Increased serum β_2 -microglobulin concentrations in hyperthyroid states

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Abstract

Serum β_2 -microglobulin concentrations were determined in 21 untreated hyperthyroid patients (12 with Graves' disease, and nine with toxic nodular adenoma) and in 20 healthy controls. All subjects had normal serum creatinine concentrations and urine analysis. Both total and free thyroid hormones were significantly higher in the hyperthyroid groups than in controls. β_2 -microglobulin concentrations were significantly increased in both groups of hyperthyroid patients compared with controls. No difference was found in the thyroid hormone and β_2 -microglobulin concentrations between both sets of patients. The β_2 -microglobulin and thyroid hormone concentrations were not correlated. These data show that hyperthyroidism is another cause of increased β_2 -microglobulin production along with viral infections, immunologically mediated diseases, and malignant neoplasms. The increased serum β_2 -microglobulin concentration in thyroid hyperfunction is probably related to metabolic rate, even if autoimmunity might contribute to its overproduction.

β_2 -microglobulin is a low molecular weight protein (11 600) found on the surface of lymphocytes and other nucleated cells, where it constitutes the light chain of class I histocompatibility antigens.¹ Free molecules are also detectable in the plasma as products of cell turnover, particularly from lymphocytes. The serum concentration of β_2 -microglobulin closely depends on renal function because the kidneys are the main site of clearance.² Increased concentrations of β_2 -microglobulin have been found in viral infections, including human immunodeficiency virus infection, malignancies, especially lymphoproliferative diseases, and in autoimmune disorders.³⁻⁵ Conflicting data have been reported about the serum concentrations of β_2 -microglobulin in thyroid diseases and the pathogenesis of this is still disputed.⁶⁻⁹ We therefore carried out a study of serum β_2 -microglobulin concentrations in two groups of hyperthyroid patients, 12 with Graves' disease and nine with toxic nodular adenoma, and compared them with normal subjects.

Methods

Twenty one patients with untreated hyper-

thyroidism were studied: 12 had Graves' disease (11 women and one man, age range 38-70 years) and nine had toxic nodular adenoma (three women and six men, age range 40-74 years). Diagnostic criteria for hyperthyroidism were increased concentrations of free thyroid hormones and undetectable concentrations of serum thyroid stimulating hormone (TSH). Graves' disease and toxic nodular adenoma were differentiated according to the usual clinical and scintigraphic data. All the patients had normal urine analysis and serum creatinine concentrations, and were unaffected by other diseases.

Twenty healthy subjects of comparable age constituted the control group. Blood samples were taken at 08.00 h after an overnight fast for measurements of serum TSH, T4, T3, free T4 (FT4), free T3 (FT3), creatinine, and β_2 -microglobulin. TSH was determined by an immunoradiometric assay (reagents from Cis International, France; lower detection limit 0.02 mU/l); T4, T3, FT4 and FT3 were determined by radio immunoassay (reagents from Mallinckrodt, West Germany; Biodata, Italy; Clinical Assay-Baxter Division, USA; and Becton Dickinson, USA, respectively); β_2 -microglobulin by a latex agglutination photometric immunoassay, LAPIA (reagents from Eiken Chemical, Japan; reference values 0.8-2 mg/l), using an automatic analyser (LA-System 2000, Poli Diagnostici, Italy); and serum creatinine by an autoanalyser method.

Statistical analysis was performed by the Mann-Whitney U test for unpaired data and linear regression analysis.

Results

Results expressed as mean (SEM) are given in the table. Both patient groups had significantly higher concentrations of both total and free thyroid hormones than the controls, while no difference was detected among the patients. Serum creatinine concentrations were significantly lower in Graves' disease than in toxic nodular adenoma and controls. Serum β_2 -microglobulin was significantly higher in both Graves' disease (2.23 (0.12) mg/l; $p < 0.01$) and toxic nodular adenoma (2.39 (0.28) mg/l; $p < 0.01$) than in controls (1.17 (0.11) mg/l), while no difference existed between the two groups of hyperthyroid patients. No significant correlation was detected between β_2 -microglobulin and both thyroid hormones and serum creatinine in each of the three groups and in the group of hyperthyroid patients as a whole.

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Thyroid function, serum creatinine, and β_2 -microglobulin concentrations in 21 hyperthyroid patients

	T3 (nmol/l)	T4 (nmol/l)	FT3 (pmol/l)	FT4 (pmol/l)	Serum creatinine μ mol/l	β_2 - microglobulin (mg/l)
Graves' disease (n = 12)	4.82 (0.83)	227.53 (23.77)	17.21 (3.52)	52.66 (9.49)	44.25 (6.10)	2.23 (0.12)
Toxic nodular adenoma (n = 9)	4.34 (0.41)	181.97 (16.59)	16.05 (1.63)	18.85 (8.42)	54.17 (3.05)	2.39 (0.28)
Controls (n = 20)	2.08 (0.13)	120.28 (28.93)	4.39 (0.44)	14.14 (1.59)	65.62 (3.81)	1.71 (0.11)
Graves' disease v controls	<0.01	<0.001	<0.001	<0.001	<0.01	<0.01
Toxic nodular adenoma v controls	<0.001	<0.01	<0.001	<0.001	<0.01	<0.01
Graves' disease v Toxic nodular adenoma					<0.05	

Discussion

Increased β_2 -microglobulin concentrations have been reported in both inflammatory and neoplastic diseases, particularly of lymphoid origin, as well as in renal failure²⁻⁵; recently it has been shown that serum β_2 -microglobulin is of prognostic value in patients with HIV infection.¹⁰ β_2 -microglobulin has also been determined in autoimmune thyroid disease. In chronic thyroiditis β_2 -microglobulin measurements have given conflicting results,^{6,9} while in Graves' disease β_2 -microglobulin was clearly raised, but the cause of its increased production is unknown, and both immune processes and endocrine changes have been suggested as possible explanations.^{8,9}

It is well known that Graves' disease has an immune mediated pathogenesis with changes in both T and B cell activities and their interactions.¹¹ Activated T cells are increased in untreated patients; the suppressor-effector activity of CD8+ cells or suppressor-inducer function of CD4+ 2H4+ cells in thyroid glands are considerably impaired when compared with those in peripheral blood. These changed ratios may lead to increased activation of B lymphocytes.^{12,13} Therefore, an increase in serum β_2 -microglobulin in Graves' disease might be a direct consequence of this lymphocytic derangement. Furthermore, the reduction of β_2 -microglobulin occurring during treatment with methimazole might be due to the effect of this drug on immune processes.¹⁴ On the other hand, the high concentrations of β_2 -microglobulin reported in toxic nodular adenoma^{8,9} suggest that hyperthyroidism itself induces this through a metabolically mediated increase in β_2 -microglobulin production. This hypothesis is further supported by the significant decrease of β_2 -microglobulin during antithyroid treatment, both in Graves' disease and toxic nodular adenoma.⁸

Our data show that patients with untreated hyperthyroidism have significantly higher concentrations of serum β_2 -microglobulin than controls (Graves' disease v controls and toxic nodular adenoma v controls $p < 0.01$). As serum creatinine was normal in all subjects, the increased serum β_2 -microglobulin in hyperthyroid patients is due to overproduction. There was no difference in thyroid hormones and β_2 -microglobulin con-

centrations between the group with Graves' disease and the group with toxic nodular adenoma, which also supports the hypothesis that the increased serum β_2 -microglobulin concentrations represent mainly a hormonal effect rather than an expression of autoimmune dysfunction. As reported by Lervang and Mulder,^{8,9} we have not found any correlation between β_2 -microglobulin and thyroid hormone concentrations and therefore β_2 -microglobulin can not be considered a reliable indicator of the degree of thyroid hyperfunction. The lack of correlation between serum β_2 -microglobulin and thyroid hormone concentrations might also suggest an additional role for immunological processes in the increase in β_2 -microglobulin production.

In summary, our findings show that hyperthyroidism must be borne in mind when interpreting increased serum β_2 -microglobulin concentrations.

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