Netherlands
The Journal of Medicine
PUBLISHED IN COLLABORATION WITH THE NETHERLANDS ASSOCIATION OF INTERNAL MEDICINE

MISSION STATEMENT

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.

EDITORIAL INFORMATION

Editorial office 'The Netherlands Journal of Medicine'
Geeralien Derksen-Willemsen
Radboud University Nijmegen Medical Centre
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

CITED IN

Biosis database; embase/excerpta medica; index medicus (medline) science citation index, science citation index expanded, isi alerting services, medical documentation services, current contents/clinical medicine, PubMed.

VAN ZUIDEN communications
Alphen aan den Rijn, the Netherlands

Contents

Cover
Graphic art made by Lia Stouten. For details about the artist, her work and how to order see elsewhere in this journal.

Subscriptions
General information
An annual subscription to The Netherlands Journal of Medicine (ISSN 0300-2977) consists of 11 issues. Issues within Europe are sent by standard mail and outside Europe by air delivery. Cancellations should be made, in writing, at least two months before the end of the year.

Subscription fee
The annual subscription fee within Europe is € 650, for the USA € 665 and for the rest of the world € 765. Subscriptions are accepted on a prepaid basis only and are entered on a calendar year basis.

Payment method
Please make your check payable to Van Zuiden Communications B.V., PO Box 2122, 2400 CC Alphen aan den Rijn, the Netherlands or you can transfer the fee to ING Bank, account number 67.89.10.872, Castellumstraat 1, Alphen aan den Rijn, the Netherlands, swift-code: ING BNL 2A. Do not forget to mention the complete delivery address of the Journal.

Claims
Claims for missing issues should be made within two months of the date of dispatch. Missing issues will be mailed without charge. Issues claimed beyond the two-month limit must be prepaid at back copy rates.

Orders, preprints, advertising, changes in address, author or general enquiries
Please contact the publisher.

Van Zuiden Communications B.V.
PO Box 2122, 2400 CC Alphen aan den Rijn
The Netherlands
Tel.: +31 (0)172-47 61 91, fax: +31 (0)172-47 18 82
E-mail: njm@zuidencomm.nl
Internet: www.njm-online.nl

EDITORIAL

The Netherlands Journal of Medicine's hit list: best cited articles in 2003

J.P.H. Drenth*, P. Smits, T. Thien, A.F.H. Stalenhoef

Department of Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, *corresponding author: tel. +31 (0)24-361 47 60, fax: +31 (0)24-354 01 03, e-mail JoostPHDrenth@CS.com

The scientific world we live in is changing. We no longer rely on the hardcopy of a Journal for scholarly information, instead we just log on to the web and try to find the article that fits our needs. We introduced open access to the *Netherlands Journal of Medicine* (NJM) at the beginning of August, 2005.[1] We did so because we believe that open access serves readers and scientists best. The content of the NJM is now readily available via PubMed (www.pubmed.gov) as well as via the Publisher's website (www.njm-online.nl). We believe that this will attract a wider audience and enable us to disseminate relevant clinical knowledge on a global platform.

The benefits for the Journal are clear: open access enhances the visibility of the Journal and we hope that this translates into an increase in the quantity and quality of submitted manuscripts. On the other hand, open access benefits the authors and readers as well. Evidence shows that usage increases when access is more simple, and maximising the usage of the scientific information benefits society. Papers that are freely accessible online are more easily available and enjoy a higher visibility, which leads to higher citation rates.[2] A by now classic study analysed possible factors that were responsible for higher citation rates for *British Medical Journal* (BMJ) articles. In 1999, the BMJ enjoyed free open access and for a cohort of papers that were published in that year, Perneger calculated the 'hit count' and number of citations these articles received in the following years.[3] Indeed the hit count in the first week after publication correlated significantly with the number of subsequent citations. This phenomenon might be new for biomedical scientists, but it has been known for years among physicists and mathematicians. The correlation between hit counts and subsequent citations appears to be so consistent that an online usage/citation correlator has been created that allows the prediction of citation counts two years later on the basis of the downloads of today (http://citebase.eprints.org/analysis/correlation.php). Consequently, the number of early hits is a potentially useful measure of the scientific value of published medical research papers.

Facilitated by the former publisher, the *Netherlands Journal of Medicine* was available on the web from September 1999 until December 2001. The online content of the Journal was only available via institutional subscription, which limited its access. Despite these obstacles, the electronic usage of the Journal grew quickly, illustrated by the hit counts which increased from only 200 a month at the beginning of 2000 to 1600 a month by the end of 2002.[4] In recent years, we have witnessed an enormous explosion of Internet technology and the data provided here are a mere reflection of this. The electronic traffic to our Journal (for a large part facilitated by its open access) has exceeded our expectations. The vast majority of articles are accessed and downloaded directly via PubMed, and in the first three months the hit count easily exceeded 3000 every month. This illustrates the popularity of PubMed as a search interface but also that the Journal is a viable and interesting source for valuable clinical information. In the near future, we hope to provide you with more detailed information down to the level of individual articles.

Now let us focus our attention on the most popular articles from 2003. In 2003 the Journal published 20 reviews, 22 original articles, 28 case reports and 15 other reports. A count on Web of Science interface (ISI Web of Knowledge), on 15 October 2005, revealed that a total of 45 articles (53%) yield citations and the majority of papers received less than two citations. The level of non-citations is

on a par with that seen for surgical publications but higher than that for immunological journals.[5] The ten most cited articles received on average 4.9 citations within two years after publication (*table 1*). The table contains six reviews, three original articles and one case report. This finding is in line with the notion as reiterated elsewhere that reviews attract the most citations. The authors on this list have to be applauded because they have succeeded in pickking up many citations in a time when the Journal was only limited (*table 1*).

As Editors, we continuously strive for improvement in the content as well as design of the Journal.[6] We aim for publication of important new scientific developments that affect the clinical practice of internists. The Journal attracts a large range of clinical manuscripts and the list shown here reflects the variety of subject matter published by the Journal that has succeeded in attracting attention. The most frequently cited article from 2003, written by Dr Ingrid M. Jazet and colleagues from Leiden University Medical Centre, describes the role of adipocyte secretory products in relation to insulin resistance and obesity. It is well written and equally well illustrated and highly topical, all important reasons why it is best cited.[7] The Editorial Board congratulates these authors on their achievement.

We feel that by publication of both citation rates and hit counts for articles we single out those articles that made the cut. We plan to keep track of both types of impact in the future and will inform the reader accordingly.

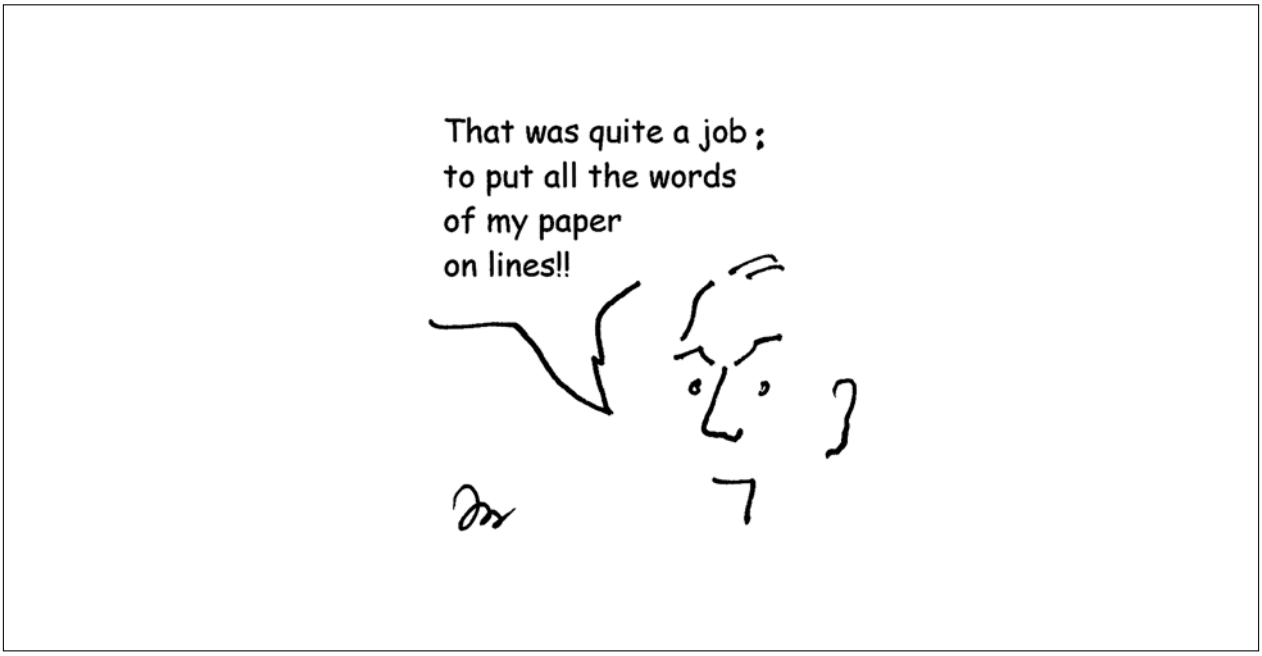
REFERENCES

1. Drenth JP. A watershed for the Netherlands Journal Medicine: open internet access. Neth J Med 2005;63(7):239-40.
2. Lawrence S. Free online availability substantially increases a paper's impact. Nature 2001;411(6837):521.
3. Perneger TV. Relation between online "hit counts" and subsequent citations: prospective study of research papers in the BMJ. BMJ 2004;329(7465):546-7.
4. Hoepelman AI. The Netherlands Journal of Medicine: end of a fruitful period and a new start. Neth J Med 2001;59:267-9.
5. Weale AR, Bailey M, Lear PA. The level of non-citation of articles within a journal as a measure of quality: a comparison to the impact factor. BMC Med Res Methodol 2004;4:14.
6. Thien T, van der Meer JW, Stalenhoef AF, Smits P. Why publish in the Netherlands Journal of Medicine? Neth J Med 2003;61:99.
7. Jazet IM, Pijl H, Meinders AE. Adipose tissue as an endocrine organ: impact on insulin resistance. Neth J Med 2003;61(6):194-212.

Table 1 *Highly cited articles from the Netherlands Journal of Medicine published in 2003*

Author [reference]	Title	Pages	# Citations
Jazet IM, Pijl H, Meinders AE[7]	Adipose tissue as an endocrine organ: impact on insulin resistance	194-212	10
Van Vonderen MG, Bos JC, Prins JM, Wertheim-van DP, Speelman P[8]	Ribavirin in the treatment of severe acute respiratory syndrome (SARS)	238-41	6
Arend SM, Breedveld FC, van Dissel JT[9]	TNF-alpha blockade and tuberculosis: better look before you leap	111-9	5
Bleeker-Rovers CP, Bredie SJ, van der Meer JW, Corstens FH, Oyen WJ[10]	F-18-fluorodeoxyglucosepositron emission tomography in diagnosis and follow-up of patients with different types of vasculitis	323-9	5
Riksen NP, Keuning JJ, Vreugdenhil G[11]	Rituximab in the treatment of relapsing idiopathic thrombocytopenic purpura	262-5	5
Baas SJ, Endert E, Fliers E, Prummel MF, Wiersinga WM[12]	Establishment of reference values for endocrine tests. III: Primary aldosteronism	37-43	4
Becker A, van der Does FE, van Hinsbergh VW, Heine RJ, Bouter LM, Stehouwer CD[13]	Improvement of glycaemic control in type 2 diabetes: favourable changes in blood pressure, total cholesterol and triglycerides, but not in HDL cholesterol, fibrinogen, Von Willebrand factor and (pro)insulin	129-36	4
Van Bommel EF[14]	Renal replacement therapy for acute renal failure on the intensive care unit: coming of age?	239-48	4
De Fost M, Aerts JM, Hollak CE[15]	Gaucher disease: from fundamental research to effective therapeutic interventions	3-8	3
Loffeld RJ, van der Putten AB[16]	The yield of UGIE: a study of a ten-year period in the 'Zaanstreek'	14-8	3

8. Van Vonderen MG, Bos JC, Prins JM, Wertheim-van DP, Speelman P. Ribavirin in the treatment of severe acute respiratory syndrome (SARS). Neth J Med 2003;61(7):238-41.
9. Arend SM, Breedveld FC, van Dissel JT. TNF-alpha blockade and tuberculosis: better look before you leap. Neth J Med 2003;61(4):111-9.
10. Bleeker-Rovers CP, Bredie SJ, van der Meer JW, Corstens FH, Oyen WJ. F-18-fluorodeoxyglucose positron emission tomography in diagnosis and follow-up of patients with different types of vasculitis. Neth J Med 2003;61(10):323-9.
11. Riksen NP, Keuning JJ, Vreugdenhil G. Rituximab in the treatment of relapsing idiopathic thrombocytopenic purpura. Neth J Med 2003;61(7):262-5.
12. Baas SJ, Endert E, Fliers E, Prummel MF, Wiersinga WM. Establishment of reference values for endocrine tests. III: Primary aldosteronism. Neth J Med 2003;61(2):37-43.
13. Becker A, van der Does FE, van Hinsbergh VW, Heine RJ, Bouter LM, Stehouwer CD. Improvement of glycaemic control in type 2 diabetes: favourable changes in blood pressure, total cholesterol and triglycerides, but not in HDL cholesterol, fibrinogen, Von Willebrand factor and (pro)insulin. Neth J Med 2003;61(4):129-36.
14. Van Bommel EF. Renal replacement therapy for acute renal failure on the intensive care unit: coming of age? Neth J Med 2003;61(8):239-48.
15. De Fost M, Aerts JM, Hollak CE. Gaucher disease: from fundamental research to effective therapeutic interventions. Neth J Med 2003;61(1):3-8.
16. Loffeld RJ, van der Putten AB. The yield of UGIE: a study of a ten-year period in the 'Zaanstreek'. Neth J Med 2003;61(1):14-8.



Drenth, et al. The Netherlands Journal of Medicine's hitlist.

Netherlands
The Journal of Medicine

How to optimise interventions for problem drinking among hospital outpatients?

M.J. Emmen[1*], H. Wollersheim[2], G. Bleijenberg[3], G.M. Schippers[4]

[1]Netherlands Institute for Health Services Research (NIVEL), Utrecht, the Netherlands, [2]Centre for Quality of Care Research and [3]Expert Centre for Chronic Fatigue, Radboud University Nijmegen Medical Centre, Nijmegen, the Netherlands, [4]Amsterdam Institute for Addiction Research, Amsterdam Medical Centre, the Netherlands, [*]corresponding author: tel.: +31 (0)30-272 98 29, fax: +31 (0)30-272 97 29

ABSTRACT

In this article several suggestions on how to optimise interventions for problem drinking among hospital outpatients are enumerated. These interventions are especially important for patients with diagnoses that are alcohol related. The intervention has to be brief and easy to integrate into medical specialist's routine practice; an active role for the medical specialist and flexible involvement of a specialised nurse are suggested. Key elements of the intervention are:

- **early identification of problem drinking;**
- **raising the issue of problem drinking;**
- **assessment of the drinking behaviour;**
- **reaching an agreement about change;**
- **follow-up;**
- **evaluation of the change.**

A feasible and attractive option is integrating the intervention into a broader lifestyle intervention. Those who perform the brief alcohol intervention need to be specially educated and trained.

KEYWORDS

Alcohol consumption, alcoholism, brief intervention, hospital outpatients, prevention

INTRODUCTION

Medical specialists in hospitals frequently encounter patients who drink above safe health limits (>14 units/week for women and >21 units/week for men). Especially if patients have medical complications that are related to their problematic alcohol use, the medical specialist has to intervene in the alcohol problems alongside the patient's medical treatment. Although interventions for problematic alcohol use are described in guidelines such as the 'Guideline problematic alcohol use from the Dutch College of General Practitioners',[1] medical specialists are not used to intervening structurally in alcohol-related problems. Most lack the skills to intervene appropriately and successfully. Because of time restraints and low expectations on effect, lifestyle interventions are considered a waste of time. Medical specialists usually restrict themselves to warnings, i.e. to unidirectional advice about lifestyle. This is often not sufficient. The question arises as to how alcohol problems among hospital patients can be dealt with in a more structured way during medical practice. In this article we will give suggestions on how interventions for problem drinking among hospital outpatients can be optimised, based on relevant literature and our own research experience. We will refer to the type of intervention, target population and to the question who can best provide the intervention. This is followed by a description of the important elements of a brief alcohol intervention among hospital outpatients including an example. Training should be an important facilitator of the intervention.

TYPE OF INTERVENTION, TARGET GROUP AND PROVIDER

Type of intervention

To stimulate medical caregivers to perform an intervention

to reduce alcohol consumption among their patients, the intervention needs to be brief and easy to integrate into daily hospital medical practice. The majority of the patients with mild or moderate alcohol problems might profit from such an intervention.[2,3] Those who fail to change their drinking behaviour can be referred to specialised treatment with a higher level of intensity.
Most brief interventions comprise assessment, advice, counselling with educational elements, and some form of written information. They are less time-consuming than intensive alcohol treatment and are generally delivered by professionals other than specialists in substance abuse.[4] They are often 'opportunistic', since their aim is to modify drinking behaviour in patients whose primary interest is not discussing their drinking behaviour. Most brief interventions aim for moderate or harm-free drinking rather than total abstinence.
Although various studies have reported about the use of brief alcohol interventions in general practice,[5,6] less studies examined brief alcohol intervention in the hospital setting. In a review of the literature regarding studies performed in the general hospital setting, we found only eight controlled trials.[7] Two of these studies were performed among outpatients. Although one of these outpatient studies found a reduction in alcohol consumption and a decrease in γ-glutamyltransferase (GGT),[8] and the other a decrease in sickness allowance days,[9] both studies had major methodological weaknesses. So the evidence for the effectiveness of such brief interventions is not convincing. However, various arguments underscore the need for a brief intervention that is structured, flexible and feasible. The chronic character of many alcohol problems needs to be taken into account. A single intervention by one medical specialist during one or two consultations might not be sufficient to have a lasting effect on chronic disorders.[2] An alcohol intervention embedded in a chain of repeated interventions, preferably in cooperation with other caregivers, might eventually lead to better results. A short, feasible motivational advice may help the doctor-patient interaction. Finally, whether they like it or not, medical doctors are regularly confronted with patients who continue their drinking habit that is in flagrant contradiction to their health. The causal or contributing effects of heavy drinking on somatic illnesses is strong and undisputed. As such, medical specialists cannot neglect this behaviour. It seems simply unethical to disregard it.
So, how should the intervention be performed?
Although brief interventions for problem drinking are also performed among hospital patients who attend the accident and emergency department or came straight to a clinic for treatment of injuries,[10-12] we focus more on the medical specialist in the chronic care setting. In acute care settings the population more often consists of younger drinkers who drink too much on one occasion (binge drinkers) instead of the chronic excessive drinkers. Often less time is available for intervention, so follow-up of an intervention can become difficult. If the patient's injury is related to the use of alcohol, the intervener should primarily pay attention to that injury. All these factors make brief interventions in the acute care different from those we describe in our article

Target group

Brief alcohol interventions could also be effective for problem drinkers with nonalcohol-related complaints. However, it can be questioned who will be the best person to perform this form of prevention. We think it can be useful if medical specialists who identify excessive drinkers with health problems that are neither directly nor indirectly related to excessive alcohol use at least make a remark about the healthy drinking limits, and ask the general practitioner to deal with it further.

Provider of the intervention

Brief interventions in the hospital setting can be performed by different healthcare providers such as medical specialists,[8] psychologists,[13] specialised nurses,[13-16] or combinations of these.[9,17]
We doubt whether psychologists should be the secondary reference to provide a brief intervention in the hospital setting. Elvy and colleagues (1988) studied a brief intervention in which hospital inpatients were approached by a psychologist who confronted them with their self-reported drinking problems and asked whether they would accept referral to an alcoholism counsellor.[13] Although patients who received the intervention improved in terms of self-reported alcohol problems, no differences in reduction in alcohol consumption were found compared with those who did not receive the intervention. We also failed to find evidence for the effectiveness of adding a brief motivational intervention for problem drinking provided by a psychologist to physician's advice among hospital outpatients.[18] The two-session intervention focused on enhancing motivation by perceiving consequences of excessive use and reflecting on them. After six months there were no differences between the patients who did and those who did not receive the intervention.
Evidence suggests that nurses are effective at reducing excessive drinking in the primary healthcare setting.[19] Nurses performed approximately half of the interventions evaluated in the World Health Organisation study of brief interventions in primary healthcare.[19] This study showed that their simple advice and brief counselling had a significant effect on reducing alcohol consumption, especially among males. Another primary care study also found a reduction in alcohol consumption after very brief advice and counselling delivered by a nurse practitioner.[20]
Less studies evaluated brief interventions for problem

drinking performed by nurses in the hospital setting, and the effects are less convincing. Three studies that evaluated brief alcohol interventions performed by a (specialised) nurse among hospital inpatients reported no effects on alcohol consumption.[14-16] However, an intensive interview by a specialised nurse led to a reduction in alcohol-related problems and a reduction in the biochemical marker GGT.[14] After an audiovisual presentation of information on alcohol and a booklet offered by nursing staff a significanty larger proportion of patients experienced a decrease in their alcohol-related health problems compared with a control group.[15] So the effects of nurses providing the brief intervention for problem drinking among hospital patients are mixed. Nevertheless, because nurses with a specialisation in mental health counselling regularly provide treatment in organisations dealing with substance use disorders, specialised nurses can be considered quite suitable to be employed for this task in outpatient clinics as well.

Based on the positive effects of brief alcohol interventions performed by the general practitioner,[5,6] it seems likely that a hospital intervention for problem drinking is most effective when it is performed, or at least initiated, by the medical specialist himself. This was the case in the only hospital intervention study with clear positive effects.[8] A motivated medical specialist gave his patients personal advice and reinforced this four times within eight weeks. Also, in a recent study among outpatients with high cardiovascular risk, we demonstrated that targeting several risk behaviours such as excessive drinking, smoking, unhealthy eating habits and inactivity by a medical specialist in internal medicine appeared to have positive although small effects.[21]

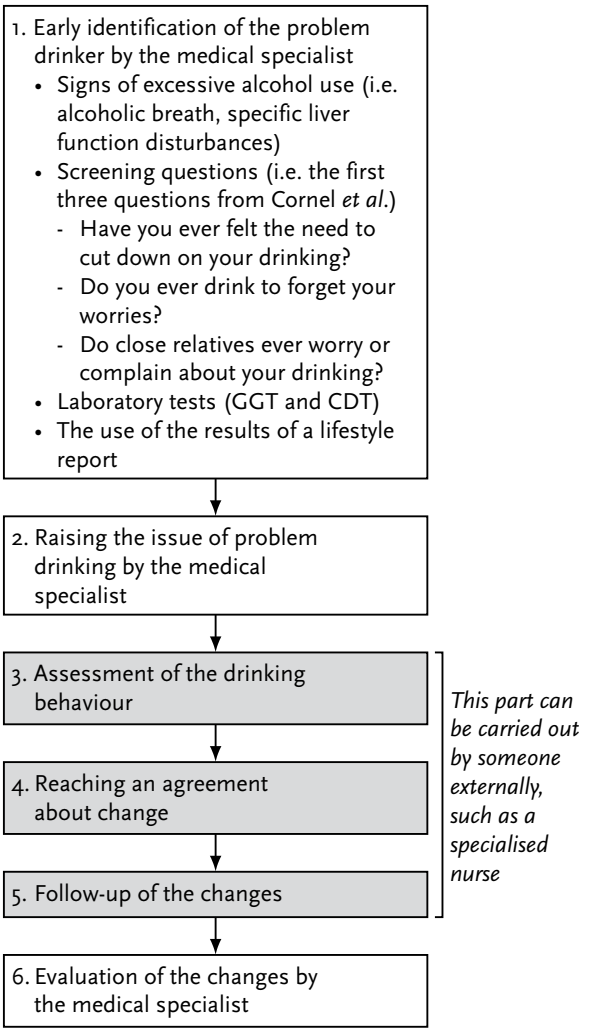
However, lack of time, knowledge or motivation, doubts about effectiveness and inadequate skills often prevent medical specialists from performing brief interventions to promote patient health.[22-24] A feasible alternative might be that they pass on the intervention to another care provider after they have established rapport with the identified problem drinker. These care providers can be trained more extensively and can save costs if they take over tasks that are now carried out by the medical specialist. Research in primary healthcare has demonstrated positive effects when screening and raising the issue of a drinking problem by the physician were combined with an intervention by a nurse.[25] This could be a valuable combination in the hospital setting too.

KEY ELEMENTS OF A BRIEF ALCOHOL INTERVENTION AMONG HOSPITAL OUTPATIENTS

Based on the guide 'Helping patients with alcohol problems', published by the National Institute on Alcohol Abuse and Alcoholism,[26] and in line with the recently published Dutch guidelines for intervention in smoking behaviour,[27] and inspired by our own experiences, we have developed a stepwise approach for brief, structured intervening in problem drinking among hospital outpatients. The six key elements of a brief alcohol intervention are (*figure 1*):

- early identification of problem drinking;
- raising the issue of problem drinking;
- assessment of the drinking behaviour;
- reaching an agreement about changing the drinking behaviour;
- follow-up;
- evaluation of the change.

Figure 1 *The six key elements of a brief alcohol intervention in the hospital setting*



Early identification of problem drinking

Early identification of problem drinking is important since brief interventions are most effective if started early.[2] The medical specialists are in a favourable position to identify the problem drinker during the first diagnostic consultation. Therefore, they should question all patients regarding their alcohol consumption. However, many patients do not present their alcohol use as a problem. Not only disorders such as reflux oesophagitis, liver cirrhosis, pancreatitis, peripheral neuropathy, hypertension, fatigue and depression, but also a variety of social and behavioural complications can serve as clues to the presence of problem drinking.[28,29]

Screening questionnaires, such as the first three questions from an interval scale measuring the severity of problem drinking by Cornell and colleagues,[30] or the four questions from the CAGE questionnaire,[31] can be used to facilitate the early identification of problem drinkers. The administration of the three screening questions from Cornell's scale takes 25 seconds. The administration of the four questions from the CAGE takes 32 seconds. Given the good psychometric qualities, we would recommend the first three questions from Cornell's interval scale.[30] The AUDIT is a useful screening questionnaire too,[32] but two minutes are required for the administration of this ten-item questionnaire and another minute for the interpretation of the scores. Altogether this takes too much time. In our study regarding the effectiveness of a brief psychological motivational alcohol intervention among hospital outpatients, internal medicine residents did a structural screening. They used the Cornell scale for all patients who consumed alcohol. About 70% of the participating residents reported that they found it difficult to ask the sensitive alcohol-related questions to patients with complaints that were obviously not alcohol related or to patients who stated that they only drank sporadically. They were concerned about offending these patients. In general, they had fewer problems with the screening if patients drank regularly or had probable alcohol-related complaints. Other researchers found similar problems with universal screening among general practitioners.[33] Therefore we would like to advocate a greater alertness in identifying problem drinking than screening all patients structurally.

The screening questions could be supported by the use of biochemical markers of excessive alcohol consumption such as an elevated GGT or carbohydrate-deficient transferrin (CDT).[34] The cut-off value for the % CDT (axis-shield % CDT assay) is ≥2.6%. However, for both markers the predictive value for diagnosing alcohol abuse is not high.[34] If elevated, these markers can be valuable during follow-up. They can be used to motivate patients who have successfully lowered their consumption and in whom the test normalised.

Raising the issue of problem drinking

Raising the issue of problem drinking sensitively is the next step. Since problematic alcohol use is associated with more stigmas than, for example, tobacco use, and patients can feel ashamed, the topic should be raised non-moralistically. This part of the intervention will be most convincing if medical specialists do it, since they are the experts to emphasise the relation between the patient's alcohol use and medical symptoms. After mentioning the (possible) influence of 'use of alcohol' on the patient's complaints, the specialist can ask the patient to discuss his/her drinking behaviour. Rollnick and colleagues suggest that words such as 'problem' or even 'concern' can best be avoided and that 'use of alcohol' is the safest phrase to use.[35] They also advise that if the subject is raised and the patient is feeling threatened, it can be good to give a patient time to think it over, coming back to it later. Yet, this could mean an extra consultation.

Assessment of the drinking behaviour

The following step is the assessment of the drinking behaviour. Although in our experience medical specialists can be trained to assess patient's drinking behaviour within five minutes, it could be an option to involve a specially trained nurse for this part of the intervention. Based on the biopsychosocial model of health and illnesses developed by Engel,[36,37] we suggest examining the drinking behaviour from a biological, psychological and social perspective. The biological perspective means examining the relation between patient's alcohol use and medical symptoms. The psychological perspective deals with where, when and how much the patient drinks, his cognitions (ideas and opinions about alcohol use), and emotions (how the patient feels when drinking alcohol). The social perspective concerns the self-reported influences on the patient's social environment; how the social environment confirms, accepts or rejects the patient's drinking behaviour, and with whom and where the patient drinks.

Reaching an agreement about change

After the assessment, the medical specialist or specialised nurse tries to reach an agreement with the patient about changing the risk behaviour. The advice provided to the patient depends on the severity of the complaints and the patient's drinking history. Based on the guidelines to help patients with alcohol problems published by the National Institute on Alcohol Abuse and Alcoholism[26] the following advice is recommended: reducing alcohol consumption below the national health limit (in the Netherlands: ≤3 U/day for men and ≤2 U/day for women) for patients with mild or moderate alcohol problems and abstaining from alcohol for patients with severe alcohol-related diagnoses, alcohol dependency, or a long drinking history.

After the advice, the patient should be given the opportunity to react. The medical specialist gauges the patient's readiness to change by asking what the patient thinks and if he is ready to cut down or to abstain. According to the transtheoretical model of behaviour change the patient is stimulated to move through a series of changes from not thinking about change (precontemplation), to being unsure about it (contemplation), ready for change (preparation), engaged in change (action) and keeping the change going (maintenance).[38,39] If a patient is not ready to change, the medical specialist can restate concern about the patient's health and reaffirm his willingness to assist the patient when he is ready to change his drinking behaviour. Although this patient will not immediately change his drinking behaviour, offering the advice might have caused a change in the patient's thinking about the risky drinking behaviour. If a patient is ready to try to cut down or to abstain, the patient and care provider can negotiate a feasible behavioural change goal. Patients are more likely to change their drinking behaviour when they are involved in goal setting.[40] The care provider can enhance the commitment by noting the mutual agreement down in the patient's medical record, and by announcing that he will return to the subject at the next consultation.

Follow-up

The fifth step of a brief intervention is a follow-up at the next consultation. The care provider asks the patient how he has progressed with his behaviour change and reinforces any progress toward reduction in alcohol consumption. It is important to enhance the patient's confidence, so the patient will feel able to change his drinking behaviour.[40] If a patient has not reached his treatment goals, the care provider should explore the reasons for this. New feasible goals can be set and new agreements can be made.

The role of these follow-up sessions in which patient's progress is monitored should not be underestimated. Interventions for excessive drinkers seem to be more effective when extended by one or more follow-up sessions.[41,42] Both effective brief interventions in the primary care,[5,6,25] and the only successful hospital intervention,[8] included several follow-up sessions.

Evaluating the change

The sixth and last step of the intervention is the evaluation of the change by the medical specialist. If someone else performed the assessment, reached the agreement and did one or more follow-up sessions, the medical specialist needs to be informed about the results, so he can evaluate how a patient has progressed. To prevent patients from relapsing and to better maintain the established changes in drinking behaviour, the medical specialist can inform the patient's general practitioner and eventually other health providers about the agreement of change and results by a letter. A copy of the letter can be sent to the patients. This written document might enhance patient commitment.

For those patients who have had several unsuccessful attempts at changing their drinking behaviour, the medical specialist should consider referral to a specialist in substance abuse or a self-help group such as the AA (Alcoholics Anonymous). Again the specialist can send a copy of the referral letter to the patient.

BRIEF ALCOHOL INTERVENTIONS AS PART OF A BROADER LIFESTYLE INTERVENTION

Integrating alcohol assessment in the context of a broader lifestyle assessment will probably make it more acceptable to both internists and nurses and less threatening for the patients.[43] Recently, we studied the implementation and effect of brief behavioural feedback intervention in hospital outpatients.[21] The intervention was performed by medical specialists in internal medicine and directed at patients with lifestyle-related complaints, in particular those with a high cardiovascular risk profile. The intervention was brief and easy to perform, it took about one to five minutes, seemed to be feasible to implement, and had small but significant positive effects. The intervention involved not only the reduction of excessive alcohol consumption, but also modification of smoking, physical inactivity and poor dietary habits.[21]

To deliver the intervention, the medical specialists first had to invite patients to complete a computerised lifestyle assessment including questions about smoking, physical inactivity, poor dietary habits and alcohol consumption and about patient's readiness to change these behaviours. This pilot study reported on the use of a computer programme called CLAFI (Computerised Lifestyle Assessment and Feedback Intervention). In this programme, patient's assessment scores are presented in a personal lifestyle feedback report. The scores on the different health behaviours are calculated and transformed into risk scores for the four behaviour domains. The risk scores are visualised by traffic lights: red for risky behaviour, orange for behaviour which is not really harmful yet, but could be improved, and green for healthy behaviour. The traffic lights are accompanied by educational messages such as 'Smoking is harmful for your health, you'd better stop' (red colour). For each behaviour that was 'risky' or 'could be improved', the patient's motivation to change is presented as well. This information about patients' motivation to change can be very useful for the medical specialists who have to provide feedback to their patients.

In a next consultation, the medical specialist offers the personal feedback report to the patients. We support the medical specialists by providing an instructive checklist, as part of the programme, to couple the report with verbal comments and advice. The feedback report makes risk behaviour immediately visible for the medical specialist and the patient, and places it in the frame of lifestyle in general. This facilitates in particular the key elements of identifying the lifestyle problems and raising the issue and can be followed by further assessment and an agreement on changing behaviour.

TRAINING

Although nurses and physicians in specialised healthcare settings indicate they are often confronted with alcohol problems, they consider early recognition and treatment of heavy drinking as less appropriate and showed poor knowledge of the content of brief alcohol interventions.[23] Research shows that general practitioners who received more education regarding alcohol abuse are more likely to manage patients with alcohol-related harm.[44] Also training in alcohol counselling skills is important to give them a sense of competence to intervene with problem drinkers.[45] A controlled trial conducted among emergency medicine residents demonstrated that these elements are also relevant in the training of specialists.[46] A four-hour didactic video and skills-based workshop significantly improved the residents' knowledge and practice with regard to patients with alcohol problems.
We developed a five-hour training programme for medical specialists to perform the brief alcohol intervention described earlier, implying both raising alertness, educating and counselling, and referral. The trainers were psychologists and experienced medical specialists. The training transfers the relevance, effects and content of a brief alcohol intervention in the context of a biopsychosocial model of health and illnesses.[36,37]
Because it is preferable to involve nurses in brief alcohol interventions in general healthcare, a training programme is needed to help them screen and educate patients, perform brief interventions and support the treatment of patient resistance.[47] An adaptation of our training programme has now been designed and is being used in a running implementation project in Amsterdam and Nijmegen.

CONCLUSION

The combination of identifying the problem drinking and raising the issue of a drinking problem by the specialist with the assessment of the drinking behaviour, reaching an agreement about change and follow-up by a specialised nurse needs further consideration. Finally, medical specialists should evaluate the change and consider informing other care providers, or referring patients who have had several unsuccessful attempts at changing their drinking behaviour to specialised alcohol treatment. To stimulate the medical specialist and nurses to perform the intervention, it should be brief, easy to perform, fit into their workflow, and be focused on patients with complaints which are directly or indirectly related to excessive alcohol use. Moreover, it is important to educate both medical specialists and nurses about the relevance and effects of brief alcohol intervention and to train them in how to apply those interventions.
Future research can best be focused on the effectiveness of brief alcohol interventions among hospital outpatients in routine practice. For example in randomised controlled multicentre trials, where hospitals are randomised to evaluate the intervention against usual care. Such studies should include a process analysis of daily routines that might reveal factors that influence the successful implementation of the interventions and help tailoring the service.

ACKNOWLEDGEMENT

The research is funded by ZonMw 'Netherlands Organisation for Health Research and Development', (project no.: 31000017).

REFERENCES

1. Cornel M, van Olst EJ, Willink AE, Hoeksema JCM, Bloemen JR, van der Laan JR. NHG-Standaard Problematisch alcoholgebruik [Guidelines of the Dutch College of General Practitioners Problematic alcohol use]. Huisarts Wet 1990;33:280-5.
2. Moyer A, Finney JW, Swearingen CE, Vergun P. Brief interventions for alcohol problems: a meta-analytic review of controlled investigations in treatment-seeking and non-treatment-seeking populations. Addiction 2002;97:279-92.
3. Institute of Medicine. Broadening the base of treatment for alcohol problems. Washington DC, US: National Academy Press; 1990.
4. Heather N. Brief intervention strategies. In: Hester RK, Miller WR, editors. Handbook of alcoholism treatment approaches: Effective alternatives. Needham Heights, MA,US: Allyn & Bacon; 1995. p. 105-22.
5. Ballesteros J, Gonzalez-Pinto A, Querejeta I, Arino J. Brief interventions for hazardous drinkers delivered in primary care are equally effective in men and women. Addiction 2004;99:103-8.
6. Poikolainen K. Effectiveness of brief interventions to reduce alcohol intake in primary health care populations: a meta-analysis. Prev Med 1999;28:503-9.
7. Emmen MJ, Schippers GM, Bleijenberg G, Wollersheim H. Effectiveness of opportunistic brief interventions for problem drinking in a general hospital setting: systematic review. BMJ 2004;328:318-20.

8. Maheswaran R, Beevers M, Beevers DG. Effectiveness of advice to reduce alcohol consumption in hypertensive patients. Hypertension 1992;19:79-84.
9. Persson J, Magnusson PH. Early intervention in patients with excessive consumption of alcohol: a controlled study. Alcohol 1989;6:403-8.
10. Antti-Poika I, Karaharju E, Roine R, Salaspuro M. Intervention of heavy drinking--a prospective and controlled study of 438 consecutive injured male patients. Alcohol Alcohol 1988;23:115-21.
11. Longabaugh R, Woolard RE, Nirenberg TD, et al. Evaluating the effects of a brief motivational intervention for injured drinkers in the emergency department. J Stud Alcohol 2001;62:806-16.
12. Smith AJ, Hodgson RJ, Bridgeman K, Shepherd JP. A randomized controlled trial of a brief intervention after alcohol-related facial injury. Addiction 2003;98:43-52.
13. Elvy GA, Wells JE, Baird KA. Attempted referral as intervention for problem drinking in the general hospital. Br J Addict 1988;83:83-9.
14. Chick J, Lloyd G, Crombie E. Counselling problem drinkers in medical wards: a controlled study. BMJ 1985;290:965-7.
15. Rowland N, Maynard AK. Standardized and alcohol education: a hit or miss affair? Health Promotion Int 1993;8:5-12.
16. Watson HE. A study of minimal interventions for problem drinkers in acute care settings. Int J Nurs Stud 1999;36:425-34.
17. Heather N, Rollnick S, Bell A, Richmond R. Effects of brief counselling among male heavy drinkers identified on general hospital wards. Drug Alcohol Rev 1996;15:29-38.
18. Emmen MJ, Schippers GM, Bleijenberg G, Wollersheim H. Adding psychologist's intervention to physicians' advice to problem drinkers in the out-patient clinic. Alcohol Alcohol 2005;40:219-26.
19. Babor TF, Grant M, Acuda W, et al. A randomized clinical trial of brief interventions in primary care: summary of a WHO project. Addiction 1994;89:657-60.
20. Ockene JK, Adams A, Hurley TG, Wheeler EV, Hebert JR. Brief physician- and nurse practitioner-delivered counseling for high-risk drinkers: does it work? Arch Intern Med 1999;159:2198-205.
21. Emmen MJ, Peters E, Elving LD, et al. A brief behavioral feedback intervention in hospital outpatients with a high cardiovascular risk. Patient Education and Counselling. In press. Epub 2005 Jan 4.
22. Brull R, Ghali WA, Quan H. Missed opportunities for prevention in general internal medicine. CMAJ 1999;160:1137-40.
23. Kaariainen J, Sillanaukee P, Poutanen P, Seppa K. Opinions on alcohol-related issues among professionals in primary, occupational, and specialized health care. Alcohol Alcohol 2001;36:141-6.
24. Schwartz JS, Lewis CE, Clancy C, Kinosian MS, Radany MH, Koplan JP. Internists' practices in health promotion and disease prevention. A survey. Ann Intern Med 1991;114:46-53.
25. Israel Y, Hollander O, Sanchez-Craig M, et al. Screening for problem drinking and counseling by the primary care physician-nurse team. Alcohol Clin Exp Res 1996;20:1443-50.
26. National Institute on Alcohol Abuse and Alcoholism. Helping patients with alcohol problems: A health practitioners guide. 2004 February NIH Publication No.:04-3769.
27. Van Weel C, Coebergh JW, Drenthen AJM, et al. Richtlijnen voor medici en paramedici bij de behandeling van tabaksverslaving [Review]. Ned Tijdschr Geneeskd 2005;149(1):17-21. Erratum in Ned Tijdschr Geneeskd 2005;149(12):672.
28. Isaacson JH, Nielsen C, Urbanic R, Challgren E. Markers for Patients with Alcohol Problems in an Outpatient General Medicine Clinic. Subst Abus 1999;20:141-7.
29. O'Connor PG. The General Internist. Alcohol Res Health 1994;18:110-6.
30. Cornel M, Knibbe RA, van Zutphen WM, Drop MJ. Problem drinking in a general practice population: the construction of an interval scale for severity of problem drinking. J Stud Alcohol 1994;55:466-70.
31. Ewing JA. Detecting alcoholism. The CAGE questionnaire. JAMA 1984;252:1905-7.
32. Babor TF, De La Fuente JR, Saunders J, Grant M. AUDIT: the Alcohol Use Disorders Identification Test. Guidelines for use in the primary health care. Geneva: World Health Organization; 1989.
33. Beich A, Gannik D, Malterud K. Screening and brief intervention for excessive alcohol use: qualitative interview study of the experiences of general practitioners. BMJ 2002;325:870-2.
34. Aithal GP, Thornes H, Dwarakanath AD, Tanner AR. Measurement of carbohydrate-deficient transferrin (CDT) in a general medical clinic: is this test useful in assessing alcohol consumption. Alcohol Alcohol 1998;33:304-9.
35. Rollnick S, Mason P, Butler C. Health Behaviour Change: A guide for practitioners. Edinburgh: Churchill Livingstone; 1999.
36. Engel GL. The need for a new medical model: a challenge for biomedicine. Science 1977;196:129-36.
37. Engel GL. The clinical application of the biopsychosocial model. Am J Psychiatry 1980;137:535-44.
38. Prochaska JO, Diclemente CC. Toward a comprehensive model of change. In: Miller WR, Heather N, editors. Treating addictive behaviors: Processes of Change. New York: Plenum Press; 1986. p. 3-27.
39. Prochaska JO, Diclemente CC, Norcross JC. In search of how people change. Applications to addictive behaviors. Am Psychol 1992;47:1102-14.
40. Miller WR, Rollnick S. Motivational interviewing: Preparing people to change addictive behavior. New York: The Guilford Press; 1991.
41. Humphreys K, Tucker JA. Toward more responsive and effective intervention systems for alcohol-related problems. Addiction 2002;97:126-32.
42. McAvoy BR, Kaner EF, Lock CA, Heather N, Gilvarry E. Our Healthier Nation: are general practitioners willing and able to deliver? A survey of attitudes to and involvement in health promotion and lifestyle counselling. Br J Gen Pract 1999;49:187-90.
43. Graham AW. Screening for alcoholism by life-style risk assessment in a community hospital. Arch Intern Med 1991;151:958-64.
44. Anderson P, Kaner E, Wutzke S, et al. Attitudes and management of alcohol problems in general practice: descriptive analysis based on findings of a world health organization international collaborative survey. Alcohol Alcohol 2003;38:597-601.
45. Ockene JK, Wheeler EV, Adams A, Hurley TG, Hebert J. Provider training for patient-centered alcohol counseling in a primary care setting. Arch Intern Med 1997;157:2334-41.
46. D'Onofrio G, Nadel ES, Degutis LC, et al. Improving emergency medicine residents' approach to patients with alcohol problems: a controlled educational trial. Ann Emerg Med 2002;40:50-62.
47. Lock CA, Kaner E, Lamont S, Bond S. A qualitative study of nurses' attitudes and practices regarding brief alcohol intervention in primary health care. J Adv Nurs 2002;39:333-42.

Netherlands
The Journal of Medicine

No clear effect of diabetes education on glycaemic control for Turkish type 2 diabetes patients: a controlled experiment in general practice

P.J.M. Uitewaal[1*], A.J.J. Voorham[2], M.A. Bruijnzeels[3], A. Berghout[4], R.M.D. Bernsen[5], P.H. Trienekens[6], A.W. Hoes[7], S. Thomas[5]

[1]Department EGG, Municipal Health Service, The Hague, the Netherlands, [2]Community Interventions Sector Health Promotion, Municipal Health Service Rotterdam Area, the Netherlands, Departments of [3]Health Policy and Management, and [5]General Practice, Erasmus Medical Centre, Rotterdam, the Netherlands, [4]Departments of Internal Medicine, Endocrinology, Medical Centre Rotterdam South, the Netherlands, [6]Practitioners Laboratory, Rotterdam Foundation (STAR), Rotterdam, the Netherlands, [7]Department of Clinical Epidemiology and General Practice, Julius Centre for General Practice and Patient-Oriented Research, University Medical Centre Utrecht, the Netherlands, [*]corresponding author: tel.: +31 (0)70-353 71 94, fax : +31 (0)70-353 72 92, e-mail: p.uitewaal@ocw.denhaag.nl

ABSTRACT

Background: In Turkish immigrant diabetics, problems with communication and cultural differences may hinder delivery of diabetes care.

Methods: In a prospective controlled study, the effect of an ethnic-specific diabetes education programme on glycaemic control and cardiovascular risk factors in Turkish type 2 diabetes patients was assessed, by comparing Turkish diabetics who were offered the education programme with Turkish diabetics offered routine care only (control group). From 16 general practices (31 GPs) in Rotterdam, 104 Turkish type 2 diabetes patients were recruited, 85 of whom could be assessed at one-year follow-up. Glycaemic control, lipid concentrations, blood pressure and body mass index were measured.

Results: Compared with the control group, mean HbA_{1c} in the intervention group decreased by 0.3% (95% CI -0.8 to 0.2). A significant decrease in HbA_{1c} was observed in women with HbA_{1c} >7% at baseline (-0.9%; 95% CI -1.73 to -0.09) but not in the other subgroups studied. Serum lipid concentrations, blood pressure and body mass index remained unchanged in the intervention group.

Conclusion: Ethnic-specific diabetes education by Turkish female educators has no obvious beneficial effect on glycaemic control or cardiovascular risk profile. More focus on specific patient selection and gender equality between educators/ patients may prove worthwhile.

KEYWORDS

Diabetes mellitus, education, ethnic groups

INTRODUCTION

Type 2 diabetes has a high prevalence among ethnic groups in Western society.[1-4] Together with ageing of the population, it is expected that the prevalence of type 2 diabetes will further increase in these groups in the coming decade. Diabetes education is an essential part of diabetes care.[5] Problems with communication and cultural differences may hinder delivery of optimal diabetes care to ethnic groups.[6]

The Turkish population is one of the largest ethnic minority groups in the Netherlands. Most of the older Turkish inhabitants are first-generation immigrants who came to the Netherlands in the 1960s and 1970s. They live in a relatively traditional manner and their proficiency in the Dutch language is limited. The available data show that the prevalence of type 2 diabetes in the Turkish population is about twice as high as that in the indigenous Dutch population and that compared with Dutch type 2 diabetes patients, glycaemic control in Turkish diabetics is poorer.[4,7]

We developed an ethnic-specific education programme: an education programme tailored to the traditions and

specific habits of the Turkish diabetes patients (treated by their GP in general practices) and also taking the low level of education in this group into account. The programme was carried out by Turkish female health educators. This study assessed whether the diabetes education programme has a beneficial effect on glycaemic control and cardiovascular risk factors in Turkish type 2 diabetes patients.

PATIENT AND METHODS

The study followed a prospective controlled experimental design. Turkish type 2 diabetes patients from seven practices (13 GPs) in the southern part of Rotterdam formed the intervention group and were offered routine care together with ethnic-specific diabetes education. For the control group Turkish type 2 diabetes patients were recruited from nine practices (18 GPs) located in a comparable ethnic and socioeconomic area in the northern part of Rotterdam, who were offered routine care only. All practices were fully computerised.
Approval for this study was obtained from the Ethics Committee of the Erasmus Medical Centre, Rotterdam.

Patients

An inventory of all type 2 diabetes patients who were treated for their diabetes by the GP exclusively was made from the computer-based patient records and, if present, disease register. Patients were identified as type 2 diabetics if they were specifically marked in the patient records as having type 2 diabetes, or using oral antidiabetic medication or insulin. Patients were considered Turkish on the basis of their surname, as assigned by a Turkish assistant.[7] All Turkish type 2 diabetes patients younger than 75 years and treated for diabetes by their GP were eligible. Excluded were patients who, according to their GP, were too ill to follow the intervention programme, and patients planning to go abroad for more than six months during the study period. A Turkish-speaking assistant, who was not aware of which group the patients were allocated, approached the patients to invite them to participate. After informed consent and baseline measurements, patients were informed by letter whether they were allocated to the intervention or the control group.

Intervention

The two Turkish health educators, both of Turkish origin, who spoke both Turkish and Dutch fluently, were regarded as representatives of the target population (peers). They were trained educators and had experience in educating in a primary care setting. They received an additional training about diabetes management. Because of their Turkish background, the educators could be seen as peers and were thought able to translate advice on diabetes into understandable and (culturally) acceptable (ethnic-specific) advice for Turkish diabetes patients.[8] The health educators were supervised by a Dutch psychologist, both individually and together with other to health educators.
A new diabetes programme was developed, based on basic elements of known Dutch diabetes education programmes (e.g. what is diabetes, general advice on diet, physical exercise and self-care), taking the characteristics of this specific group of Turkish diabetes patients, such as low education and a traditional way of living, into account. The planned nine-month programme included seven individual educational sessions and three group sessions. The individual sessions consisted of four sessions with the educator and patient together and three 'triangle' sessions with the GP, educator and patient present, to discuss the three-monthly assessment of the glycaemic control and cardiovascular risk factors. Patients were encouraged to have one of the individual sessions with the dietician and one with the partner present, although this was not obligatory. Afterwards, the educator and patient discussed the triangle sessions. During the intervention, group sessions were organised separately for men and women. The educators were allowed to adjust the number of the education sessions according to the needs of the individual patient. Individual and group sessions took place in the general practice.
The programme was based on three principles: peer education, tailoring, and the Health Education Model.[9] Education focused on attainment of self-care skills and behavioural change strategies. During the individual sessions the educators were assigned to investigate the patient's attitude regarding important diabetes-related behaviour (e.g. diet, exercise and medical drug compliance) according to the model, in order to prioritise the therapeutic goals. During the individual sessions patients were invited to arrange an appointment together with a dietician to discuss dietary rules and the patient's partner to discuss social support. In each session, the therapeutic goals were re-evaluated and adjusted to the patient's personal experiences and problems hampering attainment of the goals. The first group session was mainly to discuss experiences and the patients received general information about diabetes. During the second group session the treatment of diabetes and self-care behaviour were discussed. Main topics in the third group session were prevention of diabetes-related complications and care of the feet (this intervention and also the results on behavioural outcome measures are described in detail elsewhere).[8,10]

Outcome measures

Plasma glucose, total cholesterol, HDL cholesterol, and triglyceride were measured every three months with the 950 AT ORTHO diagnostics. Glycated haemoglobin was

determined by the Variant-1 Biorad. LDL cholesterol was calculated using the Friedewald formula.[11] All blood samples were taken in the fasting state using venous blood samples. The research assistants were instructed to measure systolic and diastolic blood pressure (Korotkoff V) on the left arm of the seated patient twice with a two-minute interval using a mercurial blood pressure monitor and calculate the mean of the two measurements. Weight and height were measured to calculate the body mass index (BMI).

Since allocation to the intervention or control group was not random, differences in diabetes care between the two groups were considered as a potential confounder. In order to adjust for this confounder, features of diabetes care in the participating practices were assessed by analysing the medical records of all listed Turkish diabetes patients (including patients not in this study) in the participating practices, as described in a previous study.[7] From an inventory of all type 2 diabetes patients made from a computer-based patient record, and if present, disease register, all Turkish patients were selected who had been treated exclusively by the GP and were known to have had diabetes for at least 3.5 years and who could be followed for two years before the intervention took place. Indicators of diabetes care were: 1) the mean number of recommendations from the Dutch GP guidelines on diabetes that were carried out (maximum 8), 2) the number of diabetes-related referrals of Turkish diabetes patients, and 3) the percentage of medication adjustments within three months after registration of increased plasma glucose levels (fasting ≥8.0 mmol/l, nonfasting ≥10.0 mmol/l).[12]

Statistical analysis

The main effect parameter was change in HbA_{1c} between baseline measurement and one-year follow-up. Power calculations were based on the assumption that the study should be able to detect a clinically relevant improvement in HbA_{1c} of 0.6% in the intervention group, based on an intention-to-treat analysis. With a 5% significance level and a power of 90%, 50 patients were required in each group.

To adjust for potential confounding, multivariate linear regression analyses were carried out with change from baseline as outcome variable, and HbA_{1c} at baseline, gender, age, years since diagnosis, mode of treatment, and the indicators of diabetes care as potential confounders. Because essential data were missing for some patients due to loss to follow-up, we first carried out an intention-to-treat analysis, followed by an intention-to-treat analysis on the dataset obtained by multiple imputation for missing data. Multiple imputation for non-response replaces each missing value by two or more plausible values.[13]

Subgroup analyses

To acquire additional information we decided in advance to perform subgroup analyses for patients with HbA_{1c} ≤7% (good glycaemic control) and HbA_{1c} >7 at baseline, and for male and female patients separately.

RESULTS

Table 1 gives the baseline characteristics of the 104 patients included in the study: 38% were men, mean age was 52 (SD 6.0) years, mean number of years since diagnosis of diabetes was 6.0 (SD 4.6), and mean HbA_{1c} was 8% (SD1.6). There were no significant differences between the intervention and control group.

Features of care for in the intervention and control practices (before the intervention)

Analysis of the medical records of all listed Turkish diabetes patients yielded the following results. The mean number of guideline recommendations carried out (maximum 8) in the intervention practices was 2.0 (SD 2.0) per patient *vs* 2.7 (SD 1.7) per patient in the control practices. During the two-year registration before the intervention, 25% of the Turkish diabetes patients in the intervention practices were referred for diabetes treatment to hospital-based diabetes clinics *vs* 9.6% in the control practices. Within three months after measuring poor plasma glucose, medication was adjusted in 75% of the cases in the intervention practices *vs* 57% of the cases in the control practices.

Loss to follow-up

Of the 104 patients who signed informed consent, five patients (three in the intervention and two in the control group) did not attend the laboratory for baseline measurements and dropped out before the intervention. Another 14 patients (12 in the intervention and two in the control group) were lost to follow-up. Reasons for not completing the follow-up measurements were: refused (5), stayed abroad for a longer period (4), moved or changed physician (4), unable to be contacted (1) (*figure 1*).

The intervention

The mean number of education sessions visited by 38 patients with known baseline and follow-up measurements was 9.3 (SD 3.9) of the ten planned sessions. Ten of the 38 patients had a session with the dietician present.

Glycaemic control

Table 2 shows change in glycaemic control and cardiovascular risk factors after one year. There were no significant differences in the change in HbA_{1c} and fasting plasma between patients in the intervention and control group.

Table 1 *Patient characteristics and baseline measurements of type 2 diabetes patients in the intervention (I) and control (C) group; data are mean (SD), or number of patients (percentage)*

	n (I/C)[1]	Intervention group	Control group
Age (years)	53/51	50.6 (9.3)	53.5 (6.2)
Men (number)	53/51	21 (40)	19 (37)
Years of education	37/41[2]		
• No education		14 (38)	14 (34)
• One to six years		20 (54)	22 (54)
• More than six years		3 (8)	5 (12)
Income	38/39[2]		
• <1000 €/month		26 (68)	32 (82)
• >1000 €/month		12 (32)	7 (18)
Number of years since diagnosis	53/51	6.0 (4.2)	6.1 (5.0)
Body mass index (kg/m^2)	48/47[2]	32.8 (5.2)	31.6 (4.5)
Smokers (number)	48/46[2]	10 (21)	9 (20)
Treatment for diabetes (number)	53/50		
• Diet		9 (17)	5 (10)
• Sulphonylureas		23 (43)	21 (42)
• Metformin		6 (11)	9 (18)
• Combined oral hypoglycaemic agents		13 (25)	15 (30)
• Insulin		2 (4)	- (0)
HbA_{1c} (%)	50/49	8.2 (1.7)	7.9 (1.6)
Fasting plasma glucose (mmol/l)	50/49	10.4 (3.0)	9.8 (3.3)
Total cholesterol (mmol/l)	50/49	5.3 (1.1)	5.5 (1.0)
HDL cholesterol (mmol/l)	50/49	1.1 (0.4)	1.0 (0.3)
LDL cholesterol (mmol/l)	49/43[3]	3.1 (1.0)	3.4 (0.9)
Triglyceride (mmol/l)	50/49	2.5 (1.8)	2.7 (1.5)
Blood pressure (mmHg)			
• Systolic	48/48[2]	136 (17)	141 (22)
• Diastolic	48/48[2]	88 (10)	89 (10)
Urinary albumin (number)	48/49[2]		
• >50		10 (21)	8 (16)
• >300		5 (10)	2 (4)

[1]Baseline laboratory data were obtained from 50 patients in the intervention group and from 49 patients in the control group, and were missing in five patients (3 intervention, 2 control) who signed informed consent. [2]Missing data due to incomplete dataset. [3]Due to high triglyceride level (>4.5 mmol/l) the LDL cholesterol could not be calculated in eight patients.

Compared with the control group, mean HbA_{1c} in the intervention group decreased by 0.3% (95% CI -0.8 to 0.2) and fasting plasma glucose decreased by 0.9 mmol/l (95% CI -2.2 to 0.3). Adjustment for baseline value (HbA_{1c}), patient features (age, gender, years since diagnosis and use of medication) or practice features did not substantially alter these findings.

Table 3 gives the results of subgroup analyses for change in HbA_{1c} after one year for patients with baseline HbA_{1c} ≤7% (good glycaemic control) and patients with baseline HbA_{1c} >7%, for all patients, and for males and females separately. A significant effect of the intervention was only seen in women with increased plasma glucose levels (0.87%; 95% CI -1.73 to -0.09).

Figure 1 *Flow chart*

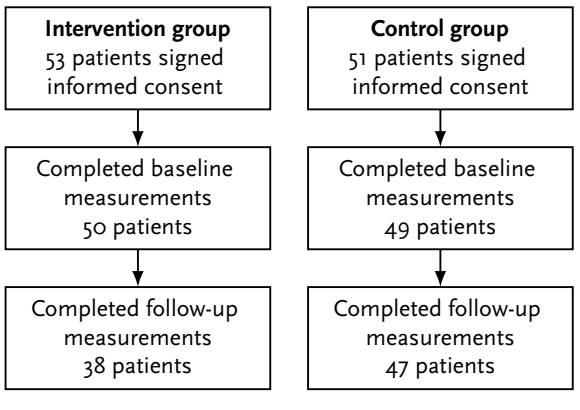


Table 2 *Glycaemic control and cardiovascular risk factors in 85 Turkish diabetes patients with completed datasets: outcome measurements at baseline, and one year after baseline measurements, and mean change from baseline measurements in both groups*[1]

	Intervention group (n=38)			Control group (n=47)			Mean differences (95% CI)
	Baseline	After 1 year	Change from baseline	Baseline	After 1 year	Change from baseline	
HbA_{1c} (%)	7.9 (1.4)	7.6 (1.2)	-0.3 (1.3)	8.0 (1.6)	8.0 (1.5)	0.03 (0.9)	-0.3 (-0.8 to 0.2)
Fasting plasma glucose (mmol/l)	10.1 (3.0)	8.8 (2.9)	-1.3 (3.2)	9.9 (3.3)	9.7 (2.8)	-0.4 (2.5)	-0.9 (-2.2 to 0.3)
Total cholesterol (mmol/l)	5.1 (1.0)	5.0 (1.0)	-0.1 (0.7)	5.5 (1.0)	5.5 (1.0)	-0.1 (0.6)	-0.1 (-0.4 to 0.2)
HDL cholesterol (mmol/l)	1.2 (0.3)	1.1 (0.3)	-0.1 (0.2)	1.0 (0.3)	1.1 (0.3)	0.1 (0.1)	0.1 (0.05 to 0.2)
LDL cholesterol (mmol/l)	3.0 (0.9)	3.0 (0.9)	-0.1 (0.8)	3.4 (0.9)	3.3 (0.9)	-0.2 (0.7)	0.1 (-0.2 to 0.5)
Triglycerides (mmol/l)	2.3 (1.9)	2.0 (1.1)	-0.3 (1.3)	2.7 (1.6)	2.5 (1.9)	-0.2 (1.2)	0.17 (-0.7 to 0.4)
Body mass index (kg/m^2)	33.0 (5.7)	32.3 (4.9)	-0.2 (1.7)	31.7 (4.5)	30.9 (4.4)	-0.5 (1.1)	0.3 (-0.3 to 1.0)
Blood pressure (mmHg)							
• Systolic	136 (18)	131 (16)	-5 (13)	141 (22)	142 (25)	1 (22)	-6 (-15 to 2)
• Diastolic	88 (11)	85 (11)	-4 (8)	89 (10)	87 (12)	-2 (12)	-1 (-6 to 4)

Values are adjusted – for HbA_{1c} at baseline and patient characteristics (age, gender, years since diagnosis, mode of treatment: diet alone or use of oral hypoglycaemic agents – mean values (SD) and mean differences between changes from baseline in the intervention and control group (95% CI). [1]Fourteen patients (12 in the intervention and 2 in the control group) with completed baseline measurements were lost to follow-up. Reasons for this were: refused (5), stayed abroad for a longer period (4), moved or changed physician (4), unable to be contacted (1).

Cardiovascular risk factors

No significant differences in the changes of plasma lipid levels, blood pressure and BMI in favour of the intervention group were observed at one-year follow-up.

The analyses based on the 104 patients who entered the study with missing values imputed by means of multiple imputation yielded similar results for the outcome measurements HbA_{1c} and cardiovascular risk factors.

DISCUSSION

In this study targeting first-generation Turkish immigrants with type 2 diabetes, bicultural education in general practice had no obvious beneficial effect on either glycaemic control parameters or cardiovascular risk factors.

An improvement in HbA_{1c} of 0.6% in the intervention group, on which the power calculations were based, was not achieved; the study group was too small to detect an improvement as small as 0.3%. The expected larger improvement was based on the assumption that nearly all Turkish diabetes patients would have HbA_{1c} levels >7%. However, this was not the case in 26 (31%) of the 85 patients with completed datasets, which made an improvement of 0.6% more difficult to reach.

The finding that the intervention was slightly more effective in women warrants some discussion. Firstly, the low HbA_{1c} level at baseline in the male patients in both the intervention (HbA_{1c} 7.7%) and control group (HbA_{1c} 8.0%) with completed datasets, and the small number of men might explain why no significant decrease in HbA_{1c} in men could be shown. Secondly, the influence of gender inequality between the female educator and the male patients might explain the lack of effect in men. A former study showed the positive influence of gender equality on the effectiveness of health education.[14] In our study, both of the Turkish educators were female and (for cultural reasons) Turkish male patients may feel less inclined to take advice regarding behavioural changes from women. Indeed, another report of this study showed that the Turkish females experienced more change in behaviour than the Turkish men.[8] Attention to gender equality should be considered in future studies, possibly by making the contents of the message more gender specific. Although no studies have been performed to prove this, it seems quite possible that the susceptibility for behavioural advice differs between Turkish men and women.

Table 3 *Subgroup analyses for change in mean HbA_{1c} one year after baseline measurements in patients in the intervention and control group for patients with HbA_{1c} ≤7.0% at baseline (good glycaemic control) and for patients with HbA_{1c} >7.0% at baseline: in all patients, and in males and females separately*

Patient group	n	HbA_{1c} in % (SD) at baseline	HbA_{1c} in % (SD) at one year	Difference between intervention and control[1]	
				β	95% CI
All patients					
• Intervention	38	7.9 (1.4)	7.6 (1.2)	-0.30	(-0.74 to 0.14)
• Control	47	8.0 (1.6)	8.0 (1.4)		
Male patients					
• Intervention	14	7.7 (1.3)	7.6 (1.3)	-0.09	(-0.75 to 0.57)
• Control	19	8.0 (1.7)	7.9 (1.3)		
Female patients					
• Intervention	24	8.0 (1.5)	7.6 (1.1)	-0.49	(-1.11 to 0.13)
• Control	28	8.0 (1.5)	8.0 (1.6)		
Patients with HbA_{1c} ≤7%					
• Intervention	10	6.5 (0.5)	6.9 (0.9)	0.25	(-0.34 to 0.84)
• Control	16	6.7 (0.3)	7.0 (0.8)		
Patients with HbA_{1c} >7%					
• Intervention	28	8.4 (1.3)	7.9 (1.2)	-0.53	(-1.09 to 0.04)
• Control	31	8.6 (1.5)	8.5 (1.5)		
Male patients with HbA_{1c} >7%					
• Intervention	10	8.2 (1.0)	7.8 (1.3)	0.06	(-0.78 to 0.90)
• Control	14	8.6 (1.8)	8.2 (1.5)		
Female patients with HbA_{1c} >7%					
• Intervention	18	8.6 (1.4)	7.9 (1.1)	-0.87	(-1.73 to -0.09)
• Control	17	8.7 (1.4)	8.7 (1.5)		

[1]**Adjusted for HbA_{1c} at baseline and patient characteristics (age, gender, years since diagnosis, mode of treatment: diet alone or use of oral hypoglycaemic agents).**

The first methodological limitation of this study was the absence of randomisation, which was not possible for three reasons. First, the bicultural educators were already working in the participating intervention practices and Turkish patients were familiar with the facility; exclusion of diabetes patients from this facility for a longer period was not considered an option. Secondly, the number of patients per general practice would be too small to arrange group education within each general practice. Thirdly, the danger of contamination between patients of the control and intervention group was considered too large, particularly because older Turkish patients living in one district form close networks.

A second limitation concerns the dropout. Because we were unable to follow up 15 of the 53 patients who dropped out of the intervention, it was impossible to perform a traditional intention-to-treat analysis. Reasons for dropping out were diverse and many patients dropped out before or early on in the intervention, and only five patients dropped out for education-related reasons. We believe, however, that the possibility of bias induced by selective dropout is very limited. Importantly, this is illustrated by analysis of the dataset obtained by multiple imputation for missing data, which yielded similar results on both HbA_{1c} and cardiovascular risk factors.

To our knowledge this is the first study to assess the effect of ethnic-specific diabetes education on glycaemic control in Turkish diabetes patients. Although the results show that our educational approach has no clear effect on glycaemic control or cardiovascular risk factors, the study yielded some interesting findings. A substantial proportion of patients in good glycaemic control, the high dropout and the larger effect in women suggest an even more tailored approach. The fast growing numbers of diabetes patients from non-Western ethnic minority groups in West Europe, and the difficulty that physicians experience in treating these patients groups warrant further study.

REFERENCES

1. Marshall JA, Hamman RF, Baxter J, et al. Ethnic differences in risk factors associated with the prevalence of non-insulin-dependent diabetes mellitus. Am J Epidemiol 1993;137:706-18.
2. Carter JS, Pugh JA, Monterrosa MD. Non-insulin-dependent diabetes mellitus in minorities in the United States. Ann Intern Med 1996;125:221-32.
3. Weijers RNM, Bekedam DJ, Oosting H. The prevalence of type 2 diabetes and gestational diabetes mellitus in an inner city multi-ethnic population. Eur J Epidemiol 1998;14:693-9.
4. Uitewaal PJ, Manna DR, Bruijnzeels MA. Prevalence of type 2 diabetes mellitus, other cardiovascular risk factors, and cardiovascular disease in Turkish and Moroccan immigrants in North West Europe: a systematic review. Prev Med 2004;39:1068-76.
5. Elasy TA, Ellis SE, Brown A, Pichert JW. A taxonomy for diabetes educational interventions. Patient Educ Couns 2001;43:121-7.
6. Hawthorne K, Tomlinson S. Pakistani Moslems with type 2 diabetes mellitus: effect of sex, literacy skills, known diabetic complications and place of care on diabetic knowledge, reported self-monitoring management and glycaemic control. Diab Med 1999;16:591-7.
7. Uitewaal PJM, Bruijnzeels M, Bernsen R, Voorham T, Thomas S. Diabetes care in Dutch general practice: differences between Turkish immigrants and Dutch patients. Eur J Public Health 2004;14:15-8.
8. Voorham AJJ, Uitewaal PJM, Bruijnzeels M. Het effect van voorlichting in de eigen taal aan Turkse diabetespatiënten. Tijdschr Soc Gezondheidsz 2002;80:514-20.
9. De Vries H, Dijkstra M, Kuhlman P. Self-efficacy: the third factor besides attitude and subjective norm as a predictor of behavioural intentions. Health Educ Res 1988;3:273-82.
10. Uitewaal P, Bruijnzeels M, de Hoop T, et al. Feasibility of diabetes peer education for Turkish type 2 diabetes patients in Dutch general practice. Patient Educ Couns 2004;53:359-63.
11. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the distribution of low-density lipoprotein cholesterol in plasma without the use of the preparative ultracentrifuge. Clin Chem 1972;18:499-502.
12. Rutten GEHM, Cromme PVM, Zuidweg J, Mulder JD. Huisarts en diabetes type 2: een verantwoording voor de NHG standaard. Huisarts Wet 1989;32:7-13.
13. Rubin DB, Schenker N. Multiple imputation in health care database: an overview and some applications. Stat Med 1991;10:585-98.
14. Voorham AJJ, Kocken PL. Kenmerken van de voorlichter bij het effect van seniorenvoorlichting. Tijdschr Soc Gezondheidsz 2000;78:303-8.

The editors wish to express their gratitude to the following reviewers *of the Netherlands Journal of Medicine* for their contribution:

C.G.M.I. Baeten, I. ten Berge, F. Boers, W.A. de Boer, E.F.H. van Bommel, W. van den Bosch, A. Brand, S.J.H. Bredie, M.J. Bruno, M.J.M. Bonten, M. Castro Cabezas, R. van Crevel, S. Croockewit, O.J. Cluysenaer, C.J. Cohen Tervaert, J. Deinum, R.H.W.M. Derksen, M. Drent, L. Elving, B. van Engelen, L.G.J.B. Engels, J. Galama, R.O.B. Gans, H. van Goor, D.E. Grobbee, H. van Hamersvelt, J. van Hattum, M. den Heijer, Y. Heijdra, R. Heine, A. Hermus, J. van der Hilst, A. Hoepelman, N. Hoogerbrugge, K. Ingels, E. de Jong, P.E. de Jong, P.A. Kager, C.G.M. Kallenberg, P.W. Kamphuisen, B. Kiemeney, R.J. de Knegt, J.J. Kolkman, H.A. Koomans, K. Kramers, E.J. Kuipers, B-J. Kullberg, P. de Leeuw, A.J. van der Lelij, R. Loffeld, K. Lovas, A.H. van den Meiracker, D. van de Mheen, B. Michels, R.P.J. Michels, C.J.J. Mulder, M. Netea, P. Netten, W. Oyen, M. van Oijen, G. Pop, C. Punt, D.S. Postma, J. Radder, J. Raemaekers, L.J.M. Reichert, C.J. de Rijks, J.A. Romijn, M. Russel, G.E.H.M. Rutten, J.M.J.I. Salemans, H.P. Sauerwein, A.V.M. Schattenberg, H. Schouten, H.C. Schouten, P.D. Siersema, J. Smeets, J.W.A. Smit, P. Soetekouw, R.W. Stockbruegger, F. Sweep, E. Stroes, P.M.J. Stuyt, C. Tack, H.W. de Valk, A. van der Ven, Th. Wagener, P.J. Wahab, E. van der Wall, E.E. van der Wall, C. van Weel, J.J. Weening, J. Wetzels, W.M. Wiersinga, J.C.M. Witteman, H. Wollersheim, H. van de Worp.

Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Establishment of reference values for endocrine tests. Part IV: Adrenal insufficiency

E. Endert, A. Ouwehand, E. Fliers, M.F. Prummel, W.M. Wiersinga*

Department of Endocrinology and Metabolism, Academic Medical Centre, University of Amsterdam, PO Box 22660, 1100 DD Amsterdam, the Netherlands, *corresponding author: tel: +31 (0)20-566 60 71, fax: +31 (0)20-691 76 82, e-mail: w.m.wiersinga@amc.uva.nl

ABSTRACT

Background: The short Synacthen test, the overnight metyrapone test and the insulin tolerance test are frequently used in the evaluation of patients suspected of adrenal insufficiency. In the present study, we established reference values for these diagnostic tests, as well as for baseline morning plasma cortisol and adrenocorticotrophic hormone (ACTH).

Methods: We studied 50 subjects recruited from the general population, equally distributed according to sex and age between 20 and 69 years. A short ACTH stimulation test (250 μg Synacthen iv), an overnight metyrapone test (2.0, 2.5, or 3.0 g given orally depending on body weight at 23.30 hours) and an insulin tolerance test (0.15 U/kg actrapid iv) were performed. Reference intervals are given as the means ± 2SD of observed hormone concentrations after logarithmic transformation.

Results: The following reference values were established: 09.00 hr plasma cortisol 150 to 802 nmol/l, 09.00 hr plasma ACTH 8 to 93 ng/l, peak plasma cortisol after Synacthen 591 to 1113 nmol/l, peak plasma cortisol after insulin-induced hypoglycaemia 557 to 1015 nmol/l, and plasma 11-deoxycortisol after metyrapone 197 to 759 nmol/l.

Conclusion: We established reference values for diagnostic tests that are useful in the evaluation of patients suspected of primary or secondary/tertiary adrenal insufficiency.

KEYWORDS

ACTH, adrenal insufficiency, cortisol, insulin, metyrapone, Synacthen

INTRODUCTION

Adrenal insufficiency is a rather rare disease. Primary adrenal insufficiency has a prevalence of 93 to 140 per million, and the estimated prevalence of central adrenal insufficiency is 150 to 280 per million.[1] Primary adrenal insufficiency in the Netherlands is mostly caused by autoimmune adrenalitis, whereas central (secondary and tertiary) adrenal insufficiency is usually the result of pituitary/hypothalamic tumours, surgery or irradiation. Glucocorticoid deficiency gives rise to mainly nonspecific symptoms, whereas orthostatic hypotension and brown discolouration of skin and mucosa develop only in advanced disease. The existence of other autoimmune endocrine disorders or hypothalamic/pituitary disease, however, may give a clue to the existence of adrenal insufficiency. If clinical suspicion has been raised, it is important to demonstrate accurately the absence or presence of adrenal insufficiency. Measurement of cortisol and adrenocorticotrophic hormone (ACTH) in a single blood sample is, however, inconclusive in many instances for a number of reasons. First, the time of sampling is important in view of the circadian rhythm of cortisol and ACTH. Another potential bias is that both cortisol and ACTH are stress hormones: elevated plasma concentrations may occur at a difficult venipuncture or in stressed patients. These confounding factors call for blood sampling under standard conditions. But even then, a normal plasma cortisol concentration does not reliably rule out glucocorticoid deficiency. In order not to miss the diagnosis which puts the patient at risk of developing a potential life-threatening Addison crisis, many centres rely on dynamic function tests of the hypothalamic-pituitary-adrenal axis in view of their higher sensitivity.

Administration of synthetic ACTH (Synacthen) releases cortisol from the adrenal gland: a reduced cortisol response indicates primary adrenal failure if plasma ACTH (measured under standard conditions) is elevated, or central adrenal failure if plasma ACTH is not elevated. A normal increase in plasma cortisol in response to Synacthen, however, still does not completely rule out the possibility of central adrenal insufficiency. To this end, an insulin tolerance test or a metyrapone test can be performed. The insulin-induced hypoglycaemia is a potent stimulus for the release of corticotrophin-releasing factor (CRH) and subsequently ACTH and cortisol; it is, however, an unpleasant test and contraindicated in patients with ischaemic heart disease or epilepsy. Metyrapone given orally is better tolerated, although it may cause nausea and headache. Metyrapone inhibits the enzyme 11β-hydroxylase in the adrenals and thereby the conversion of 11-deoxycortisol into cortisol; the drop in plasma cortisol is an effective stimulus for the release of ACTH, which enhances adrenal steroidogenesis: plasma 11-deoxycortisol concentrations increase but plasma cortisol levels remain low because of the enzymatic blockade.

Although in principle each laboratory should establish their own reference values, this recommendation is not always followed in practice. Consequently, reference values supplied by the manufacturer of a particular assay kit are used in many cases, or values are derived from the literature. The situation is even worse with regard to dynamic stimulation and suppression tests as only few institutions endeavour to establish the reference range of responses in subjects without the disease under scrutiny. This unfortunate state of affairs is, however, quite understandable as it will not be feasible, especially for smaller institutions, to perform all these tests in a reference population.

We decided to establish reference values for the following endocrine tests used in the evaluation of adrenal insufficiency: morning (09.00 hour) plasma ACTH, cortisol and 11-deoxycortisol, Synacthen test, insulin tolerance test, and metyrapone test. These tests were performed under standardised conditions in 50 subjects recruited from the general population not suspected of having adrenal sufficiency.

SUBJECTS AND METHODS

Subjects

Volunteers were recruited by advertisement in a local newspaper with a free house-to-house distribution in the Amsterdam region. Responders were asked by telephone whether they satisfied the inclusion and exclusion criteria. Inclusion criteria were age between 20 and 69 years and self-proclaimed general good health. Exclusion criteria were pregnancy or lactation, parenteral drug abuse, alcohol abuse, the use of oestrogens or corticoids, cardiovascular disease, diabetes mellitus, and epilepsy. Subjects were invited to our department where they were interviewed about drinking and smoking habits, and the use of drugs and medication. Weight, height and blood pressure were measured. Pregnancy was excluded in all female subjects by a urine human chorionic gonadotropin test (hCG). Subjects were divided per decade into five age groups. Each age group consisted of five men and five women. Informed consent was obtained from all subjects and the study was approved by the hospital's ethics committee.

Tests

Synacthen test

The Synacthen test was performed in the postabsorptive state and in recumbent position, starting between 08.30 and 09.30 hours. An indwelling venous catheter was inserted (t = -30 min) in an antecubital vein, and blood samples were taken at t = -15 min and t = 0 min for measurement of ACTH (EDTA blood, tubes were put immediately on ice) and cortisol and 11-deoxycortisol (heparin blood). Additional blood samples were taken at t = 30 min and t = 60 min for measurement of cortisol after intravenous administration of 250 μg tetracosactin (Synacthen; Novartis Pharma; Arnhem, the Netherlands) at t = 0 min. Plasma samples were stored at -20°C until assay.

Metyrapone test

After completion of the Synacthen test, metyrapone capsules of 250 mg (Metopiron, Interpharm BV, Almere, the Netherlands) were distributed to the volunteers. They were asked to swallow the capsules the same evening at home at 23.30 hours with a glass of milk or yoghurt. The administered dose was 2.0 g (body weight <70 kg), 2.5 g (body weight 70 to 90 kg), or 3.0 g (body weight >90 kg), corresponding to 8, 10 and 12 capsules respectively. Next morning blood samples were taken in the postabsorptive state at 09.00 hours for measurement of ACTH (EDTA blood) and cortisol and 11-desoxycortisol (heparin blood). Plasma samples were stored at -20°C until assay. Blood pressure and pulse rate were recorded after the venapuncture.

Insulin tolerance test

The insulin tolerance test was performed in the postabsorptive state and in a recumbent position, starting between 08.30 and 09.30 hours. An indwelling venous catheter was inserted (t = -30 min) in an antecubital vein, and blood samples were taken at t = -15 min and t = 0 min. Additional blood samples were taken at t = 15, 30, 45, 60 and 75 min after intravenous administration of insulin 0.15 U/kg (Actrapid, Novo Nordisk, Mainz, Germany) at t = 0 min. Plasma samples for measurement

of cortisol were stored at -20°C until assay. Criteria for a valid test result were neuroglycopenic symptoms lasting for at least ten minutes and a blood glucose concentration of <2.2 mmol/l.

Analytical methods

All hormone measurements were done in duplicate. ACTH was determined by an immunoluminometric assay (Nichols Institute Diagnostics, San Juan Capistrano, CA, USA) with a detection limit of 1 ng/l; the intra-assay CV was 5.0%, the inter-assay CV 7.5%. Plasma cortisol was measured by an enzyme immunoassay (Diagnostic Products Corporation, Los Angeles, CA, USA) with a detection limit of 50 nmol/l; the intra-assay CV was 4.4%, the inter-assay CV 7.4%. Crossreactivity of 17-OH-progesterone and 11-deoxycortisol in the cortisol assay is 0.2 and 1.6% respectively; a rise of plasma 11-deoxycortisol up to 820 nmol/l as observed after metyrapone will thus hardly affect serum cortisol values. Plasma 11-deoxycortisol was determined by a radioimmunoassay (ICN Pharmaceuticals, Diagnostic Division, Orangeburg, NY, USA); the intra-assay CV was 3.7%, the inter-assay CV 9.4%. Samples of a particular subject were assayed in the same run, but samples of different persons were assayed in different runs to include inter-assay variation in the establishment of reference values.

Statistical methods

Alcohol use was defined as ingestion of alcohol-containing beverages at least twice daily, and smoking as daily smoking. Hormone values below the detection limit of the assays were included in the analyses as having the value of 50% of the detection limit. In the Synacthen test and the insulin tolerance test basal values were calculated as the mean of t = -15 and t = 0 min. The absolute increase in cortisol was calculated as the highest observed cortisol value after Synacthen or insulin administration, respectively, minus the basal cortisol value; the relative increase in cortisol was the absolute increase in cortisol divided by the basal cortisol value.

Sex differences and the effects of smoking and alcohol were tested by the Mann-Whitney U test, the effect of age by the Kruskal-Wallis test. The Wilcoxon matched-pairs test was used to compare the two baseline levels of ACTH and cortisol in the Synacthen test. Spearman's rank correlation analysis was used to evaluate possible correlations between baseline cortisol values and the increase in cortisol. If hormone concentrations were not normally distributed, logarithmic transformation to normality was performed in order to calculate reference intervals.

The SPSS 9.0 statistical package was used. In all analyses, p values <0.05 were considered statistically significant.

RESULTS

Subject characteristics

Mean age of the 50 healthy volunteers was 44±15 years (range 20-69). Seven (14%) were smokers and seven (14%) used alcohol. The body mass index ranged from 18.8 to 39.4 (median 25.4) in the 25 males, and from 18.3 to 37.4 (median 26.5) in the 25 females.

Synacthen test (*table 1*)

ACTH concentrations at t = -15 (range 6 to 160 ng/l, median 26) were higher than at t = 0 (range 8 to 82 ng/l,

Table 1 *Results of diagnostic tests for adrenal insufficiency in 50 healthy volunteers*

		Mean	Median	Range
Morning (09.00 hr) plasma cortisol	nmol/l	378	325	125-950
Morning (09.00 hr) plasma 11-deoxycortisol	nmol/l	6.0	5.6	2.6-14.9
Morning (09.00 hr) plasma ACTH				
• Females	ng/l	25	21	10-76
• Males	ng/l	40	33	11-116
Synacthen test (250 µg iv)				
• Peak plasma cortisol	nmol/l	821	800	620-1280
• Absolute cortisol increase	nmol/l	443	452	110-830
• Relative cortisol increase	%	150	143	16-516
Metyrapone test				
• Plasma cortisol	nmol/l	180	145	<50-540
• Plasma ACTH	ng/l	297	233	42-960
• Plasma 11-deoxycortisol	nmol/l	407	410	140-820
Insulin tolerance test				
• Peak plasma cortisol	nmol/l	761	744	568-1037
• Absolute cortisol increase	nmol/l	361	370	112-600
• Relative cortisol increase	%	111	95	12-324

median 23) (p=0.002). Baseline ACTH values (the mean of t = -15 and t = 0) ranged from 10 to 116 ng/l with a median of 24; they were higher in males (range 11 to 116 ng/l, median 33) than in females (range 10 to 76 ng/l, median 21) (p=0.007).
Plasma cortisol concentrations at t = -15 (range 130 to 930 nmol/l, median 340) were higher than at t = 0 (range 120 to 970 nmol/l, median 310 (p=0.005). Baseline plasma cortisol values ranged from 125 to 950 nmol/l with a median of 325; there was no sex difference. After stimulation with ACTH 1-24 (250 µg Synacthen iv) peak cortisol values (range 620 to 1280 nmol/l, median 800) were reached at t = 30 in three subjects and at t = 60 in 47 subjects. The absolute and relative increase in plasma cortisol is depicted in *figure 1*. The cortisol increase was indirectly related to baseline cortisol: the higher the baseline cortisol, the lower the increase (r=0.63, p<0.001) (*figure 2*). Sex, age, smoking and alcohol had no effect on the cortisol response to exogenous ACTH.

Metyrapone test (*table 1*)
Ingestion of the metyrapone capsules was reasonably well tolerated: only a few subjects said they had noticed nausea or slight headache. The response of plasma ACTH, cortisol and 11-deoxycortisol concentrations to metyrapone is depicted in *figure 3a* and *3b*. ACTH and 11-deoxycortisol increased in all subjects. Cortisol decreased in all but seven subjects. Plasma ACTH had risen in each of these seven subjects from 18 ± 9 ng/l to 134 ± 64 ng/l (median ± SD), on average by a 8.5-fold increase; plasma 11-deoxycortisol prior to metyrapone was <15 nmol/l in all seven subjects, and increased after metyrapone to 140 and 180 nmol/l respectively in two subjects and to >250 nmol/l in the other five.

Insulin tolerance test (*table 1*)
One participant was excluded from the analysis because no hypoglycaemia occurred. All remaining 49 subjects developed neuroglycopenic symptoms; nadir blood glucose concentrations varied from 0.5 to 2.4 mmol/l. Two subjects had nadir blood glucose levels of 2.2 and 2.4 mmol/l respectively; they were maintained in the analysis because both demonstrated clear neuroglycopenia, and their peak serum cortisol values were well within the observed range of the other subjects. Spontaneous recovery of hypoglycaemia was observed in everyone. The

Figure 1 *Plasma cortisol concentrations at baseline and after stimulation with exogenous ACTH 1-24 (250 µg Synacthen iv) in 50 healthy subjects*

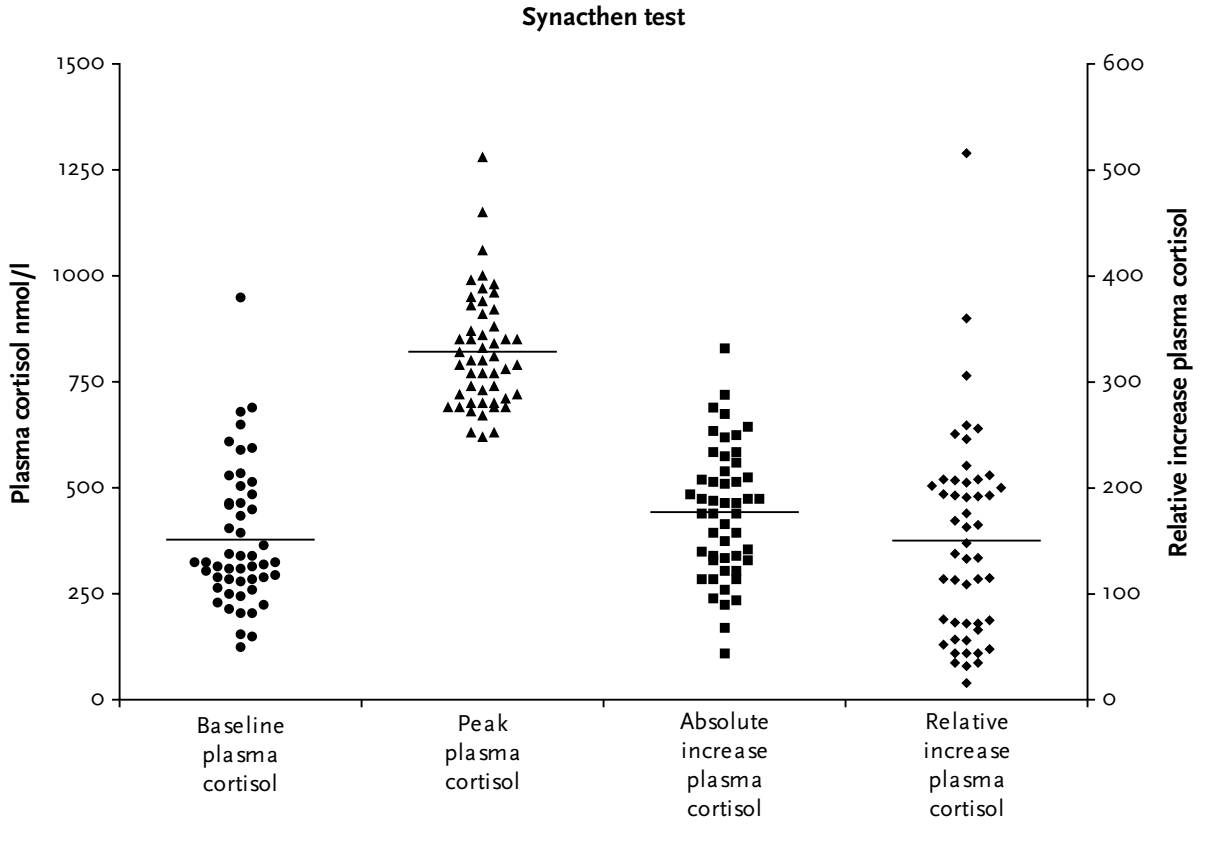


Figure 2 *Relationship between baseline plasma cortisol and the absolute increase in plasma cortisol after stimulation with exogenous ACTH 1-24 (250 μg Synacthen iv) in 50 healthy subjects*

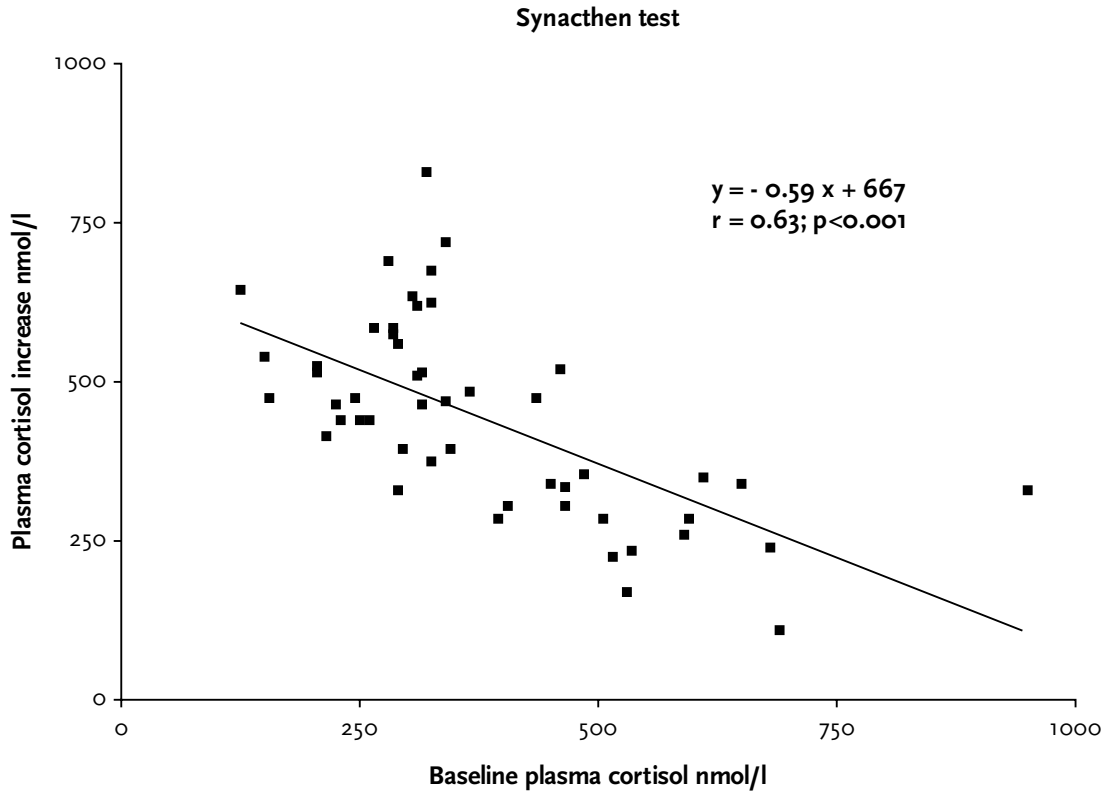


Figure 3a *The response of plasma ACTH (left panel) and cortisol (right panel) to metyrapone (2.0, 2.5 or 3.0 g orally depending on body weight, taken the previous evening) in 50 healthy subjects*

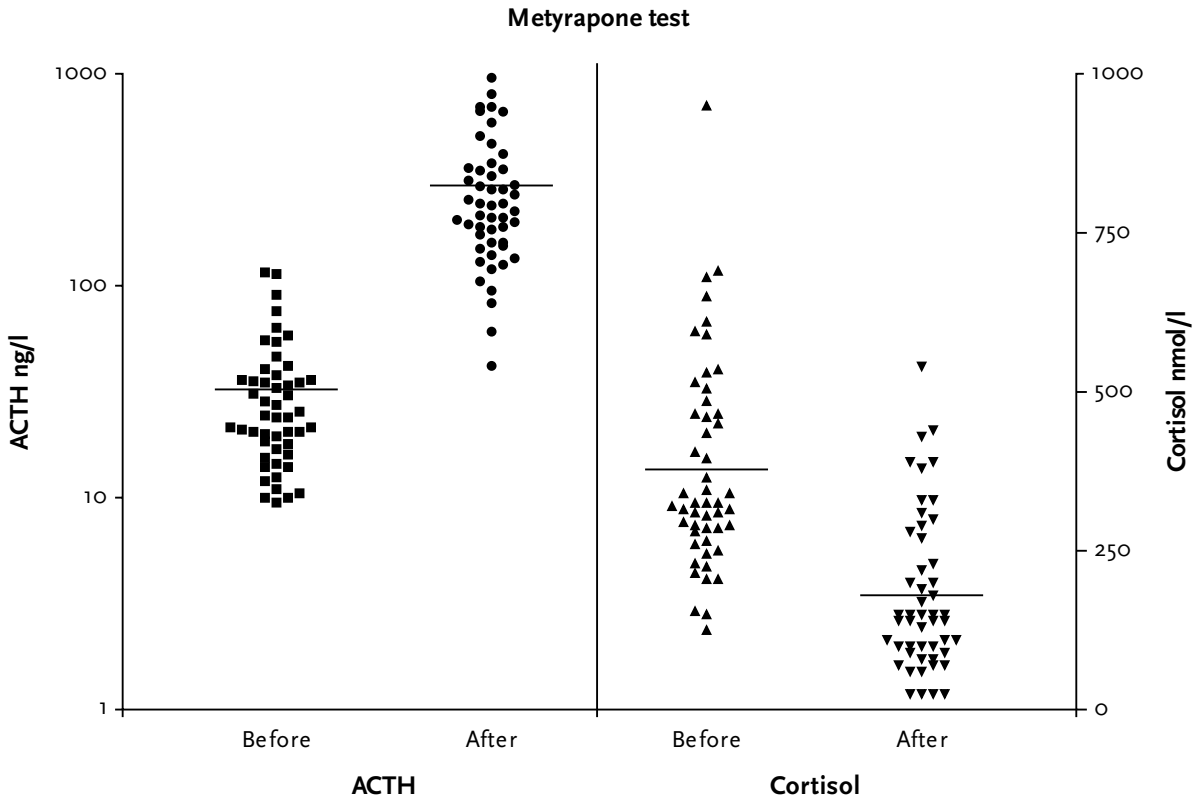
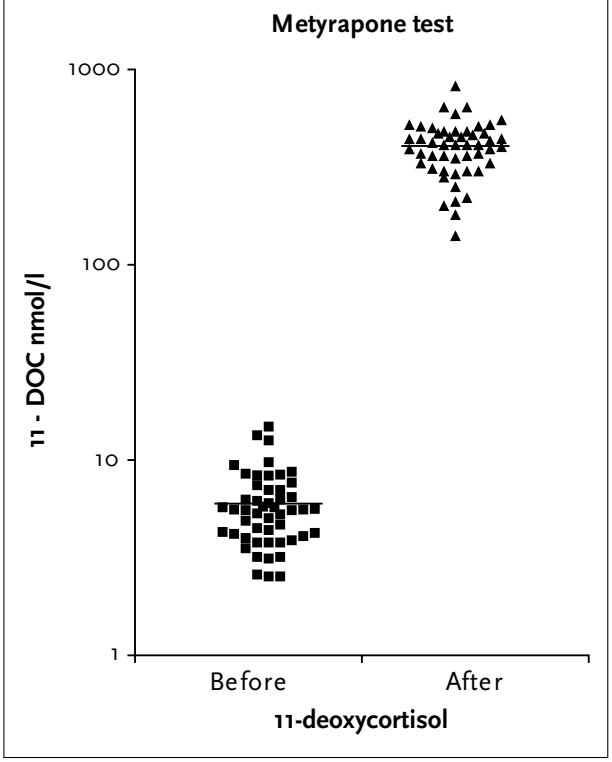


Figure 3b *The response of 11-deoxycortisol to metyrapone (2.0, 2.5 or 3.0 g orally depending on body weight, taken the previous evening) in 50 healthy subjects*



response of plasma cortisol to insulin-induced hypoglycaemia is depicted in *figure 4*.

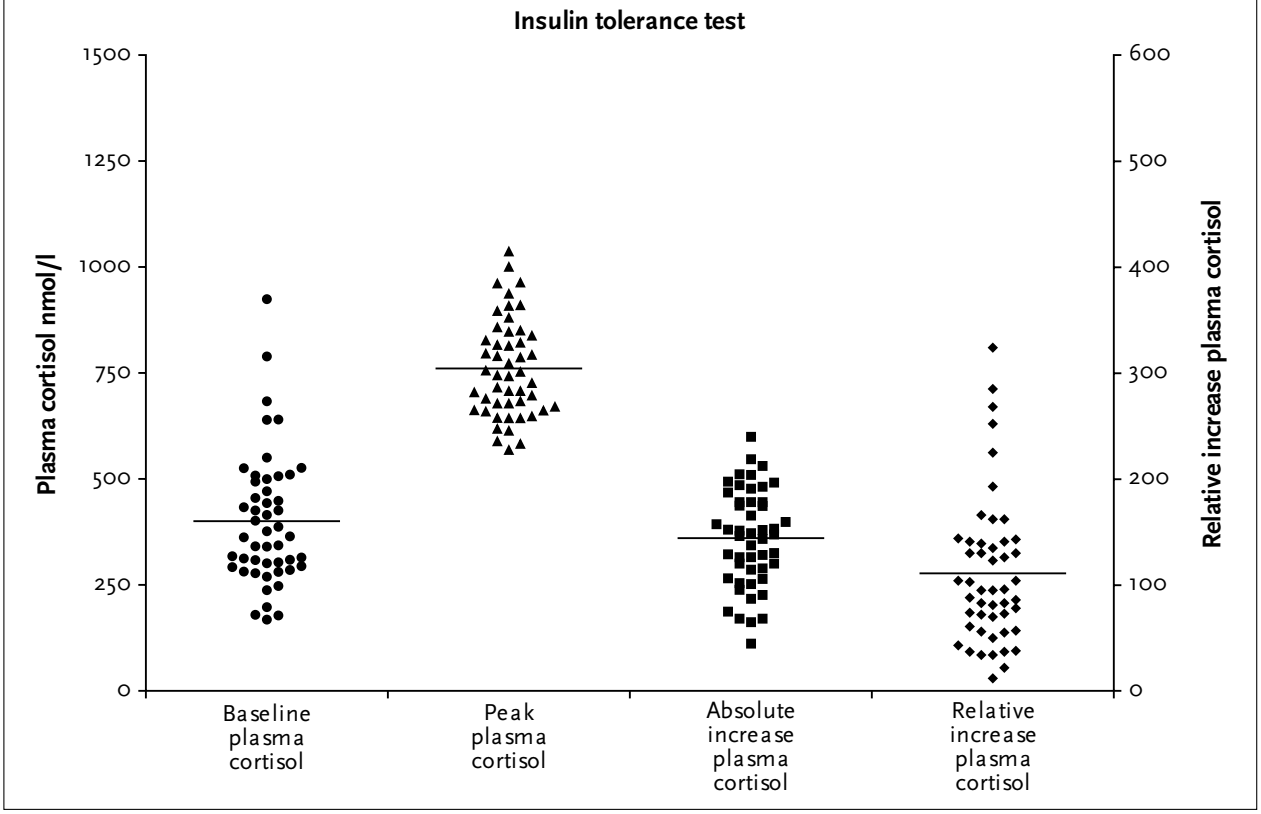
Reference values

Baseline hormone concentrations and stimulated hormone concentrations in the three dynamic tests had no normal distribution. In order to obtain reference values, all hormone concentrations were log-transformed, and from these values the mean - 2SD and the mean + 2SD were calculated. Back transformation of these numbers provided the reference interval, listed for each test in *table 2*. Reference intervals of morning (09.00 hour) plasma cortisol, 11-deoxycortisol and ACTH were derived of baseline measurements in the Synacthen test.

DISCUSSION

The morning (09.00 hour) values of plasma cortisol and ACTH obtained in the present study are in good agreement with those reported in a previous paper by our group in 1998, in which reference values for tests aimed at evaluation of hypercortisolism were established from the results of 50 subjects likewise recruited from the general population.[2] Plasma cortisol concentrations (median and range in nmol/l) prior to CRH in the 1998 study were

Figure 4 *Plasma cortisol concentrations at baseline and after insulin-induced hypoglycaemia (0.15 U/kg Actrapid iv) in 49 healthy subjects*



380 (140 to 980) and 340 (140 to 986) at t = -15 and t = 0 min, respectively, and corresponding figures in the present study prior to Synacthen are 340 (130 to 930) and 310 (120 to 970). Baseline plasma ACTH (median and range in ng/l) was 24 (7 to 73) for males and 17 (1 to 76) for females in the 1998 study, and 33 (11 to 116) and 21 (10 to 76), respectively, in the present study. (It should be noted that plasma ACTH concentrations throughout the 1998 paper were falsely given as pmol/l, whereas the units in reality were ng/l; we apologise for this error). The sex difference in plasma ACTH was again observed in the present study. The reference intervals of morning plasma cortisol and ACTH (obtained under standardised concentrations) are very similar in both studies, which is reassuring in terms of internal consistency between our studies over time.

It has been argued that adrenal insufficiency is proven if cortisol at 09.00 hours is <100 nmol/l, and is ruled out if cortisol at 09.00 hours is >500 nmol/l, provided the subject is not stressed, not pregnant and not using oestrogens.[1,3,4] In such cases no further tests are required except a plasma ACTH to differentiate between primary and central adrenal insufficiency. We do not, however, advocate starting with a single blood sample for measurement of cortisol, but favour proceeding immediately with the Synacthen test under standardised conditions as described above. The advantage of this approach is that the effect of diurnal variation and stress on plasma cortisol and ACTH is minimised, and that if there is a subnormal cortisol response to Synacthen the baseline ACTH value allows a definite diagnosis of primary or central adrenal failure, thereby speeding up the diagnostic process. The advantages of our recommendation outweigh, in our opinion, its disadvantages (we do perform more laboratory tests then in hindsight are strictly necessary – but we have abandoned random cortisol measurements). According to our tests results, the Synacthen test can be considered normal if peak plasma cortisol is >590 nmol/l (*table 2*). The increase in cortisol is directly related to baseline cortisol (*figure 2*), in agreement with literature data.[1,5] Calculation of the absolute and relative increase in cortisol could be useful in view of the overlap between the upper limit of cortisol and the lower limit of peak cortisol after Synacthen; its usefulness remains, however, to be demonstrated as others have not found added value from such calculations.[6] Our cut-off level of peak cortisol corresponds well with the value of 500 to 600 nmol/l usually stated in the literature.[1,4-7] The vast majority of patients with primary adrenal failure have peak cortisol levels below this cut-off value, whereas only a few have cortisol levels >550 nmol/l albeit associated with high ACTH levels.[6] Our protocol might thus have a high diagnostic accuracy for primary adrenal insufficiency. With normal plasma ACTH levels, a recent meta-analysis concluded that at clinically useful cut-off peak cortisol levels between 500 and 600 nmol/l (where specificity is approximately 95%), a subnormal peak cortisol level substantially increases the likelihood that the patient has central adrenal insufficiency.[6] Conversely, a normal peak cortisol only modestly decreases the likelihood of central adrenal insufficiency, particularly if the pretest probability is high. Thus, the diagnostic accuracy of the 250 μg Synacthen test for central adrenal insufficiency is limited (sensitivity only 57% at a specificity of 95%, positive likelihood

Table 2 *Reference values of diagnostic tests in the evaluation of adrenal insufficiency*

		Reference interval (mean ± 2SD)*
Morning (09.00 hr) plasma cortisol	nmol/l	150-802
Morning (09.00 hr) plasma 11-deoxycortisol	nmol/l	5.5-12.6
Morning (0.900 hr) plasma ACTH	ng/l	8-93
Synacthen test (250 μg iv)		
• Peak plasma cortisol	nmol/l	591-1113
• Absolute cortisol increase	nmol/l	189-907
• Relative cortisol increase	%	27-526
Metyrapone test		
• Plasma cortisol	nmol/l	<50-640
• Plasma ACTH	ng/l	64-907
• Plasma 11-deoxycortisol	nmol/l	197-759
Insulin tolerance test		
• Peak plasma cortisol	nmol/l	557-1015
• Absolute cortisol increase	nmol/l	165-702
• Relative cortisol increase	%	24-340

*Calculated after logarithmic transformation of hormone concentrations to obtain a normal distribution.

ratio 11.5 and negative likelihood ratio 0.45), and the test is more helpful for ruling in than for ruling out central adrenal insufficiency.[6] It follows that with a high pretest probability of central adrenal insufficiency and a normal cortisol response to Synacthen, other tests with better sensitivity should be performed.[6]

The insulin tolerance test has long been regarded the gold standard for the diagnosis of central adrenal insufficiency. Our test results indicate that if adequate hypoglycaemia is reached, plasma cortisol should rise above 557 nmol/l (*table 2*). This value is in good agreement with the cut-off levels of 550 nmol/l commonly stated in the literature.[1,8-13] We refrained from measuring the ACTH response to insulin-induced hypoglycaemia because measuring the ACTH response does not seem to provide added clinical value.[11,13] One advantage of the insulin tolerance test is that it allows simultaneous evaluation of both GH deficiency and ACTH deficiency. The test, however, is unpleasant and serious side effects do happen, although fortunately only very rarely. This explains our preference for the metyrapone tests. Good concordance between the results of the metyrapone test and the insulin tolerance test has been reported in several studies, one study even claiming superiority of the metyrapone test.[8,14-15]

Our results of the overnight single-dose metyrapone test indicate that the next morning, the plasma 11-deoxycortisol should rise >197 nmol/l (*table 2*). This cut-off level is in good agreement with the threshold value of 200 nmol/l commonly stated in the literature.[1,8,14-16] The test was in general well tolerated, and no low blood pressures have been recorded after metyrapone. In patients with central adrenal insufficiency, however, hypotension in the early morning hours may develop after administration of metyrapone the previous evening; as a precaution we therefore hospitalise patients suspected of central adrenal insufficiency for one night, and discharge them with hydrocortisone replacement if the blood pressure is low the morning after blood withdrawal. The test in the healthy volunteers of this study was performed in outpatient clinics. A check on the ingestion of metyrapone by the volunteers at home was done by measuring plasma cortisol and ACTH the next morning. The expected fall in plasma cortisol was not observed in seven subjects, but incompliance with intake of metyrapone tablets seems unlikely in view of their 8.5-fold increase in plasma ACTH as compared with a mean 9.8-fold rise of plasma ACTH in the whole group and their substantial rise of plasma 11-deoxycortisol after metyrapone.

A low-dose Synacthen test employing 1 μg instead of 250 μg intravenously has been advocated in many studies over the last decade: the 1 μg dose already gives a maximal cortisol response, and the 1 μg test could be superior to the 250 μg test for diagnosing central adrenal insufficiency because the obtained plasma ACTH levels are more physiological.[17-21] A recent meta-analysis, however, concluded that available data do not clearly establish the superiority of the 1 μg over the 250 μg Synacthen test in secondary adrenal insufficiency.[6] The 1 μg test requires accurate dilution of Synacthen which comes in 250 μg ampoules, and frequent carefully timed venous blood sampling; it is thus much more liable to errors than the 250 μg test, which is more robust and easier to perform. Consequently, we refrained from establishing a peak cortisol response to 1 μg Synacthen.

In summary, we have established reference values for 09.00 hour plasma cortisol and ACTH, and for response to three dynamic tests (Synacthen test, metyrapone test, and insulin tolerance test) to be applied in the biochemical diagnosis of adrenal insufficiency. Clinically useful cut-off levels are likely a peak plasma cortisol of 550 nmol/l after either Synacthen or insulin-induced hypoglycaemia, and a plasma 11-deoxycortisol of 200 nmol/l after metyrapone. The validity of these cut-off levels should be evaluated in patients undergoing these tests because of suspected adrenal insufficiency from which discrimination values can be derived.

REFERENCES

1. Arlt W. Allolio B. Adrenal insufficiency. Lancet 2003;361:1881-93.
2. De Bos Kuil MJJ, Endert E, Fliers E, Prummel MF, Romijn JA, Wiersinga WM. Establishment of reference values for endocrine tests. I: Cushing's syndrome. Neth J Med 1998;53:153-63.
3. Hägg E, Asplund K, Lithaer F. Value of basal plasma cortisol assays in the assessment of pituitary adrenal insufficiency. Clin Endocrinol 1987;26:221-6.
4. Le Roux CW, Meeran K, Alaghband-Zadeh J. Is a 0900-h serum cortisol useful prior to a short synacthen test in outpatient assessments? Ann Clin Biochem 2002;39:148-50.
5. Patel SR, Selby C, Jeffcoate WJ. The short Synacthen test in acute hospital admissions. Clin Endocrinol 1991;35:259-61.
6. Dorin RI, Qualls CR, Crapo LM. Diagnosis of adrenal insufficiency. Ann Intern Med 2003:139:194-204.
7. Clark PM, Neylon I, Raggat PR, Sheppard MC, Stewart PM. Defining the normal response to the short Synacten test: implications for the investigation of hypothalamic-pituitary disorders. Clin Endocrinol 1998:49:287-92.
8. Courtney CH, McAllister AS, McCance DR, et al. The insulin hypoglycaemia and overnight metyrapone tests in the assessment of the hypothalamic-pituitary-adrenal following pituitary surgery. Clin Endocrinol 2000:53:309-12.
9. Schmidt IL, Lahner H, Mann K, Petersenn S. Diagnosis of adrenal insufficiency: Evaluation of the corticotropin-releasing hormone test and basal serum cortisol in comparison to the insulin tolerance test in patients with hypothalamic-pituitary-adrenal disease. J Clin Endocrinol Metab 2003;88:4193-8.

10. Maghnie M, Uga E, Temporini F, et al. Evaluation of adrenal function in patients with growth hormone deficiency and hypothalamic-pituitary disorders: comparison between insulin-induced hypoglycemia, low-dose ACTH, standard ACTH and CRH stimulation test. Eur J Endocrinol 2005;152:735-41.
11. Borm K, Slawik M, Seiler L, et al. Is the plasma ACTH concentration a reliable parameter in the insulin tolerance test? Eur J Endocrinol 2003;149:535-41.
12. Gonzalbez J. Villabona C, Ramon J, et al. Establishment of reference values for standard dose short synacthen test (250 μg), low dose short synacthen test (1 μg) and insulin tolerance test for assessment of the hypothalamic-pituitary-adrenal axis in normal subjects. Clin Endocrinol 2000;53:199-204.
13. Tuchelt H, Dekler K, Bähr V, Oelkers W. Dose response relationship between plasma ACTH and serum cortisol in the insulin hypoglycaemia test in 25 healthy subjects and 109 patients with pituitary disease. Clin Endocrinol 2000;53:301-7.
14. Steiner H, Bähr V, Exner P, Oelker PW. Pituitary function tests: comparison of ACTH and 11-deoxycortisol responses in the metyrapone test and with the insulin hypoglycemia test. Exp Clin Endocrinol 1994;102:33-8.
15. Fiad TM, Kirby JM, Cunningham SK, MCKenna TJ. The overnight single-dose metyrapone test is a simple and reliable index of the hypothalamic-pituitary-adrenal axis. Clin Endocrinol 1994;40:603-9.
16. Soule S, van Zyl-Smit C, Parolis G, et al. The low dose ACTH stimulation test is less sensitive than the overnight metyrapone test for the diagnosis of secondary hypoadrenalism. Clin Endocrinol 2000;53:221-7.
17. Tjordjmann K, Jaffe A, Grazas N, Apter C, Stern N. The role of the low dose (1microgram) adrenocorticotropin test in the evaluation of patients with pituitary diseases. J Clin Endocrinol Metab 1995;80:1301-5.
18. Mayenknecht J, Diederich S, Bähr V, Plockinger U, Oelkers W. Comparison of low and high dose corticotropin stimulation tests in patients with pituitary disease. J Clin Endocrinol Metab 1998;83:1558-62.
19. Abdu TAM, Elhadd TA, Neary R, Clayton RN. Comparison of the low dose short Synacthen test (1 μg), the conventional dose short Synacthen test (250 μg), and the insulin tolerance test for assessment of the hypothalamo-pituitary-adrenal axis in patients with pituitary disease. J Clin Endocrinol Metab 1999;84:838-43
20. Dickstein G. Hypothalamo-pituitary-adrenal axis testing: nothing is sacred and caution in interpretation is needed. Clin Endocrinol 2001;54:15-6.
21. Suliman AM, Smith TP, Labib M, Fiad TM, KcKenna TJ. The low-dose ACTH test does not provide a useful assessment of the hypothalamic-pituitary-adrenal axis in secondary adrenal insufficiency. Clin Endocrinol 2002;56:533-9.

Netherlands
The Journal of Medicine

CASE REPORT

Myelotoxicity and hepatotoxicity during azathioprine therapy

N.K.H. de Boer*, C.J.J. Mulder, A.A. van Bodegraven

Department of Gastroenterology and Hepatology, VU University Medical Centre, Amsterdam, the Netherlands, *corresponding author: tel.: +31 (0)20-444 06 11, fax: +31 (0)20-444 05 54, e-mail: KHN.deBoer@vumc.nl

ABSTRACT

Azathioprine is a frequently used immunosuppressant for managing inflammatory bowel disease (IBD). In recent years the hepatotoxic profile of thiopurines has been recognised. We report the case of a 40-year-old man with Crohn's disease treated with azathioprine. After taking azathioprine (2.2 mg/kg daily) for two years, his liver function tests were found to be elevated. Moreover, a myelodepression was established as platelet and leucocytes counts were lowered. The 6-thioguaninenucleotide level was 738 picomoles/8 x 10^8 per red blood cell, which is well above the proposed upper limit of efficacy and associated with an increased risk of developing a myelodepression. Genotyping of the enzyme thiopurine methyltransferase revealed no mutant alleles. The ultrasonography and CT scan showed signs of portal hypertension (spleen 17 cm and widened splenic vein). A liver biopsy was performed and an incomplete septal liver cirrhosis was found. An upper endoscopy revealed oesophageal varices (grade 2 to 3). Autoimmune and viral liver diseases were ruled out by laboratory parameters. After cessation of therapy, all laboratory parameters normalised. Therefore, azathioprine is believed to be the causative factor for inducing the liver cirrhosis. Continuous monitoring of patients taking thiopurines is mandatory. The role of 6-thioguaninenucleotide levels in inducing myelotoxicity and hepatotoxicity is discussed.

KEYWORDS

Azathioprine, Crohn's disease, hepatotoxicity, liver cirrhosis, myelotoxicity, 6-thioguaninenucleotides

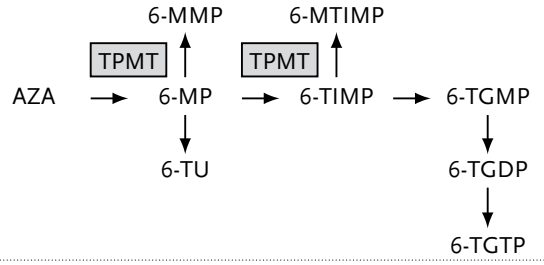
INTRODUCTION

Azathioprine (AZA) and 6-mercaptopurine (6-MP) have gained a prominent place as an immunosuppressive maintenance therapy for Crohn's disease (CD). However, their therapeutic role has been under discussion because of toxicity. Adverse effects may occur in 15 to 30% of patients.[1,2] AZA-induced hepatotoxicity is believed to be a rare adverse event. Hepatitis is considered to be an idiosyncratic reaction to AZA. Nodular regenerative hyperplasia (NRH), veno-occlusive disease, peliosis hepatis, fibrosis and sinusoidal dilatation are regarded as signs of dose-dependent hepatotoxicity.[3-8] During the complex metabolisation process of AZA and 6-MP, multiple metabolites are generated (*figure 1*).[9] The pharmacologically active metabolites are the 6-thioguaninenucleotides (6-TGN), which are believed to induce apoptosis of activated T lymphocytes,[10] hence leading to suppression of the overactive immune defence mechanisms. The proposed range of 6-TGN is 235 to 450 picomoles/8 x 10^8 per red blood cell (RBC).[11] High 6-TGN levels (>450 picomoles/8 x 10^8 RBC) have been associated with an increased risk of developing a myelodepression and high levels of the methylated product of 6-MP (6-methylmercaptopurine (6-MMP)) with hepatotoxicity.
Here we describe a patient who developed histological liver abnormalities combined with a myelodepression most likely caused by the use of AZA.

CASE REPORT

In 2000 the diagnosis of CD of the ileum and jejunum with perianal fistulas was established in a 35-year-old man.

Figure 1 *Thiopurine metabolism*



Azathioprine (AZA) undergoes a rapid nonenzymatic conversion in the liver yielding 6-mercaptopurine (6-MP). Following intracellular uptake, 6-MP is metabolised by three enzymes (xanthine oxidase, thiopurine methyltransferase (TPMT) and hypoxanthine phosphoribosyl transferase). Xanthine oxidase and TPMT catalyse the reaction of 6-MP to 6-thiouric acid (6-TU) and 6-methylmercaptopurine (6-MMP), respectively. The hypoxanthine phosphoribosyl transferase enzyme system is responsible for the formation of 6-thioinosine-monophosphate (6-TIMP) which may ultimately be transformed into the pharmacologically active 6-thioguaninenucleotides: 6-thioguanine-monophosphate (6-TGMP), 6-thioguanine-diphosphate (6-TGDP) and 6-thioguanine-triphosphate (6-TGTP).

A steroid pulse therapy was administered to induce remission. However, in December 2000 a surgical ileocaecal resection was performed due to intractable symptoms caused by a stenosis of the terminal ileum. Postoperative therapy with calcium, vitamin D, H_2-receptor antagonist, vitamin B12 and AZA was initiated. AZA was given in doses of 200 mg a day (2.2 mg per kg). The disease remained quiescent and regular laboratory controls were normal (*table 1*). In December 2003 abnormal laboratory parameters were found as liver function tests were elevated. Leucocyte and platelet counts were found to be below the reference limits (*table 1*). No physical complaints were mentioned by the patient. As AZA was believed to be the causative factor, an abdominal ultrasound was performed, and the level of 6-TGN/6-MMP and the status of the enzyme thiopurine methyltransferase (TPMT) were determined. The examination by abdominal ultrasound revealed an enlarged spleen (17 cm) and a distended diameter of the splenic vein (1.9 cm). The hepatic parenchyma showed no abnormalities. The 6-TGN was found to be 738 picomoles/8 x 10^8 RBC.[12] Determination of the 6-MMP level was not carried out due to technical failure. TPMT genotyping revealed no mutant alleles (TPMT*1/*1). Autoimmune and viral liver diseases were ruled out by laboratory parameters. Alcohol use was repeatedly denied. Subsequently, a CT scan was performed but no novel insights were obtained. A fine needle liver biopsy was performed in May 2004 and the specimen was stained with haematoxylin and eosin, (silver)reticulin and trichrome. An incomplete septal cirrhosis was found microscopically without signs of primary sclerosing cholangitis, peliosis hepatis, veno-occlusive disease or NRH. Oesophageal varices (grade 2 to 3) were found by upper gastrointestinal endoscopy. Treatment with a β-receptor antagonist (propranolol 10 mg twice daily) was initiated as primary prophylaxis for oesophageal bleeding. All laboratory tests normalised after cessation of AZA (*table 1*). The α-fetoprotein level was not increased. The disease has remained in remission to date. Abdominal ultrasounds and upper gastrointestinal endoscopies are performed at regular intervals.

DISCUSSION

The metabolism of thiopurines has partly been elucidated in recent years. Several metabolites have been held responsible for induction of adverse events. The enzyme TPMT plays a key role in the bioavailability of 6-TGN. High TPMT activity may lead to elevated levels of 6-MMP, which have been associated with hepatotoxicity (>5700 pmol/8 x 10^8 RBC) and refractoriness on therapy.[9] A diminished TPMT activity will likely result in shunting 6-MP away from 6-MMP towards overproduction of 6-TGN. Levels of 6-TGN >450 pmol/8 x 10^8 red blood cells (RBC) induced by AZA or 6-MP therapy have been associated with an increased risk of developing myelotoxicity (e.g. leucopenia or thrombocytopenia).[13] Despite shortage of conclusive evidence, 6-TGN levels between 235 and 450 pmol/8 x 10^8 RBC are currently considered to corre-

Table 1 *Laboratory parameters*

Test	December 2000	December 2003	March 2005	Normal values
Aspartate aminotransferase (U/l)	12	57	25	<40
Alanine aminotransferase (U/l)	19	53	26	<45
Gamma-glutamyltransferase (U/l)	15	85	26	10-50
Alkaline phosphatase (U/l)	86	141	97	40-120
Bilirubin (unconjugated) (μmol/l)	10	35 (0.28)	16 (0.23)	<20
Haemoglobin (mmol/l)	9.5	7.7	9.5	8.7-11
Leucocytes (x 10^9/l)	17.2	2.1	8.1	3-10
Platelets (x 10^9/l)	303	64	161	150-400

spond with an increased likelihood of optimal therapeutic response. The 6-TGN levels during AZA (2 to 2.5 mg/kg) and 6-MP (1 to 1.5 mg/kg) therapy vary between individuals but in most cases they are found to be between 200 and 500 pmol/8 x 10^8 RBC.[14] These observations may explain the leucopenia and thrombocytopenia of our patient as the 6-TGN level was 738 picomoles/8 x 10^8 RBC, which is well above the proposed upper limit of efficacy. However, the diminished platelet count may also be explained by the splenomegaly due to the portal hypertension. The relatively high 6-TGN level is not explained by the TPMT status as no mutant alleles were found by genotyping.[15] Additionally, the medication used by our patient is not expected to influence the metabolism of AZA.[11] The possibility of an AZA overdose can not be ruled as the 6-MMP level was not available. An adequate clarification for the elevated 6-TGN is not available.

In recent years the hepatotoxic potential of thiopurines, in particular 6-thioguanine (6-TG), has been discussed in literature. The use of 6-TG in IBD patients has currently been abandoned due to its presumed hepatotoxic profile, as it has been associated with the induction of NRH.[16] The higher occurrence of histological liver abnormalities during 6-TG treatment in comparison with AZA or 6-mercaptopurine (6-MP) may be explained by the significantly higher levels of 6-TGN reached by 6-TG. In the past, it was demonstrated that AZA may lead to veno-occlusive disease due to dose-dependent toxicity to murine sinusoidal endothelial cells and hepatocytes.[17] Additional different pharmacokinetic characteristics or a different first-pass effect may play a role as well. Interestingly, there is a clear predominance of hepatic lesions in male patients which raises the question of a genetic predisposition.[16] The hypothesis that high 6-TGN levels are hepatotoxic may provide an explanation why our patient developed an incomplete septal cirrhosis. Moreover, this concept may provide a clue why hepatotoxicity is reported to be relatively rare during AZA and 6-MP therapy as the majority of IBD patients will have much lower 6-TGN levels during AZA or 6-MP treatment compared with our patient. However, an underestimation of histological liver abnormalities caused by AZA or 6-MP therapy may be expected, since the current practice is to stop the drug without performing a liver biopsy when finding elevated liver function tests during AZA or 6-MP treatment. Furthermore, not all histological liver abnormalities lead to derangement in liver function tests.

Our case illustrates the potential toxicity of AZA and stresses the need for continuous close monitoring of patients taking thiopurines in general. Routinely performed laboratory controls including full white blood counts and liver function tests seem mandatory.

REFERENCES

1. Pearson DC, May GR, Fick GH, Sutherland LR. Azathioprine and 6-mercaptopurine in Crohn disease. A meta-analysis. Ann Intern Med 1995;123:132-42.
2. Candy S, Wright J, Gerber M, Adams G, Gerig M, Goodman R. A controlled double blind study of azathioprine in the management of Crohn's disease. Gut 1995;37:674-8.
3. Fonseca V, Havard CW. Portal hypertension secondary to azathioprine in myasthenia gravis. Postgrad Med J 1988;64:950-2.
4. Haboubi NY, Ali HH, Whitwell HL, Ackrill P. Role of endothelial cell injury in the spectrum of azathioprine-induced liver disease after renal transplant: light microscopy and ultrastructural observations. Am J Gastroenterol 1988;83:256-61.
5. Daniel F, Cadranel J, Seksik P, et al. Azathioprine induced nodular regenerative hyperplasia in IBD patients. UEGW 2004; A221.
6. Russmann S, Zimmermann A, Krahenbuhl S, Kern B, Reichen J. Veno-occlusive disease, nodular regenerative hyperplasia and hepatocellular carcinoma after azathioprine treatment in a patient with ulcerative colitis. Eur J Gastroenterol Hepatol 2001;13:287-90.
7. Sterneck M, Wiesner R, Ascher N, et al. Azathioprine hepatotoxicity after liver transplantation. Hepatology 1991;14:806-10.
8. Holtmann M, Schreiner O, Kohler H, et al. Veno-occlusive disease (VOD) in Crohn's disease (CD) treated with azathioprine. Dig Dis Sci 2003;48:1503-5.
9. Dubinsky MC, Lamothe S, Yang HY, et al. Pharmacogenomics and metabolite measurement for 6-mercaptopurine therapy in inflammatory bowel disease. Gastroenterology 2000;118:705-13.
10. Tiede I, Fritz G, Strand S, et al. CD28-dependent Rac1 activation is the molecular target of azathioprine in primary human CD4+ T lymphocytes. J Clin Invest 2003;111:1133-45.
11. Al Hadithy AF, de Boer NK, Derijks LJ, Escher JC, Mulder CJ, Brouwers JR. Thiopurines in inflammatory bowel disease: pharmacogenetics, therapeutic drug monitoring and clinical recommendations. Dig Liver Dis 2005;37:282-97.
12. Lennard L, Singleton HJ. High-performance liquid chromatographic assay of the methyl and nucleotide metabolites of 6-mercaptopurine: quantitation of red blood cell 6-thioguanine nucleotide, 6-thioinosinic acid and 6-methylmercaptopurine metabolites in a single sample. J Chromatogr 1992;583:83-90.
13. Schutz E, Gummert J, Mohr FW, Armstrong VW, Oellerich M. Azathioprine myelotoxicity related to elevated 6-thioguanine nucleotides in heart transplantation. Transplant Proc 1995;27:1298-1300.
14. Lowry PW, Franklin CL, Weaver AL, et al. Measurement of thiopurine methyltransferase activity and azathioprine metabolites in patients with inflammatory bowel disease. Gut 2001;49:665-70.
15. Lennard L. TPMT in the treatment of Crohn's disease with azathioprine. Gut 2002;51:143-6.
16. Dubinsky MC, Vasiliauskas EA, Singh H, et al. 6-thioguanine can cause serious liver injury in inflammatory bowel disease patients. Gastroenterology 2003;125:298-303.
17. DeLeve LD, Wang X, Kuhlenkamp JF, Kaplowitz N. Toxicity of azathioprine and monocrotaline in murine sinusoidal endothelial cells and hepatocytes: the role of glutathione and relevance to hepatic venoocclusive disease. Hepatology 1996;23:589-99.

Netherlands
The Journal of Medicine

Between hands and feet

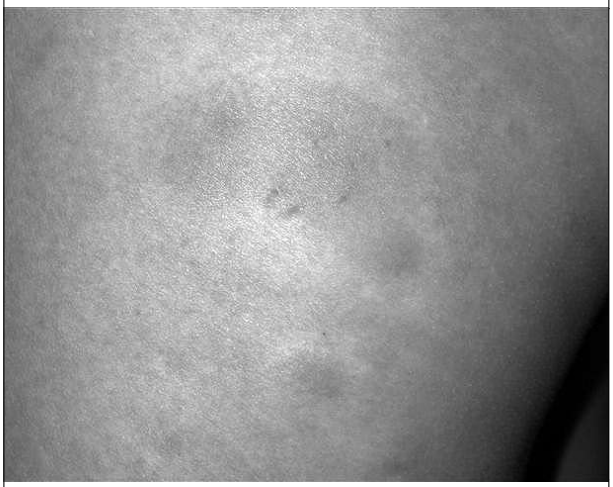
F. Stam[1*], T. van Meurs[2], C. Koley[3]

Departments of [1]Internal Medicine, [2]Dermatology and [3]Pathology, VU University Medical Centre, Amsterdam, the Netherlands, [*]corresponding author: tel.: +31 (0)20-4444 39 58, fax: +31 (0)20-444 43 13, e-mail: f.stam@vumc.nl

CASE REPORT

A 21-year-old woman presented in the month of February with a three-day history of several violaceous, pruritic, indurated plaques on her thighs with a diameter ranging from 2 to 5 cm. Her medical history revealed chronic constipation, for which fibres had been prescribed. On examination, except for the skin changes (*figure 1*) no abnormalities were found. The patient worked as a secretary and rode horses as a hobby. Laboratory investigation showed normal values for ESR, white blood cell differentiation, serum creatinine and urinary analysis.

Figure 1 *A raised violaceous plaque on the lateral thigh*



A colour version of this photo quiz can be found on our website www.njmonline.nl.

WHAT IS YOUR DIAGNOSIS?

See page 453 for the answer to this photo quiz.

Netherlands
The Journal of Medicine

A severe (type II) hepatopulmonary syndrome in a patient with idiopathic portal hypertension and treatment with paroxetine

Ş. Yilmaz[1*], M. Dursum[1], F. Canoruç[1], K. Bayan[1], A. Karabulut[2], H. Akay[3]

Departments of [1]Gastroenterology, [2]Cardiology and [3]Radiology, Faculty of Medicine, Dicle University, Diyarbakir, Turkey, [*]corresponding author: tel.: +90412 2488001, fax: +90412 2488523, e-mail:drserif@dicle.edu.tr

ABSTRACT

The hepatopulmonary syndrome has been defined as chronic liver disease accompanied by abnormal pulmonary gas exchange, which might result in arterial deoxygenation, and widespread intrapulmonary vasodilation. Although it has been pointed out that hepatopulmonary syndrome occurs in liver cirrhosis, there are a few studies in the literature reporting noncirrhotic portal hypertension as a cause of hepatopulmonary syndrome. Currently, liver transplantation is the only effective therapy for such patients. On the other hand, there is also a proposal about considering paroxetine, a potent nitric oxide synthase inhibitor, for use in the hepatopulmonary syndrome. We present a patient with severe (type II) hepatopulmonary syndrome caused by idiopathic portal hypertension and discuss the consequences of paroxetine therapy.

KEYWORDS

Hepatopulmonary syndrome, paroxetine

INTRODUCTION

Hepatopulmonary syndrome (HPS) is recognised by progressive pulmonary complications that include severe liver disease and/or portal hypertension, abnormal arterial oxygenation, and presence of intrapulmonary vascular dilatations.[1] There might be severe hypoxaemia with arterial PO_2 <60 mm Hg (8 kPa), dyspnoea, cyanosis, digital clubbing, orthodeoxia and platypnoea in these patients. Its incidence in patients with liver cirrhosis is about 10%,[2] and in the literature this rate is 10 to 20% in patients who are candidates to liver transplantation.[3,4] A few cases of noncirrhotic portal hypertension (NCPH) complicated by HPS have been published.[5,6] Therefore the cirrhosis is not a strict criterion for HPS identification. We present here a patient with a classical presentation of severe HPS, which was caused by idiopathic portal hypertension, and we discuss the effect of paroxetine therapy on this syndrome.

CASE REPORT

An 18-year-old male patient was admitted to our clinic at the beginning of 2004. He had fever, fatigue, and dyspnoea. His symptoms were intermittent and alleviated after antibiotic therapy, which he had been receiving since the previous year. In many attacks, cyanosis, palpitations and intolerance to exercise also occurred. He had also been suffering from a depressed mood on a daily basis for a period of three months. He had been hospitalised because of Brucella disease one year earlier. There was no history of pica. Physical examination revealed cachexia, pale conjunctiva, frank cyanosis of the tongue, lips and the distal part of extremities, finger clubbing, splenomegaly, and spider nevus on his shoulder. Laboratory findings revealed the following: haemoglobin 6.4 mmol/l, haematocrit 0.31, white blood count 1.9 x 10^9/l, platelet count 83 x 10^9/l, and erythrocyte sedimentation rate 75 mm/h. Serum aspartate aminotransferase was 0.89 U/l, alanine aminotransferase 0.71 U/l, lactic dehydrogenase 4.04 U/l, alkaline phosphatase 4.6 U/l, γ-glutamyl-

transpeptidase 1.66 U/l, total bilirubin 11.9 μmol/l, iron concentration 7.09 μmol/l, total iron binding capacity 75.6 μmol/l, transferrin saturation rate 9%, albumin 39 g/l, and globulin 32 g/l. Reticulocytes count, seruloplasmin, thyroid hormones, cortisol, and corticotropin levels were normal. Haemoglobin and protein electrophoresis were also normal. Serum markers for hepatotropic and nonhepatotropic viruses, ANA, anti-LKM-1, anti-SLA, pANCA, and AMA-M_2 were all negative. Prothrombin time was 15 seconds, activated partial thromboplastin time, protein S and antithrombin III were normal, but protein C level was low (36.6%). Analysis of the sweat chloride value was normal in duplicate. In DNA analysis, gene mutation for cystic fibrosis (ΔF 508 and ΔTA 1677) was absent. Respiratory function test was compatible with moderate restriction. The alveolar-arterial oxygen gradient (A-aPO_2) was 68 mmHg (9 kPa) in upright position. Partial arterial oxygen tension (PaO_2) was 53 mmHg (7 kPa) in supine position and 45 mmHg (6 kPa) in sitting position (orthodeoxy). Response to 100% inspired oxygen was 54 mmHg (7.2 kPa). Arterial blood gas values in upright position revealed pH 7.47, PCO_2 29 mmHg (3.8 kPa), SaO_2 81%, and HCO_3 23 mmol/l. The carbon monoxide diffusing capacity (DL_{CO}) of the lung was 42.4 (% predicted). Electrocardiogram and posteroanterior lung X-ray and thorax high resonance computerised tomography were normal. Macroaggregated albumin (^{99m}Tc-MAA) scintigraphy revealed heterogeneous radioactivity distribution in the lung fields. There was obvious tracer uptake over the brain, spleen and bilateral kidneys, with shunt fraction of 20%. Standard echocardiogram revealed normal findings. Contrast echocardiography showed microbubbles after four heart beats (late opacification) in left heart chambers with 4+ degree of opacification (*figures 1A* and *1B*). He did not tolerate transoesophageal echocardiography. Cardiac output was calculated and found to be 8 l/min on cardiac catheterisation by the Fick method. The results of this procedure are summarised in *table 1*. The value of hepatic venous pressure gradient (HVPG) was 6 mmHg. The endoscopy showed grade 2 to 3 oesophageal varices and portal gastropathy. Doppler ultrasonography of abdominal-portal system revealed a normal-sized liver, normal parenchymal echogenity, dilated portal vein (*figure 2*), mild splenomegaly and splenic venous dilatation (*figure 3*). There was no image of cavernous transformation of the portal vein. Liver biopsy showed noncirrhotic liver parenchyma with normal architecture, dilated sinusoids and portal space, degenerated hepatocytes, periportal-portal inflammation (*figure 4*), porto-portal bridging fibrosis and sclerosis (*figure 5*). In the light of all these parameters, the diagnosis of HPS caused by NCPH was made. He also fulfilled all the criteria for major depression, according to the psychological consultation. We gave him paroxetine (Seroxate® tb) 20 mg a day orally for six months because

Figure 1A *Microbubbles in right heart chambers in contrast echocardiogram*

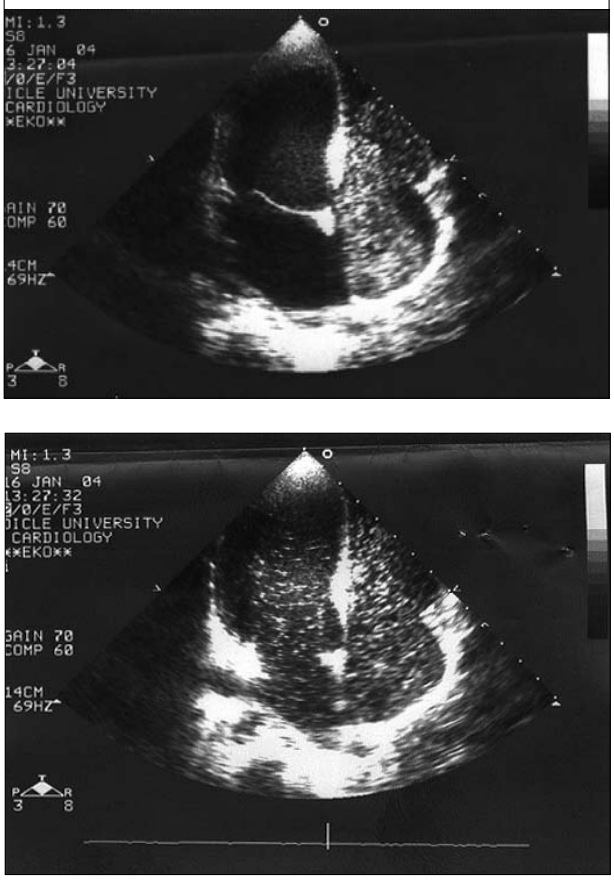


Table 1 *Parameters obtained from cardiac catheterisation*

Angiography	Pressures (mmHg)	SAO_2 (%)	PAO_2 (mmHg)
Pulmonary artery	20/10	67	40
Right ventricle	20/0	69	40
Right atrium	5 (mean)	70	40
Aorta	100/70	87	56

Figure 2 *Liver ultrasonogram: dilated portal vein without cavernous transformation*

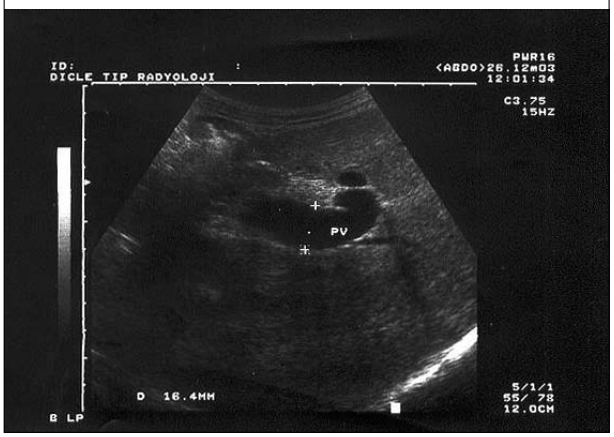


Figure 3 *Spleen ultrasonogram: splenomegaly with dilated splenic vein*

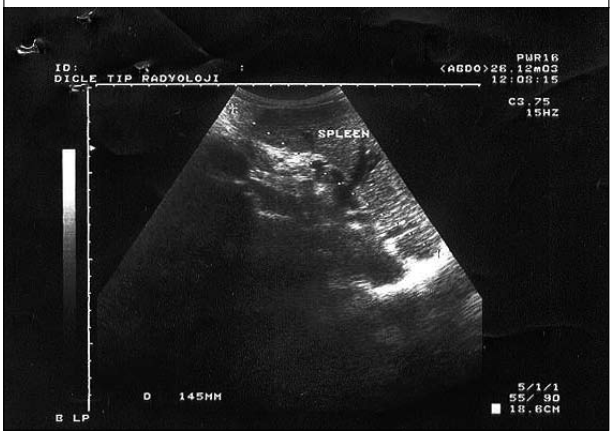


Figure 4 *Liver biopsy shows portal-periportal inflammation, and hepatocellular degeneration (HE x 200)*

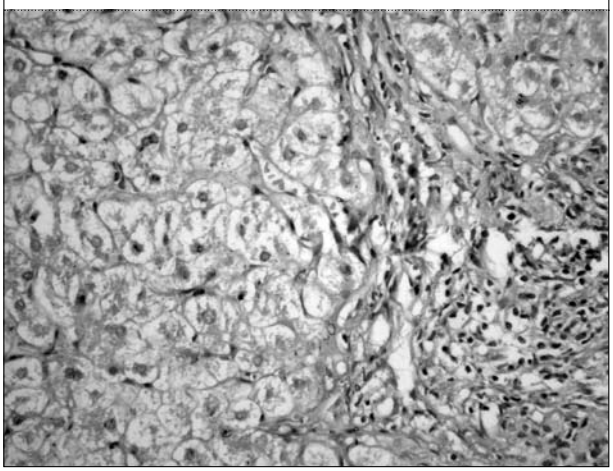
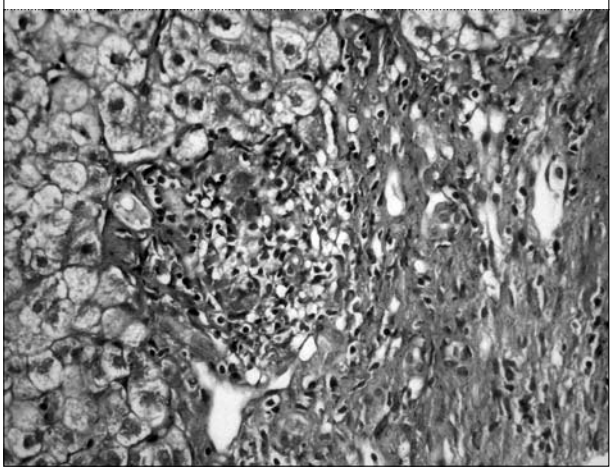


Figure 5 *Liver biopsy shows periportal fibrosis with Masson's trichrome staining (x 200)*



of its antidepressant effect and the possibility of NO-synthetase inhibition resulting in a decrease in intrapulmonary shunting. The blood gas parameters at the end of treatment are summarised in *table 2*.

Table 2 *Results associated with before and after paroxetine treatment*

		Results	
		Before	**After**
A-aPO_2 gradient		68	75
100% O_2 test (PaO_2-mmHg)		54	61
PaO_2 (mmHg)	Supine	53	40
	Upright	45	35
SaO_2 (%)	Supine	83	65
	Upright	81	63

DISCUSSION

In the definition of hepatopulmonary syndrome, the presence of cirrhosis is still frequently one the criteria[7-9] but it is obvious that HPS is also seen in patients with noncirrhotic portal hypertension.[10] Recently, in a study performed by Kaymakoglu *et al.*, it was pointed out that HPS might occur in both liver cirrhosis and noncirrhotic portal hypertension and that portal hypertension is the predominant pathogenic factor related to HPS.[6] However, pathogenesis of HPS is still obscure. This is likely to be a manifestation of decreased hepatic clearance or increased hepatic production of circulating cytokines and other vascular growth mediators such as endothelins, nitric oxide (NO), and prostaglandins. Increased sensitivity to these mediators is another theory. The major role was attributable to the potent vasodilating mediator nitric oxide. Besides, endothelin-1 increases inducible NO syntheses and plays an important part in intrapulmonary vasodilatation in HPS.[11] As we mentioned above, for NCPH, severe liver dysfunction is not mandatory for intrapulmonary vasodilatation. The other reasons for an impaired oxygenation because of shunting are pleural spider naevi, intrapulmonary A-V shunts and portopulmonary venous anastomoses.

Arterial hypoxaemia is described as PaO_2 <70 mmHg (9.3 kPa) in blood gas analysis; <60 mmHg (8 kPa) reflects severe hypoxaemia. Hypoxia is believed to result from an inability of oxygen to diffuse to the centre of dilated vessels up to tenfold in diameter in HPS.[12] Low level of PaO_2 does not reflect gas exchange disturbance in liver disease alone, because of hyperventilation and hyperdynamic circulation in cirrhosis. Therefore, measuring the A-aPO_2 gradient is better, and a level >20 mmHg (2.6 kPa) is pathological and important in HPS diagnosis. It was 68 mmHg (9 kPa) in our patient. On the other hand, 100% oxygen inspiring test (breathing 100% oxygen through a mouthpiece and wearing nose clips for 20 minutes in the sitting position) is another supplement. The test of supplementation with 100% oxygen distinguishes HPS type I from type II. In type I, there is a close to normal response

to the administration of oxygen (PaO_2 >400 mmHg (53.3 kPa)), but in type II, an inadequate response to this regimen.[4] In the study carried out by Kaymakoglu *et al.*, there were three patients with HPS in the NCPH group and all of them had levels >150 mmHg (20 kPa). This level was 54 mmHg (7.2 kPa) in our patient, which is compatible with type II HPS and reflects a severe intrapulmonary shunt. The cases reported to have HPS caused by NCPH in the literature were not as severe as our patient. Contrast echocardiography is one of the best modalities confirming intrapulmonary dilatations.[7] Positive echocardiogram for HPS was defined by the detection of delayed visualisation of microbubbles in the left heart chambers after three to six contractions. If microbubbles are visualised after one to two contractions, this reflects intracardiac right-to-left shunting. There was a result compatible with the intrapulmonary shunt in our patient with a higher degree of opacification (4+), compared with the cases in the study of Kaymakoglu *et al.*, and this result may also support the severity of shunting. Pulmonary angiography is the most invasive procedure in diagnosis of HPS and shows emboli and/or other causes of hypoxemia. There are two patterns in angiographic examination of HPS patients.[12] In type I, there is a normal vascular structure, spongiform, spotted image, and patients respond to 100% oxygen supplementation test. In type II, there are vascular dilatations such as arteriovenous communications and a poor response to treatment by medications or transplantation.

As we previously stated, our patient had severe HPS. The portal hypertension was of unknown origin. There was no evidence of liver cirrhosis. There was a prehepatic intrasinusiodal portal hypertension pattern in data obtained from hepatic venous catheterisation in our patient wedged hepatic venous pressure (WHVP) and HVPG normal. No portal or splenic venous thrombosis was found in the imaging studies. Schistosomiasis was also excluded by microscopic findings. There was no history of medication or herbal abuse in our patient. We could not detect any pattern compatible with partial nodular transformation in imaging studies. Serum markers for early primary biliary cirrhosis and primary sclerosing cholangitis were negative. Furthermore, there were no signs of myeloproliferative disease or sarcoidosis. Finally, there was no evidence of congenital hepatic fibrosis cholangitis.

Idiopathic portal hypertension (IPH) is also called noncirrhotic portal fibrosis or hepatoportal sclerosis, and known as a conditon in which liver function is preserved. However, patients with IPH who develop hepatic failure late after the illness have been reported.[13] The pathogenesis of the portal hypertension in these patients is unknown. Some investigators believe that the principal abnormality is in the portal venules. Microthrombi in the portal venules or sclerosis of the portal veins may be seen. High portal venous flow and increased intrahepatic resistance are also present. Pathologically, the following findings were present: alterations in small vessels, regarded as the initial lesion, and changes in liver architecture consisting of fibrosis and/or nodule formation, regarded as secondary. However, in obstructive portal venopathy, the suspected initial lesion is not always found in a biopsy specimen.[14] When an obvious venular obstruction is not seen, many endogen factors consist of cytokines, and activated coagulation factors may cause stellate cell activation followed by perisinusoidal fibrosis. There are prothrombotic disorders in approximately 50% of these patients and this phenomenon may play a crucial role in the pathogenesis of IPH.[15] HVPG is normal or moderately elevated in patients with IPH. In the light of these data we conclude that our patient has IPH with protein C deficiency, with preserved liver function and exclusion of liver cirrhosis.

The struggle to find the underlying disease is the essential approach in the treatment of HPS. The strategy to remove circulating vasodilators by for instance allium sativum, indomethacin, and almitrine bismesylate was found to have marginal effects. Embolotherapy can be tried in patients with type II HPS who have widespread intrapulmonary vascular dilatations.[16] Transjugular intrahepatic portosystemic shunting may improve levels of PaO_2 and may be feasible, especially to gain time for liver transplantation. Severe hypoxaemia used to be considered a contraindication to liver transplantation, but liver transplantation is still the single proven treatment option to cure HPS nowadays.[17]

As suggested in the literature[18] we treated our patient with paroxetine, a selective serotonin reuptake inhibitor with nitric oxide synthase blocking properties. We gave this drug for six months because of HPS and major depression. His depressive mood responded to the treatment, but we saw no improvement in blood gas parameters (summarised in *table 2*), Tc-99-m MAA scintigram, contrast echocardiogram or in clinical status. Paroxetine was given to the patients with HPS caused by cirrhosis in the mentioned study. The unknown pathogenesis of portal hypertension in noncirrhotic patients makes it difficult for as to know how to treat them. In the light of our findings, we presume that NO may play a minor role in HPS caused by IPH. On the other hand, lack of response to NO-reducing agents may be explained by progression of the liver disease. We could not perform the second liver biopsy because of a low platelet count (43000/μl). There is an increasing trend towards extrahepatic portal vein thrombosis in patients with this disease, and anticoagulant therapy is proposed to maintain portal vein patency.[15] Our patient had high-grade oesophageal varices that were prone to bleed and thrombocytopenia, so we did not consider giving him anticoagulant therapy. Finally

our patient, who has a poor prognosis, is now in the liver transplantation programme because there is no other effective treatment available in our country.

CONCLUSIONS

This case supports the literature about HPS caused by noncirrhotic portal hypertension. The findings in our patient were rather severe when compared with cases of HPS caused by NCPH reported in the literature. Treatment with paroxetine did not alter the course of the disease. There is thus a need for a more extensive cohort of noncirrhotic portal hypertensive patients with these features, and studies on many other treatment options to overcome the controversial points.

NOTE

A color version of this case report can be found on our website www.njmonline.nl.

REFERENCES

1. Krowka MJ. Hepatopulmonary syndrome: recent literature (1997 to 1999) and implications for liver transplantation. Liver Transpl 2000;6(4 Suppl 1):S31-5.
2. Naeije R, Melot C, Hallemans R, et al. Pulmonary hemodynamics in liver cirrhosis. Semin Respir Med 1985;7:164-71.
3. Martinez GP, Barbera JA, Visa J, et al. Hepatopulmonary syndrome in candidates for liver transplantation. J Hepatol 2001;34:651-7.
4. Lima BL, Franca AV, Pazin-Filho A, et al. Frequency, clinical characteristics, and respiratory parameters of hepatopulmonary syndrome. Mayo Clin Proc 2004;79(1):42-8.
5. Babbs C, Warnes TW, Haboubi NY. Non-cirrhotic portal hypertension with hypoxaemia. Gut 1988;29(1):129-31.
6. Kaymakoglu S, Kahraman T, Kudat H, et al. Hepatopulmonary syndrome in noncirrhotic portal hypertensive patients. Dig Dis Sci 2003;48(3):556-60.
7. Gaines DI, Fallon MB. Hepatopulmonary syndrome. Liver Int 2004;24(5):397-401.
8. Pomier-Layrargues G. TIPS and hepatic encephalopathy. Semin Liver Dis 1996;16:315-20.
9. Meyer CA, White CS, Sherman KE. Diseases of the hepatopulmonary axis. Radiographics 2000;20(3):687-98.
10. De BK, Sen S, Biswas PK, et al. Hepatopulmonary syndrome in inferior vena cava obstruction responding to cavoplasty. Gastroenterology 2000;118(1):192-6.
11. Asbert M, Gines A, Gines P. Circulating levels of endothelin in liver cirrhosis. Gastroenterology 1993;104:1485-91.
12. Castro M, Krowka MJ. Hepatopulmonary syndrome. A pulmonary vascular complication of liver disease. Clin Chest Med 1996;17(1):35-48.
13. Bernard PH, Le Bail B, Cransac M, et al. Progression from idiopathic portal hypertension to incomplete septal cirrhosis with liver failure requiring liver transplantation. J Hepatol 1995;22:495-9.
14. Wanless IE. Micronodular transformation (nodular regenerative hyperplasia) of the liver: a report of 64 cases among 2,500 autopsies and a new classification of benign hepatocellular nodules. Hepatology 1990;11:787-97.
15. Hillaire S, Bonte E, Denninger MH, et al. Idiopathic non-cirrhotic intrahepatic portal hypertension in the West: a re-evaluation in 28 patients. Gut 2002;51(2):275-80.
16. Poterucha JJ, Krowka MJ, Dickson ER. Failure of hepatopulmonary syndrome to resolve after liver transplantation and successful treatment with embolotherapy. Hepatology 1995;21:96-100.
17. Lange PA, Stoller JK. The hepatopulmonary syndrome. Effects of liver transplantation. Clin Chest Med 1996;17:115-23.
18. Altschuler EL, Kast RE. Paroxetine for hepatopulmonary syndrome? Med Hypotheses 2004;62(3):446-7.

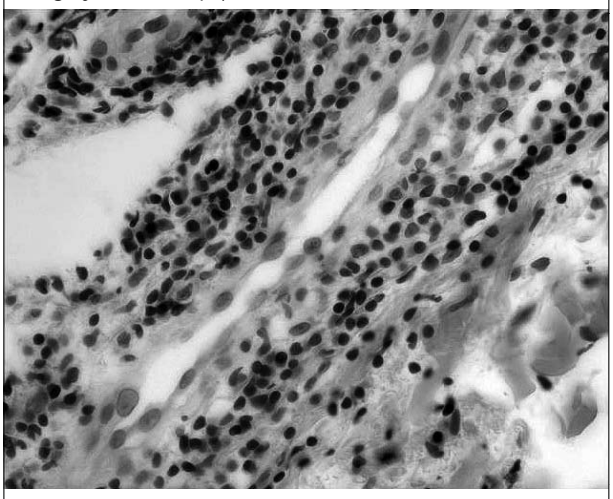
ANSWER TO PHOTO QUIZ (ON PAGE 447)

BETWEEN HANDS AND FEET

DIAGNOSIS

The typical distribution of the skin lesions in a young woman who rode horses in the winter pointed to the diagnosis of rider's pernio.[1] Pernio is well known to occur on the hands and/or feet, but other parts of the body exposed to cold can also be affected. This diagnosis was confirmed by a skin biopsy (*figure 2*), which showed slight oedema of the papillary dermis as well as perivascular mononuclear cell infiltrates in the dermis. There was also diffuse fluffy oedema of the vessel walls and swelling of vascular endothelial cells. The mononuclear infiltrate of the vascular walls is suggestive of a lymphocytic vasculitis. In the literature rider's pernio has also been nicknamed 'equestrian cold panniculitis'[2] and 'winter kibes in horsy women'.[3] Especially young, obese, horse-riding women, who compromise the skin vascularisation of the buttocks and thighs with tight-fitting uninsulated riding pants, are affected in the winter time.[4] The lesions appear one to three days after horse riding in the winter and subside spontaneously without scarring in several weeks, which was also the case in our patient. To prevent another episode the patient was advised to wear several layers of thick clothing instead of a pair of jodhpurs.[5]

Figure 2 *Perivascular mononuclear cell infiltrate and fluffy oedema of the vessel wall with swelling of vascular endothelial cells (Haematoxylin-eosin stain: original magnification x 40)*



A colour version of this photo quiz can be found on our website www.njmonline.nl.

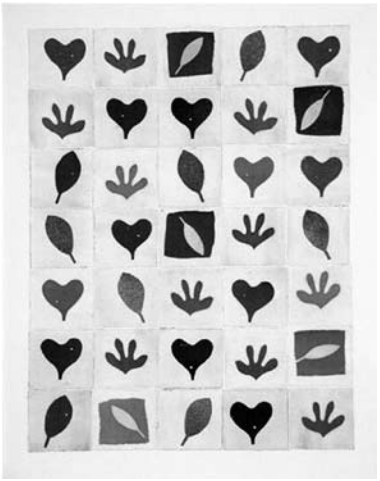
REFERENCES

1. Petri M, Niordson AM. Rider's pernio. Panniculitis with vasculitis provoked by cold. Ugeskr Laeger 1982;144:2091-2.
2. Beacham BE, Cooper PH, Buchanan CS, Weary PE. Equestrian cold panniculitis in women. Arch Dermatol 1980;116:1025-7.
3. [No authors listed]. Winter kibes in hosey women [Editorial]. Lancet 1980;2:1345.
4. Weedon D. Skin Pathology. Churchill Livingstone. Second edition. 2002. p. 250-251.
5. Dowd PM. Reactions to cold. In: Burns T, Breatnach S, Cox N, Griffiths C (editors). Rook's Textbook of Dermatology. 7th edition. Massachusetts: Blackwell Science; 2004. p. 23.1-17.

ABOUT THE COVER

'Lied van de lente'

Lia Stouten



Lia Stouten (1951) specialises in creating graphic art in limited editions. The etching plates, which are made of zinc, are cut and several clear colours are applied. Her work has affinity with Japanese and Eastern art. By means of simple, colourful materials, nature is powerfully but subtly presented in this work. Forms of plants, colours of landscapes, dreams, culture and nature are her sources of inspiration. This year, for example, she showed her work at the International Mini-Print in the National Palace of Culture in Sofia, Bulgaria and also in Lisbon, Portugal.
Since 1999 she has received many assignments for institutions and galleries all over the country. Her last assignment was for the new gallery Skarsterlan in Joure. An original print (size 46 x 60 cm) is available at a price of € 230 and can be ordered from Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands or by e-mail: Galerie-unita@planet.nl or www.galerie-unita.com.

BOEKAANKONDIGING

Waar zouden we zijn zonder infecties? Essays over infectieziekten

Dit boek is uitgebracht ter gelegenheid van het tienjarig bestaan van het bureau van de Landelijke Coördinatiestructuur Infectieziekten (LCI).

De auteurs van dit boek laten zien dat infectieziekten een zeer belangrijke rol spelen bij alle facetten van de samenleving.

In het eerste hoofdstuk wordt duidelijk gemaakt dat de mens als wandelende voedingsbodem in vivo nooit van zijn micro-organismen af zal komen; mens en microbe hebben elkaar immers nodig.
Andere hoofdstukken laten zien dat infectieziekten niet alleen ellende maar ook veel moois hebben voortgebracht. Micro-organismen bewonen niet alleen alle uithoeken van ons lichaam, maar nemen ook in geestelijk opzicht bezit van ons. Dat was niet alleen in het verleden zo, toen infectieziekten ook in de westerse landen bovenaan stonden op de ladder van doodsoorzaken bij jonge mensen, maar ook in de huidige tijd van westerse weelde en rijkdom. Ook nu worden wij steeds weer geconfronteerd met oude en nieuwe ziekteverwekkers, ondanks goede hygiëne, vaccinaties en antimicrobiële middelen.

Waar zouden we zijn zonder infecties? Essays over infectieziekten

Redactie: J. van Steenbergen, J. van Everdingen
Uitgever: Belvédère/Medidact,
Alphen aan den Rijn
Jaar: 2005
ISBN: 90-8523-087-x
Prijs: € 32,00 per stuk, inclusief BTW, exclusief verzendkosten

Bestellen via:
www.vanzuidencommunications.nl

BOEKAANKONDIGING

Immuuntherapie van hematologische ziekten

In de eerste editie van dit boek hebben de eindredacteuren geprobeerd het zich snel uitbreidende veld van de immuuntherapie bij zowel maligne als benigne hematologische ziekten te beschrijven.
Dit is gedaan door in verschillende hoofdstukken, naar ziektebeeld ingedeeld, de meest recente pathofysiologische bevindingen en therapeutische applicaties door een groot aantal auteurs, allen experts op het door hen beschreven gebied, te laten samenvatten. De eindredacteuren hebben getracht eenheid in de hoofdstukken te bewerkstelligen. Het moge echter duidelijk zijn dat de persoonlijke mening van de auteurs doorklinkt in de diverse hoofdstukken.
Het boek is met name bedoeld voor hematologen, oncologen, fellows in opleiding, geïnteresseerde algemeen internisten en gespecialiseerde verpleegkundigen en uiteraard voor een ieder met belangstelling voor immuuntherapie van hematologische ziekten.

Immuuntherapie van hematologische ziekten

Redactie: G.J. Ossenkoppele, A.A. van de Loosdrecht
Uitgever: Van Zuiden Communications B.V.,
Alphen aan den Rijn
Jaar: 2005
ISBN: 90-8523-088-8
Prijs: € 49,00 per stuk, inclusief BTW, exclusief verzendkosten

Bestellen via:
www.vanzuidencommunications.nl

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

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

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

Preparation of manuscripts
Type all pages with double spacing and wide margins on one side of the paper. To facilitate the reviewing process, number the lines in the margin and the pages.
Subheadings should not exceed 55 characters, including spaces.
Abbreviations: Measurements should be abbreviated according to SI units. All other abbreviations or acronyms should be defined on the first appearance in the text. Use a capital letter for generic names of substances and materials.
A *Covering letter* should accompany the manuscript, identifying the person (with the address, telephone number, fax number and e-mail address) responsible for negotiations concerning the manuscript. The letter should make it clear that the final manuscript has been seen and approved by all authors. Conflicts of interest, commercial affiliations, consultations, stock or equity interests should be specified. In the letter one to three sentences should be dedicated to what this study adds. All authors should sign the letter.

Divide the manuscript into the following sections: Title page, Abstract, Keywords, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

The *Title page* should include authors' names, degrees, academic addresses, correspondence address, including telephone number, fax number, e-mail address and grant support. Also the contribution of each author should be specified.
The title should be informative and not exceed 90 characters, including spaces. Avoid use of extraneous words such as 'study', 'investigation' as well as priority claims (new, novel, first). Give a running title of less than 50 characters. If data from the manuscript have been presented at a meeting, list the name, date and location of the meeting and reference and previously published abstracts in the bibliography. Give a word count (including references, excluding tables and legends) at the bottom of this page.

The *Abstract*, not exceeding 250 words, should be written in a structured manner and with particular care. In original articles, the Abstract should consist of the following paragraphs; Background, Methods, Results and Conclusion. They should briefly describe the problem being addressed in the study, how the study was performed and which measurements were carried out, the most relevant results, and what the authors conclude from the results.

Keywords: Include three to five keywords.

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

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

The *Results* should be presented precisely, without discussion.

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

Acknowledgement: All funding sources should be credited here. Also a statement of conflicts of interest should be mentioned.

References should be numbered consecutively as they appear in the text (after the punctuation and in square brackets). Type the reference list with double spacing on a separate sheet. References should be in the language they are published in, conform the 'Vancouver' style for biomedical journals (N Engl J Med 1991;324:424-8). Journal abbreviations should conform to the style used in

the Cumulated Index Medicus. Examples:

1. Smilde TJ, van Wissen S, Wollersheim H, Kastelein JJP, Stalenhoef AFH. Genetic and metabolic factors predicting risk of cardiovascular disease in familial hypercholesterolemia. Neth J Med 2001;59:184-95.
2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

Please note that all authors should be listed when six or less; when seven or more, list only the first three and add et al. Do not include references to personal communications, unpublished data or manuscripts either 'in preparation' or 'submitted for publication'. If essential, such material may be incorporated into the appropriate place in the text. Recheck references in the text against the reference list after your manuscript has been revised. The use of bibliographic software programmes that are designed to generate reference lists such as Reference Manager© or Endnote© is highly encouraged. Authors can use the predefined output 'Vancouver' style from these programmes.

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

Figures must be suitable for high-quality reproduction. Submit line drawings made in Word or other computer programmes but not in a PowerPoint file. Indian ink drawings or sharp, strongly contrasting photographic prints on glossy paper are also acceptable. Lettering should be complete, of professional quality, and of a size appropriate to that of the illustration of drawing, with the necessary reduction in size taken into account. Figures should be no larger than 12.5 x 18 cm. Submit half-tone illustrations as black-and-white prints on glossy paper, with as much contrast as possible. Identify each figure on the back with a typed label, which shows the number of the figure, the name of the leading author, the title of the manuscript and the top of the figure. Colour figures are occasionally possible and will be charged to the authors.
Legends for figures should be typed, with double spacing, on a separate sheet.

Case reports
Case reports containing concise reports on original work will be considered for publication. Case reports which are relevant for understanding the pathophysiology or clinical presentation of disease may also be accepted under this heading. Articles published in this section should be no longer than 1000 words, and supplied with a summary of about 60 words, preferably no more than two figures and/or tables, and no more than 15 references.

Letters to the editor
The editorial board will consider letters to the editor referring to articles previously published in the Journal. Letters should be no more than 500 words.

Books for reviewing
The editorial board will consider review papers of books.

Submission
Manuscripts should be sent to the Editor in chief, Prof Dr Anton F. Stalenhoef, Radboud University Nijmegen Medical Centre, Department of General Internal Medicine, 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. Manuscripts should be submitted in four complete sets; authors should retain one copy. Rejected manuscripts will not be returned to the author unless specially requested at the time of submission.

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

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

Proofs
Proofs will be sent to the authors to be carefully checked for printer's errors. Changes or additions to the edited manuscript cannot be allowed at this stage. Corrected proofs should be returned to the editorial office within two days of receipt.

Offprints
These are not available. The first author receives a sample copy of the Journal with the published article.