between the two groups. Body weight decreased by -1.8 kg in the exenatide group, and increased by 1.0 kg in the placebo group (between-group difference -2.7 kg, p<0.001). There was no effect on serum lipid measurements, but there was a significant decrease in systolic and diastolic blood pressure, which was only observed in the exenatide group (the between-group difference in systolic blood pressure was 4.4 mmHg and in diastolic blood pressure 3.4 mmHg, both in favour of the exenatide group). The rate of hypoglycaemia was similar in the two groups. In total 26 participants in the exenatide group and 22 in the placebo group withdrew; 13 participants in the exenatide group and one in the placebo group withdrew because of adverse events. Nausea, diarrhoea, vomiting, headache and constipation occurred more in the exenatide group than in the placebo group. Baseline characteristics differed with regards to gender (more females in the exenatide group, 49 *vs* 36%), and prestudy oral antihyperglycaemic agents used (more participants on metformin alone in the placebo group (75 *vs* 66%), and more participants on metformin plus pioglitazone in the exenatide group (17 *vs* 7%)), and HbA1c levels (8.35 in the exenatide group *vs* 8.53% in the placebo group). After adjustment for these variables, none affected the primary outcomes.

In a post-hoc analysis of 137 exenatide and 122 placebo participants of this study, it was investigated whether baseline HbA1c, baseline body weight, and diabetes duration had an effect on the outcome of glycaemic control and weight loss.[9] Exploratory subgroup analyses revealed that users of exenatide had greater HbA1c reductions compared with optimised insulin glargine alone, irrespective of baseline HbA1c (p<0.001). Also, greater HbA1c reductions were seen in the exenatide users with longer diabetes duration (9-15 and >15 years) and those with lower BMI (BMI <30 and 30-36 kg/m^2) (p<0.01). Irrespective of baseline HbA1c or BMI, exenatide users lost more weight than those on placebo (p<0.05). Exenatide users with longer diabetes duration (>15 years) lost the most weight (p<0.001).

A 38-week trial of adding liraglutide to metformin followed by a randomised, open-label investigation of further intensification with systematically titrated basal insulin detemir was performed by De Vries *et al.*[10] This study was performed in 202 office- or hospital-based sites in Belgium, Canada, France, Germany, Italy, the Netherlands, Spain, the UK and the US between March 2009 and April 2010. The trial comprised a 12-week run-in period during which liraglutide was started and uptitrated to 1.8 mg, followed by a 26-week, randomised, two-armed, parallel-group period for participants not achieving an HbA1c <7.0%. Sulphonylurea use was discontinued before the study and metformin was continued. Participants were randomised to receive insulin detemir (randomised treatment group) added to metformin and liraglutide, or continued metformin and liraglutide (randomised

control group). Participants who had achieved an HbA1c <7.0% were the observational group. A total of 988 participants entered the 12-week run-in period, 987 were exposed to liraglutide, 168 withdrew during the run-in period, of whom 92 due to adverse events (76 gastrointestinal). Therefore, 821 participants entered the 26-week randomisation period, of whom 498 entered the observational group, and 323 were randomised, 162 receiving insulin and 161 not. In total, of these 821, 80 participants withdrew, of whom 19 due to adverse events (evenly distributed among the groups). Participants reaching the target had a shorter diabetes duration, lower HbA1c and fasting plasma glucose levels (FPG), and more had been treated with metformin only before enrolment. HbA1c was reduced by 1.3% in the observational group and by 0.6% in the randomised groups. Body weight decreased by 3.5-4.4 kg, FPG by 1.0-2.0 mmol/l. Nausea was the most frequently reported adverse event in the run-in period, but there was also one case of acute pancreatitis, and one subject was diagnosed with papillary thyroid carcinoma. In the randomised groups, adding insulin detemir reduced HbA1c by a further 0.51% *vs* an increase of 0.02% in the placebo group (p<0.0001). Mean FPG decreased by 2.1 mmol/l in the detemir group *vs* 0.4 mmol/l in the placebo group. The detemir group lost 0.16 kg body weight *vs* 0.95 kg in the placebo group (p=0.03). HbA1c <7% was achieved by 17 *vs* 43% (p<0.0001), and ≤6.5% by 6 *vs* 18% (p=0.0016) in the placebo and detemir group respectively. The composite endpoint (HbA1c <7% and no weight gain and no hypoglycaemia) was reached by 21% in the detemir and 9% in the control group. There were not many hypoglycaemic events and no major hypoglycaemia. No significant changes in blood pressure and lipids were found, except for a larger reduction in free fatty acids in the detemir group (-0.11 *vs* -0.003 mmol/l, p=0.002). More adverse events and increased lipase were found in the detemir group, but without signs or symptoms. HbA1c reduction was 1.1% overall in the observational group, FPG decreased by 2.1 mmol/l, and weight by 4.8 kg. Adverse events were found in 81% of the observational group, 49 serious of which 45 were considered unlikely to be caused by the study drug, and without obvious pattern. No major and 9.0% minor hypoglycaemia occurred. The authors mention that perhaps more participants might have reached the target HbA1c level if the run-in period had lasted longer or with a lower FPG target for insulin titration. Furthermore, the study used the highest liraglutide dose; maybe there would have been less withdrawals if it had been allowed to return to the 1.2 mg dose. Also, there was no active comparator or masked placebo.

Until now, there are no studies in which addition of exenatide or liraglutide to basal insulin has been compared with another comparator. In one study (Clinicaltrials NCT00960661), addition of exenatide bid to existing treatment with insulin glargine and metformin is compared with addition of thrice-daily insulin lispro. The results of this study are expected in the Spring of 2013. To evaluate the differences between GLP-1 analogues and other possible treatments, we really need long-term comparative studies between active treatment modalities. It can be doubted whether studies, in which the addition of a GLP-1 analogue *vs* placebo is studied (as in NCT01617434) really will advance our knowledge about the benefits of combined insulin/GLP-1 analogue treatment compared with existing therapies.

UNCONTROLLED STUDIES/ OBSERVATIONS

Several uncontrolled, nonrandomised, mostly retrospective reports derived from clinical practice have been published.[11-19] Data of these studies are summarised in *table 1*. Most studies reported a decrease in HbA1c, weight, and insulin dose upon addition of GLP-1 to insulin therapy. There are several problems with these studies. First, participation was voluntary so there is a risk of selection bias. No strict protocols as in randomised studies are followed and diabetes treatment changes were individually tailored. Glycaemic improvements in the ABCD study were possibly attenuated by concurrent reductions in other hypoglycaemic agents such as insulin.[16] Not all data were always available on all patients, possibly leading to bias. Larger reductions in HbA1c and weight could possibly be due to the additional start or intensification of lifestyle interventions. There were no control groups, and all studies were observational.

The ABCD trial was analysed again with patients on whom baseline diabetes treatment details and three-month HbA1c and/or weight data were available.[20] These patients were grouped as: Group 1 (non-insulin users, n=2427), Group 2 (insulin continued, n=927), and Group 3 (insulin stopped, n=319). The authors found that at three months, the mean HbA1c reduction for Group 1 was 0.90 ± 1.57% (p<0.001), for Group 2 0.51 ± 1.51% (p<0.001), and for Group 3 0.00 ± 1.91% (p=0.968), and weight loss was -4.1 ± 4.6 kg, -4.6 ± 5.0 kg and -6.6 ± 5.2 kg (all p<0.001). Among insulin-treated patients, increasing insulin dose reduction led to less HbA1c reduction, but more weight reduction.

GLP1 ANALOGUES IN TYPE 1 DIABETES

We identified a few studies which assessed the effects of GLP-1 analogue treatment in type 1 diabetes. The rationale is that the effect of GLP-1 on glucagon, appetite

Table 1. *Summary of nonrandomised, mostly uncontrolled and retrospective studies*[11-19]

Study & author	Data source	Cases	Controls	Study duration	Comparison	Results	Weight	Insulin dose	Adverse events
Observational, retrospective Viswanathan 2007 [11]	Medical records (outpatient clinic)	Group A: 38 patients who took EXE regularly	Group B: 14 patients who discontinued EXE due to insurance, personal or economic reasons	Mean follow-up 26 weeks	Group A vs Group B	Group A: mean HbA1c ↓ by 0.6±0.2% (p=.007) In Group A, but not Group B, ↓ of TC by 8.5±3.3% (p=.03), TG by 26±7.6% (p=.01), SBP by 9.2±3.3 mmHg (p=.02), hsCRP by 34±14.3% (p=.05)	Mean body weight ↓ by 6.46±0.8 kg (p<.001) in Group A and ↑by 2.4±0.6 kg in Group B (p<.001)	Insulin dosage requirement ↓for rapid-acting and mixed insulins (p<.02)	Not reported
Observational, retrospective Sheffield 2008 [12]	Electronic medical records (outpatient clinic)	EXE added to insulin, n=124 (out of 134)	None	1 year follow-up	Before and after start of EXE	↓ in HbA1c of 0.87% after a year (p<.001)	Mean weight ↓ 5.2 kg (p<.001)	45% stop of pre-meal insulin (p<.001) 9 U ↓mean pre-meal insulin doses (p=.0066), ↓ in median number of daily insulin injections from 2 to 1 (p=.0053) 59% discontinuation of SU (p=.0088)	14 patients (10%) experienced (mostly mild) hypoglycaemia, 48 patients (36%) discontinued EXE due to AE mostly gastrointestinal
Observational, retrospective Yoon 2009 [13]	Medical records	EXE added to insulin, n=188 (out of 268) Excluded: 38 discontinued EXE < 2 mo, 30 lost to follow-up, 12 no evaluable data	None	Up to 27 mo	Before and after start of EXE	Mean change in HbA1c -0.54 to -0.66 % (p<0.001 to p=0.020). Slight rise after 18 mo	Mean weight ↓2.4-6.2 kg (p<0.001, p<0.01). Slight rise after 18 mo. Positive correlation between weight loss and decrease in insulin TDD	-18.0 U/day at 0-6 mo, and -14.8 U/day at 6-12 mo (p<0.001), mainly prandial doses 11 patients stopped insulin	26 discontinued due to AE, mainly gastrointestinal; hypoglycaemia in 4.0% Two serious AEs: acute renal failure not attributed to EXE, and pancreatitis
Prospective audit of clinical protocol use of EXE in people with type 2 DM, obesity and progressive weight gain on insulin therapy Nayak 2010 [14]	Outpatient clinic	EXE added to insulin, n=174, n=160 analysed	None	6-12 mo, n=160 completed 6 mo, n=57 completed 12 mo	Before and after start of EXE	No change in HbA1c, SBP fell from 141 ± 19 to 136 ±22 mm Hg at 6 mo	Weight ↓ 10.7± 5.7 kg at 6 mo, and 12.8±7.5 kg at 12 mo	Insulin TDD ↓ from 144±90 to 51±55 U/day at 6 mo, and 55±53 U/day at 12 mo. 25% came off insulin at 3 mo	14 (8%) discontinued EXE because of intolerable gastrointestinal AE, in others AE mainly gastrointestinal. One patient died after 6 mo due to cardiac events
Observational, retrospective Lane 2011 [15]	Chart review, outpatient clinic	LIRA 1.2 or 1.8 mg daily, added to high-dose insulin ± metformin, n=15 2 patients used EXE before the study (was discontinued)	None	12 weeks	Before and after start of LIRA	HbA1c ↓1.4 ± 0.7% (p=0.0001)	Weight ↓ 5.1 ±3.9 kg (p=0.0001), range -12.2 to +0.36 kg.	↓ of insulin TDD by 28% (range -100 to +30 U/day, mean change in insulin TDD -53±35 U/day, p=0.0001)	No severe episodes of hypoglycaemia

Study & author	Data source	Cases	Controls	Study duration	Comparison	Results	Weight	Insulin dose	Adverse events
Nationwide EXE audit Thong 2011 (ABCD) [16]	4857 patients from 126 centres across the United Kingdom	Total n=1921 (n = 1257 insulin at baseline with EXE, and n = 664 insulin started after EXE initiation)	n=2936 not on insulin during EXE	1 year, median follow-up 31 weeks	HbA1c, weight: insulin at baseline with EXE vs not on insulin during EXE, AE and treatment satisfaction: all patients with EXE and insulin vs EXE wo. Insulin	Mean HbA1c ↓ after 6 mo: 0.51 ± 0.06% vs 0.94 ± 0.04%, difference p<0.001 HbA1c ↓ of ≥1%: 34.2% versus 49.0%, p<0.001	Mean weight ↓ 5.8±0.2 kg versus 5.5±0.1 kg, difference ns	Insulin TDD reduced by 42±2 U/day 209 (16.6%) came off insulin, 32.1% off SU, 54.3% off TZD	More insulin-treated patients discontinued EXE (31 vs 14%, p<0.001), had gastrointestinal AE (28 vs 25%, p=0.008), hypoglycaemia (9 vs 6%, p<0.001), and treatment dissatisfaction (21 vs 6%). Treatment dissatisfaction associated with start of insulin during EXE therapy, and with more injections per day
Observational, retrospective Levin 2012 [17]	National US insurance claims database (the Integrated Health Care Information Services Impact database)	At least one prescription claim each for insulin GLA and EXE 3 groups: n=141, EXE followed by GLA (EXE+); n=281, GLA followed by EXE (GLA+); n=31, GLA and EXE initiated together (GLA+EXE)	None	1 year	EXE+ versus GLA+ and GLA+EXE versus GLA+	HbA1c: GLA+EXE: -1.2% EXE+ -0.9% GLA+ -0.4%, all p<0.01 HbA1c ↓ in GLA+EXE and EXE+ sign. higher than in GLA+ HbA1c <7% at 1 year: GLA+ 28.1%, EXE+ 31.2%, GLA+EXE 48.3%, higher in GLA+EXE than GLA+ (p=0.0196)	No data available	No data available	No significant rise in number of hypoglycaemic events No data on AE
Observational, retrospective Levin 2012 [18]	US chart review	n=44: GLA added after EXE (EXE/GL) n=121: EXE added after GLA (GL/EXE)	None	24 mo	EXE/GL vs GL/EXE	HbA1c ↓ pooled -0.7% (p<0.001) 33% achieved HbA1c ≤7.0%.	Weight unchanged in EXE/GL, ↓in GL/EXE (-2.5±6.7 kg, p=0.001)		Hypoglycaemia frequency similar in both treatment groups. No data on adverse events
Observational, retrospective Lind 2012 [19]	Medical records (outpatient clinic)	n=61 analysed Use of insulin (multiple injections 52%, basal only 34%, premixed 12%), combined with metformin (68.9%) or SU (1.6%) 40 patients started on LIRA, 21 on EXE	None	Average follow-up time 7 mo	Before and after start of LIRA or EXE	Mean HbA1c ↓ 1.0% (p<0.001) Treatment satisfaction higher than with previous regimen (DTSQ)	Weight ↓ by a mean of 7.1 kg (p<0.001)	Insulin therapy discontinued in 5 patients, insulin doses on average ↓ by a mean of 38.6 U	4 of 65 discontinued GLP-1 analogue use because of AE (2 nausea, one fatal MI, one acute sepsis affecting the liver) One severe hypoglycaemic event, number of symptomatic hypoglycaemias low and less than with previous regimen (DTSQ)

EXE=exenatide; LIRA=liraglutide; GLA=glargine; SU=sulphonylureas; mo=months; vs=versus; AE=adverse events; wo.=without; ↓=decrease; ↑=increase; TC=total cholesterol; TG=triglycerides; SBP=systolic blood pressure; DTSQ=Diabetes Treatment Satisfaction Questionnaire; TDD=total daily dose; ns=not significant; TZD=thiazolidines; DM=diabetes; MI=myocardial infarction.

and the GI system may assist in achieving more stable control and reduction of body weight. A study by Raman *et al.* analysed the response to a mixed meal after a single dose of exenatide 1.25 or 2.5 µg in combination with insulin or insulin alone in eight subjects with type 1 diabetes.[21] The insulin dose was reduced by 20% in those receiving exenatide. The authors observed reduced postprandial hyperglycaemia (p<0.0001), and a lower delta plasma glucose area under the curve in the early postprandial period (1.25 µg *vs* insulin alone: p<0.008, 2.5 µg: p<0.007). Gastric emptying was delayed but the authors do not mention how much delay they found. There was no difference in glucagon concentration between the groups. Another study reported that liraglutide added to insulin therapy in 14 patients with type 1 diabetes during one week reduced mean fasting and mean weekly glucose concentrations (p<0.01), and reduced glycaemic excursions, while lowering the basal and bolus insulin dose.[22] Prior to starting liraglutide 0.6 mg, glucose control was intensified until stable doses of insulin were reached. The insulin dose was decreased by 25% for basal insulin and 33% for bolus insulin at the onset of liraglutide therapy. Six patients discontinued liraglutide after one week, because they were not able to continue continuous glucose monitoring due to the costs. In eight patients liraglutide was continued for 24 weeks and increased to 1.2 and 1.8 mg daily after one and two weeks respectively. The effects remained, HbA1c decreased from 6.5% to 6.1% (p=0.02), and they also lost body weight (-4.5 ± 1.5 kg, p=0.02). Patients reported a reduction in appetite and food intake following liraglutide. This was not a double-blind, placebo-controlled study. A short-term study (4 weeks) reported that treatment with liraglutide in type 1 diabetic patients reduced the insulin dose with improved or unaltered glycaemic control.[23] Ten C-peptide positive and 10 C-peptide negative patients were treated with liraglutide plus insulin for four weeks, and ten C-peptide negative patients served as a control group and were treated with insulin monotherapy. Insulin dose decreased more in C-peptide positive patients. Total area under the curve of glucagon after a mixed meal test followed by exercise decreased significantly (p=0.002) in liraglutide-treated patients. Once more, adverse events were mainly gastrointestinal. Almost all liraglutide-treated patients lost weight, -2.8±0.3 kg in C-peptide positive and -1.8 ± 0.6 kg in C-peptide negative patients. In one retrospective study, it is foreseen that patients with type 1 diabetes on treatment with either continuous subcutaneous insulin infusion (CSII) or multiple (four or more) injections of insulin per day on continuous glucose monitoring system (CGMS) will be included. These patients were treated with liraglutide in addition to insulin. Data are not yet available (NCT01299012).

SIDE EFFECTS

The most commonly reported adverse events in all studies were nausea, vomiting and diarrhoea, and in most studies these complaints were mainly present during the initial weeks of treatment. In the study by de Vries *et al.*, nausea was the most frequently reported adverse event in the run-in period, but there was also one case of acute pancreatitis, and one subject was diagnosed with papillary thyroid carcinoma.[10] Ryder *et al.* described the main results of the ABCD nationwide exenatide audit in an earlier article.[24] They mentioned four cases of pancreatitis, of which, after scrutiny, one could be related to the use of exenatide, and the other three had alternate causes. Furthermore, 14 cases of acute renal failure were reported, six as a result of nausea, vomiting or diarrhoea resulting in dehydration. Two had an underlying renal impairment or nephropathy, in one there was a probable other cause, and one could not be clarified by the contributor. In four cases there was no reported alternative cause other than the use of exenatide. There were 13 cases of allergy reported, of which five anaphylactic-like reactions. In a review on the safety and efficacy of once-weekly GLP-1 analogues, Madsbad *et al.* found that gastrointestinal side effects seem to be less with the exenatide once weekly formulation than with exenatide bid, and less with liraglutide than with exenatide bid, probably related to peak concentrations of the drug.[25] On the other hand, antibodies seem to be most frequent with exenatide once weekly. In studies in rodents, C-cell hyperplasia was found during administration of liraglutide and exenatide, but in humans there are as yet no data indicating an association between treatment with GLP-1 analogues and C-cell cancer. Also, cases of pancreatitis have been published, but in most cases patients had other factors predisposing to pancreatitis, and the risk of pancreatitis does not seem to be higher in GLP-1 analogue users than in patients with diabetes mellitus who are treated with other drugs.[25]

CONCLUSION

There is limited approval for the combination of use of insulin and GLP-1 analogues. The FDA and EMA approved the addition of exenatide to existing insulin glargine treatment, either alone or in combination with metformin and/or pioglitazone, while also the addition of insulin detemir to existing liraglutide therapy has been approved. However, these combinations are not reimbursed in the Netherlands. Also, the addition of a GLP-1 analogue to existing multiple insulin injection regimens has not yet been approved. There is a limited amount of evidence, but all studies available show a decline in HbA1c and in

body weight, perhaps less in the insulin users than in the non-insulin users, but at the same time a decline in insulin dose, except for the study by Buse *et al*.[7] The ABCD study showed more side effects in the insulin group.[16] Side effects are mainly gastrointestinal, and no new side effects were encountered in the group of patients using a combination of a GLP-1 analogue with insulin, compared with users of GLP-1 analogue monotherapy or a GLP-1 analogue in combination with other oral blood glucose lowering drugs. One has to be aware, however, that the number of patients treated is limited, and study duration was never longer than one year. Pancreatitis occurred in some studies, but remained rare. There was also one patient who was diagnosed with a small thyroid cancer.

Adding GLP-1 analogues to insulin has the benefit of reducing HbA1c as well as weight, while we know that the major problem with uptitrating insulin is weight gain.

Further randomised trials will be needed to confirm what was found in these (mostly observational) studies.

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REVIEW

Biologics for rare inflammatory diseases: TNF blockade in the SAPHO syndrome

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ABSTRACT

Introduction: SAPHO is an invalidating syndrome characterised by Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis. The low prevalence and heterogeneous presentation often leads to a significant diagnostic delay. Here, we provide an up-to-date overview of current insights into the pathogenesis and different treatment options. In addition, we describe the effects of anti-TNF treatment in three refractory cases.

Case reports: Patient A is a 25-year-old female with hidradenitis suppurativa, inflammatory back pain and painful joints. After diagnosis, anti-TNF treatment was started resulting in clinical improvement. Patient B is a 44-year-old woman who presented with acne, palmoplantar pustulosis and anterior chest wall pain. Bone scintigraphy showed increased uptake at the anterior chest wall. Treatment with bisphosphonates resulted in temporary improvement and subsequent treatment with anti-TNF induced long-term clinical improvement. Patient C is a 37-year-old woman with palmoplantar psoriasis, relapsing hidradenitis and inflammatory back pain. MRI revealed osteitis of the pubic bone. Anti-TNF was started for SAPHO syndrome. However, despite a clinical response, our patient discontinued treatment, resulting in rapid deterioration. Anti-TNF treatment was re-introduced followed by clinical improvement.

Conclusion: These case reports illustrate, consistent with the current literature, that TNF blockers can be considered for treatment of refractory SAPHO syndrome.

KEYWORDS

SAPHO, synovitis, acne, pustulosis, hyperostosis, osteitis, hidradenitis suppurativa, anti-TNF.

INTRODUCTION

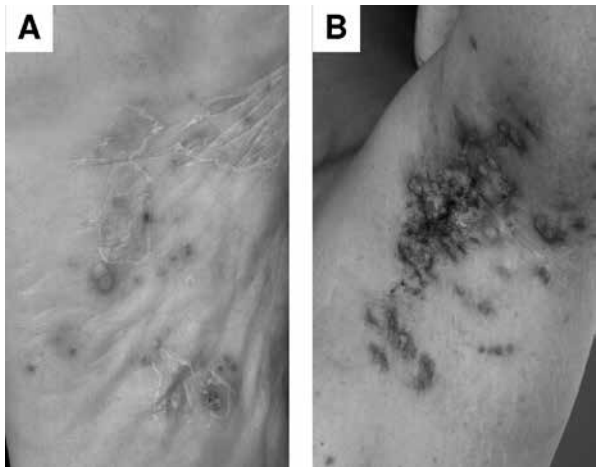
SAPHO syndrome is a relatively unknown disease that was first described in 1987 by A.M. Chamot.[1] The acronym SAPHO stands for: Synovitis, Acne, Pustulosis, Hyperostosis and Osteitis. The diagnosis is often missed or delayed due to the low prevalence and heterogeneous presentation with symptoms of the skin, joints and bones. Recent insights into the pathogenesis of SAPHO and the evidence that TNF blockade can be effective for virtually all manifestations of the disease, allude to the fact that early recognition and treatment of this syndrome will improve the health and quality of life of SAPHO patients. In this report, we describe the cases of three patients with different clinical presentations who were all diagnosed with SAPHO syndrome and successfully treated with TNF blockers.

CASE REPORTS

Case 1

Patient A is a 25-year-old woman who was known with recurrent hidradenitis suppurativa of the armpits and groins for more than ten years. In 2008 pustular skin lesions on the palms of the hands and soles of the feet occurred (*figure 1A*). Simultaneously, she developed arthralgia and inflammatory back pain, accompanied by morning stiffness. The back pain improved with movement. On physical examination we observed extensive scarring in the armpits and groins together with moderately active hidradenitis (*figure 1B*). In addition, she had arthritis of the left sternoclavicular joint. Laboratory tests revealed an elevated erythrocyte sedimentation rate (ESR, 84 mm in the first hour) and normocytic anaemia (haemoglobin 6.9 mmol/l). Genetic testing indicated that the HLA-B27 gene was absent and X-rays of the sacroiliac

Figure 1. *Typical skin lesions in SAPHO syndrome: palmoplantar pustulos footpad (A) and hidradenitis suppurativa in the axilla (B)*

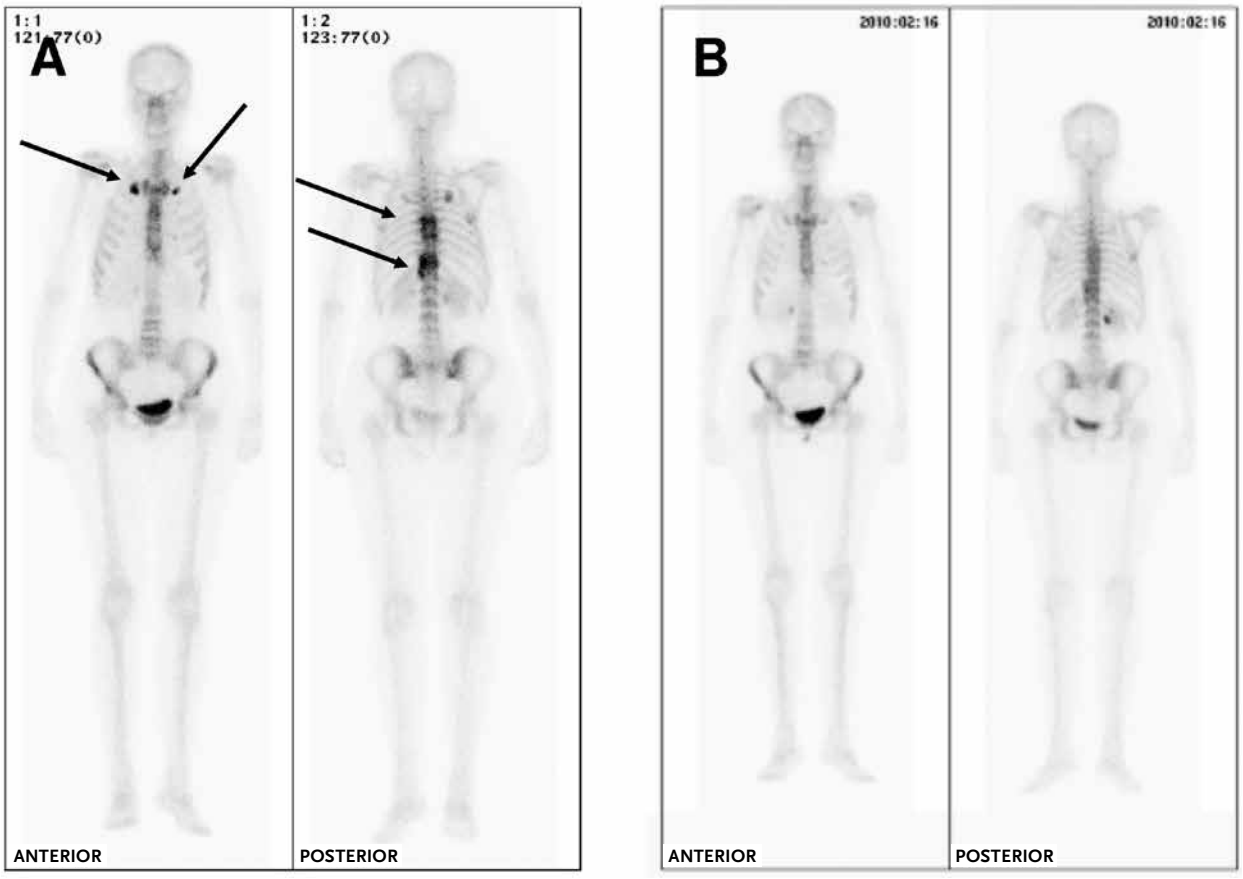


joints showed no sacro-iliitis. Given the combination of synovitis, hidradenitis and pustulosis, SAPHO syndrome was diagnosed. Local treatment of the pustular skin lesions including surgery and antibiotics (azithromycin) did not persistently improve her symptoms. Subsequent systemic treatment with NSAIDs and prednisolone also proved ineffective. Therefore, she started on TNF blockade (infliximab 5 mg/kg every 8 weeks) in September 2009. This resulted in a rapid improvement of both the skin lesions and the arthritis. In six weeks time the ESR decreased to 25 mm in the first hour.

Case 2

Patient B is a 44-year-old woman who presented with pustular skin lesions and thoracic pain in 2004. She also experienced low back pain with morning stiffness lasting approximately one hour. In addition, she was regularly subfebrile, but did not have weight loss or night sweats. On physical examination a swelling of the right sternoclavicular joint was found. We also observed an extensive acneiform rash on her face, hands and feet. After dermatological consultation a skin biopsy was performed and the diagnosis of palmoplantar pustulosis was made. Laboratory tests showed a slightly elevated ESR (32 mm in the first hour). A chest X-ray revealed syndesmophytes of the thoracic spine and scintigraphy demonstrated increased uptake of technetium at the first costochondral

Figure 2. *Scintigraphy before (A) and two years after (B) initiation of treatment with infliximab. The arrows point out the increased uptake (osteitis) of technetium at the first costochondral junction, the sternoclavicular joints and thoracic vertebrae*



junction and the sternoclavicular joints on both sides (*figure 2A*). Besides this, there was enhanced uptake at the site of several thoracic vertebrae. The diagnosis of SAPHO was made and because NSAIDs in combination with topical glucocorticoids were not effective, alendronate was started at a dose of 70 mg once weekly for six months, as this has been described to be effective in some cases.[2,3] After a temporary improvement, the symptoms recurred and the patient was treated with a single-dose regimen of pamidronic acid 90 mg. This resulted in temporary improvement of her bone pain but had no effect on the skin lesions. Therefore, we decided to initiate treatment with TNF blockade (infliximab 5 mg/kg every 8 weeks). A few days after the first infusion the skin lesions disappeared and her back pain improved substantially. Also, her fatigue decreased and the patient was free of almost all her symptoms with this treatment. Interestingly, scintigraphy also showed a decrease in osteitis (*figure 2B*).

Case 3

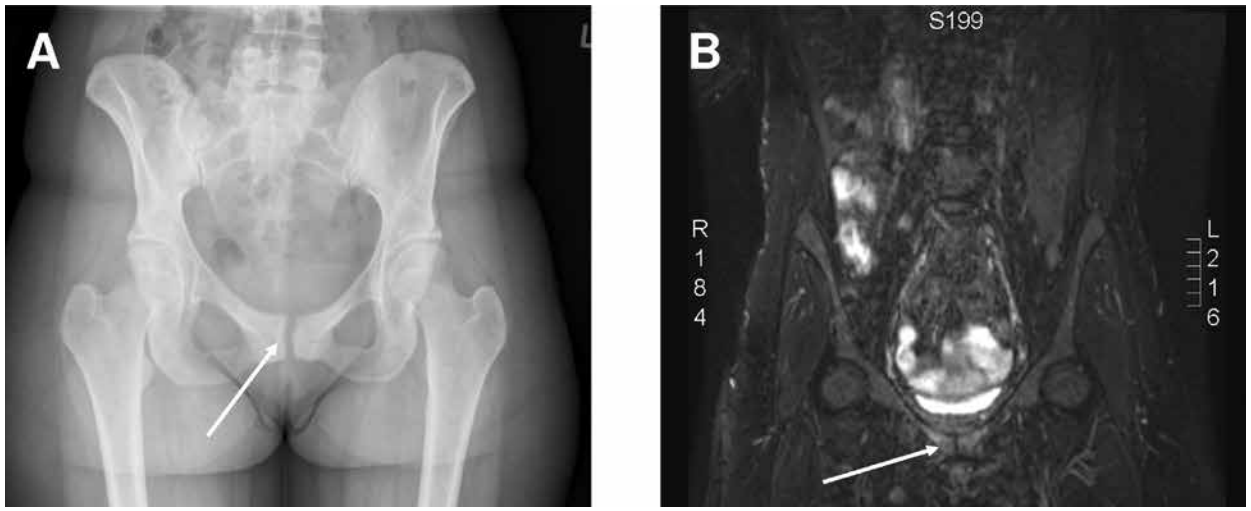
Patient C is a 37-year-old woman who had been diagnosed with palmoplantar psoriasis in 1999. In 2005 she developed hidradenitis suppurativa in the groin and genital region. In 2007 she visited the rheumatology outpatient clinic with inflammatory back pain. Physical examination revealed limited mobility of the lumbar spine (Schober test 10-12.5 cm). However, she did not have active skin lesions at that time. Laboratory tests showed an ESR of 21 mm in the first hour and HLA-B27 was negative. On a conventional X-ray of the pelvis no evidence for a sacro-iliitis was observed, but there was an irregular aspect of the os pubis (*figure 3A*). An MRI scan of the pelvis was compatible with osteitis pubis (*figure 3B*). Subsequently, the diagnosis of SAPHO syndrome was made and after insufficient improvement on NSAIDs she started on TNF blockade (infliximab 5 mg/kg every 8 weeks) in early 2010. Despite a good clinical response the patient did not want to continue treatment. After discontinuation of infliximab, a rapid and strong increase in her back pain and pelvic pain occurred, as well as a significant increase in fatigue. Therefore, anti-TNF treatment was restarted and her complaints decreased again.

BACKGROUND

As illustrated by the three cases, the interval between the symptoms and final diagnosis of SAPHO syndrome is usually very long, sometimes even years. This is mainly due to two factors. Firstly, the disease is rare (data on the exact incidence and prevalence are lacking) and therefore often unknown. Secondly, the clinical presentation is heterogeneous and patients may therefore present to different specialists. As illustrated by case 3, the various manifestations (pustulosis and osteitis) do not necessarily coincide. The variation in clinical presentation is also evident from the different names that were given to the disease spectrum before 1987. The best known names are: pustulotic arthro-osteitis, acne-associated arthropathy, sternocostoclavicular hyperostosis (SCCH) and chronic recurrent multifocal osteomyelitis (CRMO). CRMO is currently recognised as the paediatric manifestation of the disease.

Cohort studies indicate that SAPHO syndrome is more common in women than in men (2:1).[4] Approximately 70% of patients have anterior chest wall pain,[4,5] which is regarded as the most characteristic feature of the disease. Affected patients may present with pain, tenderness, and swelling of the sternum and its articulations. Upon imaging hyperostosis and osteitis are often observed.

Figure 3. *Conventional radiologic (A) and MRI (B) image of osteitis pubis in SAPHO syndrome. The arrows indicate the irregular aspect of the os pubis*



Next to sternoclavicular involvement, the entire axial skeleton can be affected, in particular the sacroiliac region (24-48%), spine (approximately 33%) and the symphysis pubis (7%).[6] Vertebral involvement is particularly characterised by the occurrence of discitis, asymmetric paravertebral calcifications and syndesmophytes. The bone damage is often associated with inflammation of adjacent joints such as the sternocostal and sternoclavicular joints. Peripheral arthritis occurs in 4-36% of patients and is also regarded as a local extension of a primary bone disorder. Often a non-specific sterile inflammation is observed when a bone biopsy is performed.[7]

Skin abnormalities are present in 55-80% of patients. These can occur simultaneously with the joint complaints, prior to the skeletal disorders, or may occur up to several years after the first articular symptoms. In 70% of the cases, the skin lesions occur prior to the development of skeletal abnormalities. Palmoplantar pustulosis is the most observed skin disorder (50-55%) and sometimes occurs in conjunction with psoriasis vulgaris, although psoriasis vulgaris can also occur alone. Approximately 25% of patients have severe acne which can present as acne conglobata or acne fulminans. In addition, other skin disorders such as hidradenitis suppurativa can occur. The association with neutrophilic dermatoses such as pyoderma gangrenosum and Sweet's syndrome is rare. The natural course of SAPHO syndrome is characterised by variable disease activity with exacerbations and remissions. Sometimes it leads to a serious, debilitating condition with persistent pain. Only a minority of patients have a self-limiting course of the disease.[7]

DIAGNOSIS

SAPHO syndrome is primarily a clinical diagnosis based on the occurrence of a combination of typical skin disorders with bone pain and/or synovitis, often at the level of thoracic spine and pelvis (*table 1*). There is a limited role for laboratory testing: in about half of the cases the ESR and CRP values are elevated.[5] In contrast, imaging is extremely useful in the investigation of bone pain. Although conventional radiographs may show signs of osteosclerosis, erosions and hyperostosis, computed tomography (CT) is much more sensitive to detect these abnormalities. Scintigraphy can also be useful in establishing the diagnosis. In literature, a sensitivity of 93% is reported.[6] In active disease the typical 'bull's head sign' can be observed: increased technetium 99m uptake at the area of the manubrium sterni and the sternoclavicular joints resembles a bull's head. Magnetic resonance imaging (MRI) may, in addition to signs of osteitis, also provide evidence for enthesitis.

Table 1. *Criteria for SAPHO syndrome*

1. Osteoarticular manifestations in combination with palmoplantar pustulosis and/or severe acne
2. Hyperostosis with or without skin manifestations
3. Chronic recurrent multifocal osteomyelitis of the axial and peripheral skeleton with or without skin manifestations
4. Exclusion criteria:
a. Infectious osteomyelitis or septic arthritis
b. Infectious palmoplantar pustulosis
c. Palmoplantar keratoderma blennorhagica

Differential diagnosis with related disorders is often difficult as SAPHO shows a broad overlap with related conditions. The skin manifestations of SAPHO often resemble palmoplantar pustolosis, psoriasis, or hidradenitis suppurativa. In that case the actual diagnosis is based on the simultaneous presence of bone or joint symptoms. From an articular perspective, SAPHO syndrome is clinically related to spondyloarthritis based on a) an association with psoriasis and inflammatory bowel disease, b) the occurrence of osteitis of the sternum, spine, and pelvis, and c) asymmetric peripheral arthritis.[8] However, dactylitis, arthritis of the proximal interphalangeal joints and uveitis do not belong to the inflammatory features found in SAPHO syndrome. Also, HLA-B27 positivity does not occur more frequently in patients with SAPHO syndrome than in the general population. Finally, SAPHO syndrome sometimes shows similarities with Behcet's disease, but uveitis, ulcers, and thromboembolic events usually do not occur (reviewed in Magrey and Khan[7]).

PATHOPHYSIOLOGY

The underlying aetiological and pathophysiological mechanisms of SAPHO syndrome are not yet elucidated. SAPHO syndrome is considered to be a polygenic autoinflammatory disorder in which an abnormal, strong reaction of the innate immune system to pathogens gives rise to chronic sterile inflammation. In this respect SAPHO syndrome also shows similarities with spondyloarthritis, Behcet's disease and hidradenitis suppurativa.

A genetic contribution to the development and course of the disease is supported by the observation of familial clustering.[9-11] The genes that appear to play a role in SAPHO syndrome are located on chromosome 18 (cmo locus): LPIN2 and NOD2. LPIN2 encodes lipin 2 which may be involved in modulating apoptosis of polymorphonuclear cells.[12] Mutations in the NOD2 gene are also associated with inflammatory bowel disease and may lead to an abnormal immune response to bacterial

peptidoglycans via activation of the pro-inflammatory transcription factor nuclear factor-κB (NF-κB).[13,14] In SAPHO syndrome it is hypothesised that an occult disseminated infection or an abnormal systemic immune response to low virulence bacteria such as *Proprionibacterium acnes* is a trigger for a chronic inflammatory response with mainly production of IL-8, IL-18 and TNF.[7] This is substantiated by the presence of skin lesions in SAPHO syndrome and also by the fact that this commensal skin bacterium has been demonstrated in cultures of the affected bone lesions.[15] The hypothesis is further supported by the fact that some patients improve under chronic antibiotic therapy.[16] In agreement with the concept that SAPHO is an autoinflammatory rather than autoimmune condition, autoantibodies do not appear to play a role in the pathogenesis of the disease.[17]

TREATMENT

The natural history of SAPHO syndrome is not well defined. Although a minority of patients have a self-limited course, the majority have either a relapsing-remitting pattern or chronic indolent pattern. A number of therapies have been reported to be useful in patients with SAPHO syndrome.[18] Several case reports and descriptions of small case series indicate that NSAIDs improve osteoarticular pain. There are also reported beneficial effects of colchicine, glucocorticoids and disease modifying anti-rheumatic drugs (DMARDs) such as methotrexate and sulphasalazine. However, there are no double-blind, randomised controlled trials to substantiate the effectiveness of these drugs. Interestingly, in 2009 an intervention study demonstrated that patients with positive cultures for *Proprionibacterium acnes* can improve using azithromycin or clarithromycin. After discontinuation of the antibiotics this effect is nullified.[16]

In recent years, many case reports have appeared on the use of bisphosphonates in the treatment of SAPHO syndrome, in which both partial and complete remission have been described.[2,3] The beneficial effect of bisphosphonates may result from possible anti-inflammatory activity and inhibition of bone turn-over.[19] However, this treatment has little or no effect on the skin lesions.[3]

The clinical and pathophysiological relationship of SAPHO syndrome with spondyloarthritis, psoriasis and Behcet's disease has led to the use of TNF blockade in this syndrome. In line with our descriptions, case reports and case series often demonstrate a marked improvement in the clinical picture and the inflammatory response.[20] However, also in TNF blockade no double-blind randomised placebo-controlled trials have been performed to confirm these observations. The largest case series of 45 SAPHO syndrome patients treated with TNF inhibitors[21] indicates that skin, joint and bone symptoms respond to TNF inhibition, although it is not clear whether this treatment is permanently effective. Another problem is the reimbursement of this treatment, as SAPHO syndrome is not a registered indication for TNF blockers. In the current financial regulations of the Dutch healthcare system, the reimbursement of TNF blockade for unregistered indications is difficult, if not impossible. Nevertheless, given the impossibility to carry out randomised clinical trials in this rare and heterogeneous disease, and the reported clinical improvement after treatment with TNF antagonists, the use of TNF blockade should be considered in severe and treatment-resistant patients.[22]

Recently, an autoinflammatory disease based on deficiency of the interleukin-1-receptor antagonist was described under the name DIRA.[23] This disease is associated with sterile multifocal osteomyelitis, periostitis and pustulosis, which looks similar to SAPHO. Interestingly, DIRA patients exhibit a good response to anakinra, an interleukin 1 (IL-1) receptor antagonist. The positive effects of this drug in a disease with overlapping clinical features prompted investigators to evaluate the effects of anakinra in SAPHO syndrome. Anakinra proved to be beneficial in five out of six SAPHO patients, two of which previously failed to respond to TNF blockers.[24]

CONCLUDING REMARKS

SAPHO syndrome is a rare disease which should be considered in patients presenting with acne or pustular skin disease in combination with chest and/or bone pain. The diagnosis relies on the clinical picture in combination with imaging (bone scintigraphy, CT or MRI) to detect osteitis. Treatment consists of NSAIDs and sometimes bisphosphonates, although the latter have no effect on skin disease. In refractory cases TNF blockade or IL-1 receptor antagonist treatment may be considered.

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ORIGINAL ARTICLE

Identification of modifiable risk factors for acute kidney injury after cardiac surgery

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ABSTRACT

Objectives: Acute kidney injury (AKI) is a common problem after cardiac surgery and is associated with an increase in morbidity, mortality and duration of hospital stay. With this study we aimed to identify potential risk factors for cardiac surgery associated AKI (CS-AKI) in a single-centre population with a special focus on modifiable risk factors.

Methods: Retrospective single-centre cohort study of 565 consecutive patients who underwent isolated coronary artery bypass grafting (CABG) with the use of cardiopulmonary bypass. AKI was defined by the AKIN classification. Known risk scores were applied when possible.

Results: Of the population, 14.7% were diagnosed with AKI. When considering baseline characteristics we found a significant difference in age, preoperative estimated glomerular filtration rate (eGFR) and chronic kidney disease (CKD) stage and urgency of surgery between the CS-AKI group and the control population. Regarding the intraoperative characteristics, patients with CS-AKI had a significantly lower haematocrit and were more likely to receive a transfusion of packed cells. Postoperative administration of furosemide and packed cell transfusions were also associated with AKI. We found no differences in other characteristics (history of diabetes mellitus, history of congestive heart failure, sex, body mass index (BMI), history of cardiac surgery, low cardiac output and need for intra-aortic balloon pump (IABP), duration of cardiopulmonary bypass (CPB) and cross clamping).

Conclusion: In our series we could identify intraoperative administration of packed cells and postoperative administration of furosemide or packed cells as potentially modifiable risk factors in the development of AKI.

KEYWORDS

Acute renal injury (AKI), cardiac surgery, haematocrit, modifiable risk factors, transfusion

INTRODUCTION

Acute kidney injury (AKI) is common in hospitalised patients and is associated with an increase in morbidity and mortality as well as an increase in the duration of the hospitalisation.[1] Moreover, AKI is associated with a higher risk for advanced chronic kidney disease (CKD) and end-stage renal disease in the long term.[2] Cardiac surgery associated AKI (CS-AKI) is a well-described problem and recent studies report an incidence of 2-30% depending on the definition.[3] CS-AKI is the result of a complex of different pathophysiological mechanisms leading to a global decrease in renal function causing a rise in serum creatinine (sCr). Many independent risk factors for CS-AKI were defined but in general the cause of AKI is multifactorial as these risk factors reduce functional renal reserve. As such, AKI, and especially worse cases, seldom come alone and are generally part of multiple organ dysfunction syndrome or even multiple organ failure. CS-AKI is seen in patients undergoing different operations varying from isolated revascularisation or valve replacement to extensive, combined procedures, cardiac transplantation and the use of assist devices.

After sepsis, cardiac surgery is the second most important cause of AKI in intensive care patients[4] and AKI is an independent risk factor for mortality.[3,5] When renal replacement therapy (RRT) is needed in this group mortality exceeds 50%.[5] Several algorithms were suggested to predict the risk of CS-AKI, but definitions of AKI as

well as the included risk factors are diverse and difficult to reproduce. Since the introduction of the RIFLE classification by the Acute Dialysis Quality Initiative (ADQI) in 2004,[6] a more uniform definition of AKI gives the opportunity to compare different studies. A modification by the Acute Kidney Injury Network (AKIN) in 2007[7] made the classification more sensitive and included the additional criterion of time (AKI developing within 48 hours). Both classification systems have been validated in different populations of cardiac surgery patients and have shown to correlate with short-term outcome.[8]

With this study we aimed to identify possible risk factors for CS-AKI in a single-centre population of 565 patients who underwent isolated CABG with a special focus on modifiable risk factors. Furthermore, we evaluated the performance of several known risk scores.

MATERIALS AND METHODS

We conducted a retrospective, observational, single-centre cohort study and reviewed the cases of 578 consecutive patients who underwent isolated CABG with the use of cardiopulmonary bypass during an 18-month period between June 2009 and November 2010. All patients were adults. Patients on chronic dialysis (n=2), with a history of renal transplantation (n=2) or with survival <24 hours after surgery (n=6) were excluded. One patient underwent concurrent aortic valve surgery, for one patient insufficient data were available and one patient needed a cardiac assist device and these patients were also excluded. Data were extracted from the cardiac surgery electronic database and the electronic data management system used in the intensive care unit. After exclusion 565 patients were withheld for further analysis. In the perioperative period, the following parameters were examined: demographic characteristics, diabetes mellitus, CKD stage, history of cardiac surgery, history of congestive heart failure, history of low cardiac output, urgency of surgery, intraoperative lowest haematocrit, intraoperative and postoperative packed cell transfusion, sCr (at admission, and every 24 hours for a minimum of 48 hours and a maximum of seven days and after eight weeks), estimated glomerular filtration rate (eGFR), postoperative administration of furosemide, duration of cardiopulmonary bypass (CPB) and cross-clamping, need for intra-aortic balloon placement (IABP), need for RRT, duration of AKI and global physical functioning eight weeks after surgery. During the aforementioned period there were no changes in anaesthesia, CBP technique or fluid protocol.

AKI was defined by the AKIN criteria (*table 1*)[7] and eGFR was estimated with the Cockcroft-Gault formula and the Modification of Diet in Renal Disease (MDRD) formula.

Table 1. *AKIN criteria*[7]

	Serum creatinine criteria	Urine output (UO) criteria
Stage 1	Increased sCr x 1.5 or ≥0.3 mg/dl	UO <0.5 ml/kg/h x 6 hours
Stage 2	Increased sCr x 2	UO <0.5 ml/kg/h x 12 hours
Stage 3	Increased sCr x 3 or sCr ≥4 mg/dl (with acute rise ≥0.5 mg/d)	UO <0.3 ml/kg/h x 24 hours or anuria x 12 hours

Patients who receive renal replacement therapy (RRT) are considered to have met the criteria for stage 3 irrespective of the stage they are in at commencement of RRT.

Classification of AKI was based on changes in sCr alone and assessed by two different persons. Discrepancies were solved by consensus. Baseline kidney function as described by CKD stage was classified according to the criteria of the Kidney Disease Outcomes Quality Initiative (K/DOQI, *table 2*)[9] with an exception for CKD stage I, which could not be determined because of lacking data concerning proteinuria or history of kidney injury. History of diabetes mellitus was defined as the need for medication to lower the glycaemia. Congestive heart failure was defined by clinical signs of decompensation or signs of congestion with cardiac ultrasound (decreased variation of vena cava inferior with respiration and/or a dilated vena cava inferior). Low cardiac output was defined as a left ventricle ejection fraction below 40%. Urgency of surgery was classified as urgent (within 24 hours after initial diagnosis) or non-urgent. The EuroSCORE is the preoperative risk stratification model with the highest discriminatory power for both 30-day and one-year mortality after open heart surgery. This model is based on 17 predictors of mortality and uses information regarding the patient, cardiac status and type of surgery.[10] Usefulness of several other risk scores specific for the prediction of the need for RRT or other forms of AKI in our population was also evaluated (Cleveland score,[11] Mehta score[12] and AKICS/ Simplified Renal Index (SRI) score).[13]

Table 2. *Chronic kidney disease stages*[1]

Stage	Criteria
1	GFR >90 ml/min/1.73 m² with persistent albuminuria >30 mg/24 h
2	GFR 60-89 ml/min/1.73 m²
3	GFR 30-59 ml/min/1.73 m²
4	GFR 15-29 ml/min/1.73 m²
5	GFR <15 ml/min/1.73 m² or end-stage renal disease

[1]**Applicable when present for three or more months, irrespective of cause; GFR = glomerular filtration rate.**

STATISTICS

Data were analysed using SPSS 20. Continuous variables are listed as mean ± standard deviation and were analysed by an unpaired T-test. Categorical variables are listed as frequencies and were analysed by χ^2 test. Univariate and multivariate logistic regression was applied to evaluate potential modifiable risk factors associated with AKI. In a first approach all variables that were significantly different between the group with AKI and the group without AKI were included as covariates in a univariate analysis. Age, eGFR, and haematocrit were transformed into binary variables. For this purpose, a cut-off point was determined using ROC analysis. Next, a multivariate model was constructed with significant covariates. A p-value ≤0.05 was considered statistically significant.

RESULTS

Comparison of patient characteristics

Patient characteristics are reported in *table 3*. Our database covers >97% of information except for information considering duration of CPB and cross-clamping, which is only known for 46% of the patients. We performed no correction for missing data but there was no difference in the occurrence of AKI between the two groups when we compared the group with known CPB duration with the group without. The majority of the patients were male with a mean age of 67 ± 9.6 years, and 83 patients (14.7%) were diagnosed with AKI. RRT was necessary in two of them (0.4%) and both patients died during the initial admission. Subgroups of different stages of AKI were too small for further statistical analysis (AKIN stage 2: 4 patients; AKIN stage 3: 3 patients). First an univariate analysis including associated factors was assessed (*table 4*) followed by a multivariate model including potentially modifiable risk factors (*table 5*). Transfusion both intraoperatively and postoperatively and the administration of furosemide remained significant.

Evaluation of different scoring systems

In our population only the SRI score[13] was applicable for specific renal risk scores and was determined for 551 patients (98%). The Mehta score and Cleveland score were not applicable, mainly because of lack of data and differences in the definitions used. For mortality risk scores, the EuroSCORE was determined for all patients but three and was significantly higher in patients suffering from AKI.

Table 3. *Patient characteristics (univariate analysis)*

Characteristics	No AKI (n=482) 85.3%	AKI (n=83) 14.7%	p
Baseline			
• Age (years) (n=565)	66.5 ± 9.4	69.9 ± 10.2	0.05
• Female sex (n=565)	89 (18.5%)	16 (19.3%)	0.86
• BMI (kg/m²) (n=565)	27.3 ± 4.2	28.6 ± 4.7	0.06
• eGFR (ml/min/1.73m²) (n=565)	87.9 ± 30.9	74.8 ± 34.0	< 0.01
• CKD stage (n=565)	1.3 ± 1.2	1.9 ± 1.2	< 0.01
• Diabetes mellitus (n=565)	88 (18.3%)	16 (19.3%)	0.70
• History of cardiac surgery (n=565)	6 (1.2%)	3 (3.6%)	0.11
• Congestive heart failure (n=550)	23 (4.9%)	6 (7.4%)	0.35
• Ejection fraction < 40% (n=553)	16 (3.4%)	6 (7.4%)	0.26
• IABP (n=565)	8 (1.7%)	1 (1.2%)	1
• Urgent surgery (n=563)	24 (5.3%)	11 (13.4%)	0.03
• EuroSCORE (n=562)	3.6 ± 2.6	5.2 ± 3.5	< 0.01
• SRI score (n=551)	0.5 ± 0.7	0.8 ± 1	< 0.01
Perioperative			
• Transfusion of packed cells (n=565)	56 (11.6%)	21 (25.3%)	<0.01
• Lowest haematocrit (%) (n=565)	24.8 ± 2.1	24.1 ± 3.1	<0.01
• Duration of cardiopulmonary bypass (min) (n=266)	90.2 ± 26.9	85.8 ± 26.7	0.56
• Duration of cross clamping (min) (n=266)	35.3 ± 13.5	34.1 ± 14.1	0.56
Postoperative			
• Administration of furosemide (n=563)	289 (60%)	70 (84.3%)	<0.01
• Transfusion of packed cells (n=563)	78 (16.3%)	35 (42.2%)	<0.01

AKI = acute kidney injury; BMI = body mass index; CKD = chronic kidney disease; eGFR = estimated glomerular filtration rate; IABP = intra-aortic balloon pump; SRI = Simplified Renal Index.

DISCUSSION

In our population we found a relatively low incidence of AKI in comparison with other studies. Possible factors are a short duration of cardiopulmonary bypass and low mean EuroSCORE. We found a significant association between the development of CS-AKI with several previously described risk factors such as preoperative eGFR and CKD stage, but not for diabetes mellitus, need for IABP, or duration of CPB and cross-clamping. Possible explanations are the low incidence of the need for IABP and the relatively short CPB and cross-clamping time in both groups. We were only able to test one renal risk score in our population (SRI score) and we only found a difference in univariate analysis. Transfusion both intraoperatively and postoperatively and the administration of furosemide appear to play a significant role in the development of CS-AKI. As preoperative haematocrit is associated with the lowest intraoperative haematocrit,[14] we suggest that this could be a potentially controllable risk factor for AKI

Table 4. *Factors associated with acute kidney injury, univariate analysis*

	Units of increase	Regression coefficient (β_1)	OR (95% confidence interval)	p
eGFR <60 ml/ min/1.73 m²	0 (≥60) 1 (<60)	2.53	1.53-2.16	< 0.01
Age >70 (per year)	0 (≤70) 1 (>70)	2.00	1.25-3.21	< 0.01
Urgent surgery	0 (not urgent) 1 (urgent)	2.95	1.39-6.28	<0.01
Haematocrit <20% during CPB	0 (haemato-crit ≥20%) 1 (haemato-crit <20%)	2.75	1.15-6.55	=0.02
Transfusion of packed cells during surgery	0 (no transfusion) 1 transfusion	2.58	1.46-4.55	<0.01
Diuretics after surgery	0 (no diuretic) 1 diuretic	3.56	1.92-6.61	<0.01
Transfusion of packed cells after surgery	0 (no transfusion) 1 (transfusion)	3.76	2.28-6.19	<0.01
Creatinine > 1 mg/dl	0 (≤1 mg/dl) 1 (>1 mg/dl)	2.94	1.82-4.77	<0.01

CPB = cardiopulmonary bypass; eGFR = estimated glomerular filtration rate; OR = odds ratio.

Table 5. *Potentially modifiable risk factors: multivariate analysis*

	Units of increase	Regression coefficient (β_1)	OR (95% CI)	p
Diuretics after surgery	0 (diuretic) 1 (diuretic)	3.44	1.82-6.51	<0.01
Transfusion of packed cells during surgery	0 (no transfusion) 1 (transfusion)	2.20	1.19-4.07	=0.01
Transfusion of packed cells after surgery	0 (no transfusion) 1 (transfusion)	2.98	1.77-5.01	<0.01
Haematocrit	0 (haematocrit ≥ 20%) 1 (haematocrit <20%)			=0.43
Intercept (β_0)	-0.01			

as well. Possible mechanisms are that transfused red blood cells (RBCs), being deficient in 2,3-diphosphoglycerate, have an inability to properly load and unload oxygen. Additionally, stored RBCs are less supple and deformable and may physically obstruct the smaller capillaries, leading to further organ ischaemia. Furthermore, transfused RBCs have an artificially shortened lifespan, and their haemolysis leads to an increase in circulating free iron.[15] One should be careful in transfusing these patients with a possible role for optimising the haematocrit preceding surgery or predonation of packed cells as recently suggested by Karkouti *et al.*[16] A confounding factor, however, is the amount of blood loss during surgery which is not known for our population. Although postoperative transfusion of packed cells is a significant risk factor for CS-AKI this can also be a mere surrogate marker for sicker or older patients with a higher bleeding risk. Use of diuretics in an attempt to prevent CS-AKI has not shown any benefits and Lassnigg *et al.* also report detrimental effects with an increase in the incidence of AKI.[17] Another report stated that the use of diuretics in an attempt to restore urine output can only indicate the severity of AKI and does not improve functional outcome.[18] Our study has several shortcomings, one of them being the lack of power, partly secondary to the large number of confounding factors in CS-AKI. Another important issue is the use of surrogate markers, for example for kidney function. Serum creatinine comes into play as a marker for decreasing kidney function when already more than 50% of kidney function has been lost and is only useful after a steady state is reached. Creatinine clearance is a better marker although again with considerable delay.[19] Repeated four-hour creatinine clearance measurements in critically ill patients allow earlier detection of AKI, as well as progression and recovery compared with plasma creatinine[20] but this information was not available for our population. Although eGFR was estimated both by the Cockroft-Gault and MDRD formulas only the values derived from the first formula were reported as in the majority of earlier studies. Considering earlier recognition of AKI using biomarkers several potentially useful markers are under investigation. An ideal biomarker is specific for AKI, has a high sensitivity in the early stages of disease, correlates with disease severity and has prognostic value.[21] In the field of cardiac surgery, kidney injury molecule-1 (KIM-1) and neutrophil gelatinase associated lipocalin (NGAL) are getting much attention. KIM-1 is a transmembranous protein expressed in dedifferentiated proximal tubule cells after ischaemia or toxicity but not in normal tissue. This makes urinary KIM-1 a possible diagnostic marker differentiating between renal AKI on the one side and prerenal AKI or CKD on the other. In a population of 103 cardiac surgery patients KIM-1 turned out to be superior when compared with other urinary biomarkers (Cystatin C, interleukin 18 and urinary NGAL) in the early detection of AKI.[22] NGAL is a transport molecule expressed in neutrophils and epithelial cells. In AKI transcription of NGAL in the kidney increases and both urinary and serum NGAL are early markers of AKI with a slight superiority for urinary NGAL. Increase in NGAL correlates with the risk of the need for RRT. Since individual sensitivity and specificity of biomarkers is low, a combination of both

markers could be useful as a predictor of AKI.[19,21] A recent meta-analysis concerning prevention of CS-AKI showed that none of the studied pharmacological interventions (dopamine, fenoldopam, calcium channel blockers, natriuretic peptides, diuretics and N-acetylcysteine) can significantly reduce mortality. Only fenoldopam and natriuretic peptides can possibly influence occurrence of AKI and the need for RRT positively. Overall the quality of the included studies was poor with a total of 4605 patients for 49 studies with a wide variation of definitions used.[23] In conclusion, although several patient characteristics and intraoperative measures cannot be influenced, there is a role for modifying risk factors such as preoperative haematocrit, intraoperative transfusion of packed cells and postoperative administration of packed cells and diuretics. Future research is warranted to standardise AKI criteria and further development of risk assessment algorithms could improve outcome prediction for this important clinical problem after major cardiac surgery.

EARLIER PRESENTED DATA (ABSTRACTS)

Annual Congress of the European Society of Intensive Care Medicine (ESICM) October. 2011 Berlin: Short-term morbidity of coronary artery bypass grafting due to acute kidney injury. Intensive Care Medicine 2011; Suppl 1: S60. Annual Congress of the American Society of Nephrology (ASN) November 2011, Philadelphia: Identification of potentially controllable risk factors for acute kidney injury after cardiac surgery. J Am Soc Nephrol 2011; 22: 130A.

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ORIGINAL ARTICLE

Causes of death in intensive care patients with a low APACHE II score

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ABSTRACT

Background: Little is known about the actual causes of death of patients with a low APACHE II score, but iatrogenic reasons may play a role. The aim of this study was to evaluate the demographics, course of disease, and causes of death in this specific group of ICU patients.

Methods: For this retrospective observational study, adult patients (>18 years) admitted to the ICU were included.

Results: During the 47-month study period, 9279 patients were admitted to our ICU, of which 3753 patients had an APACHE II score ≤15. Of the latter group of patients, 131 (3.5%) died during their hospital stay. Their median (IQR) APACHE II was 12 (11-14) and their main reason for ICU admission was respiratory insufficiency (47%). Both in patients with and without limited therapy, haemodynamic insufficiency was the main cause of death (50 and 69%, respectively). Three patients died directly related to medical interventions.

Conclusion: Most patients with an APACHE II score lower than 15 who died were admitted to the ICU because of respiratory insufficiency. The main cause of death was haemodynamic insufficiency following limited therapy because of an unfavourable prognosis. In less than one out of 1000 cases of this low-risk group of patients death was related to iatrogenic injury.

KEYWORDS

APACHE, causes of death, iatrogenic disease, intensive care, mortality

INTRODUCTION

The Acute Physiology and Chronic Health Evaluation II (APACHE II) system is a severity of disease classification system for adult patients admitted to the intensive care unit (ICU). The APACHE score, based on several patient characteristics (including age and comorbid conditions) and 12 physiological parameters obtained during the first 24 hours following ICU admission, represents the severity of illness and is closely correlated with hospital mortality.[1] However, the APACHE II score should not be used for individual treatment decisions.[2] There is a good correlation between the APACHE II score and risk of death in large groups of patients, but the individual mortality risk predicted by the score varies considerably with the underlying diagnosis.[3] Although the APACHE II score has a moderate predictive accuracy,[1,4,5] it appears superior compared with other scoring systems.[6-9] The APACHE II score has proven its value for monitoring quality of care and for conducting clinical studies as it enables comparison of outcomes among groups of critically ill patients.[1,10]

According to the original database, hospital mortality of patients with an APACHE II score of 15 is up to 21%.[1] Other factors, not included in the APACHE II scoring system, seem to play a role in the mortality outcome for this low-risk group of patients. Although the role of the APACHE II score in prediction of death has been studied widely, we are not aware of any studies that examined the causes of death in patients with a low APACHE II score. Our hypothesis is that iatrogenic causes could be a potentially relevant factor and that a more detailed analysis of this group of patients may function as a valuable quality control measure. The aim of the present study is to describe the demographic characteristics, courses of their disease, and cause of death in this specific group of patients with a predicted low mortality rate.

MATERIALS AND METHODS

Patient population

We retrospectively evaluated the medical records of all patients admitted to the adult ICU of Radboud University Nijmegen Medical Centre between January 2004 and December 2008 with an APACHE II score ≤15 who died during their hospitalisation up to 30 days after being discharged from the ICU. For all patients, the APACHE II score was manually recalculated from the worst physiological and laboratory parameters in the first 24 hours after ICU admission. Patients who were admitted to the ICU more than once within 30 days were evaluated based upon their APACHE II score during their first ICU stay.

Data collection

Medical records were examined by one of three investigators for each patient. Pre-admission data were documented in a case record form to minimise inter-observer variability. Collected data included patient demographics such as age, sex, height and weight. The recalculated APACHE II score was documented, along with the date of admission, diagnosis at admission, reason for ICU admission, type of admission (elective versus emergency) and comorbidities.

Comorbidities were defined in relation to a specific index condition according to the seminal definition of Feinstein.[11] The question which condition should be designated as the index and which as the comorbid condition is not always self-evident and was therefore defined as the disease that prompted the need for critical care. Indexes were classified according to organ system as were any distinct additional entities. Once included in the study, the remainder of the case record form was designed to register a patient's course of disease (improving, stable or worsening), including possible risk factors related to death and complications.

Patients admitted to the ICU may be subject to many complications related to advanced monitoring and therapy. All relevant complications were assessed including possible medical omissions during a patient's ICU admission. Medical omissions were defined as the failure to do something required by the patient's condition in the acute situation, which may have contributed to the patient's death. Iatrogenic complications were defined as adverse effects that were not associated with the index condition or any of the patient's recorded comorbid conditions. These were likely related to medical treatment and resulted in either significant morbidity or mortality. Significant morbidity was defined as the need for reoperation, transfusion, systemic inflammatory response syndrome (SIRS), sepsis, acute respiratory distress syndrome, respiratory or haemodynamic insufficiency, continuous veno-venous haemofiltration or extra corporeal membrane oxygenation.

Data documentation was completed with registration of the number of admissions to the ICU, duration of the ICU stay in days, hospital mortality and cause of mortality. If available, the autopsy report was examined to obtain a better insight into the course of disease and cause of death. If clinical data were incomplete, the patient was excluded from the study. To ensure a uniform assessment of the gathered data, patient data and conclusions were reviewed by all three primary investigators. A database containing the data of all patients was used for further calculations.

Statistics

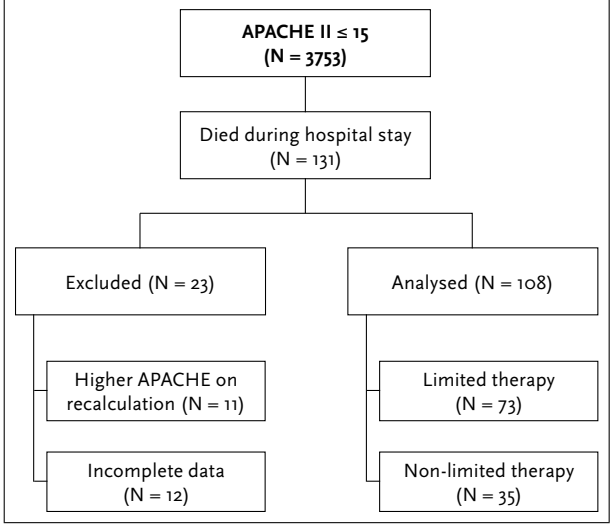
Calculations were computed using commercially available software (Excel, release 11.5.5, Microsoft Corporation). Data are expressed as number of patients (%), or median and interquartile range (IQR) or mean ± SD, depending on its distribution.

RESULTS

Demographic data

During the 47-month study period, 9279 patients were admitted to the ICU of the Radboud University Nijmegen Medical Centre, of which 3753 patients had an APACHE II score ≤15. Of 3753 patients, 131 (3.5%) died during their hospital stay. From this group of patients, 23 were excluded from further analysis, 11 because of an APACHE II score ≥20 after recalculation and 12 patients because of incomplete data. The remaining 108 patients who died were included in the study (*figure 1*). The median (IQR) APACHE II score of this group of patients was 12 (11-14). The demographic characteristics of the patients are illustrated in *table 1*.

Figure 1. *Flowchart of study population*



Reasons for ICU admission and length of stay

Indications for ICU admittance are depicted in *figure 2*. The most frequent indications for ICU admittance were respiratory insufficiency (47%), postoperative monitoring (27%) and haemodynamic instability (20%). The median (IQR) hospital length of stay was 13 (4-31) days, including 9 (3-7) days on the ICU.

Comorbidity and risk factors for complications or death

The three most frequently occurring comorbidities were circulatory (hypertension, ischaemic heart disease, atherosclerosis), respiratory (chronic obstructive pulmonary disease, pneumonia), and cancer, 68%, 22% and 22%, respectively (*table 2*). Besides these pre-ICU-admission risk factors, several risk factors occurred during the ICU stay. The most frequent risk factor was the use of vasoactive medication (74%). The other monitored risk factors during the ICU stay are listed in *table 2*.

Table 2. *Comorbidity and risk factors for complications or death*

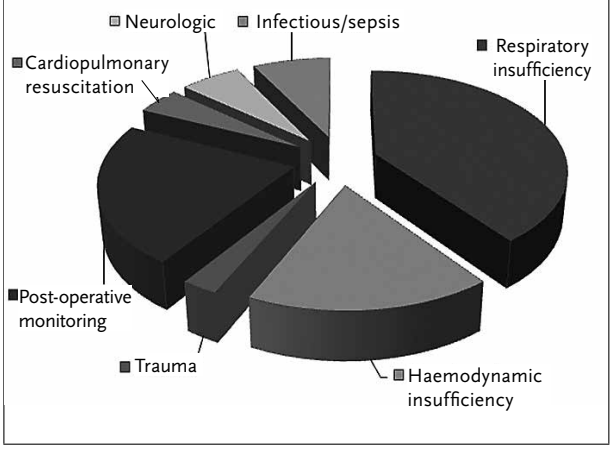
Variable	N (% of cases)
Chronic comorbidity	
Haemodynamic problems	73 (68%)
Cancer	24 (22%)
Respiratory problems	24 (22%)
Neurological status	21 (19%)
Infection	13 (12%)
Renal disease	12 (11%)
Immunosuppressive medication	7 (6.5%)
Diabetes mellitus	7 (6.5%)
Obesity	6 (5.5%)
Risk factors for complications	
Vasoactive medication	80 (74%)
Trauma	32 (30%)
Sepsis	16 (15%)
Cardiopulmonary resuscitation	10 (9%)
Mechanical ventilation	6 (5.5%)

Table 1. *Demographics characteristics of patients*

Variable	Value
Total number of patients	9279
Patient with APACHE ≤15	3753 (40.4%)
Number of patients who died	131 (1.4%)
Patients included	108
Sex	
Male	67 (62%)
Female	41 (38%)
Age (years)	61.6 ± 15.0
Height (cm)	171 ± 0.7
Weight (kg)	74.6 ± 1.9
BMI (kg/m²)	25.4 ± 0.9
APACHE II	12 (11-14)
SAPS	43 (35-51)

Data are expressed as mean ± SD or median and interquartile range or as number (%).

Figure 2. *Reason for ICU admission*



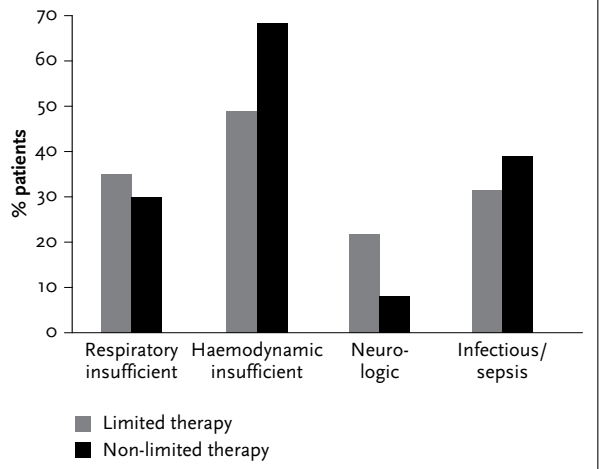
In 77% of the cases, the cause of death was directly related to the ICU admission diagnosis. In 23% of the patients, death was due to development of a new diagnosis during ICU stay or unexpected complications. In this group relevant complications were bleeding, vascular insufficiency (ischaemia, necrosis), renal failure, brain damage and multi-organ dysfunction syndrome.

Mortality

Of the complete group of patients who died during hospital stay, 75% died in the ICU after 7 (IQR 3-15) days. The remainder of the patients died on the ward 8 (IQR 3-26) days after their ICU admission. Post-mortem examination was performed in 34% of the patients.

Seventy-three patients who died (68% of total) were judged to have an unfavourable prognosis and died following limitations of therapy (*figure 3*). It is true that the decision to limit therapy may eventually result in the death of a patient; however, this is not always the cause. To illustrate what percentage of patients die, e.g., of shock (e.g. following termination of vasopressor therapy), or because of respiratory insufficiency (e.g. following detubation), the consequence of limitation of therapy was taken as the ultimate cause of death in this group of patients. Shock related to low cardiac output or low blood pressure was labelled haemodynamic insufficiency, and this was the main cause of death in patients both with and without treatment limitations. Next were infectious causes and respiratory failure due to pneumonia, acute respiratory distress syndrome (ARDS), or exacerbation of their chronic

Figure 3. *Cause of death*



obstructive lung disease (COPD). These patients died with a clinical picture of hypoxia or hypercapnia.

In three patients an iatrogenic event was directly related to the death of the patient. One patient died of arterial pulmonary bleeding following Swan-Ganz catheter insertion on the Cardiac Care Unit. Another patient suffered from intestinal perforations due to abdominal surgery and died following abdominal septic shock. The third patient developed catheter-related bacteraemia with *Pseudomonas* spp. following renal replacement therapy and died of haemodynamic insufficiency. The courses of these patients are described as 'illustrative cases' and available in the online supplement.

DISCUSSION

To the best of our knowledge, this is the first study describing the course of disease and cause of death in ICU patients with a low risk of death as predicted by the APACHE II score. Major reasons to conduct this study were our interest in the fate of this category of patients and to examine our quality of care, as our hypothesis was that iatrogenic damage may be a potentially relevant factor in this low-risk group of patients. We found that most patients with an APACHE II score ≤15 who eventually died were admitted to the ICU because of respiratory insufficiency. In most patients, death was preceded by limitations of therapy because of a perceived unfavourable prognosis. Both patients with and without limited therapy ultimately died in the ICU because of haemodynamic insufficiency. Although medical records were analysed with special attention to complications of medical interventions and possible omissions related to the outcome of the patient, only three such cases were identified. To our knowledge, there are no reports that quantify the incidence of lethal complications of medical interventions. In our view, further insight into the reasons for death in patients with a low APACHE score could serve as an evaluation of the quality of care and more published data from other ICUs and countries is necessary to be able to benchmark different units.

The use of death among low-risk groups as a quality control is not a novel concept as shown in a study conducted by Hannan *et al.*[12] In this study they reviewed 8109 charts within a defined subset of in-hospital deaths in New York hospitals and found that patients who died in low-mortality risk groups (with a risk of death <0.5%) were 5.2 times more likely to be associated with quality of care problems than other patients who died. Other indications for 'care departed from professionally recognised standards' were: cardiopulmonary arrest (OR 3.4), renal failure (OR 3.2) and infection (OR 3.0).

However, our approach to use low Apache II scores for measuring quality of care in ICU patients is novel. The APACHE II score is extensively used in both research and the clinic, but so far no study has described the demographics and causes of death in patients predicted to have a small chance of dying. Two possibilities appear likely to explain the mortality in this group of patients. First, the APACHE score might lack specificity in certain groups of patients resulting in a false-negative prediction of a small chance of dying for a given patient. Second, the APACHE score was correct considering the condition of the patient during ICU admission, but a patient's condition can deteriorate during the ICU stay, resulting in his/her unfavourable outcome. In addition, as a recent study showed that the benefit of an ICU admission is substantially lower in patients with a lower severity of illness,[13] death due to iatrogenic reasons may play a role, especially in these patients with a low chance of dying.

Although in the majority of cases cause of death could be directly related to the conditions present during ICU admission, we observed a discrepancy between the primary reason for ICU admission, being respiratory insufficiency, and haemodynamic insufficiency as the most frequently observed cause of death. This is most likely related to the natural course of the disease. For example, in a pneumonia patient, the pulmonary problems may subside, while septic shock or multi-organ failure may become present in a later phase. Naturally, patient outcome not related to the reason for ICU admission is difficult to predict during the first 24 hours following ICU admission. While this was only the case in approximately a quarter of the patients, it does explain the limited predictive value of the APACHE score, especially in patients with a low score. Another example illustrating this issue concerns triage decisions. It was recently reported that of patients who were evaluated as

'too sick' or 'too old' to be admitted to an ICU, the 90-day survival rate on the general ward was approximately 20%.[13] It appears plausible that the survival percentage of the group of patients expected to have an unfavourable prognosis could have been higher if they had indeed been admitted to an ICU. Naturally, other factors that were not reported and that go beyond life expectancy, such as quality of life, may also have played a role in the decision not to admit a patient to the ICU. Nevertheless, findings such as these are of major importance to evaluate our processes of care. In the present study, most patients died following limitation of therapy. Although a decision to limit further therapy is carefully taken and always in consensus with the physicians involved, we must remain vigilant about its justice and correctness.

Several limitations of the study should be addressed. First, we acknowledge that the choice to use an APACHE ≤15 is completely arbitrary. Nevertheless, it appears unlikely that another cut-off value would alter the results to a significant extent. Second, inter-observer variability is a theoretical limitation. It is recognised that the APACHE score has a high inter-observer variation,[14] limiting the sensitivity and specificity of its predictive value. Importantly, we used data from the Netherlands Intensive Care Evaluation, for which training in data acquisition is mandatory and improvements of training have been determined.[15] In our study, the data were collected by three individual observers who were instructed on how to use the case record form. As we prospectively acknowledged that inter-observer variability might occur, patient data and conclusions were reviewed by all three primary investigators following data collection. Also, in patients for which an autopsy report was not available the cause of death was retrospectively retracted from the charts and reviewed by the investigators until consensus. In addition, it was not possible to analyse the consequences of nosocomial infections, drug interactions or side effects, nutritional disturbances, acid-base problems or psychological complications. Finally, this study is a single-centre study. Therefore, it may not allow generalisation to other centres due to institution-based differences in treatment, termination of treatment and admission policies.

In conclusion, most patients with a low APACHE II score who did not survive died following limitations of therapy. Haemodynamic insufficiency as a consequence of shock related to low cardiac output or low blood pressure was the main cause of death in this group. Without limitation of therapy haemodynamic insufficiency was also the main cause of death, followed by infection/sepsis and respiratory insufficiency. Only a small proportion of patients died directly related to iatrogenic events.

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CASE REPORT

MIDD or MELAS: that's not the question

MIDD evolving into MELAS: a severe phenotype of the m.3243A>G mutation due to paternal co-inheritance of type 2 diabetes and a high heteroplasmy level

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ABSTRACT

Maternally inherited diabetes and deafness (MIDD) and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) are different syndromes, but are caused by the same m.3243A>G mutation in mitochondrial DNA. Why some patients develop MIDD while others MELAS is unknown, but may be related to heteroplasmy level. Progression from MIDD to MELAS has not been described. Here we report a patient with MIDD who over time developed severe insulin resistance and symptoms and signs consistent with MELAS. The most likely explanation here was paternal co-inheritance of type 2 diabetes in combination with a high heteroplasmy level. The present case showing evolution of MIDD to MELAS supports the concept that both syndromes can be regarded as two phenotypes of the same disease.

KEYWORDS

Insulin resistance, m.3243A>G mutation, MELAS, MIDD, heteroplasmy

INTRODUCTION

Maternally inherited diabetes and deafness (MIDD) and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) are both caused by a maternally inherited m.3243A>G mutation in the mitochondrially encoded tRNAleucine 1 (UUA/UUG) gene.[1,2] MIDD accounts for 0.5-3% of diabetes mellitus (DM) and is characterised by decreased insulin secretion and sensorineural hearing loss.[3,4] In contrast, MELAS is a more severe syndrome, characterised by stroke-like episodes, encephalopathy, myopathy and lactic acidosis in blood and/or cerebral spinal fluid.[1,5,6] Both syndromes are associated with a broad spectrum of other symptoms, including depression, heart disease (cardiomyopathy) and Alport-like renal disease.[3-6] It is not clear why some patients develop MIDD, and others MELAS, but it has been suggested that the level of heteroplasmy (the presence of a mixture of mutant and normal mtDNA in a cell) plays a role.[6-8] Although some papers have reported neuromuscular involvement in MIDD,[3,9] progression from MIDD to MELAS has not been described in Caucasians.
Here we describe a male patient with the m.3243A>G mutation and an MIDD phenotype who over time developed a strikingly progressive insulin resistance and eventually evolved into MELAS. This case illustrates that mitochondrial diseases are multisystem disorders and that clinical signs and symptoms might alter over time. Apart from that it emphasises the importance of considering genotyping in DM patients, especially when the patient is young, has a positive family history or additional signs suggesting MIDD or MELAS.

CASE REPORT

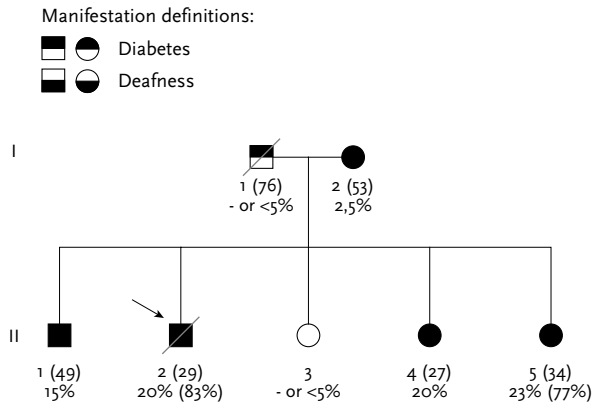
The proband -body mass index 24 to 27 throughout adult life- was diagnosed with hypertension and DM at 29 years, and sensorineural deafness at 33 years. His family,

which we have described previously, showed a high coseggregation of DM and deafness.[10] The m.3243A>G mutation was detected by targeted mutation analysis, with a blood leucocyte heteroplasmy of 20% in the proband (*figure 1*). His mother suffered from insulin-dependent DM and deafness, his father had type 2 DM treated with oral medication. The clinical course in the second generation was variable, ranging from no symptoms at all (II-3) to progressive disease in II-1, II-4 and the proband, who showed the most severe clinical picture.

His diabetes was characterised by progressive insulin resistance, for which he needed increasing doses of a rapid-acting insulin analogue ranging from 60 units per day at age 40, to 420 units at age 62. Nevertheless the Hba1c had exceeded 86 mmol/mol over the last ten years. To reach normoglycaemia, he was finally hospitalised monthly, for one week, to be treated with intravenous insulin up to 200 units per day. During these weeks he felt much better, especially concerning complaints of progressive muscle pain for which he eventually needed morphine. Ankle-brachial index was normal and he had no peripheral neuropathy or rhabdomyolysis. Serum triglyceride levels exceeded 10 mmol/l despite treatment with gemfibrozil and acipimox. Atorvastatin was stopped because of the myalgia. There was only mild background retinopathy and no renal failure or proteinuria.

His clinical picture worsened and at age 51 he developed MELAS with stroke-like episodes consisting of transient hemiparesis, headache, aphasia and reduced consciousness. There was no evidence of cerebral ischaemia on repeated CT scans, performed directly or within one week after an episode. An MRI could not be performed because of a cochlear implant. His cognitive function declined during the course of the disease. He suffered from right ventricular failure of unknown cause at age 49. Serum lactate was elevated (3.9 mmol/l) increasing to 4.9 mmol/l after a six-minute walk test, performed at age 60 at the end of a week of intravenous insulin. The walking distance was far below expected (212 m, expected 631 ± 93 m). A muscle biopsy showed decreased mitochondrial energy production, with lowered substrate oxidation and ATP production (19.1 nmol/h. mUCS; normal 34.5-67.5). Many COX-negative fibres were seen, indicating mitochondrial myopathy (*figure 2*). The muscle heteroplasmy level was 84%. He died at age 62 of aspiration pneumonia after a stroke-like episode.

Figure 1. *Pedigree of the family with the m.3243A>G mutation*



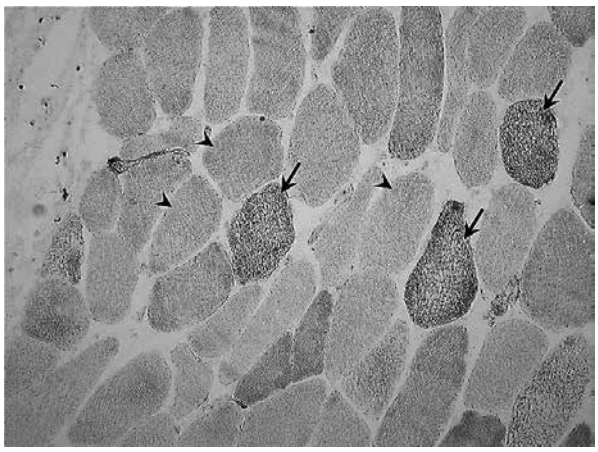
Roman numbers indicate generations. The proband is indicated by an arrow. The first line below the symbol represents identification number, with in parenthesis the age of onset of DM. The second line displays heteroplasmy levels in peripheral blood leucocytes and, in parenthesis, if available, in muscle.

DISCUSSION

Here we describe an MIDD patient who clinically evolved to MELAS over time. This is highly unusual and has not been described before in a Caucasian patient. Observational studies of Caucasian MIDD patients just showed absence of typical MELAS manifestations.[2,3,9] Furthermore, while MIDD has been associated with a predominant insulin secretion defect,[4,6,7] this patient developed extreme insulin resistance over time.

The explanation for these two features may be dual. Firstly, the MIDD phenotype may have evolved into a much more severe MELAS phenotype with severe insulin resistance in addition due to co-inheritance of type 2 diabetes from his father ('double gene dose').[11] A similar, albeit milder, phenotype was observed in the family members II-1 and II-4 who also show progressive insulin resistance,

Figure 2. *Muscle biopsy of the proband with cytochrome c oxidase (COX) staining*



Many COX-negative fibres (arrowheads) and a few COX-positive fibres (arrows) are present, indicating mitochondrial myopathy.

with average daily insulin doses of 250 and 120 units, respectively.

A second potential explanation is the high heteroplasmy level of the m.3243A>G mutation in muscle tissue (84%), which may cause a mitochondrial respiratory chain defect leading to reduced insulin-stimulated glucose metabolism and thus insulin resistance.[7,12,13,14] Mitochondrial dysfunction may also lead to stroke-like episodes, right ventricular failure and the severe hypertriglyceridaemia due to failure to metabolise free fatty acids.[3,4,6,12,14]

The present case demonstrates that a high muscle mutation load of 84% is a better predictor for the severe phenotype than the relatively low blood mutation load of 20%. This also seems the case in II-4, who does not meet all the MELAS criteria, but suffers from severe depression, has cerebral spinal fluid lactic acidosis and myopathy with a muscle heteroplasmy level of 77%. Heteroplasmy levels differ considerably amongst various tissues and the phenotypic variability of the m.3243A>G mutation is, at least in part, due to the varying levels of heteroplasmy.[4,6-8,13,15] Leucocytes are mostly used to determine heteroplasmy levels, in which they can be quite low and also tend to decline upon ageing.[4,15] The mutation load in more slowly dividing tissues such as muscle is higher,[7,15] and has a stronger relationship with phenotype.[4,8,13] Urinary epithelial cells may provide a reliable non-invasive alternative to perform mutation analysis.[16]

Interestingly, this case also demonstrates that muscle pain, which somewhat resembles ischaemic pains, was less severe when glucose control was optimised by intravenous insulin treatment. This observation suggests that muscle pain in MELAS is related to intracellular energy metabolism.

Treatment options, beside symptomatic relief and rehabilitation, are limited to treatment with L-arginine, an important mediator of cerebral vasodilation which can improve frequency and severity of stroke-like episodes, and the antioxidant coenzyme Q10.[6] The latter also acts as an electron carrier in the mitochondrial respiratory chain. It may therefore improve the mutation-associated dysfunction of the respiratory chain in mitochondria, but was not effective in our patient. Metformin is contraindicated because of the risk for lactate acidosis.[6]

CONCLUSION

This case history illustrates the severe and progressive clinical phenotype that may arise from the m.3243A>G mutation. Severe insulin resistance may occur, possibly determined by co-inheritance of type 2 diabetes. Furthermore, we show that MIDD patients may develop MELAS over time, which supports the concept that MIDD and MELAS in fact are two phenotypical expressions of one disease.

ACKNOWLEDGEMENTS

We thank Professor C.J. Tack for the discussions and suggestions regarding the manuscript.

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Netherlands
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PHOTO QUIZ

Keratoconjunctivitis, pharyngeal ulcera, hypoxaemia and fever

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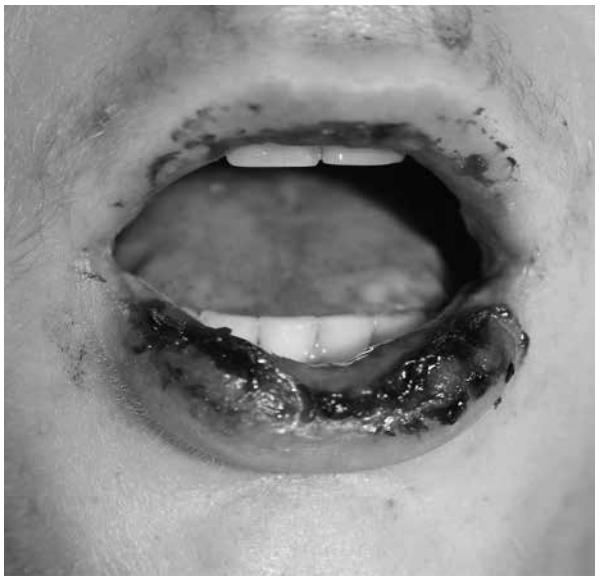
CASE REPORT

A 20-year-old Caucasian male presented at our clinic with fever, a sore throat, coughing, red swollen eyes, photophobia, blurred vision and crusted lips for ten days. He had no relevant medical history and was not taking any medication. On physical examination the patient was febrile (39.4°C) without dyspnoea. The ophthalmologist diagnosed a bilateral keratoconjunctivitis (*figure 1*). Furthermore, he had a severe stomatitis with crusted swollen lips (*figure 2*) and pharyngitis. No lymphadenopathy or genital ulcers were present. Blood analysis showed a mild leucocytosis (10.5 x 10^9/l, 73.7% neutrophils) and elevated C-reactive protein (127 mg/l).

Figure 1. *Red swollen eyes*

Figure 2. *Crusted lips with ulcera on the lips and tongue*



Arterial blood gas analysis showed hypoxaemia (PO_2 57 mmHg). The chest X-ray revealed an increased density in the right lower lobe, suggestive of a small infiltrate.

WHAT IS YOUR DIAGNOSIS?

See page 468 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

A 24-year-old woman with skin ulceration and strawberry gums

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CASE REPORT

A 24-year-old woman was referred by her general practitioner to the dermatologist and the internist because of a three-month history of skin ulcers on her face and right arm. She had also noted redness and swelling of her gingiva in the last four weeks (*figure 1*). She had already been treated with several oral and topical antibiotics without effect. Two weeks before she developed general malaise with low-grade fever, nose obstruction and epistaxis. She had no arthralgias or gross haematuria. On examination, she had three deep ulcerations with a purple margin on her left cheek, on her chin and on the inner side of her right upper arm. She also had erythematous swollen gingiva with petechiae looking like the surface of a strawberry. Besides the skin ulceration and mucosal lesions, examination was not remarkable. On laboratory investigation, C-reactive protein was 21 mg/l and there was a mild leucocytosis (11.9 x10^9/l). Renal and hepatic function tests and urinary sediment were normal. A chest X-ray revealed no abnormalities.

WHAT IS YOUR DIAGNOSIS?

See page 469 for the answer to this photo quiz.

Figure 1A. *Erythematous swollen gingiva with petechiae looking like the surface of a strawberry*

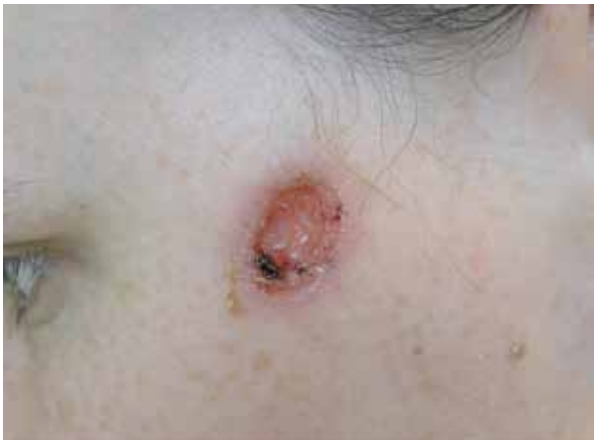

Figure 1B. *Deep skin ulceration with a purple margin on the left cheek*

Netherlands
The Journal of Medicine

PHOTO QUIZ

Fever and back pain

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CASE REPORT

An 80-year-old female patient was admitted to our hospital with malaise, fever, pancytopenia (haemoglobin 3.7 mmol/l, leucocytes 0.4 x 10^9/l, platelets 12 x 10^9/l) and increased C-reactive protein (120 mg/l) two weeks after an episode of vomiting and diarrhoea. Her medical history revealed multiple myeloma for which she received palliative chemotherapy. Blood cultures yielded *Salmonella typhimurium* and she was treated with ciprofloxacin. After initial improvement, the patient again developed fever and ceftazidime was started. Blood cultures remained negative. Two weeks after discharge, she was once more admitted with fever and blood cultures again yielded *Salmonella typhimurium*. The strain had become ciprofloxacin resistant, but was susceptible to third-generation cephalosporins. Abdominal ultrasound, transthoracic echocardiography and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed no signs of abdominal abscesses, endocarditis, osteomyelitis or an endovascular source for the recurrent bacteraemia. The patient was treated with ceftriaxone for one week, trimethoprim-sulphamethoxazole for four weeks (eradication therapy), followed by low-dose prophylactic trimethoprim-sulphamethoxazole. Myeloma treatment was continued.

Three months later she presented with fever and backache. She had stopped taking the trimethoprim-sulphamethoxazole two weeks before admission, for unknown reasons. The physical examination was unremarkable. Laboratory results showed a C-reactive protein of 122 mg/l and pancytopenia. Chest X-ray and urinalysis were normal. Broad-spectrum treatment with piperacillin/tazobactam was started. Blood cultures were again positive for *Salmonella typhimurium*. Antibiotics were switched to oral trimethoprim-sulphamethoxazole. A contrast-enhanced computed tomography (CT) scan of the abdomen was performed to rule out an intra-abdominal source of infection (*figure 1*).

WHAT IS YOUR DIAGNOSIS?

See page 470 for the answer to this photo quiz.

Figure 1. *Contrast-enhanced computed tomography of the abdomen, transverse (A) and frontal (B) sections*

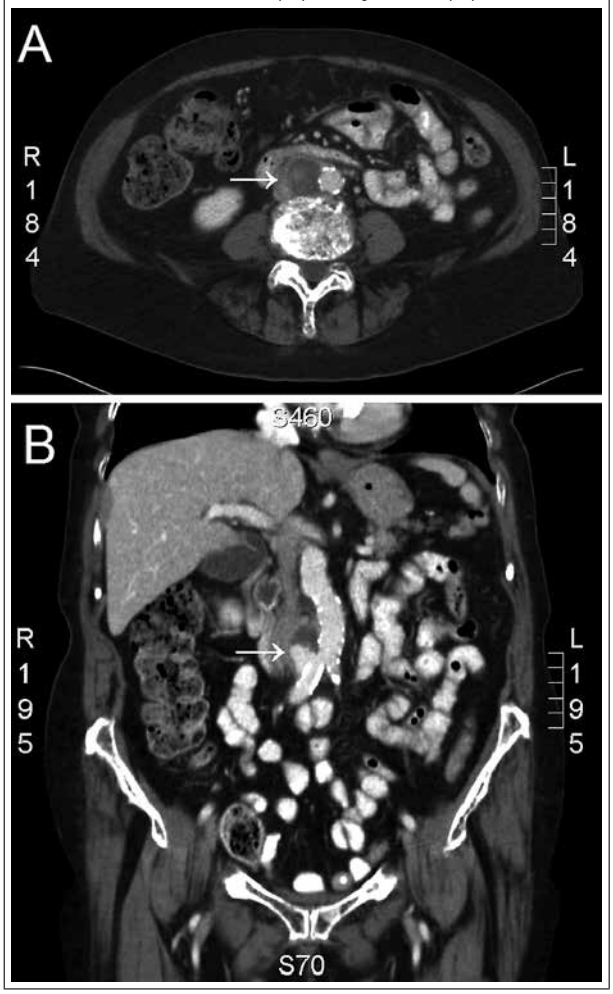

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PHOTO QUIZ

A 55-year-old man with pruritic skin nodules

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A 55-year-old Caucasian man hailing from Syracuse, NY, USA presented with pruritic skin nodules for the past six months. The lesions initially started on the back and then spread all over the body. The patient denied fever, chills, loss of weight or appetite; a review of systems was otherwise negative. He had no significant past medical history and was not on any medications. He had never travelled outside the USA to any developing nations. On physical examination, multiple non-tender, fungating, weeping lesions with an erythematous base and multiple plaques were noted on the back, trunk, abdomen, upper and both lower limbs (*figure 1*). Laboratory tests revealed a persistently high leucocyte count ranging between 12,000-17,000/µl; peripheral smear did not show any abnormal cells. Hepatic and renal function tests were normal. A punch biopsy of the skin lesion was performed.

Figure 1. *Multiple nodules over the torso*

WHAT IS YOUR DIAGNOSIS?

See page 471 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

PHOTO QUIZ

Palmar necrosis during the treatment of acute myeloid leukaemia

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CASE REPORT

A 32-year-old man was admitted to the haematology department for the treatment of acute myeloid leukaemia. He had no other significant medical history. He received a second induction cycle of chemotherapy consisting of cytarabine (1000 mg/m^2 twice daily, day 1-6), amsacrine (120 mg/m^2 once daily, day 4-6) and clofarabine (10 mg/m^2 once daily, day 1-5). In addition, because this treatment causes prolonged agranulocytosis, antimicrobial prophylaxis was given consisting of fluconazole 50 mg once daily, feneticilline 250 mg 4 times/day, ciprofloxacin 500 mg twice daily and tobramycin 120 mg 3 times/day for the prevention of yeasts, gram-positive cocci, gram-negative rods and selective digestive tract decontamination, respectively.

Figure 1. *Erythema with necrosis on the palm of the left hand*

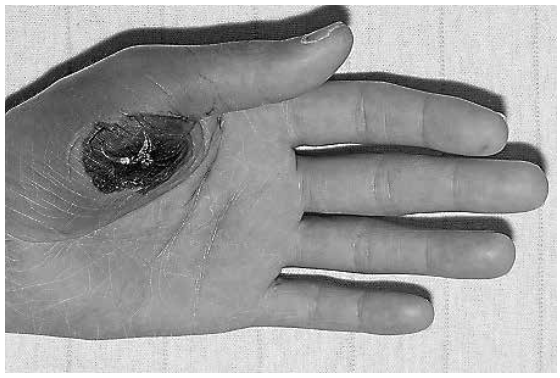
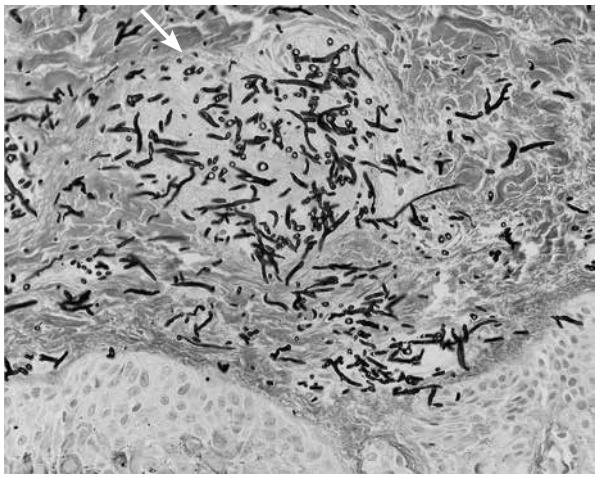


Figure 2. *Skin biopsy (x 200 objective)*



After 16 days, without previous trauma, the patient developed a progressive tender and erythematous macule with induration and central necrosis on the palm of his left hand (*figure 1*). He had no fever. Laboratory results showed the following: haemoglobin 5.4 mmol/l, leucocytes < 0.1 x 10^9/l and thrombocytes 33 x 10^9/l. A skin biopsy was taken (*figure 2*).

WHAT IS YOUR DIAGNOSIS?

See page 472 for the answer to this photo quiz.

ANSWER TO PHOTO QUIZ (PAGE 463)

KERATOCONJUNCTIVITIS, PHARYNGEAL ULCERA, HYPOXAEMIA AND FEVER

DIAGNOSIS

Our patient presented with fever, keratoconjunctivitis, stomatitis, pharyngitis and a respiratory tract infection. A chest computed tomography confirmed the diagnosis of pneumonia.

The differential diagnosis included a primary herpes simplex infection, other viral infections or a bacterial infection. Our patient was empirically treated with acyclovir and amoxicillin-clavulanic acid intravenously. Extensive testing (cultures, serology, polymerase chain reaction (PCR) revealed a positive *Mycoplasma* complement binding reaction of >1:128 and a positive *Mycoplasma* pneumonia PCR on a throat swab. Therapy was subsequently switched to azithromycin for five days after which the symptoms resolved completely.

Mycoplasma pneumoniae is a small organism frequently causing upper respiratory tract infections, but also pneumonia. Infection rates are highest among adolescents.[1] Although *M. pneumoniae* usually causes a mild self-limiting disease, there are case reports describing fulminant *M. pneumoniae* pneumonia.[1,2] Extrapulmonary manifestations, as seen in our case, are also reported in the literature. These include pharyngitis, otitis and sinusitis. Rare manifestations are dermatological disorders, conjunctivitis, stomatitis, arthralgia and haemolysis.[1,3] Latsch *et al.* reported on two adolescents with conjunctivitis, genital erosions, exudative and ulcerative stomatitis (without skin lesions) due to an acute *M. pneumoniae* infection.[4] Clinicians should include diagnostic tests for *M. pneumoniae* infection in patients presenting with fever, pneumonia, conjunctivitis, or mucocutaneous lesions.

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ANSWER TO PHOTO QUIZ (PAGE 464)

A 24-YEAR-OLD WOMAN WITH SKIN ULCERATION AND STRAWBERRY GUMS

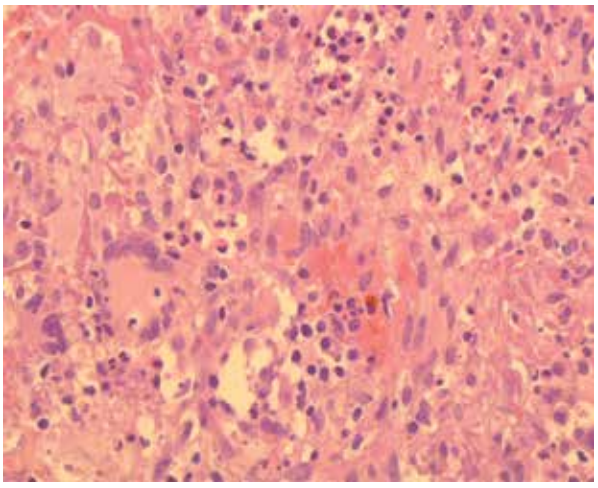
DIAGNOSIS

Granulomatosis with polyangiitis (GPA), previously known as Wegener's granulomatosis, was considered the most appropriate diagnosis based on the clinical picture. Skin biopsy of the lesion on her right arm showed active folliculitis with giant cell reaction and therefore did not contribute to the diagnosis. However, biopsy of the nasal mucosa showed extensive chronic, granulomatous, ulcerating inflammation with vasculitis (*figure 2*), confirming the diagnosis of granulomatosis with polyangiitis. In addition serum anti-PR3 (cANCA) antibodies were positive (4.9 kU/l, reference <2 kU/l) .

GPA is a rare granulomatous necrotising vasculitis of small vessels, affecting vascular structures especially of the upper airways, lungs and kidneys. Patients usually present with constitutional symptoms including fever, migratory arthralgias, malaise, anorexia, nose obstruction, dyspnoea and weight loss.[1] GPA is also known to cause mucosal lesions. Strawberry gums, as found in this patient, are very typical for GPA.[2] Skin lesions, in this case with the aspect of pyoderma gangrenosum, are usually non-specific. Other cutaneous manifestations of GPA are palpable purpura, nodules, petechiae and delayed healing of excision wounds.[3] The American College of Rheumatology criteria for the classification of Wegener's granulomatosis are abnormal urinary sediment (red cell casts or greater than five red blood cells per high power field), abnormal findings on chest radiograph (nodules, cavities, or fixed infiltrates), oral ulcers or nasal discharge, and granulomatous inflammation on biopsy. For purposes of classification, a patient is said to have Wegener's granulomatosis if at least two of these four criteria are present. The presence of any two or more criteria yields a sensitivity of 88.2% and a specificity of 92.0%.[4]

This case illustrates that recognition of the very typical strawberry gums as a manifestation of GPA may lead to an early diagnosis and treatment.

Figure 2. *HE-stained slide of nasal mucosal biopsy shows granulomatous vasculitis*



ACKNOWLEDGEMENTS

We would like to thank Mrs. R.P. Aliredjo for providing the slide of the nasal mucosal biopsy.

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ANSWER TO PHOTO QUIZ (PAGE 465)

FEVER AND BACK PAIN

DIAGNOSIS

The CT scan showed a saccular dilatation at the bifurcation of the abdominal aorta to the right common iliac artery and the diagnosis of infected aneurysm due to *Salmonella typhimurium* infection was made.

Infected or mycotic aneurysms are rare lesions.[1] However, about 10-25% of patients older than 50 years who present with non-typhoidal *Salmonella* bacteraemia develop infectious endarteritis or mycotic aneurysm, due to pre-existing atherosclerosis and/or immunodeficiency.[2] *Salmonella* vascular infections most often involve the aorta, femoral or iliac arteries.[1] Symptoms include fever, back pain, chest pain or abdominal pain. Recurrent bacteraemia is present in 85% of cases.[3]

CT angiography is the diagnostic modality of choice. Signs of aortitis are an irregular arterial wall, periaortic oedema or soft-tissue mass and (uncommonly) periaortic gas. After aneurysm formation, signs of an infectious nature are an unusual location, saccular shape, rapid growth and disrupted arterial wall calcification.[4] The sensitivity of FDG-PET for detection of vascular infection is unknown.[4]

The patient's physical condition prohibited surgical resection of the infected aneurysm.[3] However, good results have been obtained with combined endovascular aneurysm repair and lifelong antibiotics.[5] Therefore, therapy was switched to ceftriaxone intravenously and the patient received an endovascular graft. After four weeks, ceftriaxone was replaced by oral trimethoprim-sulphamethoxazole but was later switched to oral azithromycin because of nausea attributed to the continuous use of trimethoprim-sulphamethoxazole.[6] Myeloma treatment was interrupted. At follow-up, six months after discharge, the myeloma was slowly progressing but no signs of infection were present with the azithromycin maintenance therapy.

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ANSWER TO PHOTO QUIZ (PAGE 466)

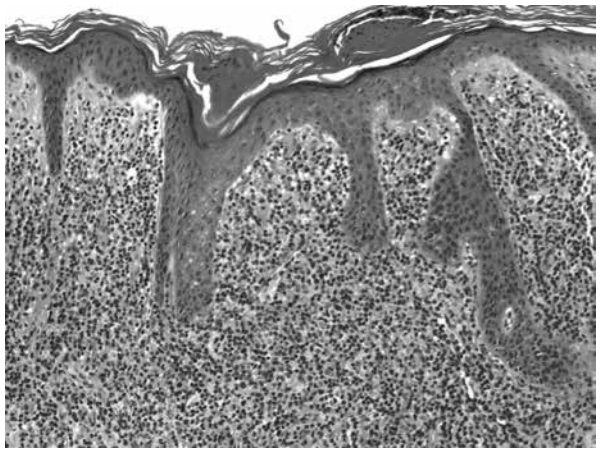
A 55-YEAR-OLD MAN WITH PRURITIC SKIN NODULES

DIAGNOSIS

Mycosis fungoides

Punch biopsy of the lesion showed an upper dermal lymphoid infiltrate consisting of medium to large lymphoid cells with irregular or folded nuclear contours, some with prominent nucleoli and a variable amount of cytoplasm (*figure 2*). Immunohistochemistry showed diffuse strong staining for CD3, CD4 and CD5 with scattered positivity for CD7 and CD8; CD20 highlighted a few background B cells and CD30 was negative. A diagnosis of mycosis fungoides (MF) was made. Radiology was negative for solid organ involvement. The patient was staged as MF Stage III (T4 N0 M0 B0) and treatment was initiated with cyclophosphamide, methotrexate, and prednisone. External beam radiation was also used for local control. The patient responded well with marked improvement in the size of the lesions and remains under follow-up.

Figure 2. *Skin biopsy HE stain*



Mycosis fungoides is an extranodal indolent non-Hodgkin's lymphoma of T-cell origin that is characterised by skin involvement. The incidence of MF is approximately six cases per million per year, accounting for about 4% of all cases of non-Hodgkin's lymphoma. Peak age of presentation is about 55 to 60 years, with a 2:1 male to female ratio.[1] MF may often resemble skin disorders such as eczema, psoriasis, parapsoriasis, photodermatitis, or drug reactions; hence a high clinical suspicion should be maintained. For advanced stage MF, treatment approaches include both local skin directed therapies as well as systemic cytotoxic chemotherapy.[2]

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ANSWER TO PHOTO QUIZ (PAGE 467)

PALMAR NECROSIS DURING THE TREATMENT OF ACUTE MYELOID LEUKAEMIA

DIAGNOSIS

Microscopic examination of the skin biopsy revealed numerous mycelial filaments, which occluded the blood vessels (black arrow in *figure 2*). On culture *Aspergillus fumigatus* was grown.

Since a dermal mycosis was suspected in this immunocompromised patient, treatment with voriconazole 200 mg twice daily was initiated before the results of the skin biopsy were available. Amphotericin B 0.7 mg/kg/day was added 48 hours later because of rapid progression and was stopped after normalisation of neutrophil counts. The erythema resolved within a week. The central necrosis made surgical debridement with skin grafting necessary, after which the patient completely recovered. Voriconazole will be continued throughout immunosuppressive therapy following allogeneic stem cell transplantation.

Cutaneous manifestations are uncommon in aspergillosis, with a reported incidence of <5%.[1] Cutaneous aspergillosis may present as a primary infection after skin injury, for instance near intravenous access sites, burns or at sites with occlusive dressing. More often, it can be secondary when arising by spread from extracutaneous sites such as the lungs.[2] The initial skin lesion can rapidly lead to necrosis due to angioinvasion. *Aspergillus fumigatus* induces vascular invasion by microfilament rearrangement in endothelial cells and this results in endocytosis. In the vascular lumen the hyphae can cause endothelial damage and stimulate tissue factor activity with subsequent intravascular obstruction and thrombosis.[3]

During the cutaneous aspergillosis this patient experienced no signs of involvement elsewhere and a chest X-ray was normal. However, he had recovered from diffuse cytarabine skin toxicity before the cutaneous aspergillosis developed, which presumably was the porte d'entrée.

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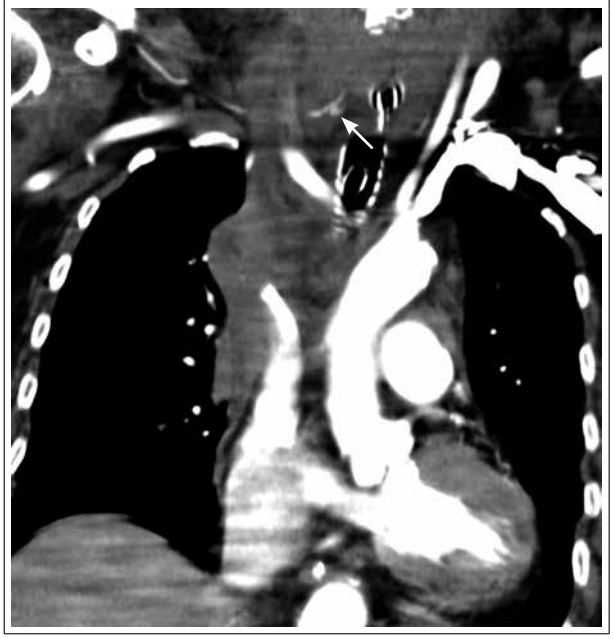
ERRATUM

In the Photo Quiz 'Rapid widening of the mediastinum after coronary angiography' by Seubert et al., published in Neth J Med. 2012 November; 70(9):415, 419, the white arrow in *figure 2* appeared in the wrong place in the printed issue of the Journal. The arrow pointed to the trachea and not to the site of bleeding that was situated above. In this corrected figure 2, the arrow is in the right place. We apologise for this confusion.

Figure 2. *Computed tomography of the chest with contrast shows an active bleeding focus in the right inferior thyroid artery*



Netherlands
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SPECIAL REPORT

Binary ultrasonography for the internist: yes or no, that's the question!

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ABSTRACT

The authors discuss the pros and cons with regard to ultrasound for the internist. They state that ultrasonography is seldom used by internists and they suggest several reasons for this. After a brief review of the literature they conclude that using ultrasound would probably benefit patients and would lead to a more rapid diagnosis and an increase in safety while performing invasive diagnostic and therapeutic interventions. The authors suggest that internists use ultrasound in a different way compared with radiologists, cardiologists, etc. They introduce the term binary ultrasound: ultrasound should be used to answer clinical questions with a yes or a no.

KEYWORDS

Ultrasonography, diagnosis, intervention

INTRODUCTION

In the last few years there have been many discussions about implementing ultrasonography for the internist. Up to now, no clear decision has been taken. In this article we will ponder about the reasons for this hesitation and suggest a new role for ultrasound in internal medicine: binary ultrasound.

THE CURRENT SITUATION

Up to now, there is no training curriculum in ultrasound for internists in the Netherlands. This is in contrast to many countries around us where ultrasonography is often performed by internists. Many specialists in the Netherlands have adopted ultrasonography in their daily practice. Urologists, gynaecologists, cardiologists and pulmonologists rely on their echographic skills for analysing the anatomy and functionality of the organs that they are studying. We see that ultrasonography is beginning to enter the field of some subspecialities of internal medicine with great hesitation: endocrinologists are echoing the thyroid, vascular internists measure the carotid artery intima media thickness with the aid of ultrasound, intensivists use ultrasound for determining cardiac output and filling status.

So what are the reasons that internists have not accepted ultrasound as an integral part of their examinations? There have been no investigations into this issue, but we will try to find an answer and suggest new avenues to explore.

Firstly, there is probably a misunderstanding about what ultrasonography means for the internist. It goes without saying that radiologists will always be better at performing an ultrasound of the liver, the kidneys or other internal organs, and that cardiologists will always outperform us in investigations of the heart, etc. We suggest that ultrasound for the internist should be limited to answering simple questions with a 'yes' or a 'no'. We coin the term binary ultrasound.

From the literature it appears that answering clinical questions with a yes or a no is a viable way of thinking; emergency ultrasound was approximately 86% sensitive and 98% specific to detect abdominal fluid and 96% sensitive and 100% specific to detect pleural fluid.[1] The overall sensitivity and specificity for detecting hydronephrosis in patients with a renal colic amounted to 87% and 82%, respectively.[2] Assessment of the diameter of the inferior vena cava, and its variations during respiration,

correlate with central venous pressures that were measured invasively.[3,4] A short training session in emergency ultrasound appeared accurate to detect abscess formation in the presence of a soft tissue infection,[5] and bedside soft tissue ultrasound altered the management in 56% in patients with cellulitis.[6]

Some of the questions that can be answered with a yes or a no are:

- Is there free fluid in the abdomen?
- Is there a postrenal obstruction?
- Is there pleural fluid?
- Is there a pericardial effusion?
- Is there intravascular volume depletion?
- Is there abscess formation in the presence of a soft tissue infection?

Of course, an internist with the aid of ultrasound cannot answer all clinical questions with a yes or a no: 'Is the bile duct dilated?' for instance is a far more difficult question to answer.

There may be doubts about the reliability of the above-mentioned application of ultrasonography or whether these skills can only be learned after an extensive training program. The American College of Emergency Physicians has described precise pathways for training in core applications of emergency ultrasound, including the evidence for these core applications. It appears that a limited number of examinations is enough to reliably perform several of the core applications. Based on a long experience in core emergency ultrasound training, the American College of Emergency Physicians recommends that a trainee should obtain at least 25 documented and reviewed cases in each of the core applications with a range of 25-50 cases, whereas a minimum number of ten examinations are recommended for an ultrasound-guided procedure examination. So, binary ultrasound can be learned within a limited timeframe.[7]

DIAGNOSING COMMON INTERNAL MEDICAL PROBLEMS

Ultrasonography has a central role in diagnosing many major problems. For instance, in hypotension, ultrasonography is very helpful in determining cardiac filling status, rightward deviation of the intraventricular septum, tamponade, and free fluid in the pleural space or abdominal cavity. These diagnoses can be determined with good reliability by asking questions that can be answered with a simple yes or no (e.g. is there any pericardial fluid?) after which more dedicated investigations can be ordered. Ultrasound is also very good in determining filling status through determining whether the inferior caval vein is dilated.[3]

The diagnostic value of immediate goal-directed ultrasound to identify causes of nontraumatic, undifferentiated hypotension in the emergency department has been shown by Jones *et al*.[8] They found this protocol resulted in fewer viable diagnostic aetiologies and a more accurate physician impression of the final diagnosis within 15 minutes after presentation.

Unknown to many, ultrasound of the lungs is also able to determine whether the lungs are ventilated through visualisation of the pleura.[9]

PERFORMING INVASIVE PROCEDURES

Ultrasonography is becoming an indispensible tool in invasive procedures. There is accumulating evidence that ultrasonographic guidance improves patient safety and procedural success.[10] For instance, it has been shown in the literature that internal jugular cannulation for the placement of haemodialysis catheters is safer with ultrasonography.[11] In addition to this: one of us failed 14 times in 155 catheterisations of the internal jugular vein and hit an artery seven times. Furthermore there were four localised haematomas.[12]

Ultrasonography in diagnosing and treating pleural effusions is very valuable and saves a lot of x-rays.[13] Ultrasound guidance improved the success rate of paracentesis and identified a number of patients in whom the procedure could not be performed. A short training program was sufficient to learn to use ultrasound in these instances.[14]

We would like to propose that the time that internists perform procedures blindly is slowly coming to an end.

THE FUTURE

We suggest that internists will have to learn what we coin as a new term: binary ultrasonography. Internists can use ultrasonography to answer clinical questions with a yes or a no to improve their diagnostic skills in addition to their other skills. Furthermore, internists will use ultrasonography as an aid in performing invasive procedures.

We propose that ultrasonography for the internist becomes so important that it will be performed in many instances before the results of laboratory investigations become available. This will be especially the case in treating the acutely ill medical patient; many protocols will in the future have a new structure: 1. History; 2. Physical examination; 3. Ultrasonography; 4. Lab results; 5. Additional investigations. This will lead to better patient care.

These principles have consequences. Firstly, the basics of ultrasonography will have to be taught in the beginning of the training of the internists and, secondly, ultrasound competencies have to be described for every aspect of the training of the internist and implemented in the training when appropriate.

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1 DAG WERKEN
1 DAG BIJKOMEN

EEN NIERPATIËNT MOET ER VEEL VOOR OVER HEBBEN OM EEN BEETJE NORMAAL TE LEVEN.
Ze was 14 toen bij haar een nierziekte werd ontdekt. Inmiddels is Charlotte Trieschnigg 35 en na twee niertransplantaties moet ze nu opnieuw dialyseren. Dit is voor haar de enige manier om in leven te blijven. Charlotte slaapt vier nachten per week in het ziekenhuis om te dialyseren. Dat is heel zwaar maar toch heeft Charlotte het ervoor over om zo toch een beetje normaal te kunnen leven. De Nierstichting zet alles op alles om nierpatiënten een betere kwaliteit van leven te geven. Daarnaast werken we er keihard aan om nierziekten te voorkomen. Dat kunnen we echter niet alleen.

WAT HEEFT U OVER VOOR EEN NIERPATIËNT? STEUN ONS!
KIJK WAT U KUNT DOEN OP NIERSTICHTING.NL

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

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