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CLINICAL STUDY

Health status in patients with sub-clinical hypothyroidism

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Abstract

Objective: Sub-clinical hypothyroidism (SCH) is a common disorder. People with this condition may have symptoms which could affect their perception of health. Therefore, the perceived health status of people with SCH was assessed and compared with population-matched norms.
Design: A prospective cross-sectional survey.
Methods: Seventy-one adults with SCH, age range 18–64 years were studied. Perceived health status was measured by the Short Form-36 (SF-36) version 2 questionaire, which has been validated in a UK population setting. The SF-36 has eight scales measuring physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health. Their SF-36 scores were compared with UK normative data after matching for age and sex and are reported as z-scores.
Results: Scores of all eight SF-36 scales were significantly lower in people with SCH compared with the normative population. A negative score (compared with zero of the normative population) indicates worse health status. The most significantly impaired aspects of health status were vitality and role limitations due to physical problems (role physical scale) with z-scores (95% confidence intervals) of −1.01 (−0.74 to −1.29) and −0.73 (−0.43 to −1.04) respectively. Thyroid autoimmunity did not influence the results.
Conclusion: Perceived health status is significantly impaired in people with SCH when compared with UK normative population scores. This needs to be taken into consideration by clinicians when managing patients with this disease.

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Introduction

Sub-clinical hypothyroidism (SCH) is a biochemical diagnosis and refers to patients with elevated thyroid stimulating hormone (TSH) levels and a normal free thyroxine (fT4) level (1). It is a common disorder with prevalence rates quoted between 5.8 and 17.4% depending on the age of the population studied (1–3). The presence of symptoms of hypothyroidism in patients with SCH when compared with the general population is controversial due to the non-specific nature of many hypothyroid symptoms, which are also common to many other conditions, and due to the different types of patient samples studied (3–7).

The lifetime prevalence of depression in patients with SCH is double that of the general population and has been reported to reduce the efficacy of antidepressant treatment (8); it is associated with anxiety (9) and changes in mood and cognitive functioning (10). There is also evidence that exercise capacity may be impaired due to significant reduction of exercise-related stroke volume, cardiac index, vital capacity and reduced anaerobic thresholds (11). All these factors may affect subjective perception of health status.

Subjective health status is a key component in the evaluation of any medical condition and therapeutic intervention (12). In patients with SCH, symptoms may contribute to perceived impairment of health-related quality of life (13). Health status can be measured by the widely used generic Short Form-36 (SF-36) questionaire. As there have been some concerns about the wording and layout of the original SF-36 (14), the developers have designed a second version – the SF-36v2. The normative data for the SF-36v2 in the UK was obtained from a postal survey of patients randomly selected from general practitioner records, which achieved a response rate of 64.4% ($n = 8889$). The SF-36v2 was shown to have improved reliability and reduced floor and ceiling effects compared with the previous version of the SF-36 (15). Respondents were also asked to report demographic details and any long-term illnesses, and 36.6% reported a chronic long-standing illness. In the present study, we therefore assessed the health status of people with SCH

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using the SF-36v2 and compared it with UK normative population scores.

Patients and methods

Patients

One hundred consecutive community living adults with SCH were recruited over a 5-month period from primary care practices after identification from the laboratory database. Inclusion criteria were people with SCH over 18 years of age. Exclusion criteria were people with ischaemic heart disease, cerebrovascular disease, neurological disease, diabetes mellitus, chronic renal impairment, known psychological illnesses such as schizophrenia, bipolar affective disorder and depression, previous history of thyroid disease or previous thyroxine therapy, asthma, and pregnancy, so as to reduce the effect of other co-morbid conditions on perceived health status. All participants except one had had at least three abnormal thyroid function tests (TSH >4 mU/l with normal fT4 levels) consistent with SCH, their thyroid status having been checked previously due to hypothyroid symptoms, or SCH was an incidental finding. All participants gave written informed consent and the Gateshead ethics committee approved the study. Only 71 patients (mean age ($\pm$S.D.) 48.7 years ($\pm$9.67), range 23–64; 15 males) in the 18 to 64 year age group were considered for comparison with the UK SF-36v2 normative data, as normative data are not available for older adults. The mean$\pm$S.D. TSH concentration was 6.6 ± 2.5 mU/l, range 4.1–16 (normal reference range: 0.4–4.0 mU/l) and the mean$\pm$S.D. fT4 concentration was 13.9 ± 1.9 pmol/l, range 10.3–19 (normal reference range: 9–25 pmol/l). The frequency of other chronic diseases was: hypertension 9.5%, hypercholesterolaemia 1.3% and arthritis (osteoarthritis, gout or rheumatoid arthritis) 21.9%. Results of two participants found to be on treatment for asthma were not included in the analyses. The results of 27 participants aged 65 to 80 years were used for within-SCH group comparisons.

SF-36v2

Perceived health status was evaluated by the SF-36v2 questionnaire. The questionnaire is composed of 36 items, 35 of which are classed into eight scales of varying length. For each SF-36v2 dimension, raw item scores are coded, summed and transformed on to a scale ranging from 0 (worst possible perceived health status) to 100 (best possible health status). The single item on perceived changes in health status over the previous 12 months was not considered in the present study. The degree of divergence from the scores for the normative population of an individual patient or specific patient population can be measured using a z transformation, taking into account the effects of age and gender. For each SF-36v2 scale, a z-score was calculated by subtracting the mean scale score of the normative population sample (matched for age and sex) from the scale score of the study group and dividing this difference by the standard deviation of the normative population sample. This was carried out individually for each participant for each scale and the overall group mean was calculated. A z-score value of 0 corresponds to the mean value of the normal population, a z-score value of -1 or -2 corresponds to one or two standard deviations below the normal population respectively. Z-scoring was preferred to the 0–100 based scoring algorithm to compare with the UK normative scores because it provides a basis for meaningful comparison across scales and for easier interpretation (16, 17). Control values were obtained in relatively large numbers from random samples of the UK population aged between 18 and 64 years ($n = 8889$), as described above. This procedure has previously been used in the UK in the study of health status in patients with different diseases such as Parkinson's disease and multiple sclerosis (18), heart failure and left ventricular systolic dysfunction (19) and low back pain, menorrhagia, suspected peptic ulcer and varicose veins (17), and elsewhere in thyroid disease (20).

Biochemical tests

The tests were performed at the Queen Elizabeth Hospital Biochemistry Laboratory. Serum was collected using standard sampling tubes containing separating gel. TSH and fT4 were measured by an electro-chemiluminescence immunoassay 'ECLIA' using Roche Elecsys E170 immunoassay analysers (Roche Diagnostics, UK). The Elecsys TSH test had been calibrated against the 2nd IRP WHO Reference Standard 80/558. The Elecsys fT4 test had been calibrated against Enzymuntest fT4. This, in turn, was calibrated using equilibrium dialysis. Thyroid autoimmunity was determined by the quantitative measurement of anti-thyroid peroxidase autoantibodies (anti-TPO) by ELISA (ORGENTEC Diagnostika GmbH, Mainz, Germany) with a cut-off value of 50 IU/ml.

Statistical analyses

Data were analysed by one researcher (SR). Means$\pm$ S.D. were used to report descriptive data and 95% confidence intervals (95% CI) were used to report the difference in the means between the study participants and the normative population. A 95% CI is significant if the interval range does not cross zero, signifying that the two populations are different (21). Student's unpaired *t*-test was used to compare the subgroup means and Bonferroni's post hoc multiple comparison test for observed means was carried out to ensure that multiple *t*-tests did not show a significant difference where none exists, i.e. to reduce type I error (22).

Z-scores were also used to report transformed scores as discussed previously. A mean z-score <0.2 was considered clinically non-significant, between 0.2 and 0.5 as a small difference, between 0.5 and 0.8 as a moderate difference and >0.8 as a large difference (23, 24).

Correlation analysis (Spearman's rho for non-parametric data or Pearson's r for parametric data) was used to assess the relationship between each SF-36 scale measured and biochemical and demographic parameters. Internal consistency reliability - that is, the extent to which there is a correlation between items on a scale – was assessed by Cronbach's alpha, an inter-item correlation statistic, with a value range of 0–1 (25). Levels of >0.9 are usually agreed to signify excellent internal consistency reliability (26). A P value of <0.05 was taken as statistically significant. SPSS version 11.0 was utilised for computing the statistics (SPSS Inc., Chicago, IL, USA).

Results

In comparison with a large UK population reference group, scores on all eight scales of the SF36v2 were found to be significantly reduced (Table 1). The difference was attenuated but still significant when people with SCH and other chronic diseases (e.g. arthritis, hypertension and hypercholesterolaemia) were excluded from the analyses ($n = 24$). Z-scores for all 71 participants studied were significantly lower than the normative data for all scales of the SF-36 but only the vitality (VT) scale showed a large difference, that is >0.8 (Fig. 1).

The rest of the z-scores showed either moderate (role physical (RP), general health (GH), social functioning (SF) and role emotional (RE)) or small (physical functioning (PF), bodily pain (BP) and mental health (MH)) differences. When analysed separately for men ($n = 15$) and women ($n = 56$), the results of the z-score analysis showed that women tended to have lower scores for all scales compared with men, although not significantly so (Fig. 2). Men had significantly lower z-scores in all scales except PF when compared with men from the UK norms (Fig. 2) whereas women had significantly lower scores on all scales.

Table 1 Differences in absolute SF-36 scores in patients with SCH compared with age- and sex-matched normative data.

	SCH subjects (mean±S.D.; $n = 71$)	UK normative population (mean±S.D.; $n = 8660$)	Difference in means (95% CI)
PF	76.05±24.98	87.99±19.65	11.94 (7.4–16.48)
RP	68.32±29.74	87.17±22.01	18.85 (13.76–23.94)
BP	68.63±27.02	78.8±23.01	10.17 (4.86–15.48)
GH	60.07±22.26	71.06±20.43	10.99 (6.28–15.7)
V	37.15±23.81	58.04±19.6	20.89 (16.37–25.41)
SF	69.52±27.47	82.77±23.24	13.25 (7.89–18.61)
RE	72.48±26.84	85.75±21.18	13.27 (8.38–18.16)
MH	63.35±18.85	71.92±18.15	8.57 (4.39–12.75)

SF-36 score range: 0 to 100 (poor to excellent health status). PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

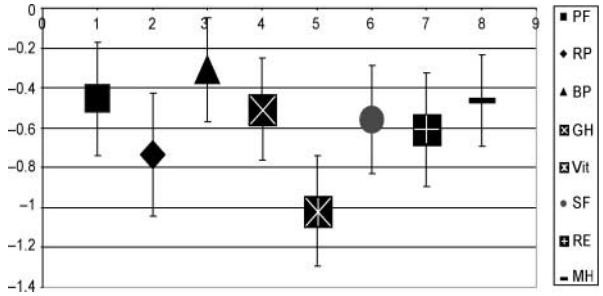

Figure 1 SF-36v2 scale scores of patients with SCH (mean with 95% confidence interval) compared with age- and sex-matched controls in a UK cohort (zero line). Note: a negative z-score indicates lower health status in the SCH group compared with normative data. PF, physical functioning; RP, role physical; BP, bodily pain; GH, general health; VT, vitality; SF, social functioning; RE, role emotional; MH, mental health.

Health status scores did not differ in people with thyroid autoimmunity, as determined by the presence of anti-TPO antibodies ($n = 39$), although the two groups were well matched for age, sex and biochemical thyroid function tests. None of the scales of the SF-36v2 correlated with either TSH or fT4 levels. As expected, TSH values correlated significantly with fT4 ($r = -0.238$, $P = 0.04$). The z-scores for the VT scale correlated significantly with age ($r = 0.35$, $P = 0.002$), which was statistically significant after Bonferroni correction requiring a P value of 0.006 (0.05/8). Comparison of absolute scores of older people with SCH (aged 65–80 years) ($n = 27$) with the younger group studied ($n = 71$) showed that the older group had significantly impaired health status only for the PF, RP and BP

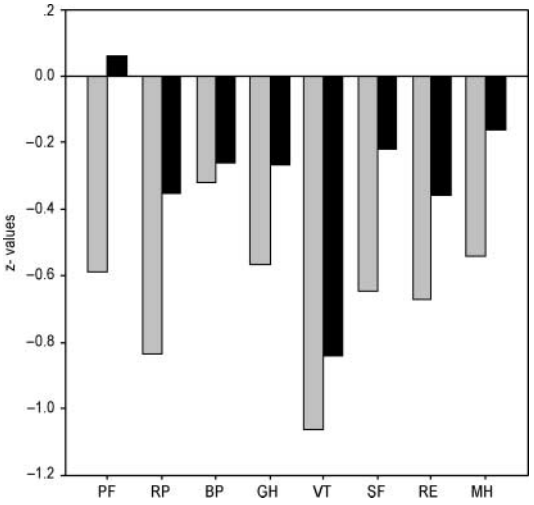

Figure 2 Sex differences in z-scores for each SF-36 scale for patients with SCH ($n = 71$). Solid bars, males; shaded bars, females.

scales (difference in means (95% CI): 17.72 (6.4 − 29.04), 13.93 (1.32 − 26.54) and 14.93 (2.97 − 26.89) respectively).

Cronbach's alpha coefficient ranged from 0.91 to 0.93 signifying excellent internal consistency reliability for all eight SF-36 scales in this sample of patients with SCH.

Discussion

Perceived health status is more than just the presence or absence of disease or symptoms and encompasses social, physical and emotional dimensions. Clinicians do not routinely assess patients' perceptions of their health status, but it is increasingly being argued that the patient's perspective is as valid as that of the clinician in evaluation of a medical condition and its outcomes (27). We have shown for the first time that patients with SCH perceive significant impairment of their health status, as measured by all eight scales of the SF-36v2. The normative data in this study for comparison of scores for all scales comprised a random sample from the general population and not a disease-free population. Hence it is probable that some of these individuals had thyroid disease and therefore the results obtained in this study may well be an underestimation of the true value. This is all the more likely since 36.6% of the normative population reported chronic long-standing illness (patients with chronic diseases are more likely to respond to a postal health survey than disease-free individuals), whereas patients with such conditions, apart from hypertension, arthritis and hypercholesterolaemia, were excluded in the present study.

Bianchi and colleagues recently reported that there were no differences in perceived health status (as measured by the SF-36 and the Nottingham Health Profile instruments) between their Italian patients with SCH, and age- and sex-matched Italian population norms (20). The results reported in this paper are different from their observations. This may be due to the different population and normative data used in the analysis as well as the fact that the comparison sample in the present study was younger owing to the lack of normative data for people older than 64 years in the UK.

Limitations of this study are that patients were not identified from a screening programme and were recruited from primary care practices. Thus patients with presence of symptoms at the higher end of the scale and/or with other co-morbidities were more likely to have been studied. However, the results obtained still remain significantly different from the normative scores even when data were analysed after excluding people with other chronic conditions. It is quite possible that some conditions such as hypertension and hypercholesterolaemia are 'silent' and hence affect health status the least (28). Also, it would seem that men tend not to have any impairment of physical functioning as compared with normative scores for men of the same age. We have no direct explanation for this and further research is required. Also, older people (>64 years) with SCH have significantly lower scores on the physical scales (PF, RP and BP) when compared with younger people. This was not an unexpected finding as others have obtained significant age gradients in some SF-36 subscales (29), but the lack of normative data for comparison with this older group is disappointing, especially since SCH is more prevalent in older people (30). There is some recent evidence that SCH may not adversely affect the very old in terms of disability, cognitive function and survival (31). Although it is clear from this study that people with SCH have impaired perceived health status, it is yet to be clarified whether normalizing serum TSH level would improve it. Previous studies have had conflicting results in improving symptoms and health-related quality of life (4, 7, 32–34). It has also been shown that people on adequate doses of L-thyroxine exhibit impaired psychological well-being (35).

In conclusion, we have shown that perceived health status is significantly impaired in people presenting with SCH and this should be considered when managing this condition.

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References

1 Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA & Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *Journal of Clinical Endocrinology and Metabolism* 2002 **87** 489–499.

2 Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, Evans JG, Young E, Bird T & Smith PA. The spectrum of thyroid disease in a community: the Whickham survey. *Clinical Endocrinology* 1977 **7** 481–493.

3 Canaris GJ, Manowitz NR, Mayor G & Ridgway EC. The Colorado thyroid disease prevalence study. *Archives of Internal Medicine* 2000 **160** 526–534.

4 Nystrom E, Caidahl K, Fager G, Wikkelso C, Lundberg PA & Lindstedt G. A double-blind cross-over 12-month study of L-thyroxine treatment of women with 'subclinical' hypothyroidism. *Clinical Endocrinology* 1988 **29** 63–75.

5 Eden S, Sundbeck G, Lindstedt G, Lundberg PA, Jagenburg R, Landahl S & Svanborg A. Screening for thyroid disease in the elderly. Serum concentrations of thyrotropin and 3,5,3′-triiodothyronine in a representative population of 79-year-old women and men. *Comprehensive Gerontology. Section A, Clinical and Laboratory Sciences* 1988 **2** 40–45.

6 Zulewski H, Muller B, Exer P, Miserez AR & Staub JJ. Estimation of tissue hypothyroidism by a new clinical score: evaluation of patients with various 11 grades of hypothyroidism and controls.

Journal of Clinical Endocrinology and Metabolism 1997 **82** 771–776.
7 Cooper DS, Halpern R, Wood LC, Levin AA & Ridgway EC. L-Thyroxine therapy in subclinical hypothyroidism. A double-blind, placebo-controlled trial. *Annals of Internal Medicine* 1984 **101** 18–24.
8 Saddock BJ & Saddock V. Psychological factors affecting medical conditions. In *Kaplan and Saddock's Comprehensive Textbook of Psychiatry*, pp 1765–1888. Eds A Stoudemie & JS McDaniel. Philadelphia: Lippincott Williams and Willens, 2000.
9 Sait Gonen M, Kisakol G, Savas Cilli A, Dikbas O, Gungor K, Inal A & Kaya A. Assessment of anxiety in subclinical thyroid disorders. *Endocrine Journal* 2004 **51** 311–315.
10 Hendrick V, Altshuler L & Whybrow P. Psychoneuroendocrinology of mood disorders. The hypothalamic–pituitary–thyroid axis. *Psychiatric Clinics of North America* 1998 **21** 277–292.
11 Kahaly GJ. Cardiovascular and atherogenic aspects of subclinical hypothyroidism. *Thyroid* 2000 **10** 665–679.
12 Working for Patients. Secretaries of State for Health, England and Wales, Northern Ireland, and Scotland. London: HMSO, 1989.
13 Jaeschke R, Guyatt G, Cook D, Harper S & Gerstein HC. Spectrum of quality of life impairment in hypothyroidism. *Quality of Life Research* 1994 **3** 323–327.
14 Jenkinson C & McGee H. Patient assessed outcomes: measuring health status and quality of life. In *Assessment and Evaluation of Health and Medical Care*. Ed. C Jenkinson. Buckingham: Open University Press, 1997.
15 Jenkinson C, Stewart-Brown S, Petersen S & Paice C. Assessment of the SF-36 version 2 in the United Kingdom. *Journal of Epidemiology and Community Health* 1999 **53** 46–50.
16 Ware JE Jr, Kosinski M, Gandek B. *SF-36 Health Survey: Manual and Interpretation Guide*. Lincoln, RI: QualityMetric Incorporated, 2000.
17 Garratt AM, Ruta DA, Abdalla MI, Buckingham JK & Russell IT. The SF-36 health survey questionnaire: an outcome measure suitable for routine use within the NHS? *British Medical Journal* 1993 **306** 1440–1444.
18 Riazi A, Hobart JC, Lamping DL, Fitzpatrick R, Freeman JA, Jenkinson C, Peto V & Thompson AJ. Using the SF-36 measure to compare the health impact of multiple sclerosis and Parkinson's disease with normal population health profiles. *Journal of Neurology, Neurosurgury and Psychiatry* 2003 **74** 710–714.
19 Hobbs FD, Kenkre JE, Roalfe AK, Davis RC, Hare R & Davies MK. Impact of heart failure and left ventricular systolic dysfunction on quality of life: a cross-sectional study comparing common chronic cardiac and medical disorders and a representative adult population. *European Heart Journal* 2002 **23** 1867–1876.
20 Bianchi GP, Zaccheroni V, Solaroli E, Vescini F, Cerutti R, Zoli M & Marchesini G. Health-related quality of life in patients with thyroid disorders. *Quality of Life Research* 2004 **13** 45–54.
21 Gardner MJ & Altman DG. Confidence intervals rather than *P* values: estimation rather than hypothesis testing. *British Medical Journal (Clinical Research Edition)* 1986 **292** 746–750.
22 Norman GR & Streiner DL. *Biostatistics: The Bare Essentials*. Hamilton: B.C. Decker Inc., 2000.
23 Cohen J. *Statistical Analysis for the Behavioural Sciences*. New York: Academic Press, 1977.
24 Kazis LE, Anderson JJ & Meenan RF. Effect sizes for interpreting changes in health status. *Medical Care* 1989 **27** S178–S189.
25 Cronbach LJ. Coefficient alpha and the internal structure of tests. *Psychometrica* 1951 **41** 1395–1401.
26 Nunally JC & Bernstein IH. *Psychometric Theory*. New York: McGraw-Hill, 1994.
27 Leplege A & Hunt S. The problem of quality of life in medicine. *Journal of the American Medical Association* 1997 **278** 47–50.
28 Stewart AL, Greenfield S, Hays RD, Wells K, Rogers WH, Berry SD, McGlynn EA & Ware JE Jr. Functional status and well-being of patients with chronic conditions. Results from the Medical Outcomes Study. *Journal of the American Medical Association* 1989 **262** 907–913.
29 Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T & Westlake L. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. *British Medical Journal* 1992 **305** 160–164.
30 Braverman LE & Utiger RD. The epidemiology of thyroid diseases. In *Werner's and Ingbar's The Thyroid: A Fundamental and Clinical Text*, pp 467–473. Philadelphia: JB Lippincott-Raven, 2000.
31 Gussekloo J, Van Exel E, De Craen AJ, Meinders AE, Frolich M & Westendorp RG. Thyroid status, disability and cognitive function, and survival in old age. *Journal of the American Medical Association* 2004 **292** 2591–2599.
32 Jaeschke R, Guyatt G, Gerstein H, Patterson C, Molloy W, Cook D, Harper S, Griffith L & Carbotte R. Does treatment with L-thyroxine influence health status in middle-aged and older adults with subclinical hypothyroidism? *Journal of General Internal Medicine* 1996 **11** 744–749.
33 Kong WM, Sheikh MH, Lumb PJ, Naoumova RP, Freedman DB, Crook M, Dore CJ, Finer N & Naoumova P. A 6-month randomized trial of thyroxine treatment in women with mild subclinical hypothyroidism. *American Journal of Medicine* 2002 **112** 348–354.
34 Meier C, Staub JJ, Roth CB, Guglielmetti M, Kunz M, Miserez AR, Drewe J, Huber P, Herzog R & Muller B. TSH-controlled L-thyroxine therapy reduces cholesterol levels and clinical symptoms in subclinical hypothyroidism: a double blind, placebo-controlled trial (Basel Thyroid Study). *Journal of Clinical Endocrinology and Metabolism* 2001 **86** 4860–4866.
35 Saravanan P, Chau WF, Roberts N, Vedhara K, Greenwood R & Dayan CM. Psychological well-being in patients on 'adequate' doses of L-thyroxine: results of a large, controlled community-based questionnaire study. *Clinical Endocrinology* 2002 **57** 577–585.

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