Excess Triiodothyronine as a Risk Factor of Coronary Events

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Background: Abnormalities in cardiac function, eg, arrhythmias and congestive heart failure, often accompany thyrotoxicosis. A relationship between thyroid hormone excess and the cardiac complications of angina pectoris and myocardial infarction (MI) remains largely speculative.

Methods: The results of thyroid function studies on blood samples drawn from a total of 1049 patients (aged 40 years or older) immediately on emergency medical admission were related to frequencies of angina pectoris and myocardial infarction as determined according to current diagnostic algorithms. After 3 years, those patients who had initially presented with angina pectoris or acute MI were observed for subsequent coronary events; of these (n=185), 98% of the subjects (n=181) could be reevaluated.

Results: On hospital admission, the relative rate of angina pectoris and MI was markedly high (odds ratio, 2.6; 95% confidence interval, 1.3-5.2; P=.007) in patients with elevated serum free and total triiodothyronine (T₃) levels. An initially elevated free T₃ level was a risk factor for subsequent coronary events during the 3-year follow-up (adjusted odds ratio, 4.8; 95% confidence interval, 1.3-17.4; P=.02).

Conclusions: An elevation of serum free T₃ levels at hospital admission is associated with a 2.6-fold greater likelihood of the presence of a coronary event. Moreover, an initially elevated T₃ level is associated with a 3-fold higher risk of developing a subsequent coronary event during the next 3 years. Excess T₃ seemed to be a factor associated with the development and progression of acute myocardial ischemia.

The relative importance of these various factors in regard to cardiac functioning in the thyrotoxic state has not yet been determined, especially as to whether beneficial or deleterious effects have greater impact. Therefore, we have designed this study to test the hypothesis of whether thyroid hormone excess is related to the cardiac complications of angina pectoris and MI.

**SUBJECTS AND METHODS**

**PATIENT POPULATION AND STUDY DESIGN**

This study was based on the evaluation of 1049 patients from the population of Lübeck, Germany, and its vicinity. All persons aged 40 years or older presenting to the medical emergency treatment center at the Medical University of Lübeck from January 1 to April 30, 1995, were included, with the exception of those who had received intravenous vasopressor or mechanical respiration, as well as those who had been resuscitated following cardiac arrest prior to admission (21 patients). Characteristics of the 1049 patients on hospital admission are given in Table 1. Heparin had not been administered to any patient before phlebotomy, not even by the referring emergency physician. As the university hospital is 1 of 2 facilities serving the area, emergency admissions are made to this institution on odd-numbered days of the month while the second hospital admits on respective even-numbered days of the month. This special allocation system in Lübeck allowed for drawing an approximately 50% sample of all patients presenting for emergency medical care with a minimum of potential selection bias. Every patient gave written consent. The consent form and the study protocol have been approved by the local ethics commission.

After 3 years, from January 1 to April 30, 1998, we did follow-up evaluations of those patients who had initially presented with angina pectoris or AMI. Of these (n=185), 98% of the subjects (n=181) could be recalled and reevaluated. Baseline characteristics of the 181 patients who completed the follow-up are given in Table 1.

**HORMONAL MEASUREMENTS**

Serum thyroxine (T₄) and T₃ concentrations were determined from blood samples drawn immediately after arrival in the emergency department and prior to any intravenous therapy, including administration of heparin. Ascertainment of the respective free T₄ and T₃ (FT₄ and FT₃, respectively) and total T₄ and T₃ (TT₄ and TT₃, respectively) serum concentrations was accomplished using enzyme immunossays (Boehringer Mannheim Immunodiagnostica, Mannheim, Germany). Total serum T₄ and T₃ levels were measured for comparative purposes to rule out possible laboratory inaccuracies in determination of the respective free hormone concentrations. The reference intervals for our laboratory were FT₄, 4.5 to 9.0 pmol/L (3.6-9 pg/mL); FT₃, 10 to 25 pmol/L (0.8-1.9 ng/dL); TT₄, 1.2 to 2.7 nmol/L (0.8-1.8 ng/mL); and TT₃, 58 to 151 nmol/L (4.5-11.7 pg/dL). These intervals correspond to those established by Gerhardt and Keller, who used the same type of assays on a population from nearby Scandinavia. Thyrotropin (TSH) was measured using an immunoluminometric assay (Brahms Diagnostica, Berlin, Germany; reference interval, 0.2-3.5 mU/L). The samples were analyzed either on the day of hospital admission or, after immediate storage at −20°C, within 72 hours following admission.

**DIAGNOSTIC PROCEDURES**

On hospital admission, angina pectoris, and AMI were diagnosed on the basis of acute symptoms, electrocardiographic (ECG) classification, cardiac enzymes, and patient history related to coronary heart disease. Angina pectoris was diagnosed if acute chest pain at rest had arisen within 12 hours prior to hospital admission and at least 1 of the following 3 criteria for “suspected ischemia” was present: (1) angina, based on a standardized questionnaire; (2) history of a possible infarction based on the same questionnaire, or (3) positive ECG signs according to the items of the Minnesota code. A diagnosis of definite MI was based on current World Health Organization diagnostic algorithms according to the MONICA study protocol.

Information on possible interfering variables was collected in a structured interview with each patient, through contact with the general practitioner, from earlier hospital records, or from current laboratory tests and ECGs. We assessed the presence of the classic risk factors (hypercholesterolemia; history of hypertension, diabetes, or smoking), drug effects (prehospitalization medication, contact with iodine-containing contrast agents), and coexisting diseases (atrial fibrillation documented in ECG at admission; history of thyroid or liver disease).

In the cohort study, the occurrence of subsequent coronary events up to 3 years after initial evaluation was assessed by using the current World Health Organization diagnostic algorithm for AMI. Patients who had initially presented with angina pectoris were observed for the occurrence of MI; patients who had initially presented with MI were observed for the occurrence of coronary death (<28 days after initial evaluation) or recurrent MI (≥28 days after initial evaluation). Information on coronary events and on possible interfering variables was collected in a structured interview with the patient’s general practitioner, from hospital records, autopsy findings, in a structured telephone interview with each surviving patient, and through contact with family members of each patient who had died. Coronary revascularisation procedures (percutaneous transluminal coronary angioplasty, stent, bypass) during the 3-year follow-up were assessed; however, in case of a recurrent coronary event, only procedures prior to the respective event were included in the analysis. Investigators collecting the data on events during follow-up were blinded to thyroid status.

**STATISTICAL ANALYSIS**

The data were evaluated using logistic regression analyses to estimate odds ratios (ORs) and their 95% confidence intervals. Odds ratios were calculated to analyze the relationship between the results of the thyroid function tests and the occurrence of coronary events. These ORs were adjusted for age and sex. Additional covariates (hypertension, diabetes, smoking, hypercholesterolemia, liver disease, atrial fibrillation, etc) were conditionally selected in a forward stepwise procedure. Calculations were done using the SPSS statistics program, version 6.0 (SPSS Inc, Chicago, Ill).
Among the 1049 patients examined, elevations of serum FT3, or serum FT4, levels, or suppressed serum TSH levels were found in 60, 99, and 108 patients, respectively (Table 1). Most of these patients had 2 or 3 of these thyroid function alterations corresponding to the strong associations between FT3, FT4, and TSH (Table 2). There were 109 respective diagnoses of angina pectoris and 76 cases of AMI. Using bivariate analysis, we found elevated FT3 levels consistently correlated with both angina pectoris and MI (Table 3). If FT3 level was considered a continuous variable, the correlation with angina pectoris and MI was also significant (regression coefficient, 0.0148; SE, 0.0056; P = .008). The multivariate logistic regression revealed an adjusted OR of 2.6 (95% confidence interval, 1.3-5.2; P = .007) for the occurrence of angina pectoris or MI in the presence of elevated serum FT3 levels (Table 4).

As possible interfering variables, the classic risk factors, eg, history of hypertension, smoking, or elevated low-density lipoprotein cholesterol, were significant at ORs of 1.7, 1.5, and 1.9, respectively. Atrial fibrillation was more frequent in patients with suppressed TSH levels (age-adjusted OR, 2.2; 95% confidence interval, 1.3-3.8; P = .004; no further predictors of atrial fibrillation could be identified using a stepwise forward logistic regression model). Nonetheless, there seemed to be no relationship between atrial fibrillation and the manifestation of coronary events after application of the logistic regression model to our data (Table 4). Finally, the occurrence of documented liver disease also showed no effect on the incidence of coronary events in the logistic regression.

A summary of the substances having potential influence on thyroid function that appeared in the histories of the 60 patients with elevated serum FT3 levels (amiodarone, β-adrenergic antagonists, glucocorticoids, carbamazepine, salicylates, furosemide, radiocontrast agents) is given presented in Table 5. Contact with iodine-containing contrast agents within 6 months prior to admission was reported by 9 (15%) of the 60 patients. In total, 140 (13%) of the 1049 patients reported having received contrast substances (Table 1).

Assessments of TT3 levels, performed to confirm the validity of the laboratory analyses in the determination of hypertriiodothyrominemia, supported the results of the FT3 studies. In the subgroup of 60 patients with elevated serum FT3 levels, we also found increases in TT3 concentrations, above the reference range in 48 (80%) of these patients, and within the upper third of the reference range in 12 (20%).

In the cohort study, elevated TT3 levels were confirmed to be strongly related to coronary events during the 3-year follow-up. Using bivariate analysis we found elevated FT3 levels as a risk factor for subsequent coronary events. The crude relative risk was 3.0 (95% CI, 1.3-7.1); the crude OR, as an estimate of the relative risk, was 4.0 (95% CI, 1.2-12.7; P = .01) (Table 5). Because of strong associations between FT3, FT4, and TSH, we used a multivariate model with thyroid function alterations conditionally selected in a forward stepwise procedure (inclusion criterion, P < .10). Of thyroid function alterations, only FT3 was a significant risk factor for subsequent coronary events: FT3, FT4, and TSH with P values of .02, .19, and .16, respectively. After adjustment for other known risk factors and potentially confounding variables, the multivariate logistic regression revealed an adjusted OR of 4.8 (1.3-17.4; P = .02) for the occurrence of subsequent coronary events in patients with initially elevated FT3 levels (Table 6).
Our data demonstrate a strong association between excess T3 and the rate of manifestation of coronary events, i.e., angina pectoris or MI. A relatively large number of patients (60) presented with T3 excess (Table 1). Angina pectoris or MI was diagnosed in 1 of 5 presenting patients (Table 1). Logistic regression analysis, as presented in Table 4, revealed an unexpectedly high adjusted OR of 2.6 for the occurrence of angina pectoris or MI in the presence of elevated free T3 levels.

The coastal region of northern Germany, where Lübeck is situated, is an iodine-deficient area.16 As expected, we observed a markedly higher rate of elevated T3 levels in our patients than in hospital admissions in geographic areas with an adequate iodine supply.17 For 3 reasons, iodine deficiency offers a unique opportunity to study the effects of thyroid hormone excess in a patient population. First, thyrotoxicosis, especially with excess T3, occurs more frequently in iodine-deficient areas.18 Second, slight elevations in serum T3 levels, as occurred in few patients in our study, also occur in iodine-deficient areas owing to adaptive changes, including an increased conversion of T4 to T3 in thyroidal and extra-thyroidal tissues, and an increased secretion of TSH.19 Rarely, serum TSH levels may be normal in the presence of slightly elevated T3 levels because T3 is not very effective as an inhibitor of TSH secretion.20,21 Third, hypertriiodothyroninemia has been documented to occur as a precursor to thyrotoxicosis in some patients.22 Thus, it is possible that we detected an early stage of evolving thyrotoxicosis in some patients that had led to hospital admission for, e.g., cardiac complications.

Possible interfering variables also known to affect the rate of coronary events or levels of T3 have also been taken into consideration in our calculations. The classic risk factors, i.e., hypertension, smoking, and hypercholesterolemia, were, as expected, shown to be indepen-
dent risk factors in the regression model. As previously described by other researchers, we found low serum TSH levels associated with atrial fibrillation but atrial fibrillation not associated with coronary events, making an interfering effect of atrial fibrillation unlikely. As another factor, liver disease may fundamentally alter thyroid hormone metabolism, but our analysis demonstrated no relationship between liver disease, thyroid hormones, and coronary events. Finally, with the exception of 1 patient taking amiodarone, no clinically relevant pharmacological effects could be established for the patients with T3 excess. In conclusion, we consider it improbable that interfering effects could have been the basis of the observed relationship between thyroid function and coronary events.

Based on these cross-sectional data, with all due caution and recourse to knowledge outside of this study, we may raise some conjectures as to the nature of the relationship. On the one hand, it may be that the T3 excess found in our patients is the precipitating cause of the coronary events, reflecting the direct action of T3 on the heart. Indeed this may be the major mechanism operative in the relationship evidenced in our data. On the other hand, coronary events in return might also have affected thyroid function. While we found no evidence in the literature that the acute stress associated with coronary events could have led to T3 excess, there is enough evidence that nonthyroidal diseases, such as coronary events, could lead...
to a low serum T3 concentration,20-31 Typical changes in nonthyroidal illness include the decrease in extrathyroidal conversion of T4 to T3 accompanied by a decreased serum TSH level. This type of association, however, failed to explain our data because one would expect a coronary event to be associated with low T3 levels, but this was not what we observed. In spite of the likelihood of these T3-lowering effects, ie, altered thyroid function in nonthyroidal illness, we found T3 levels elevated after coronary revascularization. The effect of elevated T3 levels on subsequent coronary events was independent of any of these potentially confounding factors. The results from the cohort study provide evidence for the prognostic value of excess T3.

In conclusion, we could demonstrate that an elevated T3 concentration at hospitalization is associated with a 2.6-fold greater likelihood of the presence of a coronary event. Moreover, an initially elevated T3 level is associated with a 3-fold higher risk of developing a subsequent coronary event during the next 3 years. Excess T3 seemed to be a factor associated with the transition from chronic coronary artery disease to AMI.

Accepted for publication March 17, 2000.
We are indebted to H. H. Raspe, MD, PhD, F. S. Keck, MD, and H. Djonlagic, MD, for their invaluable suggestions, and to J. Levejohann, MD, and S. Sommer for their help in data collection.

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