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Conscious sedation for endoscopic procedures

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ABSTRACT

Despite the fact that gastrointestinal endoscopy is a safe procedure, significant complications can occur. According to the literature most complications are related to sedation and compared with perioperative mortality under general anaesthesia, the mortality for this procedure appears high. Strict implementation of existing guidelines is warranted.

In this issue, Bosch et al. report on a stepwise sedation procedure with midazolam and fentanyl for the insertion of central venous catheters. They conclude that such an approach is safe and effective. Apart from the insertion of catheters, conscious sedation is frequently applied during invasive procedures in internal medicine, such as biopsies, punctures and endoscopy procedures. Within this field the administration from sedatives and narcotics by non-anesthesiologists has been a matter of debate for many years. In 1986 a report of the Dutch Health Council for the use of sedation in dentistry was published. The Committee concluded that initial treatment should begin with reassurance and support to bring the patient to a state where the medical treatment offered is accepted. In most cases this should be enough. If this does not work, it may be necessary to obtain sedation by means of pharmacological agents. The report gives useful definitions about general anaesthesia and ‘conscious sedation’.

General anaesthesia is described as a method that induces a reversible and controllable depression of certain functions of the central nervous system causing unconsciousness. Fear and pain are absent and vital reflexes are depressed or absent. ‘Conscious sedation’ is described as a method that induces a reversible and controllable depression of certain functions of the central nervous system, during which the patient remains conscious. The maintenance of verbal and non-verbal communication and intact vital reflexes during conscious sedation is crucial. Both ventilatory and cardiovascular function has to be maintained. Despite these definitions the line between sedation and general anaesthesia is not always clear in practice. Although the use of conscious sedation in endoscopies is widespread, there are large regional differences. In one survey conducted in the United States only 2.2% of endoscopies were performed without routine use of conscious sedation, whereas in some European countries the majority of endoscopic procedures are performed without sedation. Recently Bonta et al. found that echo-endoscopic investigation of the oesophagus and stomach without sedation was feasible and acceptable for both endoscopists and patients. However, the overall tolerance of patients was significantly better during sedation with midazolam.

Despite the fact that gastrointestinal endoscopy is a safe procedure, significant complications can occur as a result of instrumentation with a frequency of 0.1% for upper endoscopies and 0.2% for colonoscopy. According to a rather old study by Silvis et al. cardiopulmonary complications are more common than bleeding or perforation and may account for over 50% of all reported complications. In a more recent study the rate of cardiopulmonary events was 2 per 1000 cases. The 30-day mortality was 1 per 2000 cases and included aspiration pneumonia, pulmonary embolism and myocardial infarction. Arrowsmith et al. used data from the American Society for Gastrointestinal Endoscopy’s computer-based management system to compare the rates of serious cardiorespiratory complications.
and death associated with the use of midazolam and diazepam. Data were analysed from 21,011 procedures. Serious cardiorespiratory complications and death occurred in 5.4 and 0.3 per 1000 procedures, respectively. The authors concluded that concomitant use of narcotics and urgent and emergency procedures increased the risk of serious cardiorespiratory events.

When we compare these results with postoperative mortality these numbers seem quite high. In a Dutch survey of 62,969 procedures in a University Hospital, including neurotrauma and emergency surgery, 314 patients (0.5%) died within seven days of the operation.\textsuperscript{15} Death was related to both anaesthesiological and surgical factors in 14 patients (2.2 per 10,000 operations). Other studies estimate anaesthetic mortality rates to be as low as 0.05 per 10,000 anaesthetics for in-hospital surgical procedures depending on the ASA classification of the patient.\textsuperscript{15} For outpatient anaesthesia D’Eramo et al. found an overall mortality rate of 1 in 85,000 patients.\textsuperscript{15} Although mortality seems a clear endpoint, results may be biased by study methods (voluntary reporting) and differences in definitions or the postoperative observation period. Furthermore, it remains difficult to compare surgery during general anaesthesia with endoscopic procedures.

To my knowledge there are no figures available from the Dutch situation about complications during endoscopic procedures. However, it must be concluded that compared with postoperative mortality after general surgery the mortality for a merely diagnostic procedure such as endoscopy appears high.

Recently, studies have been published about the use of ultra-short-acting hypnotic agents such as propofol for endoscopic procedures. Propofol is a useful intravenous anaesthetic agent. It causes a reduction in blood pressure predominantly resulting from vasodilatation. After the injection of propofol apnoea commonly occurs and for varying duration. One of the greatest problems with the administration of sedative agents is the interindividual variability of the sensitivity for these agents. The dose that causes no effect in one patient may cause deep sedation in another patient. Also agitation may be interpreted as not enough sedation, but may actually be caused by hypoxia. Although in a recent publication the authors stated that they did not experience major complications with the use of propofol, the need for short-lasting mask ventilation was significantly increased.\textsuperscript{15} Maintenance of the airway is one of the most important tasks of the anaesthesiologist or emergency physician. It cannot be overemphasised that this life-saving technique seems much easier than it often is in clinical practice and that this technique needs extensive education and training. There is, in my opinion, an important fundamental difference in responsibility in applying mask ventilation in an emergency situation compared with the elective administration of a sedative agent in an elective case.

Given the information that the majority of cardiopulmonary complications as a result of endoscopies relate to ‘conscious sedation’, strict monitoring of the patient and a good understanding of the pharmacology and side effects of the agents that are administered as well as the role of pharmacological antagonists is important. Personnel should be trained in life support skills and advanced life support should be available within five minutes. Guidelines by the American Association of Anesthesiologists and the American Society for Gastrointestinal Endoscopy should be implemented.\textsuperscript{16-17} Despite the fact that it is not specifically mentioned in the guidelines of the American Society for Gastrointestinal Endoscopy monitoring patients by a specially trained person other than the endoscopist can probably prevent many cardiorespiratory complications.\textsuperscript{16}

The routine assistance of an anaesthesiologist for low risk patients undergoing standard upper or lower endoscopic procedures is not warranted and is certainly cost-prohibitive. In the future, ‘conscious sedation’ during diagnostic procedures might be an interesting role for anaesthetic physician assistants. In my view, the person who assists the gastroenterologist with conscious sedation should be part of the local anaesthesia department and should have continuous experience in administering anaesthesia and maintaining the airway. After sedation patients should recover in an area equipped with appropriate monitoring and resuscitation equipment. The procedure will become even safer if the patients are under close attendance by skilled personnel during the recovery period until discharge criteria are fulfilled.

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Scheffer. Conscious sedation for endoscopic procedures.
Examination of the urinary sediment is a simple and indispensable tool in the diagnostic approach to patients with asymptomatic haematuria. Various glomerular and nonglomerular diseases can cause haematuria. A well-trained expert can distinguish between these two forms of haematuria by examining the urinary sediment under a simple light microscope. In glomerular haematuria, dysmorphic erythrocytes and erythrocyte casts are found, whereas in nonglomerular haematuria the erythrocytes are monomorphic and erythrocyte casts are absent. However, few people have sufficient expertise in the examination of the urinary sediment, and consequently this investigation is performed far too seldom. A few years ago, a simple method of fixation of the urinary sediment became available. Fixed specimens can be stored at room temperature for at least two weeks, which enables the sending of a fixed specimen to an expert examiner by regular mail. In this way, the urinary sediment can more frequently be used as the initial investigation in the diagnostic route of patients with asymptomatic haematuria.

Persistent or intermittent haematuria is an alarming symptom for the patient and his doctor. Haematuria can be caused by a number of conditions, including infections and stone disease of the urinary tract, malignant disorders, coagulation disorders and intrinsic renal diseases (for example glomerulonephritis). The medical history and physical examination might provide clues that point towards the diagnosis. On the other hand, determining an adequate diagnostic strategy will be more difficult when additional symptoms are missing. This asymptomatic haematuria can be macroscopic or microscopic, the latter being usually discovered coincidentally. In the case of asymptomatic haematuria, most patients are sent for urological evaluation, most likely because of concern for a malignancy of the urogenital tract. This urological evaluation usually consists of imaging of the urinary tract (ultrasound, intravenous urography, CT scan), blood and urine chemistry, urine cytology and cystoscopy. However, a urological evaluation is inappropriate when glomerular disease is present. In that case other diagnostic instruments, such as renal biopsy, will be necessary to disclose the nature of the disease. Since examination of the urinary sediment can help to differentiate between glomerular and nonglomerular forms of haematuria, it is an important tool in patients with asymptomatic haematuria. Birch and Fairley were the first to show that examination of the urinary sediment by phase-contrast microscopy can help in the discrimination between glomerular and nonglomerular forms of haematuria. Nowadays, examination of the urinary sediment is mostly used to screen for urinary tract infection or to confirm the presence of haematuria. Most prevailing diagnostic algorithms for the analysis of asymptomatic haematuria advise extensive urological evaluation, whereas only a few stress the role of the urinary sediment as a diagnostic instrument. In a recently published diagnostic algorithm, the urinary sediment was not mentioned at all. By following such a strategy, the majority of serious urological pathology will be disclosed. Unfortunately, in many studies a definite...
urinary sediment.

Furthermore, many patients with nephrological diseases will remain unidentified, and a considerable number of patients will endure inappropriate and often repeated urological testing. We estimated on the basis of a retrospective study that about 25% of 134 patients referred to a urology department for the analysis of asymptomatic haematuria most likely had glomerular disease and thus underwent inappropriate urological testing [unpublished data]. Therefore, examination of the urinary sediment in patients with haematuria is mandatory, preferably before a patient is referred to a medical specialist. In this review we stress the importance of this simple, cheap and informative test as a diagnostic tool in patients with asymptomatic haematuria. Furthermore, we bring into notice a method of fixation of the urinary sediment that allows preservation of the urinary specimen for two weeks at room temperature.

**Prevalence of Asymptomatic Haematuria**

The prevalence of asymptomatic microscopic haematuria has been determined in unselected populations, as well as in screening studies of selected populations. Woolhandler and co-workers reviewed five population-based studies, and mention a prevalence of asymptomatic haematuria of 0.19 to 16.1%. The variation in the reported prevalence in these studies most likely reflects differences in the populations screened. Part of these differences might also be explained by the methods used to detect microscopic haematuria (dipstick versus microscopic analysis of the urinary sediment). Mohr and co-workers found a prevalence of 15% in a population that consisted of men older than 35 years of age and postmenopausal women. Briton reported the presence of occult haematuria in 20.1% of men over 60 years of age undergoing screening for bladder cancer using dipstick tests. Various studies have shown that the prevalence of asymptomatic haematuria increases with age, whereas others found no correlation between advanced age and the prevalence of occult haematuria.

**The Dipstick Test**

Evaluation of a urinary specimen should start with a dipstick test. The dipstick provides semiquantitative information about the presence of different components in the urine, such as erythrocytes, leucocytes and protein. Most tests are able to detect the presence of 25 to 50 erythrocytes per µl urine which is equivalent to 2 to 3 erythrocytes per high power field on microscopic examination. The test has a sensitivity of 93 to 96% and a specificity of about 60 to 80% for detecting erythrocytes in the urine. The negative predictive value of the test is about 98%. Because of its high sensitivity, the chances of finding erythrocytes in a urinary sediment are limited when the dipstick test is negative for erythrocytes. Therefore, urinary specimens need no further examination for haematuria when the dipstick test for erythrocytes is negative. The number of urinary samples that can be discarded for microscopic examination in this way also depends on the prevalence of haematuria in the test population. Due to its poor specificity, a considerable number of urinary samples remain containing little or no erythrocytes at all on microscopic examination despite a positive dipstick.

Myoglobinuria, poorly washed glassware, the presence of oxidising agents in the urine (e.g. povidine) and bacterial contamination are common causes of a false-positive dipstick test, whereas urinary samples that contain ascorbic acid or formaldehyde, or have low pH (<5.1), can lead to a false-negative dipstick test.
that osmotic changes alone did not lead to the formation of dysmorphic erythrocytes, whereas a change in urinary osmolality in combination with a haemolytic environment did. After this change of shape has taken place, erythrocytes cannot return to their original shape and thus appear as dysmorphic erythrocytes in the urine. Acanthocytes or G1 cells are erythrocytes with blebs and bulbs on their membrane. Some authors consider the presence of acanthocytes more specific for glomerular disease than dysmorphic erythrocytes. In a study by Dinda et al., the presence of >4% acanthocytes in the urine resulted in both a specificity and sensitivity of 100% for diagnosing glomerular disease compared with 100 and 90%, respectively, for dysmorphic erythrocytes. However, they observed a mean percentage of acanthocytes in their patients with glomerular disease of 20.6% of all red cells, a figure that is exceptionally high. In our experience, finding more than 4% of acanthocytes in a urinary sample is uncommon, even in patients with glomerular disease. We therefore regard acanthocytes as a subtype of dysmorphic erythrocytes and count them as such. Finally, the urinary sediment of patients with glomerular haematuria is characterised by the presence of a large variety of erythrocyte shapes. There is heterogeneity in shape and size of the erythrocytes, and also cell fragments can be found. Usually, at least three different shapes of erythrocytes are present in the urine of patients with glomerular disease, giving rise to a polymorphic picture (figure 1). This is in contrast with nonglomerular haematuria in which all red cells are similar in shape (isomorphic), resulting in a monomorphic pattern (figure 2).

Although there is no consensus in the literature on the upper normal limit of erythrocytes in a urinary specimen, most investigators consider two to three red cells per high power field to be the upper limit of normal. We consider urinary samples that contain three or more erythrocytes per high power field to be pathological, and examine them for erythrocyte morphology. We then estimate the percentage of dysmorphic erythrocytes, after evaluating 100 red cells in the urinary sample. The study by Birch and Fairley did not delineate the percentage of dysmorphic urinary red cells required for the sample to be classified as dysmorphic and subsequent reports have varied on this issue with figures from 20 to 80%. However, in a previous study of fresh urinary sediments from 107 patients with known urological or nephrological causes of haematuria, we found that a value of 40% dysmorphic erythrocytes was a reliable cut-off point for differentiating between glomerular and nonglomerular haematuria. At this value, the sensitivity for diagnosing a urological cause of the haematuria was 100% and the specificity 66.7%. By including the absence of erythrocyte or haemoglobin casts as an additional parameter, the specificity rose to 88.1%. Consequently, we consider samples with more than 40% dysmorphic erythrocytes to be suggestive for glomerular haematuria, and definitely glomerular when the dysmorphic pattern is accompanied by the finding of erythrocyte or haemoglobin casts. When monomorphic haematuria is accompanied by erythrocyte or haemoglobin casts, a combination of a urological and a nephrological cause of the haematuria should be suspected. To summarise, glomerular haematuria is characterised by the presence of erythrocyte casts with more than 40% dysmorphic erythrocytes in a polymorphic pattern, whereas in nonglomerular haematuria, less than 40% dysmorphic red cells are found, a monomorphic pattern exists and erythrocyte casts are absent.

Phase-contrast microscopy is believed to be a superior method to bright-field microscopy for detecting dysmorphic erythrocytes. Phase-contrast microscopy showed a sensitivity of 90% and a specificity of 100% for detecting glomerular haematuria, compared with 82 and 100%
with bright-field microscopy, when a cut-off point of 20% dysmorphic erythrocytes was used as indicator for glomerular haematuria and renal biopsy was used as the gold standard for diagnosing glomerular disease. Provided that the settings of a light microscope are optimal (with lowering of the condenser lens), bright-field microscopy and phase-contrast microscopy appeared equally effective in differentiating glomerular from non-glomerular haematuria. We prefer the standard light microscope because it is easily accessible and can be used in every reasonably equipped laboratory. Examination of a urinary sediment by standard light microscopy is also easier to perform and less time-consuming compared with phase-contrast microscopy. Inter-observer variability in the examination of urinary sediments is considered a major limitation for both forms of microscopy. In a study by Raman et al., two independent observers differed in their interpretation of dysmorphic erythrocytes on 38% of occasions using phase-contrast microscopy. However, the second observer had only limited experience, and unfortunately the correlation did not improve during the course of the study. After sufficient training of both observers, we found an excellent inter-observer variation using bright-field microscopy (correlation coefficient 0.90, kappa: 0.77). In a prospective study, trained laboratory personnel came to a different observation in 26% of 115 samples compared with an experienced nephrologist. This resulted in a difference in conclusion on the source of the haematuria in only 4% of cases (unpublished data). We therefore believe that after special training, an excellent agreement in the examination of the erythrocyte morphology can be reached between different observers.

**Fixation of the Urinary Sediment and Central Examination**

As stated before, ample experience is necessary for adequate evaluation of the urinary sediment. Expertise is difficult to obtain because most physicians see too few patients with unexplained haematuria, and they therefore only seldom examine urinary specimens for erythrocyte morphology. Furthermore, we have observed that without special training the routine examination of urinary sediments by laboratory personnel is not reliable for differentiating between glomerular and nonglomerular haematuria [unpublished data]. As a consequence, microscopic evaluation of the urinary sediment is often lacking in the diagnostic work-up of unexplained haematuria. For several years now, a method of fixation of the urinary specimen is easily available. A formaldehyde-containing fixative solution called CellFIX™, also used for the fixation of mononuclear cells in flow cytometry, proved useful for the fixation of urinary elements. We assessed this method of preservation in 46 patients referred for the analysis of asymptomatic haematuria to a urology department. Part of a urinary sample was studied within three hours after voiding, and another part was added to a small container filled with 0.2 ml of CellFIX™. The fixed sample was kept for ten days at room temperature before examination. Both samples were evaluated for red cell morphology and scored for the presence of casts. There was a highly significant correlation between the percentage of dysmorphic red cells in the fixed and fresh samples ($r=0.87$, $p<0.0001$). The mean difference of the percent scores of dysmorphic erythrocytes was $2.9 \pm 10.5\%$, which was not significantly different from zero (figure 3). Furthermore, no difference in the presence of casts was observed between the fixed and the fresh samples. Taken together, this fixation technique makes it possible to keep the specimen at room temperature for a minimum of ten days without changes in numbers or morphology of red cells and casts.

![Figure 3](image-url)  
**Figure 3**  
Percentages of dysmorphic erythrocytes in fresh and fixed sediments ($n=46$)  
Mean scores of fresh and fixed against their difference (broken lines are mean ± 2 SD).

The preparation of fixed urinary sediment is a simple procedure that can easily be performed at the general practitioner’s office or in laboratory facilities that offer diagnostic services. Subsequently, these samples can be sent to an experienced laboratory, or be stored until examination by experienced individuals is available. Detailed instructions for making a fixed urinary sediment can be found in table 1. The examination of urinary samples in central laboratories with sufficient expertise will lead to a more effective diagnostic route for patients with asymptomatic haematuria.
RECOMMENDATION

Based on the fact that the prevailing diagnostic algorithms for the analysis of asymptomatic haematuria are not very efficient and that a considerable number of patients undergo inappropriate urological evaluation, we make a plea for a diagnostic strategy that includes the examination of the urinary sediment. Since the urinary sediment has proven to be a suitable diagnostic tool in differentiating glomerular from nonglomerular haematuria, it should be used early in the diagnostic route of patients with asymptomatic haematuria. We therefore recommend that patients who present with asymptomatic haematuria follow the algorithm displayed in figure 4.

CONCLUSION

Examination of the urinary sediment is a simple, cheap, noninvasive and reproducible test with a great discriminatory potential to differentiate between glomerular and nonglomerular forms of haematuria. Someone with suffi-
cient expertise, for example a specially trained technician in a central diagnostic laboratory, should perform it. Ideally, examination of the urinary sediment should be done before referral of the patient to a medical specialist.

ACKNOWLEDGEMENTS

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REFERENCES

The prevention and treatment of overweight and obesity
Summary of the advisory report by the Health Council of the Netherlands

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ABSTRACT
This article presents the highlights of an advisory report on the prevention and treatment of overweight and obesity. The report, which was produced by the Health Council of the Netherlands, incorporates the most recent developments and projected scientific breakthroughs in this field.

The prevalence of overweight and obesity has taken on epidemic proportions. In the Netherlands, as elsewhere, there is a steady rise in the number of individuals suffering from overweight or obesity. Since it is associated with serious health problems, obesity (and to a lesser extent overweight) leads to increased costs for the healthcare system.

Food consumption surveys and studies on time trends in physical activity patterns have revealed that the increased prevalence of obesity is due to an increasing lack of exercise, combined with relative overconsumption. A healthy diet (including plenty of fruit, vegetables and cereal products) and at least one hour a day of moderate physical activity are recommended for the maintenance of energy balance and for the prevention of weight gain.

While genetic factors play a part in the development of overweight and obesity, environmental factors appear to be of overriding importance. The so-called 'obesogenic environment' prompts individuals to eat more and to take less exercise.

There are still no effective intervention strategies for the prevention of weight gain. However, the explosive increase in the prevalence of obesity and of its associated serious medical problems demands a common-sense approach involving preventive interventions, which are based on modern views of health promotion. These interventions require a broad coalition of actors, in which local and national authorities, industry, the healthcare system and the population at risk must each shoulder their own share of responsibility.

The primary aim of obesity treatment should be a long-lasting weight loss of about 10%. Even this relatively small weight loss can produce significant health gains. Treatment methods must involve an integrated (lifestyle) approach, dependent on the amount of overweight involved and on the presence of comorbidity. Obesity should be treated chronically and prevention of weight regain must be part of any obesity treatment programme.

INTRODUCTION
This article is a summary of an advisory report by the Health Council of the Netherlands (Health Council of the Netherlands, publication 2003/07, 2003). The report was requested by the Minister of Public Health, Welfare and Sport, who wanted an inventory of the most recent developments and projected scientific breakthroughs in the prevention and treatment of overweight and obesity.

Definition of overweight and obesity
According to the WHO definition, adults are defined as obese (or severely overweight) if they have a body mass index (BMI) of 30 kg/m² or more. Those with a BMI
The value of between 25 and 30 kg/m² are considered to be overweight. The BMI is defined as an individual’s mass (in kg) divided by the square of their height (in meters).

**Increasing prevalence in the Netherlands**

Throughout the world, the prevalence of overweight and obesity has taken on epidemic proportions. In the Netherlands, the steady rise (increasing prevalence) in the number of individuals suffering from overweight and obesity (figure 1) is comparable with the situation in other European countries. This increase is less pronounced than in the United Kingdom and Germany, for example. On average, 40% of Dutch adults are overweight, while 10% of the adult population is obese. It is estimated that 1 to 1.5% of adults suffer from morbid obesity (BMI ≥40).

![Figure 1](image_url)

**Figure 1**

*Long-term trends in the prevalence of obesity (BMI ≥30 kg/m²) among Dutch men and women aged 37-43*

The extent of the overweight epidemic is also clearly reflected in the increased prevalence of overweight during childhood. On average, 13% of boys and 14% of girls in the Netherlands are overweight. It seems that the most marked increase in prevalence occurs in young children above the age of three. If this trend continues, it is estimated that 15 to 20% of adults in the Netherlands will be obese by 2015.

Overweight and obesity are more common among the poorly educated, and in population groups of Turkish and Moroccan origin.

**Health risks**

While the health risks associated with obesity have been well documented, much less is known about those associated with moderate overweight. One of the first health effects to result from weight gain is insulin resistance, which disrupts the normal action of insulin. Insulin resistance plays a key role in the development of metabolic syndrome. This syndrome is characterised by abdominal obesity and a number of associated metabolic anomalies, such as insulin resistance, dyslipidaemia and hypertension. These anomalies in turn form the basis for the development of disorders such as cardiovascular diseases and type 2 diabetes mellitus and its complications. These disorders are also associated with reduced physical activity and a nutritional pattern of high saturated fat, low vegetable/fruit, and low-fibre products.

Other health risks that are associated with overweight and obesity are various types of cancer, gall-bladder diseases, arthrosis, respiratory problems, gout, infertility, menstrual disorders and foetal defects. The greater the overweight, the greater the risk of such comorbidity.

Table 1 contains an estimate of the health risks to which obese adults are exposed. The relative risk ratios (RR) give a rough indication of the strength of the correlation between obesity and its associated diseases. The population attributable risks (PAR) indicate the percentage of the occurrence of other diseases, which could be prevented if there was no obesity. The table clearly shows that, in both sexes, type 2 diabetes mellitus is associated with the highest RRs and PARs.

<table>
<thead>
<tr>
<th>Disease</th>
<th>WOMEN PREVALENCE</th>
<th>RR</th>
<th>WOMEN PAR (%)</th>
<th>MEN PREVALENCE</th>
<th>RR</th>
<th>MEN PAR (%)</th>
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</thead>
<tbody>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>12.7</td>
<td>52.9</td>
<td></td>
<td>5.2</td>
<td>26.3</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.2</td>
<td>23.5</td>
<td></td>
<td>2.6</td>
<td>12.0</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.2</td>
<td>17.4</td>
<td></td>
<td>1.5</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>Cancer of the colon</td>
<td>2.7</td>
<td>14.0</td>
<td></td>
<td>3.0</td>
<td>14.5</td>
<td></td>
</tr>
<tr>
<td>Angina pectoris</td>
<td>1.8</td>
<td>7.1</td>
<td></td>
<td>1.8</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Gall-bladder diseases</td>
<td>1.8</td>
<td>7.1</td>
<td></td>
<td>1.8</td>
<td>6.4</td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer</td>
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<tr>
<td>Osteoarthritis</td>
<td>1.4</td>
<td>3.7</td>
<td></td>
<td>1.9</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.3</td>
<td>2.8</td>
<td></td>
<td>1.3</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

Of all the health risks deriving from obesity, the increased prevalence of glucose intolerance and type 2 diabetes mellitus is particularly worrying. Type 2 diabetes mellitus has even been reported in North American children and adolescents. This represents an ominous development, in view of the macrovascular (heart disease, stroke, limb amputation) and microvascular (kidney failure, blindness) sequelae.
In addition, obesity is often accompanied by psychological and social problems, as well as a reduced quality of life. The morbidity associated with obesity (and, to a lesser extent, with overweight) leads to numerous (medicinal) treatments and additional work disability, as well as increased costs for the healthcare system.

**ANALYSIS OF DETERMINANTS OF OVERWEIGHT AND OBESITY**

In order to counteract the increasing prevalence of overweight and obesity, it is of the utmost importance that the causes of this epidemic be identified and understood. Important determinants of overweight and obesity have been revealed by data from studies into long-term trends in food habits and daily physical activity patterns, as well by findings concerning the influence of energy intake and energy expenditure on the energy balance. In addition, genetic, biological, psychological, social and environmental factors strongly influence the choice that individuals make with regard to diet and activity pattern.

**Small changes, major consequences**

For millions of years, the human race was accustomed to a hunter-gatherer lifestyle, which is characterised by high daily energy expenditure. In general, food was scarce and energy intake was attuned to eating as much as was available. Under these circumstances, the regulation of body mass was always adjusted to a low energy intake and a high expenditure of energy. On a long-term basis, the energy intake and expenditure seem to stay in balance under physiological control (figure 2).

For the past 100 years, however, a substantial part of the world’s population has experienced the reverse situation, having a high-energy intake (overconsumption of energy) and low energy expenditure (physical inactivity). Where there is low energy expenditure, the energy balance is disturbed and becomes positive and as a consequence the body mass increases. In this situation, body mass can only be controlled by cognitive strategies. It appears that energy intake can only keep energy expenditure in balance when daily energy expenditure is not too low. Over extended periods of time, even a marginally positive energy balance will lead to major changes in body weight. This means that overweight can easily develop when energy intake is only slightly higher than energy expenditure. A surplus of only 20 kcal a day over the course of one year results in a weight gain of one kilogram. This means that overweight can easily develop when energy intake only slightly exceeds energy expenditure. The increased body mass will partly compensate for the higher energy intake, since it involves an increase of about 15 kcal a day in energy expenditure, even more in obese subjects.

**Lack of exercise and relative overconsumption**

National food consumption surveys reveal that there was a fall in average energy intake in the Netherlands from 1987/1988 to 1997/1998. This is illustrated in table 2, which shows the mean energy intake for the total Dutch population in three surveys held every five years between 1987 and 1998.

Mean energy intake, which was assessed by questioning individuals about their diet (food anamnesis), shows a declining trend. This applies to individuals of both sexes and all ages. Further analysis of these data showed that, over this ten-year period, nonalcoholic beverages, nuts and snacks increased their relative shares of the total energy intake.

Quantitative data on the energy expenditure of the Dutch population are scarce, and have mostly been derived from questionnaires and interviews. While food intake questionnaires are characterised by underreporting, subjective physical activity measurements are prone to overreporting. Furthermore, data from questionnaires and interviews given to children below the age of 12 have limited validity. While movement counters or heart rate monitors are more objective (and more valid), they can only be used for a limited period of time.
Recent trend reports\textsuperscript{15,16} concluded that half of the Dutch population is inactive. One limitation of trend reports, however, is that they are mostly based on questionnaires which focus purely on more intensive activities, such as sport. Physical activity at work, commuting between school/work, and relatively low-intensity daily activities such as walking, gardening and cycling were not always included.

The only longitudinal study to be carried out in the Netherlands demonstrated a clear decrease in physical activity (42\% in boys and 17\% in girls) in individuals aged between 13 and 17, followed by a slower decline up to the age of 32.\textsuperscript{17}

Other indications of decreased energy expenditure in the general population are the increase in modern inactive recreational activities (TV, PC, scooter, automobile) and the fact that children spend less time playing outdoors.\textsuperscript{18}

In view of the increased prevalence of overweight, the extent of this decline in physical activity must more than compensate for the fall in energy intake. It therefore seems likely that the increased prevalence of overweight and obesity is due to an increasing lack of exercise, combined with relative overconsumption.

**Influence of energy intake and expenditure on the energy balance**

If overweight is to be prevented, it is essential that energy intake be attuned to energy expenditure. A high-fat diet carries a greater risk of overconsumption than a low-fat diet.\textsuperscript{19} The exact types of carbohydrates consumed are also important, although the way in which this affects the regulation of the energy balance is not yet fully understood. Nevertheless, there is strong evidence that the sugars contained in energy-rich drinks (especially soft drinks) can easily lead to a positive energy balance. In addition, epidemiological studies have revealed a clear connection between a low-fibre diet and the risk of overweight.

Various other dietary factors can also affect energy intake, such as the energy density of the diet,\textsuperscript{20} portion size,\textsuperscript{21} meal frequency\textsuperscript{22} and ‘snacking’ behaviour.\textsuperscript{23}

The diet that provides the best chance of maintaining the energy balance is one with a low energy density, and which includes plenty of fruit, vegetables and cereal products.

In terms of preventing an increase in body mass, daily exercise of moderate intensity seems to be more important than very high intensity exercise, which leads to exertion.\textsuperscript{24} Activities that involve a moderate degree of exertion can be sustained for longer periods of time. As a result, these activities achieve a relatively high degree of fat oxidation. Energy expenditure by weight-bearing physical activities (such as walking, stair climbing, jumping) increases with body mass. Obese adolescents indulge in less daily physical activity than their non-obese peers, but their total energy expenditure is the same.\textsuperscript{25}

The current Dutch standard for healthy levels of exercise\textsuperscript{26} stipulates a minimum of thirty minutes of moderate exertion for adults and sixty minutes for children and adolescents, preferably every day but on no less than five days per week. Moderately intensive activities result in an energy output of three to eight times the resting metabolic rate (3-8 MET). These recommendations are based on the preventive effect on chronic diseases such as cardiovascular diseases, COPD, and type 2 diabetes mellitus. The relative risks for these diseases in inactive subjects are three to five times higher compared with active subjects. However, recent investigations indicate that this amount and intensity of exercise does not seem to be sufficient to prevent weight gain in the general population.\textsuperscript{27-29} The Health Council’s Committee feels that, in order to achieve this, individuals must engage in at least one hour of moderate physical activity a day. This is probably also sufficient to keep moderately overweight adults from becoming obese. Obese subjects must exercise for at least 60 to 90 minutes a day to ensure that any weight loss is permanent.

**Obesogenic environment more important than genetic factors**

The recent epidemic of overweight and obesity is very unlikely to have a genetic basis. This is because it has developed in just two generations, too short a time for significant gene mutations to take effect.\textsuperscript{30} While genetic factors do play a part in the development of overweight and obesity, the influence of environmental factors appears to be of overriding importance. As yet, very few of the genes responsible for susceptibility to the development of overweight have been identified. The part played by interactions between genes or interactions between genes and lifestyle factors is also poorly understood.
Little targeted research has been carried out into the influence of specific behavioural determinants or environmental factors which underpin high-risk behaviour associated with the development of overweight (overconsumption and an inactive lifestyle). With regard to eating behaviour, it has been established that food preferences are often acquired at an early age and that preferences for energy-rich foods are easily acquired. In addition, research into eating behaviour and physical exercise has shown that many people are unaware of how much they eat and of how little exercise they take. Individuals must therefore develop an adequate awareness of their own eating behaviour and patterns of physical exercise. This is an essential first step in the instigation of behavioural changes. Furthermore, interactions between parents and children, role-model behaviour by parents, and rules imposed during upbringing are major factors that can affect the development of overweight in children.

There is strong evidence that various physical, economic and sociocultural factors (the so-called ‘obesogenic environment’) prompt individuals to eat large amounts of food and to take little exercise. For example, various studies of children have found a link between the number of hours spent watching television and the development of overweight. There is a major correlation between the higher prevalence of obesity in population groups with a low socioeconomic status and environmental factors which tend to impede healthy behaviour.

Effective preventive intervention strategies

An intervention strategy that can effectively prevent undesirable weight gain has yet to be devised. Nevertheless, some short-term interventions have been carried out at schools in various countries and the reported results reveal a slight beneficial effect on the prevalence of overweight in children. It is not known whether this is a short-term or long-term effect, however. The effectiveness of interventions which target environmental factors (in areas such as housing, transport systems, education, pricing and fiscal measures, and available foods) has also been too poorly studied to enable a verdict to be reached.

There has been scarcely any systematic research into the effectiveness of preventive interventions used in accordance with modern views on health promotion. The latter dictate that interventions be attuned to the specific behavioural determinants and environmental factors which underpin high-risk behaviour, and that interventions in the field of information provision and education be combined with regulations and environmental factors (so-called intervention mapping).

The aim of interventions must be both to increase habitual levels of daily physical activity and to reduce energy intake. The development and implementation of such intervention programmes requires a broad coalition of actors, in which local and national authorities, industry, the healthcare system and the population must each shoulder their own share of responsibility.

Integrated approach to the treatment of obesity

According to international guidelines, the primary aim of obesity treatment should be to achieve a long-lasting weight loss of about 10%. Even this relatively small weight loss can produce significant health gains. These international guidelines are based on a careful analysis of the strength of evidence presented in the available scientific literature on the identification, evaluation and treatment of overweight and obesity. Practical guidelines on obesity in children have been drawn up in much the same way. A treatment protocol should also be drafted for all concerned healthcare professionals in the Netherlands, as a matter of urgency.

In international guidelines there is consensus regarding treatment criteria. Those eligible for treatment include all subjects with a BMI ≥30 kg/m² and those with a BMI of between 25 and 30 kg/m² and an increased health risk. This risk could be due to the presence of type 2 diabetes mellitus, hypertension, hyperlipidaemia, sleep apnoea or the central localisation of body fat. Alternatively, it could be related to a family history of increased health risk.

While other moderately overweight subjects do not require special treatment, it is important to avoid further weight gains. Significant health gains can even be achieved by maintaining a constant, albeit slightly elevated body weight. All subjects with a BMI ≥40 kg/m² should be treated.

Dependent on the amount of overweight involved and on the presence of comorbidity, there is the option of an integrated approach. This aims to bring about changes both in terms of behaviour (diet and physical activity) and cognition, in some cases in combination with pharmacological or surgical therapy. The only effective strategy for obese children appears to be behaviour therapy in groups, in which the parents also participate.

On the basis of strict selection criteria, individuals with extreme overweight are eligible for medicinal or surgical treatment. Surgical treatment may be the solution in some cases of extreme obesity. Both treatment strategies must be used in combination with a weight management programme. There have been favourable reports about both medicinal treatment and surgical treatment, based on weight loss and improvements in terms of health risk factors and quality of life. Data on long-term results are only available for surgical treatment.

The major problem with current obesity treatment is that any weight loss achieved is not usually long lasting. The suspension of treatment negates its effects. This does not mean that obesity is untreatable. What it does show is that the treatment was effective but that it was terminated.
prematurely. While there have been very few studies into the effectiveness of longer duration treatments (exceeding two years), some studies have described cases of long-lasting weight loss spanning periods of several years. While the treatment prospects for obese patients have improved in recent years, it should be pointed out that the beneficial results obtained only apply to a limited group of patients and then only for the duration of their treatment.

**CONCLUSIONS AND RECOMMENDATIONS**

The prevalence of overweight and obesity has taken on epidemic proportions: on average, 40% of Dutch adults are overweight (BMI ≥25) and 10% are obese (BMI ≥30). There is an increased prevalence of overweight in childhood, and obesity is more common in poorly educated and immigrant populations. Obesity and, to a lesser extent, overweight are associated with serious health problems and lead to increased costs for the healthcare system. The most alarming trends are the increasing prevalence of overweight and obesity in children and adolescents, and the increasing prevalence of type 2 diabetes mellitus. In addition, obese subjects run a greater risk of comorbidity with cardiovascular diseases, various types of cancer, respiratory problems, infertility, etc. Furthermore, obesity is often accompanied by psychological and social problems, as well as a reduced quality of life.

Over extended periods of time, overweight can easily develop when the energy balance is only slightly positive. There are clear indications of a substantial decline in the level of daily physical activity among the population of the Netherlands in recent years. There has also been a fall in average energy intake. It therefore seems likely that the increased prevalence of overweight and obesity is due to an increasing lack of exercise, combined with relative overconsumption. The prevention of overweight requires a good balance between the intake and expenditure of energy. Relatively small increases in energy expenditure, combined with relatively small decreases in energy intake can prevent weight gain. A daily food intake, which includes plenty of fruit, vegetables and cereal products (with a low energy density), together with at least one hour of moderate physical activity, provides the best chance of maintaining the energy balance and preventing weight gain. Obese subjects must exercise for at least 60 to 90 minutes a day to ensure that any weight loss is permanent.

While genetic factors play a part in the development of overweight and obesity, they cannot account for the present epidemic. Psychological, social and environmental factors are more likely determinants. There is strong evidence that the so-called ‘obesogenic environment’ prompts individuals to eat more and to take less exercise.

An intervention strategy that can effectively prevent weight gain has yet to be devised. However, in view of the explosive increase in the prevalence of obesity and of its associated serious medical problems, the Committee feels that development of preventive intervention programmes based on a common-sense approach should be given high priority. These preventive interventions should be based on modern views on health promotion, combining interventions in the field of information provision, regulations and environmental factors. Interventions should be attuned to the specific behavioural determinants and environmental factors which underpin high-risk behaviour in the target population, and should be aimed at increasing habitual levels of daily physical activity and reducing energy intake. The development and implementation of such intervention programmes requires a broad coalition of actors, in which local and national authorities, industry, the healthcare system and the population must each shoulder their own share of responsibility.

Obesity treatment should be targeted on a realistic weight loss. The primary aim should be to achieve a long-lasting weight loss of about 10%. Even this relatively small weight loss can produce significant health gains. Dependent on the amount of overweight involved and on the presence of comorbidity, an integrated (lifestyle) approach is needed, aimed at bringing about changes both in terms of behaviour (diet and physical activity) and cognition, in some cases in combination with pharmacological or surgical therapy. The only effective strategy for obese children appears to be behaviour therapy in groups, in which the parents also participate. While treatment prospects for obese patients have improved, it must be realised that the beneficial results obtained only apply to a limited group and then only for the duration of their treatment. Accordingly, obesity should be chronically treated and prevention of weight regain must be part of any treatment programme. A treatment protocol should also be drafted for all concerned healthcare professionals in the Netherlands, as a matter of urgency.

In view of the complexity and severity of the obesity problem, further research is required in many subfields, such as monitoring the prevalence of obesity in relation to long-term trends in energy intake and expenditure; the individual and social causes of overweight and obesity; the interaction between genetics and environment; product development; improvements of the obesogenic environment aimed at increasing physical activity and decreasing energy.
intake; well-designed, effective preventive interventions; and long-term, effective treatment methods. In both the primary healthcare system and the child healthcare system, priority should be given to research into the efficacy of early identification and preventive intervention in moderately overweight adults and children, where there are additional risk factors, such as metabolic syndrome.

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The full report, with an executive summary in English (on which this publication is based), should be cited as follows: Gezondheidsraad. Overgewicht en Obesitas. Den Haag: Gezondheidsraad, 2003; publicatie nr. 2003/7. It can be downloaded from www.gr.nl.

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Stepwise sedation is safe and effective for the insertion of central venous catheters

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ABSTRACT

Background: The introduction of a central venous catheter in haemodialysis patients is an unpleasant procedure for the patient. Intravenous sedation is accepted practice in complicated endoscopic procedures but not often used in haemodialysis patients.

Methods: We developed a protocol for the use of stepwise sedation in these patients with the use of midazolam and fentanyl.

Results: Stepwise sedation with midazolam and fentanyl was used in 155 procedures. No or minor movements were observed in 94% of 154 procedures. 88% of the 155 procedures were graded as very easy or easy. No or only very slight recall of the procedure were noted in 86% of 133 procedures. Only in 7% of 132 procedures were the patients able to recollect most of the procedure. No, or only a small amount of pain was recollected in 93% of 131 procedures. The most important complication was a slight decrease in oxygen saturation in 23 procedures. In the second part of the study we compared the effects of sedation with midazolam alone versus the combination of midazolam and fentanyl for the introduction of Tesio catheters. Amnesia, ease of procedure and the recollection of pain were equivalent. Oxygen desaturation occurred significantly less often with the use of midazolam alone.

Conclusion: We conclude that stepwise sedation is effective and safe in haemodialysis patients and leads to a complete amnesia for the procedure.

INTRODUCTION

Insertion of central venous catheters is often performed in dialysis patients, mostly for temporary access, but with increasing frequency for permanent vascular access as well.1,2 Even though the insertion is fraught with many possible complications, such as pneumothorax, arterial puncture and haemorrhage, it is considered to be a relatively safe procedure and can be performed in an outpatient setting.1 The procedure itself is creates some amount of discomfort for the patient. He has to lie flat, mostly in a head-down position, drapes are applied and the procedure may be painful. Furthermore, the patient is not allowed to move, or even scratch his nose. Some procedures take little time but increasingly catheters are tunnelled subcutaneously and this leads to a more complicated and longer procedure.

Intravenous sedation with either midazolam or diazepam is accepted practice in complicated endoscopic procedures, such as colonoscopy or endoscopic retrograde choledochopancreaticography.3 We could not find references in the literature concerning the role of sedation in dialysis patients. The use of intravenous sedation is not without theoretical dangers in these patients. Firstly many dialysis patients are old and it has been shown that the clearance of midazolam, at least in older men, is slower than in younger men. Furthermore, midazolam and its metabolites are excreted mainly by the kidneys, leading to higher plasma levels in patients with renal insufficiency.6 Because we had favourable results with intravenous sedation in some patients, we designed the following observational study.
MATERIALS AND METHODS

All dialysis patients who had to have a central venous catheter inserted in the dialysis department between July 1996 and February 2001 were included. A peripheral venous cannula was inserted if no central venous catheter was present. Oxygen saturation and heart rhythm were monitored during the procedure. From 1 July 1996 to 31 July 1999, fentanyl and midazolam were used for sedation and from 1 August 1999 to 1 February 2001 midazolam alone was used. While talking to the patient, a test dose of midazolam and a dose of fentanyl (50 μg; until 31 July 1999) were given. Old patients with multi-system disease received 1 or 2 mg midazolam; younger patients 3 to 5 mg. Iodine was applied and allowed to dry. During this time the effect of the first dose was observed and if the patient had not yet fallen asleep a second dose of midazolam was given. After the application of local anaesthesia (lidocaine 1%), iodine was applied for the second time and drapes were applied. If necessary a third dose of midazolam was given. Extra amounts of midazolam were given if the patient woke up during the procedure (for instance if the procedure took a long time). Intranasal oxygen was given if the saturation dropped below 85%. Directly after the insertion two items were scored: 1) The movements of the patient during the procedure on a scale from 0 (no movement) to 5 (extreme unrest) and 2) the ease of the insertion on a scale from 1 (very easy) to 5 (very difficult). At the first dialysis session the patient was asked about recollection of the procedure and the amount of pain experienced during the procedure, both on a scale from 0 to 5. During the procedure the patient was monitored with regard to the following parameters: heart rate, heart rhythm, blood pressure, oxygen saturation. Flumazenil was immediately available if necessary. The first part of our study describes our experiences with stepwise sedation in all patients. In July 1999 the decision was made to omit the fentanyl from the protocol and give only midazolam. We compared our observations between the two time periods to determine whether the administration of fentanyl was necessary. This part of the analysis has been restricted to the introduction of Tesio catheters to obtain a more homogenous picture. All procedures were done by experienced nephrologists or by an experienced junior doctor. The locations for vascular access were chosen by the attending nephrologist. In the beginning of the study some subclavian veins were chosen for short-term access. Later, most catheters were introduced into the internal jugular vein. Femoral veins were chosen if a serious bleeding risk was present (for instance in thrombotic thrombocytopenic purpura) or if an infected catheter was present in the internal jugular vein or had recently been removed.

RESULTS

All patients

Between July 1996 and February 2001, 155 catheters (Tesio, Medcomp, Harleysville, Pennsylvania 125; double-lumen catheter 29; single lumen 1) were inserted in 98 patients. In 28 patients, more than one catheter was inserted and two patients received five catheters. The average age of the patients was 60.2 years (range 17-93 years). The insertion sites were the right internal jugular vein (64), left internal jugular vein (14), right subclavian vein (26), left subclavian vein (29) and right femoral vein (22). The average cumulative dose of midazolam was 7.2 mg (0-23 mg) and the average dose of fentanyl was 51 μg (0-1500 μg).

In 14 patients there was a problem with inserting the catheter into the chosen vein. In twelve of these patients a second vein was cannulated immediately (for instance, failure to cannulate the right internal jugular vein, followed by successful introduction into the right subclavian vein). In two patients the procedure was stopped and a catheter was introduced the next day into a different vein. This was done when a vein on the other side had to be chosen and an X-ray of the thorax was needed to rule out a pneumothorax or haematothorax. In 23 procedures there was a decrease in oxygen saturation below 85% for which the administration of oxygen was necessary. A minor complication occurred in 17 procedures during the insertion: self-terminating ventricular tachycardia (1), arterial puncture (7), extravascular position of the catheter (1), apnoea for which flumazenil was given (1), leakage of the lumen of the catheter (2), and minor bleeding at insertion site (4). The main complications are listed in Table 1. Movements were scored in 154 of the 155 procedures. No or minor movements (grade 0-2) were noted in 94% of 154 procedures (figure 1). Insertion with little difficulty (grade 1-3) was noted in 88% of 152 scored procedures (figure 2). No or only very slight recall of the procedure were noted in 86% of 133 procedures. Only in 7% of 132 procedures were the patients able to recollect most of the procedure. No, or only a small amount of pain was recollected in 93% of 131 procedures.

Table 1
Complications in 155 consecutive catheter insertions

<table>
<thead>
<tr>
<th>COMPLICATION</th>
<th>NUMBER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desaturation (oxygen administration)</td>
<td>23</td>
</tr>
<tr>
<td>Flumazenil administration</td>
<td>1</td>
</tr>
<tr>
<td>Local haematoma</td>
<td>4 (no blood transfused)</td>
</tr>
<tr>
<td>Arterial puncture</td>
<td>7</td>
</tr>
<tr>
<td>First time failure to cannulate</td>
<td>14 (12 times immediate cannulation of different vein; 2 catheters introduced the next day)</td>
</tr>
</tbody>
</table>
Midazolam versus midazolam and fentanyl in Tesio catheters

Between 1 July 1996 and 31 July 1999, 47 Tesio catheters were inserted; from 1 August 1999 to 1 February 2002, 78 Tesio catheters were inserted. Sedation with midazolam alone proved to lead to equal ease of the procedure and similar amnesia and pain experience. The number of cases of oxygen desaturation differed significantly (table 2).

**DISCUSSION**

In this observational study we have shown that stepwise sedation is effective in obtaining excellent amnesia and pain relief at catheter insertion in this group of patients. It is unfortunate that not all procedures were scored. Especially the recall of the procedure and the recollection of pain was not always scored, since this was done the next day by the nurse who was responsible for the haemodialysis session. However we feel that enough patients were scored to draw some conclusions.

The most important point in our study is that the sedation was titrated in every patient in a stepwise fashion. The first dose was administered before the application of iodine and subsequent doses were given after observation of the effects of every dose. Every step in the preparation before the actual insertion, such as the drying of the iodine, the administration of lignocaine and the positioning of the drapes, takes several minutes so that there is enough time to observe the level of sedation before the actual catheter insertion. The major complication was a drop in oxygen saturation, which resolved without further sequelae after the administration of oxygen. Flumazenil was given only once. The fentanyl was probably an important reason for these desaturations. In the second part of the study, we demonstrated clearly that the number of oxygen

**Table 2**

Comparison of sedation with either midazolam alone or the combination of midazolam and fentanyl in the insertion of Tesio catheters (125 procedures)

<table>
<thead>
<tr>
<th>MEDICATION</th>
<th>MIDAZOLAM (N=47)</th>
<th>COMBINATION (N=78)</th>
<th>P VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Midazolam (mg)</td>
<td>7.7</td>
<td>7.9</td>
<td>p=n.s.</td>
</tr>
<tr>
<td>Fentanyl (µg)</td>
<td>0</td>
<td>86.9</td>
<td></td>
</tr>
<tr>
<td>Desaturation (&lt;85%)</td>
<td>1</td>
<td>18</td>
<td>p=0.0014</td>
</tr>
<tr>
<td>Complication</td>
<td>1</td>
<td>13</td>
<td>p=0.02</td>
</tr>
<tr>
<td>No movement</td>
<td>42 (46)</td>
<td>70 (78)</td>
<td>p=1.0</td>
</tr>
<tr>
<td>Easy insertion</td>
<td>39 (45)</td>
<td>69 (78)</td>
<td>p=0.78</td>
</tr>
<tr>
<td>No recall</td>
<td>27 (33)</td>
<td>64 (70)</td>
<td>p=0.19</td>
</tr>
<tr>
<td>No pain after procedure</td>
<td>27 (34)</td>
<td>35 (70)</td>
<td>p=0.39</td>
</tr>
</tbody>
</table>

The number between brackets refers to the number of patients scored.
desaturations decreased significantly in the patients who received midazolam alone. So, it can be concluded that stepwise sedation can be performed safely in patients with renal insufficiency. Furthermore, sedation with midazolam alone is sufficient to achieve adequate results. Since almost all patients remained perfectly still during the procedure, we feel that this protocol leads to an easier introduction of the catheter. This, however, has not been tested. And lastly, we would like to stress that all insertions were done under close observation of the patient and monitoring of oxygen saturation, heart rate and rhythm.

REFERENCES

A 79-year-old male presented with general weakness and tiredness. The further work-up yielded the diagnosis of pancytopenia, without signs of a myeloproliferative process or myelofibrosis. The pancytopenia was treated with androgen and later with blood transfusions. About one year later his condition deteriorated with fever, progressive jaundice and a clearly palpable liver, with a picture of multiple clarifications on the scintigraphy. Shortly after, the pancytopenia worsened further (haemoglobin 2.2 mmol/l, leucocytes $1.7 \times 10^9$/l and thrombocytes $5 \times 10^9$/l). A haemorrhagic diathesis developed and the patient died. The post-mortem examination revealed a liver of 3750 grams with a striking picture on macroscopy: tumourous red foci, leading to a browner macroscopic appearance. On microscopy this picture consisted of spaces filled with blood and separated by liver and Kuppfer cells (figures 1A and 1B).

What is your diagnosis?

See page 27 for the answer to this photo quiz.

Acknowledgement

We acknowledge Professor J.H.J.M. van Krieken of the Department of Pathology of the University Medical Centre St Radboud, Nijmegen for his assistance with the pictures.

A colour version of this photo quiz can be found on our website www.njmonline.nl.
Osteonecrosis in patients with testicular tumours treated with chemotherapy

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ABSTRACT

The role of antiemetics is invaluable in allowing cancer patients to complete, otherwise possibly intolerable, chemotherapy. In the Perugia Consensus Conference it was decided that the recommended antiemetic regimen in the prevention of acute emesis induced by a single high, low and repeated doses of cisplatin is a serotonin receptor antagonist plus dexamethasone. We describe three testicular cancer patients who were cured with chemotherapy but developed bilateral osteonecrosis of the femoral head 17, 22 and 55 months after chemotherapy. It is very likely that the dexamethasone used in the antiemetic drug regimen contributed to the development of osteonecrosis in these patients. Osteonecrosis is a serious side effect of antiemetic treatment with dexamethasone and this serious complication should be incorporated in the current guidelines. Patients should be informed about the risk of osteonecrosis when taking dexamethasone as an antiemetic drug. A recommendation to add corticosteroids to serotonin receptor antagonists only after demonstrated nausea in chemotherapy regimes with low-dose cisplatin (20 mg/m2) for five days seems justified.

INTRODUCTION

The role of antiemetics is invaluable in allowing cancer patients to complete, otherwise possibly intolerable, chemotherapy. With the use of serotonin receptor antagonists, a major breakthrough in antiemetic treatment, namely complete protection against vomiting, was achieved in 40 to 60%. Combination with dexamethasone was shown to increase complete protection against vomiting in 70 to 90% of patients. Nowadays, a serotonin receptor antagonist plus dexamethasone is the regimen of choice in the prevention of acute emesis induced by single high and low and repeated doses of cisplatin. In this report we present three patients who developed osteonecrosis of the femoral heads after treatment with chemotherapy for their testicular tumours.
Diazepam was added to the antiemetic regimen due to persistent nausea and vomiting. In the first cycle the patient received 20 mg of dexamethasone a day only once because of vomiting. The total dose of steroids given was equivalent to 2.21 g of prednisolone. In 1992 the fistula was closed as well as the anus praeter naturalis. After recovery from surgery the patient complained about erectile dysfunction. There were no signs of persistent or recurrent testicular cancer. In October 1995 the patient complained about pain in the right hip. In January 1996, bilateral osteonecrosis of the femoral heads was diagnosed on conventional radiographs and MRI (55 months after the end of chemotherapy). Initially a rotation osteotomy according to Sugioka was performed on the right side. In December 1998 treatment by bone impaction grafting after removal of the osteonecrotic bone was performed on the left side. Finally, in December 2000 the patient underwent total hip replacement on the right side.

Patient B
A 28-year-old man with stage IIa nonseminoma of the right testis with rising serum tumour marker levels after orchidectomy (good prognosis according to the International Germ Cell Consensus Classification Group (IGCCCG) classification) was treated with three cycles of BEP (bleomycin 30 mg days 2, 8 and 15, etoposide 100 mg/m² days 1 to 5, cisplatin 20 mg/m² days 1 to 5) and one cycle of EP (same regimen without bleomycin) from November 1998 until January 1999. Nausea and vomiting were controlled with a combination of ondansetron 8 mg and dexamethasone 10 mg intravenously during the first five days of the cycle. In addition dexamethasone was continued for an additional two days at a dose of 3 mg twice daily. Ondansetron 8 mg and dexamethasone 10 mg were also given once just prior to the second gift of bleomycin (day 8) in the first cycle at the outpatient clinic to treat existing nausea and vomiting. The total dose of steroids given to the patient during treatment was equivalent to 1.61 g of prednisolone. Treatment was unremarkable except for one episode of leucopenic fever for which patient was admitted to hospital for a short period. Postchemotherapy restaging showed normal serum tumour markers in the presence of residual disease on abdominal CT scan. In March 1999, a retroperitoneal lymph node resection was performed. Pathological examination revealed mature teratoma. Thereafter, the patient has remained free of recurrence. In December 2000 (22 months after completion of chemotherapy) the patient reported progressive pain in his right hip. A radiograph of his right hip suggested signs of osteonecrosis of the femoral head. An MRI showed bilateral osteonecrosis of the femoral heads. A bone scan scintigraphy excluded the presence of metastatic disease. The bilateral femoral head necrosis has so far been managed conservatively.

Patient C
A 29-year-old man with stage IIa seminoma (IGCCCG: good risk) was treated with three cycles of BEP (bleomycin 30 mg days 2, 8 and 15, etoposide 100 mg/m² days 1 to 5, cisplatin 20 mg/m² days 1 to 5) given three-weekly between August and October 1999. During the first five days of every cycle, ondansetron 8 mg intravenously once or twice daily and dexamethasone 10 mg intravenously once daily were used as antiemetics. Dexamethasone was continued orally for an additional two days at a dose of 3 mg twice daily. He received a dose of steroids equivalent to 1.16 g of prednisolone over the three cycles of BEP (using a conversion rate of 0.8 mg dexamethasone = 5 mg prednisolone). He achieved a complete remission. However, in March 2001 (17 months after completion of chemotherapy) the patient complained about pain in the left hip. Conventional radiographs as well as MRI (figure 1) showed bilateral hip osteonecrosis. Medical history was unremarkable with no prior steroid use. The BMI of 27.7 kg/m² and the use of four units of alcohol a day were the only other risk factors for avascular bone necrosis.

Figures 1A (right hip) and B (left hip)
Coronal T1-weighted spin echo MR images of both hips
A serpentine line of very low signal intensity demarcates a large area of low signal intensity in both femoral heads, representing osteonecrosis (Association de la Recherche de la Circulation Osseuse Stage III).
Decompression surgery was applied to the right hip. The left hip was treated conservatively.

**DISCUSSION**

We report three patients who received chemotherapy because of testicular cancer and who developed bilateral osteonecrosis of the femoral heads. Osteonecrosis is not a specific disease entity but the final common pathway of a number of conditions mostly leading to an impairment of the blood supply to the bone. Diseases or conditions associated with or leading to osteonecrosis are numerous (table 1).

The association between therapy for a malignancy and the development of osteonecrosis of the femoral head was first presented by Ihde and DeVita in 1975, a report followed by many other reports of patients developing osteonecrosis while being treated for Hodgkin’s disease or lymphoma. In solid tumours, osteonecrosis is infrequently reported. The publications concern testicular cancer and breast cancer and to a lesser extent endometrial cancer, ovarian cancer and prostate cancer. Despite the relative rarity of testicular cancer, approximately 75% of the reported cases in adults occurred in this group. Possible explanations for this include the lack of recognition in other patient groups and the specific effects of chemotherapy used to treat testicular cancer. Various manifestations of late vascular toxicity have been reported in survivors of testicular cancer. The most well-recognised occurrence of chronic small-vessel damage in patients treated with chemotherapy for testicular cancer is Raynaud’s phenomenon, which occurs in 23 to 43% of the patients. Damage to the autonomic nervous system vessels caused by cisplatin or vinblastine (both known to have neurotoxic side effects) that innervates the peripheral smooth muscle is involved in the pathogenesis of Raynaud’s phenomenon. Another example of vascular toxicity is the capillary damage of the nailfold which could be visualised by capillary microscopy, even in asymptomatic patients treated with bleomycin. It can be hypothesised that these vascular effects may contribute to the development of osteonecrosis. Although age is not a known risk factor for the development of osteonecrosis, it is striking that osteonecrosis is also described more frequently in Hodgkin patients who are generally of a similar young age to testicular cancer patients. Young patients probably have a more active lifestyle after treatment of their initial disease. More and active weight bearing on the femoral head will increase the risk of femoral head collapse leading

<table>
<thead>
<tr>
<th>Conditions which can cause osteonecrosis of the femoral head</th>
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<tbody>
<tr>
<td>Trauma</td>
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<tr>
<td>Haemoglobinopathies: sickle-cell disease</td>
</tr>
<tr>
<td>Polycythaemia</td>
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<tr>
<td>Gaucher’s disease</td>
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<td>Fabry’s disease</td>
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<td>Caisson disease</td>
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<td>Congenital and developmental conditions: Ehler-Danlos syndrome</td>
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<tr>
<td>Legg-Calvé-Perthes disease</td>
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<td>Radiotherapy</td>
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<tr>
<td>Hypercortisolism: Cushing’s disease</td>
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<tr>
<td>Corticosteroid medications</td>
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<tr>
<td>Hyperparathyroidism</td>
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<tr>
<td>Excessive alcohol consumption</td>
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<tr>
<td>Coagulation disorders</td>
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<tr>
<td>Hyperlipidaemia</td>
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<tr>
<td>Vasculitis: systemic lupus erythematosus</td>
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<tr>
<td>Giant cell arthritis</td>
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<tr>
<td>Gout and hyperuricaemia</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>Pregnancy</td>
</tr>
</tbody>
</table>

**Figures 1C (right hip) and D (left hip)**

*Coronal T2-weighted gradient echo, fat-suppressed MR images of the same patient*

The serpentine line (black; see arrow) is now surrounded by a narrow zone of high signal intensity (oedema; white), known as ‘the double-line sign’. This is considered highly specific for osteonecrosis.
to a higher degree of complaints. Based on three reports, in which testicular cancer patients were followed after chemotherapy, the crude incidence of osteonecrosis was estimated at 1.5% (95% confidence interval 0.9-2.1%). The incidence of asymptomatic osteonecrosis was 9% (confidence interval: 2-20%) in a small group of patients who previously received chemotherapy because of testicular cancer. The incidence of symptomatic osteonecrosis was 3.8% in the same group.

Corticosteroids, used as antiemetic therapy, are considered to be the main cause of the development of osteonecrosis in patients with solid tumours. In our report, all three patients were treated with dexamethasone combined with ondansetron as antiemetics. In the literature a few cases have been reported in which osteonecrosis developed after chemotherapy without previous administration of dexamethasone. This finding suggests that cytotoxic drugs contribute to the development of osteonecrosis. Several mechanisms are thought to play a role in the development of corticosteroid-induced osteonecrosis.

Firstly, the number of adipocytes in the femoral head of rabbits treated with corticosteroids is increased. This increase in adipocytes correlates with a higher intra-osseous pressure in the femoral head, probably because the efferent veins are compressed by the increased fat content and the afferent arterial flow continues (Sterling mechanism). Furthermore, apoptosis of osteoblasts as well as of osteoclasts is increased with the use of corticosteroids. Finally, corticosteroids stimulate the differentiation of bone marrow stem cells into adipocytes. This leads to a lower number of osteoblasts and therefore a decreased repair and remodelling of osteonecrotic bone.

There is no strict time-dose relationship between corticosteroids and the occurrence of osteonecrosis. Our patients were on corticosteroids in prednisone-equivalent doses of 1.16 to 2.21 g. In the literature, prednisone-equivalent doses ranging from 0.61 to 9.01 g have been reported. Although there are no studies that compare the risks of short to medium-acting steroids, such as prednisone with dexamethasone, it is likely that the latter places the patient at a higher risk due to longer serum and biological half-life.

Winquist et al. reviewed 28 patients with osteonecrosis after treatment for testicular cancer. In three patients onset of osteonecrosis was acute while in 23 patients it was delayed, by a mean of 26 months (range: 12-47 months), after chemotherapy. In our three patients osteonecrosis developed 17, 22 and 55 months after chemotherapy. Although the femoral head is affected most frequently, Harper et al. reported a patient with testicular cancer who in addition to osteonecrosis of the femoral head also suffered from osteonecrosis of the scaphoid and both medial femoral condyles. In the study by Winquist et al., bilateral femoral head involvement was found in 70%. In all our patients bilateral femoral head necrosis was diagnosed. Control of emesis is important in protocol dose adherence. In a double-blind study 531 patients were randomised to one of four intravenous doses of dexamethasone (4-8-12-20 mg) in combination with 8 mg of ondansetron. Complete protection from vomiting was significantly superior in patients who received 20 mg compared with those who received 4 and 8 but not 12 mg. In a meta-analysis of 3791 patients enrolled on 22 randomised trials in which dexamethasone plus a serotonin antagonist was compared with placebo treatment plus a serotonin antagonist superiority of the dexamethasone arm was found. Although these steroid-associated complications are uncommon, they are devastating (sometimes even requiring total hip replacement) especially in young patients with potentially curable malignancy. The addition of dexamethasone to the antiemetic regime is inevitable to achieve optimal treatment. As no evident dose response has been documented, the lowest effective dose of dexamethasone should be used.

In the American Society of Cancer Oncology guidelines concerning antiemetics as well as in the Perugia Consensus Conference regarding the optimal antiemetic treatment osteonecrosis due to corticosteroids is not mentioned. Although the development of osteonecrosis in patients treated with chemotherapy is probably multifactorial, the likely contribution of corticosteroids should have warranted the incorporation of this potential side effect in the guidelines. Patients should be informed about the increased risk of osteonecrosis when treated with chemotherapy for which dexamethasone is used for antiemetic treatment. In addition, osteonecrosis should be included in the differential diagnosis of patients who have been treated with chemotherapy and who present with hip pain. At the onset of hip complaints in a patient treated with corticosteroids, MRI should be performed if plain X-rays show no significant signs of any disease. In the late stages of osteonecrosis, radiographs and CT scanning are sufficient to prove the existence and the extension of the disease; MRI is then no longer necessary. Finally, a recommendation to add corticosteroids to serotonin receptor antagonists only after demonstrated nausea in chemotherapy regimes with low-dose cisplatin (20 mg/m²) for five days seems justified.

References


**ANSWER TO PHOTO QUIZ (ON PAGE 22)**

**A MAN WITH PANCYTOPENIA AND LIVER COMPLICATIONS**

**DIAGNOSIS**

This picture is classical for peliosis hepatis, which is very seldom seen. Peliosis hepatis consists of blood-filled cysts in the liver and it differs from haemangiomatosis by the absence of fibro-endothelial partitions. The pathogenesis of peliosis is unclear, but it is hypothesised that there may be a dilatation of the sinuses caused by loss of reticulin filaments between the sinuses and liver cells.

There are associations with some infectious agents (e.g. *Bartonella henselae*) and with androgens (e.g. 17alpha-alkylated androgens), as in the present case. Peliosis may sometimes be seen in the spleen and induce bleeding complications. Liver biopsy in such a patient is very dangerous.

ABSTRACT

We report a 36-year-old woman with primary hypothyroidism revealed by postpartum amenorrhoea-galactorrhoea associated with hyperprolactinaemia and suprasellar pituitary enlargement on magnetic resonance imaging (MRI). On thyroid hormone replacement therapy all clinical, biochemical, radiological and endocrine abnormalities disappeared. Hyperplasia of pituitary thyrotrophs and/or lactotrophs seems to be responsible for the pituitary enlargement seen on MRI.

INTRODUCTION

Amenorrhoea, galactorrhoea and hyperprolactinaemia in a young woman usually suggests a prolactinoma of the anterior pituitary. Hyperprolactinaemia is present in one-third of primary hypothyroid patients. Less commonly, galactorrhoea and amenorrhoea is associated with primary hypothyroidism. Rarely, amenorrhoea, galactorrhoea and hyperprolactinaemia in primary hypothyroid patients are associated with an enlarged pituitary gland leading to diagnostic confusion with prolactinomas. We report a patient with primary hypothyroidism associated with postpartum galactorrhoea, amenorrhoea and pituitary gland enlargement as well as her clinical course during L-thyroxine replacement therapy.

CASE REPORT

A 36-year-old woman, gravida 2 para 2, was referred to our hospital in 2001 for analysis of amenorrhoea and galactorrhoea since her last pregnancy in 1997. The patient had a normal pregnancy and delivery in December 1997. After a nursing period of six weeks, secretion of milk persisted associated with amenorrhoea. Serum prolactin concentration (PRL) was 103 μg/l (normal 0-20 μg/l). Thyroid function was not tested at that time. She was treated with conventional doses of bromocriptine for nearly twelve months, leading to cessation of galactorrhoea and normal periods. After discontinuation of therapy all symptoms returned. After a brief period of oral anticonception therapy, during which periods were regular, the patient discontinued this medication as well and was seen by a gynaecologist in 2001 for amenorrhoea and galactorrhoea. The external and internal genitalia were normal. On examination bilateral galactorrhoea was confirmed. Again prolactin was 103 μg/l. Magnetic resonance imaging (MRI) revealed a 14 x 20 x 12 mm pituitary macroadenoma extending to the suprasellar cisterna without compression of the chiasma (figure 1). With this information the patient was sent to the department of endocrinology. Typical clinical signs suggesting hypothyroidism were noticed on physical examination. There was no palpable thyroid tissue. Milk could easily be expressed from the breasts. Thyroid function tests were consistent with primary hypothyroidism. The serum free T4 (FT4) was 3.9 pmol/l (normal 10.0-24.0 pmol/l) and thyroid stimulating hormone (TSH) >75 mU/l (normal 0.40-4.00 mU/l). Basal serum prolactin (PRL) was elevated: 103 μg/l (normal 0-20 μg/l). Luteinising hormone (LH) was < 1 U/l and oestadiol (E2) was <0.07 nmol/l. The remaining dynamic tests of the hypothalamic-pituitary axis were normal, including growth hormone and ACTH.
Substitution therapy with L-thyroxine was started, gradually increasing to 125 µg daily. During the next ten months the galactorrhoea resolved and menstrual bleeding resumed. Serum free T4 concentration became normal at 18.7 pmol/l. TSH and prolactin concentrations returned to normal, at concentrations of 2.5 mU/l and 20 µg/l respectively. LH concentration was 4.5 U/l and E2 0.36 nmol/l. MRI of the sellar region was repeated after six months of treatment. MRI demonstrated a marked decrease in the size of the pituitary mass within the sella turcica. After one year of treatment with L-thyroxine repeated MRI showed normal dimensions of the pituitary gland and the bony structures surrounding it (figure 2).

**DISCUSSION**

This case illustrates that primary hypothyroidism in a female may present by amenorrhoea, galactorrhoea and hyperprolactinaemia. Amenorrhoea appears to be caused by suppression of the hypothalamic GnRH secretion by prolactin leading to low gonadotropin and oestradiol levels. The cause of hyperprolactinaemia in primary hypothyroidism is less clear. Several mechanisms have been proposed. At least four factors may contribute to hyperprolactinaemia in primary hypothyroidism. Firstly, the elevated prolactin could be attributed to increased PRL secretion under the influence of TRH, which stimulates TSH as well as PRL secretion.

Secondly, prolactin clearance may be decreased in hypothyroid patients. Thirdly, a study by Foord et al. demonstrated that cultured anterior pituitary cells from hypothyroid rats have a reduced sensitivity to the inhibitory action of dopamine and dopamine agonists on prolactin production, possibly by a defect at the level of the dopamine receptor or at the post receptor level. Fourthly, thyroid hormone itself may also play an important role in the cause of hyperprolactinaemia. Davis et al. noticed that 3,5,3’-triiodothyronine reduces prolactin messenger RNA levels in rodent pituitary cells. Decreased circulating thyroid hormone levels might stimulate prolactin synthesis. The pathophysiological mechanisms in primary hypothyroidism that lead to hyperprolactinaemia might involve factors acting on prolactin receptors as well as on prolactin gene expression. The pituitary enlargement in primary hypothyroidism may be explained by lactotroph and/or thyrotroph hyperplasia; severity and duration of hypothyroidism being of influence. In view of the potent negative regulation of dopamine on prolactin cells, compression of the pituitary stalk due to hyperplasia of the pituitary can also lead to a moderate hyperprolactinaemia. In our patient this seems to be unlikely as the other dynamic hypothalamic-pituitary tests were normal.
Hypothyroidism and hyperprolactinaemia with pituitary enlargement can cause diagnostic difficulties. Coexistence of primary hypothyroidism and a pituitary macroadenoma as well as primary hypothyroidism associated with hyperprolactinaemia and pituitary enlargement should be taken into account. The resolution of the pituitary enlargement and the resumption of the menstrual cycle after replacement therapy with L-thyroxine strongly argues against the possibility of a coexisting macroadenoma and favours the second possibility.

**CONCLUSION**

In a female patient with amenorrhoea, galactorrhoea and hyperprolactinaemia associated with enlargement of the pituitary gland, primary hypothyroidism should always be excluded as a possible cause.

**REFERENCES**


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**Table 1**

*The course of serum FT₄, TSH, PRL, LH and E₂ in a young woman with primary hypothyroidism before and after ten months of treatment with L-thyroxine*

<table>
<thead>
<tr>
<th></th>
<th>FT₄ (PMOL/L)</th>
<th>TSH (MU/L)</th>
<th>PRL (µg/L)</th>
<th>LH (U/L)</th>
<th>E₂ (NMOL/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before</td>
<td>3.9</td>
<td>&gt;75.0</td>
<td>103</td>
<td>&lt;1</td>
<td>&lt;0.07</td>
</tr>
<tr>
<td>After</td>
<td>18.7</td>
<td>2.5</td>
<td>20</td>
<td>4.5</td>
<td>0.36</td>
</tr>
</tbody>
</table>
After the monograph about ‘Essentiële Hypertensie’ by Lips in 1956, there is now a second Dutch textbook called ‘Handboek Hypertensie’ under the leadership of Birkenhäger and De Leeuw. This is a multi-author book and is much broader than just essential hypertension. The book contains 30 chapters and is divided into six parts:

1) General aspects comprises three chapters: one about the measurement of blood pressure, both the standard sphygmomanometry and the more sophisticated noninvasive ambulatory blood pressure monitoring (ABPM); the second chapter is about the risk of high blood pressure and the reduction of this risk by antihypertensive drug treatment; and the third chapter gives an overview about the nutritional factors and ends with some general advice.

2) Secondary hypertension with chapters on phaeochromocytoma, on mineralocorticoid aspects in hypertension, and on renal artery stenosis with its different aspects of diagnosis and of subtypes and methods of treatment (PTRA or stent). It is striking that in this chapter the most frequent form of secondary hypertension is not discussed, namely nephrogenic hypertension due to renal parenchymatous diseases.

3) Primary or essential hypertension with pathophysiological themes: the haemodynamic or volume theory, neurohumoral influences, endothelial resistance and finally the genetic influence theory.

4) The consequences, in particular for the heart thus left ventricular hypertrophy, carotid intima-media thickness, and the damage to the kidney are discussed in separate chapters. Here there is no mention of the target organ damage that can be observed in the eyes using fundoscopy or by measuring the ankle-brachial index.

5) Then the treatment section follows with chapters about nonpharmacological treatment and subsequently chapters about diuretic pharmacotherapy, selective α1-antagonists, β-blockade with different properties (selectivity, partial agonistic activity, etc), calcium antagonists and the subgroups, angiotensin-converting enzyme inhibitors, angiotensin II, and subtype 1 receptor antagonists. This section finishes with a chapter about the interactions of antihypertensive drugs with NSAIDs and about antihypertensive drug compliance and the pharmacogenetic factors.

6) In the last part four chapters about hypertension in special categories are presented: in pregnancy, in children, in the elderly and in blacks. The last two chapters in this section are about hypertensive crisis and preoperative hypertension. Almost all the subjects dealt with in this book are of importance for the daily care of patients with hypertension. One can always find some criticisms, but as a whole I am very positive about the contents of this book, the more so as this is the first edition. Thus, some suggestions can be made to the editors and authors for future editions. I have already suggested a few points for some of the chapters. A general comment is that the draft of the different chapters varies. For example, the chapters about phaeochromocytoma and about patient compliance with antihypertensive medication are more extensive than others. The same holds for the number of references per chapter, varying from less than 10 to more than 150.

There are some careless mistakes which will be easy to correct in the next edition, for example the top text of figure 2.8A should refer to cardiovascular mortality. Also the terms white-coat hypertension and white-coat effect are used interchangeably but they clearly refer to different patients. The registration in figure 1.3C does not show a white-coat hypertension. On page 41 a reference number 58 is given but on page 43 the last reference number is 51. Also the alphabetical register can be improved; for instance, when looking for M-mode, one finds pages 154, 171 and 174, but pages 154 and 171 are part of a reference list, whereas on page 174 the precise explanation about M-mode is presented. Despite these and other minor points, the book can be recommended to internists with different subspecialties such as nephrology, endocrinology, vascular medicine and clinical pharmacology, but also to cardiologists.
ABOUT THE COVER

‘Face’

Jim Siegel

Chicago-born Jim Siegels studied Graphic Design and Fine Arts in New York City at the School of Visual Arts, where he received a B.F.A. before embarking on a ten-year artistic stay on the small Dutch island of Saba. He moved to the Netherlands with his family and settled in the town of Nijmegen. Jim is now working from an atelier in the village of Beek where he continues to explore his artistic perspectives. Most of his work is oils on canvas and wood assemblages, but he doesn’t shy away from unusual methods. Recently he has started a series of lino cuts, using an unorthodox style which he calls ‘Floating Prints’. When making this linoleum print, he starts by cutting the separate elements: eye, nose, mouth and chin. During the printing process, like assembling a collage, he rearranges these elements to create a unique and different face each time. In this series he has made four multicolour prints. No two prints are the same, just like each human face is different. Of one particular assembly he made four mono-colour prints.

An original print, size 57 x 78 cm, from this limited edition (4) is available at a price of € 180.
You can order the print at Galerie Unita, Rijksstraatweg 109, 6573 CK Beek-Ubbergen, the Netherlands, by e-mail: galerie-unita@planet.nl or see the internet site: www.galerie-unita.com.
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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.

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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 pages; also we would appreciate seeing the line numbers in the margin (Word: page set-up - margins - layout - line numbers). Divide the manuscript into the following sections: Title page, Abstract, Introduction, Materials and methods, Results, Discussion, Acknowledgements, References, Tables and Figures with Legends.

A Covering letter should accompany the manuscript, identifying the person (with the address, telephone and telex numbers, 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, any commercial affiliations, consultations, stock or equity interests should be specified. In the letter 1-3 sentences should be dedicated to what this study adds. All authors should sign the letter.

The Title page should include authors’ names, degrees, academic addresses, address for correspondence including telephone, fax and e-mail, 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.

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 proprietary names of substances and materials. At first mention of a chemical substance, use the correct chemical designation as well as the generic name.

The Abstract, not exceeding 200 words, should be written in a structured manner and with particular care, since this will be the only part of the article studied by some readers. In original articles, the abstract should consist of four paragraphs, labelled 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.

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 finding sources should be credited here. Also a statement of conflicts of interest should be put here.
References should be numbered consecutively (in square brackets) as they appear in the text. Type the reference list with double spacing on a separate sheet. References should accord with the system used in Uniform requirements for manuscripts submitted to biomedical journals (N Engl J Med 1991;324:424-8).

Examples:


Please note that the first six authors should be listed; 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 reference list after your manuscript has been revised.

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. India 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 topside 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.

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Brief 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 be supplied with a summary of about 60 words, preferably no more than two figures and/or tables, and no more than 15 references.

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