

Over- and Under-Treatment of Hypothyroidism Is Associated with Excess Mortality: A Register-Based Cohort Study

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Objective: This study investigated the association between hypothyroidism and mortality in both treated and untreated hypothyroid patients, and the consequences of over- and under-treatment with respect to mortality.

Patients and Methods: This was a register-based cohort study of 235,168 individuals who had at least one serum thyrotropin (TSH) during 1995–2011 (median follow-up 7.2 years). Hypothyroidism was defined as at least two measurements of TSH >4.0 mIU/L within a half year spaced by at least 14 days, or one measurement of TSH >4.0 mIU/L and two filled prescriptions of levothyroxine the following year. All-cause mortality rates were calculated using multivariable Cox regression analysis adjusted for age, sex, and comorbidities using the Charlson Comorbidity Index.

Results: Mortality was increased in untreated hypothyroid individuals ($n=673$; hazard ratio [HR]=1.46 [confidence interval (CI) 1.26–1.69]; $p<0.001$) compared to euthyroid controls. Results remained significant even when subdividing according to mild (TSH >4.0 mIU/L and ≤ 10 mIU/L; $p<0.001$) and marked hypothyroidism (TSH >10 mIU/L; $p=0.002$). Mortality was increased in both treated and untreated hypothyroid individuals for each six months a patient had increased TSH (HR = 1.05 [CI 1.02–1.07], $p<0.0001$, and HR = 1.05 [CI 1.02–1.07], $p=0.0009$, respectively). In patients who received levothyroxine, the HR for mortality increased by a factor 1.18 ([CI 1.15–1.21]; $p<0.0001$) for each six months a patient exhibited decreased TSH. This finding was essentially unchanged after stratification by disease severity (mild or marked hypothyroidism) and age (older and younger than 65 years).

Conclusions: Mortality was increased in untreated but not in treated hypothyroid individuals, independently of age and severity of hypothyroidism. Duration of decreased TSH in treated individuals had a greater impact on mortality than did duration of elevated TSH. These results stress the need for close monitoring of treatment in individuals receiving thyroid hormone replacement therapy.

Keywords: hypothyroidism, thyroid, register-based, treatment, mortality

Sammenhængen mellem hypothyroidisme og dødelighed har længe været debatteret, men mange studier tager ikke højde for konsekvensen af varighed af thyreoidea-dysfunktion, behandling, og overbehandling. Dette studie tager udgangspunkt i 275.000 individer der i perioden 1995 til 2011 har fået målt TSH mindst én gang. Vi fandt øget mortalitetsrisiko i ubehandlede hypothyroide individer, men ikke i de behandlede. Ydermere fandt vi, at dødelighed per halve år med høj TSH var øget i såvel behandlede som ubehandlede individer. Som mål for overbehandling fandt vi, at mortalitetsrisikoen var øget per halve år med lav TSH i de behandlede individer. I betragtning af, at nyere studier finder en høj grad af overbehandling af hypothyroide patienter viser disse resultater os, at mens behandling af hypothyroidisme er associeret med lavere dødelighed, er det vigtigt, at der sigtes efter at opnå og bibeholde TSH-værdier indenfor normalområdet.