MANOEL RICARDO ALVES MARTINS

O ESTADO SOMATOTRÓFICO É UM DETERMINANTE IMPORTANTE DA AÇÃO DO HORMÔNIO TIROIDEANO EM CRIANÇAS COM DEFICIÊNCIA DE HORMÔNIO DE CRESCIMENTO: IMPLICAÇÕES PARA A TERAPIA COM LEVOTIROXINA NO HIPOTIROIDISMO CENTRAL

Tese apresentada à Universidade Federal de São Paulo – Escola Paulista de Medicina para a obtenção do Título de Doutor em Ciências

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Abreviações

ANOVA	Analysis of variance
CH	Central hypothyroidism
CTRL	Control
D1	Type I deiodinase
D2	Type II deiodinase
D3	Type III deiodinase
DXA	Dual energy X-ray absorptionmetry
ET	Ejection time
FT_4	Free thyroxine
GH	Growth Hormone
GHD	Growth Hormone deficient
ICT	Isovolumic contraction time
IFMA	Immunofluorimetric
IGF-I	Insulin-like Growth Factor I
IRT	Isovolumic relaxation time
L-T_4	Levothyroxine
OFF GH	Non GH-replaced GHD children
ON GH	GH-replaced GHD children
REE	Resting Energy Expenditure
SE	Standard error
T_3	Triiodothyronine
T_4	Tetraiodothyronine
TH	Thyroid Hormone
TSH	Thyroid Stimulating Hormone
TT_3	Total Triiodothyronine

Dedicatória

Dedico essa tese a Lígia. Por tudo. Para sempre.

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Sumário

GROWTH HORMONE (GH) REPLACEMENT IMPROVES THYROXINE BIOLOGICAL EFFECTS: IMPLICATIONS FOR MANAGEMENT OF CENTRAL HYPOTHYROIDISM

Short title: GH improves thyroxine biological effects

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Abstract

Context: The biological significance of GH-induced changes in serum TH concentrations is unknown. It has been suggested that serum FT_4 should be targeted at the high normal range during GH replacement.

Objective: To evaluate the effects of GH replacement on thyroxine biological effects.

Hypothesis: If GH modulates thyroxine biological effects, serum FT_4 should be targeted accordingly.

Design/Setting: Observational (Study 1) and interventional (Studies 2-3)/Outpatient.

Patients: 32 GHD patients (13 off GH; 22 on L-thyroxine).

Interventions: Study 2: Levothyroxine to increase FT_4 (>1.0ng/dL). Study 3: GH administration or withdrawal.

Main outcome measures: FT_4, TT_3, myocardial isovolumic contraction time (ICT) and resting energy expenditure (REE).

Results: Study 1: OFF GH and ON GH groups had similar FT_4, but OFF GH showed lower TT_3 (P<0.01) and REE (P=0.02), higher ICT (P<0.05) than ON GH and controls. On GH, ICT and REE correlated only with TT_3 (r=-0.48, r=0.58, P<0.05). Off GH, ICT correlated only with FT_4 (P<0.01).

Study 2: Off GH, levothyroxine intervention increased FT_4 (P=0.005), TT_3 (P=0.012), decreased ICT (P=0.006), increased REE (P=0.013); ICT and FT_4 changes correlated (r=-0.72, P=0.06). On GH, levothyroxine increased FT_4 (P=0.0002), TT_3 (P=0.014),

REE (P=0.10), decreased ICT (P=0.049); REE and TT_3 changes correlated (r=0.60, P=0.05).

Study 3: GH decreased FT_4, increased TT_3, decreased ICT, increased REE (P<0.05). REE correlated (P<0.05) with IGF-I (r=0.57), TT_3 (r=0.64). ICT correlated only with TT_3 (r=-0.47).

Conclusions: GH replacement improves the biological effects of thyroxine. Serum FT_4 should be targeted at the high normal range in GHD patients only off GH replacement.

Introduction

Central hypothyroidism (CH) is a common disorder in patients with hypothalamic-pituitary disease. It results from decreased stimulation of an otherwise normal thyroid gland by a decreased and/or biologically less active TSH (1;2). At diagnosis, serum TSH levels in CH may be decreased, normal or slightly elevated, and consistently decline to low/undetectable levels during physiological levothyroxine replacement (3). Thus, both diagnosis and adequacy of levothyroxine replacement in CH have to rely on serum T_4 levels, which show intraindividual variations much narrower than the normal reference range (4). In addition, GH deficiency (GHD) is usually present in patients with CH and GH replacement is known to change serum concentrations of thyroid hormones (TH), decreasing T_4 and increasing T_3 through peripheral mechanisms (5-9).

In practice, a low serum T_4 in patients with hypothalamic-pituitary disease is highly specific, but insensitive, to diagnose CH given the high prevalence of CH in that population. Biochemical markers of peripheral TH action like cholesterol, sex hormone-binding protein, angiotensin-converting enzyme, carboxyl-terminal telopeptide of type I collagen, osteocalcin, and bone GLA protein have all been proved insufficiently sensitive and/or specific in the diagnosis and management of CH (10). Furthermore, optimum T_4 levels during levothyroxine replacement in CH have not been established through biological markers of TH action. Notwithstanding, targeting serum T_4 levels to the high normal reference range, both in children receiving GH or in any patient with CH irrespective of GH replacement, has been widely recommended (11).

Resting energy expenditure (REE), on the other hand, is very sensitive to changes in TH concentrations and relatively easy to measure using indirect calorimetry

(12), but REE is also influenced by GH (13). More recently, we have shown that the isovolumic contraction time (ICT), a sensitive and specific marker of TH action in the heart (14;15), was increased in nearly all adult patients with hypothalamic-pituitary disease and low FT_4 levels, in 38% of those with normal FT_4 and that increasing serum FT_4 levels within the normal range with levothyroxine normalized ICT in most patients (16;17).

The aim of the present study was to investigate the biological significance of the changes in serum TH concentrations that occur during GH replacement in GHD children and adolescents using both ICT and REE as biological markers of TH action.

Subjects and Methods

Subjects

The study protocol was approved by the local ethical committee and written informed consent was always obtained.

Patients: Thirty-two patients (21 males; age: 15.8±5.7 yr, range: 6-23 yr) with hypothalamic-pituitary disease followed at our Neuroendocrine Clinic were consecutively enrolled (Table 1).

Thirty patients had GHD (GH<10.0 μg/L after clonidine and insulin-induced hypoglicemia), 17 on GH replacement with recombinant human GH (0.035 mg/kg/day sc)]; 22 had CH, all on levothyroxine (50-125 μg/day po); 8 had ACTH deficiency (cortisol<18 μg/dL after insulin-induced hypoglicemia), all on prednisone (2.5-5.0 mg/day po); 12 had gonadotrophic deficiency, all on sexual steroid replacement. Hormone replacements were kept unchanged for ≥3 months before the study.

Controls: Twenty-three age- and sex-comparable healthy subjects (13 males; age: 12.6±3.8 yr, range: 5-19 yr).

Study 1: Influence of GH replacement on basal serum TT_3, ICT and REE

All patients underwent an initial evaluation after a 10-12 h overnight fasting, starting with indirect calorimetry, followed by blood collection, dual energy X-ray absorptionmetry (DXA) and echocardiographic evaluation.

Study 2: Influence of GH replacement on the responses of serum TH, ICT and REE to levothyroxine intervention

Eight GHD patients (3 off/5 on GH) with low FT_4 (<0.7 ng/dL) and 10 GHD patients (4 off/6 on GH) with FT_4 between 0.7-1.0 ng/dL were reevaluated after starting and/or increasing levothyroxine (by 12.5-25 μg each 5-6 weeks) until FT_4 reached 1.0-1.54 ng/dL.

Study 3: Influence of GH intervention on serum TH, ICT and REE

Patients who started (n=4) or stopped (n=3) GH replacement after basal evaluation or after levothyroxine intervention were reevaluated using the same protocol after 5-6 weeks of changing GH status. Replacement of other hormones was kept unchanged.

Hormone Assays

Hormones were measured, in duplicate, in serum.

Free T_4

Immunofluorimetric assay (Delfia, Wallac Oy, Turku, Finland). Sensitivity: 0.16 ng/dL. Intraassay and interassay coefficients of variation: 4.4% and 6.1%, respectively. Normal reference values: 0.7–1.54 ng/dL.

Total triiodothyronine

Immunofluorimetric assay (Delfia Wallac Oy, Turku, Finland). Sensitivity: 20 ng/dL. Intraassay and interassay coefficients of variation: 3.0%. Normal reference values: 80-210 ng/dL.

Insulin-like growth factor–I (IGF-I)

Immunoradiometric assay (DSL, Texas, USA). Sensitivity: 0.8 ng/mL. Intraassay and interassay coefficients of variation: 1.5–3.4% and 1.5–8.2%, respectively.

Echocardiographic Examination

A complete 2-dimensional and Doppler echocardiogram was performed using a 2.0- to 2.5-MHz transducer (HDI 5000, Philips, Andover, Mass, USA). ICT and other measurements in the same patient were made by the same echocardiographist (F.C.D. or V.A.M.) without knowledge of patient´s data, as previously described (16).

Resting Energy Expenditure (REE)

REE was measured using the Vista Mini-CPX metabolic system (Vacumed, Ventura, CA, USA) linked to a gas analyzer CO2/O2 Vacumed Turbofit connected to a computer and monitored by Vista Turbofit 4.0 software as described elsewhere (12). Estimated REE was calculated by an equation (18) using fat-free mass (DXA, QDR 4500, Hologic Inc, Wartham, MA, USA). REE was expressed as measured/estimated REEx100.

Data analysis

Statistical analyses: GraphPad Prism 4.03 (www.graphpad.com). Comparisons: paired or unpaired *t* test (2 groups) or ANOVA (>2 groups) followed by Student-Newman-Keuls test. Correlations: Pearson´s test. Significance: 0.05. Results: mean±SE.

Results

Study 1: Influence of GH replacement on basal TT_3, ICT and REE

Twenty-four patients (14 ON/10 OFF GH) had FT_4 within the normal reference range, including 14 patients with CH receiving levothyroxine and similarly distributed between ON GH and OFF GH subgroups (7/14 *vs.* 7/10, *P*=0.42). Eight patients had low FT_4 (5 ON/3 OFF GH), all with undertreated CH.

Patients with normal FT_4 levels

As shown in Figure 1, no difference in FT_4 was observed between OFF and ON GH groups (0.99±0.07 ng/dL *vs.* 0.98±0.04 ng/dL, respectively, *P*=0.89), which reflected a similar target of serum FT_4 (midnormal range) in our patients with CH taking levothyroxine irrespective of GH replacement. FT_4 levels were 13% lower in both groups as compared to controls (1.12±0.03 ng/dL, *P*<0.05).

TT_3 was lower in OFF as compared to ON GH patients (109.1±7.4 ng/dL *vs.* 141.1±9.7 ng/dL, *P*<0.01) or controls (156.3±5.2 ng/dL, P<0.001), but similar between ON GH patients and controls (*P*>0.05). TT_3/FT_4 ratios were significantly lower in OFF GH (114.7±10.3, *P*=0.02), but not in ON GH patients (148.1±13.8, P=0.55), as compared to controls (140.4±5.2).

ICT was similar in ON GH patients and controls (39±3.6 ms *vs.* 38±2.9 ms, P=0.91) but higher in OFF (49±2.8 ms) as compared to ON GH patients (*P*=0.049) and controls (*P*=0.032).

REE was lower in OFF GH patients as compared to controls (88%±5.8% *vs.* 104%±3.5%, *P*=0.02), and lower, but not significantly, when compared to ON GH

patients (98±3.5, *P*=0.14). ON GH patients and controls showed similar REE (*P*=0.26).

Patients with low FT_4 levels

FT_4 levels were similar in patients with low FT_4 on GH and the only three patients off GH (0.54±0.08 ng/dL *vs.* 0.53±0.04 ng/dL, respectively, *P*=0.84), but both groups had lower FT_4 (*P*<0.001) as compared to controls.

TT_3 was not different in OFF and ON GH patients with low FT_4 (110.7±23.1 ng/dL *vs.* 97.6±13.0 ng/dL, *P*=0.61), but was lower in both groups as compared to controls (156.3±5.2 ng/dL, *P*<0.05 and *P*<0.001, respectively).

ICT was increased in OFF as compared to ON GH patients (65.0±1.5 ms *vs.* 41.4±6.7 ms, *P*<0.05) or controls (*P*<0.01), but no significant difference in ICT was observed between ON GH patients and controls (41.4±6.7 ms *vs.* 38±2.9 ms, *P*>0.05).

REE was decreased in OFF as compared to ON GH patients (69%±2.5% *vs.* 93.4%±5.9%, *P*<0.05) or controls (104%±3.5%, *P*<0.01), but not between ON GH patients and controls.

Correlations between ICT, REE and TH levels

As shown in Figure 2, ICT was inversely correlated with FT_4 in OFF (r=-0.79, *P*< 0.01) but not in ON GH (r=-0.12, *P*=0.64) and with TT_3 in ON (r=-0.48, *P*=0.04) but not in OFF GH (r=-0.11, *P*=0.73) groups. REE was correlated with TT_3 in ON (r=0.58, *P*=0.01) but not in OFF GH (r=-0.17, *P*=0.59) groups. REE showed no significant correlations with FT_4 in either ON (r=0.07, *P*=0.78) or OFF GH groups (r=0.30, *P*=0.32).

Study 2: Response to levothyroxine intervention

Non GH-replaced patients

As shown in Figure 3, FT_4 increased from 0.68±0.06 ng/dL to 1.33±0.11 ng/dL (*P*=0.005), TT_3 increased from 110±11.4 ng/dL to 146±14.9 ng/dL (P=0.012), ICT decreased from 60±2.3 ms to 37±2.5 ms (*P*=0.0006), and REE increased from 80.0±6.2 to 93.4±4.9 (*P*=0.013) after levothyroxine in non GH-replaced patients. As compared to controls, levothyroxine intervention resulted in a 19% higher FT_4 (1.33±0.11 ng/dL *vs.* 1.12±0.03 ng/dL, *P*=0.0127) but similar TT_3 (146±14.9 ng/dL *vs.* 156.3±5.2 ng/dL, *P*=0.43), ICT (37±2.5 ms *vs.* 38±2.9 ms, *P*=0.81) and REE (93.4±4.9 *vs.* 103.8±3.5, *P*=0.15). None of the 7 non GH-replaced patients showed abnormal ICT or REE suggestive of excessive levothyroxine replacement.

In the 3 patients with low FT_4, ICT was high and decreased to the normal reference range, whereas REE was low and increased to the normal reference range in two patients after levothyroxine. In the 4 patients with FT_4 between 0.7-1.0 ng/dL, both FT_4 and TT_3 increased, within the normal reference ranges or slightly above (FT_4 in one patient), ICT decreased, from high to normal in two and within the normal range in another two patients, whereas REE increased only slightly, within the normal reference range in three, and remained below that range in one patient.

GH-replaced patients

As shown in Figure 4, FT_4 increased from 0.72±0.06 ng/dL to 1.25±0.07 ng/dL (*P*=0.0002), TT_3 increased from 117.9±12.0 ng/dL to 149.5±11.0 ng/dL (*P*=0.014), ICT decreased from 41.4±4.0 ms to 32.3±3.4 ms (*P*=0.049), and REE increased from 99.3±4.3 to 109.4±6.3 (*P*=0.09) in GH-replaced patients after levothyroxine. As compared to controls, levothyroxine intervention resulted in a 12% higher FT_4 (1.25±0.07 ng/dL *vs.* 1.12±0.03 ng/dL, *P*=0.06), but similar TT_3 (117.9±12.0 ng/dL *vs.* 156.3±5.2 ng/dL, *P*=0.53), ICT (32.3±3.4 ms *vs.* 38±2.9 ms, *P*=0.21) and REE (109.4±6.3 *vs.* 103.8±3.5, *P*=0.49). After levothyroxine intervention, four patients showed high REE values, one of which with a low ICT, suggesting levothyroxine excess. TT_3 levels were slightly increased in two of them but in none of the remaining 7 patients who did not show REE or ICT values compatible with levothyroxine excess. FT_4 was slightly increased in only one of those 4 patients, as well as in another one of the remaining seven patients. As a subgroup, these 4 patients presented increased TT_3 (180.3±20.5 *vs.* 131.0±8.0 ng/dL, *P* = 0.03) but similar FT_4 (1.18±0.14 *vs.* 1.29±0.09 ng/dL, *P*=0.51) and IGF-I (119.5±19.3 *vs.* 254.0±143.5, *P*=0.51) levels as compared to the seven patients without abnormalities in REE and/or ICT suggestive of levothyroxine excess.

In the 5 patients on GH replacement and low FT_4, both TT_3 and REE were low in one and ICT was high in another patient (with the lowest FT_4). After levothyroxine, these two patients increased FT_4, TT_3, ICT and REE values into the normal reference ranges. In the remaining 3, levothyroxine intervention resulted in normal FT_4 and TT_3 levels in two patients, one of which with a low ICT, and slightly high FT_4 and TT_3 with a high REE in another one. In the 6 patients with FT_4 levels between 0.7-1.0 ng/dL before levothyroxine, one patient had low TT_3, high ICT and REE at the lower limit, and another one had a slightly increased REE with the

lowest ICT and the highest TT_3 before levothyroxine intervention. In the former, FT_4 increased, and both TT_3 and ICT, but not REE, were corrected after levothyroxine. In the latter, FT_4 increased to the mid-range, TT_3 and REE increased slightly and ICT remained unchanged.

Correlations between changes in ICT, REE and TH after levothyroxine intervention

ICT

Changes in ICT after levothyroxine intervention showed a strong inverse correlation with changes in FT_4 levels (r=-0.72, *P*=0.06) in non GH-replaced but not in GH-replaced patients (r=-0.38, *P*=0.25) (Figure 4, top). Changes in ICT showed no significant correlations with changes in TT_3 in GH-replaced (r=0.08, *P*=0.82) and non GH-replaced patients (r=0.17, P=0.61).

REE

Changes in REE after levothyroxine intervention showed a positive correlation with changes in TT_3 (r=0.60, *P*=0.05) in GH-replaced but not in non GH-replaced patients (r=0.15, *P*=0.75) (Figure 4). Changes in REE showed no significant correlation with changes in T_4 in GH-replaced (r=0.12, *P*=0.72) and non replaced patients (r=0.39, *P*=0.39).

Study 3: Influence of GH intervention on TH, ICT and REE

Seven GHD patients with FT_4 within the normal reference range were evaluated both on GH and off GH replacement. As expected, IGF-I levels were higher during GH replacement (558±140 ng/mL *vs.* 122±40 ng/mL, *P*=0.0082).

As shown in Figure 5, FT_4 decreased from 1.36±0.08 ng/dL to 1.09±0.09 ng/dL (*P*=0.031) (-25%), TT_3 increased from 111.0±7.0 ng/dL to 147.9±13.3 ng/dL (*P*=0.003) (+ 33%), TT_3 to FT_4 ratio increased from 82.7±5.8 to 143.3±18.9 (*P*=0.01) and became similar to controls (140.4±5.2, *P*=0.84), whereas ICT decreased from 38.9±3.0 ms to 29.9±3.1 ms (*P*=0.048) and REE increased from 76.0±3.7 to 92.4±6.4 (*P*=0.036) after GH replacement. ICT remained within the normal reference range. REE values were low (< 80%) in 5 patients before GH and remained low in two during GH replacement (both with the lowest T_3 values).

Correlations between biological markers of TH action (ICT, REE) and TH and IGF-I concentrations

When all ICT and REE values observed along a wide range of IGF-I concentrations (4–1011 ng/mL) obtained by changing somatotrophic status in seven GHD patients, ICT showed no significant correlations with IGF-I (r=-0.01, P=0.98) or FT_4 (r=0.34, *P*=0.23), but tended to correlate inversely with TT_3 levels (r=-0.47, P=0.09).

REE showed positive correlations with IGF-I (r=0.57, *P*=0.03) and TT_3 (r=0.64, *P*=0.01), but not with FT_4 levels (r=-0.22, *P*=0.44) (Figure 6).

Discussion

Although the effects of GH replacement on thyroid hormone concentrations are well established (9), their biological significance remains unclear. Because serum FT_4 levels usually decrease during GH replacement therapy, it has been widely recommended that FT_4 levels should be targeted to the upper mid-range of reference levels with levothyroxine to avoid impairment of linear growth due to hypothyroidism. Undoubtly, GH replacement can lower FT_4 levels to the hypothyroid range and unmask CH in some GHD patients, which should prompt levothyroxine replacement. However, targeting a high normal FT_4 level in patients with normal FT_4 levels is completely empirical and ignores the fact that serum concentrations of T_3, the bioactive form of TH, usually increases during GH therapy (10;11;19).

Changes in FT_4 levels within the reference range, as seen in primary subclinical hypothyroidism and hyperthyroidism, are able to change pituitary TSH secretion and affect other target organs (20). These subclinical states represent mild thyroid disfunctions that, in the long run, have been variably shown to affect quality of life and/or morbi-mortality indexes (21). Considering that patients with CH usually have GHD and frequently other pituitary hormone deficiencies, both under and over replacement of levothyroxine in these patients are likely to have even more deleterious consequences than in patients with primary hypothyroidism.

In study 1, we have shown that GH-replaced GHD children with normal FT_4 levels had higher TT_3 levels as compared to patients without GH replacement with similar FT_4 levels. In study 3, using the same group of patients on and off GH, we confirmed that GH replacement decreased FT_4 and increased TT_3 levels. In both studies, these changes resulted in TT_3/FT_4 ratios indicating that untreated GHD is a

state of decreased T_4 to T_3 conversion that can be fully corrected by GH replacement. GH-induced changes in serum TH levels result from peripheral mechanisms, as they have been shown in children on fixed doses of levothyroxine and undetectable TSH levels (9). In addition, GH had no effect on thyroid gland secretion since serum thyroglobulin levels were unnaffected by GH replacement in study 3 (data not shown). Similar studies in children with unequivocal GHD have also shown decreased T_4 (5;7;9;22;23) and increased T_3 levels (5;7;9;22;24) during GH replacement. In contrast, these changes have been shown to occur only transiently in children with GHD diagnosed by less strict criteria (25), whereas no changes have been found in non-GHD short children receiving GH (26). These differences are likely to reflect the more dramatic change in somatotrophic status that take place when severely GHD patients are replaced with GH as compared to partially or non GHD patients.

The effects of GH replacement on serum TH levels seem to be mediated directly by GH and not via IGF-I, as T_3 levels remained unchanged after IGF-I administration to patients with GH insensitivity due to mutations in the GH receptor (27). Also, a much higher increase in serum T_3 levels has been shown after GH than after IGF-I in GHD patients (28). The sites where GH affects TH metabolism in humans are not known. The peripheral metabolism of TH is under control of three monodeiodinases (D1-3), with different tissue distribution, substrate preference, and kinetics (29). The monodeiodination of T_4 to generate T_3 (activation pathways) is mediated by either D1 or D2, whereas monodeiodination of T_4 to generate reverse T_3 as well as of T_3 to generate T_2 (inactivation pathways) are mediated by D3 (29). In humans, GH actions on peripheral TH metabolism could take place in one or more sites since GH receptors are expressed in several organs and tissues that express predominantly one or more TH deioidinases: liver and kidney (D1),

skeletal and heart muscle and brown adipose tissue (D2), and brain (D1, D2 and D3). The decreased conversion of T_4 to T_3 observed in untreated GHD, which is accompanied by increased rT_3 (9), indicates a physiological role of endogenous GH in peripheral conversion of TH in humans. Further studies are necessary to define which TH activation pathway is controlled by GH.

Hitherto, the biological consequences of GH-induced changes in serum FT_4 and T_3 levels had not been studied. In our observational study (study 1), we have shown that non GH-replaced GHD patients had increased ICT and decreased REE as compared to GH-replaced patients with similar FT_4 levels. In contrast, GH-replaced GHD patients showed ICT, REE and T_3 levels similar to controls, in spite of slightly but significantly lower FT_4 levels than controls, indicating that targeting a high normal FT_4 is unnnecessary to avoid hypothyroidism in most GH-replaced GHD patients. The heart is one of the most sensitive organs to variations in plasma TH levels (30). ICT or other systolic time intervals are increased in patients with primary hypothyroidism and decreased in patients with hyperthyroidism and can be corrected by restoring normal TH/TSH levels by proper treatment (14;31;32). In a preliminary report, we found a surprisingly high prevalence of increased ICT in adult patients with hypothalamic-pituitary disease and normal FT_4 levels, most of them with non GH-replaced GHD. Increasing T_4 levels within the reference range with levothyroxine corrected ICT in nearly all those patients (16;17), indicating that measurement of ICT in patients with hypothalamic-pituitary disease and normal FT_4 levels may be useful both to detect subclinical hypothyroidism and to determine optimal individual serum FT_4 levels during levothyroxine replacement.

In study 3, administration of GH to GHD patients not only decreased FT_4 and increased T_3 levels, as expected, but also improved peripheral markers of TH action, shortening ICT and increasing REE. In this study, ICT was much more

correlated with T_3 (r=- 0.46, *P*=0.09) than with IGF-I (r=- 0.01, *P*=0.98), indicating that ICT reflected TH and not intrinsic GH action in the heart. This effect of GH on ICT could result from GH-induced local conversion of T_4 to T_3 in the heart and/or GH-induced increased serum T_3 levels. Altogether, these data indicate that somatotrophic status modulates TH action in the heart. On the other hand, REE, which has been shown to reflect both intrinsic and indirect (via T_3) actions of GH, correlated with both T_3 (r=0.64, *P*=0.01) and IGF-I levels (r=0.57, *P*=0.03) in this study. Contrary to the widespread concern of inducing hypothyroidism during GH replacement, this study shows that declining FT_4 and increasing T_3 levels within the normal reference, as tipically observed in GHD children, usually improves TH biological effects.

In study 2, we tested the empirical recommendation of targeting a high normal serum FT_4 level in patients with central hypothyroidism, especially in GHD children receiving GH replacement therapy. In effect, mean FT_4 levels reached 1.25 ng/dL, T_3 levels and REE increased and ICT decreased in both GH-replaced and non GH-replaced patients. These effects were observed in patients starting the study with low FT_4 and normal or low T_3, increased ICT and decreased REE, as well as in those with FT_4 between 0.7 and 1.0 ng/dL and normal or low T_3, normal or high ICT and low or normal REE. However, as expected from the positive influence of GH on peripheral markers of TH action showed in studies 1 and 3, abnormal ICT and/or REE indicating excessive TH replacement were observed only in GH-replaced patients (4/11 patients). Interestingly, levothyroxine overreplacement could also be identified by increased TT_3 levels in two of these four patients, but not by FT_4, which is in agreement with our findings that both REE and ICT correlated with TT_3 but not with FT_4 in GHD patients on GH replacement. On the other hand, only ICT was significantly correlated with FT_4 but

not with TT_3 in non-GH replaced GHD patients. Altogether, these observations indicate that targeting a high normal serum FT_4 level may compensate for decreased TH conversion in non GH-replaced GHD children, but may be unnecessary or even harmful in GH-replaced children.

In conclusion, our study demonstrated that GH status is a major determinant of thyroxine biological effects and should be considered in the interpretation and adjustment of serum FT_4 levels in GHD children. A statistically appropriate target value for serum FT_4 in GH-replaced children has no biological reason to be different from controls, thus a serum FT_4 in the midnormal range should suffice for most patients. Conversely, a higher target serum FT_4, into the upper normal range seems biologically more appropriate when GH is not being replaced. Serum TT_3 levels should also be monitored to detect excessive levothyroxine replacement during GH therapy. Finally, ICT and REE could be used to better define thyroid status and establish individual targets of serum T_4 levels in GHD patients.

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Table 1 – Clinical data of 32 patients with hypothalamic-pituitary disease (on GH: patients 1-19; off GH: patients 20-32) at the beginning of the study

#	Age	Sex	CH*	L-Thyroxine	Other Deficiencies	Etiology/Imaging
1	7	F	-	-	GH	Arachnoid Cyst
2	16	M	-	-	GH	Ectopic Neurohypophysis
3	15	M	+	+	GH	Idiopathic
4	6	M	-	-	GH	Ectopic Neurohypophysis
5	8	M	+	+	GH, LH, ACTH	Ectopic Neurohypophysis
6	11	M	-	-	ADH	Idiopathic DI
7	14	M	+	+	GH	Pilocytic Astrocitoma
8	19	M	-	-	GH	Ectopic Neurohypophysis
9	10	F	-	-	GH	Idiopathic
10	20	F	+	+	GH, LH, ACTH, ADH	Rathke´s Cyst
11	19	M	+	+	GH, LH	Absent Pituitary Stalk
12	6	M	+	+	GH	Prop-1 Mutation
13	12	M	+	+	GH	Idiopathic
14	9	M	+	+	GH	Prop-1 Mutation
15	14	M	-	-	GH	Idiopathic
16	18	F	+	+	GH, LH, ACTH	Craniopharyngioma
17	19	M	+	+	GH	Idiopathic
18	6	F	+	+	GH, ACTH	Absent Pituitary Stalk
19	17	M	+	+	-	Macroprolactinoma
20	22	F	+	+	GH, LH, ACTH	Prop-1 Mutation
21	21	F	+	+	GH, LH, ACTH	Prop-1 Mutation
22	21	M	+	+	GH, LH	Craniopharyngioma/RT
23	22	M	-	-	GH, ADH	Hypothalamic Germinoma
24	22	M	-	-	GH	Macroprolactinoma
25	20	F	+	+	GH	Macroprolactinoma
26	19	M	+	+	GH, ACTH, ADH	Craniopharyngioma
27	19	M	-	-	GH, LH, ADH	Infundibuloneurohypophysitis
28	23	F	+	+	GH, LH	Medulloblastoma/RT
29	9	F	+	+	GH, ACTH	Craniopharyngioma
30	21	M	+	+	GH, LH	Idiopathic
31	18	M	+	+	GH, LH, ADH	Dysgerminoma
32	23	F	+	+	GH, LH	Craniopharyngioma

*CH = Central hypothyroidism

Figure 1: Serum FT_4 levels (A), serum TT_3 levels (B), Isovolumic Contraction Time (ICT) (C) and Resting Energy Expenditure (REE) (D) in children with hypothalamic-pituitary disease and normal FT_4 according to GH status: ON GH (17 GH-replaced GHD and 2 GH-sufficient) and OFF GH (13 non GH-replaced GHD) and in 23 normal controls (CTRL). Values are mean ± SE.

Figure 2: Correlations between Isovolumic Contraction Time (ICT), Resting Energy Expenditure (REE %) and serum TH levels and in two groups of children with hypothalamic-pituitary disease according to somatotrophic status: OFF GH (n = 13, left side) and ON GH (n = 19, right side).

Figure 3: Response of serum FT_4 levels (A), serum TT_3 levels (B), Isovolumic Contraction Time (ICT) (C) and Resting Energy Expenditure (REE) (D) to levothyroxine intervention in 7 non GH-replaced GHD children (left side) and 11 GH-replaced GHD children with serum FT_4 levels < 1.0 ng/dL (right side). Horizontal bars represent mean values. Dotted lines represent normal reference ranges.

Figure 4: Correlations between changes in Isovolumic Contraction Time (ICT) and serum FT_4 levels (top) and between Resting Energy Expenditure (REE) and serum TT3 levels (bottom) after levothyroxine intervention in two groups of GHD children according to GH replacement.

Figure 5: Response of serum FT_4 levels (A), serum TT_3 levels (B), Isovolumic Contraction Time (ICT) (C) and Resting Energy Expenditure (REE) (D) to GH replacement in 7 GHD children with normal serum FT4 levels. Horizontal bars represent mean values. Dotted lines represent normal reference ranges.

Figure 6: Correlations between Isovolumic Contraction Time (ICT, left) or Resting Energy Expenditure (REE, right) and serum IGF-I (top) and TT_3 (bottom) levels in seven children with growth hormone deficiency (GHD) on and off GH replacement.

Figure 1

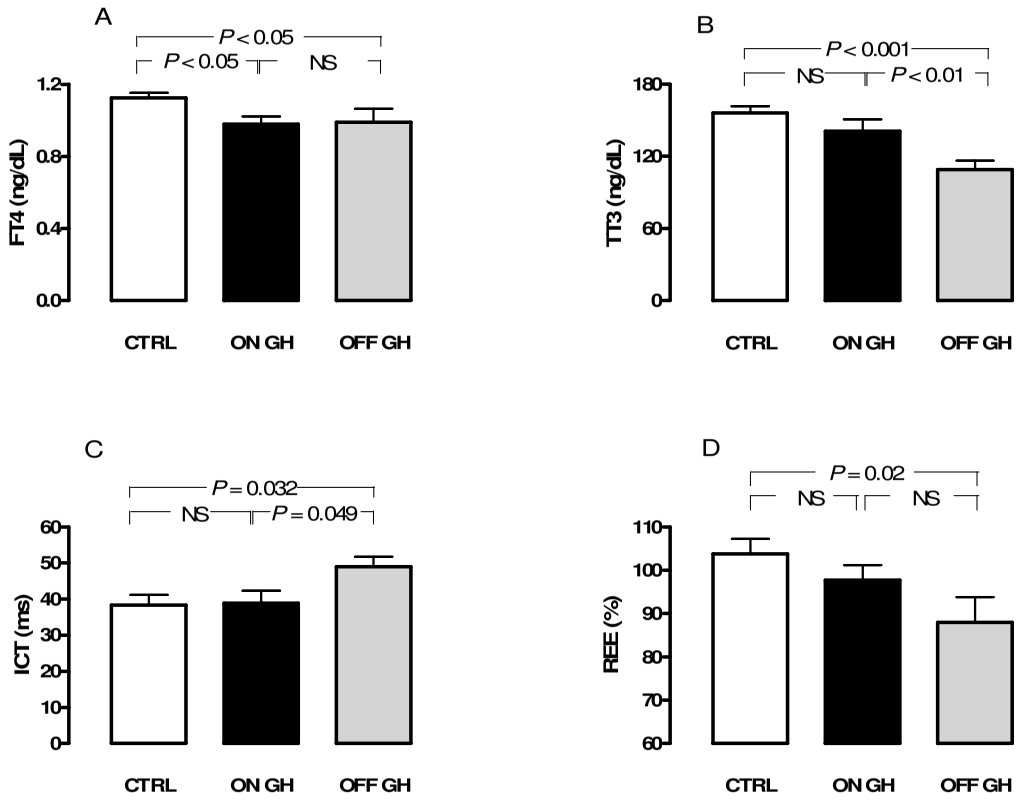

A
P < 0.05
P < 0.05
NS
FT4 (ng/dL)
1.2
0.8
0.4
0.0
CTRL
ON GH
OFF GH
B
P < 0.001
NS
P < 0.01
TT3 (ng/dL)
180
120
60
0
CTRL
ON GH
OFF GH
C
P = 0.032
NS
P = 0.049
ICT (ms)
60
50
40
30
20
10
0
CTRL
ON GH
OFF GH
D
P = 0.02
NS
NS
REE (%)
110
100
90
80
70
60
CTRL
ON GH
OFF GH

Figure 2

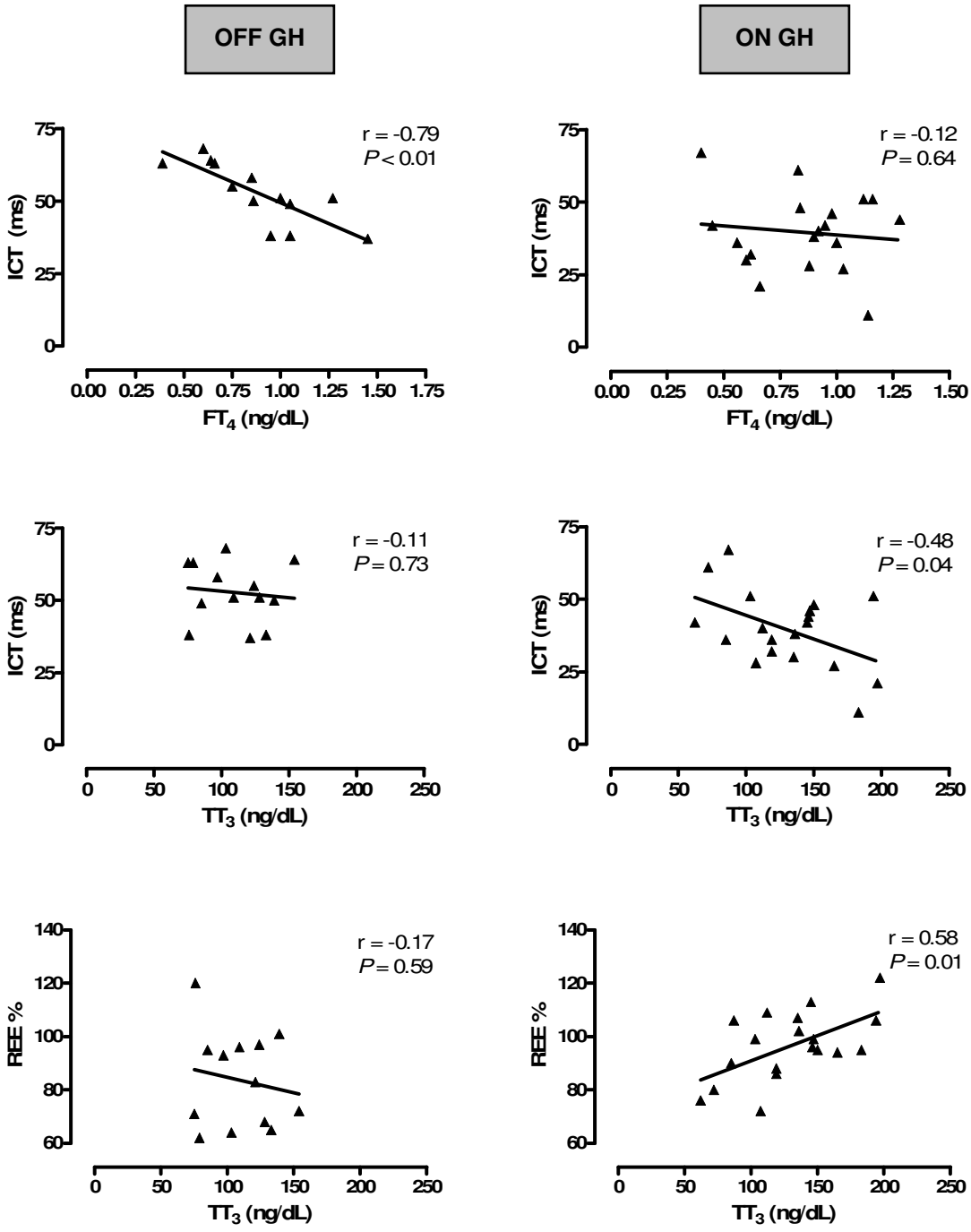

OFF GH
ON GH
ICT (ms)
FT4 (ng/dL)
r = -0.79
P < 0.01
r = -0.12
P = 0.64
TT3 (ng/dL)
r = -0.11
P = 0.73
r = -0.48
P = 0.04
REE %
r = -0.17
P = 0.59
r = 0.58
P = 0.01

Figure 3

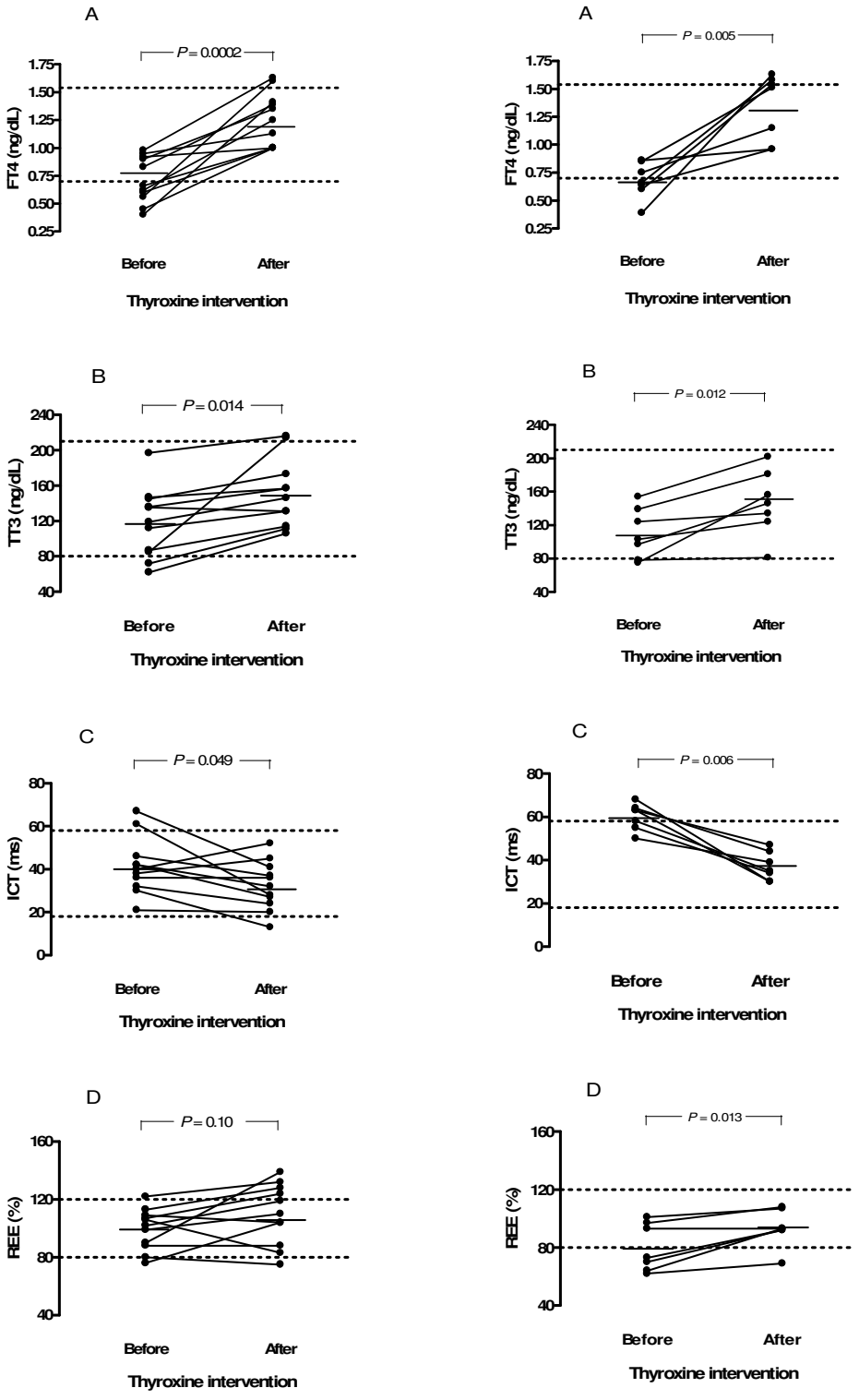

A
P = 0.0002
FT4 (ng/dL)
1.75
1.50
1.25
1.00
0.75
0.50
0.25
Before
After
Thyroxine intervention
A
P = 0.005
FT4 (ng/dL)
1.75
1.50
1.25
1.00
0.75
0.50
0.25
Before
After
Thyroxine intervention
B
P = 0.014
TT3 (ng/dL)
240
200
160
120
80
40
Before
After
Thyroxine intervention
B
P = 0.012
TT3 (ng/dL)
240
200
160
120
80
40
Before
After
Thyroxine intervention
C
P = 0.049
ICT (ms)
80
60
40
20
0
Before
After
Thyroxine intervention
C
P = 0.006
ICT (ms)
80
60
40
20
0
Before
After
Thyroxine intervention
D
P = 0.10
REE (%)
160
120
80
40
Before
After
Thyroxine intervention
D
P = 0.013
REE (%)
160
120
80
40
Before
After
Thyroxine intervention

Figure 4

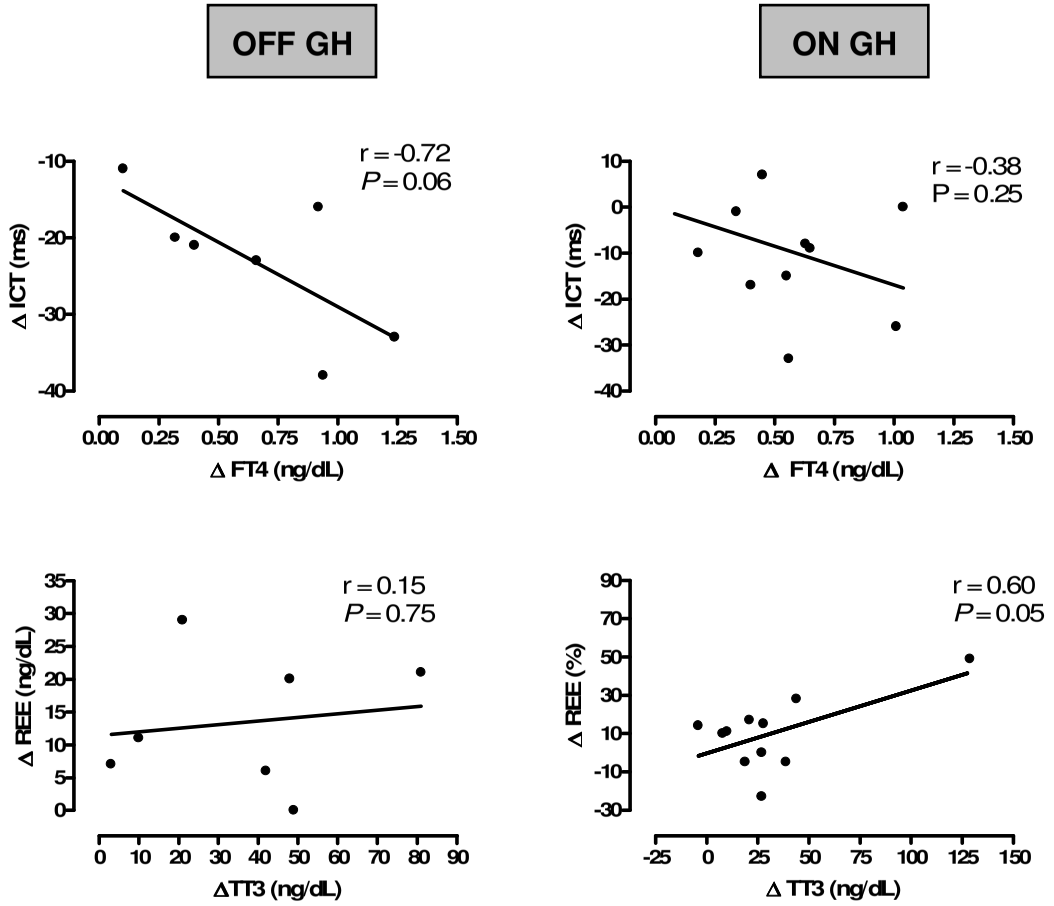

OFF GH
ON GH
r = -0.72
P = 0.06
Δ ICT (ms)
Δ FT4 (ng/dL)
r = -0.38
P = 0.25
Δ ICT (ms)
Δ FT4 (ng/dL)
r = 0.15
P = 0.75
Δ REE (ng/dL)
ΔTT3 (ng/dL)
r = 0.60
P = 0.05
Δ REE (%)
Δ TT3 (ng/dL)

Figure 5

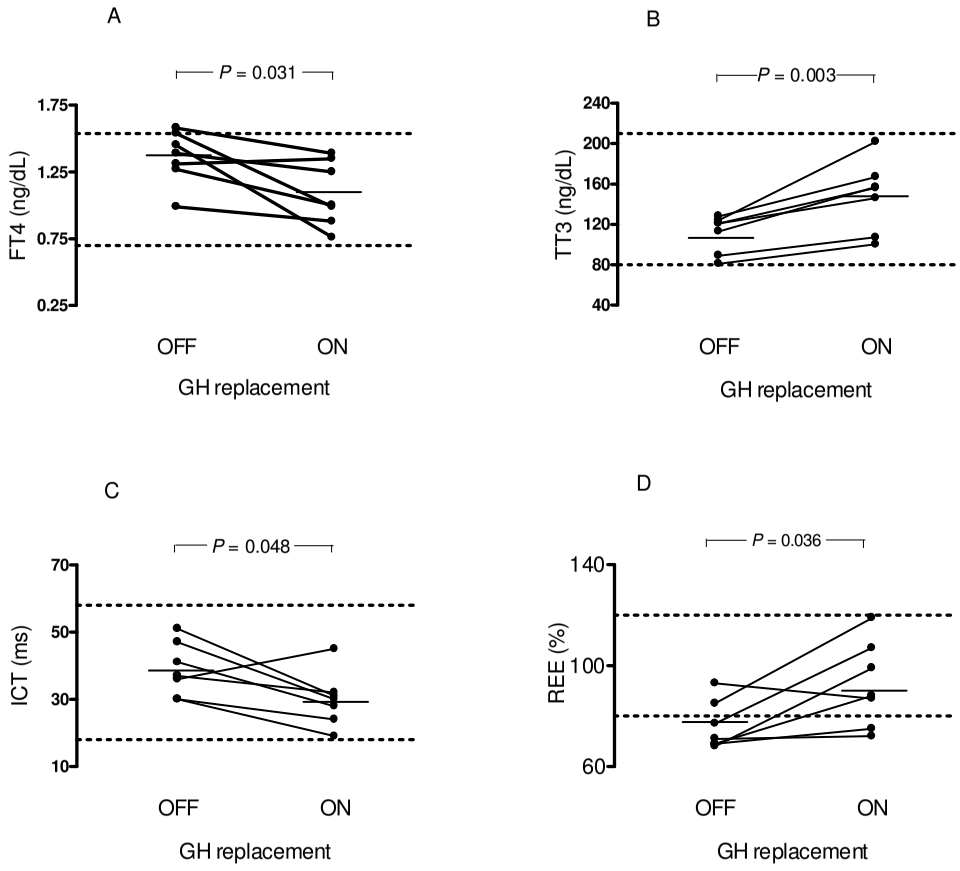
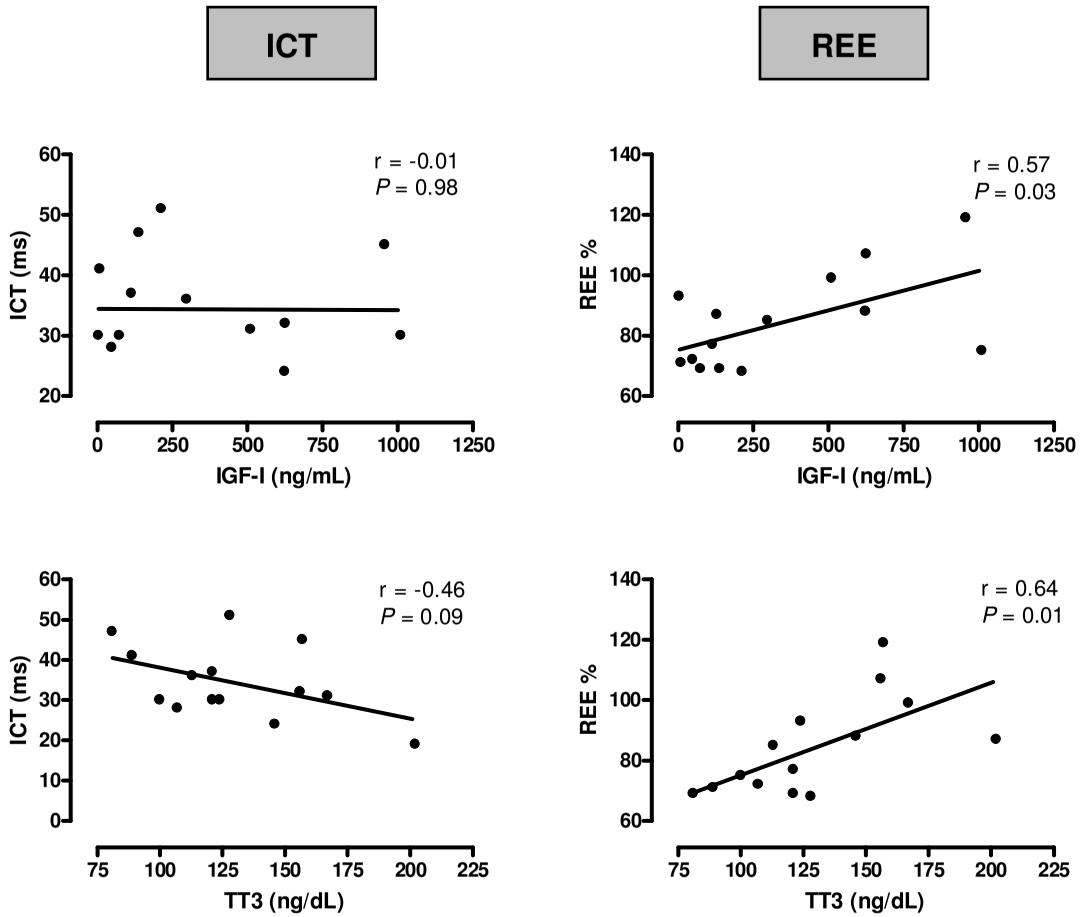

A
P = 0.031
FT4 (ng/dL)
1.75
1.25
0.75
0.25
OFF
ON
GH replacement
B
P = 0.003
TT3 (ng/dL)
240
200
160
120
80
40
OFF
ON
GH replacement
C
P = 0.048
ICT (ms)
70
50
30
10
OFF
ON
GH replacement
D
P = 0.036
REE (%)
140
100
60
OFF
ON
GH replacement

Figure 6


ICT
REE
r = -0.01
P = 0.98
ICT (ms)
IGF-I (ng/mL)
r = 0.57
P = 0.03
REE %
IGF-I (ng/mL)
r = -0.46
P = 0.09
ICT (ms)
TT3 (ng/dL)
r = 0.64
P = 0.01
REE %
TT3 (ng/dL)

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