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The mission of the journal is to serve the need of the internist to practice up-to-date medicine and to keep track with important issues in health care. With this purpose we publish editorials, original articles, reviews, controversies, consensus reports, papers on speciality training and medical education, book reviews and correspondence.

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Editorial office 'The Netherlands Journal of Medicine'
Geerlrien Derksen-Willemsen
University Medical Centre St Radboud
Department of General Internal Medicine 541
PO Box 9101, 6500 HB Nijmegen
The Netherlands
Tel.: +31 (0)24-361 04 59
Fax: +31 (0)24-354 17 34
E-mail: g.derksen@aig.umcn.nl

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Supporting smoking cessation in the medical specialist practice

G.M. Schippers

Amsterdam Institute for Addiction Research (AIAR), PO Box 3907, 1001 AS Amsterdam, the Netherlands, tel: +31 (0)20-4087870, fax: +31 (0)20-4087862, e-mail: schippers@aiar.nl

ABSTRACT

Although smoking cessation reduces the cardiovascular risk of smoking, why this is so is still uncertain. Nevertheless, because they are strongly and authoritatively involved in much of the serious health damage caused by smoking, medical specialists should do all they can to support their patients in stopping. This indispensable support can be improved, however, when specialists adopt more motivational and behaviour change promoting attitudes and communicative techniques.

Reporting negative evidence can be frustrating. Van den Berkmortel et al., in this issue, were not able to show significant changes over time in intima-media thickness of the femoral and carotid arteries in relation to nonsmoking or smoking cessation. They had to reject the hypothesis that this parameter plays an indicative role in the explanation of the rapid reduction in cardiovascular risk after smoking cessation. Supporting smoking cessation can be frustrating as well. For this study the authors recruited 127 smokers with the intention to stop from the general population. Although they do not report on that, I presume the selection was based on the participants real and strong motivation, and on the provision of some kind of support in their quitting attempts. Nevertheless, only slightly more than a quarter of those 127 remained nicotine-free in the two-year study period. Frustrating perhaps, but such figures are to be expected in supporting smoking cessation - and actually not a bad score. Smoking cessation is a serious and difficult endeavour, which is undertaken by many every year, but only with success by a few. Can medical specialists be of help?

They should, because smoking is seriously detrimental to health. About 20% of all cancer deaths worldwide are caused by smoking. Smoking causes 80 to 90% of lung cancers with a relative risk in men of over 20 and in women of over 10. Smoking is responsible for most cancers of the bladder, pancreas, oesophagus, and kidneys. Over 80% of chronic obstructive lung disease can be attributed to smoking with a relative risk in both male and female smokers of about 10. The relative risk for cardiovascular disease is about 10 in smokers aged 30 to 50 years, but this risk declines with increasing age as death rates from heart disease also rise in nonsmokers. Across all ages, about 20% of cardiovascular deaths can be attributed to smoking. However, because cardiovascular disease is so common in the population, smoking-attributable deaths from cardiovascular diseases (ischaemic heart disease, claudication, and stroke) outnumber smoking-attributable deaths from all other causes, including lung cancer.

Smoking is a cause of peripheral vascular disease, cataracts, and gastric and duodenal ulcers, and contributes to Crohn’s disease. Smoking increases the risk of cerebrovascular disease in a dose-response manner, for both haemorrhagic and ischaemic cerebral infarction, which occurs in conjunction with an increase in atherosclerosis of the carotid arteries. Smoking markedly accelerates atherosclerosis in the abdominal aorta and occlusive disease in its branches. Aortic aneurysm, peripheral vascular disease and renal artery stenosis are increased in smokers. Cigarette smoking is an independent risk factor in the development of atherosclerosis in the internal pudendal and penile arteries of young men with impotence.
Numerous respiratory diseases are strongly related to cigarette smoking. Cigarette smoking is estimated to contribute to over 80% of cases of chronic obstructive pulmonary disease (COPD), and the amount and duration of cigarette smoking directly influences the progression of COPD. Asthma and respiratory infections are not caused by tobacco smoke but are worsened by exposure to cigarette smoke.

Medical practice should provide support in smoking cessation, because health benefits strongly from cessation. At all ages, the risk of ischaemic heart disease in individuals without known coronary heart disease decreases after cessation, particularly in the first two to three years. Thereafter, the rate of decline decreases, but in about ten years former smokers reach the same risk level as never-smokers. The risk for the first myocardial infarction declines quickly to reach that of never-smokers by the third or fourth year. For smokers who already have coronary heart disease, cessation is also very effective in reducing the risk of further acute coronary events. The risk of coronary heart disease is substantially and relatively rapidly reversible on cessation of smoking. One year after quitting, the risk of coronary heart disease decreases by 50%, and within ten years, the relative risk of dying from coronary heart disease for an ex-smoker approaches that of a never-smoker. Among patients with peripheral artery disease, smoking cessation improves exercise tolerance, reduces the risk of amputation after peripheral artery surgery, and increases overall survival.

Both the duration of smoking and the amount smoked are significant predictors of lung function impairment. The Lung Health Study found a reduced rate of decline in lung function and fewer respiratory symptoms in those who remained quitters over the five-year duration of the trial. The benefit was also seen in heavy smokers, older smokers and smokers with poor baseline lung function.

Can internists be of help in supporting smoking cessation? Since many smokers ask for medical help, whether or not for smoking-related diseases, and since they have relatively many contacts, they are particularly suited to do smoking cessation interventions. When delivered by medical professionals, such interventions are usually well accepted by the patients and lead to better results than when given by nonmedical personnel. Therefore, in accordance with the British and American guidelines, the Partnership Stoppen met Roken, a cooperation of the Ministry of Health, the Nederlandse Huisartsenvereniging and the Orde van Medisch Specialisten recently put together the Dutch Guidelines for the Treatment of Tobacco Dependence (Draft version: CBO 2003 http://www.cbo.nl/product/richtlijnen/folder 20021023121843/concepttabaksversl.pdf). The Dutch guidelines see hospital outpatients as important targets for cessation support interventions, comparable with the primary care patients (p. 22). Parallel to the Minimal Intervention Strategy for Primary Physicians, a cardiologist version (C-MIS) and a lung specialist version (L-MIS; Wagena & Kotz in press) have been designed and tested; the C-MIS was found to be effective for patients with cardiac diseases after three months. Van de Meer et al. present evidence that short interventions by medical specialists are effective for COPD patients. A combination of psychological and pharmacological interventions are more effective than one of the two in isolation. However, due to lack of studies, no specific psychological interventions can be indicated. Because MIS versions for cardiologists were not proven to be effective in the long run, Van Berkel recommends the use of more intensive interventions, including the prescription of supportive medications, with a preference for bupropion and, when registered, for nortryptilin, which attenuates the change of success. The components ask, advise, assess and arrange are seen as essential and form the basis of the MIS protocols. Rice and Stead, in their Cochrane review on nursing interventions, present evidence that these components are preferably followed by frequent telephone contacts. The concerted action of a warning specialist, possibly prescribing antismoking medication and a dedicated nurse, specialised in supporting smoking, provides a strong combination.

Although there is ample evidence for their effectiveness, the degree of effect these interventions have is limited. Professional support will double (brief advice) or triple (face to face more intensive support) the number of ‘spontaneous’ quitters. In hospital outpatients this means 8 to 10% successful quitters instead of 2 to 4%. Referral to a smoking cessation specialist can enhance this number to 15 to 20%. Although the systematic application of these measures in hospital outpatient clinics will make a substantial contribution to public health and is highly cost-effective (Beleidsdocument Partnership 2004), since many persons visit yearly, the majority of those to whom the intervention is delivered will not respond. Approximately 70 to 80% of patients will be unaffected, even if given proper support.

Should this be a reason for the medical specialist not intervening in the outpatient hospital setting? Many doctors will be tempted not to intervene, but we think they should. Even if eight out of ten smokers do not respond immediately to an intervention, given the number of quitters yearly, some of them will do so, sooner or later. Furthermore, for ethical reasons medical specialists cannot refrain from raising the topic in their contacts with the patient.
Most specialists are aware of this and do raise the topic of smoking, although often not in a very structural and patient-friendly way. Patients are simply ordered to stop smoking, without expressing much trust, without distinguishing the motivational stage, and without giving real support. In the ‘failing’ patients this can lead to resistance and denial, in the ‘failing’ doctors to helplessness, reluctance, and even cynicism. Fortunately, more adequate ways of communication are available. Making use of the technique of motivational interviewing they can, more elegantly, assess the readiness to change, promote the confidence to start changing, and take away the resistance, without this costing much extra time or energy. These techniques of communication need to be trained, however, since they are not part of the initial education of many doctors. Fortunately, there are training procedures available for medical specialists to fill in these gaps. A good example is the cursus interactieve consultvoering (CIC), developed by the Medical Faculty of Radboud University Nijmegen, which is not only for smoking cessation, but also applicable for support in other lifestyle changes, such as reducing drinking, dieting, and medication compliance. The implementation of such trainings is highly recommended, therefore.

REFERENCES


Schippers. Supporting smoking cessation in the medical specialist practice.
Use of intermediate cardiovascular endpoints in intervention studies: not as easy as it seems?

M.L. Bots

Julius Center for Health Sciences and Primary Care, University Medical Centre Utrecht, Heidelberglaan 100, Internal post number D.01.335, 3584 CX Utrecht, the Netherlands, tel: +31 (0)30-2509352, fax: +31 (0)30-2505485, e-mail: m.l.bots@jc.azu.nl

In the current issue of the Journal, Van den Berkmortel and coworkers’ report on the effect of smoking cessation on cardiovascular risk reduction, as estimated by assessment of progression of carotid intima-media thickness (CIMT) and arterial stiffness. Much to the authors’ surprise, their nonrandomised study among 33 subjects who stopped smoking for at least two years, 55 persistent smokers and 50 never-smokers showed no difference in rate of change in CIMT or arterial stiffness across the groups after two years of intervention. The intriguing question of the paper is whether the finding is true or may be attributed to potential flaws of the study, focussing on design and analytical procedures, the choice of the endpoint and the power of the study.

The most desirable study design to evaluate the efficacy of interventions on cardiovascular risk is a randomised controlled trial (RCT). However, in the case of smoking this is ethically not possible. Therefore, an approach should be sought that at least tries to resemble an RCT in design and data analytic approach as closely as possible. Ideally, subjects should be analysed in a ‘intention to treat’ fashion, i.e. final analyses are based on the groups as these were at the start of the study. In the paper by Van den Berkmortel and coworkers, a considerable number of ‘dropouts’ occurred, in particular in the intervention group: from 127 smokers at baseline to 33 completers. The study should be designed in a way that the number of evaluable patients is the same at the end of the study. In studies using intermediate endpoints this may be achieved by having end of study measurements performed in those who dropped out during the study. The extent to which this approach was taken is unclear from the paper. Finally, in order to compare non-randomised groups of patients with respect to outcome in a valid manner, multivariate regression models may be applied to adjust for differences at baseline that may lead to different progression rates. Apart from baseline CIMT and alcohol consumption, the authors reported the absence of significant differences across groups at baseline. However, a multivariate analysis would have been appreciated in the paper in addition to the current data presented.

Ideally, one would tend to study smoking effects using cardiovascular events as primary outcome. Yet, using established intermediate endpoints, such as CIMT and arterial stiffness, the sample size of the study and possibly the duration of the study may be considerably reduced. The pros and cons of the final choice of the primary endpoint in a study like the one by Van den Berkmortel has recently been discussed in detail for CIMT measurements. Rather than providing estimates of CIMT progression for all carotid segments separately, there is strong view towards using the mean maximum CIMT as primary outcome. There is considerable variation in the CIMT measurement, which has been attributed to variability due to individuals, sonographers and readers. Obtaining CIMT measurements from various carotid segments, i.e. common and internal carotid artery and carotid bifurcation, near and far wall, left and right carotid artery, and averaging those estimates will likely reduce measurement variability and increase precision of the associations. Recent unpublished analyses from a large multicentre trial indeed showed that reproducibility of CIMT measurements improved considerably when the estimate was based on several measurements as compared with one measurement. Furthermore, rather than subtracting the follow-up measurement from the baseline measurement to obtain a progression estimate, an approach
might be considered in which all in-between measurements are taken into account. The information was collected by Van den Berkmortel, yet not analysed in this manner. In a study where the main focus is on change over time in the outcome parameter, information on reproducibility is essential. The cornerstone of reproducibility is the data based on repeat scans, i.e. where subjects are being examined twice with some time interval (weeks) in between the examinations. Such data reflect variability due to subjects, sonographers, readers and equipment. It is also important to have these repeat scans performed, not only at baseline, not only at the end of the study, but also during the study. In a trial as reported, it should be shown that the reproducibility between readers and that within a reader is good. However, we know that there are ‘thick’ and ‘thin’ readers. This means that using the same B-mode images, the reading by reader 1 leads to a higher CIMT estimate compared with the reading by reader 2. What is important for estimates of change over time is that the proportion thick/thin readers remains constant over time. Otherwise, progression estimates tend to become artificially large or small. When, however, the mix thick/thin readers changes over time but equally across the intervention groups it will unlikely affect the comparison across groups. As pointed out by Van den Berkmortel and coworkers, their reproducibility seems good although the data indicating reproducibility over time were not reported. Yet, in almost all of their progression estimates of CIMT, the direction is towards ‘regression’, which might be indicative of either drift within readers or change in the thick/thin readers mix over time.

When embarking on an intervention study, the assumed effect of the intervention on the primary outcome of the study and the variability of the progression rate, apart from the alpha and power, are the driving forces of the sample size. Van den Berkmortel and coworkers unfortunately did not provide information on sample size assumptions. Based on the start of the study with 127 subjects to intervene upon and the 50 nonsmoking control subjects, one may come up with an effect size of ~100% (no progression in the intervention group compared with controls), assuming a two-sided alpha of 0.05, a 80% power, a two-year CIMT progression of 0.02 mm, and a standard deviation (SD) of the progression rate of 0.05. If we assume an SD of 0.02 (table 2 in Van den Berkmortel’s paper), the effect of quitting smoking should be around a 60% reduction in progression. However, based on the literature, the annual difference in CIMT progression between quitters and those continuing to smoke is around ~0.0035 for white middle-aged women and ~0.0014 mm for white middle-aged men, constituting much smaller differences in effect than assumed above. In fact, the study by Van den Berkmortel and coworkers was based on the comparison of 35 quitters (instead of 127) with 50 controls. The posterior power calculation, assuming a 100% reduction, indicated a power of 47%. This may indicate that there is a large probability of falsely saying that ‘it is true that quitting smoking has no effect on progression of CIMT or arterial stiffness’.

In conclusion, the authors are to be complimented on their efforts to conduct a study on the effects of quitting smoking on progression of CIMT and arterial stiffness. There may be some possibilities to perform further analyses on the data in order to reduce measurement variability. Yet, the study is likely underpowered to conclude that quitting smoking has no effects on progression of CIMT or arterial stiffness. In light of the adverse effects of smoking on cardiovascular and cancer risk, the authors are correct to conclude that ‘Despite the study results, cessation of smoking should be recommended’.

REFERENCES

On the 2nd of March 2004, Willem Erkelens, a longstanding member of the editorial board, died at the age of 62 years. Willem was professor of internal medicine at the University Medical Centre in Utrecht and one of the most prominent internists in the Netherlands. As a clinician, a scientist and a teacher, he contributed greatly to internal medicine and to the Netherlands Journal of Medicine.

His critical approach, his knowledge of internal medicine as well as his wit were among his strong personal traits. Over the last 30 years Willem Erkelens published at least 20 papers in the Netherlands Journal of Medicine, most of which were original articles dealing with his favorite scientific topics, diabetes and lipid metabolism.

Among Professor Erkelens’ most recent accomplishments, his initiative and effort to rephrase the physicians’ oath should be mentioned. The new oath is a meaningful, contemporary text, really confronting the physician with the do’s and don’ts in medicine.

The Editors are grateful for his contributions and will remember him because of his qualities as a doctor, teacher, scientist and friend.
Nonalcoholic steatohepatitis

P.L.M. Jansen

Department of Gastroenterology and Hepatology, Academic Medical Centre, PO Box 22660, 1100 DD Amsterdam, the Netherlands, e-mail: pljansen@amc.uva.nl

ABSTRACT

Nonalcoholic steatohepatitis (NASH) is an underdiagnosed liver disease characterised by steatosis, necroinflammation and fibrosis. This disease may eventually develop into cirrhosis and hepatocellular carcinoma. NASH is highly prevalent among obese individuals and among patients with diabetes mellitus type 2. Nonalcoholic fatty liver (NAFL), a precursor of NASH, is the main cause of elevated serum liver enzymes among the general population. Insulin resistance is a major aetiological factor in NASH. Gradual weight loss, physical exercise and drugs that improve insulin sensitivity are potential therapies.

Asymptomatic individuals with some degree of hepato-megaly may have NAFL but even without any signs or symptoms, the liver may contain too much fat. This became apparent in the screening of potential donors for living-related liver transplantation wherein histological examination of a liver biopsy is a standard procedure. Completely asymptomatic persons may have a steatotic liver and have to be excluded from liver donation. Steatotic livers show a high degree of initial poor function and have an impaired capacity to regenerate. Steatosis is also more common than hitherto realised in the elderly.

The transition of NAFL to NASH is not clearly demarcated. In both conditions liver enzymes may be elevated and the liver fat content, as diagnosed by ultrasonography, may be equal. Inflammation and fibrosis are features of NASH. Thus, for the differentiation of NAFL and NASH, a liver biopsy is needed. NASH is a major cause of so-called cryptogenic liver cirrhosis. The diagnosis of NASH is missed in these patients because the steatosis often disappears once cirrhosis develops. The prognosis of NASH-related cirrhosis was worse than that of hepatitis C-related cirrhosis in one study (three-year survival 50 vs 70%), but showed no difference in another study. Both conditions may give rise to hepatocellular carcinoma and both may recur after liver transplantation.

PATHOLOGY

The pathology of NASH was first described by Ludwig. The pathology of NASH was first described by Ludwig. It is characterised by macrovesicular steatosis, hepatocellular inflammation and fibrosis.
cellular ballooning and mild lobular inflammation with scattered polymorphonuclear leucocytes and monocytes (table 1). Perisinusoidal or pericellular (chickenwire) fibrosis is present, in particular in acinar zone 3. Mallory bodies are occasionally seen but are not necessary for the diagnosis. Liver histopathology in alcoholic liver disease and NASH is very similar. Cholestasis is not a feature of NASH but often occurs in alcoholic liver disease. Likewise central-central and central-portal bridging necrosis frequently occurs in alcoholic liver disease but is uncommon in NASH. Macrovesicular steatosis is a common feature of a variety of liver diseases including hepatitis C, Wilson’s disease, alcoholic liver disease, primary biliary cirrhosis and toxic liver injury (table 2). All features of NASH may be present in hepatitis C but then the inflammation and fibrosis are mainly localised in the portal or perportal areas. Ballooning degeneration, Mallory’s hyaline and fibrosis are discriminating features suggestive of progressive NASH.

Table 1
Histopathology of NASH

- Necessary components
  - Steatosis (macro > micro)
  - Hepatocellular ballooning
  - Mixed mild lobular inflammation
- Usually present
  - Zone 3 perisinusoidal/pericellular fibrosis
  - Zone 1 hepatocellular glycogenated nuclei
  - Small lipogranulomas, acidophil bodies, PAS-positive Kupffer cells
- Maybe present
  - Mallory’s hyaline
  - Hepatocellular iron granules in zone 1
  - Megamitochondria
- Unusual for NASH
  - Predominantly microvesicular steatosis
  - Sclerosing hyaline necrosis
  - Veno-occlusive lesions, phlebosclerosis, perivenular fibrosis
  - Portal changes
  - Acute/chronic cholestasis


ASSOCIATIONS
NASH is associated with central obesity, diabetes type 2, syndrome X (obesity, dyslipidaemia, insulin resistance and hypertension), polycystic ovary syndrome and hyper-triglyceridaemia. Almost all patients with NASH are insulin resistant. It is clear that insulin resistance must play a key role in the pathogenesis of NASH. However, insulin resistance, hyperinsulinaemia and hyperglycaemia are not limited to NASH but also occur in other liver diseases such as hepatitis C. In contrast to alcoholic liver disease, liver pathology in patients with NASH does not disappear upon complete abstinence. As for obesity, a person does not have to be morbidly obese to have NASH. In moderately overweight patients with elevated serum liver enzymes (BMI >25 kg/m²), NASH with septal liver fibrosis was present in 30% and cirrhosis in 11%. NASH is related to diabetes mellitus type 2 but its true incidence among these patients is unknown. NASH is increasingly recognised among obese children.

DIAGNOSIS
NASH is an underdiagnosed disease. For its diagnosis a liver biopsy is required. This undoubtedly constitutes a threshold for its detection among obese and diabetic popula-
ations. Indeed a liver biopsy in obese people carries an increased risk. Moreover, a liver biopsy is too invasive for screening purposes. Ultrasonography misses about one third of cases. Most patients with NASH have elevated serum aminotransferases and many have some degree of hepatic steatosis. However, normal liver enzymes and a normal liver size do not exclude the diagnosis. Elevated liver enzymes in target groups, such as obese persons, patients with diabetes mellitus type 2 and patients on total parenteral nutrition, should raise the level of suspicion and this may lead to a more frequent diagnosis of NASH. It is clear, however, that new diagnostic markers or noninvasive procedures to detect and quantify liver fat are needed. Magnetic resonance proton spectroscopy of the liver may be such a procedure.

PATHOGENESIS

In the pathogenesis of NASH two steps or ‘hits’ can be recognised (figure 1). Fat accumulation in the liver is the sine qua non, the ‘first hit’. Fat per se is not toxic and fat accumulation is to a certain degree a physiological response. In many species fat in the liver constitutes a rapidly mobilisable source of energy. For instance, migratory birds increase their liver (and body) weight considerably before migration. During the long migratory flights, triglycerides are hydrolysed and free fatty acids (FFA) are used as energy source for muscle action. However, fat in the liver is not innocuous. Fat makes the liver vulnerable to endotoxins and ischaemic reperfusion damage and fat impairs liver regeneration. Fat in the liver causes hepatic insulin resistance. Activation of a serine kinase cascade that leads to a defect of insulin signalling may be the underlying mechanism. Furthermore, insulin-mediated activation of sterol regulatory element-binding protein 1 (SREBP-1) stimulates lipogenic enzymes in and outside the liver.

Meanwhile apolipoprotein synthesis in the liver is impaired and this leads to a reduced production of very-low-density lipoprotein (VLDL), a lipoprotein that constitutes a rate-determining step in hepatic lipid export. Despite the active oxidation of FFA, influx and synthesis outweigh FFA degradation and secretion, the net effect being hepatic fat accumulation.

Reactive oxygen species (ROS) and inflammation represent the ‘second hit’. FFAs can in fact deliver both hits. When in abundance as in over-nutrition, FFAs in the liver contribute to the synthesis of triglycerides and the hepatic accumulation of fat. In addition, the oxidation of FFAs in mitochondria and peroxisomes contributes to ROS generation. FFAs are ligands for the peroxisomal proliferator-activated receptor α, PPARα. This stimulates mitochondrial and peroxisomal β-oxidation as well as the expression of several cytochrome P450s, in particular Cyp2E1 and Cyp4A.

CYP2E1 and CYP4A are elevated in patients with NASH. This shows that in these patients PPARα is indeed activated. PPARα is a master-regulator of FFA metabolism in the liver. PPARα-knockout mice on a high-fat diet develop severe hepatic steatosis. In contrast, activation of PPARα in mice on a high-fat diet prevents triglyceride accumulation. Oxidation of FFAs helps to clear the fat and the massive amounts of ROS produced under these conditions does not seem to harm the mouse liver. Thus, although ROS production and oxidative stress may set the scene for development of NASH, inflammation is a major additional factor in the transition of NAFL to NASH. FFAs may also play a key role here. FFAs directly stimulate lckβ/NFkB, factors involved in the inflammation cascade. Moreover, adipose tissue expresses TNFα, interleukin 6 and inducible nitric oxide synthase (iNOS). Therefore obesity is a pro-inflammatory condition and likewise in obese persons the liver is exposed to cytokines produced in their adipose tissues. Moreover, TNFα and interleukin 1 and 6 reduce the activity of Jun N-terminal kinase and this inactivates insulin receptor substrate with insulin resistance as a consequence. Thus insulin resistance is both cause and consequence of NASH.

Whether intestinal dysmotility and bacterial overgrowth also contribute to NASH is controversial. Bacterial overgrowth of the small intestine has been reported in NASH and conditions with bacterial overgrowth such as jejunoileal bypass cause NASH. It can be hypothesised that lipohilic endotoxins from the gut may accumulate in the fat of hepatocytes from where they are slowly but continuously released. This stimulates Kupffer cells to produce TNFα, interleukin 1 and 6 and the profibrotic cytokine TGFβ. TGFβ stimulates the transformation of hepatic stellate cells into collagen-producing myofibroblasts. In addition, chemokines are produced that attract monocytes and neutrophils which greatly contribute to the perpetuation of oxidative stress and cell injury.

Adiponectin deficiency may be important in the development of NASH. Adiponectin (also known as 30-kDa adipocyte complement-related protein; Acrp30) is a hormone produced by peripheral adipose tissue. It circulates in the blood in a globular form and as a full-length molecule. Liver and muscle have adiponectin receptors. Stimulation of the adiponectin receptor in the liver leads to the activation of AMP-activated protein kinase and PPARα. Thus, adiponectin increases fatty acid β-oxidation thereby decreasing the hepatic triglyceride content and ameliorating insulin resistance. Adiponectin-deficient mice show an increased sensitivity to carbon tetrachloride-induced liver damage. The liver damage in these mice could be significantly attenuated by administration of recombinant adiponectin.

Also other studies show that adiponectin has a protective effect on liver damage. Adiponectin-deficient mice show an increased sensitivity to carbon tetrachloride-induced liver damage. The liver damage in these mice could be significantly attenuated by administration of recombinant adiponectin.

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Also other studies show that adiponectin has a protective effect on liver damage. Adiponectin-deficient mice show an increased sensitivity to carbon tetrachloride-induced liver damage. The liver damage in these mice could be significantly attenuated by administration of recombinant adiponectin.

Thus, although ROS production and oxidative stress may set the scene for development of NASH, inflammation is a major additional factor in the transition of NAFL to NASH. FFAs may also play a key role here. FFAs directly stimulate lckβ/NFkB, factors involved in the inflammation cascade. Moreover, adipose tissue expresses TNFα, interleukin 6 and inducible nitric oxide synthase (iNOS). Therefore obesity is a pro-inflammatory condition and likewise in obese persons the liver is exposed to cytokines produced in their adipose tissues. Moreover, TNFα and interleukin 1 and 6 reduce the activity of Jun N-terminal kinase and this inactivates insulin receptor substrate with insulin resistance as a consequence. Thus insulin resistance is both cause and consequence of NASH.
effect on the liver where it decreases necrosis and inflammation. In NASH, obesity and type 2 diabetes mellitus, adiponectin production is decreased. In the absence of this protective factor the liver is vulnerable to the action of cytokines and ROS.

THERAPY

Treatment of NASH has to be seen against this pathophysiological background (table 3). Lifestyle adjustments should be tried first: weight reduction in combination with exercise is the most rational remedy. Unfortunately compliance in obese people is low and episodic rapid weight loss, followed by binge eating and weight gain, is counterproductive. Thus, diets may often make things worse, in particular when they lead to a yo-yo effect on body weight. Programmed exercise would be a rational therapy. It diverts the fatty acids away from the liver to be metabolised in the muscles and it decreases insulin resistance.

Diets with polyunsaturated fatty acids are effective and have a sound physiological background. Polyunsaturated fatty acids stimulate PPARα and repress the sterol regulatory element-binding protein SREBP-1. Indeed, disruption of the SREBP-1 gene in leptin-deficient ob/ob mice causes a reduction of lipogenesis and clearance of liver fat but did reduce obesity and insulin resistance. Polyunsaturated fatty acid-enriched diets in ob/ob mice reduced both hepatic steatosis and insulin resistance.

Stimulation of PPARα by drugs could be an effective therapy. Gemfibrozil showed a positive effect in a small pilot study. A recent study showed that arachidyl-amido-cholanoic acid, a liver-specific agent with presumed PPARα...
agonistic activity, prevents diet-induced fatty livers in rodents.66 Drug therapy should aim at several levels and it is unlikely that a single drug could do the job. Anti-inflammatory, antioxidative, cytoprotective and lipolytic agents have been tried but given alone none of these have been shown to be very effective. For example, supplementation with vitamin E is ineffective54 but vitamin E in combination with vitamin C has shown to reduce fibrosis in a small randomised study.67 Current trials focus on drugs that increase insulin sensitivity. Metformin was successfully tried in an animal model of NASH, the leptin-deficient ob/ob mouse.68 In an uncontrolled clinical trial metformin improved insulin resistance, decreased aminotransferase levels and reduced hepatomegaly69 but larger randomised controlled studies are needed to prove its effect. The PPARγ ligand troglitazone also showed benefit in NASH patients but later was implicated in severe liver toxicity.70,71 Rosiglitazone has been tried with success in a small uncontrolled trial. Twenty-five of 30 patients with NASH completed 48 weeks of treatment. Serum aminotransferase levels and necroinflammatory score, steatosis and fibrosis improved but an undesirable weight gain occurred in 67% of these patients.72 A recent trial showed that pioglitazone may be effective.73 The thiazolidinediones have a direct effect on PPARγ in hepatic stellate cells. Activation of PPARγ in hepatic stellate cells retards collagen synthesis and fibrosis both in vitro and in vivo.74 Thus, PPARα and PPARγ agonists, as well as drugs that stimulate adiponectin release from adipose tissue, may hold promise for treatment of NASH. Activation of PPARα to stimulate β-oxidation in muscle may be another way to go.75 Finally, decompensated NASH-related cirrhosis is an indication for liver transplantation76 and this condition is rapidly becoming a common indication for liver transplantation.

**CONCLUSION**

NASH is an underdiagnosed disease. The incidence among patients with diabetes mellitus type 2 and obese people is particularly high. NASH may lead to progressive liver
disease, cirrhosis and hepatocellular carcinoma. It also occurs in obese children. For its unequivocal diagnosis a liver biopsy is necessary. Insulin resistance, steatosis, oxidative stress and inflammation play a major role in its pathogenesis and disease progression. Gradual weight reduction and exercise programmes constitute the most rational therapies but are hard to sustain. Medical therapy aims at amelioration of the insulin-resistant state and for this various drugs are under trial. The role of adiponectin and its possible therapeutic implications needs to be investigated.

REFERENCES


Video capsule endoscopy: procedure, indications and diagnostic yield

S.A.C. van Tuyl¹, E. J. Kuipers², R. Timmer¹, M.F.J. Stolk¹*  

¹Department of Gastroenterology, St. Antonius Hospital, PO Box 2500, 3439 EM Nieuwegein, the Netherlands, tel: +31 (0)30-6099111, fax: +31 (0)30-6056357, e-mail: m.stolk@antonius.net,  
²Department of Gastroenterology, Erasmus University Medical Centre, Rotterdam, the Netherlands, *corresponding author

ABSTRACT

Video capsule endoscopy (VCE) is a new noninvasive imaging technique for the complete small bowel. It provides good to excellent visualisation of the mucosa of the small bowel and has a high diagnostic yield in selected patients with gastrointestinal blood loss of suspected small bowel origin and in patients with Crohn’s disease. In comparison with small bowel X-ray and push enteroscopy, diagnostic yield appears to be superior. Although VCE is becoming increasingly popular, good studies on its clinical implications and application are only just emerging. In this paper we review the possibilities and limitations of clinical application of VCE.

INTRODUCTION

In the late 19th century, gastroenterology was among the first recognised medical specialities. Gastroenterologists had a great need for visualisation of the gastrointestinal tract but for a long time they were only equipped with rigid endoscopy and bowel X-ray. The introduction of flexible endoscopy in the early 1970s largely changed medical practice, with one exception. The small bowel distal of Treitz’s ligament to the terminal ileum remained a blind spot for endoscopy. Several important diseases such as Crohn's disease, angiodysplasias and tumours are frequently found in this part of the small bowel and often lead to clinical symptoms, such as bleeding or obstruction. Until recently the small bowel was examined by enteroclysis, computed tomography, push enteroscopy or by peroperative enteroscopy. VCE is a new diagnostic tool that can provide images of the entire small bowel in a noninvasive way.

Several papers and numerous abstracts have been published on the use of VCE. In this review the technical aspects of the procedure, indications and diagnostic yield will be discussed.

PROCEDURE OF VIDEO CAPSULE ENDOSCOPY

The video capsule is a small device with a diameter of 11 mm and a length of 26 mm which can be swallowed. It contains six light-emitting diodes, a lens, a colour camera chip and two batteries. The colour camera chip can operate at very low levels of illumination. In the rear dome of the capsule a transmitter and an antenna are located. The capsule obtains two images per second and transmits the data to eight aerials attached to the abdominal wall of the patient. These aerials are connected to a recording device. The recorder and a battery are worn in a belt around the waist. After an overnight fast, the patient swallows the capsule, which is propelled by intestinal peristalsis (figure 1). Four hours after ingestion of the capsule, a light meal and a drink are allowed. During the procedure patients can move around freely. After seven to eight hours an indicator on the recorder shows if the capsule has run out of power. The capsule is finally passed with the stools and is not reusable. Eight hours after capsule intake, the recorder is connected into the workstation to download the images which are converted into a movie. Data are reviewed by looking at an operator-determined number of images per second with dedicated software. The best results are obtained in a dark environment because this enhances
Images with abnormalities can be selected and stored for review in a separate file. For an experienced investigator it takes about 45 minutes to interpret all the images. In our experience the learning curve comprises about ten investigations. Interobserver agreement appears to be high. Several software applications are available such as automated red detection, which enables fast selection of images with blood, and capsule localisation, which facilitates anatomic localisation of abnormalities. These applications need further development but might enhance diagnostic efficacy in the future.

**Indications and Contraindications**

The most important indication for VCE is obscure gastrointestinal bleeding of suspected small intestinal origin. Patients with iron-deficiency anaemia, melaena or haematochezia are good candidates for VCE when gastroduodenoscopy and colonoscopy are normal (figure 2). Another important indication is suspected small bowel Crohn’s disease (figure 3). The indications for VCE will probably expand in the near future based on ongoing research in patients with other diseases, such as celiac disease, small bowel tumours, Rendu-Osler-Weber disease, polyposis syndromes and small bowel transplantation.

The main contraindication is the presence or suspicion of small bowel stenosis due to previous gastrointestinal surgery, a tumour or fibrotic strictures. This may lead to capsule retention and obstruction. In patients who have undergone gastric surgery or with gastroparesis, the capsule can be placed endoscopically in the small intestine at the start of the investigation. Other contraindications for VCE are difficulty with swallowing, pregnancy or the presence of implanted electronic medical devices such as pacemakers.

**Passage, Retention and Obstruction**

Stomach passage takes an average of 34 minutes and the small intestine is passed in about four hours. This means that the average passage to the caecum takes 4.5 hours. Visualisation of the complete length of the small bowel up to the caecum is achieved in 80% of the patients. In the remaining 20%, batteries are worn out before the capsule reaches the caecal valve. In the newer-generation capsule, improved batteries with a life-span of eight instead of six hours have been introduced. This is likely to increase the proportion of patients with complete small bowel visualisation. In 0 to 5% of patients, retention of the capsule proximal to a previously undiagnosed obstruction is reported. This generally does not produce any symptoms because real

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**Figure 1**
**Duodenal mucosa with characteristic villi**

**Figure 2**
**Small intestinal angiodysplasia**

**Figure 3**
**Ileal ulceration in a patient with Crohn’s disease**
impaction of the capsule seldom occurs.15,16 The capsule can remain in the intestines for at least three months. If the capsule is retained in the stomach or colon, it can be removed endoscopically. Otherwise, surgery is necessary to remove the capsule. During surgery, serious abnormalities are usually found at the level of obstruction, such as fibrotic or inflammatory stenosis or tumour.

**DIAGNOSTIC YIELD**

Most studies on diagnostic yield of VCE comprise patients with obscure occult or overt gastrointestinal bleeding (OGIB). Combined data from several studies show that the diagnostic yield in this patient population varies between 60 and 92%.3-9,14,16 This is very high when taking into account that all patients were extensively examined by other means before capsule endoscopy was applied. Unfortunately, however, most studies do not classify lesions as possibly or definitely responsible for haemorrhage. This might cause considerable bias in assessing diagnostic yield. In our experience, the most frequent finding in OGIB is small bowel angiodysplasia.14 In patients with Crohn’s disease, with or without suspected small bowel involvement, the diagnostic yield varies between 60 and 70%.10-13 Capsule endoscopy frequently reveals previously undiagnosed ulcers or focal villous denudation (figure 4).17 If in the near future capsule endoscopy were to gain acceptance as a first-line diagnostic tool, diagnostic yield would be likely to decrease in less strictly selected cases, such as patients with intestinal bleeding more than ten days before video capsule endoscopy16 or patients with abdominal pain and no other abnormalities.

**COMPARISON WITH OTHER TECHNIQUES**

Several studies have compared diagnostic yield of capsule endoscopy with small bowel X-ray examination.8,11 Enteroclysis in patients with OGIB has a diagnostic yield of 20% and in Crohn’s disease of 37%, while capsule endoscopy has a yield of 85 and 70% respectively. This is not surprising since enteroclysis will not easily detect flat or mucosal abnormalities. Other investigators have compared the yield of VCE and push enteroscopy.4,7,18 Push enteroscopy is a technique by which a dedicated long endoscope is introduced as far as possible in the small intestine in a sedated patient. Push enteroscopy appears to be inferior to VCE with regard to diagnostic yield (about 35% vs about 65%) since the capsule examines the whole small bowel and push enteroscopy only the upper part. A serious advantage of push enteroscopy is that when abnormalities are found, biopsies can be taken and therapeutic interventions such as plasma argon coagulation can be carried out. Diagnostic yield of video capsule endoscopy is comparable with intraoperative enteroscopy, which offers visualisation of the complete small intestine. This is, however, invasive and is likely to carry a higher risk of complications.19 Recently, a new double-balloon endoscope was introduced enabling visualisation of the entire small bowel. The technique is based on sequential inflation and deflation of two balloons, one attached to the tip of the endoscope, the other to an overtube, allowing stepwise progression of the tip of the endoscope through the small bowel. With this endoscope biopsies can be taken and therapeutic interventions can be performed.20,21 Future research will certainly focus on the comparison between VCE and this technique.

**CLINICAL IMPLICATIONS OF VCE**

To date, very few published data are available on the long-term effects of video capsule endoscopy results on patient outcome. Data from several preliminary reports suggest that VCE changes clinical decisions and treatment in 25 to 87% of patients.16-22 The clinical implications vary widely, due to different patient populations, different criteria for measuring effects, short follow-up periods and lack of a gold standard for diagnosis and treatment. However, clinical implications are still impressive since before the advent of VCE all treatment options were usually exhausted for these patients. Controlled long-term follow-up studies for distinct indications are needed to establish the real clinical value of VCE. It also appears that VCE performs optimally in strictly selected patient populations. Application in a general population will grossly decrease its yield.
CONCLUSION

VCE is a promising diagnostic tool for noninvasive investigation of the small bowel. The most important current indications are OGIB with or without anaemia with negative gastroscopy and colonscopy, and suspicion of small bowel Crohn’s disease. The diagnostic yield of VCE appears to be high and is probably superior to enteroclysis and push enteroscopy. However, the yield may decrease when it is performed as a first-line diagnostic tool. The major disadvantage of the procedure is the inability to take biopsies or perform coagulation of bleeding spots. Long-term follow-up studies are needed to evaluate the impact of VCE on disease management and on patient health. Only then can its position in medical management of OGIB and Crohn’s disease be established.

REFERENCES

ABSTRACT

Background: The inverse relation between high-density lipoprotein cholesterol (HDL-C) and cardiovascular (CV) disease underscores the need for clinical evaluation of the effect of HDL-C increasing drugs on the prevalence of CV disease.

Methods: We review the efficacy of Niaspan on serum lipids and the occurrence of side effects either alone or in combination with statins, in randomised controlled trials (RCT) and comparative cohort trials (CCT).

Results: In four RCTs, low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and lipoprotein(a) (Lp(a)) were decreased by 13, 26, and 17%, respectively, whereas HDL-C increased by 18%. In four CCTs a combination of Niaspan and statins showed an additional 22% reduction in LDL-C, 8% in TG and 6% in Lp(a) levels, compared with Niaspan monotherapy. Statin therapy had a minor additional effect of 1% on a total of 25% HDL-C increase during Niaspan treatment. Flushes occurred in 69% of the patients without any additional toxicity during combination therapy.

Conclusion: Niaspan effectively raises HDL-C with concomitant beneficial effects on TG and LDL-C. Niaspan can be combined safely with statins and is also effective in patients with combined dyslipidaemia and type 2 diabetes mellitus. Trials on CV endpoints evaluating the effect of statins with Niaspan are urgently needed to settle whether this combination can confirm the high expectations for cardiovascular outcome.

INTRODUCTION

During the last two decades the beneficial effect of statin therapy on cardiovascular morbidity and mortality has been confirmed in numerous large primary and secondary prevention trials that included an unprecedented number of patients, exceeding 65,000 subjects. Recent reports continue to extend the importance of low-density lipoprotein cholesterol (LDL-C) lowering in showing that even subjects with apparently ‘normal’ cholesterol benefit from statin treatment. However, in spite of this breakthrough, between 65 and 80% of all coronary events cannot be prevented by statin therapy, at least not during the intervention period of most trials. This disappointing percentage has intensified the search for novel drug targets to further improve cardiovascular outcome. Amongst these, strategies aimed at increasing high-density lipoprotein cholesterol (HDL-C) levels hold great promise.

The importance of HDL-C as a pivotal defence mechanism against atherosclerosis has been substantiated by population studies, showing that the level of HDL-C is a powerful and independent inverse predictor of premature CHD. In line, low levels of HDL-C are the most commonly encountered dyslipidaemia in patients with premature myocardial infarction, ranging up to 40% in prevalence. The impact of low HDL-C as atherogenic risk factor increases dramatically when viewed against the background of the worldwide epidemic of obesity and the metabolic syndrome. Based on available data, it can be calculated that coronary risk increases by 1 to 2% for every 1% reduction in HDL-C level. In spite of these strong observational findings, the implications of increasing HDL-C levels for cardiovascular outcome remain to be established. The lack of selective and efficacious drugs to increase HDL-C forms the main
reason for the lack of intervention studies. Lifestyle interventions, such as smoking cessation, exercise and alcohol use, are associated with only a modest increase of HDL-C.

Pharmacological modalities that raise HDL-C are statins, fibrates and nicotinic acid and its derivate. Statins increase the concentration of HDL-C by up to 5 to 10%. Fibrates lower plasma triglyceride by up to 50% and increase HDL-C by 5 to 25%, mainly through activation of the PPARα nuclear receptor. Indeed, intervention studies using fibrates have provided evidence that increasing HDL-C may constitute an important pharmaceutical target for cardiovascular prevention. Thus, in the VA-HIT trial, gemfibrozil significantly reduced CHD events from 21.7% in the placebo group to 17.3% in the active treatment group.8 In this trial, LDL-C levels were not significantly lowered, whereas HDL-C levels were increased significantly. In addition, multivariate regression analysis showed that the increase in HDL-C was the only lipoprotein change that predicted benefit.9 These data are supported by the outcome of the Helsinki Heart Study (HHS).10 In this study, the primary endpoint (CHD events) was significantly reduced in the gemfibrozil group (2.7%), compared with the control group (4.1%). The results of these studies stress the need for further studies on the effects of pharmacological interventions resulting in increased HDL-C levels on CHD.

One of the oldest and most potent HDL-C increasing drugs is niacin. Niacin was first introduced as a lipid-lowering agent in 1954.11 The mechanism by which niacin affects lipids and lipoproteins involves several pathways. Niacin stimulates the synthesis of both apo A-I and apo A-II.12 In addition, it has been suggested that niacin reduces hepatic lipase activity, resulting in reduced hepatic removal of this particle.13 Niacin also decreases the rate of hepatic very-low-density lipoprotein cholesterol (VLDL-C) and LDL-C synthesis, without affecting faecal excretion of fats, sterols, or bile acids. Shortly after its introduction, immediate-release niacin (IR-niacin) was shown to have beneficial effects on cholesterol and lipid metabolism. Despite its efficacy in increasing HDL-C and lowering triglycerides (TG), its side effects precluded broader clinical use of IR-niacin in patients.14 The most common side effects were flushing and skin rash.15 In an attempt to minimise potential side effects, slow-release formulations of niacin (SR-niacin) have been developed without great success.16,17 Besides an unfavourable side-effect profile, SR-niacin also proved to be less efficacious in treating dyslipidaemias compared with IR-niacin.18 The most recently developed compound in this class is Niaspan, an extended-release form of niacin. During the last five to six years, Niaspan was tested in numerous clinical trials, addressing safety and efficacy, both as monotherapy and in combination with other lipid-lowering drugs, such as statins and fibrates. In the next section, we will discuss the clinical trials conducted with Niaspan from 1996 until January 2004.

MATERIALS AND METHODS

A literature search of the MEDLINE database (1996 to January 2004), using the keywords niacin, nicotinic acid, lipoproteins, statins and coronary artery disease, was performed. The search was restricted to studies published in English-language journals, conducted in human subjects, and classified as clinical trials in the MEDLINE database. For inclusion, a study had to meet the following criteria: (i) random allocation of study participants to extended-release niacin vs a placebo-control group or random allocation of study participants to extended-release niacin vs extended-release niacin in combination with a statin, (2) changes in lipid profile as the primary endpoint, and (3) studies which included patients treated with an HMG-CoA reductase inhibitor were required to have an LDL-C level of at least 3.4 mmol/L (130 mg/dl). The contents of 138 abstracts or full-text manuscripts identified during our literature search were reviewed by one author (R.B.) for inclusion. Of these abstracts and manuscripts, 18 Niaspan treatment trials were identified. Other publications included reviews and secondary analysis of data from the 18 published trials. Four RCTs and four CCTs studies matched the inclusion criteria. The highest dose and the longest treatment period were selected to calculate the pooled effect on serum lipids in this analysis. The data collected for the measurement of the weighted mean difference for continuous data were: (1) the mean change in serum lipids (LDL-C, TG, lipoprotein(a) (LP(a)) and HDL-C) from baseline to follow-up in millimoles per litre (mmol/l), (2) the standard deviation (SD) of the mean difference, and (3) the number in each comparison group (n) at follow-up. Estimates of the average effect of Niaspan on serum lipid values and 95% confidence intervals (95% CI) were calculated with models based on random-effects model.

RESULTS

Efficacy and safety of Niaspan in randomised, placebo-controlled trials

The general characteristics of the four randomised, placebo-controlled, double-blind trials included in this analysis are presented in table 1.18,19 A total of 522 patients met the inclusion criteria for RCTs with Niaspan. The total duration of treatment was 70 weeks with a mean follow-up time of 18 weeks. The mean age was 55 years with a male-to-female ratio of 1.8. The mean dosage was 1.5 g Niaspan per day (1-3 g/d). One trial was conducted in patients with secondary dyslipidaemia in type 2 diabetics,19 whereas the other
three trials were conducted in patients with hypercholesterolaemia.18-20,22 In the trial by Grundy et al.,21 participants were included if they were taking statins, provided that their LDL-C was at least 3.4 mmol/l (130 mg/dl). Analysis showed significant changes in lipid profile: 13% mean reduction in LDL-C (95% CI -12.76 [-2.96 to -22.55]), 26% mean reduction in triglycerides (95% CI -25.91 [-20.89 to -30.93]), 17% mean reduction in Lp(a) (95% CI -17.36 [-17.81 to -16.90]), and an 18% mean increase in HDL-c (95% CI 17.86 [13.39 to 22.32]). The highest dose of Niaspan (3 g/day) resulted in an HDL-C increase of 28% (95% CI [27.59 to 39.66]). The effects of various doses of Niaspan on HDL-C or shown in table 2. Overall 69% of the study participants experienced flushes vs 10% of the participants who were allocated to placebo (RR 6.12, 95% CI 4.10-9.13, p<0.00001).

In the Niaspan treatment group, 22 patients (RR 6.87, 95% CI 1.53-30.85) experienced pruritus and/or rash whereas one patient in the placebo group complained of this symptom. There were seven patients with increased transaminase levels (>2 times the upper reference limit) in the Niaspan treatment group (RR 3.51, 95% CI 0.63 to 19.49, p=0.15) and none in the placebo group. Myopathy (defined as CPK >10 times the upper reference limit with myalgia) was not evident in either group. Twenty subjects (10%) in the placebo group discontinued the study compared with 116 patients (34%) in the Niaspan treatment group (p<0.00001). The most common reason for discontinuation of the drug was the occurrence of skin flushes.

**Efficacy and safety of Niaspan in comparative cohort studies**

Four comparative, uncontrolled, open-label trials with Niaspan were included in this analysis.23-26 The general characteristics are presented in table 1. A total of 1153 patients met the inclusion criteria for CCTs with Niaspan vs Niaspan and statins. The total duration of treatment was 164 weeks with a mean follow-up time of 41 weeks. The mean age was 57 years with a mean female ratio of 2.9. The mean dosage was 2 g Niaspan per day (1.3 to 2.8 g/d). One trial was conducted in patients with diabetes type 2 and secondary dyslipidaemia,25 whereas in two trials patients with hypercholesterolaemia and in one trial patients with combined hyperlipidaemia were included. Analysis showed significant changes in lipid profile: 22% more reduction of LDL-C in favour of the Niaspan and statin combination treatment group vs the Niaspan monotherapy group (95% CI 21.99 [21.75, 22.41], p<0.00001), 8% more reduction in TG in favour of the Niaspan and statin combination treatment group (95% CI 8.28 [7.89, 8.67], p<0.00001), 6% more reduction in Lp(a) in favour of the Niaspan monotherapy group (95% CI -5.91 [-6.93, -4.88]; p=0.10), and a modest change of a 1% higher increase in HDL-C (p<0.0001) in favour of the Niaspan and statin combination treatment groups (95% CI 0.81 [0.60 to 1.02]). Overall 63% of patients who received Niaspan monotherapy experienced flushes vs 60% of patients who were allocated to the Niaspan and statin combination treatment group. A total of 33% of patients experienced pruritus and/or rash in the Niaspan monotherapy group vs 13% of patients in the Niaspan and statin combination treatment group (p=0.006). There were 14 patients with increased transaminase levels (>2 times the upper reference limit) in the Niaspan monotherapy group compared with six patients in the Niaspan and statin treatment group (NS). In the Niaspan monotherapy group, 323 subjects (50%) discontinued the study compared with 138 patients (29%) in the

**Table 1**

**General characteristics of randomised controlled trials and comparative cohort trials with Niaspan**

<table>
<thead>
<tr>
<th>SOURCE</th>
<th>YEAR</th>
<th>n, M/F</th>
<th>AGE (YEARS)</th>
<th>DOSE PER DAY</th>
<th>DURATION (WEEKS)</th>
<th>DYSLIPIDAEMIA</th>
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<tr>
<td>RCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Goldberg et al.18</td>
<td>1998</td>
<td>149 (3.1)</td>
<td>54</td>
<td>N 1.5 g</td>
<td>16</td>
<td>HC</td>
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<tr>
<td>Morgan et al.19</td>
<td>1998</td>
<td>96 (1.6)</td>
<td>50</td>
<td>N 1 &amp; 2 g</td>
<td>16</td>
<td>HC</td>
</tr>
<tr>
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<td>1998</td>
<td>149 (3.1)</td>
<td>54</td>
<td>N 1.5 g</td>
<td>16</td>
<td>HC</td>
</tr>
<tr>
<td>Grundy et al.21</td>
<td>2002</td>
<td>146 (1.4)</td>
<td>60</td>
<td>N 1 g &amp; N.i.5 g</td>
<td>16</td>
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<td>592 (1.9)</td>
<td>55</td>
<td></td>
<td>16</td>
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<tr>
<td>Capuzzi et al.22</td>
<td>1998</td>
<td>723 (2.3)</td>
<td>54</td>
<td>N 2 g &amp; S 10-20 mg</td>
<td>95</td>
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<td>Hunninghake et al.24</td>
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<td>175 (1.1)</td>
<td>59</td>
<td>N 2 g &amp; L 20-40 mg</td>
<td>28</td>
<td>HC</td>
</tr>
<tr>
<td>Van et al.25</td>
<td>2002</td>
<td>31 (5.9)</td>
<td>59</td>
<td>N 2.8 g &amp; A 80 mg</td>
<td>16</td>
<td>DM type 2</td>
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<tr>
<td>Capuzzi et al.26</td>
<td>2003</td>
<td>224 (2.6)</td>
<td>5</td>
<td>N 1.3 g &amp; R 10-40 mg</td>
<td>24</td>
<td>(F)CH</td>
</tr>
<tr>
<td>Pooled</td>
<td></td>
<td>1153 (2.9)</td>
<td>57</td>
<td></td>
<td>41</td>
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</tr>
</tbody>
</table>

**RCT** = randomised placebo controlled trial, **CCT** = comparative cohort trial, n = number of subjects, M/F = male/female ratio, N = Niaspan, A= atorvastatin, L= lovastatin, R= rosuvastatin, S = (any) statin, HC = hypercholesterolaemia, DM type 2 = secondary dislipidaemia in patients with diabetes mellitus type 2, (F)CH = (familial) combined hyperlipidaemia.
The most common reason for discontinuation was the occurrence of skin flushes.

DISCUSSION

These pooled data show that Niaspan has a distinct beneficial effect on the lipid profile in patients with hypercholesterolaemia, combined hyperlipidaemia and secondary dyslipidaemia in type 2 diabetes, including a net change of 0.20 mmol/l (18%) increase in HDL-C as well as significant LDL-C, TG and Lp(a) lowering. Combination therapy of Niaspan and statin does not convey additional toxicity, whereas the efficacy of both drugs is additive. The most important side effect of Niaspan is skin flushing, the severity of which decreases significantly over time.23 In spite of previous reports on insulin resistance during Niaspan therapy, this phenomenon appears to be clinically insignificant in the currently pooled studies, which also include a study in type 2 diabetic patients.27 Overall, Niaspan has proven to be an efficacious HDL-C increasing drug, which is able to fill an important gap in the currently available lipid-modulating pharmacological arena.

Clinical perspective

In the past decade, large statin trials have proven to be beneficial for cardiovascular prevention. Despite these successes more than 70% of coronary events cannot be prevented by statins. This concerning number, plus the epidemiological findings in large-scale prospective studies demonstrating an inverse relation between HDL-C and CHD, has to some extent directed the search for new therapeutic targets. In recent years increasing HDL-C on top of statins has emerged as a therapeutic option that holds great promise for cardiovascular prevention. Especially patients with the metabolic syndrome consisting of a low HDL-C, patients with CHD and patients with genetically determined low isolated HDL-C are expected to benefit from this new and promising therapeutic option in the years to come. Expectations have increased after completion of surrogate endpoint studies, showing a significantly greater reduction of carotid arterial intima-media thickness (IMT) during statin/colestipol/niacin therapy compared with statin monotherapy.28-30 In line, HDL-C increasing strategies have also been associated with improvements in endothelial function.31 Unfortunately, clinical endpoint studies showing survival benefit during combination therapy are scarce. Available data from, for instance, the VA-HIT study have predicted a 1 to 2% additional reduction in cardiovascular events for every 1% increase in HDL-C level.13 Extrapolation of these estimates would result in reductions in cardiovascular morbidity and mortality as high as 65 to 75% if statins are combined with drugs inducing a 20 to 30% increase in HDL-C.

Brown et al. reported outcome data from the FATS study, in which combinations of niacin/colestipol or lovastatin/colestipol were evaluated vs conventional therapy with placebo or colestipol, assessed in 176 patients.32 In the Niacin combination therapy group, HDL-C increased by 41%, whereas cardiovascular event rate was reduced by 72% at ten-year follow-up. In the HATS study, 160 patients with CHD, low HDL-C and normal LDL-C levels, were treated with simvastatin combined with either niacin (SR-niacin or IR-niacin) or placebo. The combination of

Table 2

<table>
<thead>
<tr>
<th>INDEX</th>
<th>DOSE NIASPAN (MG/DAY)</th>
<th>NIASPAN (n)</th>
<th>PLACEBO (n)</th>
<th>HDL-C (MMOL/L)</th>
<th>NET CHANGE (95% CI)</th>
<th>PERCENT CHANGE (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Goldberg et al.</td>
<td>3000</td>
<td>46</td>
<td>34</td>
<td>1.16</td>
<td>0.32</td>
<td>28</td>
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<tr>
<td>Morgan et al.</td>
<td>1000</td>
<td>39</td>
<td>37</td>
<td>1.11</td>
<td>0.14 -0.04 to 0.32</td>
<td>13</td>
</tr>
<tr>
<td>Morgan et al.</td>
<td>2000</td>
<td>41</td>
<td>37</td>
<td>1.11</td>
<td>0.17 0.002 to 0.3</td>
<td>15</td>
</tr>
<tr>
<td>Knopp et al.</td>
<td>1500</td>
<td>74</td>
<td>72</td>
<td>1.16</td>
<td>0.18 0.05 to 0.34</td>
<td>16</td>
</tr>
<tr>
<td>Grundy et al.</td>
<td>1000</td>
<td>45</td>
<td>49</td>
<td>1.06</td>
<td>0.24 0.14 to 0.34</td>
<td>23</td>
</tr>
<tr>
<td>Grundy et al.</td>
<td>1500</td>
<td>52</td>
<td>49</td>
<td>1.06</td>
<td>0.21 0.15 to 0.25</td>
<td>14</td>
</tr>
<tr>
<td>Pooled</td>
<td>297</td>
<td>278</td>
<td></td>
<td>1.12</td>
<td>0.20 0.15 to 0.25</td>
<td>14</td>
</tr>
</tbody>
</table>

CI = 95% confidence interval, n = number of subjects treated with either Niaspan or placebo. To convert values for HDL cholesterol from millimoles per litre to milligram per decilitre, multiply by 38.7. Net change is expressed as the change during active treatment minus the change during control.
In conclusion, randomised trials with Niaspan on top of statin therapy, evaluating the effect on clinical endpoints, are urgently awaited to settle whether this combination, having been proven safe and effective, can indeed live up to the high expectations for cardiovascular outcome.

ACKNOWLEDGEMENT

The authors wish to thank Dr Mark McGovern from Kos Pharmaceuticals, Florida, USA, for his efforts and contribution to this study.

REFERENCES


No, no! You can't stop smoking by yourself... You need my professional help!
Two years of smoking cessation does not reduce arterial wall thickness and stiffness

F.W.P.J. van den Berkmortel1,2,*, H. Wollersheim1, H. van Langen3, T.J. Smilde1, J. den Arend1, Th. Thien1

1Department of Medicine, Division of General Internal Medicine, 2Division of Medical Oncology 550, 3Clinical Vascular Laboratory of the University Medical Centre, University Medical Centre, St Radboud, PO Box 9101, 6500 HB Nijmegen, the Netherlands, tel:+31 (0)24-3615215, fax: +31(0)24-3540788, e-mail: f.vandenberkmortel@onco.umcn.nl, *corresponding author

ABSTRACT

Background: Smoking cessation rapidly reduces cardiovascular risk. The pathophysiological mechanisms involved are still being debated. We measured structural and functional arterial wall properties of the femoral and carotid arteries after smoking cessation to investigate their possible role in cardiovascular risk reduction.

Methods: Out of 127 smokers, 33 proved to stop smoking for two years. They were compared with 50 nonsmokers and 55 persistent smokers in a prospective study. Cross-sectional compliance and distensibility coefficients as well as intima-media thickness of both carotid arteries and of the right common femoral artery were measured ultrasonographically at baseline and 3, 6, 12 and 24 months after smoking cessation. The nonsmoking and persistent smokers group were measured twice at an interval of 24 months.

Results: Persistent smoking and two years of smoking cessation did not affect cross-sectional compliance and distensibility coefficients. Although at baseline intimal-medial layers were thicker in smokers, the change over time in intima-media thickness did not differ significantly between all three groups.

Conclusion: Two years of smoking cessation was not accompanied by a slower progression or a regression in intima-media thickness nor by an improved cross-sectional compliance or distensibility coefficient. Nevertheless, smoking cessation should be recommended as it reduces cardiovascular risk rapidly after smoking cessation.
femoral artery as well as of both carotid arteries. To study the effect of smoking and its cessation exclusively, the study population consisted of subjects free from symptomatic atherosclerotic disease and without further concomitant cardiovascular risk factors.

METHODS

Subjects
Altogether, 367 applicants responded to three advertisements in daily and weekly papers in the surroundings of Nijmegen, a medium-sized city (150,000 inhabitants) in the Netherlands. From this group 127 smokers with the intention to quit smoking during the study (QS), 60 persistent smokers (PS) and 56 nonsmokers (NS) met the inclusion criteria and agreed to participate. The QS still smoked from the time of inclusion to the first measurement. Smokers smoked at least five cigarettes a day for at least five years. Nonsmokers had either never smoked or had smoked previously, but not in the preceding five years. To be sure that we exclusively studied the effect of smoking, much attention was paid to include only subjects free of symptomatic atherosclerotic disease and without additional cardiovascular risk factors. Therefore, the following criteria for exclusion were applied: 1) demonstrated cardiovascular diseases; 2) irregular heart rhythm disturbances other than sporadic premature beats on electrocardiograms; 3) use of antihypertensives, lipid- or glucose-lowering medications or hormonal medicines including oral contraceptives; 4) absence of cardiovascular risk factors defined as obesity (body mass index >30 kg/m²), hypertension (systolic blood pressure exceeding 160 mmHg and/or diastolic blood pressure exceeding 95 mmHg) defined at two separate occasions, diabetes mellitus (history or symptoms of diabetes mellitus or nonfasting plasma glucose >11.1 mmol/l), hypercholesterolaemia (nonfasting total serum cholesterol >6.5 mmol/l) or a decreased ankle-arm pressure index (ankle-arm pressure index <0.85).

All participants filled in a questionnaire concerning their health, smoking behaviour and underwent a thorough physical examination to check if inclusion criteria were fulfilled, including a blood survey and electrocardiogram. The Medical Ethics Committee of the University Medical Centre of Nijmegen gave their approval to this study. All participants gave written informed consent.

Study design
The PS and NS were invited twice at an interval of 24 months for measurements of intima-media thickness (IMT) and arterial wall dynamics. The QS were measured before and 3, 6, 12 and 24 months after smoking cessation. The inclusion procedure for all participants as well as all dynamic vessel wall measurements were performed by the same person (FvdB) to aim at maximal accuracy. To avoid diurnal differences subsequent measurements were performed at the same time of day. Subjects were not allowed to smoke or to drink caffeine-containing beverages for one and ten hours prior to investigation, respectively. At each visit participants were asked about their health, smoking behaviour and use of medication. Morning urine samples were collected 3, 6, 12 and 24 months after smoking cessation for cotinine measurements.

Measurement of intima-media thickness
All scans were performed using a Biosound Phase 2 real-time scanner equipped with a 10 MHz transducer according to a validated protocol. IMT can only be determined accurately in the far wall position, because only the far wall IMT is defined by leading edges which enables correct ultrasonographic representation. Therefore, the far walls of the following sites were measured: 1) the distal 1 cm of the straight part of both common carotid arteries; 2) the right and left carotid bulb (from 1 cm proximal to the level of the flow divider); 3) the proximal 1 cm of both internal carotid arteries and 4) the right common femoral artery, 1 cm proximal of the bifurcation into the deep and superficial femoral artery.

All ultrasound scans were performed by three well-trained sonographers who regularly participate in quality control measurement sessions. The inter-sonographer variability that was determined in a group of subjects with normal IMT ranged from 2.5 to 6.4%. The coefficient of variation for subjects with increased IMT varied between 2.5 and 8.2%. Images were analysed using a semi-automatic software programme (Eurequa; TSA Company, Meudon, France) as previously described. Three measurements were made at each scan site. The average of the measurements was taken. The measurements were calculated by two readers with an inter-reader variability of less than 2%.

Measurement of dynamic vessel wall properties
Cross-sectional compliance (CC) and distensibility coefficients (DC) of separate arteries were assessed by measuring diameters (D) and diameter changes (ΔD) ultrasonographically using a vessel wall movement detector (Wall Track System®, Maastricht, the Netherlands) as described by the groups of Hoeks and Reneman. The system used in this study consisted of an ultrasound device with a 7.5 MHz transducer (Scanner 200, Pie Medical) and a data acquisition system, connected to a personal computer. All measurements were performed by one sonographer (FvdB), according to a protocol validated in our clinic. Tracings were recorded at the following sites: 1) the right and left common carotid arteries (2 cm proximal of the bulb), 2) the right common femoral artery (at least 1 cm proximal of the bifurcation into the deep and superficial femoral artery).
Smoking cessation

Smokers were not allowed to use nicotine replacement therapy during the 24-month cessation period. Smokers who had initially stopped were phoned weekly during the first three months for support. Thereafter they were contacted fortnightly.

Smoking cessation was considered successful when the participant stated being completely abstinent in addition to urinary cotinine concentrations below 300 ng/ml.

Quantitative measurements of metabolites of nicotine in urine

Concentrations of cotinine and 3-hydroxycotinine in urine samples were determined by the commercially available Double Antibody Nicotine Metabolite kit (EURO/DPC Ltd, United Kingdom: quality system ISO 9001/EN29001/BS 5750 part I) using liquid-phase radioimmunoassay.

Subjects with urinary nicotine metabolite concentrations exceeding 300 ng/ml were considered smokers. The cut-off value was determined by EURO/DPC Ltd, United Kingdom.

Data analysis

Statistical differences in baseline characteristics and structural and functional vessel wall variables between groups were analysed using a Mann-Whitney U test.

The effect of smoking on dynamic vessel wall properties and intima-media thickness was analysed firstly by Friedman tests followed by Wilcoxon signed-rank tests. P values less than 0.05 (two-sided) were considered significant.

RESULTS

Initially 127 QS (mean age: 43 ± 8 years) joined the study. Of the 44 subjects (35%) who completed the study, 11 were excluded because of: 1) admitting cigarette use (n=2), 2) urinary cotinine level exceeding 300 ng/ml (n=5), 3) use of oral contraceptives (n=2), 4) use of beta-adrenoceptor antagonists (n=2). Finally, 29% (n=37) of the smoking cessation attempts could be considered successful but 26% (n=33) were evaluable. From the PS and the NS, five and six subjects, respectively, were excluded due to the following reasons: 1) use of hormonal suppllement therapy or oral contraceptives (3 NS), 2) use of cholesterol-lowering medication (2 NS), 3) occurrence of a transient ischaemic attack (1 PS), 4) smoking cessation (1 PS), 5) death from unknown cause (1 PS), 6) lost from follow-up (1 NS and 2 PS).

Demographic data of the initial groups have been described earlier.14,22 The baseline characteristics of the eligible subjects are shown in table 1. Groups were very similar except for weekly alcohol consumption which was significantly higher in both smoking groups. PS had significantly more pack-years compared with QS (p=0.007).

To assess the effect of smoking cessation on IMT and arterial wall stiffness we first compared the changes of these parameters after 24 months between groups. In table 2 baseline values and the changes of IMT of all investigated arteries are shown.

Table 1

Baseline characteristics of the groups of smokers who quit (QS; n=33), persisting smokers (PS; n=55) and nonsmokers (NS; n=50) who successfully completed the study.

<table>
<thead>
<tr>
<th>GROUP</th>
<th>QS (N=33)</th>
<th>PS (N=55)</th>
<th>NS (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>43 ± 8</td>
<td>47 ± 11</td>
<td>46 ± 11</td>
</tr>
<tr>
<td>Number of males (%)/ females</td>
<td>18 (55)/15</td>
<td>34 (62)/21</td>
<td>26 (52)/24</td>
</tr>
<tr>
<td>Alcohol intake (units/week)</td>
<td>15 ± 12†</td>
<td>15 ± 17†</td>
<td>6 ± 10</td>
</tr>
<tr>
<td>Number of pack-years‡</td>
<td>19 ± 10¶</td>
<td>28 ± 17</td>
<td></td>
</tr>
<tr>
<td>Body mass index at inclusion (kg/m²)</td>
<td>23.3 ± 2.3</td>
<td>23.0 ± 3.0</td>
<td>23.6 ± 2.5</td>
</tr>
<tr>
<td>Body mass index after 24 months (kg/m²)</td>
<td>25.2 ± 2.5</td>
<td>23.6 ± 4.3</td>
<td>24.0 ± 2.6</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>127 ± 12</td>
<td>129 ± 14</td>
<td>130 ± 14</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>77 ± 7</td>
<td>79 ± 8</td>
<td>79 ± 8</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>68 ± 10</td>
<td>70 ± 11</td>
<td>65 ± 11</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.22 ± 0.93</td>
<td>5.04 ± 0.75</td>
<td>4.87 ± 0.92</td>
</tr>
<tr>
<td>Blood glucose (mmol/l)</td>
<td>5.16 ± 0.97</td>
<td>5.18 ± 0.81</td>
<td>4.95 ± 0.85</td>
</tr>
</tbody>
</table>

* Data are presented as mean ± S.D. † Calculations are performed with the assumption that one pack contains 25 cigarettes; ‡ p< 0.001, ¶p<0.01, §p<0.05 compared with NS; †p<0.01 compared with PS (Mann-Whitney U test).
**Table 2**
Baseline intima-media thickness (IMT) of both carotid arteries and of the right femoral artery and changes in these parameters in 24 months. Data are presented as mean ± SD.

![Table](https://example.com/table2.png)

**Table 3**
Baseline cross-sectional compliance (CC) and distensibility coefficients (DC) of both carotid arteries and of the right femoral artery and changes in these parameters in 24 months. Data are presented as mean ± SD.

![Table](https://example.com/table3.png)
In figures 1b and 1c the percentual changes after 3, 6, 12 and 24 months of smoking cessation in CC and DC of both common carotid arteries and of the right femoral artery when compared with baseline values are presented. Smoking cessation of a varied duration was not accompanied by significant changes in these parameters.

DISCUSSION

To our surprise, two years of smoking cessation was not accompanied by significant changes in arterial wall structure and in arterial wall function and therefore these changes cannot explain the rapid reduction in cardiovascular risk, as reported in the literature. This is the first longitudinal long-term study in which the effect of smoking cessation on structural and functional vessel wall properties is prospectively evaluated in a large cohort of QS. Moreover, the cohort consisted of a well-defined population sample in which most confounding factors were conscientiously excluded and smoking cessation was maximally objectified.

Demographic characteristics, IMT and arterial wall dynamics of the initial groups did not differ from the data of the reduced QS group (from 127 to 33 subjects) described here. In both the initial and the final QS and PS groups, the weekly alcohol consumption was more than twice that in NS, which reflects different lifestyles which in turn can affect vascular wall properties. The association between smoking and drinking alcohol has been noted before. IMT was thicker in smokers as reported earlier. Although PS smoked heavier at baseline, IMT was less enlarged in this group compared with the QS. Perhaps latent smoking-related disease was already present in the QS which intentionally motivated this group to stop smoking (all subjects participated voluntarily). Only ‘healthy’ smokers who did not suffer from cardiovascular disease or cardiovascular risk factors other than smoking were studied to examine the influence of smoking as a single factor on vascular wall properties. The deliberate selection of healthy smokers might provide another explanation of this remarkable finding.

Except for the IMT of the right common carotid artery no significant differences in IMT progression were seen between groups. Right common carotid artery IMT showed significant regression of similar magnitude in both the PS and QS when compared with the NS. As this was an isolated observation which could not be explained properly, we considered it accidental and due to multiple comparisons. Our data are in accordance with a six-year follow-up study performed by Belcaro et al. who could not detect increased IMT progression of the carotid bulbs and of the femoral bifurcation segment in persistent smokers of similar age. The percentage of missing values due to measurement

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difficulties at the site of the internal carotid arteries and the carotid bulbs were 34 and 50% respectively. Crouse et al. reported 35% of missing values when IMT of the internal carotid artery was measured.\textsuperscript{7} Other studies also encountered the problem of missing values to the same degree as we did the present study.\textsuperscript{27,28}

We included 27 ex-smokers in the nonsmoking group which may have affected outcome. It has been described that former smokers have IMT values intermediate to those measured in smokers and never-smokers.\textsuperscript{15-19} However, comparisons between 27 ex-smokers and the 23 never-smokers in the NS group revealed no difference.

Analysis of measurements performed at variable points of time after smoking cessation in the successfully QS (n=33) yielded similar findings. Although percentual changes compared to baseline were negative in the common carotid arteries and in the bulbs on both sides (shown in figure 1a), no significant differences nor trends were found. As we performed quantitative measurements (thickness) to describe arterial wall structure, changes in qualitative parameters (plaque morphology), which are difficult to quantify, could still be involved in the decreased cardiovascular risk in smokers.

We found that dynamic vessel wall properties of carotid and femoral arteries were not affected by chronic smoking, which is in accordance with one other study.\textsuperscript{19} However, as the arterial tree is heterogeneous no conclusions concerning other arteries can be drawn.

Age has a major influence on CC and DC of the elastic common carotid arteries but not on CC and DC of the muscular femoral arteries.\textsuperscript{40} Indeed, two years of aging was associated with significant decreases in CC and DC of the carotid arteries, while CC and DC of the femoral artery increased during the same time period. A possible explanation for the significant increase in femoral arterial wall dynamics (pointing to less stiffening) might be an improvement in lifestyle factors, which are known to affect functional femoral arterial wall properties.\textsuperscript{45,46} Participation in lifestyle intervention studies such as the present one inevitably attracts people who care about their health. Possible positive changes in our study may have been counteracted by the significant increase in body weight after smoking cessation.\textsuperscript{53-55}

Studies in which the effect of weight on dynamic vessel wall properties was evaluated yielded conflicting results.\textsuperscript{45-48} Yet, it is difficult to believe that a minor weight gain (8%) caused a complete attenuation of the positive effects of smoking cessation.

In conclusion, although IMT is thickened in chronic smokers no difference in IMT progression could be shown after two years of smoking cessation when compared with results in persistent smokers and in nonsmokers. Furthermore, neither chronic smoking nor two years of smoking cessation has an effect on arterial wall stiffness in a carefully selected population of smokers without additional cardiovascular risk factors. Therefore, the improvement in arterial vessel wall structure and function does not explain the rapid cardiovascular risk reduction after smoking cessation. The risk reduction should, more likely, to be ascribed to haemostatic and/or endothelial factors.

**ACKNOWLEDGEMENTS**

This research project was financially supported by grant NHS 94.035 from the Dutch Heart Foundation, the Netherlands.

**REFERENCES**


Berk mortel FWPJ van den, et al. Smoking cessation and arterial wall thickness and stiffness.
ABSTRACT

Background: The combination of oxaliplatin, 5-fluorouracil (5FU) and leucovorin (LV) has shown to be active and safe as first- or second-line chemotherapy for metastatic colorectal cancer (MCC).

Patients and Methods: The outcome of patients with MCC who had progressive disease after at least two lines of palliative chemotherapy and who were subsequently treated with oxaliplatin, 5FU and LV was reviewed. Patients received FOLFOX3 consisting of oxaliplatin (85 mg/m²) on day 1, LV (500 mg/m²) as a two-hour infusion on days 1 and 2, and 5FU (3000 mg/m²) as a 46-hour infusion starting on day 1 in a cycle of two weeks.

Results: A total of 28 patients were treated with a median number of 9.5 cycles (range 1-24) at a mean dose intensity of 73%. Six patients discontinued treatment due to toxicity, of whom three had sensory neuropathy grade 2. Six patients experienced grade 3 toxicity: nausea (1), vomiting (1), diarrhoea (1), leucopenia (2) and thrombocytopenia (1); grade 4 toxicity was not observed. Twenty-five patients were evaluable for response, of whom four achieved a partial response (response rate 14%, based on intention to treat). The median progression-free survival was 5.8 months and the median overall survival was 8.5 months.

Conclusion: For heavily pretreated patients with MCC, the FOLFOX3 regimen is a fairly safe and effective treatment.

INTRODUCTION

In Western countries colorectal cancer is the second most common cause of cancer mortality. Approximately half of all colorectal cancer patients ultimately die of progressive metastatic disease. In the Netherlands, colorectal cancer was diagnosed in 8200 patients in 1998, resulting in 4200 deaths. As compared with best supportive care, chemotherapy may result in improved survival and delay of onset of tumour-related symptoms of advanced colorectal cancer. For decades, systemic treatment has consisted of 5-fluorouracil (5FU) and leucovorin (LV). Nowadays, the introduction of new agents, such as irinotecan, oxaliplatin and oral fluoropyrimidines, has expanded the therapeutic options for patients with metastatic colorectal cancer (MCC).

Oxaliplatin is a member of the platinum family, inhibiting DNA replication and transcription through the formation of DNA adducts. Oxaliplatin is active in colorectal cancer both as a single agent and in combination with other anticancer agents. As a single agent in second-line therapy, partial responses and stable disease were reported in 10 to 11% and 24 to 42% of patients, respectively. Median progression-free survival (PFS) was 4.6 to 4.8 months and median overall survival (OS) was 8.5 to 10 months. Oxaliplatin in combination with 5FU and LV as first-line therapy resulted in promising response rates (RR) of 51 to 58%, a median PFS of 8.0 to 9.8 months, and a median OS of 16.2 to 19.9 months. The same combination as second-line therapy after 5FU showed an RR of 20 to 45%, a median PFS of 4.6 to 7 months and a median OS of 10 to 17 months.

Thus far, various regimens with oxaliplatin, 5FU and LV have been investigated, consisting of weekly, two-weekly and three-weekly schedules, using different 5FU infusion schedules (bolus and/or continuous infusion) at constant or chronomodulated rates, and at different doses. The French group of De Gramont et al. reported the results...
of FOLFOX2, consisting of a regimen of oxaliplatin and LV as a two-hour infusion on day 1, followed by a 46-hour continuous infusion of 5FU, every two weeks. Other groups have investigated various FOLFOX regimens in phase II studies, using a similar time schedule as in FOLFOX2, but at different doses. A large randomised study by Goldberg et al. in 795 previously untreated MCC patients has recently shown improved survival for FOLFOX4 over the combination of irinotecan and bolus 5FU with leucovorin. The optimal way of combining oxaliplatin with 5FU/LV has, however, not yet been established.

Oxaliplatin was registered for MCC in the Netherlands in 1999. At that time, we started using oxaliplatin for pretreated MCC patients in a FOLFOX3 schedule, based on two studies by Andre et al. To investigate the efficacy and safety of this regimen as (at least) third-line chemotherapy, we retrospectively reviewed the charts of patients treated at our institute.

**PATIENTS AND METHODS**

**Patients**
The charts of all patients with MCC at our hospital who were treated with FOLFOX3 after having progressed on at least two previous lines of palliative chemotherapy were reviewed. The diagnosis of MCC had been made by histological evidence of adenocarcinoma of the colon or rectum. The patient’s history, a physical examination including the performance status, a chest X-ray, a CT scan of the abdomen, blood chemistry and a complete blood cell count were assessed at baseline.

**Treatment**
Chemotherapy consisted of oxaliplatin (85 mg/m²) with LV (500 mg/m²) as a two-hour infusion on day 1, immediately followed by 5FU (3000 mg/m²) as a 46-hour continuous infusion and LV (500 mg/m²) as a two-hour infusion on day 2 in a cycle of two weeks (the FOLFOX3 regimen). Treatment was given until progression or the occurrence of unacceptable toxicity. Standard antiemetics consisted of ondansetron and dexamethasone, both given intravenously at a dose of 8 mg 30 minutes prior to chemotherapy. In general, chemotherapy was postponed for one week if the leucocyte count was <3·0 x 10⁹/l, the platelet count was <100 x 10⁹/l or if toxicity was >grade 2. In case of persisting toxicity >grade 1, the oxaliplatin dose was reduced by 80% in further cycles.

**Evaluation**
Prior to each cycle of chemotherapy, a physical examination and a complete blood cell count were performed and toxicity was assessed. Blood chemistry, including renal and hepatic function and carcinoembryonic antigen (CEA), were measured in each cycle. CT scans of metastatic lesions were performed every two to three months and in case of clinical deterioration. Tumour response was assessed according to the RECIST criteria. Toxicity was graded according to the Common Toxicity Criteria of the National Institutes of Health/National Cancer Institute, version 2.0.

**RESULTS**
This review identified 28 colorectal cancer patients at our institute who were treated according to the FOLFOX3 regimen after at least two lines of chemotherapy for metastatic disease. All patients started FOLFOX3 therapy between December 1999 and August 2002. Patient characteristics are shown in Table 1. Of notice, all patients received 5FU as part of prior chemotherapy (25 received a 5-FU/LV regimen), while 26 patients were treated with irinotecan. None of the patients were pretreated with oxaliplatin. For three patients FOLFOX3 was the sixth line of therapy. In spite of extensive pretreatment, most patients (75%) had a World Health Organisation (WHO) performance status of 0 to 1.

**Table 1**

<table>
<thead>
<tr>
<th>Characteristics of colorectal cancer patients treated with FOLFOX3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PATIENT CHARACTERISTICS</strong></td>
</tr>
<tr>
<td>No. evaluable For response</td>
</tr>
<tr>
<td>For toxicity</td>
</tr>
<tr>
<td>Age Median 53 years Range 32-72 years</td>
</tr>
<tr>
<td>Gender Male 18 Female 10</td>
</tr>
<tr>
<td>Primary tumour Colon 21 Rectum 7</td>
</tr>
<tr>
<td>Site of metastases Liver 25 Lung 14 Other 12</td>
</tr>
<tr>
<td>No. of involved sites 1 2 2&gt;2 10</td>
</tr>
<tr>
<td>WHO performance score at start 0-1 2 3 1</td>
</tr>
<tr>
<td>No. of lines of prior chemotherapy 2 3 4 5 6</td>
</tr>
</tbody>
</table>

Croles, et al. Metastatic colorectal cancer.
Toxicity
All patients were evaluable for toxicity. A total of 254 cycles was analysed with a median number of 9.5 cycles administered per patient (range 1-24). The maximum toxicities occurring per patient are listed in Table 2. In six patients toxicity caused discontinuation of therapy. Three patients stopped because of grade 2 sensory neuropathy (after 9, 11 and 11 cycles, respectively), while one patient developed angina pectoris during the 5FU infusion. The infusion was aborted in this patient, who also suffered from pre-existing heart disease. At a second gift using a prolonged infusion time, a similar reaction prevented further therapy. One other patient developed an idiosyncratic reaction in the tenth cycle, and therapy was stopped. One patient developed a transient ischaemic attack, which might have been due to 5FU.

Table 2
Worst toxicities* in 28 patients treated with FOLFOX3 (all cycles)

<table>
<thead>
<tr>
<th>TOXICITY</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10</td>
<td>13</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>15</td>
<td>10</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>20</td>
<td>5</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>16</td>
<td>5</td>
<td>6</td>
<td>1</td>
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<tr>
<td>Sensory neuropathy</td>
<td>9</td>
<td>13</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Alopecia</td>
<td>24</td>
<td>1</td>
<td>3</td>
<td>0</td>
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<tr>
<td>Laryngeal spasm</td>
<td>27</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Anaemia</td>
<td>2</td>
<td>17</td>
<td>9</td>
<td>0</td>
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<tr>
<td>Leucopenia</td>
<td>14</td>
<td>4</td>
<td>8</td>
<td>2</td>
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<tr>
<td>Thrombocytopenia</td>
<td>6</td>
<td>19</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

*No grade 4 toxicity was observed.

Grade 4 toxicities and neutropenic fever did not occur. Six patients experienced grade 3 toxicity: nausea (1), vomiting (1), diarrhoea (1), leucopenia (2) and thrombocytopenia (1). Myelosuppression was mild, with a grade 3 leucopenia occurring in only two patients after 11 and 9 cycles, respectively. One of these patients started with a grade 2 leucopenia due to previous chemotherapy. One patient developed grade 1 hand-foot syndrome during one cycle. Due to dose delay and/or dose reduction, only 21% of the patients received >90% of the scheduled oxaliplatin dose intensity during therapy. On average, patients received 73% of the scheduled oxaliplatin and 5FU dose.

Response
Twenty-five out of 28 patients were evaluable for response (Table 3). Within two weeks after the start of therapy, one patient developed symptomatic brain metastases. Two patients had to discontinue treatment early because of a transient ischaemic attack (after one cycle) and recurrent pectoral angina (after two cycles), respectively. A total of four partial responses were observed (RR 14%, 95% CI 4.3-33%, based on intention to treat), while stable disease occurred in 14 patients (50%). The median PFS was 5.8 months (95% CI 4.8-6.7) and the median OS was 8.5 months (95% CI 6.4-10.5).

DISCUSSION
The results of this retrospective analysis of the FOLFOX3 regimen indicate that the combination is well tolerated and modestly active in heavily pretreated patients with advanced colorectal cancer. All patients had previously received a 5FU-containing regimen, and all but two had received irinotecan as another line of therapy. Of notice, most patients in this study had a good performance status, which may account for the observed feasibility of this regimen in the third line. Thus far, only one preliminary Spanish study has described the outcome of FOLFOX3 as third-line chemotherapy.9 This Spanish study reported an RR of 8.6% in 23 treated patients, stable disease in 43% of patients and a median OS of 8.0 months. These results are quite similar to our series. Likewise, a majority of 76% of the patients had a good performance status. In contrast, 14 grade 3-4 toxicities (61%) and one toxic death were reported.

FOLFOX3 as second-line therapy has been investigated in two studies in patients with MCC refractory to 5-FU/LV.7,8 Andre et al. treated 30 patients who had progressed on 5FU/LV after which oxaliplatin was added to the same regimen.7 They reported an RR of 20% and stable disease in 50%. The median PFS was 6.1 months and the median OS was 13.3 months. Neutropenia grade 3-4 occurred in 20% of the patients. The main toxicity was sensory neuropathy (90%), of which 13% was grade 2. In another study, the same authors treated 40 patients with second-line FOLFOX3.
after 5FU/LV. They reported an RR of 18.4%, stable disease in 37% of patients, a median PFS of 4.6 months, and a median OS of 10.6 months. Again, the main toxic effects were sensory neuropathy (95%), of which 27.5% were grade 3. Grade 3-4 neutropenia was rare (15%). Grade 1-2 skin toxicity (hand-foot syndrome) was observed in three patients. As can be expected, the outcome of FOLFOX3 after pretreatment with only 5FU/LV is slightly better in terms of RR and OS when compared with data from FOLFOX3 as third-line treatment in our patients. The median PFS and toxicity scores, however, were similar to our results.

In contrast to the FOLFOX3 schedule, the FOLFOX4 regimen consists of a similar dose of oxaliplatin (85 mg/m²) with LV (200 mg/m²) as a two-hour infusion, followed by 5FU 400 mg/m² bolus intravenously and 5FU (600 mg/m²) as a 22-hour infusion on day 1, and the same therapy, without oxaliplatin, on day 2 of a two-weekly schedule. In a recent study by Rothenberg et al., FOLFOX4 was administered to 152 patients with progressive MCC after first-line treatment consisting of the combination of irinotecan and bolus 5FU/LV (IFL schedule). The group reported an RR of 9.9%, stable disease in 59.9% of patients and a median PFS of 4.6 months. Of note, 73% of patients treated with FOLFOX4 developed grade 3-4 adverse events, including 44% grade 3-4 neutropenia and 6% neutropenic fever. Although the efficacy of the FOLFOX4 schedule was similar to the results observed in our patients, the toxicity profile of FOLFOX4 was much more pronounced. We observed a grade 3-4 adverse event in only six patients (21%). Although the total dose of 5FU is lower than in FOLFOX3, the higher incidence of toxicity in the less pretreated FOLFOX4 group might be due to bolus 5FU infusion and/or a higher administered dose intensity (88% of the planned dose).

As previously mentioned, the best FOLFOX regimen in terms of safety and efficacy has not yet been established. In a nonrandomised fashion, FOLFOX3 and FOLFOX4 after prior 5FU/LV therapy were compared by Andre et al. FOLFOX4 resulted in an RR of 23.5%, a median PFS of 5.1 months and a median OS of 11.1 months, which did not differ significantly from FOLFOX3. With regard to toxicity, however, neutropenia was observed more frequently in FOLFOX4 than in FOLFOX3, with grade 3-4 neutropenia in 36.9 vs 15% of patients, respectively (p=0.02). Of notice, any differences in toxicity as observed in various phase II studies may be due to patient selection and FOLFOX3 and FOLFOX4 have never been compared head to head in a randomised trial.

In the palliation of heavily pretreated patients the choice of chemotherapy should not only be based on efficacy, but on the toxicity profile as well. This retrospective analysis shows that FOLFOX3 is a fairly safe and effective regimen for heavily pretreated MCC patients who have a good performance score. Currently, the oral 5FU prodrug capecitabine (Xeloda) is being combined with oxaliplatin (XELOX), which might replace FOLFOX3 in those patients without gastrointestinal symptoms from MCC.

REFERENCES
No effect of folic acid on markers of endothelial dysfunction or inflammation in patients with type 2 diabetes mellitus and mild hyperhomocysteinaemia

A.M.E. Spoelstra-de Man¹, C.B. Brouwer³, F. Terheggen³, J.M. Bollen¹, C.D.A. Stehouwer¹,², Y.M. Smulders¹,²

¹Department of Internal Medicine, ²Institute for Cardiovascular Research, VU University Medical Center, PO Box 7057, 1007 MB Amsterdam, the Netherlands, tel: +31 (0)20-4440531, fax: +31 (0)20-4444313, e-mail: y.smulders@vumc.nl, ³Department of Internal Medicine, Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands, ²corresponding author

ABSTRACT

Background: Mild hyperhomocysteinaemia is a cardiovascular risk factor in patients with type 2 diabetes mellitus. Homocysteine may exert its detrimental effects through induction of endothelial dysfunction and/or chronic inflammation. In this study, we examined the effects of homocysteine-lowering therapy with folic acid on biochemical markers of endothelial dysfunction and low-grade inflammation in patients with type 2 diabetes mellitus and mild hyperhomocysteinaemia (≥14 μmol/l).

Methods: In a randomised, double-blind, controlled trial, patients were treated with folic acid 5 mg or placebo for six months. At 0 and 6 months, albuminuria, von Willebrand factor, soluble cellular adhesion molecules, C-reactive protein, interleukin-6 and tumour necrosis factor-α were determined.

Results: Forty-one patients completed the study (folic acid 23, placebo 18). Baseline hyperhomocysteinaemia (median 17 μmol/l, range 14 to 30 μmol/l) was reduced by 29% in the folic-acid-treated group, and remained unchanged in patients receiving placebo. On average, folic acid treatment did not significantly affect any of the endothelial (e.g. von Willebrand factor: difference folic acid minus placebo +1%, confidence interval -3 to +16%) or inflammation (e.g. C-reactive protein: difference folic acid minus placebo +13%, confidence interval -42 to +52%) markers studied. Multiple regression analyses without and with adjustment for baseline differences in cardiovascular disease and ethnicity confirmed these results. An apparent beneficial effect of folic acid on albuminuria in crude analysis was attenuated by multiple adjustment (difference folic acid minus placebo -35%, confidence interval -178 to +32%, p=0.08, adjusted 0.26).

Conclusion: The data indicate that, in this group of patients with type 2 diabetes mellitus and mild hyperhomocysteinaemia, lowering homocysteine with folic acid for six months does not improve biochemical markers of endothelial dysfunction or low-grade inflammation.

ORIGINAL ARTICLE

INTRODUCTION

Mild hyperhomocysteinaemia is a recently discovered, independent risk factor for cardiovascular disease.¹ Patients with type 2 diabetes mellitus may be particularly vulnerable to the atherothrombotic effects of hyperhomocysteinaemia when compared with nondiabetic subjects.²³ The pathophysiological basis for the association between hyperhomocysteinaemia and cardiovascular disease is unclear. Studies in animals and humans suggest that hyperhomocysteinaemia increases oxidative stress inducing, amongst other things, endothelial dysfunction.⁴ Another
The increased susceptibility to hyperhomocysteinaemia of patients with type 2 diabetes mellitus is unexplained, but may relate to the association of both high homocysteine and diabetes with endothelial dysfunction and chronic, low-grade inflammation which particularly occur in individuals with type 2 diabetes whose urinary albumin excretion is increased.\(^7\)\(^8\) In addition, recent animal data suggest that homocysteine induces superoxide formation particularly in the vascular endothelium of diabetic rabbits.\(^9\)

Folic acid lowers the serum homocysteine concentration.\(^20\) However, whether this translates into clinical benefit is still unknown. Randomised controlled trials among nondiabetic individuals have shown that homocysteine-lowering treatment can improve clinical endpoints, i.e. decrease of restenosis after angioplasty,\(^11\) and decreased incidence of abnormal exercise electrocardiography tests.\(^12\)

In addition, homocysteine lowering may improve endothelium-dependent vasodilatation,\(^7\)\(^8\) although the latter is not a consistent finding.\(^14\) Studies addressing the effects of folic acid on biochemical markers of endothelial function or chronic inflammation as surrogate markers of cardiovascular disease are scarce, and show conflicting results.\(^15\)\(^16\)

In patients with diabetes mellitus the effects of folic acid treatment have only sporadically been studied, despite their reported increased vulnerability to hyperhomocysteinaemia.

In view of these considerations, we investigated the effects of treatment with folic acid on biochemical markers of endothelial dysfunction and chronic inflammation in patients with type 2 diabetes mellitus, mild hyperhomocysteinaemia and a high-normal to clearly elevated urinary albumin excretion.

**METHODS**

**Patients**

Patients aged 30 to 85 years, with a ≥1 year history of type 2 diabetes mellitus, a fasting homocysteine concentration of ≥14 \(\mu\)mol/l and a urinary albumin-to-creatinine ratio of at least 1 mg/mmol in early morning urine at initial screening were considered for inclusion. Exclusion criteria were unstable glycaemic control (defined as more than 1.5% absolute change in HbA\(1c\) during the previous year), plasma vitamin B\(_{12}\) or folate concentrations outside the reference range (see below), serum creatinine >130 \(\mu\)mol/l, blood pressure >160 mmHg and/or >95 mmHg, congestive heart failure, major invalidating disease (e.g. severe pulmonary disease, cancer), severe hyperlipidaemia (total cholesterol >7.5 mmol/l or triglycerides >5 mmol/l), and pregnancy.

**Study protocol**

Patients were randomised between treatment with 5 mg folic acid or similar placebo tablets. The random allocation sequence was generated by computer and implemented by numbered containers. Both participants and physicians were unaware of group assignment.

At baseline and at three and six months of follow-up, subjects came to the hospital in the morning, after a ten-hour fasting period. We measured blood pressure in the sitting position after ten minutes of rest with a standard clinical sphygmomanometer, blood glucose, HbA\(1c\), serum creatinine, serum total cholesterol, HDL cholesterol and triglycerides. At baseline and after six months, plasma levels of total homocysteine, vitamin B\(_{12}\), folate, von Willebrand factor, soluble E-selectin, soluble vascular cell adhesion molecule-1, soluble intercellular adhesion molecule-1, C-reactive protein, interleukin-6 and tumour necrosis factor-\(\alpha\) were measured. In addition, urinary albumin and creatinine excretion was measured in triplicate first-voided morning urine samples.\(^27\) During the study period, medication used for treatment of hypertension or hyperlipidaemia was not changed, unless the treating physician decided that blood pressure or lipids were in an unacceptable range, in which case patients were excluded.

**Laboratory analyses**

Plasma and serum aliquots were quickly separated and frozen at -30 °C and -70 °C for batched analysis. HbA\(1c\) was measured using an automated high performance liquid chromatography analyser (Diamat BioRad Laboratories, NY, USA, reference range 5.2 to 6.7%). Serum and urinary creatinine was assayed with a modified Jaffé method. Total serum cholesterol was measured using a fully enzymatic (CHOD-PAP) kinetic method. HDL cholesterol was measured with the same method after precipitation of very-low-density and low-density lipoprotein with phosphotungstic acid and magnesium ions. Serum triglycerides were determined using an enzymatic method. Total plasma homocysteine was measured with high performance liquid chromatography, using a previously described method.\(^18\) For better separation, chromatographic conditions were changed into gradient elution from 0 to 20% acetonitril in 0.1 M KH\(_2\)PO\(_4\) (pH 1.75).

Serum vitamin B\(_{12}\) and folate were measured with a competitive protein-binding assay (Dualcount Solid Phase Boil assay, DPC, Los Angeles, CA, USA; reference values 150 to 700 pmol/l and 6.8 to 39 nmol/l, respectively).

Urinary albumin was measured using a laser-nephelometric method on a Behring Nephelometer (Behringwerke, Germany).

Von Willebrand factor antigen was assayed with a modified immunoprecipitation method using polyclonal antibodies from Dako (Glostrup, Denmark) and expressed as percentage of von Willebrand factor.
detected in pooled citrate plasma of healthy controls. Soluble cell adhesion molecules were assayed in plasma by ELISAs obtained from Diaclone (Besançon, France; intracellular and intercellular assay coefficients of variation are 4.0 and 10.8% for soluble E-selectin; 4.4 and 7.6% for s-vascular cell adhesion molecule-1 (sVCAM-1); and 4.0 and 8.6% for s-intercellular adhesion molecule-1 (sICAM-1), respectively). Reference values obtained in 40 healthy volunteers were 54.3 to 126.9 ng/ml for sE-selectin, 250 to 799 ng/ml for sICAM-1 and 761 to 1510 ng/ml for sVCAM-1. C-reactive protein levels were measured in plasma by a latex-enhanced immuno-turbidimetric method (Roche Tinaquant) performed on a Roche/Hitachi modular P800. Interleukin-6 was measured in serum by a sandwich enzyme immunoassay (Quantikine High Sensitivity, R&D Systems, Oxon, United Kingdom; intra- and inter-assay coefficients of variation <11.1% and <16.5%, respectively). Tumour necrosis factor-α was measured in serum by a sandwich enzyme immunoassay (Quantikine High Sensitivity, R&D Systems, Oxon, United Kingdom; intra- and inter-assay coefficients of variation <8.8% and <16.7%, respectively).

Statistical analyses

Data are expressed as mean (standard deviation), or as median (interquartile range). We used regression models to determine differences in outcome variables between the treatment groups, and to perform multiple adjustments for potential confounders and baseline values. We constructed general scores for markers of endothelial dysfunction and of inflammatory activity to reduce the influences of biological variability of each measure. For each individual, the values of each marker were expressed as a Z score, i.e (value in the individual minus the mean value in the study population) divided by the standard deviation, a value that thus ranged from approximately -2.5 to + 2.5. The general score of endothelial marker proteins was then calculated as the mean of the Z scores for von Willebrand factor, soluble E-selectin, soluble vascular cell adhesion molecule-1, and soluble intercellular adhesion molecule-1. Likewise, the general score for inflammatory markers was calculated as the mean of the Z scores for C-reactive protein, interleukin-6, and tumour necrosis factor-α. The study was designed to have a 90% power (1-β) to detect a difference between the treatment groups the size of 1 SD of each studied variable.

RESULTS

Fifty-one patients started this study. Seven patients declined further cooperation within three months, and one was lost to follow-up. Two patients were excluded because of serious protocol violations (intake of folic acid before start of study), leaving 41 patients for final analyses (figure 1). Because of this relatively high dropout rate, and in view of the reasons for dropout, we performed on-treatment analysis of the data. Most demographic, clinical and laboratory characteristics at baseline of patients who completed the study were comparable in both treatment groups (table 1). Somewhat less patients in the placebo group were non-Caucasian or had a history of cardiovascular disease.

Six months of folic acid therapy resulted in a significant decrease in homocysteine concentration of 29%. Analysis of the crude data showed that, on average, markers of endothelial dysfunction and inflammation did not change differently between the placebo and folic acid group (table 2, figure 2). Multiple linear regression analyses using baseline-adjusted values at t=6 months as the dependent variables revealed no significant effect of folic acid compared with placebo on protein markers of endothelial dysfunction and inflammation (table 3). There was a trend towards improvement of albuminuria after six months of treatment with folic acid compared with placebo (table 3, p=0.08). However, adjustment for baseline differences in ethnicity and cardiovascular disease attenuated this result.

Blood pressure, lipid levels, vitamin B12 and HbA1c remained stable during the trial and were not affected by treatment with folic acid (data not shown).

DISCUSSION

In this randomised placebo-controlled trial of patients with type 2 diabetes mellitus, mild hyperhomocysteinaemia and high-normal to elevated urinary albumin excretion, folic
Table 1
Baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Clinical characteristics</th>
<th>FOLIC ACID (N = 23)</th>
<th>PLACEBO (N = 18)</th>
</tr>
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<tr>
<td>Age (years)</td>
<td>63.7 (8.6)</td>
<td>66.1 (8.5)</td>
</tr>
<tr>
<td>Sex (% male)</td>
<td>61</td>
<td>56</td>
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<tr>
<td>Ethnicity (% non-Caucasian)</td>
<td>35</td>
<td>17</td>
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<tr>
<td>Duration of diabetes (years)</td>
<td>11 (4-19)</td>
<td>13 (7-19)</td>
</tr>
<tr>
<td>Oral hypoglycaemic agents (%)</td>
<td>48</td>
<td>39</td>
</tr>
<tr>
<td>Body mass index (kg/m2)</td>
<td>29.3 (3.9)</td>
<td>28.8 (1.4)</td>
</tr>
<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>139.4 (22.7)</td>
<td>140.8 (15.7)</td>
</tr>
<tr>
<td>Diastolic blood pressure (mmHg)</td>
<td>76.1 (12.0)</td>
<td>75.6 (10.3)</td>
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<tr>
<td>Smoking (%)</td>
<td>39</td>
<td>50</td>
</tr>
<tr>
<td>Cardiovascular disease (%)</td>
<td>44</td>
<td>67</td>
</tr>
<tr>
<td>Use of angiotensin-converting enzyme-inhibitors or Angiotensin II-antagonists (%)</td>
<td>78</td>
<td>74</td>
</tr>
<tr>
<td>Biochemical variables</td>
<td></td>
<td></td>
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<tr>
<td>HbA1c (%)</td>
<td>7.6 (1.3)</td>
<td>7.3 (1.2)</td>
</tr>
<tr>
<td>Serum creatinine (µmol/l)</td>
<td>106 (21)</td>
<td>104 (21)</td>
</tr>
<tr>
<td>Serum cholesterol (mmol/l)</td>
<td>5.1 (1.0)</td>
<td>4.8 (1.1)</td>
</tr>
<tr>
<td>Serum triglyceride (mmol/l)</td>
<td>1.76 (1.7-1.96)</td>
<td>1.24 (0.85-2.10)</td>
</tr>
<tr>
<td>Serum HDL cholesterol (mmol/l)</td>
<td>1.1 (0.6-1.9)</td>
<td>1.1 (0.7-3.2)</td>
</tr>
<tr>
<td>Homocysteine (µmol/l)</td>
<td>17 (15-21)</td>
<td>18 (15-20)</td>
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<tr>
<td>Serum vitamin B12 (pmol/l)</td>
<td>236.6 (63.2)</td>
<td>261.5 (85.1)</td>
</tr>
<tr>
<td>Serum folate (nmol/l)</td>
<td>13.4 (4.6)</td>
<td>11.7 (3.3)</td>
</tr>
<tr>
<td>Endothelial dysfunction</td>
<td></td>
<td></td>
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<tr>
<td>Albumin excretion (mg/mmol creatinine)</td>
<td>4.8 (1.2-15.4)</td>
<td>2.2 (1.2-32.3)</td>
</tr>
<tr>
<td>Microalbuminuria (%)</td>
<td>74</td>
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<td>Macroalbuminuria (%)</td>
<td>13</td>
<td>22</td>
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<tr>
<td>Von Willebrand factor (%)</td>
<td>173 (126-231)</td>
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<td>Soluble E-Selectin (ng/ml)</td>
<td>118 (85-138)</td>
<td>139 (97-169)</td>
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<tr>
<td>S-vascular cell adhesion molecule-1 (ng/ml)</td>
<td>1347 (1070-1640)</td>
<td>1399 (1078-1576)</td>
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<tr>
<td>S-intercellular adhesion molecule-1 (ng/ml)</td>
<td>668 (598-865)</td>
<td>797 (513-1046)</td>
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<td>Inflammation</td>
<td></td>
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<tr>
<td>C-reactive protein (mg/l)</td>
<td>2.8 (1.2-5.3)</td>
<td>3.5 (1.2-15.7)</td>
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<tr>
<td>Interleukin-6 (pg/ml)</td>
<td>4.5 (2.9-5.5)</td>
<td>5.4 (3.2-10.2)</td>
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<tr>
<td>Tumour necrosis factor-α (pg/ml)</td>
<td>2.5 (2.2-3.5)</td>
<td>2.4 (1.9-3.5)</td>
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</table>

Baseline clinical and laboratory characteristics of the patients who completed the study. Continuous data are indicated as mean (standard deviation), or in case of data with skewed distributions, as median (interquartile range). Nominal data are presented as percentages.
Cardiovascular diseases = myocardial infarction, coronary artery bypass grafting, percutaneous transluminal (coronary) angioplasty, amputation or stroke.
Microalbuminuria = albumin/creatinine ratio 1 to 30 mg/mmol, macroalbuminuria = albumin/creatinine ratio >30 mg/mmol.

acid treatment for six months did not decrease the levels of putative markers of endothelial dysfunction and inflammation. Point estimates of effect size were around zero for practically all marker proteins. Albumin excretion showed some improvement in the folic-acid-treated group, but this effect was insignificant after adjustment for confounders.

The rationale for using these marker proteins is that they reflect endothelial damage (urinary albumin/creatinine ratio), regulation of platelet adhesion and aggregation (von Willebrand Factor), leucocyte adhesion (soluble E-selectin, soluble vascular cell adhesion molecule-1 and soluble intercellular adhesion molecule-1), and chronic, low-grade inflammation (C-reactive protein, interleukin-6 and tumour necrosis factor-α). Elevated plasma levels of these markers are associated with an increased risk in cardiovascular disease.19 20 Furthermore, von Willebrand factor, soluble vascular cell adhesion molecule-1, soluble intercellular
adhesion molecule-1 and tumour necrosis factor-α were previously shown to correlate with homocysteine levels in patients with diabetes mellitus.22,23 Because the sensitivity and the specificity of individual marker proteins is limited,24 we used two panels of markers for endothelial dysfunction and low-grade inflammation.

This is, to the best of our knowledge, the first study investigating two panels of markers for endothelial dysfunction and low-grade inflammation in patients with type 2 diabetes mellitus and mild hyperhomocysteinaemia. Only one study investigated a comparable patient group, but investigated other biochemical markers, i.e. of haemostatic and fibrinolytic abnormalities (plasminogen activator inhibitor type 1, protein C activity, antithrombin III activity, fibrinogen, thrombomodulin). Treatment with folic acid and pyridoxine did not decrease their levels.25

Other studies have been performed in nondiabetic populations. In general, the effects on the separate markers were comparable with our results. Administration of folic acid, in some studies combined with pyridoxine and/or vitamin B12, consistently decreased homocysteine levels. Von Willebrand factor was most frequently used as biochemical marker of endothelial dysfunction. Five out of six studies showed no effect of treatment with folic acid on vWF concentration.21-26,31 Only in one study using high-dose folic acid (10 mg) were vWF levels decreased.30 Adhesion molecules were only sporadically determined in B-vitamin intervention trials. Folic acid did not decrease their levels,27,35 except in one study, in which folic acid was combined with polyunsaturated fatty acids and oleic acid, reducing levels of VCAM-1.32 One study addressed the effect of homocysteine-lowering treatment on albuminuria.46 In this nondiabetic population albuminuria decreased by 20% after two years, which roughly approximates the crude effect size estimate in our study. However, urinary albumin-to-creatinine ratio in this other study was mostly within the ‘normal’ reference range, and subjects were treated with both folic acid and pyridoxine. Further study is clearly necessary to resolve this issue.

Very few studies, all in nondiabetic subjects, investigated the effect on inflammation markers. Levels of C-reactive protein and interleukin-6 did not decrease,15,16,29,31 TNF-α levels were not investigated.

Most studies demonstrating a beneficial effect of folic acid on endothelial dysfunction involved endothelium-dependent vasodilation rather than biochemical endothelial tests.33-35 However, the results are not unequivocal as a number of studies showed no effect of homocysteine-lowering therapy on flow-mediated dilatation.14,37,38 In patients with type 2 diabetes, local intra-arterial administration of 5-methyltetrahydrofolate (the active form of folic acid) acutely restored endothelium-dependent vasodilation.39 It is not clear, however, that this effect is related to lowering of homocysteine, as folate may improve endothelial vasomotor function by homocysteine-independent mechanisms.40

The main limitation of this trial is the relatively limited number of subjects. Nevertheless, point estimates of effect size were around zero for practically all marker proteins, making major effects on endothelial function and inflammation unlikely. Furthermore, we used combined scores consisting of sets of markers to increase statistical power.

Table 2

<table>
<thead>
<tr>
<th></th>
<th>FOLIC ACID</th>
<th>PLACEBO</th>
<th>DIFFERENCE (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>D homocysteine (%)</td>
<td>-29 (-56 to 0)</td>
<td>-10 (-27 to +35)</td>
<td>-19 (-43 to -12)</td>
</tr>
<tr>
<td>D albumin excretion (%)</td>
<td>-13 (-100 to +464)</td>
<td>22 (-64 to +104)</td>
<td>-35 (-178 to +32)</td>
</tr>
<tr>
<td>D von Willebrand Factor (%)</td>
<td>3 (-10 to +32)</td>
<td>2 (-36 to +43)</td>
<td>+1 (3 to +16)</td>
</tr>
<tr>
<td>D sE-selectin (%)</td>
<td>4 (-25 to +64)</td>
<td>5 (-43 to 123)</td>
<td>-1 (-27 to +7)</td>
</tr>
<tr>
<td>D sVCAM-1 (%)</td>
<td>-1 (-31 to +25)</td>
<td>-1 (-41 to +79)</td>
<td>0 (-15 to +10)</td>
</tr>
<tr>
<td>D sICAM-1 (%)</td>
<td>0 (-45 to +64)</td>
<td>2 (-29 to +71)</td>
<td>-2 (-11 to +15)</td>
</tr>
<tr>
<td>D C-reactive protein (%)</td>
<td>24 (-59 to +176)</td>
<td>11 (-99 to +313)</td>
<td>+11 (-42 to +52)</td>
</tr>
<tr>
<td>D interleukin-6 (%)</td>
<td>8 (-35 to +159)</td>
<td>1 (-94 to +107)</td>
<td>+7 (-58 to +42)</td>
</tr>
<tr>
<td>D TNF-α (%)</td>
<td>0 (-38 to +124)</td>
<td>-5 (-42 to +81)</td>
<td>+5 (-14 to +18)</td>
</tr>
</tbody>
</table>

Percentage change of homocysteine and marker levels after six months of treatment with folic acid/placebo, indicated as median (range), difference between both groups with 95% confidence intervals (CI).

vWF = von Willebrand factor, sE-selectin = soluble E-selectin, sVCAM-1 = soluble vascular cell adhesion molecule-1, sICAM-1 = soluble intercellular adhesion molecule-1, CRP = C-reactive protein, IL-6 = interleukin-6, TNF-α = tumour necrosis factor-α.
Nevertheless, larger studies are clearly needed to assess whether small or moderate effects of folate treatment on endothelial marker proteins exist. Another limitation is the relatively large number of patients who did not finish the trial after randomisation, making on-treatment analysis necessary. On the other hand, pathophysiological studies such as this one are less vulnerable in this respect than trials with clinical endpoints. Also, the dropout number was about equal in both patient groups and therefore probably did not significantly influence the results.

In summary, our study shows that beneficial effects of homocysteine-lowering therapy, should they turn out to exist for clinical endpoints, are not likely to be predictable by measuring biochemical markers of endothelial damage or low-grade inflammation. Patients with type 2 diabetes, in
spite of being more susceptible to mild hyperhomocysteinemia, appear to be no exception to this rule. Endothelium-dependent vasodilation is likely to be more sensitive in detecting improved endothelial function due to folate treatment.

ACKNOWLEDGEMENTS

The Dutch Diabetes Research Foundation (Diabetes Fonds Nederland) is gratefully acknowledged for financial support. We are also indebted to C. Oldenburg of the Medical Centre Molendael for her assistance in conducting this study.

REFERENCE LIST


Table 3

Effect of folic acid vs placebo treatment on outcome variables: multiple regression analysis

<table>
<thead>
<tr>
<th>DEPENDENT VARIABLE</th>
<th>MODEL I</th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>B</td>
<td>CI</td>
<td>P</td>
<td>B</td>
<td>CI</td>
</tr>
<tr>
<td>Homocystine</td>
<td>0.77</td>
<td>0.68 to 0.87</td>
<td>&lt;0.005</td>
<td>0.77</td>
<td>0.66 to 0.88</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Albuminuria</td>
<td>0.53</td>
<td>0.27 to 1.09</td>
<td>0.084</td>
<td>0.65</td>
<td>0.30 to 1.38</td>
<td>0.26</td>
</tr>
<tr>
<td>VWF</td>
<td>1.06</td>
<td>0.66 to 1.70</td>
<td>0.25</td>
<td>1.06</td>
<td>0.94 to 1.17</td>
<td>0.32</td>
</tr>
<tr>
<td>sE-selectin</td>
<td>0.91</td>
<td>0.78 to 1.07</td>
<td>0.27</td>
<td>0.90</td>
<td>0.76 to 1.08</td>
<td>0.25</td>
</tr>
<tr>
<td>sVCAM-1</td>
<td>0.98</td>
<td>0.88 to 1.11</td>
<td>0.78</td>
<td>0.97</td>
<td>0.86 to 1.11</td>
<td>0.69</td>
</tr>
<tr>
<td>sICAM-1</td>
<td>0.99</td>
<td>0.89 to 1.16</td>
<td>0.83</td>
<td>0.99</td>
<td>0.86 to 1.14</td>
<td>0.90</td>
</tr>
<tr>
<td>Panel A</td>
<td>0.62</td>
<td>0.21 to 1.79</td>
<td>0.37</td>
<td>0.53</td>
<td>0.17 to 1.73</td>
<td>0.29</td>
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<tr>
<td>CRP</td>
<td>1.12</td>
<td>0.63 to 1.90</td>
<td>0.69</td>
<td>0.95</td>
<td>0.58 to 1.92</td>
<td>0.86</td>
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<tr>
<td>IL-6</td>
<td>0.82</td>
<td>0.53 to 1.28</td>
<td>0.37</td>
<td>0.82</td>
<td>0.51 to 1.50</td>
<td>0.38</td>
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<tr>
<td>TNF-α</td>
<td>0.97</td>
<td>0.87 to 1.22</td>
<td>0.70</td>
<td>0.98</td>
<td>0.84 to 1.16</td>
<td>0.82</td>
</tr>
<tr>
<td>Panel B</td>
<td>0.90</td>
<td>0.26 to 3.16</td>
<td>0.87</td>
<td>0.61</td>
<td>0.15 to 2.36</td>
<td>0.46</td>
</tr>
</tbody>
</table>

Multiple regression analyses with B coefficients for treatment assignment (placebo = 0; folic acid = 1) as independent variable and different outcome variable levels as dependent variables.

Model 1: baseline-value-adjusted only. Model 2: after additional adjustment for baseline differences in ethnicity and cardiovascular disease.

Panel A = set of markers for endothelial dysfunction, calculated as sum of the z-scores. Panel B = set of markers for low-grade inflammation, calculated as sum of the z-scores.

sWF = von Willebrand factor, sE-selectin = soluble E-selectin, sVCAM-1 = soluble vascular cell adhesion molecule-1, sICAM-1 = soluble intercellular adhesion molecule-1, CRP = C-reactive protein, IL-6 = interleukine-6, TNF-α = tumour necrosis factor-α.

Dependent variables were ln-transformed because of ln-normal distribution. After regression analysis antilogarithmic transformation of the B coefficients and confidence interval values was performed. Because of the back transformation, B values of ≤1 indicate a negative effect of folic acid (and are thus comparable with negative B values in normal data). Confidence intervals containing 1 should be interpreted as statistically not significant.


An unusual presentation and way to diagnose hepatocellular carcinoma

V.M.J. Novotny, V.P.M. van der Hulst, P.A. van der Wouw, J.L.G. Blaauwgeers, P.H.J. Frissen

Departments of Internal Medicine, Radiology, Cardiology and Pathology
Onze Lieve Vrouwe Gasthuis, PO Box 95500, 1090 HM Amsterdam, the Netherlands,
tel: +31 (0)20-59 99 111, fax: +31 (0)20-59 93 523, Current affiliation: Department of Haematology,
University Medical Centre St Radboud, Nijmegen, the Netherlands, e-mail: p.h.j.frissen@olvg.nl,
corresponding author

ABSTRACT

A 67-year-old man with a history of chronic obstructive pulmonary disease (COPD) was admitted with acute progression of dyspnoea, productive cough, fever, elevated central venous pressure, oedema and liver enzyme abnormalities. Pneumonia with secondary right-sided congestive heart failure was considered. Additional abdominal ultrasound examination confirmed by a CT scan showed a mass in the inferior vena cava (VCI) extending into the right atrium. The central liver location and impaired haemostasis rendered liver biopsy impossible. An alternative approach was discussed and guided by two-dimensional transoesophageal electrocardiography accessing the right internal jugular vein, biopsies were taken from the atrial mass with histology suggesting the presence of a hepatocellular carcinoma as the cause of acute dyspnoea.

BRIEF REPORT

A 67-year-old male originating from Turkey was admitted to our hospital because of progressive dyspnoea and productive cough, associated with flu-like symptoms during the previous two weeks. The day before admission, his dyspnoea acutely worsened and he developed left-sided tightness of the chest. He smoked 50 cigarettes a day and was a heavy drinker up until six years ago. His medical history revealed a deep vein thrombosis of the leg five years before admission, hypertension and COPD. He was not taking any medication. On physical examination he was moderately ill, with a body temperature of 39°C, blood pressure 195/105 mmHg, a regular pulse rate at 110 beats/min and a respiration rate of 28/min. His central venous pressure was elevated. Rales were heard over the right lung with left basal pleural rubbing. Heart sounds were normal. Beside palmer erythema and slight ankle oedema no further abnormalities were found; there was no hepatosplenomegaly or ascites.

Laboratory analysis (normal values in brackets) revealed a haematocrit of 0.44 l/l, white blood cell count 12.0 x 10⁹/l with 77% neutrophils and platelets 98 x 10⁹/l. C-reactive protein 172 mg/l (<5), total bilirubin 28 µmol/l (<10 µmol/l) conjugated 13 µmol/l (<5 µmol/l), alkaline phosphatase 205 U/l (<110 U/l), lactate dehydrogenase 418 U/l (<275 U/l), alanine aminotransferase 30 U/l (<25 U/l), aspartate aminotransferase 69 U/l (<30 U/l), γ-glutamyltranspeptidase 475 U/l (< 38 U/l) and albumin 35 g/l (35-55 g/l). Electrolytes and kidney function were normal. Arterial blood gas analysis revealed pH 7.45, pCO₂ 30 mmHg, pO₂ 63 mmHg, HCO₃⁻ 20.1 mmol/l and O₂ saturation 93.5 %. ECG showed sinus tachycardia, and a Q wave in leads II and aVF, while the chest X-ray revealed basal crowding, possibly early infiltrates.

The working diagnosis was an early pneumonia with right-sided congestive heart failure in a patient with prior COPD. Initially, he was treated with antibiotics and diuretics with good clinical response. Because of the liver enzyme abnormalities and his past alcohol abuse, abdominal ultrasound examination was performed and unexpectedly revealed a mass in the VCI extending into the right atrium. A ventilation-perfusion scan showed complete absence of perfusion of the left lung circulation.

To identify the origin and nature of the obstructive mass a triphasic helical computer tomography was performed, showing a large irregularly enhancing area in the right
liver lobe continuously extending into the VCI and into the right atrium (figure 1). Thrombi were demonstrated both in the VCI proximal to the obstructing mass and in the left pulmonary artery. No other intra-abdominal abnormalities were found. Additional laboratory investigations showed a moderately elevated α-fetoprotein at 54 IU/l (<30 U/l). Partial thromboplastin time and activated thromboplastin time were both prolonged, 17 sec (<13 sec) and 46 sec (<39 sec) respectively. Antithrombin III was 43% (>75%). Anti-HBs and anti-HBc were positive, HB-s antigen and hepatitis C antibodies both negative.

Histology showed a large cell malignancy with a hepatoid pattern partly infiltrating myocardial tissue (figure 2). Differential diagnostic possibilities were a large cell carcinoma and epitheloid angiosarcoma. There was focal positivity for periodic acid-Schiff (PAS) while PAS-diastase staining was negative. Immune histochemistry was consistent with a carcinoma. Endothelial markers (CD 31, CD 39 and factor VIII) were negative, while the keratin marker (CAM 5.2) was positive. There was focal positivity for α-fetoprotein. The diagnosis of a hepatocellular carcinoma (HCC) was suggested by these findings.

In this patient with a history of alcohol abuse and past hepatitis B infection, the results confirmed the presence of an HCC continuously growing into the VCI and the right atrium, causing venous thrombosis and tumour embolism in the left pulmonary artery.

Due to the lack of curative options, the patient was treated with anticoagulants and diuretics and was discharged from hospital. After three months, the patient died of massive ascites and hepatic coma. Autopsy was not permitted.

**DISCUSSION**

Dyspnoea has a broad differential diagnosis and can be caused by pulmonary, cardiac, anatomic, or metabolic abnormalities. Here, we have presented a rare and unexpected cause of dyspnoea, due to embolism originating from an HCC extending into the VCI and right cardiac atrium. The patient had a history of COPD and heavy smoking.
Initial clinical and laboratory findings indicated an infectious pulmonary origin of the dyspnoea with right-sided congestive heart failure and secondary liver congestion. Additional analyses revealed massive pulmonary embolism caused by an HCC growing into the right cardiac atrium as a rare cause of dyspnoea. Anamnestically, this had occurred the day before admission. The histological diagnosis was eventually established using an alternative approach: an intracardiac biopsy of the tumour could be taken by accessing the right internal jugular vein guided by two-dimensional transoesophageal echocardiography. To our knowledge, extension of HCC into the heart has only been reported once before as radiological image.1

Secondary cardiac metastasis and thrombosis due to local compression of the VCI by tumour growth was seen in several malignancies such as renal cell carcinoma.2 A cardiac tumour was less likely because malignant cardiac tumours are rare. Cardiac tumours can be primary and secondary.3 Three different types have been described: mesotheliomas, angiosarcomas and rhabdomyosarcomas. Angiosarcomas are composed of malignant cells from vascular channels and usually arise in the right heart, particularly the right atrium. These may be associated with right heart obstruction and thrombosis. Mesotheliomas and rhabdomyosarcomas rarely involve the cardiac cavities. Other more common cardiac tumours such as myxoma can be seen in the right atrium (15%), but are generally seen in the left atrium (75%). The presence of these tumours may also lead to thrombosis or embolism.

Regarding this patient, the diagnosis of HCC was primarily suspected because of the absence of other intra-abdominal abnormalities, although the α-fetoprotein was only moderately elevated. Evaluating underlying risk factors,4 we had circumstantial evidence of alcoholic liver cirrhosis and a history of hepatitis B infection in a patient originating from Turkey. However, HB-s antigen carriership and hepatitis C could both be excluded. In this patient, an unusual method was used to obtain material for histology indicating that common sense combined with insight into the possibilities of available techniques can provide alternative diagnostic approaches.

REFERENCES

Gynaecomastia: is one cause enough?

W.M. Creyghton1*, M. Custers2

Department of Internal Medicine, University Medical Centre Utrecht, PO Box 85500 3508 GA Utrecht, the Netherlands, tel: +31 (0)30-25 09 574, fax: +31 (0)30-25 09 111, e-mail: w.m.creyghton@azu.nl, 1fellow internal medicine and endocrinology, 2resident internal medicine, *corresponding author

Table 1
Causes of gynaecomastia

<table>
<thead>
<tr>
<th>PHYSIOLOGICAL</th>
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<tbody>
<tr>
<td>Neonatal</td>
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<tr>
<td>Pubertal</td>
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</tr>
<tr>
<td>Ageing</td>
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</table>

<table>
<thead>
<tr>
<th>PATHOLOGICAL</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Drugs</td>
<td></td>
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<tr>
<td>Chronic disease</td>
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<tr>
<td>Liver disease</td>
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<tr>
<td>Renal failure</td>
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<tr>
<td>Malnutrition</td>
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<tr>
<td>Neoplasms</td>
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<tr>
<td>Testicular</td>
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<tr>
<td>Adrenal</td>
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<tr>
<td>Lung</td>
<td></td>
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<tr>
<td>Liver</td>
<td></td>
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<tr>
<td>Kidney</td>
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</table>

| Hyperthyroidism|                |
| Primary or secondary hypogonadism|                |
| Other endocrinological diseases|                |
| Idiopathic      |                |

Gynaecomastia can be detected in between one-third and two-thirds of men. A wide variety of causes of gynaecomastia, some physiological, some very serious, have been identified.

We present a case in which the cause of the gynaecomastia seemed obvious after history taking and physical examination but we finally ended up with a more complex combination of diagnoses. This case stresses the importance of combining history taking and physical examination with additional laboratory testing for the assessment of gynaecomastia.

INTRODUCTION

Gynaecomastia is an often-encountered entity in clinical practice. True gynaecomastia, a benign enlargement of the glandular component of the male breast, should be distinguished from pseudogynaecomastia, in which fat deposition causes the impression of enlargement of the male breast, and from male breast cancer. Slight gynaecomastia can be detected in between one-third and two-thirds of adults and even more during normal puberty. Three peaks in the age distribution of gynaecomastia can be identified: the neonatal period, during puberty, and in the adult population, especially from the ages of 50 to 80.1 Gynaecomastia has a broad range of causes, some of them very serious (table 1). Of all cases, 25% are idiopathic or related to ageing, 25% are classified as persistent after puberty, 10 to 15% are caused by drugs, 10% have a relation with nutritional factors or liver disease, 10% are caused by primary hypogonadism, and 3% are due to testicular neoplasms. The remaining cases have their origin in various diseases such as secondary hypogonadism, hyperthyroidism, lung cancer or renal disease.4 Gynaecomastia is thought to result from an oestrogen/androgen imbalance at breast tissue level, which can be caused by various pathophysiological mechanisms.3 Several recommendations have been made for the evaluation of gynaecomastia. Two key articles covering the evaluation of gynaecomastia suggest that careful history taking with specific questions about the use of medication,
drugs, and alcohol in combination with questions about the symptoms of hepatic dysfunction, decreased sexual functioning, pulmonary symptoms suggestive of lung cancer, and hyperthyroidism is sufficient in finding most conditions associated with gynaecomastia. In the absence of abnormalities on physical examination, and on laboratory assessment of hepatic, renal, and thyroid function, it has been proposed that further specific evaluation is unlikely to be useful. Neuman, however, added a measurement of testosterone and luteinising hormone (LH) in the evaluation of gynaecomastia.

We present a case in which these recommendations did not suffice. Although the patient’s symptoms seemed to lead straight to the diagnosis, he was subsequently diagnosed with a second causative disorder. Our case emphasises the importance of laboratory testing for serious causes of gynaecomastia and the fact that the laboratory results should completely fit the assumed diagnosis.

CASE REPORT

A 31-year-old previously healthy man was referred because of progressive complaints of headache during the last two months, and because he had noticed that his right eyelid had started hanging. His nipples had become sensitive and slightly enlarged. His libido had not declined. Physical examination including examination of the testicles was normal, except for gynaecomastia and a ptosis at the right side. An ophthalmologist found a temporal vision defect of the right eye.

Laboratory results showed a normal blood cell count, electrolytes, kidney and liver function. Plasma thyroid-stimulating hormone (TSH), free thyroxin, cortisol and insulin-like growth factor-I (IGF-I) were normal. Plasma prolactin was very high (102 U/l, normal <0.5). His luteinising hormone (LH) was immeasurable (normal 1-5 U/l) and follicle-stimulating hormone (FSH) was somewhat low (1.0 U/l). Surprisingly, plasma testosterone was normal (33 nmol/l, normal 10-35). An MRI scan of the brain showed a lesion in the pituitary region with compression of the optic chiasm (Figure 1).

A diagnosis of macroprolactinoma was made and treatment with an oral dopaminergic drug (cabergoline 1 mg per week) was started. Within three weeks his headache had almost disappeared, his vision returned to normal, and the ptosis was no longer present. After seven weeks, plasma prolactin level had fallen to 7 U/l, LH and FSH were < 1.0 U/l but his plasma testosterone was still 26 nmol/l. A few weeks later he told us he had noticed a painless enlargement of the left testicle; this was confirmed on physical examination. Laboratory testing showed a raised beta human chorionic gonadotropin (β-HCG, 184 U/l, normal <5), and a normal α-fetoprotein (10 μg/l, normal <15) and lactate dehydrogenase (LDH, 535 U/l, normal 300-620). A left-sided orchidectomy was performed. Microscopic evaluation showed a nonseminoma testis. A chest X-ray and a CT abdomen did not reveal any metastasis. After the orchidectomy, the β-HCG level became immeasurable and his testosterone level decreased to 2.5 nmol/l. One month after orchidectomy and four months after starting dopaminergic treatment LH, FSH and testosterone levels started climbing and finally reached normal values. His prolactin level had decreased below 0.1 U/l. A second MRI brain scan showed regression of the pituitary lesion. Thirteen months after his initial presentation he was in good health.

DISCUSSION

Our patient presented with gynaecomastia, ptosis, a temporal vision defect and an elevated serum prolactin. This immediately pointed towards a prolactinoma in the pituitary region which was confirmed by MRI. However, testosterone levels remained normal although LH levels were immeasurable. Initially, this could not be explained and did not completely fit the assumed diagnosis.

Both a testicular tumour and a prolactin-producing tumour are known causes of gynaecomastia. To our great surprise, this patient suffered from both entities at the same time. Hyperprolactinaemia inhibits pituitary release of LH, and may thus lead to hypogonadotrophic hypogonadism. Suppression of prolactin release by treatment with dopaminergic agents should lead to resumption of LH and thus testos-
The perplexing combination of immeasurable plasma LH with a ‘normal’ plasma testosterone was presumably due to testosterone production influenced by the β-HCG from the nonseminoma testis. Treating prolactinoma with a dopaminergic agent is currently the therapy of choice. In a stage I good prognosis nonseminoma testis, one can suffice with surveillance after orchidectomy. The five-year survival rate in this group is between 89 and 93%. This case illustrates that although the cause of the gynaecomastia may seem obvious after history taking, physical examination, and routine laboratory testing, laboratory testing to investigate serious causes of gynaecomastia is necessary. In case of nonphysiological gynaecomastia or doubt about physiological gynaecomastia (neonatal, pubertal, ageing/involutional) we would recommend laboratory tests for kidney function, liver function, thyroid stimulating hormone (TSH), free thyroxin (FT4), β-human chorionic gonadotropin (β-HCG), luteinising hormone (LH), testosterone and oestradiol.

**REFERENCES**

Recurrent splinter haemorrhages weeks after a tick bite

T.S. van der Werf*, J.E. Tulleken, J.G. Zijlstra

Intensive and Respiratory Care Unit, Department of Internal Medicine, Groningen University Medical Centre, PO Box 3001, 9700 RB Groningen, the Netherlands, tel: +31 (0)50-361616, fax: +31 (0)50-3613312, e-mail: t.s.van.der.werf@int.azg.nl, *corresponding author

CASE REPORT

A 52-year-old man developed fever, headache, tinnitus, and painful joints. He reported a tick bite contracted during a summer holiday in the Netherlands, followed by erythema on his left arm three weeks earlier. Initial treatment with doxycycline had failed and he had now developed signs of meningoencephalitis. Laboratory tests showed an increased white cell count (16.1 x 10^9/l), and elevated ESR (51/1h).

Upon arrival to the intensive care unit, he was intubated and mechanically ventilated because of respiratory failure apparently due to muscle fatigue and inability to keep his airway free, and to clear respiratory secretions. He developed anuric renal failure. None of the cultures grew micro-organisms that could explain his illness. Anti-\textit{Borrelia} IgM titre was >300 EU/ml (normal range <30), without detectable anti-\textit{Borrelia} IgG antibodies. Cerebrospinal fluid analysis showed pleiocytosis and elevated protein content, without red blood cells. Further tests revealed anti-\textit{Borrelia} IgM antibodies, and the diagnosis of early-onset Lyme borreliosis (with central nervous system involvement and multiorgan failure) was later confirmed by Western immunoblotting, showing reactivity towards anti-\textit{Borrelia}-IgM.

Despite three weeks of ceftriaxone treatment, his course was unfavourable, with persistent multiorgan failure, and his petechiae, which had first disappeared, recurred (\textit{figure 1}).

WHAT IS YOUR DIAGNOSIS?

See page 264 for the answer to this photo quiz.

\textbf{Figure 1}

\textit{Petechiae on the nail beds of the left hand}

A colour version of this figure is available on www.njmonline.nl
Clinicians’ autonomy till the bitter end – can we learn from the extraordinary case of Harold Shipman?

C. van Weel

Department of General Practice, University Medical Centre Nijmegen
PO Box 9101 6500 HB Nijmegen, the Netherlands, tel: +31 (0)24-3616332,
fax: +31 (0)24-3541862, e-mail: c.vanweel@hag.umcn.nl

ABSTRACT:

Harold Shipman has attained the dubious reputation of being the greatest mass murderer of modern times. A specific feature of his murders was that these were committed during regular general practice care, over a period of 20 years. There are no grounds to assume that Shipman’s case is unique in itself, or unique to British general practice and this paper analyses ways in which the medical profession can safeguard itself against future medical murderers.

The 46-year-old R.O. had had a recurrence of her asthma and was visited by her general practitioner (GP). Accompanying chest pain made the GP consider cardiac ischaemia and he administered morphine. R.O. reached the hospital in a comatose state after resuscitation following respiratory arrest. Eyebrows were raised in the hospital at the GP’s decision to administer morphine to a patient with asthma. The ‘facts’ as they presented that day in the hospital had everything for a fascinating performance review. On the one hand, a GP who, in a patient well known to him and presenting with a familiar symptom of acute shortness of breath, had considered an alternative hypothesis to explain her situation – and acted on it. One of the pitfalls of continuity of care is that practitioners find it difficult to look at ‘old’ symptoms with unbiased eyes. But on the other hand, there was the GP’s complete failure to acknowledge the well-known facts of asthma in this patient and its negative interaction with morphine. But there was no critical review of his performance; no formal enquiry was conducted at the time, nor when R.O. died 14 months later without regaining consciousness.

More than five years after the death of R.O. the GP was convicted of murdering 15 of his patients by overdosing morphine. This put the ‘facts’ on R.O. in an entirely different light, and it can now be confidently assumed that Harold Shipman killed more than 235 of his patients between 1979 and 1999, which makes him the greatest serial killer of modern times. It left general practice – and indeed the medical profession in general – in dire straits as to how this could happen and continue to happen on such a scale and for such a long time in the confines of a small community. Following the murder trial, a series of investigations have been instigated, including an international review seminar of methods to assess (general) practitioners’ continued fitness to practice and ways to approach incompetence.

This last seminar, which was held in Manchester in January 2004, presented an interesting comparison as there are clear parallels in the assessment of clinical fitness between the UK and the seminar participants (the Netherlands, US, Canada and New Zealand). In all these countries, registration and the right to practice are restricted in time and depend on proof of the practitioner’s competence. But by and large, establishing fitness to practice is based on self-reporting of their participation in continuing medical education (CME) or on performance in testing knowledge. A major gain is the establishment of a culture of accountability (a large majority of practitioners comply with self-reporting and participate in CME) and a breakdown of professional isolation. Practice-in-isolation was a major feature of the Harold Shipman case and GPs, with their extended position in the community, are particularly
vulnerable in this respect. Although in the Netherlands, for example, a minority of GPs are in single-handed practice, a substantial part of the world’s population live in remote, rural areas with a single GP – if available at all – the only representative of the medical profession.

Another aspect that has made substantial progress in the past decades has been clinical guidance. Evidence-based medicine (EBM) has truly been taken up by GPs, resulting in ever more guidelines and in the development of CME to master knowledge and skills required to perform these guidelines. But the development of quality systems for general practice is only in its early stages. EBM is a fascinating process but clinical guidance can only be as good as the available evidence. Given its specific clinical domain, there is a substantial need for clinical research in general practice.

All the countries around the table in Manchester agreed that the methods of self-reporting, knowledge testing and CME participation were only second best and assessment of actual performance was to be preferred. This offers the opportunity of personal advice for (remedial) improvement in distinct clinical areas. In this respect, experience in the Netherlands is interesting: a total practice performance method has been developed and validated, and has found its way – on a voluntary basis – to more than 3000 of the approximately 7500 GPs in the country. This may again point in this direction: GPs who had had their registration withdrawn for professional misconduct were able to start practicing in the UK before the General Medical Council could intervene, and in Spain, where it is currently possible to revoke a registration to practice. The concept of ‘incompetence’ as a mere failure to live up to professional standards is too naive, as some culprits actively avoid control and disclosure. That is the link between professional fitness to practice and Shipman. With hindsight he can hardly be regarded as anything but a shrewd opportunist, using the margins of the professional autonomy of a trusted family doctor. Hence the scandal, and public indignation that forced a strong legal-political response to professional performance. This highlights another international experience that came forward in the Manchester seminar: scandals and incidents drive the supervision of the medical profession to a large extent. What ‘Shipman’ is for the UK, was a case of failed follow-up of abnormal cervical cytology in New Zealand. As a consequence of that enquiry, patients (‘consumers’) rather than the medical profession run the supervision of the competence and professional fitness of practitioners. This comes close to the situation in the Netherlands, where the State Inspectorate of Health Care has always been a strong factor. How effective, proactive and transparent self-regulation of the medical profession can be is also demonstrated in the approach to addicted doctors in Canada. A coherent response which treats addiction for what it really is – an addictive disease and not deviant professional behaviour – has resulted in de-criminalisation of alcohol and drugs addiction to the benefit of treatment and supervised return to practice. The success of this programme is such that practitioners with a personal history of addiction are currently at less risk of addiction after successful treatment and return to practice than the ‘average’ physician.

Early in his career as GP, Harold Shipman was found guilty of morphine use and falsification of prescriptions for his own use, and that brings the story back to him. Much has changed in the supervision of medical competence since he entered the profession. To a large extent these measures will serve to further improve GPs high professional standing. But to what extent will these measures serve to identify or prevent what was after all the reason for this seminar: a ‘next Shipman’?

The participants in Manchester could readily agree on two points: ‘Shipman’ could have happened anywhere, and current procedures of professional supervision that are in place in each country would have had a hard time in identifying him. And that warrants the study of his case. It remains deeply worrying that a GP can kill and hide these killings – through medical methods – amidst colleagues, under the eyes of coroners and police, in a small community where everyone knew everyone, and with one undertaker firm responsible for most of the burials that resulted. His departure from a partnership for single-handed practice coincided with a sharp increase in the number of killings but definitely did not actually create the opportunity to kill. From practice in partnership and its resulting formal and informal peer-review protection of patients might to some extent be expected. But Shipman’s killings (and his morphine addiction) started at the time that his practice was a firm part of a partnership and his participation in peer review well documented. Consequently, a mere appeal for group practices – important as it may be for the future of (primary) care – is too simple a solution. This may indicate that what Shipman was able to do in general practice might also happen in hospital-based specialties with their partnership structure. Professional misconduct can also flourish there. A close-knit environment of peer-professionals may respond by isolating rather than addressing the undesired professional behaviour and in that way contribute to its prolonged existence.
Having said this, the highly unusual nature of the Shipman case should not be lost from sight. No one, professionals nor the public, expects GPs to be killers. But an important factor was the way Shipman’s deeds were enshrined in a strong personal bond with his victims and their families: the caring, personal doctor who visited his patients regularly and often on his own initiative, in their homes, created the conditions for most of his more than 200 killings in a period of over 20 years. This bond was so strong that many of the surviving relatives initially sided with Shipman when he was arrested.

It is here that general practice can be particularly vulnerable for the backlash of the Shipman case. The personal working relationship provides GPs with a strong method to tailor medical care to individual needs. It would be in nobody’s interests if this were to come in disrepute, but it is up to GPs – in the UK and outside – to develop open and transparent methods to account for the use they make of it. A helpful response under the circumstances could be to include in audit of GPs performances and their timely and appropriate use of the personal bond with their patients. This bond is not simply a characteristic of general practice and even less a right for GPs to intrude on their patients’ privacy.

Audit of practice death rates is another method that might be used in a more systematic way. The Shipman enquiry has made it clear that the excessively high number of deaths in his practice could have been a valuable pointer to his wrongdoings but would not in itself have proved his case. This is in line with recent experiences in the Netherlands with a nurse suspected of killing patients on a children’s ward – another indication that ‘Shipman’ is not exclusive to the primary care setting. And that brings us back to the startling situation at the beginning: although methods to safeguard quality of care and practitioners fitness to practice are improving and despite the fact that supervision by peers is becoming the rule in medicine, there is no certainty that a ‘next Shipman’ can be prevented. It is not likely that it will take another 200-odd patients’ lives next time, but it may happen again in the primary or hospital care setting.

REFERENCES
DIAGNOSIS

The photo (figure 1) shows petechiae on the nail beds, which had developed some three weeks earlier during the initial acute episode of illness. New petechiae are subtle but can be seen on the skin over the distal interphalangeal joints. Apparently, this persistent and recurrent disease activity developed despite adequate antimicrobial treatment. A skin and muscle biopsy was analysed for the presence of vasculitis, and necrotising vasculitis confirmed the suspected post-\textit{Borrelia} vasculitis.\textsuperscript{1} As there were no spirochaetae detected in the biopsy specimen, ongoing infection as a cause of his present illness was considered unlikely. Markers for systemic idiopathic collagen-vascular disease (ANA, ANCA) were all negative.

Immunosuppression was started with corticosteroids, combined with cyclophosphamide, initially combined with plasma exchange. Several weeks later, his renal function recovered and he could be weaned from the ventilator.

Tick born fevers in Europe comprise a spectrum of diseases including Lyme borreliosis (caused by \textit{Borrelia burgdorferi}). Other tick-born fevers than Lyme should be considered, such as \textit{Ehrlichia chaffeensis} which is a rickettsiosis,\textsuperscript{2} and \textit{Babesia divergens} which is a red-blood cell protozoic infestation.\textsuperscript{3}

Infections and systemic vasculitis syndromes may be quite similar in presentation,\textsuperscript{4} and in Lyme disease vasculitis may be present and the differential diagnosis with idiopathic vasculitides such as giant cell arteritis may be difficult.\textsuperscript{5} Postinfectious vasculitis may be uncommon, but should be considered if the clinical resolution of infection is unfavourable despite adequate antimicrobial treatment. Our case illustrates that the history and physical examination should be repeated if the clinical response to treatment is unexpected. Based on the clinical detection of recurrent disease activity, a diagnostic approach was selected to reach an alternative diagnosis. The presence of vasculitis without evidence of residual infection warranted immunosuppressive therapy, resulting in a favourable course of his illness.

REFERENCES

ABOUT THE COVER

‘Morphe’

Benno Derda

Benno Derda (1968) is the artist of this month’s cover of the Netherlands Journal of Medicine. Derda studied at the Academy of Arts at the University of Siegen in Germany. Since 1995, he is an independent expressive and uses different styles of art such as print graphic, sculpture and painting. His compositions originate from watching objects and forms in nature.

The technique used in ‘Morphe’ is a colour etching of four plates. An original print (20 x 14.8 cm) of this cover, 30 in edition, is available at a price of € 80. You can order a print at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek Ubbergen, the Netherlands, by e-mail: galerie-unita@planet.nl or see the website: www.galerie-unita.com.
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The language of the Journal is English. English idiom and spelling is used in accordance with the Oxford dictionary. Thus: Centre and not Center, Tumour and not Tumor, Haematology and not Hematology.

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