岩手医科大学
審査学位論文
（博　士）

Positive association of free triiodothyronine with pancreatic β-cell function in patients with prediabetes.

Running title: Positive effects of FT3 on pancreatic β-cell function

Tomoyasu Oda, MD, Haruhito Taneichi, MD, PhD, Kazuma Takahashi, MD, PhD, Hirofumi Togashi, MD, Mari Hangai, MD, Riyuki Nakagawa, MD, Mitsutaka Ono, MD, PhD, Mizue Matsui, MD, Takayoshi Sasai, MD, PhD, Kan Nagasawa, MD, PhD, Hiroyuki Honma, MD, Takashi Kajiwara, MD, PhD, Yoshihiko Takahashi, MD, PhD, Noriko Takebe, MD, PhD, Yasushi Ishigaki, MD, PhD, and Jo Satoh, MD, PhD.

Division of Diabetes and Metabolism, Department of Internal Medicine, Iwate Medical University

#Address correspondence to:
Yasushi Ishigaki, M.D., Ph.D.
Division of Diabetes and Metabolism, Department of Internal Medicine,
Iwate Medical University
19-1 Uchimaru, Morioka, 020-0023, Japan
Phone +81-19-625-5083,
Fax +81-19-625-5083,
E-mail: ishigaki@iwate-med.ac.jp

manuscript word count : 2601 words

funding sources : None

conflicts of interest disclosures : None

・This is one of the first studies to show the positive effects of thyroid hormones on pancreatic β-cell function in patients with prediabetes.

・Regulation of insulin secretion by thyroid hormones might be a new therapeutic target for managing diabetes.

Abstract

Aim

Thyroid hormone is considered to not only cause glucose intolerance but also to increase insulin secretion. Several studies have shown the effects of thyroid hormones on insulin secretion in hyperthyroid patients and euthyroid subjects with normal glucose tolerance (NGT). However, the association of thyroid hormones with β-cell function in those with impaired fasting glucose and/or impaired glucose tolerance, i.e. prediabetes, remains unclear. Therefore, we aimed to analyse the effects of thyroid hormones on β-cell function and glucose metabolism in euthyroid patients with prediabetes.

Methods

One hundred and eleven euthyroid patients underwent 75g oral glucose tolerance tests and 52 were assigned to the NGT and 59 the prediabetes group. Homeostatic model assessment β-cell function (HOMA-β), insulinogenic index, and areas under the curve of insulin and glucose [$(AUC)_{insulin}/AUC_{glucose}$] were evaluated as indices of pancreatic β-cell function.

Results

In both groups, body mass index, fasting insulin, HOMA-R and HDL-C correlated significantly with all indices of pancreatic β-cell function. Interestingly, free triiodothyronine (FT3) correlated positively with all insulin secretion indices in the prediabetes group. Multiple linear regression analysis revealed FT3 to be an independent variable showing a positive correlation with all indices of β-cell function in the prediabetes group. In contrast, no such correlation was found in the NGT group.

Conclusions

FT3 is associated with both basal and glucose stimulated insulin secretion in euthyroid patients with prediabetes. Therefore, the regulation of insulin secretion by thyroid hormones is a

potentially novel therapeutic target for the treatment of diabetes.

Introduction

Type 2 diabetes is caused by complex interactions between insulin resistance and impaired insulin secretion from pancreatic β-cells. Even in subjects categorized as being in a prediabetes, including impaired fasting glucose (IFG) and/or impaired glucose tolerance (IGT), insulin resistance already exists [1]. In response to the development of insulin resistance, pancreatic β-cells gradually proliferate along with increased insulin secretion [2]. High glucose, as well as insulin and free fatty acids [3], are considered to play key roles in promoting pancreatic β-cell proliferation during the development of insulin resistance. Although several molecular mechanisms underlying the development of insulin resistance, such as the crucial role of glucokinase and the insulin receptor pathway [4], have been investigated, which factors induce pancreatic β-cell proliferation to meet the increased demand for insulin in this state remain as yet unknown.

Generally, thyroid hormones have been considered to cause glucose intolerance, inducing enhancement of hepatic glucose production or exacerbation of insulin resistance [5]. On the other hand, hyperthyroid patients are reported to exhibit not only glucose intolerance but also increased insulin secretion [6]. Several studies have shown the effects of thyroid hormones on insulin secretion from pancreatic β-cells. Triiodothyronine (T3) is reported to inhibit pancreatic β-cell apoptosis [7] and to promote the transformation of human pancreatic ductal cells into a form similar to pancreatic β-cells [8] and to promote pancreatic acinar cell proliferation [9]. Furthermore, the mitochondrial P43 receptor, which acts as a receptor for T3, regulates insulin secretion and glucose homeostasis [10]. In addition, the mechanisms underlying the association between thyroid hormone and insulin secretion have been reported, particularly the involvement of T3 in the insulin receptor pathway in pancreatic β-cells [11, 12] as well as the relationship between thyroid hormones and the insulin transcription factor MafA

[13].

Recently, the involvement of serum thyroid hormone levels in glucose metabolism has been examined in euthyroid subjects. Taneichi et al. reported that the components of metabolic syndrome are associated with serum free triiodothyronine (FT3) levels in euthyroid subjects with type 2 diabetes [14]. Regarding the association between thyroid hormones and insulin secretion, the serum FT3 level is related to pancreatic β-cell function independently of insulin resistance in euthyroid subjects [15, 16]. However, all previous studies focused on subjects with normal glucose tolerance (NGT), and the association of thyroid hormones with β-cell function in patients with prediabetes remains unclear. Therefore, in the present study, we analyzed the effects of thyroid hormones on β-cell function and glucose metabolism in euthyroid patients with prediabetes.

Subject and Methods

Study subjects

The subjects were 178 patients recruited from May 2012 to September 2013 who had no past history of either thyroid disease or diabetes, based on the diagnostic criteria proposed by the Japan Diabetes Society [17]. Thirty-four patients with abnormal thyroid hormone levels [normal ranges: thyroid-stimulating hormone (TSH): 0.41–1.43 mIU/L, free thyroxine (FT4): 0.12–0.22 pmol/L, FT3: 3.49–5.99 pmol/L] and 33 who were revealed to have diabetes by a 75-g oral glucose tolerance test (OGTT) were excluded from this study. In total, 111 patients were analysed. This study was approved by the Institutional Review Board of Iwate Medical University on May 2012 (Approval number: H24-36).

Study protocol and assay

The patients had fasted since 21:00 the day before the test. At 9:00 on the test day,

75-g OGTT were performed and the following clinical parameters were measured i.e., fasting blood glucose, fasting insulin, glycosylated haemoglobin (HbA1c), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), triglycerides, total cholesterol, non-esterified fatty acid (NEFA), estimated glomerular filtration rate (eGFR), TSH, FT3, FT4. Thyroid hormone was measured employing an electrochemical luminescence assay using a fully automated electrochemical luminescence immunoassay analyser (Modular Analytics EE; Roche Diagnostics K.K., Tokyo, Japan). NEFA were measured by an enzymatic method with BML (JCA, BM8060, JEOL Ltd., Tokyo, Japan). During the 75-g OGTT, blood glucose and insulin were measured every 30 minutes until 120 minutes. Blood glucose was measured by an enzymatic method (Automatic Glucose Analyzer, BM9130, JEOL Ltd., Tokyo, Japan), and insulin was measured by an immune antibody method using a fully automated electrochemical luminescence immunoassay analyser (Modular Analytics EE; Roche Diagnostics K.K., Tokyo, Japan).

Glucose tolerance classification

Glucose tolerance was classified on the basis of blood glucose levels according to the WHO diagnostic criteria for diabetes (2006) [18]. NGT was defined as fasting blood glucose < 6.11 mmol/L and blood glucose levels 2 hours after glucose loading < 7.78 mmol/L. IFG was defined as fasting blood glucose ≥ 6.11 mmol/L and fasting blood glucose < 7.00 mmol/L. IGT was defined as blood glucose levels 2 hours after glucose loading ≥ 7.78 mmol/L and blood glucose levels every 2 hours after glucose loading < 11.1 mmol/L. Patients with IFG and/or IGT were considered to be in a prediabetes.

Evaluation of glucose metabolism

The following indices were used to determine pancreatic β-cell function: homeostatic model assessment beta cell function (HOMA-β), which was calculated as a ratio of fasting

insulin divided by fasting blood glucose; insulinogenic index, which was calculated as (insulin value at 30 minutes − fasting insulin) / (blood glucose value at 30 minutes − fasting blood glucose); areas under the curve $(AUC)_{insulin}/AUC_{glucose}$ [19]. For $AUC_{insulin}$ and $AUC_{glucose}$, the AUC was calculated from insulin and blood glucose levels above zero over 120 minutes using the trapezoidal rule. The homeostasis model assessment ratio (HOMA-R) was used as the index of insulin resistance and calculated as the product for fasting blood glucose and fasting insulin [20].

Statistical analysis

Quantitative data are presented as means ± standard deviation (SD). Comparisons between the subjects with NGT and prediabetes were performed employing the Mann–Whitney *U*-test and chi-square test. Spearman's rank-order correlation analysis was used to determine the correlations among variables. The associations between FT3 and pancreatic β-cell functions were determined by linear multiple regression analysis adjusted for age, sex, body mass index (BMI), fasting blood glucose, fasting insulin, and triglyceride levels. The level of significance was set at $P < 0.05$. SPSS version 21 (SPSS Japan Inc., Tokyo, Japan) was used for all analyses.

Results

Ultimately, 52 and 59 subjects were assigned to NGT and prediabetes groups, respectively. The clinical characteristics of the enrolled subjects are shown in Table 1. The values for NEFA, fasting blood glucose, blood glucose levels at 2 hours, HbA1c, fasting insulin, HOMA-β, and $AUC_{glucose}$ were significantly higher in the prediabetes than in the NGT group. HOMA-R and $AUC_{insulin}$ tended to be higher in the prediabetes than in the NGT group but the difference did not reach statistical significance. There were no differences between groups in age, BMI, eGFR, triglycerides, HDL-C, LDL-C, TSH, FT4, or FT3.

Next, we evaluated the correlations between clinical laboratory parameters and the indices of pancreatic β-cell function, such as HOMA-β, the insulinogenic index, and $AUC_{insulin}/AUC_{glucose}$, in the NGT and prediabetes groups (Table 2). BMI, fasting insulin, and HOMA-R showed positive correlations and HDL-C a negative correlation with all indices of pancreatic β-cell function in both groups. Triglycerides correlated positively with all indices of pancreatic β-cell function in the prediabetes group, while showing a correlation only with HOMA-β in the NGT group. Interestingly, FT3 correlated positively with all indices of pancreatic β-cell function in the prediabetes group (Figure 1), whereas its only correlation in the NGT group was with HOMA-β. However, other thyroid hormones, FT4 and TSH, showed no correlations with any indices of pancreatic β-cell function in either group.

We next performed multiple linear regression analysis with clinical parameters related to glucose metabolism, i.e. age, sex, BMI, fasting blood glucose, fasting insulin, triglycerides, and FT3, to identify independent variables affecting pancreatic β-cell function. Intriguingly, this analysis revealed FT3 to be an independent variable showing a positive correlation with all indices of pancreatic β-cell function in the prediabetes group (Table 3). In contrast, a similar multiple linear regression analysis revealed that FT3 was not independently associated with any indices of pancreatic β-cell function in the NGT group (HOMA-β, $\beta = 0.072$, $P = 0.160$; insulinogenic index, $\beta = -0.273$, $P = 0.093$; $AUC_{insulin}/AUC_{glucose}$, $\beta = -0.205$, $P = 0.175$).

Discussion

The results of current study indicate FT3 to correlate positively with various indices of pancreatic β-cell function (i.e. HOMA-β, insulinogenic index and $AUC_{insulin}/AUC_{glucose}$) in euthyroid patients with prediabetes. The multiple linear regression analysis adjusted for age, sex, BMI, fasting blood glucose, fasting insulin, and triglycerides, also showed similar associations

of FT3 with pancreatic β-cell function. Interestingly, these correlations disappeared after adjustment in the NGT group. These results raise the possibility of FT3 exerting a positive effect on both basal and glucose stimulated insulin secretion in patients with prediabetes.

To meet the increased demand for insulin resulting from blood glucose elevation due to the development of insulin resistance, pancreatic β-cells would proliferate and produce greater amounts of insulin, leading to the preservation of systemic glucose homeostasis [2, 3]. The mechanisms underlying pancreatic β-cell proliferation, however, remain unclear. Recently, several studies have shown involvement of the cell cycle system in β-cell proliferation. The cell cycle regulatory factor cyclin D1/D2 [21] and cyclin-dependent kinase (Cdk) 4 [22] as well as E2F1/2 [23] play roles in β-cell growth and proliferation. On the other hand, while thyroid hormones mainly play pivotal roles in the regulation of whole body metabolism, they also mediates cell proliferation and differentiation [24]. Thyroid hormones are suggested to directly affect the cell cycle,thereby promoting the proliferation and differentiation of pancreatic β-cells. Furuya et al. reported that T3 activated the cyclin/Cdk/Rb/E2F pathway via the thyroid hormone receptor α1 in rat pancreatic β-cells, leading to activation of pancreatic β-cell proliferation and differentiation of insulin-expressing cells [25]. In addition, Misiti et al. reported that T3 promoted the transformation of human pancreatic ductal cells into a form similar to pancreatic β-cells [8].

Recently, pancreatic β-cell proliferation associated with hyperglycaemia and insulin resistance was thought to be regulated by the insulin signalling in β-cells [26]. The key molecules of the insulin signalling pathway are phosphoinositide 3-kinase (PI3K) and Akt, which are related to cell proliferation, survival, and apoptosis. Intriguingly, several studies have revealed thyroid hormone involvement in the insulin signalling pathway. T3 reportedly reduced pancreatic β-cell apoptosis via activation of the PI3K/Akt pathway in insulinoma cell-lines [7]

via the thyroid hormone receptorβ1 pathway in pancreatic β-cells [12]. On the other hand, Lin et al. reported that T3 promoted phosphorylation of the insulin receptor substrate, leading to activation of PI3K and increased insulin secretion in a mouse model of type 2 diabetes [11]. In addition, they indicated that T3 also increased the expression of NeuroD, which plays a major role in insulin gene transcription. Moreover, T3 promotes expression of the transcription factor MafA, which is important for the control of β-cell specific insulin gene expressions, leading to enhanced glucose-stimulated insulin secretion in rats [13]. Taking these observations together, thyroid hormones appear to be associated with pancreatic β-cell function through several mechanisms, such as proliferation, cell cycling, insulin signalling, and transcription factor regulation. However, there is little clinical knowledge obtained from subjects with glucose intolerance. For this reason, clinical studies supporting these associations are urgently needed.

In the present study, we found no independent associations between FT3 and indices of pancreatic β-cell function in the NGT group. In contrast, previous studies showed FT3 to be independently associated with β-cell function in euthyroid NGT subjects [15, 16]. This discrepancy between outcomes might owe to characteristic differences among study subjects, i.e., healthy subjects were recruited for prior studies, while most of our subjects had metabolic disorders, such as dyslipidemia or hypertension. Excessive NEFA reportedly inhibits glucose-stimulated insulin secretion and induces apoptosis [27] in pancreatic β-cells. These abnormalities of lipid metabolism may have the potential to affect the insulin secretion profile, resulting in outcomes different from those of previous studies. In addition, the racial difference might also be an important issue. East Asian populations are considered to be sensitive to adiposity-induced disorders in regulatory mechanisms of metabolism, as compared with Western populations. Therefore, Japanese subjects tend to develop insulin resistance and disorders of adipocytokine release with mild obesity of the degree seen in our subjects

(mean BMI: 25.7) [28]. Some adipocytokines, such as interleukin-1, are known to cause deterioration of pancreatic β-cell insulin-secretion function [29]. Thus, these racial characteristics of East Asians might be involved in the differences in outcomes from previous studies of other races, such as Pima Indians. On the other hand, **t**hese adiposity-related metabolic disorders were also observed in the prediabetes group, while their serum concentrations of FT3 were significantly associated with indices of pancreatic β-cell function. In addition, indices of pancreatic β-cell function, such as HOMA-**β** and $AUC_{insulin}$, tended to be high in the prediabetes as compared with the NGT group, whereas serum FT3 concentrations did not differ significantly between the two groups. Collectively, the impact of FT3 on insulin secretion seemed to be stronger in the prediabetes than in the NGT group. The mechanisms underlying enhancement of insulin secretion in subjects with prediabetes were not elucidated herein. Generally, patients with glucose intolerance require extra insulin secretion to compensate for peripheral insulin resistance, resulting in high serum insulin concentration. Thus, constitutive hyperinsulinemia probably exerts a strong stimulatory action on the insulin receptor pathway in pancreatic β-cells, leading to enhanced FT3 function in terms of β-cell proliferation in subjects with prediabetes. Moreover, β-cell proliferation and insulin secretion increased by FT3 might positively promote further involvement of FT3 action in pancreatic β-cells. This positive feedback loop between pancreatic β-cell function and FT3 action might function as a vital defence mechanism compensating for insufficient insulin action during insulin resistance development.

The major limitation of this study is that all of the IFG and IGT data were combined into one group, the prediabetes group, because of the small number of patients with IFG. IFG is characterized by hepatic insulin resistance and increased hepatic glucose production. On the other hand, IGT tends to be characterized by impaired additional secretion of insulin and insulin

resistance in skeletal muscle [19]. The peak of insulin secretion after glucose loading is delayed in IGT as compared to IFG [30], suggesting that patterns of insulin secretion might vary widely among patients with prediabetes. In this study, only 9 patients had IFG alone, a number insufficient for comparative analysis. Further studies are needed to determine the impact of FT3 on pancreatic β-cell function in patients with IFG. In contrast to a previous report, the significant correlation between BMI and insulin responsiveness disappeared when our data were subjected to multiple linear regression analysis. The exact reason for BMI minimally impacting β-cell function is unclear. Generally, obesity is strongly associated with hyperinsulinemia. Alternatively, visceral fat accumulation is thought to frequently be accompanied by impairment of rapid responsiveness of insulin secretion, as represented by insulinogenic index [31]. These various parameters might show different relationships with the values of BMI. In addition, evaluation of abdominal fat distribution might allow us to precisely assess this issue.

Conclusion

This study is the first to reveal the association between FT3 and pancreatic β-cell function in euthyroid patients with prediabetes. FT3 is assumeed to be an accelerator of compensatory pancreatic β-cell proliferation through several mechanisms, such as β-cell proliferation and/or insulin signalling activation. To deal with the increasing numbers of patients with prediabetes and diabetes, regenerative medicine targeting pancreatic β-cells has been expected to provide novel therapeutic strategies aimed at ameliorating impaired pancreatic β-cell function. FT3 may have potential as an activator of regenerative pancreatic β-cell proliferation, contributing to protective effects against the development of diabetes. Recently, a thyroid hormone analogue without hormonal activity on the heart or hypothalamus was

developed [32]. Therefore, the regulation of insulin secretion by thyroid hormones is a potentially novel therapeutic target for the treatment of diabetes.

Acknowledgments

Author’scontributions are as follows; T.O. recruited patients, researched data and wrote the manuscript; H.T. conductedstatistical analysis, and reviewed and edited the manuscripts; H.T., M.H., M.O., R.N., M.M., T.S., K.N., H.H., T.K., H.T., N.T. and K.T. recruited patients and contributed to discussion;Y.I. contributed to discussion and reviewed the manuscripts;and J.S. managed study design, contributed to discussion, and reviewed the manuscript.

Conflict-of-interest

The authors have no conflict of interest to declare.

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Figure legend

Correlation of free triiodothyronine with HOMA-β (A) and Insulinogenic index (B) and $AUC_{0\text{-}120\ \mathbf{insulin}/\ \mathbf{Glucose}}$ (C) in Prediabetes

Table 1 Demographic characteristics of NGT and Prediabetes

	NGT	Prediabetes	P
n (males/females)	52 (24/28)	59 (25/34)	
Age (years)	53.65±16.8	57.5±14.5	0.349
BMI (kg/m^2)	25.7±6.8	25.8±5.3	0.258
Dyslipidemia (%)	31 (60)	36 (61)	0.880
Hypertension (%)	22 (42)	22 (37)	0.589
eGFR (ml min^{-1}1.73m^{-2})	87.1±20.5	80.0±12.8	0.124
Triglycerides (mmol/L)	1.45±1.75	1.39±0.91	0.436
Total cholesterol (mmol/L)	5.06±0.89	5.09±0.93	0.920
HDL cholesterol (mmol/L)	1.58±0.56	1.59±0.47	0.583
LDL cholesterol (mmol/L)	2.99±0.76	2.99±0.86	0.875
NEFA (mmol/L)	0.67±0.21	0.84±0.23	0.001
Fasting glucose (mmol/L)	5.55±0.39	5.67±0.52	0.003
2-hour glucose (mmol/L)	6.39±0.89	8.88±1.19	<0.001
HbA1c (mmol/mol)	34.7±4.63	36.1±3.71	0.017
HbA1c (%)	5.73±0.42	5.85±0.35	0.017
HOMA-R	1.83±1.32	2.62±1.80	0.124
Fasting insulin (pmol/L)	50.9±35.2	68.5±44.3	0.011
HOMA-β	72.1±48.7	83.9±52.6	0.003
Insulinogenic index	0.89±0.68	0.69±0.47	0.337
$AUC_{0\text{-}120}$insulin (pmol·hr/L)	371.6±212.5	457.0±238.9	0.062
$AUC_{0\text{-}120}$glucose(mmol·hr/L)	7.69±1.34	9.50±1.45	<0.001
$AUC_{0\text{-}120}^{\text{insulin / glucose}}$	6.86±4.20	6.68±3.56	0.805
TSH (mIU/L)	1.74±0.87	1.93±0.93	0.280
FT4 (pmol/L)	0.160±0.015	0.158±0.021	0.417
FT3 (pmol/L)	4.73±0.52	4.81±0.51	0.599

Date are presented mean value (standard deviation) . Characteristics among group were compared Mann–Whitney U test.
BMI, Body Mass Index; eGFR,estimated glomerular filtation rate; HDL, high-density lipoprotein ; LDL, low-density lipoprotein ; NEFA,nonesterified fatty acid; HOMA-R, homeostasis model assessment ratio ; HOMA-β,homeostatic model assessment beta cell function; $AUC_{0\text{-}120}$, area under the curve from 0 to 120min; TSH, thyroid stimulating hormone;FT4,free serum thyroxine; FT3;free serum triiodothyronine

Table 2 Correlation coefficients between HOMA-β, insulinogenic index , $AUC_{0\text{-}120\ insulin/\ Glucose}$ and various clinical variables

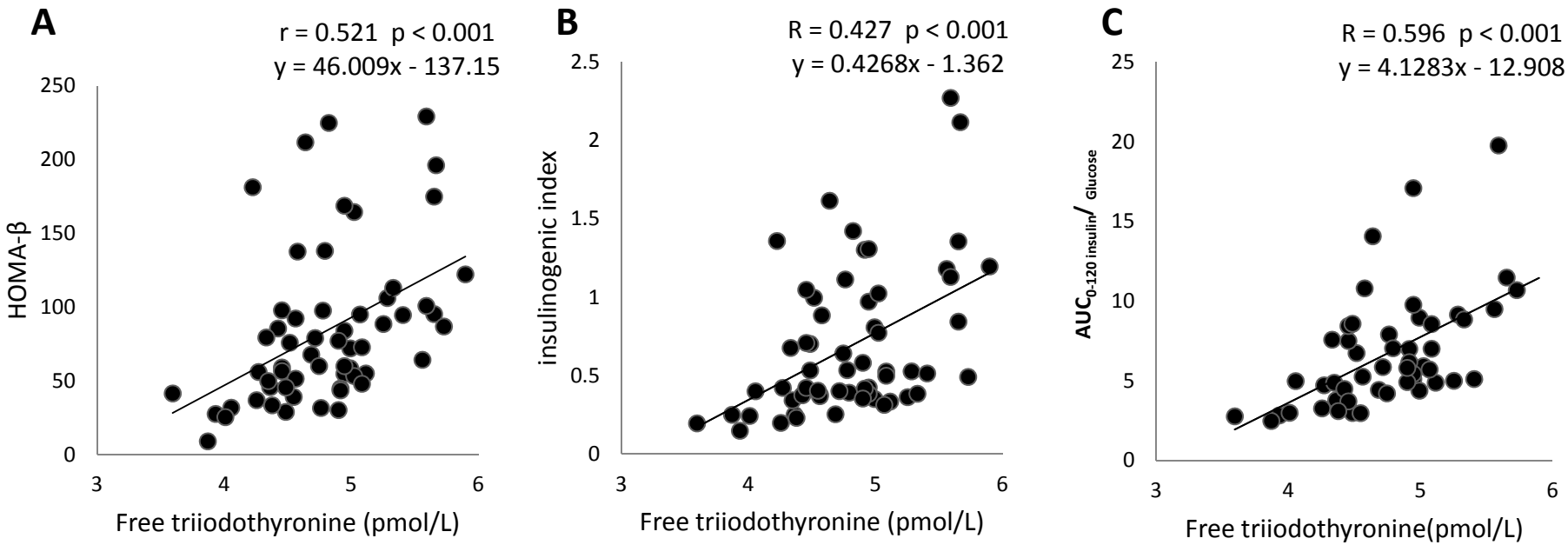
	NGT						Prediabetes					
	HOMA-β		Insulinogenic index		$AUC_{0\text{-}120\ insulin/glucose}$		HOMA-β		Insulinogenic index		$AUC_{0\text{-}120\ insulin/glucose}$	
parameter	r	P	r	P	r	P	r	P	r	P	r	P
Age (years)	-0.419	0.002	-0.319	0.021	-0.199	0.207	-0.353	0.006	-0.249	0.057	-0.221	0.145
BMI (kg/m^2)	0.795	<0.001	0.395	0.005	0.466	0.003	0.657	<0.001	0.412	0.001	0.529	<0.001
eGFR ($ml\ min^{-1}1.73m^{-2}$)	0.155	0.347	-0.046	0.779	0.082	0.618	0.101	0.482	-0.008	0.956	0.141	0.323
Total cholesterol (mmol/L)	-0.295	0.064	-0.363	0.021	-0.371	0.018	-0.084	0.564	-0.029	0.839	-0.079	0.584
Triglycerides (mmol/L)	0.434	0.002	0.131	0.364	0.264	0.099	0.504	<0.001	0.425	0.001	0.471	0.001
HDL cholesterol (mmol/L)	-0.639	<0.001	-0.448	0.001	-0.582	<0.001	-0.472	<0.001	-0.274	0.036	-0.373	0.007
LDL cholesterol (mmol/L)	-0.060	0.679	-0.076	0.602	-0.127	0.435	0.175	0.186	0.013	0.919	0.079	0.583
NEFA (mmol/L)	0.061	0.704	0.227	0.079	0.197	0.217	-0.043	0.775	0.003	0.985	0.031	0.834
Fasting glucose (mmol/L)	0.073	0.606	-0.022	0.875	0.020	0.900	-0.101	0.448	-0.006	0.962	0.133	0.353
2-hour glucose (mmol/L)	-0.048	0.734	-0.203	0.148	-0.194	0.218	-0.254	0.052	-0.336	0.009	-0.292	0.038
HbA1c (mmol/mol)	-0.107	0.451	-0.200	0.154	-0.076	0.630	0.089	0.502	0.067	0.613	0.157	0.271
HOMA-R	0.909	<0.001	0.466	<0.001	0.616	<0.001	0.857	<0.001	0.486	<0.001	0.709	<0.001
Fasting insulin (pmol/L)	0.934	<0.001	0.489	<0.001	0.646	<0.001	0.928	<0.001	0.518	<0.001	0.723	<0.001
HOMA-β	1		0.553	<0.001	0.717	<0.001	1		0.537	<0.001	0.701	<0.001
Insulinogenic index	0.553	<0.001	1		0.809	<0.001	0.537	<0.001	1		0.705	<0.001
$AUC_{0\text{-}120}$ insulin (pmol·hr/L)	0.698	<0.001	0.682	<0.001	0.962	<0.001	0.702	<0.001	0.598	<0.001	0.974	<0.001
$AUC_{0\text{-}120}$glucose(mmol·hr/L)	-0.235	0.094	-0.532	<0.001	-0.232	0.138	-0.269	0.041	-0.587	<0.001	-0.090	0.535
$AUC_{0\text{-}120\ insulin\ /\ glucose}$	0.717	<0.001	0.809	<0.001	1		0.701	<0.001	0.705	<0.001	1	
TSH (mIU/L)	-0.109	0.441	-0.199	0.157	-0.305	0.050	-0.099	0.457	-0.097	0.464	-0.079	0.584
FT4 (pmol/L)	-0.067	0.636	0.029	0.836	0.032	0.842	-0.029	0.825	0.021	0.875	0.092	0.521
FT3 (pmol/L)	0.424	0.002	0.115	0.416	0.187	0.236	0.521	<0.001	0.427	0.001	0.596	<0.001

Spearman rank order correlation.

Table3 Multiple linear regression model of free triiodothyronine concentration with HOMA-β, Insulinogenic index, and $AUC_{0\text{-}120\ insulin/\ Glucose}$ as dependent variables in subjects with prediabetes

	HOMA-β		Insulinogenic index		$AUC_{0\text{-}120\ insulin\ /\ glucose}$	
	R^2=0.948	P<0.001	R^2=0.497	P<0.001	R^2=0.666	P<0.001
Independent variable	β	P	β	P	β	P
Age	0.030	0.456	0.002	0.985	0.051	0.617
Sex	0.005	0.876	0.077	0.472	0.036	0.708
BMI (kg/m^2)	0.034	0.579	0.053	0.781	0.144	0.311
Fasting glucose(mmol/L)	-0.343	<0.001	-0.304	0.008	-0.264	0.009
Fasting insulin (pmol/L)	0.943	<0.001	0.485	0.011	0.535	0.001
Triglycerides (mmol/L)	0.229	0.820	0.093	0.429	0.125	0.217
FT3 (pmol/L)	0.109	0.005	0.269	0.025	0.275	0.012

Data are presented as β (estimated partial regression coefficient) and P values for the association of FT3 with HOMA-β, Insulinogenic index, and $AUC_{0\text{-}120\ insulin/\ Glucose}$ after adjustment for covariates. Total R^2 and P values for the entire model are given.


A
r = 0.521 p < 0.001
y = 46.009x - 137.15
HOMA-β
Free triiodothyronine (pmol/L)
B
R = 0.427 p < 0.001
y = 0.4268x - 1.362
insulinogenic index
Free triiodothyronine (pmol/L)
C
R = 0.596 p < 0.001
y = 4.1283x - 12.908
AUC0-120 insulin / Glucose
Free triiodothyronine(pmol/L)