# T3/rT3-Ratio is Associated with Insulin Resistance Independent of TSH

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**Key words**
- diabetes mellitus type 2
- insulin resistance
- thyroid function

## Abstract

Thyroid dysfunction has been shown to be associated with insulin resistance (IR). This may involve peripheral thyroid hormone metabolism, which is assumed to be reflected by the ratio triiodothyronine/reverse triiodothyronine (T3/rT3-ratio). To explore a potential association between the T3/rT3-ratio and IR we investigated pairs which differed in IR, but were matched by sex, age, body mass index (BMI), and thyroid stimulating hormone (TSH). For this purpose, matched pair analyses were embedded into a cross sectional study group. 22 pairs were matched from either the first or the third tertile of HOMA%S of a cohort of 353 euthyroid subjects with normal glucose metabolism who did not take any medication. The T3/rT3-ratio was compared in the matched pairs. The T3/rT3-ratio was significantly increased in the insulin resistant subjects compared to their insulin sensitive partners (8.78±0.47 vs. 7.33±0.33, p=0.019). Furthermore the T3/rT3-ratio was lower in men compared to women (p for the within-subject effect=0.046) both in the insulin sensitive and the insulin resistant subjects. Here we show that the T3/rT3-ratio, which is supposed to reflect the tissue thyroid hormone metabolism, is significantly increased in insulin resistant subjects. This further supports a link between thyroid function and IR.

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## Introduction

Insulin resistance (IR) is an accepted risk factor for both type 2 diabetes and cardiovascular disease [1–3]. Changes in hormonal systems are associated with altered insulin sensitivity, for example, insulin sensitivity is decreased in Cushing's disease [4] and decreased androgen levels are found in obese and insulin resistant men [5,6]. Although the precise relationships remain to be elucidated, thyroid hormones are also linked with IR. Overt hyperthyroidism is supposed to induce IR [7–9] and insulin sensitivity can be normalized by antithyroid therapy [10]. In subclinical hyperthyroidism, the association with IR is described inconsistent [11,12]. In hypothyroidism, the currently available data are even more conflicting. Insulin sensitivity has been reported to be decreased [13,14], normal [15,16], or even increased [17]. In euthyroidism, the relationship between thyroid function and IR has been addressed in only few studies. In a Dutch study cohort of 1581 euthyroid subjects, an association between free thyroxine and TSH with IR has been described [18], and low normal free thyroxine levels were associated with IR. Another study investigating the relation between TSH and IR found a positive correlation between TSH and fasting insulin (a measure of insulin resistance) in 221 healthy men, while no significant correlation with free thyroxine levels was found in this study group [19]. Recently, high normal TSH values have been described related with the metabolic syndrome [20,21] or associated with IR in women suffering from the polycystic ovary syndrome [22].

In contrast, using the euglycemic-hyperinsulinemic clamp as the gold standard for the measurement of whole-body IR, 2 further studies failed to detect a significant association between TSH and IR [23,24]. One of these studies was performed in 55 Pima Indians and described even a positive correlation between free triiodothyronine and fasting insulin [24].

Taken together, the data regarding thyroid function and IR are in part conflicting. One possible explanation might be that both TSH and the circulating thyroid hormones thyroxine (T4) and triiodothyronine (T3) levels do not adequately reflect the peripheral thyroid hormone situation.

At the tissue level, the biological activity of thyroid hormone is regulated by the deiodinases DIO 1, DIO 2, and DIO 3. DIO 1 and DIO 2 are responsible for the generation of T3 from T4, whereas DIO 3 is the major inactivating enzyme leading to an increase of reverse T3 (rT3) [25,26]. The ratio between T3 and rT3 (T3/rT3-ratio) is considered a sensitive indicator of the peripheral thyroid hormone metabolism [27]. The ratio is positively influenced by DIO 1 and DIO 2 and negatively by DIO 3. The T3/rT3-ratio is assumed to be relatively independent of the thyroidal T4 production and of variations in the serum levels of thyroid hormone binding proteins [27]. Since IR is largely dependent on the glucose metabolism of liver and muscle [28], one might assume that in the context of IR a marker of peripheral thyroid hormone status reflecting tissue metabolism of thyroid hormones is of special interest. To explore a potential relationship between the T3/rT3-ratio and IR we here investigated pairs matched by sex, age, BMI, and TSH, and at the same time maximally differing in IR as estimated by HOMA%S.

## Subjects and Methods

We investigated participants of the Metabolic Syndrome Berlin Potsdam (MeSyBePo) study cohort. The study design was approved by the local ethical committee. An oral glucose tolerance test (oGTT, 75 g glucose) was performed in all participants except patients with evident diagnosis of diabetes. Capillary whole blood glucose was measured every 30 min during the oGTT. The study has been recently described in more detail [21,29]. The study cohort for the analyses described here based on 353 subjects above 18 years of age fulfilling the following criteria:

- a TSH value in the range between 0.3 and 4.5 µU/l
- no medication
- a normal glucose metabolism, defined as the absence of known diabetes or any medication for diabetes and a fasting glucose below 5.6 mmol/l and a 2 h OGTT value below 7.8 mmol/l.

Insulin resistance was quantified by the homeostasis model assessment (HOMA%S) as described [21] and the cohort was divided into tertiles by the rank of HOMA%S. 23 pairs could be matched by sex, age, BMI, and TSH from either the first (n = 119) or the third (n = 115) tertile of HOMA%S. For the matching, a maximal deviation of 10% (TSH, BMI) or 20% (age), respectively, was allowed.

### Assays

Insulin and TSH were measured by ELISA as described [21]. Free fatty acid (FFA) and triglyceride (TG) levels were measured using colorimetric assays (Wako, Neuss, Germany or ABX Diagnostics, Montpellier, France) both on a Cobas Mira (Roche, Lörrach, Germany). Radioimmune assays (RIAs) were used to quantify reverse triiodothyronine (rT3) (Biocode Hycel, Belgium) and T3 (total triiodothyronine) (Brahms, Hennigsdorf, Germany). The minimum detectable level for the rT3 RIA is given by the manufacturer as 0.009 ng/ml. The intra-assay CV was 5.0%. The lower limit of sensitivity for the T3 RIA was given to be lower than 0.15 nmol/l. The intra-assay CV was 3.51%.

### Statistical analysis

All statistics were performed using SPSS version 14 (SPSS, Chicago, IL). Mean values and S.E.M. are given. Significance was defined as 2-tailed $\alpha < 0.05$. The matched pairs were checked for pairs with largely deviating relationship of the T3/rT3-ratios (outliers) by a stem-and-leaf plot using the ratio between the sensitive and resistant partners, respectively. One male pair was identified as an outlier and this pair was therefore removed from the analysis.

The tertiles of HOMA%S were compared by the nonparametric Kruskal-Wallis test or Chi-square test in the case of frequencies. TSH values and the T3/rT3-ratios were compared between male and female subjects by the nonparametric Mann-Whitney test. The matched pairs were compared by Student's *t*-test for paired analysis. Sexual difference in the T3/rT3-ratios were considered by a general linear model analysis, which further allowed an adjustment for differences in BMI and the smoking state.

## Results

The characteristics of the entire study group are summarized in **Table 1**. The first tertile of HOMA%S included participants with a HOMA%S from 12.2 to 93.4% (n = 119), the second tertile with a HOMA%S from 94.5 to 151.1% (n = 119), and the third tertile included subjects with a HOMA%S of >152% (n = 115). The comparison between the tertiles of HOMA%S is given in **Table 2**.

22 pairs matched by sex, age, BMI, and TSH out of either the first or the third tertile of HOMA%S were eligible for analysis (10 male pairs and 12 female pairs). Characteristics of the matched pairs are given in **Table 3**.

The T3/rT3-ratio was significantly lower in male compared to female pairs (7.43 ± 0.49 vs. 8.58 ± 0.36 ($p = 0.027$, **Fig. 1**). This difference was apparent despite similar TSH values in men and women (p for difference = 0.18) and similar HOMA%S ($p = 0.77$). The T3/rT3-ratio was significantly higher in the insulin resistant subjects as compared to their matched insulin sensitive partners (8.78 ± 0.47 vs. 7.33 ± 0.33, $p = 0.019$, **Fig. 2**).

Additionally, general linear model was calculated, which confirmed the significant difference between men and women (p for the inter-subject effect = 0.046). The relation between the insulin-resistant subjects and their insulin-sensitive partners, however, was similar in men and in women as indicated by a nonsignificant interaction term ($p = 0.153$). Adjusting for differences in the smoking state (yes/no) between the 2 partners or a restriction to the 17 pairs concordant in the smoking state did not alter the result ($p = 0.033$ or $p = 0.032$).

The matched pair design was chosen for best possible matching for age, BMI, and TSH. Nevertheless, there was a small although not statistically significant difference in BMI ($p = 0.15$, **Table 3**). Therefore, we additionally adjusted the comparison between the insulin sensitive and insulin resistant pairs for the difference in BMI which yielded unchanged results both in the entire cohort

**Table 1** Baseline characteristics of the entire study cohort

| Characteristics | n = 353 |
|---|---|
| Age (years) | 45.2 ± 0.7 |
| BMI (kg/m$^2$) | 26.3 ± 0.3 |
| WHR | 0.86 ± 0.01 |
| TSH (µU/ml) | 1.60 ± 0.06 |
| Fasting glucose (mmol/l) | 4.78 ± 0.45 |
| Fasting insulin (mU/l) | 6.82 ± 0.26 |
| HOMA%S (%) | 139.0 ± 5.0 |

BMI: body mass index; WHR: waist to hip ratio; HOMA: homeostasis model assessment

| Characteristics | Insulin resistant tertile | 2nd tertile | Insulin sensitive tertile | p-value |
|---|---|---|---|---|
| Male (female) | 63 (56) | 36 (83) | 35 (80) | <0.01 |
| Age (years) | 44.6 ± 1.2 | 45.8 ± 1.3 | 45.2 ± 1.2 | 0.72 |
| BMI (kg/m$^2$) | 29.2 ± 0.5 | 25.7 ± 0.4 | 23.7 ± 0.3 | <0.01 |
| WHR | 0.90 ± 0.01 | 0.85 ± 0.01 | 0.84 ± 0.01 | <0.01 |
| Fasting glucose (mmol/l) | 4.87 ± 0.83 | 4.74 ± 0.78 | 4.72 ± 0.70 | 0.005 |
| Fasting insulin (mU/l) | 11.44 ± 0.54 | 5.69 ± 0.07 | 3.21 ± 0.08 | <0.01 |
| TG (mmol/l) | 1.58 ± 0.09 | 1.22 ± 0.07 | 0.94 ± 0.04 | <0.01 |
| FFA (mmol/l) | 0.52 ± 0.03 | 0.59 ± 0.03 | 0.50 ± 0.02 | 0.057 |
| TSH (µU/ml) | 1.63 ± 0.11 | 1.60 ± 0.10 | 1.56 ± 0.10 | 0.81 |
| HOMA%S (%) | 66.6 ± 1.7 | 119.9 ± 1.5 | 233.6 ± 10.3 | <0.01 |

BMI: body mass index; WHR: waist to hip ratio; TG: triglycerides; FFAs: free fatty acids; TSH: thyroid stimulating hormone; HOMA: homeostasis model assessment

**Table 2** Comparison of the tertiles of HOMA%S

**Table 3** Characteristics of the matched pairs

| Characteristics | Insulin sensitive tertile (n = 22) | Insulin resistant tertile (n = 22) | p-value |
|---|---|---|---|
| HOMA%S (%) | 237.52 ± 32.71 | 69.10 ± 3,03 | <0.001 |
| insulin (mU/l) | 3.23 ± 0.18 | 10.26 ± 0.51 | <0.001 |
| fasting glucose (mmol/l) | 4.91 ± 1.57 | 4.76 ± 2.18 | 0.36 |
| FFA (mmol/l) | 0.51 ± 0.06 | 0.50 ± 0.05 | 0.86 |
| TG (mmol/l) | 1.14 ± 0.17 | 1.75 ± 0.23 | 0.03 |
| BMI (kg/m$^2$) | 26.01 ± 0.80 | 26.46 ± 0.83 | 0.15 |
| WHR | 0.87 ± 0.08 | 0.87 ± 0.08 | 0.99 |
| Age (years) | 45.72 ± 1,93 | 46.02 ± 2.08 | 0.69 |
| T3 (ng/dl) | 123.5 ± 0. 03 | 131.1 ± 0.03 | 0.09 |
| rT3 (ng/dl) | 17.51 ± 0.88 | 15.75 ± 0.88 | 0.18 |
| TSH (µU/ml) | 1.58 ± 0.16 | 1.57 ± 0.17 | 0.71 |

HOMA: homeostasis model assessment; FFAs: free fatty acids; TG: triglycerides; BMI: body mass index; WHR: waist to hip ratio; T3: total triiodothyronine; rT3: reverse triiodothyronine; TSH: thyroid stimulating hormone

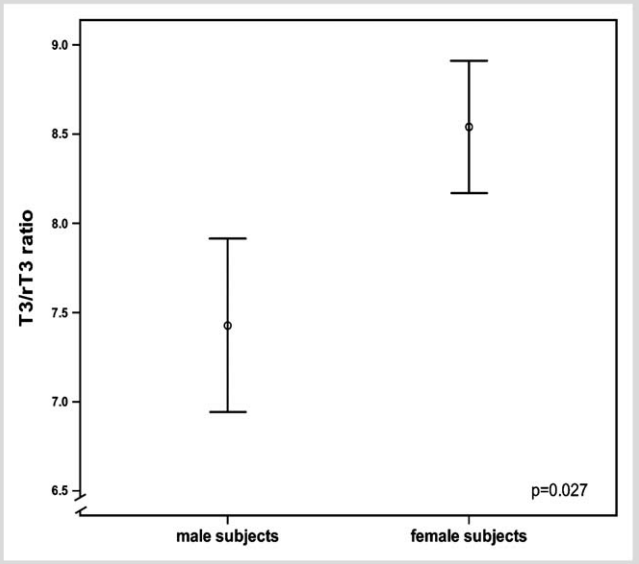


**Fig. 1** T3/rT3-ratio in males and females showing a significantly lower T3/rT3-ratio in men compared to women.

(p = 0.029) and in the subcohort restricted to the pairs concordant in the smoking state (p = 0.039).

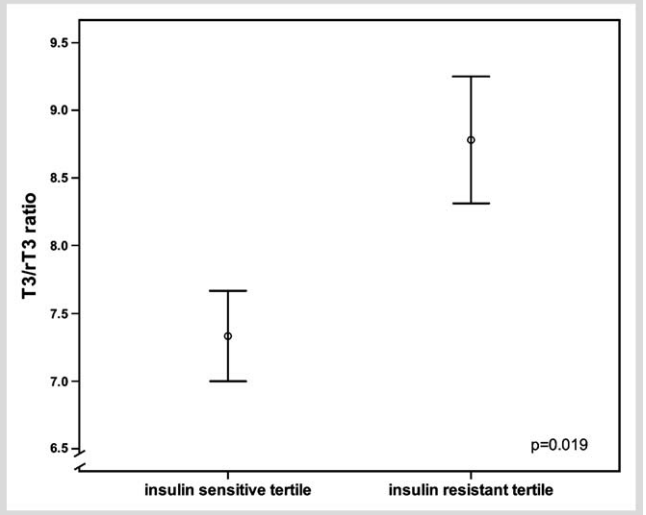


**Fig. 2** T3/rT3-ratio in insulin resistant subjects and their insulin sensitive partners. The T3/rT3-ratio was significantly increased in the insulin resistant subjects compared to their insulin sensitive partners despite comparable TSH.

## Discussion

We present here novel data concerning peripheral thyroid hormone metabolism and IR in euthyroid subjects. The T3/rT3-ratio was significantly increased in the insulin resistant subjects compared to their insulin sensitive partners despite comparable TSH values. This indicates an altered thyroid hormone metabolism with a potentially increased thyroid hormone activity in the case of IR. This difference in the T3/rT3-ratio was not explained by small and statistically nonsignificant differences in BMI between the 2 partners since a further adjustment for the difference in BMI did not alter the result.

Furthermore, the T3/rT3-ratio was significantly lower in men compared to women both in the insulin resistant and the insulin sensitive pairs. This is in agreement with data obtained in rats describing significantly lower T3 levels in male vs. female rats [30]. Furthermore, an impact of sex steroids on deiodinase activities has been described in rats [30, 31]. In humans, thyroid function in general is assumed to show only little or no gender related variations [32]. For the final conclusion, however, further studies are desirable. The difference in the T3/rT3-ratio between insulin resistant subjects and their insulin sensitive partners was similar in men and in women.

The relation between thyroid hormone and insulin sensitivity is incompletely understood. Thyroid hormone plays an essential role in several metabolic and developmental processes [33] and thyroid hormone is known to modulate carbohydrate metabolism [34], for example, by affecting cellular glucose uptake [35,36]. However, in contrast to the situation in overt hyperthyroidism that has been associated with IR [7–9] the data addressing IR in euthyroid subjects are conflicting [18,19,24]. The present findings could help to explain the so far conflicting results: TSH does not fully describe the thyroid hormonal situation, whereas the T3/rT3-ratio, which has been described as an indicator of the tissue thyroid hormone metabolism [27], appears to add further information with respect to IR. From the nonthyroidal illness syndrome it is known that disease associated changes in deiodinase activity indeed influence thyroid hormone signaling both locally and systemically [26]. Such peripheral changes in thyroid hormone deiodination could lead to the higher T3/rT3-ratio that we see in insulin resistant subjects. A limitation of the present study is that we cannot comment whether the increased T3/rT3-ratio is a cause or a consequence of IR. Insulin has been shown to upregulate DIO 2 activity in brown adipose tissue of rats [37,38], and to contribute to the regulation of DIO2 mRNA expression in human skeletal muscle [39]. Furthermore, insulin-stimulated T4 5′-deiodination has been demonstrated in rat hepatocytes [40] whereas the induction of diabetes in a rat model resulted in a decreased thyroid DIO 1 activity, which was restored after insulin treatment [31]. On the other hand, an increased T3/rT3-ratio might cause IR analogous to the situation seen in overt hyperthyroidism [7–9]. Therefore, there are theoretical arguments for a relationship in both directions.

The size of our study, which is based on a relatively small number of pairs that we could match from a cohort of 353 patients, is another potential limitation. However, there are also several strengths: (i) We used a matched pair design for optimal control of potential confounders such as age, sex, BMI, and TSH levels. The matched pair design ensured that sufficient controls (chosen from the most insulin sensitive tertile of HOMA%S) were available for the cases (chosen from the most insulin resistant tertile of HOMA%S). Furthermore, matching overcomes the disadvantage of a regression adjustment which could result in bias, for example, if linearity is wrongly assumed [41]; (ii) HOMA%S, an accepted and widely used estimate of insulin sensitivity was used [42]; (iii) The analysis was restricted to subjects with normal glucose metabolism, thereby further improving the substitute of HOMA%S as an estimate of IR; and (iv) Only subjects were included that did not take any medication to avoid any drug induced bias.

In summary, the T3/rT3-ratio was significantly lower in men vs. women. Independent from TSH, the T3/rT3-ratio was increased in insulin resistant subjects as compared to their insulin sensitive partners matched by sex, age, and BMI. Whether the observed difference in peripheral thyroid hormone metabolism is the cause or the consequence of IR remains to be elucidated.

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