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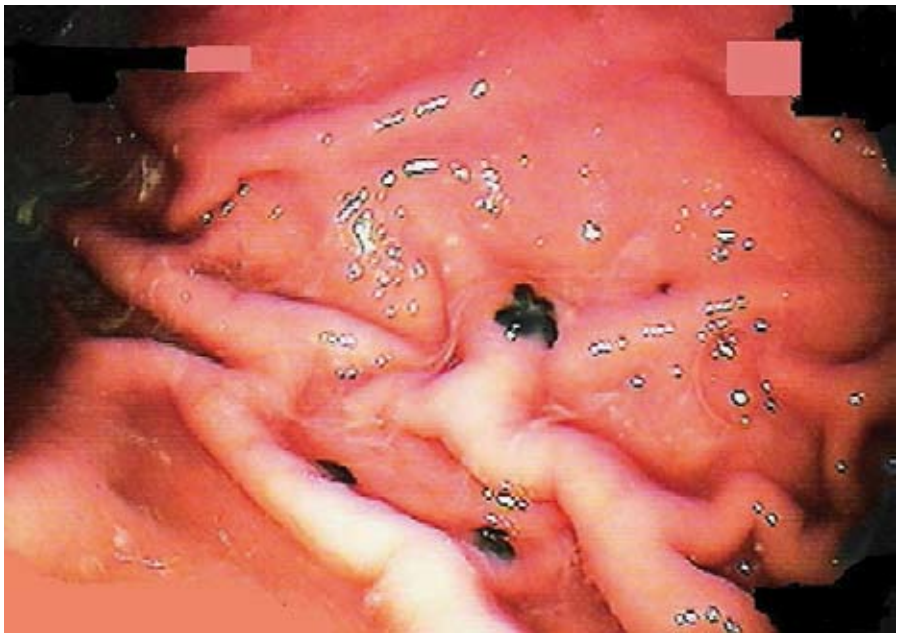

PHOTO QUIZ: Small black spots in the stomach and duodenum, see page 129

March 2008, Vol. 66, No. 3, ISSN 0300-2977

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EDITORIAL

Hypoandrogenism in obese men: pathophysiological implications *versus* practical consequences

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Hormone concentrations vary considerably within, and between, subjects, depending on factors such as gender, age, diurnal patterns, nutritional condition, medication, and nonendocrine diseases. These factors may profoundly confound the interpretation of analytical results of hormone measurements in the evaluation of endocrine diseases. In clinical endocrinology, patients present with symptoms which are carefully evaluated by a detailed medical history and physical examination. Employing this diagnostic strategy, many potentially confounding factors are identified prior to further analysis of circulating hormone concentrations. Thus, the physician can estimate the pretest likelihood of (endocrine) disease by weighing the impact of confounding by these other factors against the evidence for true hormonal secretion defects. These considerations apply to the interpretation of the low serum testosterone concentrations frequently observed in men with obesity.

In this issue of the Journal, Hofstra *et al.* report in a careful study that the majority (58%) of a cohort of obese men had plasma testosterone concentrations well into the hypogonadal range.[1] Moreover, the degree of obesity was inversely correlated with total and (calculated) free testosterone concentrations, in accordance with previous observations, such as by Lima *et al.*[2] Because testosterone is a lipophylic hormone, its transportation in blood requires binding to plasma proteins, primarily sex hormone binding globulin (SHBG). Previous studies have shown an inverse relationship between circulating SHBG concentrations and (subcutaneous) fat mass, which can fully explain the well-known reduction of circulating *total* testosterone in obese subjects.[3] In contrast, for some unclear reason, Hofstra *et al.*[1] do not find such a relationship between body fat indices and SHBG and therefore other mechanism(s) must explain low serum total testosterone levels in their study. In keeping with previous reports, for example Giagulli *et al.*,[4] this decrease in testosterone levels occurred without a compensatory increase in gonadotrophins, suggesting enhanced negative feedback restraint of gonadotrophin release. This can be explained by irreversible conversion of testosterone to oestradiol by aromatase in adipose tissue, resulting in decreased testosterone and elevated oestrogen levels in obese men. Since oestrogens, just as testosterone, exert negative feedback regulation onto the hypothalamic-pituitary system, this, at least in part, explains the biochemical pattern of hypogonadotropic hypogonadism in many obese men. This notion is strongly supported by previous observations by de Boer *et al.*, demonstrating that aromatase inhibition by letrozole normalises serum testosterone levels in severely obese men with the biochemical pattern of hypogonadotropic hypogonadism.[5] Moreover, testosterone, free testosterone and SHBG levels tend to normalise in response to weight loss,[6] indicating that the endocrine alterations in sex hormone metabolism are a consequence of obesity.

PATHOPHYSIOLOGICAL IMPLICATIONS

What are the pathophysiological implications of hypoandrogenism in obese men? Is it an endocrine epiphenomenon, merely reflecting an adaptive process balancing regulatory pathways in the face of excess fat? Or are a majority of obese men truly hypogonadal? There are at least several issues that require careful consideration in this respect. Obesity is associated with reduced fertility both in women and in men.[7] Many obese men suffer from erectile dysfunction,[8] and weight loss improves sexual function in obese males.[9] Spermatogenesis is reduced in proportion to body mass index in males.[10] Finally, hypoandrogenaemia is associated with the metabolic syndrome in men and

some data suggest that androgen therapy beneficially modifies fat distribution and ameliorates metabolic anomalies in abdominally obese men,[11] but it is unclear whether these effects were due to physiological rather than pharmacological effects of testosterone. Nonetheless, these data suggest that inhibition of pituitary-gonadal activity by excess adipose tissue provokes reproductive and metabolic anomalies in men. However, there is at present no appropriate evidence for androgen-replacement therapy and/or gonadotrophin treatment for hypoandrogenaemic obese men. For example, it is unclear if low serum testosterone levels are the proximate cause of erectile and spermatogenic anomalies and it remains to be determined if androgen replacement facilitates erectile function, whereas it most certainly will not improve spermatogenesis. Moreover, although various small-scale studies indicate that testosterone replacement beneficially impacts on various components of the metabolic syndrome in obese insulin-resistant men, it is uncertain below which serum testosterone level obese men might benefit from testosterone replacement, which dose should be used and what serum level of testosterone should be strived for, and if long-term testosterone administration is safe in obese insulin-resistant individuals. Indeed, the general uncertainty with respect to the thresholds of normal *vs* abnormal testosterone levels, as mentioned in the recent clinical practice guideline of the Endocrine Society,[12] also applies to this condition.

PRACTICAL IMPLICATIONS

Therefore, we strongly recommend against screening of sex hormone levels in obese men in general. Instead, the assessment of sex hormone levels in obese men is only indicated if there are consistent signs and symptoms of hypogonadism. We appreciate that the clinical diagnosis of androgen deficiency in men is difficult, because symptoms and signs are nonspecific and modified by age, comorbid illness, severity and duration of androgen deficiency, variation in androgen sensitivity, and previous testosterone therapy.[12] First, medical history should be thoroughly checked for symptoms of androgen deficiency. These include muscle weakness, hot flashes, reduced sexual desire, infertility, erectile dysfunction and minor trauma to the testes. Second, careful physical examination should focus on gynaecomastia, pubic, body and facial hair, and testicular atrophy. Third, we recommend obtaining blood samples for measurement of testosterone only in the morning hours on at least two occasions. There is considerable diurnal variation in serum testosterone levels, with the highest levels in the morning.[13] Moreover, the recommendation of the analysis of at least two samples is based on the reality that there is a considerable within-subject variation in testosterone levels. In general, on repeated evaluation, 30% of the men with an initially low level will have a normal level upon repeat testing.[14] Fourth, the age of the patient should be taken into consideration in the interpretation of the test results, because there is a considerable age-dependent decline in total and free testosterone levels of 35 to 50% between the ages of 20 and 80 years, which is not taken into account by the fixed range of normal values provided by many laboratories.

In a patient with signs and/or symptoms of hypogonadism low serum total and free testosterone concentrations in the face of increased luteinising hormone (LH) and follicle-stimulating hormone (FSH) levels indicate primary hypogonadism. Low serum total and free testosterone levels and (sub)normal LH and FSH values point to secondary (i.e. hypogonadotrophic) hypogonadism, which can either be a feature of obesity *per se* or a reflection of pituitary disease, requiring further evaluation of pituitary function.

We are very reluctant to treat obesity-associated low serum testosterone concentrations in the absence of any other clues for the presence of pituitary or testicular disease, because of the absence of consistent evidence that androgen replacement is safe and effective. In contrast, the available evidence does indicate that weight loss reinstates normal pituitary-gonadal function and ameliorates metabolic and reproductive anomalies in obese men.

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REVIEW

HPV-related anogenital disease and HIV infection: not always 'ordinary' condylomata acuminata

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ABSTRACT

Human papillomavirus (HPV) is responsible for various diseases in the anogenital region which range from benign condylomata acuminata to anal carcinoma. Buschke-Loewenstein tumour is a clinically 'intermediate' condition which is histologically benign but due to extensive destruction of the local tissues can show malignant behaviour. Its early recognition as a different clinical entity to 'ordinary' condylomata acuminata is important for its adequate management. Immunocompromised persons, such as those with HIV infection, have a higher incidence of HPV-related anogenital disease. Different aspects of the HPV-related anogenital disease in HIV-positive individuals are discussed.

KEYWORDS

Buschke-Loewenstein tumour, HIV, human papillomavirus

INTRODUCTION

Human papillomavirus (HPV) is a common sexually transmitted pathogen. Different HPV genotypes are associated with a whole spectrum of the specific clinical conditions. Anogenital disease can range from the benign condylomata acuminata to anal carcinoma.

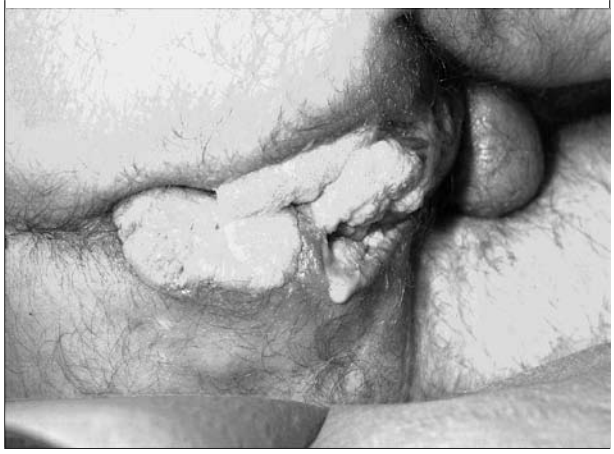
Condylomata acuminata (CA) is the commonest viral sexually transmitted disease in the world with a very low potential for malignant transformation.[1] However, under some (not yet completely understood) circumstances HPV can cause giant CA, also known as Buschke-Loewenstein tumour (BLT). BLT is typically histologically benign and does not metastasise, but it may manifest as a clinically malignant disease due to its expansive and invasive growth. Malignant transformation in the course of the disease occurs in up to 50% of the cases.[2] Although a number of cases of Buschke-Loewenstein tumour have been described in the literature, and a few reviews have summarised the information about this disease, many clinicians do not recognise this process as a different clinical entity with a different course and prognosis than CA.

We present a case of BLT in an HIV-positive patient and summarise the current information on BLT and its relation to the other HPV-related anogenital disorders with special attention to its occurrence and course in HIV-positive individuals.

A 44-year-old heterosexual Moroccan male with a history of type I diabetes mellitus and Hodgkin's lymphoma in complete remission was admitted because of extensive perianal abscesses, fever, chills, and weight loss. He had been known to be HIV positive for four years (CD4 count 491/mm^3, HIV-RNA 150,000 c/ml, no symptoms at presentation). No antiretroviral therapy was started. The patient attended his appointments regularly and reported being well. His laboratory results were stable, the CD4 count never dropped below 350/mm^3.

At admission, he appeared cachectic (BMI 18.2 kg/m^2), with multiple exophytic masses with fistulae and purulent secretion in the perineal and perianal area (*figure 1*). He admitted he had felt too embarrassed to discuss this problem earlier with his treating physician. The CT scan showed an extensive lobulated soft tissue mass between the rectum and corpora cavernosa, with multiple abscesses, and enlarged regional lymph nodes. Microscopically, a verrucous tissue covered with dysplastic epidermis, with hyper- and para-keratosis typical of condyloma acuminatum

Figure 1. *Buschke-Loewenstein tumour in the anogenital area*



was seen; the basal membrane was locally disrupted with invasive growth of dysplastic epithelium into the dermis. PCR was positive for HPV genotype 6. The diagnosis of BLT was made. The patient refused any radical surgery of his perineal disease. Radiotherapy or chemotherapy were not an option because of active infection and his poor general condition. He was treated with broad-spectrum antibiotics and incision of the abscesses. Highly active antiretroviral therapy (HAART) was started (zidovudine, lamivudine, lopinavir). Colostomy was performed which led to discernable relief of the symptoms.

Four months later he was admitted again because of severe sepsis due to major abscess formation in the condylomatous tissue. Because of his deteriorating haemodynamic and respiratory condition not responding to antibiotics and fluid resuscitation the patient eventually consented to (partial) surgical debulking of BLT. The surgical procedure was complicated by massive bleeding of the extensive wound bed. New biopsies showed an invasively growing well-differentiated spinocellular carcinoma which originated from the dysplastic epithelium of the pre-existent condylomata. Because no surgical options remained for radical removal of the tumour, treatment with a subcutaneous pegylated interferon and locally applied cidofovir cream was started, with no improvement. In the next few months the patient was reoperated several times and the newly formed abscesses were incised. The patient's condition slowly deteriorated, he suffered from progressive catabolism and relative adrenal insufficiency. Eight months after the initial admission, after the family of the patient had been consulted, all treatment was stopped and the patient died.

More than 80 different HPV genotypes have been characterised.[3] Anogenital HPV has been classified into low-risk genotypes (6 and 11) associated with 'ordinary' anogenital CA, BLT and mild intraepithelial dysplasia, and high-risk genotypes (16, 18, 31, and 45) which are found in high-grade intraepithelial neoplasia that may progress to anogenital cancer, such as cervical and anal carcinoma.[4,5] The competence of the immune system plays an important role in HPV infection as CA recurs significantly more often and within a shorter period of time after treatment in immunocompromised patients, including those with HIV infection, when compared with patients with a competent immune system.[6,7]

CHARACTERISTICS AND HISTOLOGY OF BLT

Under some (unknown) circumstances HPV 6 and 11 infection cannot be contained and leads to the development of a disfigurating cauliflower-like mass known as Buschke-Loewenstein tumour. It is described mainly in patients with an immunodeficiency (HIV infection, post-transplantation, malignancy, diabetes), during pregnancy, in persons with alcohol abuse, etc. Some local conditions (*Herpes simplex* infection, inadequate hygiene) can also be of importance.[8] It is not clear whether it is the immunological condition at the time of virus acquisition which is important for the development of an extensive disease, or whether the pre-existent HPV infection worsens during the immunosuppression.

BLT is a locally aggressive and extremely morbid condition[9] characterised by a malignant clinical course even when its histological features are benign.[10] It has a high recurrence rate varying between 18 to 67% in different case series[2,11] with an overall mortality of 21%.[2] A review by Trombetta *et al.*,[9] who studied 51 cases published in the English literature between 1958 and 2000, showed that this disease occurs more often in males than in females (ratio 2.7:1) with a mean age of patients of 43.9 years. Microscopically BLT shows thickened squamous epithelium, prominent papillomatosis, fistulous tracts, intact basement membrane, lack of anaplasia or invasion[12] and is distinguished from simple CA by the clear tendency to infiltrate the deeper tissue layers[13] and a 'pushing' rather than infiltrating effect.[9] Symptoms associated with BLT are due to the destruction of the local tissues (pain, bleeding, itching, fistulae) or due to the mechanical obstruction (ileus or problems with defecation which may lead to minimising of food intake and cachexia). Fistulas colonised with bacteria cause the formation of abscesses which can lead to sepsis. Distinction should probably be made between BLT cases presenting in the perianal area and those originating in the rectum as the latter often present only with fistula formation without an apparent exophytic tumour[9] and more often tend to exhibit malignant behaviour.[1]

BLT has much higher potency for malignant transformation than 'ordinary' CA (1.82 *vs* 30 to 56%).[1,2,9,14]

The average time to malignant transformation is five years (range 15 to 100 months).[2] This does not, however, necessarily mean a worse prognosis; in a review by Chu *et al*. patients with malignant transformation of BLT had a better prognosis than those without (33 *vs* 13 %).[2] The local tissue destruction can have fatal consequences before malignant transformation is apparent.

TREATMENT OF BLT

Treatment is often delayed because of the patient's embarrassment about visiting a doctor and fear of the consequences of the therapy. At the time of the first presentation most patients already have extensive disease. To our knowledge only one case of spontaneous regression of BLT has been reported after childbirth in a woman who was diagnosed with BLT during pregnancy.[15] Contrary to CA, conservative treatment alone usually fails. The therapeutic modalities generally used - alone or in combination - are surgery, chemotherapy and radiotherapy. No therapeutic guidelines exist as the number of reported cases is small, and various treatment modalities have been used.

A curative effect has been produced by surgical excision alone[9,10] or in combination with CO_2 surgery,[16,17] neoadjuvant chemotherapy,[14] postoperative radiation,[8,18,] combined chemoradiation [19] and local pelvis perfusion with chemotherapeutics.[2] The use of radiotherapy is still controversial because there is some evidence of anaplastic transformation and a reappearance of condylomas[19-21] as well as a lack of long-term results.[22] A combination of excision with postoperative treatment with interferon (subcutaneously[23] or intralaesionally[24]) or with a locally applied imiquimod crème[25] has also shown to be successful in some patients. Although the antiviral drug cidofovir has been used successfully for the topical treatment of genital warts in combination with surgery in HIV-positive patients,[26] no data in Buschke-Loewenstein tumour have been published.

It has become clear that the treatment of BLT must be early and aggressive to prevent local spread, extensive tissue destruction and eventually malignant transformation as potentially lethal complications. The best results are achieved with surgical therapy. The recommended techniques are either radical local excision or abdominoperineal resection.[22] There are three main problems regarding the surgical treatment: high recurrence rate (probably because of spillage of residual tumour during the operation),[2] difficult wound healing with secondary infection (due to faecal contamination) and high morbidity due to large soft tissue defects.[8,22] Most important for the appropriate management of this highly mutilating condition is the proper recognition of this clinical entity to institute the adequate therapeutic and follow-up measures as soon as possible.

HPV-RELATED DISEASE IN PATIENTS WITH HIV INFECTION

Anal disease is common in patients with HIV infection, especially in men who have sex with men (MSM). Both anal HPV infection and anal intraepithelial neoplasia (AIN) are more common in HIV-positive than in HIV-negative MSM (RR 3.7 for high-grade AIN).[27] Recurrence of anal condylomata has been more strongly associated with HIV positivity and CD4- lymphocytopenia than with persistence of HPV suggesting that HIV-negative individuals can clear the virus more easily.[28]

There seems to be a complex interaction between HIV, HPV and local mucosal immune mechanisms. HIV enhances the HPV transcription[29] and upregulates HPV E7 which influences the cellular differentiation[30] leading to the higher amounts of HPV DNA in the tissue. Furthermore, HPV causes a decrease in the number of the local macrophages, Langerhans and CD4 cells[29,31] and the impairment of the local cytokine production[32,33] resulting in impaired local immune control of HPV infection.

Because HIV seems to enhance replication of HPV one would expect that the initiation of HAART with subsequent suppression of HIV RNA should lead to the decrease in the amount of HPV in the affected mucosa followed by clinical improvement. The *sine qua non* is the good penetration of the antiretroviral drugs in the target tissues (genital of anal mucosa). The effect of HAART on the clinical course of BLT has never been studied systematically. A case describing even paradoxical worsening of BLT as a consequence of immune reconstitution syndrome after the start of HAART in a patient with low CD4 count at presentation (50/mm^3) has been reported.[34] A study in HIV-positive women showed that HAART can reduce the incidence of genital warts and vulvar intraepithelial neoplasia and this effect was mediated through the increase in CD4 cells and reduction of HIV RNA. [35]

BLT AND HIV INFECTION

Only a few cases of BLT have been published in patients with HIV infection, most of them reporting about the effect of the applied therapeutic modalities[36,37] or the co-existence of both conditions.[38-40]

ANAL CANCER AND HIV INFECTION

Anal cancer and its precursor, anal intraepithelial neoplasia (AIN), have a high prevalence in the HIV-positive population.[41] The relative risk for developing anal cancer among HIV-positive MSM is 37-times higher than for the general population.[42]

AIN can be distinguished into mild dysplasia (AIN I), moderate dysplasia (AIN II) and severe dysplasia (formerly known as carcinoma *in situ*, AIN III), [43] which can progress to anal cancer.[44] Anal cancer and high-grade AIN are associated with oncogenic or 'high-risk' HPV genotypes (16 and 18). The natural progression from AIN to anal cancer is unknown.[45] It seems that anal cancer arising from high-grade intraepithelial neoplasia is a result of a different aetiopathogenetic process than anal cancer which develops as a malignant transformation of BLT; they are associated with different HPV subtypes, the former originates typically as a flat intraepithelial lesion while the latter shows an exophytic growth very early.

It has been speculated that the higher incidence of HPV-associated cancers in HIV-positive patients could be due to the increased sexual HPV exposure. High-grade AIN can, however, also be detected in the absence of sexual risk factors in the HIV-positive individuals. When the groups of HIV-positive MSM and intravenous drug users (IVDU) without a history of anal intercourse were compared, more MSM than IVDU showed AIN of any grade (72 *vs* 36%, p<0.001) but the prevalence of high-risk AIN was similar (18 *vs* 18%).[46] The mean nadir CD4 count was significantly lower in IVDU who exhibited high-risk AIN than in those without (16 *vs* 140, p=0.03). Immunosuppression thus plays an important role in the high-risk AIN in HIV-positive persons even in the absence of anal intercourse. Similar data are reported in renal allograft recipients in the absence of receptive anal intercourse.[47] Another explanation for the higher incidence of anal cancer in HIV-positive individuals could be a higher HPV load in the affected tissues. This was shown to be significantly higher in the cervical lesions in HIV-positive than in HIV-negative women, and correlated significantly with severe immunosuppression (CD4 <200/mm^3).[48]

Immunosuppression is known to play an important role in a variety of cutaneous neoplasias.[49] Development of anal cancer in HIV-positive patients was, however, not shown to be related to lower CD4 counts.[50] Immune suppression probably plays a role in the earlier stages of HPV-associated disease but not in the established infection.[41] This might explain why no regression of high-grade AIN was observed after introduction of HAART.[50-52] It can be expected that AIN and anal cancer will probably be seen even more often in the HIV-positive population as a result of improved survival.[3]

The incidence of anal cancer in HIV-positive MSM is comparable with that of cervical cancer before the introduction of screening programmes[53] and the question raises whether such a screening would also be an effective strategy to decrease the incidence of anal malignancy. According to cost-benefit modelling, anal cytological screening in HIV-positive MSM should be cost-effective for preventing anal cancer.[54] Studies are needed to show an effect of dysplasia screening on the incidence of anal malignancy survival in HIV-positive individuals.[45]

Lowering of the prevalence of HPV infection is expected to lower the prevalence of the HPV-associated anogenital disease. One of the ways to prevent the infection with at least some of the HPV genotypes is the vaccination. The positive effect of the quadruple HPV vaccine in young women has recently been shown, with the reduction in the incidence of an HPV-associated anogenital disease and cervical cancer.[55,56] Whether the same effect could be expected in the HIV-positive population is still not known. Moreover, the effect of HPV vaccine has not yet been studied in males.

In conclusion, infection with HPV can cause various anogenital diseases with different prognosis and therapy. The proper and early recognition is essential for their adequate management to avoid unnecessary morbidity and mortality. This is of even more importance in HIV-infected individuals because the disease is more prevalent and more extensive in this population.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

High prevalence of hypogonadotropic hypogonadism in men referred for obesity treatment

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ABSTRACT

Background: Obesity can be associated with biochemical evidence of isolated hypogonadotropic hypogonadism (IHH) in men. Prevalence and severity of IHH in obese men are not exactly known.

Objective: To assess the prevalence of IHH in obese men.

Design and Subjects: Cross-sectional study of 160 obese men, BMI >30 kg/m², who applied for medical or surgical treatment of obesity in a general teaching hospital.

Main outcome measures: Total and calculated free testosterone (TT and FT) in relation to body mass index (BMI).

Results: Mean age of the study population was 43.3 ± 0.8 years (mean ± SEM), BMI ranged from 30.0 to 65.7 kg/m². TT and FT levels were inversely related to BMI (-0.48, p<0.001). Total testosterone was subnormal in 57.7% and free testosterone in 35.6% of the subjects. The group of men with IHH was more obese, had higher HbA_{1c} levels and had a 2.6 higher risk for cardiovascular disease. Decreased libido and erectile dysfunction were 7.1 and 6.7 times as common in IHH than in eugonadal obese men.

Conclusions: Reduced T levels, well into the hypogonadal range, are common in male obesity. Assessment of its clinical implications, and a search for the best mode of treatment are warranted.

KEYWORDS

Cardiovascular disease, erectile dysfunction, libido, male hypogonadism, obesity

INTRODUCTION

Ageing, obesity, and chronic illness are major factors affecting serum testosterone (T) levels in men.[1-3] The magnitude of the impact of ageing on serum T levels is well established, for obesity this is less clear.[3,4] Severe obesity may lead to isolated hypogonadotropic hypogonadism (IHH).[5,6] Several explanations have been offered to clarify the presence of reduced T levels in obese men.[5-7] One relates to the technique that is generally employed to measure serum androgen levels, i.e. measurement of total testosterone (TT) instead of free testosterone (FT). TT represents the sum of FT and T bound to albumin and sex hormone binding globulin (SHBG) and is therefore subject to variations in the concentration of the binding proteins. A profound reduction in SHBG level is commonly found in obese men, and this is a major factor causing a decrease in TT.[2,8] FT, measured or calculated by a reliable technique, is not affected by changes in SHBG. The second explanation is based on the impact of increased oestrogen production in obesity, caused by enhanced conversion of T to oestradiol (E_2) by the enzyme aromatase cytochrome P450 that is abundantly present in the adipocyte.[9,10] This increases serum E_2 which exerts a negative feedback on pituitary luteinising hormone (LH) secretion.[11-16] Excess of circulating leptin has also been identified as an LH inhibitory factor in obese men.[17] Obstructive sleep apnoea, a common complication in severe obesity, disrupts hypothalamic-pituitary function which may reduce overnight LH secretion and testosterone production.[18]

Despite the high and still increasing prevalence of obesity in men, recent guidelines on male hypogonadism do not discuss the issue of obesity-related IHH and do not provide advice whether, when and how to treat if serum T levels in obese men are well into the hypogonadal range.[19,20] The present study is the first to estimate the prevalence of obesity-related hypogonadism in men. It is based on an aselective sample of men referred for obesity treatment in a general teaching hospital.

METHODS

Subjects

One hundred and sixty obese males, referred to the departments of internal medicine and surgery for analysis and treatment of obesity, were screened for the presence of biochemical hypogonadism if their body mass index (BMI) was greater than 30 kg/m^2. The evaluation was part of a standard biochemical screening procedure to detect the main causes and metabolic complications of obesity. It was performed without prior selection and irrespective of the presence or absence of symptoms or signs of hypogonadism. In case of intercurrent or unstable disease all measurements were postponed for at least three months until the subject was feeling well again. Medical history, medication and current symptoms were recorded, with special attention for loss of libido and erectile dysfunction (ED) which were both assessed by anamnesis. General physical examination included genital inspection and estimation of testicular size. Venous blood was obtained in the fasting state between 08.00 and 10.00 hours for the measurement of serum creatinine, liver enzymes, glucose, HbA_{1c}, C-peptide, lipids, albumin, thyroid-stimulating hormone (TSH), free thyroid hormone (fT_4), luteinising hormone (LH), follicle-stimulating hormone (FSH), TT, total E_2 (TE_2), prolactin, and SHBG. If hypogonadotropic hypogonadism was diagnosed, additional measurement of early morning serum cortisol, adrenocorticotrophic hormone (ACTH) and insulin-like growth factor-1 (IGF-I) was performed to complete the evaluation of pituitary function. Pituitary hormone stimulation tests were not performed.

Exclusion criteria were liver disease (liver enzymes four times above the upper normal limit), moderate to severe renal insufficiency (serum creatinine ≥200 μmol/l), serum transferrin saturation levels >60%, medication known to affect the gonadal axis, pituitary disease, and hypergonadotropic hypogonadism.

Hormone assays and calculations

Gonadotropins and gonadal hormones were measured by electrochemiluminescene immunoassays (Roche Diagnostics, Mannheim, Germany). Interassay coefficients of variation (CV) are: LH and FSH <3%, TT <6%, TE_2 <5%. SHBG was measured by chemiluminescent enzyme immunoassay (DPC, Los Angeles, USA, reference range 13 to 71 nmol/l, interassay CV <5%). FT and bioavailable T (BT) were calculated by the method of Vermeulen *et al.* which is based on the measurement of serum albumin, total testosterone and SHBG and the use of T binding affinities to albumin and SHBG.[21] Free E_2 (FE_2) was calculated by using affinity constants for binding of E_2 with SHBG and albumin. The affinity constant of E_2 to SHBG was 3.14E+08, the affinity constant of E_2 to albumin 4.21E+04, and the affinity constant of testosterone to SHBG was 5.97E+08.[22] Reference ranges validated by in-house measurements and calculations of samples obtained from 207 healthy men, ranging in age from 20 to 60 years, are as follows: LH 2.0 to 9.0 U/l, FSH 1.5 to 12.4 U/l, TT 11 to 28 nmol/l, BT 5.2 to 13.6 nmol/l, FT 225 to 625 pmol/l, TE_2 40 to 160 pmol/l, and FE_2 1.1 to 4.7 pmol/l.

Definitions

In this study the diagnosis of isolated hypogonadotropic hypogonadism (IHH) was based on a set of biochemical criteria including an FT level below 225 pmol/l, combined with an inappropriately low LH level of less than 9.0 U/l, and no biochemical evidence of additional pituitary hormone abnormalities as assessed in early morning serum samples.

Subjects were considered to have diabetes mellitus (DM) if they received oral antidiabetics or subcutaneous insulin, or had fasting plasma glucose levels >7.0 mmol/l or HbA1c levels >6.0%.

Cardiovascular disease (CVD) was considered to be present if documented in medical history or indicated by the use of specific cardiovascular drugs (not including statins or fibrates). The spectrum of CVD present in this population comprised hypertension, coronary artery disease, heart failure, and cardiac arrhythmias.

Statistical analysis

All continuous data followed a normal distribution and are presented as means ± standard error (SE). Differences between groups were evaluated by analysis of variance and subsequently by Student's t-test, if appropriate. Relationships between variables were explored by (multiple) regression analysis. Categorical data are shown as percentages. Proportions were analysed by Fisher's exact test. Differences between IHH and non-IHH subjects were adjusted for age by logistic regression analysis. A p value <0.05 was considered statistically significant.

RESULTS

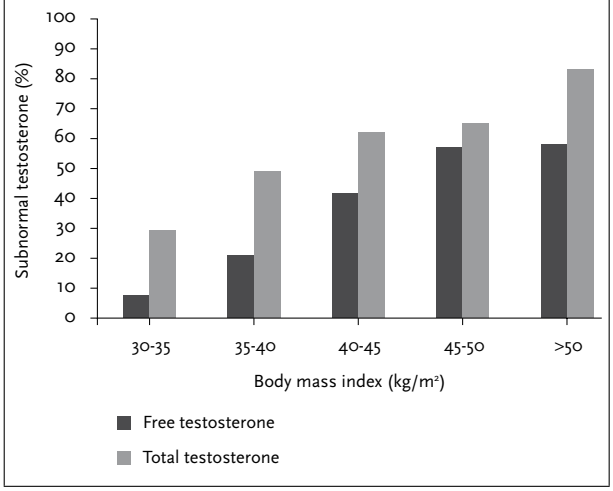
Eleven subjects were excluded for the following reasons: one because of Klinefelter syndrome, two subjects with post-orchitis hypergonadotropic hypogonadism, three had hypergonadotropic hypogonadism of unknown cause, two because of renal insufficiency, one because of chronic alcoholic hepatitis, one had a partial empty sella, and one patient because of macroprolactinoma. The final analysis comprised 149 men, mean age 43.3 ± 0.8 years (range 18 to 66 years), BMI 42.7 ± 0.7 kg/m^2 (range 30 to 65.7 kg/m^2). DM2 was present in 37% and CVD in 35%. The main manifestations of CVD were hypertension (78%), coronary artery disease (19%), cardiac arrhythmias (19%), and heart failure (7%). Twenty-seven percent used oral antidiabetics or

insulin, 33% were treated with antihypertensives, 17% took statins, 9% received thyroxin for primary hypothyroidism, 3% were treated with continuous postitive airway pressure (CPAP) for obstructive sleep apnoea and 3% were treated for depression. Mean HbA1c was 6.4 ± 0.1% (normal range 4.0 to 6.0%), fasting C-peptide 1.66 ± 0.7 nmol/l (normal value 0.36 to 1.66 nmol/l), total cholesterol 5.0 ± 0.1 mmol/l, HDL cholesterol 1.1 ± 0.1 mmol/l, and triglycerides 2.2 ± 0.2 mmol/l. Decreased libido was reported by 22.5%, erectile dysfunction (ED) by 31.7% of the subjects.

Table 1 summarises the results of hormone measurements according to BMI category. Mean age was comparable for all five categories, whereas mean BMI was significantly greater than each preceding category. Mean TT, BT and FT gradually decreased with increasing BMI, with mean declines of -1.1 nmol/category, -0.7 nmol/category and -29 pmol/category, respectively (p<0.001). TE_2 and FE_2 showed the opposite trend and gradually increased with every higher BMI category: TE_2 +11.4 pmol/category (p< 0.001), free E_2 +0.4 pmol/category (p<0.001). SHBG was already in the lowest quartile of the reference range in BMI category 30 to 35 kg/m², and remained stable at this level in the higher BMIs. Albumin tended to decrease gradually with increasing BMI (trend: -0.9 g/category, p<0.001). The ratio of FE_2 to FT increased linearly with increasing BMI (trend: +4.8 x 10^{-3}/category, p<0.0001).

TT levels <11 nmol/l were observed in 86 subjects (57.7%). BT was subnormal in 40.3% and FT levels <225 pmol/l were observed in 35.6% of the subjects. In every BMI category, the prevalence of subnormal TT levels was consistently higher than that of FT (*figure 1*). Subnormal FT levels were observed in 7.4% of cases with BMIs of 30 to 35 kg/m², in 21.0% for BMIs ranging from 35 to 40 kg/m², in 42.4% for BMIs ranging from 40 to 45 kg/m², in 58.3% for BMIs ranging from 45 to 50 kg/m², and in 59.2% of BMIs > 50 kg/m². Comparable figures were obtained if BT was used to assess androgen activity (data not shown).

Figure 1. *Prevalence of subnormal total testosterone (<11 nmol/l) and free testosterone (<225 pmol/l) levels in obese men, according to BMI category*



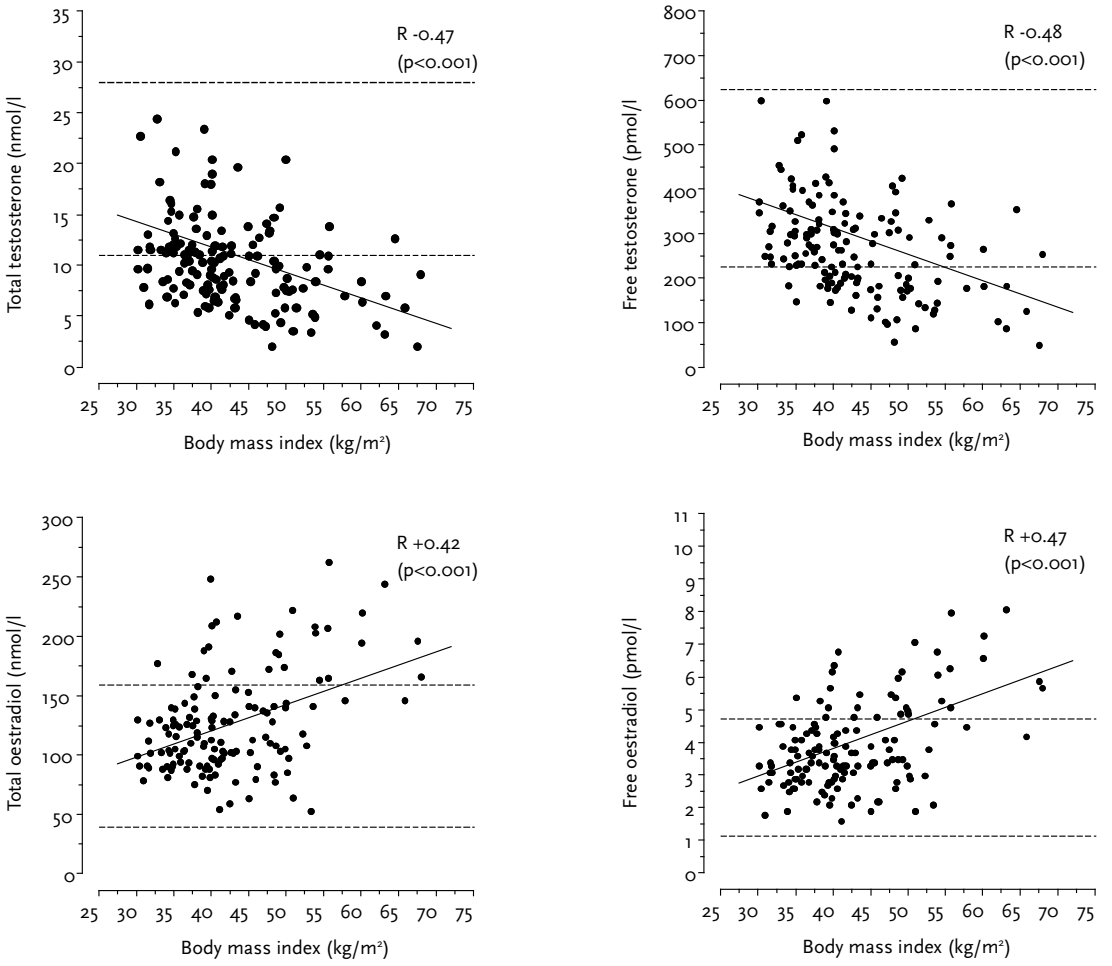
TT levels were inversely related to BMI (R -0.47, p<0.05), and positively correlated with albumin (R +0.22, p<0.005), SHBG (R +0.49, p<0.0001), and FT (R +0.85, p<0.0001). FT was only related to age (R -0.24, p<0.005) and BMI (R -0.48, p<0.0001), not to albumin or SHBG. Serum TE_2 and FE_2 levels were in the high normal range. Both were positively correlated to BMI (*figure 2*). SHBG levels were reduced to the same extent in all BMI categories (*table 1*).

Table 1. *Summary of gonadal hormone measurements in relation to BMI category*

	Reference range	Body mass index category				
		30-34	35-39	40-44	45-49	≥50
Subjects (n)		27	38	33	24	27
Age (years)		46.1 ± 1.5	42.4 ± 1.5	45.0 ± 1.9	43.8 ± 2.0	39.2 ± 1.7
BMI (kg/m²)		32.9 ± 0.4	37.8 ± 0.2	41.8 ± 0.3	47.8 ± 0.3	56.9 ± 1.1
Luteinising hormone (U/l)	2 - 9	3.5 ± 0.3	4.6 ± 0.3	4.8 ± 0.4	4.3 ± 0.4	4.0 ± 0.3
FSH (U/l)	1.5 - 12.4	4.3 ± 0.3	5.8 ± 0.6	4.7 ± 0.5	6.0 ± 0.7	5.1 ± 0.6
Total testosterone (nmol/l)	11 - 25	12.3 ± 0.9	11.3 ± 0.7	10.2 ± 0.7	9.6 ± 0.9	7.5 ± 0.6
Bio testosterone (nmol/l)	5.2 - 13.6	7.2 ± 0.4	6.9 ± 0.4	5.9 ± 0.4	5.5 ± 0.6	4.3 ± 0.4
Free testosterone (pmol/l)	225 - 625	320 ± 19	304 ± 17	262 ± 17	249 ± 26	200 ± 17
Oestradiol (pmol/l)	40 - 160	110 ± 4	122 ± 6	121 ± 7.3	130 ± 7.5	163 ± 12
Free oestradiol (pmol/l)	1.1 - 4.7	3.3 ± 0.2	3.7 ± 0.2	3.7 ± 0.2	4.1 ± 0.2	5.1 ± 0.4
Albumin (g/l)	35 - 50	41.4 ± 0.7	42.3 ± 0.4	40.9 ± 0.6	39.5 ± 0.9	38.2 ± 0.6
SHBG (nmol/l)	13 - 71	21.3 ± 1.9	19.9 ± 1.6	21.4 ± 2.1	21.7 ± 2.6	20.4 ± 1.7

Data are shown as mean values ± SE. FSH = follicle-stimulating hormone; Bio = bioavailable; SHBG = sex hormone binding globulin.

Figure 2. *Relationship between body mass index and total testosterone, free testosterone, total oestradiol and free oestradiol*



To further examine the relationships between hypogonadism and several clinical variables, the study population was divided into IHH and non-IHH men, based on an FT level of 225 pmol/l as cut-off. *Table 2* summarises the results. Mean age, BMI, HbA1c and fasting C-peptide were higher in the IHH group. The differences in TT, BT and FT remained highly significant after correction for age (p<0.001). HDL cholesterol, LDL cholesterol and triglycerides were comparable for both groups, and this remained so after exclusion of those subjects taking statins or fibrates. The prevalence of type 2 diabetes was not significantly different, but CVD was more frequent in the IHH group. The odds ratio for CVD, corrected for age, was 2.6 (95% CI 1.1 to 6.1, p<0.05) in IHH men, compared with non-IHH men. The prevalence of decreased libido and ED was considerably higher in the IHH group. Decreased libido was reported by 46.5% of the IHH men, and by 9.1% of eugonadal obese men (p<0.001). ED was reported by 61.4% of the IHH men, and by 15.9% of the eugonadal men (p<0.001). Compared with eugonadal obese men, and corrected for age, the risk of ED or decreased libido was increased by a factor 6.7 (95% CI 2.8 to 16.1, p<0.001) and 7.1 (95% CI 2.6 to 19.5, p<0.001) in IHH obese men. The use of α- and/or β-blockers was comparable for both groups, 13.0 and 14.5%, respectively.

DISCUSSION

The results of this study indicate that male obesity is frequently associated with T levels within the hypogonadal range, biochemically classified as isolated hypogonadotropic hypogonadism (IHH). The prevalence of IHH increases linearly with BMI, and exceeds 40% in subjects with BMIs of 40 kg/m² or greater, for an FT <225 pmol/l as cut-off. The data were not obtained from a completely random population of obese subjects, but were based on subjects who were referred for obesity treatment. As the latter are more likely to be symptomatic, the prevalence figures assessed in this study may be somewhat higher

Table 2. *Comparison of hypogonadal (IHH) and eugonadal (non-IHH) obese men*

	IHH	Non-IHH	P
Subjects (n)	53	96	
Age (years)	46.1 ± 1.4	40.7 ± 0.8	<0.002
Body mass index (kg/m²)	47.2 ± 1.1	39.9 ± 0.7	<0.0001
Luteinising hormone (U/l)	4.2 ± 0.3	4.4 ± 0.2	NS
FSH (U/l)	5.9 ± 0.6	4.6 ± 0.2	NS
Total testosterone (nmol/l)	6.6 ± 0.3	14.4 ± 0.4	<0.0001
Bioavailable testosterone (nmol/l)	3.6 ± 0.1	8.6 ± 0.2	<0.0001
Free testosterone (pmol/l)	162 ± 5.6	384 ± 7.9	<0.0001
Oestradiol (pmol/l)	126 ± 6.5	131 ± 4.3	NS
Free oestradiol (pmol/l)	3.8 ± 0.2	4.0 ± 0.1	NS
Free oestradiol/Free testosterone	26.9 ± 2.8	12.7 ± 0.5	<0.0001
SHBG (nmol/l)	22.3 ± 1.7	20.2 ± 1.1	NS
Albumin (g/l)	39.9 ± 0.5	41.1 ± 0.4	NS
HbA_{1c} (%)	6.7 ± 0.2	6.1 ±0.1	<0.01
Fasting glucose (mmol/l)	7.2 ± 0.7	6.7 ± 0.3	NS
Fasting C-peptide (nmol/l)	2.0 ± 0.1	1.4 ± 0.1	<0.0001
LDL cholesterol (mmol/l)	3.0 ± 0.2	3.0 ± 0.1	NS
HDL cholesterol (mmol/l)	1.1 ± 0.1	1.1 ± 0.1	NS
Triglycerides (mmol/l)	2.3 ± 0.3	2.0 ± 0.1	NS
Diabetes mellitus	46.0%	31.8%	NS
Cardiovascular disease	52.1%	23.6%	<0.002
Hypothyroidism	12.2%	5.5%	NS
Decreased libido	46.5%	9.1%	<0.0001
Erectile dysfunction	61.4%	15.9%	<0.0001

All data are expressed as mean values ± SE, or as percentages. IHH = isolated hypogonadotropic hypogonadism; NS = statistically not significant; FSH = follicle-stimulating hormone; SHBG = sex hormone binding globulin.

than in a completely random population of obese men. Nevertheless, in view of the global epidemic of obesity, obesity-related IHH is likely to be one of the most common causes for reduced serum T levels in men, next to ageing.

The calculated prevalence of hypogonadism heavily depends on the type of biochemical variable chosen to define the condition. Gross overestimation will occur if measurement of TT is used to classify serum androgenicity in obese men. In the present study reduced serum TT levels were observed in 57.7%, whereas reduced FT levels were found in 35.6%. This large discrepancy is mainly due to the decrease in SHBG that typically occurs in obesity as a result of insulin-mediated inhibition of hepatic SHBG release.[2,8,23] Therefore, it is strongly recommended not to rely on TT levels but to use FT levels, either calculated by a validated method,[21,22,24] or assessed by equilibrium dialysis.[25] The use of currently available radioimmunoassays (RIA) for FT is strongly discouraged because they are subject to the same errors as measurements of TT.[26,27]

In this study we chose to calculate the prevalence of biochemical hypogonadism based on general reference ranges obtained from men between 20 and 60 years of age. We did not use cut-off values based on data obtained from age-matched non-obese adults nor on data from normal-weight young adults. To date, there is still an ongoing debate what should be the gold standard for comparison. Several authors advocate to use the normal range of FT levels in young adults as guideline, arguing that below this limit symptoms and signs of androgen deficiency become apparent irrespective of age.[28,29] Recent guidelines appear to agree with this point of view. If normal-weight young adult data had been used as reference in the present study, this would have increased the prevalence of IHH.

One of the main questions that is raised by the results of this study is whether the high prevalence of reduced T levels in severely obese men is clinically relevant and requires therapeutic intervention. To put the findings into perspective, it is useful to compare the FT levels of obese men with those of population studies using T and SHBG assays with reference values comparable to those employed in the present study.[2,30] FT levels are at their peak between 25 and 35 years with mean values of about 400 to 450 pmol/l. After the age of 35 a gradual decline occurs. At 45 years FT will be around 300 to 350 pmol/l, and at 65 years between 200 to 250 pmol/l. Note that about a third of the obese men in the present population (mean age 46 years) had FT levels corresponding with the mean levels found in healthy men 65 years of age (*figure 2*).

The issue about the clinical impact of reduced T levels in obese men definitely requires further exploration in studies focusing on the prevalence of all clinical signs and symptoms known to be associated with hypogonadism. The present study only provides some indications. The validity of the comparison of IHH and non-IHH subjects was limited because it was hampered by an incomplete match for all relevant variables. Nevertheless, decreased libido and ED was reported about six times as frequently by IHH than eugonadal obese men. It is not likely that the differences in libido and ED can be explained by diabetes or the use of cardiovascular drugs, since the prevalence of diabetes, and the number of patients using α- or β-blokkers was similar in the eugonadal and hypogonadal men.

It was observed that cardiovascular disease was two to three times as common in IHH as compared with non-IHH obese men, and this difference remained after adjustment for age. Due to the incomplete match it remains uncertain whether the increased prevalence of CVD in IHH men is related to a higher degree of obesity, the reduced T levels or a poorer glycaemic control. Due to the cross-sectional

nature of the study it can not be established whether the increased prevalence of CVD is a cause or a consequence of hypogonadism in this specific population.

Obesity is not only characterised by a decrease in T but also by an increase in serum E_2 levels. This is visible on inspection. Obese men commonly have pseudo-gynaecomastia and reduced beard growth. Serum TE_2 and FE_2 were comparable in IHH and non-IHH men; however, the ratio of FE_2/FT in IHH men was more then twice as high as in non-IHH men. At present the clinical impact of the relatively elevated E_2 levels in hypogonadal obese men is not known. We could speculate that it may be beneficial for bone but have adverse effects on fertility.[31-34] The disturbance in E_2/T balance may also affect brain function in general, and sexual as well as nonsexual behaviour in particular.[35-38] The impact that hypogonadism and gonadal hormone therapy may have on the behaviour of obese men could be an interesting new area to explore. Hypogonadal men usually show little initiative, have lack of drive, loss of motivation, and tend to reconcile even in unpleasant situations.[39-41] Adequate treatment of hypogonadism might restore normal male behaviour and drive, which might help dealing successfully with the problem of achieving a relevant degree of weight reduction. Profound improvements of psychopathology have been observed after surgically induced weight loss, but it is not known whether this is related to weight loss per se, or secondary to hormonal changes associated with weight loss.[42]

The observation that many severely obese men have a reduced serum T raises the question whether and when treatment is required, and what should be the most appropriate mode of therapy. Recently published expert panel recommendations state that symptoms of T deficiency become manifest with FT levels between 250 and 180 pmol/l, and there is consensus that FT levels less than 180 pmol/l definitely require treatment.[19] In the present study 21% of the men had FT levels less than 180 pmol/l. The conventional mode of treatment would be androgen-replacement therapy.[43] However, because of the high conversion of T to E_2, T replacement is likely to cause a substantial rise in serum E_2, and this could have adverse somatic and psychological effects. Alternatively, treatment of obesity-related IHH might be achieved by aromatase inhibition. It is a logical choice, considering that increased aromatase activity is a key abnormality in obese men.[44,45] Another approach to treat obesity-related IHH is induction of substantial weight loss, either by low calorie diet or by bariatric surgery. The number of studies evaluating this approach is limited, results are not in full agreement and so far none of the studies were placebo-controlled.[46-50] Although successful weight loss was generally associated with a rise in SHBG and TT, complete normalisation of these parameters did not occur. FT levels often remained unchanged or increased only slightly. Several factors may explain the discrepancies between these studies, including the use of inaccurate hormone assays, differences in degree of caloric restriction, treatment periods, timing of measurements, and the failure to achieve normal body weight in many subjects.

CONCLUSION

This study has shown that many obese men have severely reduced serum T levels of a degree that is likely to have clinical implications. At present we do not know how harmful these reduced T levels are in this specific population, nor whether treatment should be started, and what might be the most appropriate mode of treatment.

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Netherlands
The Journal of Medicine

ORIGINAL ARTICLE

Deteriorating glucose tolerance status is associated with left ventricular dysfunction - the Hoorn Study

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ABSTRACT

Background: Type 2 diabetes (DM2) is associated with a greater risk of heart failure. The mechanisms underlying this association remain controversial and include diabetes-associated hypertension and obesity, impaired small and large artery function, and a distinct metabolic cardiomyopathy related to hyperglycaemia/hyperinsulinaemia. The proximate causes of heart failure are left ventricular (LV) systolic dysfunction (SDF) and diastolic dysfunction (DDF). We investigated, in a population-based cohort (n=746), the association between glucose tolerance status and SDF and DDF.

Methods and results: The study population consisted of 274 individuals with normal glucose metabolism (NGM), 174 with impaired glucose metabolism (IGM) and 298 with DM2 (mean age 68.5 years). All participants underwent an LV echocardiogram. SDF was defined as ejection fraction <55%. DDF was determined by a sum score of peak A velocity (abnormal, ≥97 cm/s), the difference between A_{pv} and A_{mv} duration (≥41 ms), and left atrial volume (≥57 ml), where cut-off values were based upon the 90th percentile in NGM. In addition, we analysed the ratio of early to late diastolic filling (E/A ratio) on a continuous scale using linear regression analyses. The age- and sex-standardised prevalences in NGM, IGM and DM2 were 13, 14 and 30% for SDF, and 26, 36 and 47% for DDF ($P_{(trend)}$ for both <0.001). After adjustment for sex, age, hypertension, body mass index, prior cardiovascular disease and (micro) albuminuria, DM2 was significantly associated with both SDF (odds ratio (95% CI) 2.04 (1.24 to 3.36)) and DDF (2.42 (1.63 to 3.60)) (90th percentile definition). This was also true for the analyses with the E/A ratio on a continuous scale (regression coefficient β (95% CI) -0.05 (-0.09 to -0.01). After adjustment for sex, age, hypertension, body mass index, prior cardiovascular disease and (micro) albuminuria IGM was not significantly associated with SDF (odds ratio (95% CI) 1.04 (0.58 to 1.88)) or DDF (1.33 (0.86 to 2.06)) using the definition based upon the 90th percentile. However, IGM was significantly associated with DDF if the E/A ratio was analysed on a continuous scale (regression coefficient β (95% CI) -0.05 (-0.10 to -0.01). Additional adjustment for brachial artery flow-mediated vasodilation or arterial stiffness, as measures of large artery function, did not materially alter the results. Hyperglycaemia and hyperinsulinaemia together explained ~30% of the association of DM2 with SDF and ~40% of that with DDF.

Conclusion: DM2 is independently associated with a 2.0-fold greater risk of SDF and a 2.4-fold greater risk of DDF. IGM was not associated with SDF, and the association with DDF was limited to the E/A ratio. These observations may therefore explain the increased risk of systolic and diastolic heart failure in elderly individuals with DM2.

KEYWORDS

Cardiovascular disease, diabetes, echocardiography

INTRODUCTION

Type 2 diabetes (DM2) is associated with an increased risk of heart failure.[1-4] The mechanisms underlying this association remain controversial, and there may be at least three possibilities. First, DM2 is often associated with hypertension and obesity, and these risk factors may in part account for the association of DM2 with heart failure.[5-7] Second, DM2 may lead to heart failure by impairing large and small artery function, because DM2 causes atherothrombotic coronary artery disease,[8] diabetic microangiopathy,[9] small and large artery endothelial dysfunction[10,11] and increased arterial stiffness.[12,13] Third, DM2 may cause a distinct metabolic cardiomyopathy related to hyperglycaemia and/or hyperinsulinaemia.[14-16]

The proximate causes of heart failure are left ventricular (LV) systolic and diastolic dysfunction. Previous studies on the association between glucose metabolism and LV function have not yielded consistent results, possibly because these studies were relatively small,[17-27] had targeted selected populations,[18,19,22-24,28] or dealt exclusively with DM2,[17-28] whilst population-based studies focused primarily on LV structure.[29-33] In addition, it is unclear whether LV dysfunction can also be detected in impaired glucose metabolism (IGM), i.e. impaired fasting glucose or impaired glucose tolerance.[29,34-36] The latter is of particular importance as investigations in IGM could give insight into the early development of DM2-related LV dysfunction.

In view of these considerations, we investigated, in a population-based cohort (n=746), the association between deteriorating glucose tolerance status on the one hand and echocardiographically determined LV systolic and diastolic function on the other. In addition, we explored the mechanisms underlying any such associations.

METHODS

Study population

For the present investigation we used data from the 2000 follow-up examination of the Hoorn Study[37] and data from the Hoorn Screening Study,[38] both of which were population-based. Details have been described elsewhere.[13] The entire study population consisted of 822 individuals (290 with a normal glucose metabolism (NGM), 187 with IGM, and 345 with DM2). Glucose tolerance status was determined by a single oral glucose tolerance test according to the 1999 WHO criteria (i.e. NGM: fasting glucose <7.0 mmol/l and post-load glucose <7.8 mmo/l; IGM: fasting glucose ≥7.0 mmol/l and postload glucose ≤11.1 mmol/l; DM2: fasting glucose ≥7.0 mmol/l and post-load glucose >11.1 mmol/l).

Echocardiography

A single ultrasound research technician blinded to the participants' clinical or glucose tolerance status obtained an LV echocardiogram according to a standardised protocol consisting of 2D, M-mode, spectral and colour flow Doppler recordings, with the use of an ultrasound scanner (HP SONOS 5500; 2-4 Mhz transducer, Andover, Massachusetts, USA). 2D recordings were performed in parasternal long- and short-axis views, and apical four- and two-chamber views.[39] Pulsed-Doppler spectral recordings were obtained with the sample volume placed at the tips of the mitral leaflets and, for the pulmonary venous flow, at the orifice of the right upper pulmonary vein. All recordings were digitally stored and analysed off-line according to international guidelines.[39]

We measured left atrial and ventricular diastolic and systolic diameters, and posterior wall (PWT) and interventricular septum thicknesses (IVS) from M-mode. Left atrial and ventricular systolic and diastolic volumes and ejection fraction were calculated from the apical four chamber view using the modified Simpson formula. Left ventricular mass was calculated as 0.8(1.04) $((EDD + IVS + PWT)^3 - EDD^3) + 0.6$ (in grams), and relative wall thickness as $(IVS + PWT)/EDD$. From the transmitral pulsed-Doppler recordings, we obtained peak E and A velocities, the ratio of early to late diastolic filling (E/A ratio) and the deceleration time E. Isovolumetric relaxation time was measured as the time from the end of aortic flow to the onset of mitral flow. From the pulmonary vein pulsed-Doppler recordings, we obtained the pulmonary vein flow A wave duration (A_{pv}) and the duration of the A wave (A_{mv}) over the mitral valve.[40] Each echocardiogram was inspected afterwards by a senior cardiologist blinded to the participants' clinical or glucose tolerance status to monitor quality of both recordings and readings.

Systolic and diastolic LV function

Normal LV systolic function was defined as ejection fraction ≥55%, and LV systolic dysfunction as ejection fraction <55%.[39] Normal LV diastolic function was defined as a sum score of 0 points, and LV diastolic dysfunction as a sum score ≥1 point, on the basis of the sum of three indices of late diastolic function, i.e., peak A velocity (0 points if <97 cm/s, 1 point if ≥97 cm/s); difference between A_{pv} and A_{mv} duration (0 points if <41 ms; 1 point if ≥41 ms); and left atrial volume (0 points if <57 ml, 1 point if ≥57 ml), where the cut-off values were 90th percentile in individuals with NGM. In addition, we analysed the E/A ratio on a continuous scale.

Other measurements

Health status, medical history, medication use and smoking habits were assessed by questionnaire.[37,38] We determined systolic and diastolic pressure, hypertension, glucose, glycated haemoglobin, insulin, serum total, high-density and low-density lipoprotein cholesterol, serum triglycerides, serum creatinine, (micro)albuminuria (as an estimate of (diabetic) microangiopathy), body mass index (BMI), waist-to-hip ratio and ankle-brachial pressure index as described elsewhere.[37,38] Insulin resistance was calculated according to the HOMA model.[41] Resting electrocardiograms were automatically coded according to the Minnesota Code.[15] Hypertension, prior cardiovascular disease and (micro) albuminuria were defined as described previously.[13,42] Endothelial function was estimated from noninvasive brachial flow-mediated vasodilation,[11,43] and central and peripheral artery stiffness from arterial ultrasonography, echocardiography and radial applanation tonometry.[12,13]

Statistical analyses

All analyses were carried out with SPSS (SPSS, Chicago, USA). We used analyses of covariance (ANCOVA), with linear contrast, to investigate trends in left atrial and ventricular mean values across categories of glucose tolerance. All statistically significant trends were tested on whether they deviated from linearity. The associations between glucose tolerance status and LV function were investigated with the use of logistic regression, in which LV dysfunction was classified as absent *vs* present (the 90th percentile definition). In addition, we analysed the E/A ratio on a continuous scale using linear regression analyses. In both these statistical methods glucose tolerance status was defined by dummy variables for IGM and DM2 with NGM as reference category. We first analysed the associations without any adjustments (crude model) and then with adjustments for potential confounders (adjusted models). As LV function is known to be affected by sex, age, hypertension and prior

Table 1. *Characteristics of the study population according to glucose tolerance status*

		Normal glucose metabolism	Impaired glucose metabolism	Type 2 diabetes mellitus	$P_{(trend)}$
No.	m/f	274 (133/141)	174 (86/88)	298 (160/138)	--
Age	years	68.5 ± 6.0	70.0 ± 6.2	66.9 ± 8.2	--
Systolic pressure	mmHg	137 ± 20	144 ± 16	148 ± 20	<0.001
Diastolic pressure	mmHg	75 ± 9	78 ± 9	79 ± 9	<0.001
Pulse pressure	mmHg	62 ± 16	67 ± 13	69 ± 15	<0.001
Mean pressure	mmHg	95 ± 11	100 ± 10	102 ± 11	<0.001
Hypertension	%	56	71	81	<0.001
Antihypertensive medication	%	25	35	51	<0.001
Total cholesterol	mmol/l	5.8 ± 1.0	5.8 ± 1.0	5.5 ± 1.1	0.003
HDL cholesterol	mmol/l	1.5 ± 0.4	1.4 ± 0.4	1.2 ± 0.3	<0.001
LDL cholesterol	mmol/l	3.7 ± 0.9	3.7 ± 0.9	3.5 ± 0.9	0.001
Triglycerides	mmol/l	1.2 (0.9-1.5)	1.3 (1.0-1.8)	1.6 (1.2-2.2)	<0.001
Lipid-lowering medication	%	13	17	20	0.03
Fasting glucose	mmol/l	5.4 ± 0.4	6.1 ± 0.5	7.7 ± 1.7	<0.001
Post-load glucose	mmol/l	5.6 ± 1.1	8.0 ± 1.6	11.7 ± 2.7	<0.001
Glycated haemoglobin	%	5.7 ± 0.4	5.9 ± 0.4	6.6 ± 0.9	<0.001
Fasting insulin*	pmol/l	46.0 (35.0-59.0)	65.5 (49.3-87.5)	83.5 (56.0-113)	<0.001
HOMA-IR*	AU	1.57 (1.16-2.04)	2.53 (1.87-3.19)	3.66 (2.54-5.47)	<0.001
Height	cm	169 ± 9	170 ± 9	169 ± 9	0.99
Weight	kg	75 ± 12	80 ± 13	83 ± 14	<0.001
Body mass index	kg/m²	26.1 ± 3.4	27.9 ± 4.0	28.9 ± 4.2	<0.001
Waist-to-hip ratio	--	0.90 ± 0.09	0.94 ± 0.08	0.96 ± 0.10	<0.001
Prior CVD	%	42	47	53	0.01
Serum creatinine	µmol/l	94.5 ± 14.1	94.8 ± 15.2	94.9 ± 19.5	0.80
(Micro) albuminuria	%	10	14	19	<.001
Smoking	%	15	18	13	0.38
SAC	ml/mmHg	1.1 ± 0.3	1.0 ± 0.3	0.9 ± 0.3	<0.001
Carotid distensibility	10^{-3} kPa^{-1}	12.8 ± 4.2	11.6 ± 4.6	10.5 ± 4.3	<0.001
Brachial FMD#	mm	0.20 ± 0.15	0.19 ± 0.18	0.13 ± 0.17	<0.001

Data are reported as mean ± standard deviation or median (interquartile range). * n=733 as 13 individuals were on insulin therapy.
SAC = systemic arterial compliance (n=695); data on other measures of central and peripheral arterial stiffness have been reported elsewhere.[12,13]
FMD = flow-mediated vasodilation (n=543).[11]

cardiovascular disease (including coronary artery disease), these variables were considered first in the adjusted models. After we had assessed the main effects, interaction terms were used to investigate whether the association between glucose tolerance status and left ventricular function differed according to sex. Individuals with impaired fasting glucose (n=64) and impaired glucose tolerance (n=116) did not significantly differ from each other with regard to any of the analyses and were therefore combined.

Results are expressed as odds ratios with their 95% confidence interval. P values <0.05 were considered statistically significant.

RESULTS

Echocardiographic examinations

Of the 822 participants, 53 did not undergo the full standardised echocardiographic protocol for logistical reasons and in 23, a qualitatively satisfactory echocardiogram could not be obtained either due to a high body mass index (n=20; body mass index of subjects with an echocardiographic examination *vs* those without: 27.3 ± 3.8 kg/m^2 *vs* 36.4 ±7.9; p<0.001) or a poor transthoracic window (n=3). Further analyses were therefore based on 746 individuals (*table 1*).

Glucose tolerance and LV systolic function

Ejection fraction and fractional shortening decreased with deteriorating glucose tolerance status ($P_{(trend)}$ for both <0.001). LV end-systolic volume increased with deteriorating glucose tolerance status ($P_{(trend)}$ = 0.007). The prevalence of LV systolic dysfunction (standardised for age and sex) in NGM, IGM and DM2 was 13, 14 and 30%, respectively ($P_{(trend)}$ <0.001) (*table 2*).

Glucose tolerance and LV diastolic function

The prevalence in NGM, IGM and DM2 of peak A velocity ≥97 cm/s was 10% (by definition), 16 and 22%, respectively; of difference between A_{pv} and A_{mv} duration ≥41 ms, 10% (by definition), 11 and 14%; and of left atrial volume ≥57 ml, 10% (by definition), 14 and 24%. The prevalence of diastolic dysfunction (standardised for age and sex) in NGM, IGM and DM2 was 26, 36 and 47% ($P_{(trend)}$ <0.001). The E/A ratio decreased with deteriorating glucose tolerance ($P_{(trend)}$ = 0.007) (*table 2*).

Odds ratios for LV systolic and diastolic dysfunction

As compared with NGM, DM2 was significantly associated with LV systolic dysfunction (OR (95% CI), 2.44 (1.55 to 3.85)). The association remained statistically significant after additional adjustment for sex, age, hypertension, prior cardiovascular disease, body mass index and (micro)

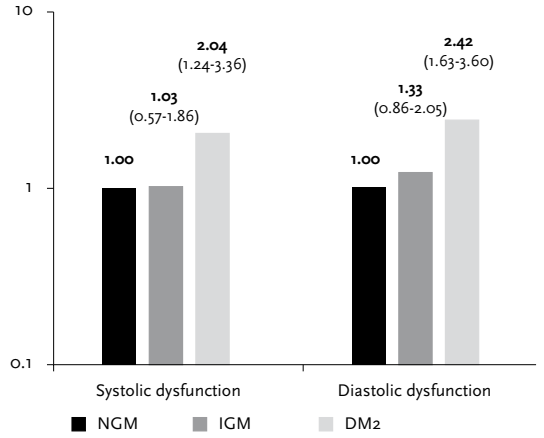
Table 2. *Left ventricular function according to glucose tolerance status*

	Normal glucose metabolism	Impaired glucose metabolism	Type 2 diabetes mellitus	$P_{(trend)}$
Prevalence of left ventricular dysfunction[a]				
Systolic dysfunction (%)	13	14	30	<0.001
Diastolic dysfunction (%)	26	36	47	<0.001
Estimates of systolic function				
Left ventricular end-systolic volume (ml)	38 (1)	38 (1)	42 (1.0)†	0.007
Ejection fraction	0.63 (0.01)	0.62 (0.01)	0.59 (0.01)†‡	<0.001
% of individuals with ejection fraction <55	13	14	30†‡	<0.001
Fractional shortening	46.9 (0.3)	46.5 (0.4)	44.7 (0.3)†‡	<0.001
Estimates of diastolic function				
Peak E velocity (cm/s)	64.7 (1.0)	65.0 (1.3)	69.1 (1.0)†‡	0.002
Peak A velocity (cm/s)	77.0 (1.0)	81.2 (1.3)#	87.2 (1.0)†‡	<0.001
% of individuals with peak A velocity ≥97	10	16#	22†‡	<0.001
E/A ratio	0.87 (0.01)	0.82 (0.02)	0.82 (0.01)†	0.007
Deceleration time E (ms)	244 (3)	237 (4)	241 (3)	0.53
Duration of A_{mv} (ms)	124 (1)	121 (1)	123 (1)	0.70
Duration of A_{pv} (ms)	139 (1)	136 (2)	144 (1)†‡	0.12
% of individuals with A_{pv}-A_{mv} ≥41	10	11	14†‡	0.20
Isovolumetric relaxation time (ms)	130 (3)	132 (4)	138 (3)	0.10
Left atrium volume (ml)	42 (1)	43 (1)	51 (1)†‡	<0.001
% of individuals with left atrium volume ≥57	10	14	24†‡	<0.001
Left ventricular end-diastolic volume (ml)	100 (1)	100 (2)	100 (1)	0.96

Data are reported as mean values (standard error) adjusted for age and sex, whereas the percentages of the individual measurements of left ventrical function were standardised for age and sex, with normal glucose metabolism as reference group. [a] For definitions see methods. †p<0.05 *vs* normal glucose metabolism. ‡p<0.05 *vs* impaired glucose metabolism. #p<0.05 *vs* =normal glucose metabolism.

albuminuria (OR, 2.04 (1.24 to 3.36)). IGM was not statistically significantly associated with LV systolic dysfunction (*table 3* and *figure 1*).
As compared with NGM, DM2 was significantly associated with LV diastolic dysfunction (OR, 2.54 (1.77 to 3.65)). The association remained statistically significant after additional adjustment for sex, age, hypertension, prior cardiovascular disease, body mass index and (micro) albuminuria (OR, 2.42 (1.63 to 3.60)). IGM was not statistically significantly associated with LV diastolic dysfunction after adjustment for hypertension and body mass index.
If we repeated the analyses with peak E, peak A and E/A ratio as continuous variables using regression analyses our results were not materially altered. However, the association between E/A ratio (i.e., a measure composed of both 'early' and 'late' diastolic dysfunction) and IGM reached statistical significance even after adjustment for prior cardiovascular disease and microalbuminuria (regression coefficient β (95% CI) -0.05 (-0.10 to -0.01) and -0.05 (-0.09 to -0.01) respectively (*table 4*; models 6 and 7).

Figure 1. *Adjusted odds ratios and their 95% confidence interval for left ventricular dysfunction across categories of glucose tolerance*



NGM = normal glucose metabolism; IGM = impaired glucose metabolism; DM2 = type 2 diabetes mellitus. NGM served as reference category. Adjustments were made for age, sex, hypertension, body mass index, prior cardiovascular disease, and (micro)albuminuria.

Results were similar when additionally adjusted for brachial flow-mediated vasodilation or measures of central and peripheral arterial stiffness (*table 3*, models 8 to 10).

To estimate the contribution of hyperglycaemia, hyperinsulinaemia and insulin resistance to the association between glucose tolerance status and left ventricular function, we compared the above analyses with those additionally adjusted for HbA1c (or fasting or postload glucose) and for insulin and insulin resistance. This showed that hyperglycaemia and hyperinsulinaemia explained 28% of the association of glucose tolerance with LV systolic dysfunction and 39% of that with LV diastolic dysfunction, with both variables contributing approximately equally (data not shown).

Additional analyses

The results of the logistic regression analyses for LV systolic dysfunction were not materially altered if the cut-off value for ejection fraction was set at 45% (data not shown).
The impact of a deteriorating glucose tolerance status on left ventricular function might be worse in women.[1] However, we found no interaction between DM2 and sex

Table 3. *Adjusted odds ratios for left ventricular dysfunction according to glucose tolerance status*

Model	Added variables	Systolic dysfunction		Diastolic dysfunction	
		Impaired glucose metabolism	Type 2 diabetes mellitus	Impaired glucose metabolism	Type 2 diabetes mellitus
1.	Crude	1.10 (0.62 to 1.95)	2.44 (1.55 to 3.85)	1.63 (1.07 to 2.46)	2.54 (1.77 to 3.65)
2.	Model 1 + sex	1.08 (0.61 to 1.93)	2.43 (1.53 to 3.88)	1.63 (1.07 to 2.46)	2.54 (1.77 to 3.65)
3.	Model 2 + age	1.10 (0.61 to 1.96)	2.38 (1.49 to 3.80)	1.50 (0.98 to 2.29)	2.98 (2.05 to 4.34)
4.	Model 3 + hypertension	1.06 (0.59 to 1.91)	2.22 (1.37 to 3.58)	1.41 (0.92 to 2.16)	2.63 (1.78 to 3.87)
5.	Model 4 + body mass index	1.06 (0.59 to 1.90)	2.13 (1.31 to 3.46)	1.33 (0.86 to 2.06)	2.46 (1.65 to 3.65)
6.	Model 5 + prior cardiovascular disease	1.04 (0.58 to 1.88)	2.08 (1.26 to 3.41)	1.33 (0.86 to 2.06)	2.44 (1.64 to 3.63)
7.	Model 5 + (micro-)albuminuria	1.03 (0.57 to 1.86)	2.04 (1.24 to 3.36)	1.33 (0.86 to 2.05)	2.42 (1.63 to 3.60)
8.	Model 5 + carotid distensibility*	0.98 (0.50 to 1.93)	2.02 (1.15 to 3.52)	1.38 (0.79 to 2.08)	2.20 (1.43 to 3.37)
9.	Model 5 + systemic compliance*	0.89 (0.45 to 1.77)	2.85 (1.67 to 4.84)	1.27 (0.77 to 2.10)	2.48 (1.59 to 3.87)
10.	Model 5 + flow mediated dilation*	1.08 (0.54 to 2.16)	3.26 (1.86 to 5.73)	1.31 (0.80 to 2.14)	2.32 (1.49 to 3.62)

Results are expressed as odds ratios (95% CI). Normal glucose metabolism serves as reference category. *For carotid distensibility: n=724; for systemic compliance: n=612; for flow-mediated dilatation: n=605.

Table 4. *Adjusted β-coefficients for conventional measures of left ventricular diastolic dysfunction*

Model	Added variables	Peak E velocity (cm/s)		Peak A velocity (cm/s)		E/A ratio (--)	
		Impaired glucose metabolism	Type 2 diabetes mellitus	Impaired glucose metabolism	Type 2 diabetes mellitus	Impaired glucose metabolism	Type 2 diabetes mellitus
1.	Crude	-0.05 (-3.31 to 3.21)	4.59 (1.76 to 7.41)	5.67 (2.08 to 9.25)	8.40 (5.29 to 11.52)	-0.07 (-0.12 to -0.03)	-0.03 (-0.08 to 0.01)
2.	Model 1 + sex	-0.00 (-3.21 to 3.20)	4.90 (2.12 to 7.68)	5.73 (2.26 to 9.21)	8.88 (5.86 to 11.90)	-0.07 (-0.12 to -0.03)	-0.04 (-0.08 to 0.01)
3.	Model 2 + age	0.31 (-2.89 to 3.51)	4.53 (1.76 to 7.30)	4.52 (1.22 to 7.82)	10.23 (7.36 to 13.10)	-0.06 (-0.10 to -0.01)	-0.05 (-0.09 to -0.01)
4.	Model 3 + hypertension	-0.07 (-3.29 to 3.15)	4.78 (0.90 to 6.66)	3.90 (0.60 to 7.20)	8.99 (6.03 to 11.94)	-0.06 (-0.10 to -0.01)	-0.05 (-0.09 to -0.01)
5.	Model 4 + body mass index	-0.80 (-4.04 to 2.43)	2.80 (-0.13 to 5.72)	3.26 (-0.75 to 6.59)	8.15 (5.13 to 11.17)	-0.05 (-0.10 to -0.01)	-0.05 (-0.09 to -0.01)
6.	Model 5 + prior cardiovascular disease	-0.62 (-3.88 to 3.12)	2.12 (-0.89 to 5.13)	2.93 (-0.40 to 6.25)	7.30 (4.25 to 10.36)	-0.06 (-0.10 to -0.01)	-0.05 (-0.09 to -0.01)
7.	Model 5 + (micro) albuminuria	-0.82 (-4.06 to 2.43)	2.75 (-0.20 to 5.71)	3.19 (-0.14 to 6.51)	7.89 (4.86 to 10.92)	-0.05 (-0.10 to -0.01)	-0.05 (-0.09 to -0.00)

Results are expressed as β-coefficients (95% CI). Normal glucose metabolism serves as reference category.

(all p values ≥0.13), which means that within our data no significant sex differences existed in the relationship between left ventricular function and glucose tolerance status. Results were not materially altered if we replaced hypertension by any of the other blood pressure variables, or if we replaced body mass index by body surface area or waist-to-hip ratio (data not shown).

The results of the logistic regression analyses for LV diastolic dysfunction were not materially altered if we excluded those with an ejection fraction <45% (n=23) (data not shown).

Results were also similar when additionally adjusted for lipid profile, use of lipid-lowering or antihypertensive medication (including ACE inhibitors), smoking, serum creatinine and LV wall motion abnormalities (data not shown).

If we replaced the P90 cut-off values for LA volume and A_{pv}-A_{mv} wave duration for published cut-off values[44,45] or chose the P95 as cut-off value, our results were not materially altered.

DISCUSSION

This study had four main results. First, as compared with NGM, DM2 was associated with a 2.0-fold greater risk of LV systolic dysfunction and a 2.4-fold greater risk of LV diastolic dysfunction. Second, these higher risks could not be explained by higher blood pressure or greater obesity, which are often observed in DM2, nor by DM2-associated impairment of large and small artery function, as estimated from the prevalence of prior cardiovascular disease and (micro)albuminuria, and from large artery endothelium-dependent vasodilation and stiffness. Third, a considerable part of LV dysfunction in DM2 (about 30 to 40%) was explained by hyperglycaemia and hyperinsulinaemia. Fourth, in this elderly population, IGM was not significantly associated with impaired LV function using the definition based upon the 90th percentile of diastolic dysfunction (DDF) parameters, but was associated with DDF using linear regression analyses with the E/A ratio on a continuous scale. These findings may thus explain why DM2 increases the risk of systolic and diastolic heart failure, and additionally argue in favour of a distinct metabolic cardiomyopathy in elderly individuals with DM2. In elderly individuals with IGM this is less clear.

Our study was comprehensive and had important advantages over previous studies on the association between glucose tolerance and LV function, which were relatively small,[17-27] targeted selected populations,[18,19,22-24,28] or dealt exclusively with DM2[17-28] whilst population-based studies focused primarily on LV structure in relation to LV systolic dysfunction.[29-33]

Our results on systolic dysfunction are in concordance with a study by Celentano *et al.*,[17] who studied 64 telephone company employees, the HyperGen Study[30] and two Strong Heart Study reports.[29,31] However, the Cardiovascular Health Study (CHS),[32] somewhat unexpectedly, did not observe systolic dysfunction in DM2.

Our study is the first to observe a clear association between DM2 and LV diastolic dysfunction in a large (Caucasian) general population-based study, designed to investigate the differences between NGM, IGM and DM2. Previous studies[18,19,22,25,29,32,36] may have failed to detect a consistent association of DM2 with LV diastolic dysfunction because of the use of echocardiographic measures of both *early* and *late* LV diastolic filling (i.e., the E/A ratio) which can be

hampered by the phenomenon of 'pseudo-normalisation' (i.e., an apparently normal LV diastolic filling pattern due to increased LA pressure, as a direct consequence of decreased LV compliance).[46] Interestingly, in our study a significant relationship did exist between the E/A ratio and glucose tolerance status. The reason for this discrepancy is not clear. However, to further overcome the phenomenon of pseudo-normalisation, we also analysed measurements of *late* diastolic performance (i.e., peak A velocity, A_{pv}-A_{mv} duration and LA volume) and combined these into a simple sum score, which has the advantage of excluding active myocardial relaxation during diastole[46] and thus providing optimal characterisation of passive stiffness of the LV chamber.

The mechanisms linking DM2 to systolic and diastolic LV dysfunction are incompletely understood. We found no evidence that DM2-associated hypertension and obesity played a role. In addition, our data do not support an important role for DM2-induced impairment of large and small artery function. However, the validity of this conclusion depends on the accuracy of the estimates of arterial function we used. For example, we used brachial artery endothelium-dependent vasodilation and (micro) albuminuria as estimates of coronary epicardial and microvascular function, respectively, and this may be insufficiently precise. Therefore, future studies to address these issues should use more sophisticated techniques.

Interestingly, indices of hyperglycaemia and hyperinsulinaemia (or insulin resistance) explained about 30 to 40% of the association between DM2 and LV dysfunction, supporting the existence, in these elderly individuals, of a distinct metabolic cardiomyopathy.[14,47,48] Hyperglycaemia and hyperinsulinaemia may impair LV function through several pathways, the relative importance of which is not completely understood. First, hyperglycaemia alters intracellular calcium homeostasis, leading to depressed contractile function.[49,50] Second, hyperglycaemia increases oxidative and carbonyl stress,[51] which may lead to a chronic, low-grade inflammatory response and cross-linking of myocardial proteins, which may promote myocardial fibrosis and impair LV compliance, effects that may be enhanced by the growth promoting properties of hyperinsulinaemia.[52,53]

It is not known whether IGM is independently associated with risk of heart failure. In our study, IGM was not associated with systolic dysfunction, and the association with diastolic dysfunction (based upon the 90th percentile definition) was explained by body mass index and hypertension. However, the association between IGM and DDF estimated from the E/A ratio remained after multivariate adjustment. Therefore, we conclude that IGM was associated with DDF but not with SDF.

Our study had several limitations. First, we cannot exclude that our results have been influenced by the co-existence of (subclinical) cardiovascular disease affecting both LV wall motion and shape. To address this concern, we adjusted for prior cardiovascular disease in our statistical analyses. Moreover, our results were not materially altered when additionally adjusted for wall motion abnormalities (data not shown). Second, our results were obtained in elderly individuals. Therefore, we may have underestimated the association of LV dysfunction with glucose tolerance due to a healthy survivor effect. Finally, as our study was cross-sectional in nature, causality should be inferred with caution and it remains to be determined whether our results can be generalised to other ethnicities.

We conclude that DM2 is independently associated with a 2.0 greater risk of LV systolic dysfunction and a 2.4 greater risk of LV diastolic dysfunction. This may explain the increased risk of systolic and diastolic heart failure in elderly individuals with DM2.

ACKNOWLEDGEMENT

This study was supported by the Netherlands Heart Foundation (grant 98154).

The authors are indebted to M.R.F.T. van Eijck-Weel for excellent assistance in both the echocardiography as well as the logistics of the study.

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Netherlands
The Journal of Medicine

CASE REPORT

Goitre and hearing impairment in a patient with Pendred syndrome

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ABSTRACT

A case is described here of a young euthyroid woman with a goitre and hearing impairment. Perchlorate discharge test showed increased washout of iodine. Genetic analysis confirmed the diagnosis of Pendred syndrome as a mutation in the *Pds* gene was found. The patient was treated with potassium iodine orally. During follow-up there where no symptoms of hyperthyroidism and the size of the goitre decreased.

KEYWORDS

Deafness, goitre, Pendred syndrome, thyroid dysfunction

INTRODUCTION

The classical triad of Pendred syndrome is congenital sensorineural hearing impairment, goitre and impaired iodine organification with an abnormal perchlorate discharge test. Pendred syndrome is the most common diagnosis in syndromal hearing impairment with an incidence of 7.5 to 10 per 100,000 people. Magnetic resonance imaging of the inner ear shows malformations of the vestibular aqueduct and endolymphatic sac. The prevalence of Pendred syndrome in the Netherlands and the optimal therapy is unknown. This autosomal recessive syndrome is not often seen by the internal medicine specialist.

CASE REPORT

A 30-year-old woman visited our outpatient clinic because of a visible goitre. She reported hearing impairment since childhood. Overall she felt well. Her menses were regular and there were no symptoms of thyroid dysfunction.

When she was 14 years old she had a thyroid operation (excision of part of the goitre) in another hospital because of enlarging of a goitre with cosmetic complaints. She was euthyroid at that time and using a Kocher's incision two cystic nodules were removed. Pathological examination showed two dysplastic nodules of follicular thyroid tissue. The follicles were full of colloid. No necrosis, inflammation or malignancy were seen. Her mother also had a goitre, but no hearing problems. She has a healthy daughter aged 2 years. There were no other family members with thyroid diseases or hearing problems.

Physical examination showed a woman with a scar in her neck from the previous thyroid operation. Her body mass index was 20 kg/m^2 and she had no signs of hypothyroidism or hyperthyroidism. She had a visible goitre. The thyroid was enlarged and felt weak with multiple palpable nodules (thyroid diameter 8 x 6.5 cm).

Laboratory tests showed a free thyroxine (T_4) level of 9.9 pmol/l (normal value 9 to 20 pmol/l) and a thyroid-stimulating hormone level of 2.5 mU/l (normal value 0.15 to 5.0 mU/l).

An X-ray of the trachea showed mild narrowing of the trachea at the level of the first thoracic vertebra with mild impression from the left side. An ultrasound of the thyroid showed multiple nodules in the left and right part of the thyroid (diameters 2.6, 2.3, 1.6 and 1.3 cm). A thyroid scintigraphy with 3.8 MBq of I^{123} was performed with imaging at 20, 60 and 90 minutes after administration of the iodine. This showed an enlarged thyroid with homogeneous uptake (*figures 1* and *2*). Sixty minutes after the iodine administration, 600 mg of perchlorate was administered and the washout was measured (perchlorate discharge test). Both the uptake and washout were increased. Increased discharge points to an organification defect as in Pendred syndrome, as is mentioned below in the discussion.

Figure 1. *Thyroid scintigraphy after iodine-123 showed homogeneous uptake*

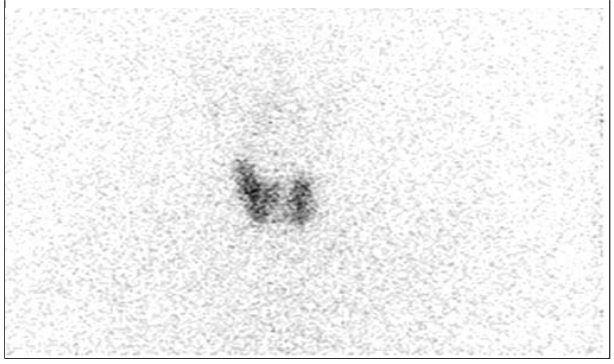
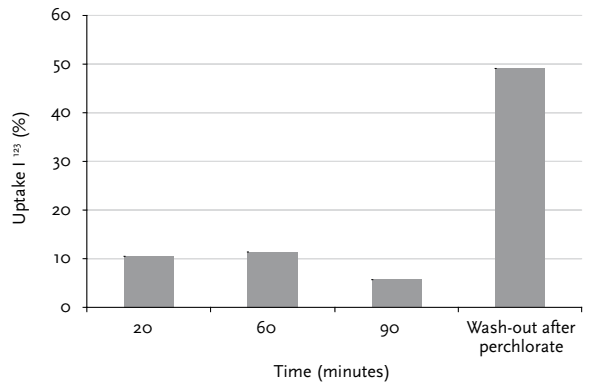


Figure 2. *Uptake measured during 20, 60 and 90 minutes follow-up*



After 60 minutes 600 mg of perchlorate was administered. A washout above 10% is suggestive of Pendred syndrome.

Molecular genetic testing showed two pathogenic mutations in the Pendred gene (SLC26A4). There was a mutation in exon 6 c.707T>C (Leu236Pro) and in intron 8 c.1001+1G>A. This confirmed the diagnosis of Pendred syndrome. She was treated with oral potassium iodine 2 mg twice daily. Two years later she was doing well and had no symptoms. She was taking oral potassium chloride, and her thyroid levels were within the normal range and the size of the goitre decreased.

DISCUSSION

Pendred syndrome was clinically recognised and concisely described in 1896 by the English general practitioner Vaughan Pendred (1869-1946).[1] A century later in 1997 Coyle and colleagues discovered the gene for Pendred syndrome.[2] This gene is located on the long arm of chromosome 7. Until now, more than 80 mutations in the *Pds* gene have been described, mostly missense mutations, but also truncations.

Pendred syndrome is an autosomal recessive disease on the base of a mutation of the PD gene (*Pds*), region SLC26A4. The *Pds* gene encodes 12 exons which forms a protein called pendrine. This protein acts as a chloride-iodine co-transporter and is expressed in the thyroid, inner ear and kidney. This transporter is closely related to a number of sulphate transporters. Pendrine functions as an ion transporter, located on the apical membrane of the thyrocytes. This transporter is responsible for the transport of iodine out of the cell into the colloid where iodination of thyroglobulin occurs. In the absence of the transporter, iodine is taken up normally by the thyrocyte, but is not efficiently bound to thyroglobulin in the colloid. A mutation of the pendrine gene gives less transport of iodine to the exocytic vesicles, in which thyroid hormone is formed, and results in impaired organification of thyroglobulin. Goitre is the most variable symptom in Pendred syndrome and is caused by impaired thyroxin production because of an organification defect. Goitre prevalence is dependent of the daily iodine intake and is, for example, seldom seen in Japan, where the daily iodine intake is high. Most patients have normal thyroid levels, but some have signs of subclinical of clinical hypothyroidism. In the kidneys, pendrine is expressed in the cortical collecting ducts and acts as a chloride-bicarbonate exchanger. However, no metabolic changes (acidosis or alkalosis) are described in patients with Pendred syndrome. Pendrine is expressed in the inner ear for regulation of the endolymphatic fluid composition. The pathophysiological mechanism of the hearing impairment is unclear. In mice knocked out for the *Pds* gene an abnormal endolymphatic duct and sac dilatation are described on the 15th embryonic day, but these mice have no goitre.[3] Magnetic resonance imaging can show dysplasia of the cochlea and vestibular aqueduct in patients with Pendred syndrome (Mondini deformity).

The perchlorate discharge test is used to diagnose Pendred syndrome. The sensitivity of this test is unknown and the test is not specific. Patients have to follow an iodine-restricted diet for two weeks. For the test iodine (I^{123}) is given orally followed by 600 mg perchlorate intravenously after which the discharge is measured. Perchlorate inhibits NIS function (sodium iodine symporter) eliminating the iodine gradient which is required for maintaining the iodine in the gland. The exit (washout/discharge) of more than 10% of the thyroidal radioiodine within two hours of administration of the perchlorate suggests on organification defect as in Pendred syndrome. The rationale for treatment with potassium iodine is that extra iodine may compensate for the insufficient iodine handling of the thyroid in Pendred syndrome.

CONCLUSION

In this case report we describe the history of a young woman with goitre and hearing impairment with an impaired perchlorate washout test. Genetic testing confirmed the diagnosis of Pendred syndrome with a mutation in the *Pds* gene. She underwent surgery in childhood that was perhaps unnecessary and is now treated with potassium iodine. After starting the therapy the goitre decreased in size.

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CASE REPORT

A young woman with a severe bilateral pneumonia as the presenting sign of an adrenal carcinoma

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ABSTRACT

A severe bilateral, culture-negative pneumonia was diagnosed in a 22-year-old woman. Additional diagnostic procedures accidentally revealed a large adrenal carcinoma and hypercortisolism. The adrenal carcinoma was surgically removed, and she received mitotane treatment. This severe and life-threatening infection was the first sign of an immunosuppressive state as part of Cushing's syndrome due to the adrenal carcinoma.

KEYWORDS

Adrenal carcinoma, Cushing's syndrome, pneumonia

CASE REPORT

A 22-year-old woman presented with high fever (>40°C) and progressive dyspnoea, pleurodynia, and abdominal pain for four days. Her medical history was uneventful and she did not complain of cough or sputum production. Physical examination revealed a high respiratory frequency of 40 breaths/min, blood pressure 160/80 mmHg, and a regular heart rate at 104 beats/min. Augmented breathing sounds were heard at the left basal lung fields. Blood tests revealed leucocytosis (16.1 x 10^9/l), and an elevated C-reactive protein (CRP) (516 mg/l). A chest X-ray showed a left-sided infiltrate with pleural effusion.

A community-acquired pneumonia was suspected and treatment was initiated with intravenous amoxicillin (1 gram, four times/day). However, her clinical condition deteriorated and she had to be transferred to the intensive care unit for assessment of potential ventilatory support. Multiple microbiological tests did not demonstrate the causative pathogen: blood cultures (4x) and pleural effusion cultures were negative. There were no signs of tuberculosis. Legionella testing of the urine was negative.

With time, she gradually recovered with an adjusted antibiotic regimen (amoxicillin-clavulanate 1000/200 mg four times/day, erythromycin 500 mg four times/day and rifampicin 600 mg three times/day), and intermittent drainage of the pleural effusion. Computed tomography (CT) showed a bilateral pneumonia with pleural effusion (*figure 1A*). Accidentally, this scan also revealed a large tumour (∅ 12 cm) of the left adrenal gland, highly suspicious for malignancy because of its size and vasoinvasive growth into the renal vein (*figure 1B*).

Hereafter, additional questioning of the patient revealed a progressive increase in weight over the last years, accompanied by irregular menstrual periods, muscle weakness, tiredness, emotional changes (e.g. confusion, agitation), and a loss of libido. A more focused physical examination indeed showed signs of centripetal obesity, with a 'buffalo hump' and 'moon-face'. These findings were accentuated when compared with previous pictures provided by the patient (*figure 2*).

Cushing's syndrome was suspected and additional tests were therefore performed (*table 1*). The test results were indicative of an excess in cortisol production: fasting morning plasma cortisol concentration and free urinary cortisol excretion in 24-hour samples were

Figure 1. *CT scan of A) thorax: bilateral pneumonia with pleural effusion and B) abdomen: a large tumour (12 cm) in the left adrenal gland, with growth into the renal vein*

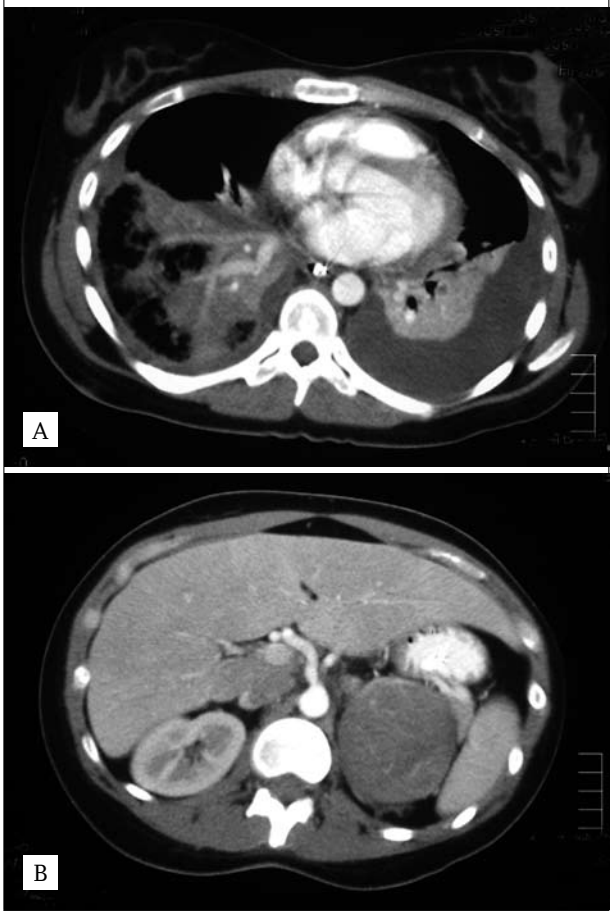
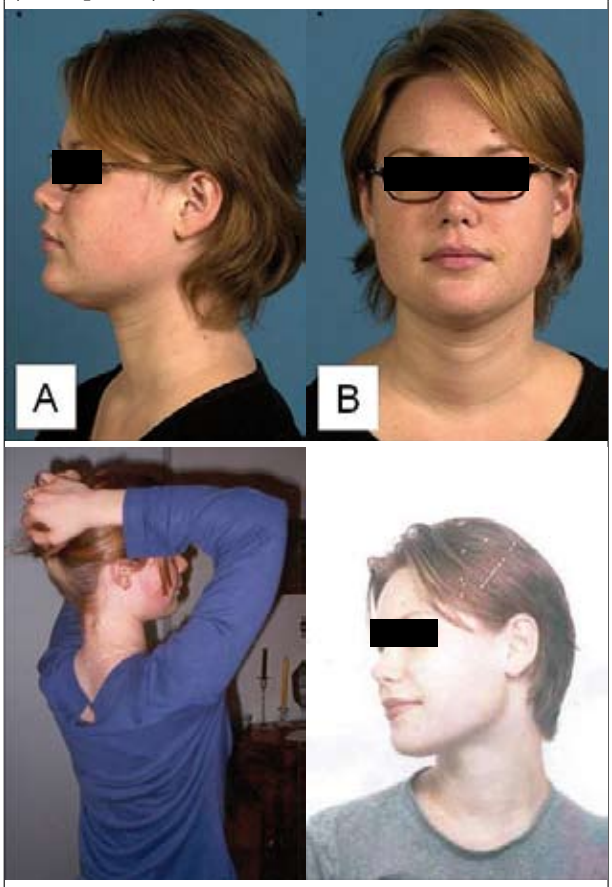


Figure 2. *Pictures of the patient during admission (upper panels), and two years before presentation (lower panels)*



A marked centripetal obesity is noted with a 'buffalo hump' (A) and 'moon-face' (B). Published with permission of the patient.

Table 1. *Biochemical tests demonstrating ACTH-independent hypercortisolism in a young woman with a severe pneumonia and a left adrenal mass*

Test	Result	Reference value
Plasma cortisol*	1.0 µmol/l	(0.22-0.50 µmol/l)
Plasma ACTH*	<4 ng/l	(4-55 ng/l)
24-hour urine cortisol excretion	1072 nmol/24 h	(<220 nmol/24 h)
Plasma cortisol* after *low* dose (1 mg) dexamethasone overnight	0.64 µmol/l	(< 0.1 µmol/l)
Plasma cortisol** after *high* dose (8 mg) dexamethasone i.v.	0.56 µmol/l delta 0.13 µmol/l	(delta >0.19 µmol/l)

***Sober concentration at 09.00 hours. ****Cortisol concentration at 16.00 hours, 7 hours after iv dexamethasone; 'delta' indicates difference between this measurement and the initial measurement of 09.00 hours.**

both elevated. Moreover, adrenocorticotropic hormone (ACTH) concentrations were undetectable. Cortisol concentrations were insufficiently suppressed after administration of dexamethasone (low and high dose), indicative of an ACTH-independent and thus adrenal source of the hypercortisolism. No clinical or biochemical evidence was found for pheochromocytoma or primary hyperaldosteronism.

The patient was referred to a university hospital for adrenalectomy. Histopathologically, an adrenal carcinoma was confirmed. After surgery, she was treated with a daily dose of 2 gram mitotane® (Ortho-para-dichlorodiphenyl dichloroethane (o,p'DDD), divided into four doses a day. She recovered completely. After three years she underwent repeat surgery for a lymph node metastasis; the resection sites were free of tumour. This time, she decided not to

take the mitotane due to severe side effects. Eighteen months later, MRI showed no signs of metastasis and she feels well.

DISCUSSION

This case illustrates a rare cause of a severe and life-threatening bilateral culture-negative pneumonia in a young woman. It demonstrates that a severe clinical course may be indicative of the presence of an immunodeficient state (e.g. haematological disorders, HIV, glucocorticoid excess). In the case presented, an adrenal carcinoma with Cushing's syndrome was the cause of the immunosuppressive state.

Cushing's syndrome

Cushing's syndrome is a synonym for hypercortisolism.[1] This excess production of cortisol can be due to ACTH-dependent (approximately 80% of the cases), or ACTH-independent causes.[2,3] *Table 2* summarises the causes, and their relative prevalence. The incidence of Cushing's syndrome as a result of adrenal carcinoma is very low (0.2 to 2 per million per year), and predominantly in the elderly.[4-6]

The presenting symptoms depend on the severity and duration of exposure to increased glucocorticoid concentrations. The diagnosis is initially often difficult, as the onset is gradual and the disease usually manifests with constitutional symptoms such as tiredness and headache. As the disease progresses, an increase in weight, progressive fatigue, and emotional liability occurs in the majority of the patients; in females, oligomenorrhoea or amenorrhoea, with hirsutism is almost mandatory. A concomitant weight loss is rare and is indicative of a malignant cause of the disease. At physical examination attention should be focused on the presence of hypertension, skin abnormalities (e.g. striae, acne, spontaneous haematoma, yeast infections), signs of centripetal obesity, proximal muscle weakness, and signs of hirsutism and virilisation.

The diagnosis is confirmed by biochemical tests: multiple screening tests in combination with plasma ACTH measurements, followed by a high-dose dexamethasone suppression test (see also *table 1*).[7,8]

These tests are important, as imaging techniques (such as CT and MRI) relatively often show 'incidentaloma' of the pituitary and of the adrenal glands (10 and 5%, respectively), without hypercortisolism.[9,10]

An increase in the rate of infections, even opportunistic ones, is the result of inhibition of the immune system that accompanies glucocorticoid excess.[11] The exact mechanism is unknown, but it seems that inhibition of CD4+ lymphocytes and cytokines plays an important role.[12,13] Several case reports have addressed severe infections as the primary symptom of hypercortisolism.[14,15] Therefore, these cases and the one we presented should be considered as an immunological endocrine emergency.

Untreated Cushing's syndrome is usually fatal as a result of thromboembolic, infectious, or hypertensive complications. At present, specific treatment is available for almost all causes, as depicted in *table 2*. For adrenal carcinoma, adrenalectomy is the therapy of choice followed by adjuvant mitotane (Ortho,para,dichlorodiphenyl dichloroethane (o,p'DDD) treatment.[16] Mitotane will completely block adrenal hormone synthesis, and therefore suppletion of glucocorticoids and mineralocorticoids is necessary. Prognosis depends on age and the presence of metastasis. Five-year survival rates differ per study, but are on average 20%.[17]

Table 2. *Causes of Cushing's syndrome [1] (excluding exogeneous supply of glucocorticoids) and their relative prevalence*

ACTH dependent	**Prevalence**
ACTH hypersecretion by corticotrophic adenoma in pituitary gland (= Cushing's disease)	68%
Ectopic ACTH secretion	12%
ACTH independent	
Adrenal adenoma	10%
Adrenal carcinoma	8%
Bilateral micro- or macro-nodular adrenal hyperplasia	1%
Pseudo Cushing's	
Alcoholism; depressive disturbances	1%*

*In our experience, the incidence of pseudo Cushing's seems higher when looking systematically for it.

CONCLUSION

In the present case, a severe bilateral pneumonia in a young woman was the result of the immunosuppressive state as a part of the Cushing's syndrome related to an adrenal carcinoma. This case illustrates that it is mandatory to find an explanation for a severe infection in young people. It can be the first sign of an underlying immunosuppressive state based on more rare causes, such as an adrenal carcinoma.

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CASE REPORT

Progressive renal disease despite immunosuppressive therapy in a patient with Wegener's granulomatosis

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ABSTRACT

We present a patient with Morbus Wegener and crescentic glomerulonephritis. Treatment with cyclophosphamide and prednisolone resulted in the disappearance of signs and symptoms of systemic inflammation. However, renal function deteriorated. Renal biopsy showed evidence of continuing capillary necrosis. Renal function improved with added plasmapheresis treatment. This case report illustrates that in patients with vasculitis necrotizing glomerulonephritis may remain active despite immunosuppressive therapy, even in the absence of extrarenal disease activity.

KEYWORDS

Crescentic glomerulonephritis, M. Wegener, vasculitis

INTRODUCTION

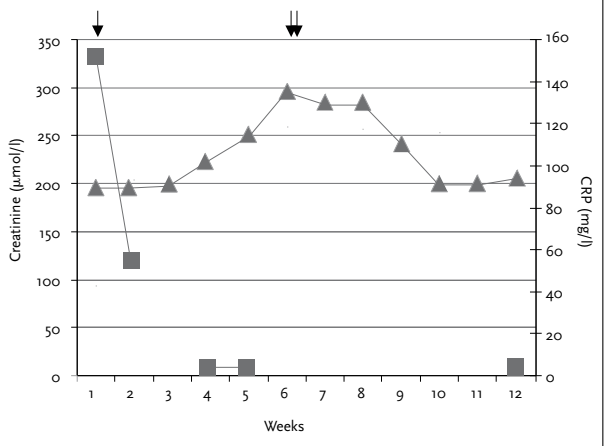
Wegener's granulomatosis is a rare disease characterised by a small vessel vasculitis in which classically the upper respiratory system, the lungs and the kidneys are involved. Renal involvement typically presents as a rapidly progressive glomerulonephritis with high morbidity and mortality.[1] Immunosuppressive therapy, if started early in the course of the disease, has improved the clinical outcome.[2] Antineutrophil cytoplasmic antibodies (ANCA) have become a valuable tool in the diagnosis of the vasculitides. A majority of patients with Wegener's granulomatosis show positive cytoplasmic ANCAs (cANCAs), which are directed against proteinase 3, a constituent of the azurophilic granules in the leucocyte. A minority of patients have antimyeloperoxidase antibodies, which provide a perinuclear ANCA staining pattern on immunofluorescence (pANCA) or even no ANCA.[3] The presence of cANCAs in a patient with upper respiratory tract symptoms and a nephritic syndrome may justify the start of immunosuppressive therapy without confirmation of glomerulonephritis by biopsy. However, a renal biopsy may be invaluable to monitor renal disease activity during treatment.

CASE REPORT

A 65-year-old male was seen three years earlier by an ear-nose-throat specialist because of extensive crusts in the nose with nasal catarrh. A biopsy specimen showed inflammation without granulomas. No specific therapy was provided. Two years later he had developed a saddle nose deformity and was referred to an internist. He had no symptoms, especially no fever, weight loss, dyspnoea or coughing. On examination he was 1.76 meter in height, 79 kg in weight and healthy looking. Further examination was unremarkable, except for the saddle nose deformation. Serum creatinine was 85 µmol/l, C-reactive protein was negative, and haemoglobin and lactate dehyrogenase (LDH) were within the normal range. ANCA was positive with a cytoplasmic pattern on immunofluorescense and positive in ELISA against proteinase 3. Urinalysis was unremarkable. Because of the apparent inactivity of the disease no specific treatment was instituted. One year later he presented with arthralgias, malaise and nose bleeding. There were no pulmonary symptoms. This time his blood pressure was elevated (180/90 mmHg) with a pulse of 90

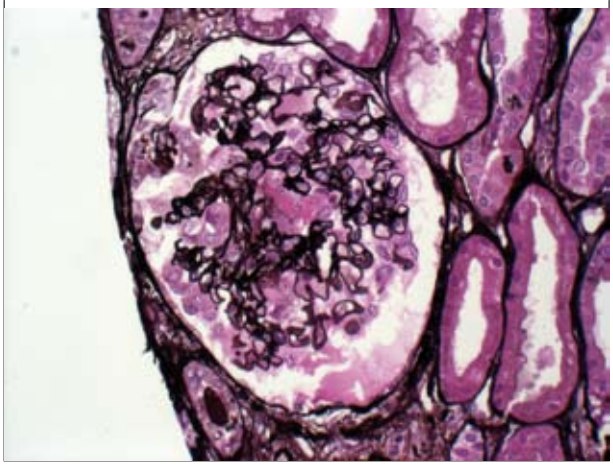
beats/min; he had blood in his nostrils and his left eye showed a conjunctivitis. Laboratory findings showed a normocytic anaemia (Hb 6.6 mmol/l), a raised creatinine of 195 µmol/l and C-reactive protein of 140 mg/l. The alkaline phosphatase was 237 U/l, the LDH 466 U/l and cANCA was positive in a titre of 16. Urinalysis showed red blood cell casts. The chest X-ray was unremarkable. A nose biopsy revealed nonspecific inflammation without granulomas. Active Wegener's granulomatosis was diagnosed and therapy was started, consisting of oral prednisolone 60 mg/day, cyclophosphamide 150 mg/day and trimethoprim-sulphamethoxazole (1:5) 480 mg/day (*Pneumocystis carinii* prophylaxis). His symptoms improved and laboratory parameters such as C-reactive protein, alkaline phosphatase and LDH normalised. In contrast, his renal function deteriorated (*figure 1*). Urinalysis showed red blood cell casts. The initial increase in serum creatinine was considered compatible with inhibition of tubular secretion of creatinine by trimethoprim, but the continuing rise prompted a renal biopsy six weeks after the start of therapy. The renal biopsy showed many glomeruli with fibrosing lesions such as fibrous and fibrocellular crescents. However, one glomerulus showed a recent capillary wall necrotising lesion characterised by an interruption of the glomerular basement membrane and fibrinous exudate in Bowman's space (*figure 2*). Because of the ongoing active renal disease plasma exchange was added to the oral therapy. Hereafter renal function improved and remained stable during follow-up (*figure 1*).

Figure 1. *Serial measurements of creatinine (triangles) and C-reactive protein (squares) before, during and after therapy*



↓Start of immunosuppressive therapy. ↓↓Start of plasma exchange (10 cycles).

Figure 2. *Glomerulus showing recent capillary wall necrosis with fibrinous exudates*



DISCUSSION

Our patient illustrates the typical presentation of Wegener's granulomatosis. Sometimes ear, nose and throat symptoms exist for years before systemic disease develops and the diagnosis is made. Our patient had nonspecific symptoms, upper respiratory symptoms and conjunctivitis. The renal manifestations with red cell casts and rapid deterioration of renal function were compatible with an extracapillary glomerulonephritis. Additionally, he developed ocular problems. Furthermore there was a normocytic anaemia, and an increased alkaline phosphatase, LDH, and C-reactive protein. Importantly cANCA with proteinase 3 specificity was present. The clinical findings in combination with the presence of the cANCA supported the conclusion that the patient was suffering from Wegener's granulomatosis. It has been established that the combination of a positive cANCA (indirect immunofluorescence) and antiproteinase 3 (ELISA) together with a systemic vasculitis provides a high sensitivity (98%) and a good specificity (73%) for Wegener's granulomatosis.[3] These specificity and sensitivity figures were used by Jennette and co-workers to estimate positive predictive values of ANCA for pauci-immune crescentic glomerulonephritis from data on more than 4000 patients who had undergone a renal biopsy. A positive ANCA in older patients (>50 years) with a rapidly progressive glomerulonephritis was extrapolated to give a positive predictive value of 99% for a pauci-immune glomerulonephritis. In elderly patients with haematuria, proteinuria and a serum creatinine between 130 to 265 µmol/l (as in our patient) the positive predictive value for a pauci-immune glomerulonephritis was 85%.[4] We felt supported by these data to start immunosuppressive therapy without performing a renal biopsy.

In our patient, the vasculitic disease activity seemed to disappear after one week of therapy. His symptoms resolved and the laboratory findings normalised except for

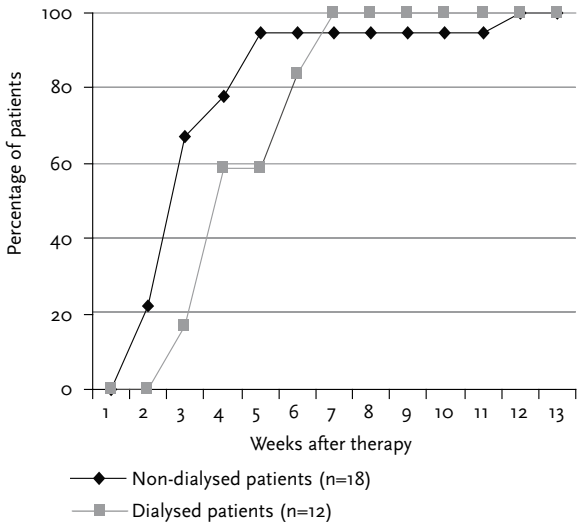
renal function. At this point we considered that the renal dysfunction could be the result of ongoing vasculitic renal activity, the effect of trimethoprim on creatinine secretion or of an intercurrent renal disease such as drug-induced tubulointerstitial nephritis. Because of his improvement in well-being and normalisation of all the other parameters we waited six weeks before performing a renal biopsy. The biopsy disclosed active glomerular cellular damage. The patient was successfully treated with ten cycles of plasma exchange. This response supports the conclusion of the biopsy and also confirms the suggested efficacy of plasma exchange when used in addition to conventional therapy in patients with severe renal disease. A pooled analysis of small studies already suggested potential benefit of plasma exchange in patients with severe renal failure.[5,6] The efficacy of plasma exchange has been proven in a recent randomised controlled trial. In this study (MEPEX) patients with ANCA-associated vasculitis and serum creatinine concentration >500 μmol/l were randomised to plasmapheresis *vs* methylprednisolone added to standard immunosuppressive therapy from the start of therapy. The results showed that renal function recovered more often in patients treated with plasma exchange than in patients treated with intravenous methylprednisolone.[7]

Reviewing our case we wondered what the optimal time for the biopsy would have been. In other words, roughly how long does it take before renal function improves after starting treatment? Therefore, we retrospectively analysed the data of our patients with biopsy-proven extracapillary proliferative glomerulonephritis treated with immunosuppressive therapy.

For the patients who responded to treatment (defined as a decrease in serum creatinine >25% or the end of dialysis treatment) we noted the time at which renal function improvement became noticeable (*figure 3*). The group of responders consisted of 14 males and 16 females with a mean age of 58 years. All patients received immunosuppressive therapy, while five patients were additionally treated with plasma exchange. Approximately one third of our patients needed dialysis treatment. In these patients a response was noted within five to six weeks, while in the nondialysed patients renal function improved within three to four weeks in all but one. Applying these results to our patient, we should have performed the biopsy no later than three weeks after starting treatment.

Obviously we cannot prove that our patient responded to plasma exchange. Our patient did not fulfil the criteria of the MEPEX study. It is not known whether renal activity is present in patients who respond to therapy, and we cannot even exclude that a later response might have occurred. However, in our retrospective study cohort all patients but one demonstrated an improvement in renal function within three weeks after starting therapy. The renal biopsy showed capillary wall necrosis, which was estimated to be less than two to three weeks old. Taken together, we felt that a wait and see policy would have increased the likelihood of more persistent kidney damage.

Figure 3. *Time to improvement of renal function after start of immunosuppressive therapy in patients with extracapillary proliferative glomerulonephritis*



In conclusion: in patients with ANCA-associated vasculitis, renal injury (necrotising glomerulonephritis) can persist despite adequate immunosuppressive therapy with prednisolone and cyclophosphamide, and should be considered even if extrarenal disease activity improves. If renal function does not improve within three weeks, a renal biopsy should be performed. In patients with vasculitis and active renal disease, addition of plasmapheresis therapy must be considered.

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The Journal of Medicine

PHOTO QUIZ

Pituitary failure due to postpartum DIC: reversible diabetes insipidus and hypogonadism

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CASE REPORT

A 30-year-old female presented with vulvar haematoma, hypertension and pancytopenia which developed immediately after childbirth. She developed polyuria in the first week after delivery and did not have any lactation. On examination, she had a 4 x 5 cm vulvar haematoma and minimal vaginal bleeding, and no signs of adrenal insufficiency. Her laboratory results were as follows: creatinine 1.3 mg/dl, aspartate transaminase 97 U/l, alanine transaminase 52 U/l, lactate dehydrogenase 680 U/l, indirect bilirubin 35.2 µmol/l, haemoglobin 5.4 mmol/l, platelets 72 x 10^9/l, leucocytes 4.7 x 10^9/l, prothrombin time 23.7 sec (11 to 14.5), activated prothrombin time 53.8 sec (24 to 40), international normalised ratio 2.18, fibrinogen 4.7 µmol/l (5.88 to 11.76), D-dimer 37.45 µg/ml (0 to 0.5), and fibrin degradation products 20 µg/ml (0 to 5). Her blood sodium was 146 mmol/l, with a plasma glucose of 5.8 mmol/l, plasma osmolality of 305 mmol/kg, simultaneous urinary density of 1007 and urinary osmolality of 244 mmol/kg. Because of her critical state, a water deprivation test was not performed. Her anterior pituitary function was within the normal limits, except for low levels of gonadotropins, with low levels of oestradiol. T1-weighted sellar magnetic resonance images (MRI) showed an enlarged and hyperintense pituitary gland that was interpreted as a haematoma.

Her polyuria, which improved with nasal desmopressin, resolved in the following days and there was no further need for treatment (*table 1*).

Table 1. *Anterior pituitary functions at initial diagnosis and after one year*

	Initial	First year
Follicle-stimulating hormone (3-14 IU/l)	0.21	6.65
Luteinising hormone (2.4-12.6 IU/l)	0.01	4.1
Prolactin (165-1008 µg/l)	560	656
Oestradiol 2 (99-881 pmol/l)	73.4	73.4
Thyroid-stimulating hormone (0.35-4.94 mIU/l)	0.692	2.659
Free thyroid hormones 3 (27.7-73.9 pmol/l)	20.2	52.7
Free thyroid hormones 4 (9-24.5 pmol/l)	11.8	12.5
Adrenocorticotrophic hormone (0-26.4 pmol/l)	3.74	3.1
Cortisol (138-635 nmol/l)	422	469
Growth hormone (0.06-5 µg/l)	0.89	0.43
Insulin-like growth factor (15.7-65.5 nmol/l)	8.5	6.6

WHAT IS YOUR DIAGNOSIS?

See page 130 for the answer to this photo quiz.

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PHOTO QUIZ

Small black spots in the stomach and duodenum

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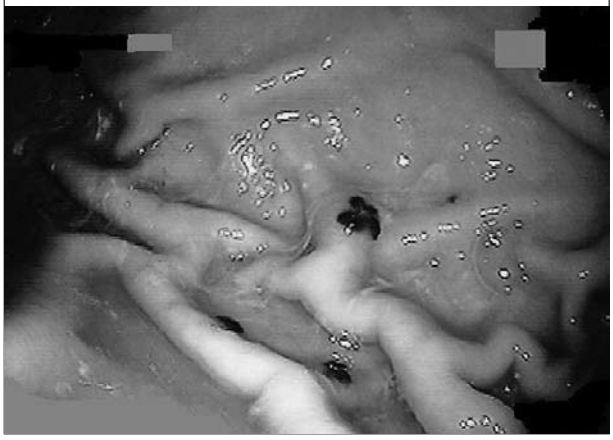
CASE REPORT

A 40-year-old female was admitted to our hospital due to nausea, vomiting, marked weight loss, and dull upper abdominal pain lasting for two months. Her past medical history was unremarkable, but prior to her admission she had taken a proton pump inhibitor, which did not relieve her symptoms. Her physical examination was normal but she was pale; a complete blood count revealed anaemia (haemoglobin 4.9 mmol/l) and an upper gastrointestinal endoscopy disclosed multiple small black spots extending over the whole stomach (*figure 1*) and duodenum. Histopathological examination of these lesions showed tumour infiltration in the gastric lamina propria containing cytoplasmic black pigment (*figure 2*).

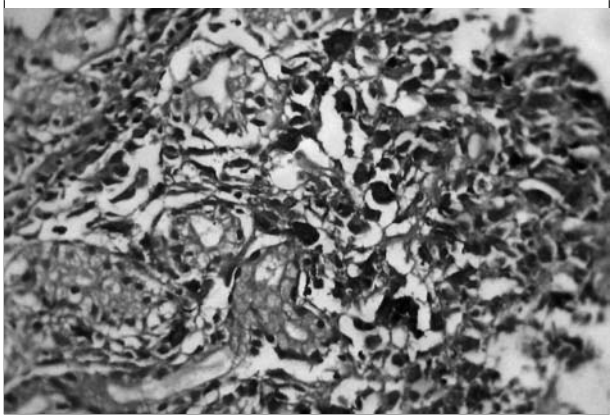
Figure 1. *Multiple black spots on the gastric body are seen*



WHAT IS YOUR DIAGNOSIS?

See page 131 for the answer to this photo quiz.

Figure 2. *Tumour infiltration in the gastric lamina propria containing cytoplasmic black pigments (HE x 40)*



ANSWER TO PHOTO QUIZ (ON PAGE 128)

PITUITARY FAILURE DUE TO POSTPARTUM DIC: REVERSIBLE DIABETES INSIPIDUS AND PERMANENT HYPOGONADISM

DIAGNOSIS

Our patient seems to be a case of reversible diabetes insipidus and irreversible central hypogonadism, which may be a result of pituitary haematoma (*figure 1*) and/or ischaemia due to disseminated intravascular coagulation. Resolution of the diabetes insipidus correlated with regression of the haematoma (*figure 2*), which was caused by haemorrhage into the pituitary. This is rarely reported.[1] However, early volume replacement may be another factor that limited the pituitary ischaemia independent of a temporary compressive effect of the haematoma. Irreversibility of gonadotropin deficiency strongly supports ischaemic damage to the pituitary as in classical Sheehan's syndrome.[2,3]

NOTE

This photo quiz was accepted as a poster at the Congress of the Society of Endocrinology and Metabolism of Turkey and presented in September 2006.

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Figure 1. *Coronal precontrast T1-weighted MR image showing an enlarged pituitary gland containing a hyperintense area*

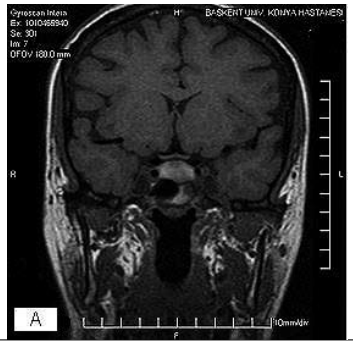
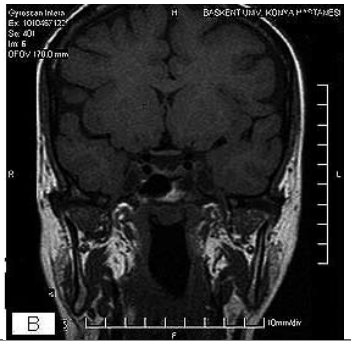


Figure 2. *Coronal T1-weighted image showing the decrease in pituitary size due to regression of haematoma*



ANSWER TO PHOTO QUIZ (ON PAGE 129)

SMALL BLACK SPOTS IN THE STOMACH AND DUODENUM

DIAGNOSIS

After the histopathological examination, the diagnosis of malignant melanoma was made in this patient. As multiple lesions were detected in both the stomach and the duodenum the patient was believed to have metastatic melanoma. However, despite a clinically extensive exploration of the skin, anal region, nose, and the eyes no primary site could be detected. The patient was put on chemotherapy consisting of dacarbazine, but died after the first cycle.

Melanoma, breast and lung cancer are the most common sites for metastasis to the stomach and small intestine,[1] but primary melanoma of the gastrointestinal tract is a very rare entity. Although the cell of origin was not identified since normal stomach epithelium lacks melanocytes, ectopic migration of melanocyte precursors or differentiation of the APUD cells (cells with a capacity for amine precursor uptake and decarboxylation) to melanocytes have been advocated as possible mechanisms.[2,3] Although we could not identify the primary tumour, the early death of our patient was accepted in favour of metastatic disease.

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Nephrogenic systemic fibrosis in stage 4 kidney disease, what is the alternative?

Dear Sir,

In a past issue, Wetzels[1] advises to avoid gadolinium-based contrast agents in patients with stage 4 and 5 kidney disease, i.e. a GFR <30 ml/min. His advice is in line with the opinion of many more authors and guidelines, such as the one proposed by the Netherlands Federation of Nephrology. All because of the risk of developing nephrogenic systemic fibrosis (NSF), which is indeed a disease to avoid.

In his argumentation, and in the argumentation of others, I miss two aspects. The first is the lack of hard evidence to support their and others' advice on gadolinium or at least some qualification of the emphasis put on the advice to avoid of gadolinium at all costs. The reported 200 to 300 cases of NSF worldwide do not outweigh the probably millions of MRI scans carried out without any problem in patients with a GFR <30 ml/min. Furthermore, as some authors claim, NSF has not been described in patients with an estimated GFR of more than 20 ml/min.[2] Why then advise patients with a GFR <30 ml/min to avoid gadolinium? Moreover, the reported incidence of NSF after exposure to gadolinium in stage 5 kidney disease is 1.5[3] to 2.4%.[4] Given the scarce reports of NSF in patients with stage 4 kidney disease, the risk of acquiring NSF in these patients would be extremely low, as the incidence of stage 4 kidney disease is far higher than the incidence of stage 5 kidney disease. Although the half-life of gadolinium is markedly prolonged in renal insufficiency, which probably contributes to the occurrence of NSF, and although it is logical to assume that patients with stage 4 kidney disease are therefore also at increased risk, this is not yet proven!

The second aspect I miss in the discussion about NSF, is the lack of weighing the avoidance of gadolinium against the toxicity of alternative diagnostic methods. How can I produce vascular images without the risk of contrast nephropathy, contrast allergy or cholesterol emboli (which has a mortality of 50%!)? Why avoid gadolinium at all costs when the alternative is at least as dangerous?

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RESPONSE

The safety of gadolinium compounds

The editorial comment was intended to bring to attention nephrogenic systemic fibrosis (NSF) as a severe side effect of gadolinium-containing contrast media in patients with chronic kidney disease.[1] The comment did not allow me to discuss all aspects extensively. I merely alluded to the guidelines formulated by Kuo *et al.*[2] Even these authors do not forbid any use of gadolinium in patients with chronic kidney disease. My conclusion was that the knowledge of NSF as potential side effect of gadolinium 'must be taken into account when considering the best diagnostic strategy in the individual patient'. This conclusion still holds, meaning that the risk of gadolinium-based imaging procedures must be weighed against the well-known risks of other procedures as put forward by Dr. Stassen.

I am concerned by one of Dr Stassen's conclusions. I do not agree with the statement that 'the reported 200 to 300 cases of NSF worldwide do not outweigh the probably millions of MRI scans carried out without any problem in patients with a GFR <30 ml/min'. NSF was only recently recognised as a problem, there must be many unreported cases. In fact, in recent months the number of case reports is rising at a staggering pace, and in a small country as Denmark a total of 24 patients have been reported until 2006. It seems that we have only seen the tip of the iceberg. Since NSF is a severe, disabling and untreatable disease, with associated mortality, we must take action.

Admittedly, risks are low in patients with a GFR >30 ml/min. The recent FDA warning has cautioned against the use of gadolinium compounds in patients with a GFR <30 ml/min. We do not know the risk in these patients. However, NSF has been described in patients with a GFR of 25 ml/min. In patients with a GFR <15 ml/min the risk of developing NSF after gadolinium exposure is estimated at 3%. Although the risk of NSF in patients with a GFR of 15 to 30 ml/min will be lower than 1%, the total number of patients at risk is large.

I suggest the following: be restrictive when ordering a diagnostic procedure in patients with a GFR <30 ml/min. Do not use linear gadolinium-contrast agents. Although cyclic compounds are relatively safe, use the lowest possible dose, and try to avoid repeated procedures. Lastly, weigh the risks and benefits of the various diagnostic procedures and select the procedure with the lowest risk. Awareness of NSF should reduce the risk of its development.

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Netherlands
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SPECIAL REPORT

Thyroid function disorders - Guidelines of the *Netherlands Association of Internal Medicine*

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ABSTRACT

Thyroid function disorders are common with a female to male ratio of 4 to 1. In adult women primary hypothyroidism and thyrotoxicosis have a prevalence of 3.5/1000 and 0.8/1000, respectively. This guideline is aimed at secondary care providers especially internists, but also contains relevant information for interested general practitioners and gynaecologists. A multidisciplinary working group, containing delegates of professional and patient organisations, prepared the guideline. According to principles of 'evidence-based medicine' available literature was studied and discussed. Considering the availability and quality of published studies a practical advice was formulated. For a full overview of the literature and considerations the reader is referred to the original version of the guideline (accessible through NIV-net). In this manuscript we have aimed to provide the practicing internist with practical and 'as evidence-based as possible' treatment guidelines with respect to thyroid function disorders.

KEYWORDS

Hyperthyroidism, hypothyroidism, thyroid function, thyroxine

INTRODUCTION

Thyroid function disorders are common with a female-to-male ratio of 4 to 1. In adult women primary hypothyroidism and thyrotoxicosis have a prevalence of 3.5/1000 and 0.8/1000, respectively.[1]

This guideline is aimed at secondary care providers, especially internists but also contains relevant information for interested general practitioners and gynaecologists. A multidisciplinary working group prepared the guideline. The members of the working group were delegates of their respective professional organisations and a delegate of the patient organisations was also a full member of the working group.

According to principles of evidence-based medicine available literature was studied and discussed. Considering the availability and quality of published studies, a practical advice was formulated. For a full overview of the literature and considerations, the reader is referred to the original version of the guideline (accessible through NIV net). In this manuscript we have aimed to provide the practising internist with practical and 'as evidence-based as possible' treatment guidelines with respect to thyroid function disorders.

DIAGNOSIS OF THYROID FUNCTION DISORDERS

With regard to thyroid *function* disorders determination of the plasma thyroid-stimulating hormone (TSH) level is the single most important measurement.[2] *Figure 1* shows the algorithm for the diagnosis of thyroid function disorders. It is important to recognise that analytical problems can occur, most frequently due to concomitant medication (*table 1*). The algorithm is most useful in an ambulant setting. In case of a serious – nonthyroidal – illness thyroid function measurements are frequently abnormal and normalise during recovery of the underlying illness.[3] Therefore, in patients with (severe) illness, thyroid function should be determined only in cases with a very high index of suspicion.[3]

Figure 1. *Diagnosis of thyroid function disorders*

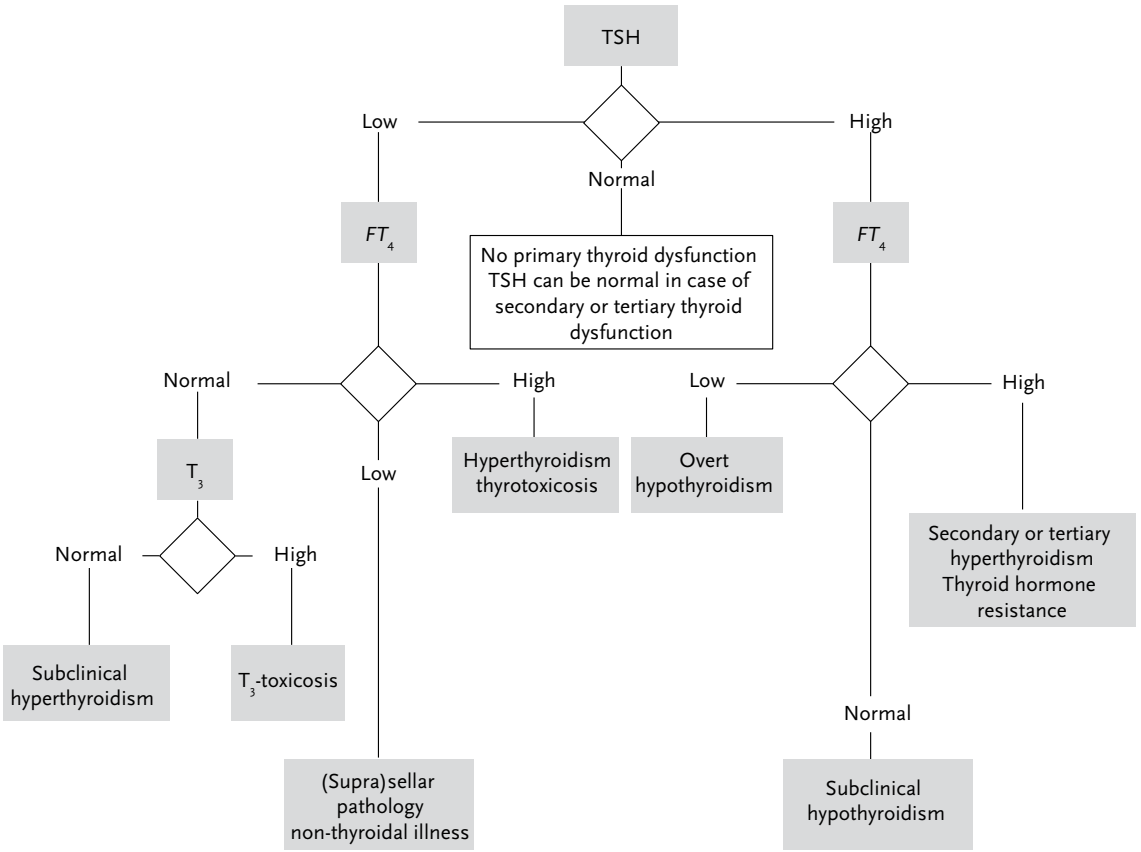

Table 1. *Analytical problems due to concomitant medication*

Inhibition of TSH secretion	Dopamine, glucocorticoids, somatostatin analogues
Inhibition of T4 secretion	Amiodarone, lithium
Stimulation of T4 secretion	Iodide, amiodarone
Impaired T4 absorption	Biliairy salts, iron, antacids, calciumcarbonat, aluminium hydroxyde, sucralfate
Stimulation of TBG synthesis	Oestrogens, opioids
Inhibition of TBG synthesis	Androgens, glucocorticoids
Inhibition of 5' deiodinase	Amiodarone, β-blockers, glucocorticoids
TBG-T4 dissociation	Frusemide, heparin

After a descriptive diagnosis of a thyroid function disorder determination of thyroid autoantibodies or thyroid scintigraphy can be helpful in establishing the exact cause of the thyroid function disorder. This is especially prudent in case of thyrotoxicosis.

TREATMENT OF THYROTOXICOSIS

There are three main causes of thyrotoxicosis: Graves' disease, toxic uni- or multinodular goitre and thyroiditis. Available treatment options are medical therapy, radioactive iodine and surgical treatment. Because the preferred treatment differs according to the cause of the thyrotoxicosis, it is important to establish a causal diagnosis. Unless the cause of the thyrotoxicosis is obvious – e.g. in case of severe Graves' orbitopathy – thyroid scintigraphy is thus advised in all cases of thyrotoxicosis.

How to do it box 1

Thyrotoxicosis: treatment options

- Graves' disease: medical, radioactive iodine, surgery[4]
- Toxic nodular goitre: radioactive iodine, surgery[5]
- Destructive thyrotoxicosis (subacute granulomatous thyroiditis, postpartum thyroiditis): wait and see, symptomatic treatment[6]

Graves' disease - treatment of thyrotoxicosis

Unless the thyrotoxicosis is very severe or a very large goitre is present, medical therapy is preferred for most patients.[7] Surgery can be especially useful in case of a very large goitre or if severe orbitopathy is present.[8] A high thyrotropin antibody titre is associated with a lower chance of permanent remission.[9,10]

Based upon the available literature propylthiouracil (PTU) and methimazole seem equally effective as antithyroid

drugs and no difference in the incidence of common adverse reactions (rash, arthralgia, gastrointestinal disturbances and altered taste) has been reported.[11-14] However, more severe and uncommon side effects such as hepatitis and ANCA-positive vasculitis are more frequently associated with PTU than with methimazole.[15] Also, methimazole can be dosed once daily improving compliance.[13] It should be noted here that both PTU and methimazole can lead to life-threatening agranulocytosis; therefore, in case of sore throat in combination with fever the use of these drugs should be postponed until agranulocytosis is excluded. Taken together we advise methimazole as antithyroid drug of choice in nonpregnant adults.

A recent meta-analysis concluded that with respect to reaching euthyroidism a block-and-replace (high-dose antithyroid) regimen is as effective as a titration (low-dose antithyroid) regimen.[16] After a treatment period of six to 18 months the relapse rates were 51% after a block-and-replace regimen and 54% after a titration regimen.[16] The incidence of adverse reactions is only marginally higher for block-replace regimens; surprisingly, this was found for minor but not for major adverse reactions.[16] We advise – based upon a more predictable lowering of thyroid hormone levels – a block-and-replace regimen for 12 to 18 months above a titration regimen in the treatment of Graves' disease in nonpregnant adults.

How to do it box 2

Graves' disease: medical therapy of thyrotoxicosis

- Methimazole starting dose 30 mg once daily[15,17,18]
- Check free thyroxine after 4-6 weeks, if in normal range add L-thyroxine full replacement dose
- Adjust L-thyroxine dose on the basis of thyroid function test results every 6-8 weeks. If test on two consecutive visits stable check thyroid function every 3 months
- Stop methimazole and L-thyroxine after 12-18 months[19-22]

A relapse of Graves' disease – after previous medical treatment – should preferably be treated with radioactive iodine.[23] In young patients with no cardiovascular history and a mild thyrotoxicosis, radioactive iodine can be given without previously rendering the patient euthyroid. In elderly patients and in those with a cardiovascular history it is advised to pretreat with antithyroid drugs until euthyroidism is achieved before treatment with radioactive iodine. Methimazole should be stopped three to five days and PTU at least 15 days prior to radioactive iodine treatment.[24-28] After treatment with radioactive iodine, antithyroid drugs should not be restarted within four days after treatment.[29] In order to prevent a worsening of symptoms – due to destruction of thyroid tissue –antithyroid treatment should be continued until at least three months after radioactive iodine treatment.[30] The risk of permanent hypothyroidism depends on the administered radioiodine dose.[31] In about 10% of patients the hypothyroidism that ensues after treatment with radioactive iodine is transient; therefore, it is advised that this is stopped six months after starting thyroxine supplementation for determination of TSH.[32] Radioactive iodine should be considered as primary therapy for Graves' disease in case of a large goitre or an unusually severe thyrotoxicosis.[7]

How to do it box 3

Graves' disease: radioactive iodine treatment

- In elderly patients and in those with a cardiovascular history pretreat until euthyroidism is achieved
- Stop methimazole 3-5 days and PTU at least 15 days prior to radioactive iodine treatment[24-28]
- In case of post-I^{131} hypothyroidism stop thyroxine 6 months after starting in order to diagnose transient post-I^{131} hypothyroidism[32]

Surgical therapy for Graves' disease should be considered in case of severe allergic reactions on antithyroid drugs, if malignancy of the thyroid is suspected and if restoration of euthyroidism needs to be achieved very quickly (e.g. in case of severe mechanical complaints.[8] Operative management should consist of subtotal or near total thyroidectomy.[8] Preoperatively, the patient should be rendered euthyroid. Typical complications – depending on the surgeons experience – are hypoparathyroidism and damage to the laryngeal recurrent nerve.[8]

How to do it box 4

Graves' disease: preoperative treatment

- Standard: usual antithyroid therapy until euthyroidism is restored (see *box 2*)
- Allergic to antithyroid drugs:
  - β-blocker until heart rate during exercise <80 /min: propranolol 80-240 mg daily
  - Iodide: start 10-14 days preoperatively: KI 50-250 mg thrice daily (1-5 drops solutio iodi spirituosa) or solutio iodi aquosa (Lugol's solution) 0.1-0.3 ml thrice daily (3-5 drops)

Graves' disease - treatment of orbitopathy

Graves' orbitopathy (GO) is associated with hyperthyroidism in 87% of patients.[33] Three percent of patients with GO are hypothyroid and 10% are euthyroid. TSH-receptor antibodies are usually present and hyperthyroidism develops in about 25% within years.[33] In those with hyperthyroidism GO presents before thyrotoxicosis in 20%, during thyrotoxicosis in 40% and after thyrotoxicosis in 40%.[33] Conversely, of all patients with Graves' thyrotoxicosis only 5 to 15% develop serious GO and 30 to 40% mild GO.[33] GO is usually bilateral; however, in 15% the orbitopathy is unilateral. Indeed, GO is the most prevalent cause of unilateral exophthalmos.[33] In patients with GO quality of life is severely impaired.[34,35] Restoration of euthyroidism generally leads to improvement of GO.[36,37] Considering the effects on GO, medical and

surgical treatment of the thyrotoxicosis are equally safe; radioactive iodine treatment, however, may exacerbate GO in 15% of patients.[38,39] Such exacerbation occurs in the first few months after 131-I treatment; fortunately, in two-thirds of patients eye symptoms are mild and transient. Steroids can prevent exacerbation of GO after radioactive iodine treatment and is advised in patients with pre-existent active GO, serious thyrotoxicosis (TT3 >5 nmol/l), high TSH-receptor antibody titres and smokers.[38,40,41]

How to do it box 5

Graves' disease: radioactive iodine treatment – preventive treatment with steroids

- Week 1-4: Prednisone 30 mg once daily
- Week 5-8: Prednisone 20 mg once daily
- Week 9-12: taper prednisone with 5 mg weekly

With respect to lifestyle, all patients with GO should be advised to quit smoking as this is associated with – more severe – GO and treatment failure.[38,42,43]

In order to further tailor immunosuppressive and surgical treatment, it is important to classify the severity and activity of GO. To this aim use of the clinical activity and NO-SPECS score is advised. For practical guidance and visual support see www.eugogo.org.

How to do it box 6

GO activity: Clinical Activity Score (amended from Mourits et al. Br J Ophthalmol 1989,73,639-4

- Spontaneous orbital pain
- Gaze evoked orbital pain
- Eyelid swelling that is considered to be due to active (inflammatory phase) GO
- Eyelid erythema
- Conjunctival redness that is considered to be due to active (inflammatory phase) GO (ignore 'equivocal' redness)
- Chemosis
- Inflammation of caruncle or plica
- Increase of ≥2 mm in proptosis
- Decrease in uniocular excursion in any one direction of ≥8°
- Decrease of acuity equivalent to 1 Snellen line

How to do it box 7

GO severity: NO SPECS score

0. **N**o symptoms or signs of GO
1. **O**nly signs, no symptoms
2. **S**oft tissue involvement (aperture in mm)
3. **P**roptosis (Hertel in mm)
4. **E**xtraocular muscle involvement (motility, double vision)
5. **C**orneal involvement
6. Sight loss (visual acuity, colour vision)

Mild GO can be treated with retrobulbar radiotherapy. This is especially effective in pain control and improving motility but has no effect on proptosis.[44,45] GO of intermediate severity can be treated with immunosuppressants (preferably with intravenous steroids).[44,45] Severe GO characterised by optical neuropathy and corneal ulceration represents the most severe manifestation of GO and should be treated with either high-dose steroids or orbital decompressive surgery.[44,45] It is strongly advised to refer patients in whom immunosuppressive or orbital decompression surgery is contemplated to specialist centres.

Iodine-induced thyrotoxicosis

Iodine excess can lead to thyrotoxicosis. Iodine intake in the Netherlands is adequate (i.e. 150 to 300 μg/day).[46] In vulnerable people such as those with a history of Graves' disease or with nodular goitre, excess iodine can lead to thyrotoxicosis: iodine-induced thyrotoxicosis (IIT).[47] Common sources of excess iodine are: iodine-containing radiographic contrast agents, amiodarone, kelp, iodine-containing multivitamins and large quantities of Japanese food.[47] IIT due to iodine-containing radiographic contrast agents and amiodarone will be discussed in more detail.

IIT after administration of radiographic contrast agents occurs in 0 to 1.2% of patients without underlying thyroid disease.[48] In patients with an underlying thyroid disorder the incidence is 5.2%.[48-51] Risk factors are higher age, nodular goitre and suppressed TSH.[48] The thyrotoxicosis is usually mild and resolves spontaneously. Prevention is possible with methimazole (20 mg once daily) and sodium perchlorate (300 mg thrice daily).[52-54] Despite treatment thyrotoxicosis is not preventable in all patients and side effects are common.[52,54] Therefore preventive treatment should be considered only in those patients at high risk for serious cardiac arrhythmia.

How to do it box 8

Prevention of contrast agent induced thyrotoxicosis

Methimazole once daily 20 mg and sodium perchlorate three times daily 300 mg

Amiodarone administration has several effects on parameters of thyroid function. Amiodarone consists for 39.3% of iodine. A dose of 200 to 400 mg daily therefore leads to a substantial iodine excess. Such an excess leads to inhibition of thyroid iodine organification (Wolff-Chaikoff effect) resulting in an increase in TSH (resulting in a TSH of about 5 to 15 mU/l) which – due to escape of Wolff-Chaikoff effect – normalises after approximately three months. Peripheral effects of amiodarone on thyroid hormone metabolism collectively lead to higher T4 and fT4 levels while TSH remains normal. During amiodarone use the upper limit of normal for T4 and fT4 should be increased by about 25%.

In the Netherlands amiodarone-induced thyrotoxicosis (AIT) occurs in 12.1% of amiodarone-treated patients.[55] The clinical picture shows a wide variety; often the presenting symptom is worsening of cardiac arrhythmia.[56,57] Development of AIT is not associated with cumulative dose. It occurs unpredictably and in a short period of time.[55] There are two types of AIT: type I and type II. As treatment differs it is important to carefully evaluate patients with AIT.

Type I is a thyrotoxicosis with hyperthyroidism occurring in patients with nodular goitre or Graves' disease. Thyroid antibodies are frequently present. As a result of increased thyroid hormone synthesis radioactive iodine uptake can still be increased and the thyroid is hypervascularised.[56]

Type II is a destruction-mediated thyrotoxicosis that results from the cytotoxic effect of amiodarone on thyroid follicular cells.[56]

Treatment can be difficult.[56,57] Type I AIT is preferably treated with methimazole 30 mg daily in combination with potassium perchlorate 500 mg twice daily.[56,58] As excess iodine renders methimazole less effective, methimazole alone does not significantly shorten the period of thyrotoxicosis in most patients. It is advised to stop administration of amiodarone if possible; unfortunately most patients are still thyrotoxic six to nine months after discontinuation of amiodarone. Radioactive iodine uptake is sometimes high enough to make radioactive iodine therapy possible. In case of type II AIT the treatment of choice is prednisone: 30 mg daily for two weeks and thereafter tapering to zero in three months.[59] In type II AIT continuation of amiodarone is usually possible.[60] In extremely therapy resistant cases thyroidectomy can be an option.[61]

How to do it box 9

Treatment of AIT

- Type I: methimazole 30 mg daily in combination with potassium perchlorate 500 mg twice daily. If possible stop amiodarone
- Type II: prednisone: 30 mg daily for two weeks and thereafter tapering to zero in 3 months. Continuation of amiodarone usually possible

Subclinical hyperthyroidism

Subclinical hyperthyroidism is a biochemical diagnosis characterised by suppressed TSH and normal free T4 and T3 concentrations.[62] When other causes of suppressed TSH – medication (steroids, dopamine), nonthyroidal illness, (supra) sellar disease – are excluded a suppressed TSH is indicative of a T4 concentration that is above the individually determined setpoint.

The prevalence of endogenous subclinical hyperthyroidism is 0.7 to 1.9%, of exogenous hyperthyroidism 1.3 to 2.0%.[63,64] Causes are nodular goitre, Graves' disease and thyroiditis.

Subclinical hyperthyroidism is statistically associated with atrial fibrillation: in subjects in the Framingham heart study with a TSH <0.1 the cumulative ten-year incidence for atrial fibrillation was 28% compared with 11% in those with normal TSH levels.[64] These findings were recently confirmed by Capolla *et al*. who found in persons with a TSH <0.4 mU/l during a period of 13 years a twofold increased incidence of atrial fibrillation compared with euthyroid subjects.[65] Besides rhythm disturbances subclinical hyperthyroidism also leads to adverse changes in echocardiographic measurements.[66] In postmenopausal women subclinical hyperthyroidism is associated with osteoporosis.[67] With regard to fractures it can be said that women with a suppressed TSH have a higher fracture incidence than women with a normal TSH.[68] Finally, the risk of dementia seems threefold increased in subclinical hyperthyroidism.[69] However, whether there is an increased mortality in patients with subclinical hyperthyroidism is controversial.

Based on the above it is advised to treat patients with subclinical hyperthyroidism if there are toxic symptoms, atrial fibrillation or osteopenia.[70] Regardless of signs and symptoms it should be considered to treat persons older than 60 years, postmenopausal women especially if TSH is <0.1 mU/l.

Thyroiditis

Thyroid inflammation can be caused by physical stimuli, micro-organisms and autoimmunity.[6] Subacute granulomatous thyroiditis and subacute lymphocytic thyroiditis will be discussed here. Postpartum thyroiditis will be reviewed separately.

Subacute granulomatous thyroiditis (Quervain's thyroiditis)[71] has an incidence that is one-fifth to one-eight of that of Graves' disease and is more common in women.[72,73] It is assumed that it is caused by a virus or by post-viral inflammation.[6] Thyroiditis presents with pain in the thyroid region often radiating to the ear accompanied by muscle pain, fatigue and symptoms of thyrotoxicosis.[74-76] Physical examination reveals a painful goitre.[74,76] In the acute phase the erythrocyte sedimentation rate is elevated (typically >40 mm) with slight anaemia and leucocytosis.[74,77] Thyroid function shows a thyrotoxicosis lasting two to ten weeks that resolves spontaneously.[74,77,78] The thyrotoxicosis is destruction mediated and is therefore self-limiting, treatment is symptomatic with aspirin (600 mg three to six times daily) and β-blockers.[74,77,79] In rare cases treatment with steroids (one week of prednisone 40 mg daily, then 30 mg to be tapered by 5 mg weekly) is needed to control pain.[77,80] There is no increased risk for development of permanent overt hypothyroidism.[6]

How to do it box 10

Symptomatic treatment of subacute granulomatous thyroiditis

- Aspirin 600 mg three tot six times daily
- β-blockers e.g. propranolol 40-120 mg or atenolol 25-50 mg daily

Subacute lymphocytic thyroiditis and postpartum thyroiditis are generally considered to be variants of Hashimoto's thyroiditis.[6] It is an autoimmune destructive thyrotoxicosis.[6] Contrary to subacute granulomatous thyroiditis it is painless and classically has a biphasic course: a thyrotoxicosis followed by a hypothyroid period.[6] As in subacute granulomatous thyroiditis the thyrotoxic phase is destruction mediated and self-limiting.[6] However, unlike subacute granulomatous thyroiditis permanent hypothyroidism develops in 6%. Importantly, hypothyroidism can develop after a prolonged period of euthyroidism. Therefore, yearly assessment of thyroid function is advised.[6]

TREATMENT OF PRIMARY HYPOTHYROIDISM

Primary overt hypothyroidism

Primary hypothyroidism is caused by a thyroid disorder and biochemically characterised by an elevated TSH and a lowered fT4.[81] Symptoms are usually vague and nonspecific, frequently occurring symptoms are cold intolerance, constipation, dry skin, low heart rate, hoarse voice and impaired mental performance.[82] In its most extreme form heart failure and coma can occur.[82] In children hypothyroidism can cause mental retardation; indeed, worldwide hypothyroidism caused by iodine deficiency is the single most prevalent cause of mental retardation.[83]

The prevalence of hypothyroidism is 0.3 to 0.4%, increasing with age and with a female predominance.[63,84,85] Usually it is on autoimmune basis. Other causes are iatrogenic (after previous treatment for hyperthyroidism), medication (amiodarone, lithium) and congenital.[82,86] Worldwide, iodine deficiency is by far the most prevalent cause of hypothyroidism.[82]

Treatment is substituting the deficient hormone, i.e. L-thyroxine.[82,87] Dose is dependent on underlying cause and weight, around 1.8 μg/kg for autoimmune hypothyroidism and about 2.0 μg/kg after (near) total thyroidectomy.[82] However, interindividual variance is large. In young and healthy patients full-dose substitution can be given at once.[82] However, in the elderly (arbitrarily defined as >60 years) and those with cardiovascular morbidity it is advised to start more slowly (25 μg with dose adjustments based on TSH every four to six weeks). Importantly, there are no differences in quality of life between a fast and slow titration schedule.[88] Thyroid hormone dose is adjusted on the basis of TSH – not fT4 – aiming for a TSH in the normal range.[87] L-thyroxine should be taken either in the morning on an empty stomach or in the evening at bedtime, in the last instance the required dose to reach euthyroidism is generally lower.[89]

Several drugs such as biliary salts, iron, antacids, calcium carbonate, aluminium hydroxyde and sucralfate interfere with thyroxine uptake.[90-95] It is advised to take these medications two to four hours apart from thyroxine. Phenytoin, carbamazepine, fenobarbital and rifampicin lead to an increased clearance of thyroxine, thus the need for thyroxine increases.[96-99]

Persistent symptoms after biochemically optimal substitution: T4/T3 combination therapy

A substantial number of treated patients have persistent symptoms despite biochemically optimal substitution.[100,101] Possibly this is because of a lack of T3 produced by the thyroid.[82]

In a recent meta-analysis of 11 studies with a total of 1216 randomised patients no significant differences with respect to body pain, depression, fear, quality of life and lipids were noted between T4/T3 combination therapy and T4 therapy.[102] In a large Dutch study patients preferred T4/T3 combination therapy in a 5:1 ratio.[103] Surprisingly this preference was not reflected in a battery of neurocognitive tests. What was related to this patient preference was weight loss. In the dose the patients preferred (T4/T3 in a ratio 5:1) 51% of the patients had a suppressed TSH, a higher heart rate and elevated bone markers. Based on the above T4/T3 combination therapy is not advised as standard therapy for primary hypothyroidism.[103]

In case of persistent symptoms after biochemically optimal substitution it is reasonable – albeit not supported by evidence – to increase the substitution dose until the TSH is low normal. Also, it is important to exclude other diseases that are associated with primary – autoimmune – hypothyroidism, such as type I diabetes mellitus, adrenal insufficiency, vitamin B12 deficiency and celiac disease.

How to do it box 11

Treatment of primary hypothyroidism

- Young and healthy patients: L-thyroxine full dose substitution: 1.8 μg/kg for autoimmune hypothyroidism and about 2.0 μg/kg after (near) total thyroidectomy
- Elderly (arbitrarily defined as >60 years) patients and those with cardiovascular morbidity: titrate more slowly: 25-50 μg starting dose
- Dose adjustments based on TSH every 4-6 weeks, aim for TSH in normal range
- When stable check TSH once yearly
- In case of persistent symptoms titrate TSH to low normal levels, exclude diseases that are associated with autoimmune hypothyroidism

Subclinical hypothyroidism

Subclinical hypothyroidism is defined as the situation in which TSH is elevated and fT4 is normal.[70] Alternative causes for such a biochemical profile are nonthyroidal illness, recovery from thyroiditis and treatment with recombinant TSH.[104] The prevalence varies between 4 and 8.5%.[70]

The risk for development of overt hypothyroidism is positively associated with TSH and the presence of TPO antibodies. If TSH is <6.0 mU/l the cumulative risk for development of overt hypothyroidism is close to zero, if TSH is between 6 and 12 mU/l this is 42.8%, and with a TSH >12 mU/l the cumulative incidence of overt hypothyroidism is 76.9%.[105] The presence of TPO antibodies can add in assessing the risk for development of overt hypothyroidism, especially if the TSH is between 6 and 12 mU/l; in this range the risk for development of overt hypothyroidism increases by 80%.[105] Outside this range the risk for development of overt hypothyroidism increases by 40%.[105]

There is one study on cardiovascular morbidity and mortality that shows no increased cardiovascular risk in patients with subclinical hypothyroidism followed for 20 years.[106] However, two recent meta-analyses did show that subclinical hypothyroidism is associated with coronary heart disease.[107,108]

Unfortunately there are no intervention studies of sufficient quality that show a positive effect of treatment.[109-113] Despite this shortcoming it seems defendable to start a trial of treatment of at least three months in case of otherwise unexplained fatigue or cognitive dysfunction in patients with subclinical hypothyroidism. It should be noted that in those older than 85 years the presence of subclinical hypothyroidism is associated with a lower mortality.[114]

Lithium-induced hypothyroidism

In about 50% of lithium-treated subjects a goitre develops.[115-118] This is most likely caused by elevated TSH levels as subclinical and overt hypothyroidism are seen in 20 to 30% and 4.4% of cases respectively.[66,115,119] Therefore, in case of lithium use we advise checking TSH every six to twelve months;[119] and – in order to prevent goitre formation – prescribe thyroxine if the TSH is >4.0 mU/l.

THYROID DYSFUNCTION DURING PREGNANCY AND POSTPARTUM

During pregnancy maternal thyroid hormone metabolism changes considerably.[120] There is an increase in iodine demand due to placental transport to the foetus.[83] Daily iodine intake during pregnancy and lactation should therefore be at least 250 µg.[83]

Under the influence of oestrogen, thyroxine-binding globulin (TBG) levels increase considerably; this leads to an increase in TT4 and TT3 concentrations.[120] In the first trimester hCG levels rise sharply and – due to the structural homology of hCG and TSH and their respective receptors – lead to a lowering of TSH (<0.4 mU/l in 10% of pregnancies).[120] Also, there is considerable placental thyroxine transport which adds to the increased thyroid hormone requirement during pregnancy.[120]

As the foetal pituitary-thyroid axis becomes functional around week 12 of gestation it follows that before this period the foetus is completely dependent upon maternal supply of thyroid hormone.[121]

Hyperthyroidism during pregnancy is most often due to gestational transient hyperthyroxinaemia. This occurs in 2 to 3% of European women and in 11% of Asian women. Graves' disease is seen in 0.01 to 0.02% of pregnancies.[122] As untreated or poorly treated hyperthyroidism is associated with obstetric complications (miscarriage, low birth weight, (pre)-eclampsia and possibly congenital malformations) and – in case of Graves' disease – with foetal and neonatal thyrotoxicosis adequate diagnosis and treatment are essential.[123-126]

Gestational transient hyperthyroidism occurs in the first trimester and is associated with hyperemesis in 50% of cases.[127,128] Women with gestational transient hyperthyroidism usually have no goitre, lack signs of thyroid eye disease and TSH receptor antibodies (TRAb) are negative. The thyrotoxicosis is usually mild, and resolves spontaneously by week 18 in most cases.[127,128]

Graves' disease should be suspected in the presence of a diffuse goitre, ophthalmopathy, thyroid dermopathy and the presence of TRAb. In women with known Graves' disease who are contemplating pregnancy the disease should preferably be treated by thyroid ablation either with radioactive iodine or surgery before pregnancy. It should be noted that for six months after radioiodine treatment pregnancy is contraindicated and euthyroidism is not always restored after one treatment.

Graves' disease diagnosed during pregnancy should be treated medically. Medical treatment of Graves' disease during pregnancy consists of monotherapy with antithyroid drugs in the lowest possible dose to achieve a fT4 concentration in the high normal range.[120] Because there are reports linking methimazole use with aplasia cutis, choanal atresia and oesophagus atresia there is a preference for the use of PTU.[129,130] It is advised to perform thyroid function tests every six to eight weeks.[120] Often it is possible to stop treatment in the third trimester.[120] In exceptionally resistant cases thyroidectomy should be considered in the second trimester. During lactation it is safe to use methimazole (<20 mg daily) or PTU (<300 mg daily).

The risk of foetal and neonatal thyrotoxicosis can and should be assessed by the measurement of maternal serum TRAb.[131] It is advised to measure these antibodies in all women with (a history of) Graves' disease. This is especially relevant in women rendered hypothyroid as a result of ablative therapy for Graves' disease.[131] TRAb can be measured in the first or second trimester and if positive should be measured again in the third trimester.[131] If TSH-receptor antibodies are present in the third trimester adequate monitoring for foetal thyrotoxicosis is mandatory.[131]

Relevant literature suggests that even relatively mild and often unrecognised maternal hypothyroxinaemia (i.e. low fT4 and normal TSH) is associated with significant and persistent impairment of neuropsychological performance in the offspring.[132,133] Unfortunately there are no prospective studies available on the effects of thyroxine supplementation regarding the long-term neurodevelopment of the infant. Moreover, determining free thyroxine levels in pregnancy has serious analytical shortcomings.[120] So, it is at present unclear how to proceed when the fT4 is low but TSH is normal.

In case of an elevated TSH – i.e. >4.0 mU/l – a significantly increased rate of obstetrical complications has been described.[134,135] Therefore, it is advised to treat subclinical hypothyroidism (TSH >4.0 mU/l) in pregnancy. Whether in case of otherwise unexplained infertility or habitual abortion, treatment of subclinical hypothyroidism has favourable results is unknown. However, based on the above it seems reasonable at least to consider thyroxine treatment.

Overt hypothyroidism (raised serum TSH and decreased free thyroxine) diagnosed during pregnancy should be immediately treated with full replacement doses of T4.[120] In women preconceptionally treated, T4 requirements during pregnancy increase on average by 50%.[120,136] Women with subclinical hypothyroidism should be advised to have thyroid function tests as soon as they have a positive pregnancy test. Women who are already using thyroxine should be instructed to increase their dosage by 30%; thereafter, dosage should be adjusted based upon thyroid function tests.[136,137] As in the treatment of hyperthyroidism it is advised to perform thyroid function tests every six to eight weeks aiming for a TSH between 1 and 2 mU/l.[136,137]

How to do it box 12

Treatment of Graves' disease during pregnancy

- Monotherapy with PTU in the lowest possible dose
- Aim for a normal TSH and a fT4 concentration in the high normal range
- Adjust dose every 4-6 weeks
- Check TSH-receptor antibodies in mother

How to do it box 13

Treatment of hypothyroidism during pregnancy

- In pregnancy treat subclinical hypothyroidism (TSH cut-off >4.0 mU/l)
- Treat overt hypothyroidism diagnosed during pregnancy immediately with full replacement doses of T4
- If hypothyroid preconceptionally: instruct to increase dosage by 30% if pregnancy is diagnosed
- Aim for a normal TSH and a fT4 concentration in the high normal range
- Adjust dose every 4-6 weeks

POSTPARTUM THYROIDITIS

Postpartum thyroiditis is a syndrome of transient or permanent thyroid dysfunction occurring in the first year after delivery, based on an autoimmune inflammation of the thyroid.[138] In the Netherlands the incidence is reported from 5.2 to 7.2%.[138] Postpartum thyroiditis classically runs a biphasic course: a thyrotoxic phase is followed by a hypothyroid phase. 'Postpartum' thyroiditis can also occur after loss of pregnancy at 5-20 weeks gestation.[138]

The thyrotoxic phase of postpartum thyroiditis is due to leakage of thyroid hormones from destroyed thyrocytes and is therefore self-limiting. The most important differential diagnosis is Graves' disease, thus a thyroid scintigraphy or determination of TSH-receptor antibodies is advised.[138]

The hypothyroid phase, developing approximately four to eight months postpartum and usually lasting four to six months, is clinically more important.[138] After a period of postpartum thyroiditis permanent hypothyroidism occurs in 12 to 61%. This can also occur after a previous period of euthyroidism, so yearly TSH determination is advised in all women after a period of postpartum thyroiditis.[138]

THYROID EMERGENCIES

Thyrotoxic crisis

Thyrotoxic crisis is a clinical syndrome characterised by a life-threatening thyrotoxicosis. Critical for diagnosis is a high level of clinical suspicion. Burch and Wartofsky have proposed a scheme that can facilitate diagnosis. Tachycardia, fever, gastrointestinal dysfunction and central nervous system dysfunction are the most prominent features. [139]

Mortality is high (10 to 75%) and therefore treatment should be instituted immediately in an intensive care unit.[139,140] Treatment should be supportive and thyroid-specific.

Supportive treatment consists of correction of hyperpyrexia with acetaminophen (aspirin can elevate T4 and T3 levels), cardiovascular support, treatment of infection and other underlying/precipitating conditions.[139,140]

Thyroid-specific treatment is aimed at reducing thyroid hormone production and action. Thyroid hormone synthesis is blocked by antithyroid drugs; both PTU and methimazole can be used (PTU 200 to 250 mg every four hours or methimazole 30 mg every six hours).[139,140] Thyroid hormone release is inhibited by iodine: Lugol's solution 10 to 15 drops every eight hours or sodium iodide or potassium iodide which can be given intravenously 0.5 to 1 gram every 12 hours.[139,140] In order to prevent iodine from being used as a substrate for thyroid hormone synthesis it should be given at least one hour after the first dose of antithyroid drugs.[139,140] Inhibition of peripheral T4 to T3 conversion is produced by giving high-dose intravenous glucocorticoids, e.g. hydrocortisone 200 to 300 mg as a loading dose followed by 100 mg every eight hours.[139,140] Blocking the effects of T4 and T3 on peripheral tissues is achieved by β-blockers; propranolol is the classic drug for this indication: 0.5 to 1.0 mg intravenously in ten minutes followed by 1 to 3 mg every hour until concomitantly administered oral propranolol (60 to 80 mg every six to eight hours) is effective.[139,140]

How to do it box 14

Treatment of thyrotoxic crisis

- Block thyroid hormone synthesis: PTU: 200 to 250 mg every 4 hours or methimazole 30 mg every 6 hours
- Inhibit thyroid hormone release – only after administration of antithyroid drugs: Lugol's solution 10 to 15 drops every 8 hours or sodium iodide or potassium iodide intravenously 0.5 to 1 gram every 12 hours
- Inhibit T4 to T3 conversion: glucocorticoids, e.g. hydrocortisone 200 to 300 mg as a loading dose followed by 100 mg every 8 hours
- Block the effects of T4 and T3 on peripheral tissues: β-blockers, e.g. propranolol: 0.5-1.0 mg intravenously in 10 minutes followed by 1-3 mg every hour until concomitantly administered oral propranolol (60-80 mg every 4 to 6 hours) is effective

Myxoedema coma

Myxoedema coma is a severe state of hypothyroidism that presents with altered mental status, respiratory insufficiency and hypothermia besides other common hypothyroid symptoms.[141] It is commonly precipitated by an acute event (e.g. infection, myocardial infarction, hypothermia, sedatives) on the background of a long-standing untreated – or insufficiently treated – hypothyroidism.[141] Laboratory investigation shows hyponatraemia, anaemia, hypoglycaemia, hypercholesterolemia, elevated LDH and creatinine kinase.[141] If secondary hypothyroidism is suspected hydrocortisone should also be given.[141] However, to establish the diagnosis determination of TSH and fT4 are essential; in this respect it is important to be aware that TSH levels can be only slightly elevated as a result of nonthyroidal illness.
Treatment should take place in an intensive care unit.[141] Thyroid hormone substitution should not be delayed until results of thyroid function tests are known. We advise supplementation of T4 and T3. T4: a loading dose of 200 to 250 μg intravenously followed by 100 μg after 24 hours and thereafter 50 μg daily (preferably oral otherwise intravenously). T3: 10 μg every eight hours until normalisation of vital function.

How to do it box 15

Treatment of myxoedema coma

- T4: a loading dose of 200 to 250 μg intravenously followed by 100 μg after 24 hours and thereafter 50 μg daily preferably orally
- T3: 10 μg every 8 hours until normalisation of vital functions

NOTE

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SPECIAL REPORT

50 years *Netherlands Journal of Medicine*

The next 10 years: 1986-1995

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In 1982, when my predecessor Leo Offerhaus asked me to join the editorial board of the Netherlands Journal of Medicine, I became acquainted with a small group of eager and enthusiastic internists who at that time were responsible for the Journal. The editor was called the 'managing editor' to illustrate the fact that it was he who really managed the Journal. The board members (who were then called the 'editors') met at regular intervals at Offerhaus' home (with coffee and cake!) to comment on new manuscripts and to discuss new ways of improving the Journal's standard. There were no formal rules, and decisions were taken in a friendly atmosphere. Especially during the winter months, however, travelling to the managing editor's house was not always easy and sometimes we got stuck in heavy snowstorms (global warming was not heard of then). The poor editor-in-chief could do nothing but wait and see if anyone would appear. There was no way of knowing who would show up and who would not, as nobody had a cellular phone in those days.

By the end of 1984, Offerhaus was facing new challenges which forced him to delegate some of the editor's work to a younger colleague and so I became 'assistant managing editor', at that time a new phenomenon at the Journal. We were lucky enough to witness an increased submission rate of good manuscripts which made it possible to publish the Journal on a monthly basis. After a risky endeavour in 1981, when it was decided to increase the number of issues from six to ten a year,[1] it was easier for us to move to a monthly publication as of 1985. When this was accomplished, Offerhaus resigned and I took over his position in January 1986. The implication was that, for the first time in the history of the Journal, the editor was not based in Amsterdam but in Rotterdam.

It was a time for change. The term 'managing editor' was abandoned and replaced simply by 'editor' to denote the editor-in-chief. The editorial board was reshaped and two associate editors were appointed to assist the editor-in-chief: Edo Meinders, who was on the verge of moving from Arnhem to Leiden, and No Vogten from Heemstede.[2] The former 'editors' were now collectively referred to as the editorial board. The three editors met every month in Utrecht or in one of their homes and the meetings of the full editorial board were limited to twice a year. The latter meetings always took place in the office of the *Nederlandsche Internisten Vereeniging* (NIV; the *Netherlands Association of Internal Medicine*) in Utrecht and were followed by dinner in 'De Kromme Elleboog'. The restaurant's name (but also the food) was particularly appreciated by Leo van der Putte who was our board member for rheumatology at the time.

The first year in office was full of challenging experiences. The most intriguing of these were the negotiations with the new publisher. For a number of reasons, it had become necessary to look for another publisher, a process that had already been started by Offerhaus in an attempt to professionalise the Journal. After many deliberations and thorough discussions with the Board of the NIV we finally chose Elsevier as our future publisher. The treasurer of the NIV had calculated that the transition to Elsevier would become a profitable venture in a few years time, although the expectations in this regard were not completely fulfilled. Judith Taylor at Elsevier was our liaison officer with whom we closely collaborated. She was instrumental in guiding the changeover from Bohn to Elsevier and in the development of new items. Besides the Netherlands Editorial Board we instituted an International Advisory Board in an attempt to make the Journal better known outside our own country. Fortunately, the number of manuscripts continued to rise and more original work found its way to the Journal. It enabled us to give the Journal a recognisable format with each issue containing an editorial, at least two original articles, a few brief reports and one or two reviews.

In January 1987, the first issue of the renewed Journal appeared. The layout had completely changed and the rather dark cover from the previous years had been replaced by a white cover with green lettering. The transition phase was accompanied by another major change. From that moment onwards, the Journal was no longer distributed exclusively in the Netherlands. Whereas the Dutch subscribers continued to receive their monthly edition, an international edition of the Journal was published bimonthly (with the articles of two issues combined, of course). This was also done to promote the Journal abroad.[3] Naturally, not everybody appreciated the new look right from the start and it took some time before people became convinced of the appropriateness of these changes.

In the same period, Mrs Stijger resigned and most of the secretarial work now had to be done by the editors themselves. However, the personal computer was rapidly conquering the world and it became much easier to print and send out standard letters. Although this may sound rather trivial to young doctors who have literally grown up with a computer, for us in those days it was still a bit of an adventure. Moreover, many processes had not yet developed to today's standards. For instance, we started to work with WordPerfect 4.0® as the word processor which lacked many of the features of the current packages. For printing we had a choice of using either matrix printers or daisywheel printers. As the quality of the former was poor, we decided to use the daisywheel system. However, printing turned out to be a tedious job when you wanted to include different fonts or styles such as italics. It meant that you had to interrupt normal printing, replace the wheel containing normal letters by the one containing the italic letters and resume printing until the next format change. No wonder the turnaround time at the editorial office was still unacceptably long. It was not until the year 1991 that we could afford a modern laser printer which marked the beginning of a new era. Yolande te Giffel became the new secretary and she handled all office matters until the Journal moved to Utrecht in January 1996.

In retrospect, the 1986-1995 period turned out to be a crucial one. The decision to change publisher, the ambition to let the Journal grow with some outlook for internationalisation and the reshaping of the Journal into a modern periodical all proved to be necessary for the survival of the Journal. Of course, these developments also went with the loss of some tradition. In the old days the great internists of our country, the men of really great stature, were awarded a special issue of the Journal as a liber amicorum. This habit was formally abandoned in 1986 after the presentation of the last liber amicorum to Professor Mandema during the lustrum festivities of the NIV in Arnhem (*figure 1*).

Figure 1. *Presentation by Dr de Leeuw (Editor-in-Chief) of the last liber amicorum (special issue of the Netherlands Journal of Medicine) to Professor Mandema in Arnhem (Musis sacrum) on 21 November 1986*

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MONTHLY NJM ONLINE HITLIST

The table lists online hits for all articles published in the December issue of the *Netherlands Journal of Medicine 2007* (available online on Pubmed since 14 December 2007).

Article	Hits
EDITORIAL	
Hereditary haemochromatosis	104
REVIEWS	
Probiotics and remission of ulcerative colitis: a systematic review	161
Changing aspects of HFE-related hereditary haemochromatosis and endeavours to early diagnosis	103
ORIGINAL ARTICLES	
Morbidity and mortality in first-degree relatives of C282Y homozygous probands with clinically detected haemochromatosis compared with the general population: the HEmochromatosis FAmily Study (HEFAS)	115
Incidence of first acute myocardial infarction in the Netherlands	111
CASE REPORTS	
Failure of CHOP with rituximab for lymphomatoid granulomatosis	127
Watery diarrhoea: an unusual manifestation of breast cancer	101
SPECIAL REPORT	
Synopsis of the Dutch multidisciplinary guideline for the diagnosis and treatment of hereditary haemochromatosis	112
LETTER TO THE EDITOR	
Spontaneous fistulisation of a liver abscess into the stomach	70
PHOTO QUIZZES	
Patient with diarrhoea, abdominal pain and weight loss	130
Blurred vision	109
MONTHLY NJM ONLINE HITLIST	
For all articles published in September 2007	102
Total	**1345**

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

Manuscripts
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2. Kaplan NM. Clinical Hypertension. 7th ed. Baltimore: Williams & Wilkins; 1998.
3. Powell LW, Isselbacher KJ. Hemochromatosis. In: Braunwald E, Fauci AS, Kasper DL, et al., editors. Harrison's Principles of Internal Medicine. 15th edition. New York: McGraw-Hill; 2001. p. 2257-61.

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