Free triiodothyronine plasma concentrations are positively associated with insulin secretion in euthyroid individuals

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Abstract

Background—Thyroid hormones (TH) may influence glucose metabolism. Hyperthyroid subjects have higher insulin secretion rates when compared with euthyroid individuals.

Objective—To evaluate the association between TH concentrations and insulin secretion in euthyroid, healthy Pima Indian adults ($n=55$, 29 ± 7 years, females/males 36/19) with normal glucose tolerance (NGT) admitted to a Clinical Research Unit.

Methods—TSH, free thyroxine (FT_4), $3,5,3'$-L-tri-iodothyronine (FT_3), and fasting plasma insulin (FPI) concentrations were measured in fasting plasma samples, percentage of body fat (%BF) by dual energy x-ray absorptiometry (DXA), acute insulin response (AIR), and incremental area under the curve (AUC) of insulin in response to a 25 g intravenous glucose tolerance test (IVGTT) and 75 g oral glucose tolerance test (OGTT) respectively and insulin action (M) during an euglycemic clamp.

Results—FT_3 concentrations were associated with FPI, AIR, and insulin AUC both before ($r=0.33$, $P=0.01$; $r=0.29$, $P=0.03$; and $r=0.35$, $P=0.008$ respectively) and after adjustment for age, sex, %BF, glucose (fasting concentrations or glucose AUC), and M ($\beta=0.09$, $P=0.01$; $\beta=0.16$, $P=0.03$; and $\beta=0.24$, $P=0.0007$ respectively). No associations were found for TSH or FT_4.

Conclusion—FT_3 was associated with several measurements of insulin secretion in euthyroid individuals with NGT. T_3 concentrations may play a role in the regulation of insulin secretion.

Introduction

Inadequate insulin secretion is an early event in the natural history of type 2 diabetes mellitus (T2DM) (1). Glucotoxicity and lipotoxicity (2), cellular nutrient overload (3), inflammatory/ immune mechanisms (4), *in utero* exposure to a diabetic environment (5), low weight at birth (6), and genetic factors (5,7) contribute to this insulin secretory dysfunction. Furthermore, a reduction in β-cell mass may be a characteristic of subjects with impaired fasting glucose and T2DM (8,9). A better understanding of these and other factors influencing β-cell mass and function is important to prevent or delay the development of T2DM.

Thyroid hormones (TH) influence glucose metabolism. Current knowledge on the role of TH in both insulin secretion and action comes mainly from studies performed during experimental or spontaneous forms of hyperthyroidism. The elevated plasma glucose concentrations observed in hyperthyroid subjects are mainly accounted for by an increase in hepatic glucose production, since insulin-mediated glucose uptake in muscle is actually enhanced (10,11). Insulin secretion rates have been reported to be enhanced in thyrotoxic individuals when they

are compared with the euthyroid situation or with control subjects (10,12–16).However, other studies have also reported no differences (17,18) or even decreased (19,20) secretion rates.

In euthyroid individuals, evidence for a physiological role of TH, if any, in insulin secretion is scarce. We aimed to investigate the association of TH with direct measurements of both insulin secretion and insulin action in euthyroid individuals with normal glucose regulation.

Subjects, materials, and methods

Subjects were members of the Gila River (Pima) Indian Community near Phoenix, AZ, USA. Participants were non-diabetic, healthy, adult full-blooded Pima, or closely related Tohono O'odham Indians who participated in an ongoing longitudinal study to identify risk factors for T2DM and obesity. Subjects in this study were part of a group (*n*=115) selected to examine the relationship of TH with energy expenditure and body weight. These subjects had normal thyroid function (based on normal serum thyroid-stimulating hormone (TSH) concentration, 0–3–4.5 mIU/l) and measurements of energy expenditure and substrate oxidation. For the present study, a subset of this group was selected if they had normal glucose tolerance (NGT) and measurements available for both insulin secretion and insulin action. Subjects were admitted to the Clinical Research Unit of the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) in Phoenix, where they were fed a standard weight-maintaining diet for at least 3 days before metabolic testing. Subjects did not smoke or take medication at the time of the study. The study was approved by the NIDDK Institutional Review Board and the Gila River Indian Tribal Council. Before participation, written informed consent was obtained.

Percentage of body fat (%BF) was measured by whole-body dual- energy x-ray absorptiometry. Glucose tolerance status was assessed by a 3-h, 75 g oral glucose tolerance test (OGTT) (American Diabetes Association 2003).Acute insulin response (AIR) was calculated as the average incremental plasma insulin concentration from the third to the fifth minute after a 25 g i.v. glucose bolus. Insulin-mediated glucose disposal rate (M) was assessed at physiologic insulin concentrations (156±36 pmol/l) during a hyperinsulinemic–euglycemic clamp and normalized to estimated metabolic body size (EMBS, fat-free mass + 17.7 kg) (21).

Frozen fasting plasma samples were used to measure TSH and free TH concentrations at Linco-Diagnostic Services Inc., St Charles, MO, USA. Plasma TSH concentrations were measured by RIA (LincoPlex). Plasma 3,5,3′-L-tri-iodothyronine (FT_3) and free thyroxine (FT_4) concentrations were measured by a solid-phase ^{125}I RIA (Diagnostic Product Corporation, Los Angeles, CA, USA) with intra-assay and inter-assay coefficient of variation (CV) values of 6 and 7.8% and 5 and 7%, respectively. Plasma glucose concentrations were measured using the glucose oxidase method (Beckman Instruments Inc., Fullerton, CA, USA). Plasma insulin concentrations were measured by two different radio-immunoassays used over time in our laboratory: Concept 4 (Concept 4; ICN, Costa Mesa, CA, USA) and Access (Beckman Instruments. Insulin assays). All measurements of insulin were normalized to the original RIA (a modified Herbert-Lau assay) using regression equations.

Statistical analyses were performed using SAS software (SAS version 9.1, SAS Institute Inc., Cary, NC, USA). All data are expressed as mean±S.D. throughout the manuscript. Incremental areas under the curve (AUC) for plasma glucose and insulin concentrations during oral glucose tolerance test (OGTT) were determined by the trapezoidal method. Non-normally distributed variables were log transformed ($\log_{10}$) to reduce skewness and then normality was re-evaluated. Pearson's or Spearman's correlation analyses were used to quantify relationships between TH concentrations and variables of interest. General linear regression models were

used to assess independent relationships of FT_3 with measurements of insulin secretion after adjustment for covariates. Level of statistical significance was set at $P<0.05$.

Results

Subjects were euthyroid young adults (Table 1). The FT_3 concentrations were associated with fasting plasma insulin (FPI), AIR, and insulin AUC both before (Fig. 1) and after the adjustment for age, sex, and %BF ($r=0.37$, $P=0.007$; $r=0.35$, $P=0.01$; and $r=0.39$, $P=0.005$ respectively). No associations between FT_3 concentrations and body fat, fasting glucose, incremental glucose AUC, or M were observed. Associations between FT_3 concentrations and FPI, AIR, and insulin AUC were additionally adjusted for glucose concentration and insulin action, the most important determinants of insulin secretion. In multiple regression analyses, FT_3 concentrations were positively associated with FPI, AIR, and insulin AUC after adjustment for age, sex, %BF, fasting plasma glucose concentrations, glucose AUC (only for the association with insulin AUC), and M (Table 2).

Neither FT_4 nor TSH concentrations were associated with FPI, AIR, fasting glucose, or M. The FT_4 concentrations were weakly associated with insulin AUC ($r=0.25$, $P=0.07$).

Discussion

In euthyroid Pima Indians with NGT, plasma concentrations of FT_3 were associated with fasting insulin and with both a direct measurement (AIR) and an estimate (insulin AUC) of β-cell function derived from intravenous glucose tolerance test (IVGTT) and OGTT respectively. These associations were independent of insulin-mediated glucose uptake and plasma glucose concentrations, both major determinants of insulin secretion.

The association between TH and insulin secretion has been investigated mainly in individuals with hyperthyroidism (10,12–19). A serendipitous, positive association between serum-FT_3 and an estimate of insulin production (calculated from the insulin clearance during the clamp and fasting insulin concentrations) was found in euthyroid, lean, healthy individuals (22). A physiological mechanism for the possible role of TH on insulin secretion has not been clearly established, however, evidence indicates that TH may affect both β-cell mass and function.

TH are critically involved in cell growth and development. Plate chondrocyte hypertrophic differentiation (23), cardiomyocyte growth (24), neuronal and glial cell differentiation (25), and primary B lymphopoiesis (26) are influenced by TH. T_3 is also a powerful inducer of pancreatic acinar cell proliferation in rodents (27). β-Cell mass is determined by a balance between β-cell replication, size, and neogenesis, and rate of β-cell apoptosis (28). *In vitro* studies of human and rodent insulinoma cell lines showed that T_3 protects from apoptosis and induces β-cell growth and proliferation (29). The latter effect was mediated by interaction of T_3 with its receptors and associated with changes in the expression of cell cycle-related proteins (29). Human pancreatic duct cells (hPANC-1) express high levels of TH receptor isoforms (30). Treatment of hPANC-1 cells with T_3 induces changes in cell morphology, promotes cell differentiation into insulin-producing β-cells, upregulates insulin and glucose transporter protein-2 transcripts, and increases insulin release into the medium (30). Furthermore, T_3 affects the splicing and secretion of β-amyloid precursor proteins (APP) isoforms (31) and represses the expression of the APP gene in neuroblastoma cells (32). Whether T_3 has a similar effect on islet amyloid polypeptide, a potential cytotoxic protein for β cells, is not known.

On the other hand, TH may also influence β-cell function. TH receptor has been identified in pancreatic β -cell lines (33). T_3-enhanced insulin release in isolated rat pancreatic islets exposed to glucose concentrations of 2–8 mmol/l, had no effect at concentrations of 12 mmol/l, and inhibited insulin release at concentrations of 16.6 mmol/l (34). T_3 promotes expression of

important proteins involved in both glucose and lipid metabolism that may influence insulin secretion. In particular, carnitine palmitoyl transferase 1 (CPT-1) expression and activity (35, 36), mitochondrial glycerol-3-phosphate dehydrogenase (mGPDH) activity (37), and levels of excitatory amino acid transporter type 1 (EAAT1) mRNA and protein (38) are increased by TH. EAAT1 and mGPDH are key components of the NADH shuttles which are essential for coupling glycolysis with mitochondrial ATP generation and triggering glucose-induced insulin secretion (39). CPT-1 is responsible for the transport of fatty acids into the mitochondria for oxidation. Accumulation of long-chain fatty acyl-CoAs is proposed to mediate the deleterious effects of chronically elevated fatty acids on insulin secretion (2). However, free fatty acids (FFAs), when not chronically in excess, are essential to the pancreatic β-cell for its normal function, in particular, for glucose-stimulated insulin secretion (40). It has been reported that hyperthyroid individuals have higher serum concentrations of FFAs, glycerol, and rates of lipolysis in adipose tissue (41,42). Whether, and how, FFA concentrations or rates of lipolysis are similarly influenced at physiological TH concentrations in euthyroid individuals and whether this favors insulin secretion is not known. Unfortunately, FFA concentrations were not available in our study population.

In summary, plasma-free T_3 concentrations were associated with direct and indirect measurements of insulin secretion independent of insulin sensitivity and glucose concentrations in euthyroid individuals with NGT. T_3 concentrations may play a role in the regulation of insulin secretion.

Acknowledgements

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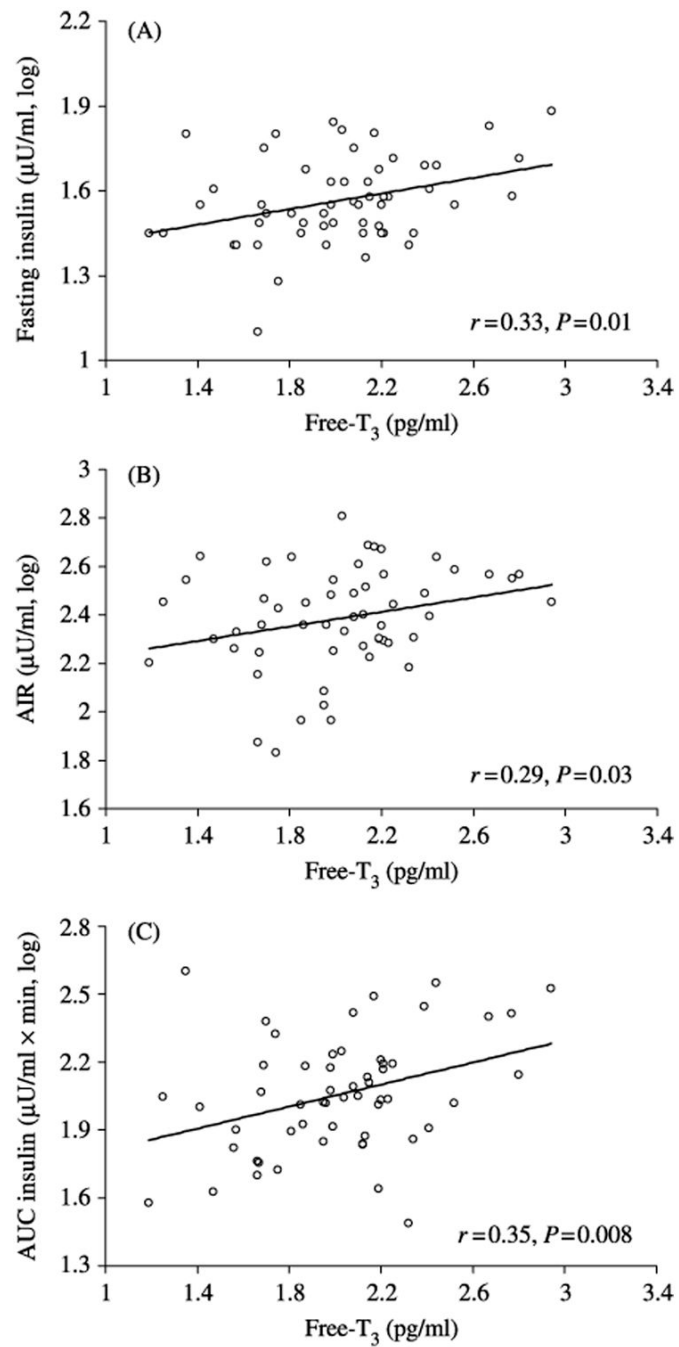
Figure 1.
Association between plasma free T_3 concentrations and fasting plasma insulin (A), acute insulin response (B), and incremental area under the curve of insulin (C). Correlation coefficients and *P* values are given.

Table 1

Subjects characteristics.

	n=55
Sex (females/males)	36/19
Age (years)	29±7
Height (cm)	168±7
Weight (kg)	93±21
BMI (kg/m^2)	33±8
Body fat (%)	32±7
Fasting plasma glucose (mg/dl)	87±10
2-h glucose (75 g OGTT, mg/dl)	105±21
Fasting plasma insulin (μU/ml)	39±14
AUC insulin (μU/ml per min)	136±85
Acute insulin response (μU/ml)	270±120
M (mg/kg EMBS min)	2.8±1.5
TSH (μIU/ml)	2.7±1.5
Free T$_4$ (ng/dl)	1.2±0.2
Free T$_3$ (pg/ml)	2±0.4

Data are mean±s.D; BMI, body mass index; OGTT, oral glucose tolerance test; AUC, Incremental area under the curve; EMBS, estimated metabolic body size; TSH, thyroid-stimulating hormone; Insulin, glucose, TSH, free T$_3$, and free T$_4$ concentrations are given in conventional units; to convert to Système Intermationale units (pmol/l, mmol/l, μIU/l pmol/l, and pmol/l respectively) multiply by 6.945, 0.055, 1, 1.54, and 12.87 respectively.

Table 2

Determinants of fasting plasma insulin, acute insulin response, and insulin AUC.

| | Fasting insulin (log$_{10}$) | | AIR (log$_{10}$) | | Insulin AUC (log$_{10}$) | |
| | R^2=0.70, P<0.0001 | | R^2=0.34, P=0.002 | | R^2=0.62, P<0.0001 | |
	β	P	β	P	β	P
Age (years)	−0.004	0.03	−0.009	0.03	−0.009	0.01
Sex (male)	0.006	0.9	−0.11	0.2	−0.16	0.02
Body fat (%)	0.01	0.0005	−0.001	0.8	−0.001	0.9
Fasting glucose (mg/ml)	0.002	0.3	−0.007	0.02	–	–
Glucose AUC (mg/dl per min)	–	–	–	–	0.004	0.004
M (log$_{10}$)	−0.38	0.001	−0.53	0.02	−0.85	0.0002
Free T$_3$ (pg/ml)	0.09	0.01	0.16	0.03	0.24	0.0007

Data are β (estimated partial regression coefficient) and P values for the association of free T$_3$ concentrations (mean±s.d. 2±0.4 pg/ml) with fasting insulin (mean±s.d. 39±14 µU/ml), AIR (acute insulin response, mean±s.d. 270±120 µU/ml), and insulin AUC (insulin area under the curve, mean±s.d. 136±85 µU/ml per min) after adjustment for covariates. Total R^2 and P values for the entire model are given. M: insulin-mediated glucose disposal rate at physiological insulin concentrations. Insulin (µUI/ml), glucose (mg/dl), and free T$_3$ (pg/ml) concentrations are given in conventional units; to convert to Système Internationale units (pmol/l, mmol/l, and pmol/l) multiply by 6.945, 0.055, and 1.54 respectively.