

Association of elevated insulin-like growth factor binding protein-1 with insulin resistance in hyperthyroidism

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Summary

OBJECTIVE Insulin-like growth factor binding-protein-1 (IGFBP-1) has a role in glucose homeostasis and is present at high concentrations in hyperthyroidism. We have investigated the relationship between IGFBP-1 concentration and glucose homeostasis in hyperthyroidism.

DESIGN Patients and controls had intravenous glucose tolerance tests (IVGTT) and/or oral glucose tolerance tests (OGTT). Patients were tested when hyperthyroid and when euthyroid whilst the controls were tested once. The IVGTT was used to assess insulin sensitivity and the OGTT to establish that the study group had abnormal glucose tolerance. The hyperthyroid patients were treated with methimazole to restore euthyroidism.

PATIENTS Ten patients (9 females) and 13 healthy controls (9 females) consented to the study. Ten patients and nine controls (7 females) had IVGTT. Six patients (5 females) and six controls (4 females) had OGTT.

MEASUREMENTS Glucose, insulin, glucagon, GH and IGFBP-1 were measured during GTT. IGF-I, free thyroid hormones, and TSH concentrations were measured basally.

RESULTS Hyperthyroid subjects were insulin resistant and 67% had impaired glucose tolerance. Fasting IGFBP-1 levels were doubled in hyperthyroid subjects compared to healthy controls and correlated positively with free T4 ($r=0.84$, $P<0.0001$), with peak glucose during the OGTT ($r=0.68$, $P<0.005$) with peak insulin during the IVGTT ($r=0.51$, $P<0.005$) and negatively with glucose disappearance constant ($r=-0.52$, $P<0.005$). IGFBP-1 was highly phosphorylated in hyperthyroid and control subjects. Fasting insulin and IGFBP-1 levels were unrelated but IGFBP-1 suppressed acutely during GTT in all groups. GH levels fell less in patients with hyperthyroidism than in normals during GTTs.

CONCLUSIONS We conclude that in hyperthyroidism thyroid hormones directly increase fasting IGFBP-1 concentration but acute regulation of IGFBP-1 by insulin is normal and that elevated fasting phosphorylated IGFBP-1 concentration is associated with insulin resistance.

The serum concentration of IGFBP-1 is modulated by prevailing thyroid hormone levels. Hyperthyroidism raises IGFBP-1 levels which return to normal with the restoration of euthyroidism (Miell *et al.*, 1994). Untreated hypothyroid patients have low IGFBP-1 levels which have been reported to rise (Angervo *et al.*, 1993b) or not change (Miell *et al.*, 1993) with the institution of thyroxine therapy. Similarly, withdrawal of thyroxine therapy in hypothyroid patients produces a fall in IGFBP-1 levels which is reversed after recommencing treatment (Angervo *et al.*, 1993c; Miell *et al.*, 1994). Under most circumstances, insulin is the main negative regulator of IGFBP-1 (Cotterill *et al.*, 1993b), probably through a direct effect on gene expression in the liver (Conover & Lee, 1990), although glucagon plays a lesser role as a positive regulator (Hilding *et al.*, 1993; Westwood *et al.*, 1995). In addition, glucose independently regulates IGFBP-1 concentration *in vitro* (Cotterill *et al.*, 1989) and *in vivo* (Snyder & Clemmons, 1990). Thyroid hormone may act directly on IGFBP-1

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concentration or indirectly by altering the concentrations of other hormones such as insulin or glucagon. IGFBP-1 is usually highly phosphorylated in human nonpregnant serum (Westwood *et al.*, 1995) which increases its affinity for IGF-I and augments its inhibitory action on IGF-I function (Coverley & Baxter, 1997); the degree of phosphorylation of IGFBP-1 in hyperthyroidism has not been reported.

There is good evidence that IGFBP-1 has an independent action in glucose homeostasis. Prolonged fasting in humans raises IGFBP-1 levels and impairs glucose tolerance (Cotterill *et al.*, 1993b) and a transgenic mouse, which overexpresses the gene for human IGFBP-1, has been described which exhibits fasting hyperglycaemia, hyperinsulinaemia and glucose intolerance (Rajkumar *et al.*, 1995); similar results were obtained by injection of IGFBP-1 into rats (Lewitt *et al.*, 1991). The mechanism by which IGFBP-1 affects glucose concentrations may be through a reduction in free IGF-I concentrations which may have a tonic glucose lowering effect (Nyomba *et al.*, 1997).

Glucose intolerance has long been recognized to accompany hyperthyroidism but the mechanisms involved are complex. Glucose concentrations are raised during oral glucose tolerance testing in hyperthyroid patients (Cavagnini *et al.*, 1974; Shen & Davidson, 1985; Taylor *et al.*, 1985; Ikeda *et al.*, 1990) and largely return to normal with the restoration of euthyroidism (Shen & Davidson, 1985). The occurrence of both raised IGFBP-1 concentrations and impaired glucose tolerance in hyperthyroidism suggests that the association may be causal. We have examined this relationship and have also explored the factors responsible for

regulating IGFBP-1 concentrations during glucose tolerance testing in hyperthyroidism.

Methods

Protocol

The protocol was approved by the Ethics Committee of Reggio Emilia and consent was given by subjects prior to participation in the study. Two cohorts were studied, thyrotoxic patients and healthy controls. Hyperthyroidism was defined as elevated free thyroid hormone levels and undetectable TSH. The hyperthyroid patients were treated with methimazole alone to restore euthyroidism, defined as a normal TSH concentration or a normal free T4 (FT4) level. Patients and controls underwent IVGTT and/or OGTT. The IVGTT was used to assess insulin sensitivity and the OGTT to establish that the study group had abnormal glucose tolerance. Patients were tested when hyperthyroid and when euthyroid whilst the controls were tested once. The median period between tests for the patients was 110 days (range 40–269). Subject details are given in Table 1 for the OGTT and Table 2 for the IVGTT.

Intravenous glucose tolerance test

An intravenous cannula was inserted and 0.5 g/kg glucose was given as a 25% solution over 3 minutes. Blood samples were taken at times – 10, – 1, 1, 3, 5, 7, 10, 15, 20, 30, 45, 60, 75, 90, 105, 120, 150, 180 minutes, separated immediately and stored at – 20°C until analysis.

	Control	Hyperthyroid	Euthyroid
Number	6	6	6
Age (year, median (range))	24.5 (22–43)	43.5 (19–59)	43.5 (19–59)
Sex	5F:1M	4F:2M	4F:2M
FT3 (pmol/l)	4.0 ± 0.9	17.6 ± 2.8 ^{bd}	3.1 ± 0.6
FT4 (pmol/l)	16.9 ± 1.4	58.8 ± 8.1 ^{bd}	16.4 ± 0.9
TSH (mU/l)	2.2 ± 0.2	ND ^{bd}	2.1 ± 0.2
Fasting blood glucose (mmol/l)	4.5 ± 0.1	4.7 ± 0.2	4.6 ± 0.2
2-h blood glucose (mmol/l)	4.7 ± 0.2	6.7 ± 0.4 ^{bd}	4.6 ± 0.2
Proportion with IGT	0/6	4/6	0/6
Peak glucose (mmol/l)	7.3 ± 0.3	9.2 ± 0.5 ^{bc}	7.4 ± 0.2
Time of peak glucose (minutes)	27.5 ± 2.5	42.5 ± 6.0	32.5 ± 2.5
Glucose AUC _{0–180} (minutes.mmol/l)	928 ± 44	1222 ± 44 ^{bd}	933 ± 33
Peak insulin (mU/l)	67.3 ± 8.7	78.0 ± 8.2 ^{ac}	65.7 ± 5.6
Time of peak insulin (minutes)	30.0 ± 0.0	55.0 ± 11.4	46.3 ± 6.3
Insulin AUC _{0–180} (minutes.U/l)	4.9 ± 0.7	7.4 ± 1.2	5.4 ± 0.4
Glucagon AUC _{0–180} (minutes.ng/l)	NT	9068 ± 652	10075 ± 1080
Nadir GH (mU/l)	0.54 ± 0.30	3.0 ± 0.81 ^{ac}	0.06 ± 0.06

Table 1 Oral glucose tolerance test: Subject characteristics and hormone concentrations

(Results as mean ± SEM unless stated otherwise; ND, not detected; NT, not tested; IGT, impaired glucose tolerance. Significance shown as follows; a, $P < 0.05$ vs. controls; b, $P < 0.01$ vs. controls; c, $P < 0.05$ vs. euthyroid; d, $P < 0.01$ vs. euthyroid).

Table 2 Intravenous glucose tolerance test: Subject characteristics and hormone concentrations

	Control subjects	Hyperthyroid patients	Euthyroid patients
Number	9	10	10
Age (year, median (range))	28 (19–43)	38.5 (25–59)*	38.5 (25–59)*
Sex	7F:2M	9F:1M	9F:1M
BMI (kg/m ²)	22.3 ± 0.3	22.3 ± 0.3 ^d	23.4 ± 0.3
FT3 (pmol/l)	4.2 ± 0.3	17.2 ± 2.0 ^{bd}	5.1 ± 0.5
FT4 (pmol/l)	16.1 ± 1.0	53.7 ± 5.5 ^{bd}	17.4 ± 2.5
TSH (mU/l)	2.2 ± 0.2	ND ^b	0.5 ± 0.2**
Peak glucose (mmol/l)	15.3 ± 1.0	16.5 ± 0.4	16.7 ± 0.3
Time of peak glucose (minutes)	3.0 ± 0.6	1.2 ± 0.2*	2.2 ± 0.4
Peak insulin (mU/l)	52.8 ± 6.6	84.3 ± 6.2**‡	52.8 ± 5.1
Time of peak insulin (minutes)	3.8 ± 0.5	1.0 ± 0.0**†	3.3 ± 0.9
Glucagon AUC _{0–180} (minutesng/l)	NT	9281 ± 1093	6248 ± 621
Glucose disappearance constant (%)	2.0 ± 0.2	1.5 ± 0.1*	1.8 ± 0.2
Nadir GH (mU/l)	2.40 ± 0.54	2.97 ± 0.75†	0.90 ± 0.24*

Results as mean ± SEM unless stated otherwise; ND, not detected; NT, not tested. Significance shown as follows; * $P < 0.05$ vs. controls; ** $P < 0.01$ vs. controls; † $P < 0.05$ vs. euthyroid; ‡ $P < 0.01$ vs. euthyroid.

Oral glucose tolerance test

An intravenous cannula was inserted and 75 g glucose was given orally. Blood samples were taken at times –15, 0, 15, 30, 45, 60, 75, 90, 105, 120, 150, 180 minutes, separated immediately and stored at –20°C until analysis.

Assays

GH, IGF-I, insulin, glucose, FT4, free T3 (FT3), and TSH were assayed as previously described (Miell *et al.*, 1994). IGFBP-1 was measured by RIA as previously described (Cotterill *et al.*, 1993a). IGFBP-1 phosphorylation status was determined using *n*-OG electrophoresis and western ligand blotting as previously described (Westwood *et al.*, 1995). C-terminal glucagon was assayed by RIA (Wellcome Research Laboratories, Belfast; intra-assay CV 5.5% at 150 µg/l and interassay 12.2% at 150 µg/l).

Calculations

Homeostasis model insulin resistance index (HOMA-R) (Matthews *et al.*, 1985; Nagasaka *et al.*, 1997) and glucose disappearance constant (GDC) were calculated as follows:

$$HOMA - R = \frac{\text{Fasting insulin (mU/l)} \times \text{Fasting glucose (mmol/l)}}{22.5}$$

$$GDC = \frac{1 - (\text{Glucose}_{30}/\text{Glucose}_{10})}{20}$$

Where glucose_{*x*} represents the glucose concentration at time *x* minutes during the IVGTT. Area-under-the-curve (AUC) calculations were made using the trapezoidal method.

The significance of differences between groups was analysed using *t*-tests; two-sided paired *t*-tests to compare the same subjects when hyperthyroid and euthyroid, and two-sided unpaired *t*-tests to compare patients to controls. Statistical significance was taken at $P < 0.05$. To allow analysis, undetectable TSH concentrations were regarded as being 0 mU/l. Data were determined to be Normally distributed prior to the use of statistical tests or descriptors such as SEM. Stepwise multiple linear regression was performed using SPSS software.

Results

Results are given as mean ± standard error with *P*-values when significant.

Prevalence of impaired glucose tolerance and diabetes

Four of the six hyperthyroid patients who had an OGTT had impaired glucose tolerance, as defined by 2 h blood glucose concentrations greater than 6.7 mmol/l (WHO Study Group, 1985), which resolved when the patients were euthyroid; all controls had normal glucose tolerance (Table 1).

Hormone concentrations during the IVGTT and OGTT

Table 1 summarizes the changes during the OGTT and Table 2 summarizes the changes during the IVGTT. There were no significant differences in the initial (time 0–10 minutes) area-under-the-curve (AUC) for glucose but insulin AUC from

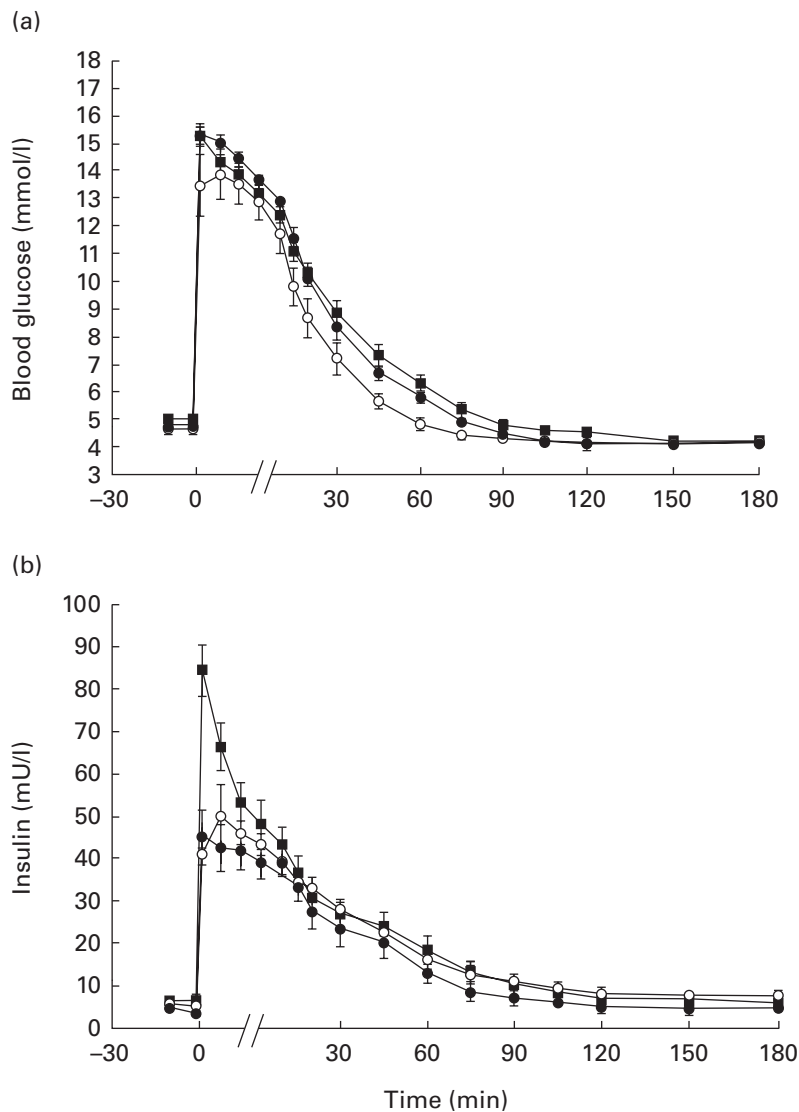


Fig. 1 a, Mean blood glucose concentrations during intravenous glucose tolerance tests in hyperthyroid patients (■, $n = 10$), euthyroid patients (●, $n = 10$) and healthy controls (○, $n = 9$). b, Mean insulin concentrations during intravenous glucose tolerance tests in hyperthyroid patients (■, $n = 10$), euthyroid patients (●, $n = 10$) and healthy controls (○, $n = 9$). Mean \pm SE.

times 0–10 minutes was significantly higher in hyperthyroid patients than in controls (Figs. 1 and 2).

IGFBP-1 concentration

Analysis of the hyperthyroid patients and normal controls demonstrated a highly significant correlation between fasting IGFBP-1 and FT4 or FT3 (FT4 and IGFBP-1, $r = 0.84$; FT3 and IGFBP-1, $r = 0.79$). Fig. 3 illustrates the relationship between IGFBP-1 and FT3 concentration. There was also a strong relationship between the change in thyroid hormone concentration and the change in fasting IGFBP-1 concentration with treatment of the hyperthyroidism (Δ FT4 and Δ IGFBP-1, $r = 0.81$; Δ FT3 and Δ IGFBP-1, $r = 0.69$).

Biochemical characterization of fasting serum IGFBP-1 from the thyrotoxic patients demonstrated that 6/7 had exclusively highly phosphorylated IGFBP-1 when thyrotoxic and when euthyroid. One patient had some non or lesser phosphorylated IGFBP-1 when hyperthyroid which was not detected when euthyroid (Fig. 4, lanes 5–6); this change may merely reflect the sensitivity of the test as the total amount of IGFBP-1 present when euthyroid was less. All normal control sera ($n = 4$) contained only highly phosphorylated IGFBP-1.

IGFBP-1 concentrations were significantly greater in hyperthyroid patients than in euthyroid patients or controls throughout the IV and OGTT. When expressed as a percentage of the baseline value, similar suppression of IGFBP-1 occurred in all groups (Fig. 5).

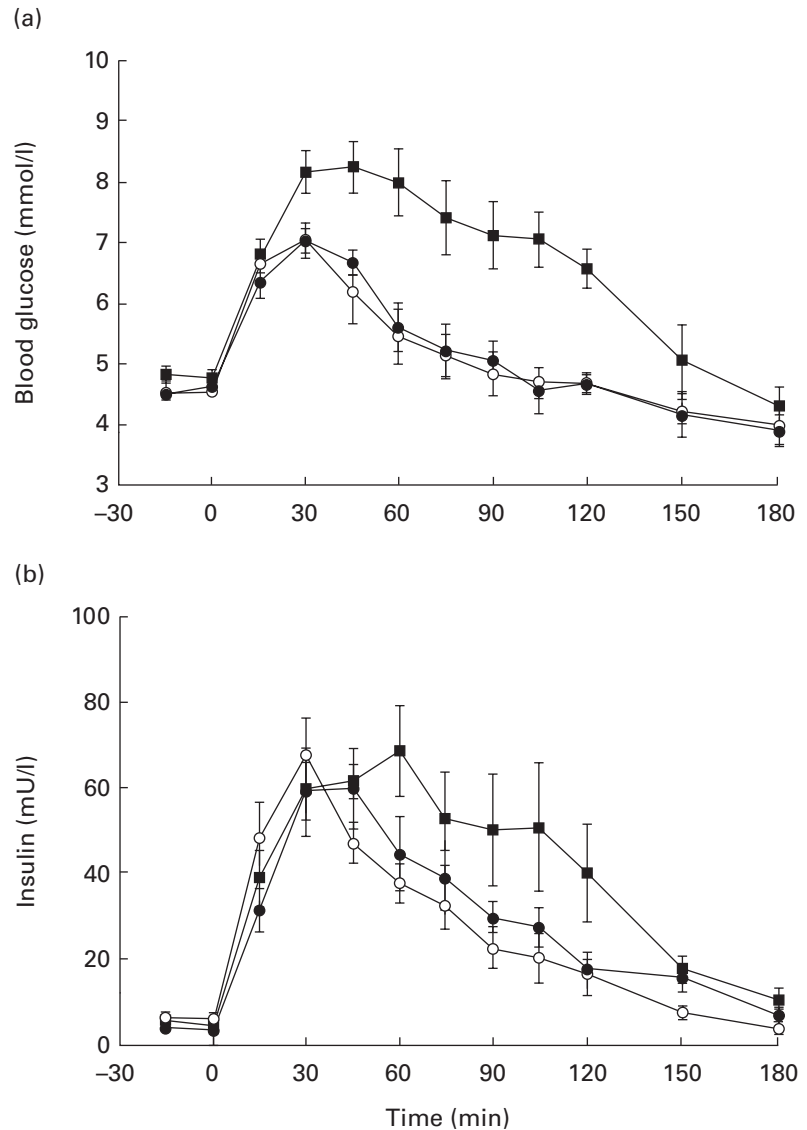


Fig. 2 a, Mean blood glucose concentrations during oral glucose tolerance tests in hyperthyroid patients (■, $n = 6$), euthyroid patients (●, $n = 6$) and healthy controls (○, $n = 6$). b, Mean insulin concentrations during oral glucose tolerance tests in hyperthyroid patients (■, $n = 6$), euthyroid patients (●, $n = 6$) and healthy controls (○, $n = 6$). Mean \pm SE.

When all subjects were combined, fasting IGFBP-1 correlated with peak glucose during the OGTT ($r = 0.68$, $P < 0.005$) and with peak insulin during the IVGTT ($r = 0.51$, $P < 0.005$) but not with fasting or AUC insulin or glucose. Fasting IGFBP-1 correlated with the GDC ($r = -0.52$, $P < 0.005$) but not with HOMA- R -values ($r = -0.05$). Stepwise multiple linear regression with GDC as the dependent variable and fasting IGFBP-1, fasting GH, AUC₀₋₁₈₀ GH and FT4 as independent variables produced the following univariate relationship:

$$\text{GDC} = (2.35 \times 10^{-2}) - (1.99 \times 10^{-4}) \times [\text{IGFBP} - 1]$$

$$R^2 = 0.28$$

IGFBP-1 levels correlated negatively with the insulin concentration

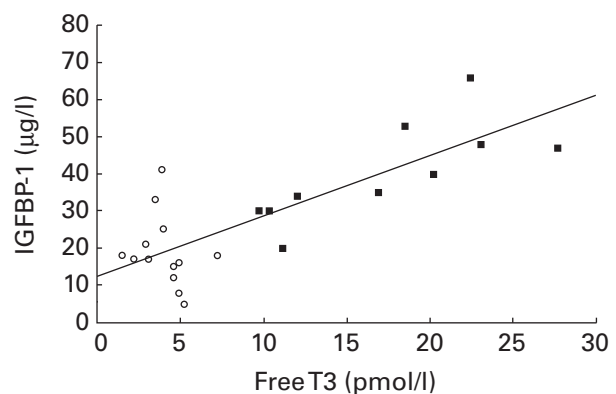


Fig. 3 Correlation of mean fasting IGFBP-1 and free T3 concentrations in hyperthyroid patients (■, $n = 10$) and normal controls (○, $n = 13$).

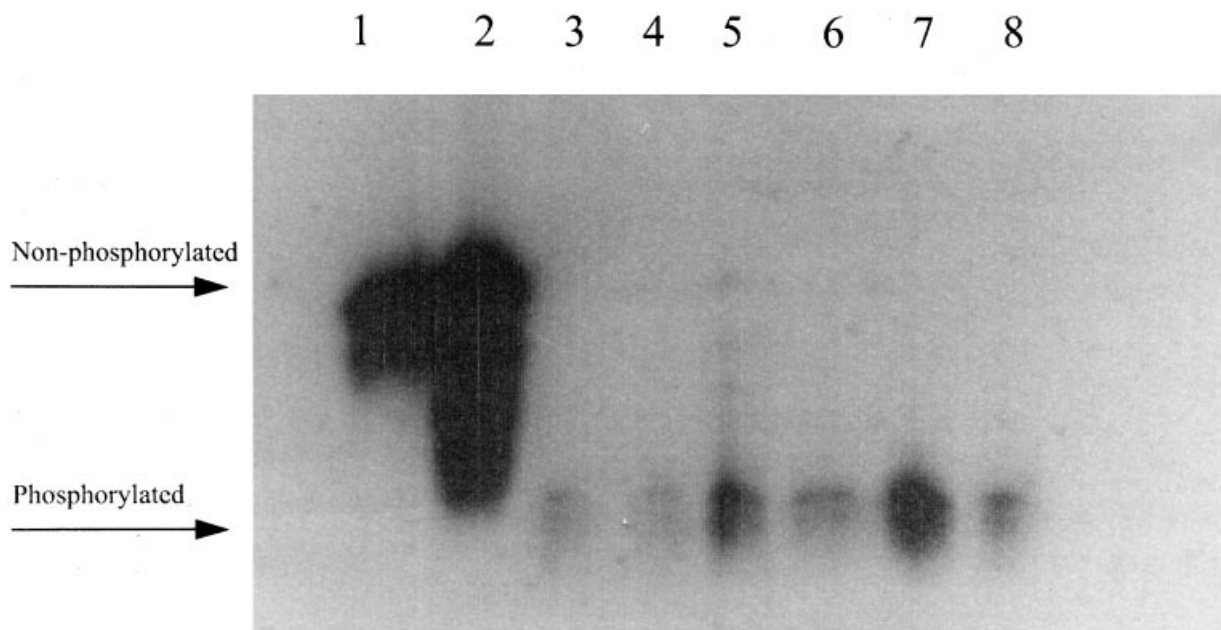


Fig. 4 Representative Western ligand blot of paired fasting sera from patients when hyperthyroid and when euthyroid. (Lane 1, nonphosphorylated recombinant IGFBP-1; 2, amniotic fluid; 3, normal control; 4, normal control; 5, patient A hyperthyroid; 6, patient A euthyroid; 7, patient B hyperthyroid; 8, patient B euthyroid).

45 minutes earlier and with the insulin concentration 60 minutes earlier in hyperthyroid patients during the OGTT ($r = -0.80$, $P < 0.02$ and $r = -0.88$, $P < 0.01$, respectively) but not in euthyroid or control subjects.

Growth hormone and IGF-I

Five of the six hyperthyroid patients who had an OGTT failed to suppress GH concentration to less than 2 mU/l whereas all the normal controls and the patients when euthyroid had normal GH suppression. GH nadir during the OGTT was higher in hyperthyroid patients than in euthyroid patients or normal controls. The GH AUC₀₋₁₈₀ during the OGTT was higher in patients when hyperthyroid (1359 ± 255 minmU/l) than when euthyroid (303 ± 72 minmU/l, $P = 0.006$). Fasting IGF-I concentrations are given in Table 3.

Discussion

IGFBP-1 concentrations in hyperthyroid patients were more than twice those in control subjects and returned to normal with the treatment of hyperthyroidism. The mechanism responsible may be a direct action of thyroid hormones on IGFBP-1 production or elimination, or may be indirect via perturbations in other hormones, such as insulin or glucagon. The strong and highly significant relationship found in this study between

IGFBP-1 concentrations and FT3 or FT4 levels suggests that thyroid hormones act directly to increase IGFBP-1. In addition, the lack of a relationship between fasting IGFBP-1 levels and fasting insulin or glucagon is against these proteins being the link between elevated thyroid hormones and IGFBP-1. Our finding that IGFBP-1 falls in an indistinguishable manner during the GTT, whether patients are hyperthyroid or euthyroid, suggests that the clearance of IGFBP-1 is not affected by hyperthyroidism and thus the predominant effect of thyroid hormones is probably to increase IGFBP-1 production. Thyroid hormones have been reported to directly increase IGFBP-1 gene expression in tissue culture (Angervo *et al.*, 1993a). The IGFBP-1 protein was found to be highly phosphorylated in hyperthyroidism, as in health, indicating that the raised IGFBP-1 concentrations in hyperthyroidism are likely to be active in binding IGF-I.

Glucose intolerance is known to be common in hyperthyroidism and our finding of impaired glucose tolerance in 66% of hyperthyroid subjects supports this. The aetiology of abnormal glucose homeostasis in hyperthyroidism is unclear with previous studies examining the roles of insulin and glucagon (Hales & Hyams, 1964; Kabadi & Eisenstein, 1980; AvRuskin *et al.*, 1985; Shen & Davidson, 1985; Müller *et al.*, 1986; Lam *et al.*, 1987; Gonzalo *et al.*, 1996). Strong evidence exists that IGFBP-1 has an independent action in glucose homeostasis with increasing concentrations leading to glucose intolerance.

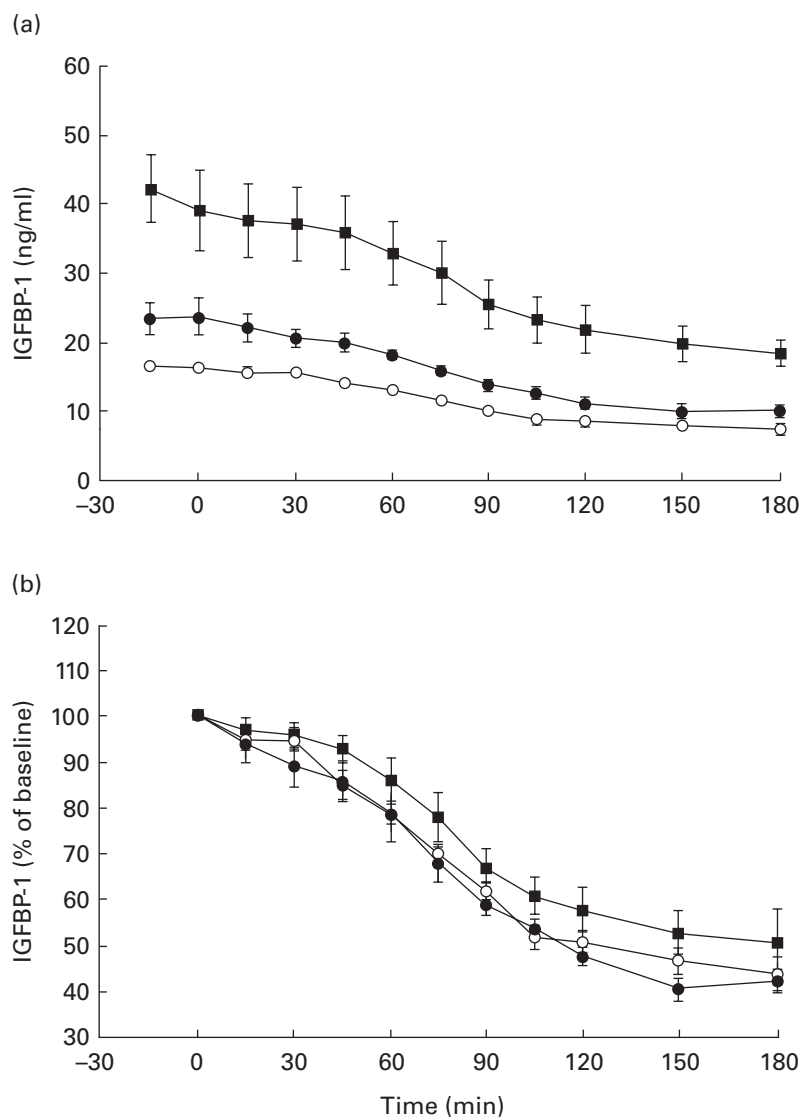


Fig. 5 a, IGFBP-1 concentrations during oral glucose tolerance tests in hyperthyroid patients (■, $n = 6$), euthyroid patients (●, $n = 6$) and healthy controls (○, $n = 6$). b, Fall in IGFBP-1 concentration (as percentage of basal value) during oral glucose tolerance tests in hyperthyroid patients (■, $n = 6$), euthyroid patients (●, $n = 6$) and healthy controls (○, $n = 6$).

We found that hyperthyroid patients had insulin resistance as evidenced by increased HOMA-*R*-values and a decreased GDC. The patient group was older than the control group for the IVGTT but this is unlikely to have had a major effect on insulin resistance as there was evidence of reversible insulin resistance (as judged by HOMA-*R* scores) at baseline in the hyperthyroid patients which decreased in the same patients when euthyroid, i.e. the insulin resistance was due to hyperthyroidism and not age. Fasting IGFBP-1 levels correlated with the GDC and predicted the peak glucose concentration during the OGTT. Euthyroidism was associated with a fall in IGFBP-1 levels and resolution of the impaired glucose tolerance despite a significant increase in BMI. The discovery of a significant

relationship between fasting IGFBP-1 concentration and GDC is potentially causal. Three lines of evidence suggest that the direction of causality is from IGFBP-1 to insulin resistance. Firstly, we found no relationship between fasting insulin (one indicator of insulin resistance) and IGFBP-1, although insulin resistance was evident from the HOMA-*R*-values. Secondly, as discussed earlier, there is ample experimental evidence in animals that IGFBP-1 has actions to cause glucose intolerance and insulin resistance. Lastly, in other conditions exhibiting insulin resistance, such as the polycystic ovary syndrome (Morris & Falcone, 1996) and noninsulin dependent diabetes mellitus (Bang *et al.*, 1994), IGFBP-1 levels are not raised, suggesting that insulin resistance is not a determinant of high IGFBP-1 levels.

Table 3 Fasting hormone concentrations in patients when hyperthyroid and when euthyroid, and in normal controls

	Control subjects	Hyperthyroid patients	Euthyroid patients
Number	13	10	10
Fasting glucose (mmol/l)	4.6 ± 0.1	5.0 ± 0.1 ^a	4.8 ± 0.1
Fasting insulin (mU/l)	5.8 ± 0.9	6.3 ± 0.9	4.3 ± 0.4
Fasting IGFBP-1 (µg/l)	18.7 ± 2.7	39.3 ± 3.9 ^{bd}	24.2 ± 1.9
Fasting IGF-I (µg/l)	119 ± 19	108 ± 8	105 ± 13
HOMA-R (mmol.mU/l ²)	1.19 ± 0.20	1.41 ± 0.22 ^c	0.90 ± 0.09
Insulin:glucose ratio (mU/mmol)	1.3 ± 0.2	1.3 ± 0.2	0.9 ± 0.2

Results as mean ± SEM; NT, not tested; HOMA-R, homeostasis model insulin resistance index. Significance shown as follows; a, $P < 0.05$ vs. controls; b, $P < 0.01$ vs. controls; c, $P < 0.05$ vs. euthyroid; d, $P < 0.01$ vs. euthyroid.

Despite varying fasting IGFBP-1 concentrations in the different patient groups, acute regulation of IGFBP-1 was normal during GTT indicating that the raised level of IGFBP-1 was not a consequence of insulin resistance. Both insulin and glucagon acutely regulate IGFBP-1, either by decreasing or increasing levels, respectively. Our findings of acutely increased insulin during the GTT, and the relationship between IGFBP-1 and 45 or 60 minute earlier insulin concentrations, indicate that insulin acutely modulates IGFBP-1 concentration in hyperthyroidism.

The increased GH levels during GTT in this study mirror the findings of previous studies of increased spontaneous GH secretion (Iranmanesh *et al.*, 1991) and decreased GH suppression during GTT (Cavagnini *et al.*, 1974) in hyperthyroidism. GH levels failed to suppress after IVGTT in hyperthyroidism (AvRuskin *et al.*, 1985). In contrast, Moller *et al.* (1996) found similar fasting GH levels in hyperthyroid patients and controls. The mechanism for the change in GH regulation is not clear. Although many factors could be responsible for this effect it seems plausible that the increase in IGFBP-1 in hyperthyroidism reduces free IGF-I levels and thus GH levels rise through a lack of negative feedback. Elevated GH levels act in opposition to insulin in glucose homeostasis and may have contributed to glucose intolerance.

We found that IGF-I levels were not affected by hyperthyroidism which is consistent with the report that artificial elevation of thyroid hormone levels, by treating normal subjects with thyroxine for 3 months, did not change IGF-I levels (Miell *et al.*, 1994). In contrast, high IGF-I levels have been described in hyperthyroidism which fell with treatment (Miell *et al.*, 1993) and withdrawal of thyroxine from thyroidectomised patients led to a fall in IGF-I levels of 18–29% (Angervo *et al.*, 1993c; Miell *et al.*, 1994). It is not clear why our results differ from other studies as the degree of hyperthyroidism was similar. The normal IGF-I concentrations seen may mask a reduced bioavailable IGF-I due to the presence of increased IGFBP-1.

In conclusion, we have found a strong relationship between hyperthyroidism and raised phosphorylated IGFBP-1 levels. This is most likely due to a direct effect of thyroid hormones on IGFBP-1 production as IGFBP-1 clearance was normal. The raised IGFBP-1 is associated with IGT, predicts the glucose response to an OGTT and is directly related to reduced glucose disappearance, suggesting that IGFBP-1 may be involved in regulating glucose disposal in hyperthyroidism. The high IGFBP-1 levels probably produce a fall in free IGF-I, which may account for the increases seen in serum GH concentration by the loss of negative feedback. In hyperthyroidism, fasting IGFBP-1 levels are reset at a higher level by a direct effect of thyroid hormones. This may act as a compensatory mechanism to the increase in fuel consumption associated with the increased metabolic rate of thyrotoxicosis, a similar compensation to that seen in the fasting state.

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