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Research Article

Deiodinases in Human Adipose Tissue from Obese Patients. Differences by Gender and Anatomical Depot

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Abstract

T3 regulates energy metabolism, glucose and lipid metabolism and several markers of adipocyte differentiation in white adipose tissue (WAT). T3 levels in tissues are regulated by the deiodinases (D1, D2, D3 or DIO1, DIO2, DIO3, respectively).

Aim: To analyze DIO1, DIO2 and DIO3 deiodinases activity and mRNA expression and T4 and T3 concentrations in omental (OM) and subcutaneous (SC) WAT from obese, evaluating the differences by gender and anatomical depot. *DIOs* mRNAs were also analyzed in lean *versus* obese subjects.

Results: In obese patients, T4 was lower only in SC WAT from obese men and T3 was lower in OM and SC WAT from obese women. In agreement, D2 activity was lower in SC WAT from obese women while D3 activity tended to increase in OM an SC WAT from obese women, explaining the lower T3 in WAT. The highest T3 was found in OM WAT from obese men together with the lowest D3 activity. *DIO1* and *DIO2* mRNA were higher in the SC WAT from both obese men and women.

DIO1 and *DIO3* mRNA were increased in OM and SC WAT from obese *vs* lean patients. *DIO2* mRNA increased only in OM from IR-Obese and was always higher in SC than in OM WAT.

DIO2 mRNA is higher in OM floating adipocytes and *DIO3* mRNA in the stromal vascular fraction.

Conclusion: In Conclusion gender and depot differences were observed in the three deiodinases studied, both in activity and mRNA expression.

ABBREVIATIONS

BAT: Brown Adipose Tissue; BSA: Bovine Serum Albumin; Camp: Cyclic AMP; DIO1, D1, Dio1: Type 1 Deiodinase; DIO2, D2, Dio2: Type 2 Deiodinase; DIO3, D3, Dio3: Type 3 Deiodinase; DTT: Dithiothreitol; HEPES: 4-(2-Hydroxyethyl)-1-Piperazineethanesulfonic Acid; NE: Norepinephrine; OM: Omental WAT; PCR: Polymerase Chain Reaction; PPAR: Peroxisome Proliferator-Activated Receptor; PTU: 6-Propyl-2-Thiouracil; qRT PCR: Quantitative Real-Time PCR; RIA: radioimmunoassay; SC: Subcutaneous WAT; SD: Standard Deviation; SEM: Standard Error Of The Mean; T3: Triiodothyronine; T4:Thyroxine; TCA: Trichloroacetic Acid; TSH: Thyrotropin; UCP1: Uncoupling Protein 1; W: Women; WAT: White Adipose Tissue.

INTRODUCTION

The deiodinases DIO1, DIO2 and DIO3 are selenoenzymes that regulate thyroid hormone concentrations in tissues, specifically T3 levels, providing the proper T3 amount required for adequate function. Two isoenzymes (DIO1 and DIO2 or D1, D2) catalyze the 5'deiodination producing T3 from T4, while DIO3 (D3) catalyzes 5-deiodination inactivating T3 and T4. DIO3 is the main pathway for T3 degradation. All of them are regulated by thyroid status and many other situations and are present in different tissues. DIO1 is abundant in liver, kidney and thyroid. DIO1 Km is in the µM range, is inhibited by PTU, decreases in hypothyroidism and increases in hyperthyroidism, except in the thyroid where DIO1 increases in hypothyroidism and is stimulated by TSH. DIO2 is present in pituitary, brain, brown adipose tissue (BAT), pineal gland, placenta and thyroid. In man, DIO2 is also present in heart and muscle [1,2]. DIO2 is PTU-insensitive, its Km is in the nM range, increases in hypothyroidism and produces T3 for local needs. The inactivating enzyme, DIO3, catalyzes the deiodination of T4 and T3 in the inner ring, leading to the inactive iodothyronines, reverse T3 and 3', 3-T2. DIO3 activities are increased during fetal life, cellular proliferation and inflammation.

In BAT, the T3, locally produced by DIO2, is important for a full thermogenic function [3] and for lipogenesis [4]. T3 is required for the differentiation program of the adipocytes [5] and for the induction of lipogenic enzymes.

D1 and D2 activities and *dio1* and *dio2* mRNA are present in rat white adipose tissue (WAT) [6,7], but little is known about deiodinases in WAT, their abundance, hormonal regulation and role or specific function in different anatomical depots in WAT. In mice brite/beige adipocytes can be induced in some WAT depots (using UCP1 as BAT marker) to increase energy expenditure (browning) [8] and *dio2* increases are also found in browning.

Many factors are involved in the regulation of deiodinases: thyroidal status, cAMP and catecholamines (norepinephrine), insulin, biliary acids, most of them have been described in several tissues and in BAT or brown adipocytes [2]. Glucocorticoids are also strong regulators of D2 activity and *dio2* mRNA in brown adipocytes [9]. For WAT the information is scarce but T3, insulin, biliary acids or agonists of the PPARgamma (tiazolidindiendiones) might play a role.

Due to the role of thyroid hormones as regulators of energy expenditure the changes of thyroid function in obesity have been studied with different results as many studies find correlations between increased serum T3 and obesity while other studies do not find such correlations [10]. But the changes in plasma T3 reflect the thyroid homeostasis of the whole organism, not the changes in the adipose tissue of the obese patients. On the other hand deiodinases have been implicated in obesity and insulin resistance, as mice with targeted disruption of *dio2* gene, when fed high diets show insulin resistance and visceral obesity, together with difficulties to burn fat [4,11] suggesting the importance of the proper function of *dio2* to avoid the progression of obesity. Several metabolic abnormalities are also observed in the *dio3* ko mice [12]. This led us to explore the presence of deiodinases in human obesity. We wanted to know about the presence and role of the deiodinases DIO1, 2 and 3 in human fat, specifically in obesity, their specific regulation in different WAT depots or differences due to gender, if any. Fat accumulation in males and females show phenotypic differences that have been described in detail.

WAT represents 15-25% of the body weight (BW) in lean subjects and this percentage rises to about 50% of BW in obese people. This represents a huge pool of T3 whose regulation influences many metabolic processes. Visceral (OM) WAT is associated to higher risk of diabetes and cardio-vascular damage. In humans, D1 activity and DIO1 mRNA are increased in subcutaneous (SC) and visceral (OM) WAT from obese patients compared to lean patients [13] and D2 activity and its *DIO2* mRNA were found in human preadipocytes [14].

The aim of the present paper is to study D1, D2 and D3 activities and *DIO1, DIO2* and *DIO3* mRNA and T4 and T3 concentrations in human SC and OM adipose tissue from obese patients and to compare *DIO1, DIO2* and *DIO3* mRNA expression in WAT from lean and obese patients.

MATERIALS AND METHODS

Samples

Human subcutaneous (SC) and omental (OM) WAT were obtained from obese patients with morbid obesity during bariatric surgery. All the protocols followed the European Community guidelines (Helsinki guidelines), previous approval by the ethics committees of our institutions and approved consent of the patients undergoing surgery following the protocols approved by the scientific societies and each Hospital Ethic committees.

For T4 and T3 determinations we used OM and SC WAT from 12 obese patients, 6 males and 6 females, using paired samples from both depots (except for one patient). The same patients samples were used for the determination of DIOs activities and *DIOs* mRNAs (Table 1).

The comparison between lean and obese patients (with and without insulin resistance, IR) was done using samples from the patients listed in Table 2.

Drugs and reagents

T4, T3 and 3, 5-diiodo-thyronine (3,5-T2), 2N-propyl-6-thiouracil (PTU) and DL-dithiothreitol (DTT) were from Sigma Chemical Co (St Louis, MO). Reverse T3 (rT3) and 3', 3-diiodothyronine (3', 3-T2) were from Henning Berlin GMBH (Berlin, Germany).

High specific activity [^{125}I]-T4, [^{131}I]-T4, [^{125}I]-T3 and [^{125}I]-rT3 (3000 mCi/mg) were synthesized in our laboratory, as already described [15]. [^{125}I]-T3 and [^{125}I]-T4 were used for the determination of thyroid hormone concentrations using highly sensitive T4 and T3 radioimmunoassays (RIAs). [^{131}I]-T4 and [^{125}I]-T3 were used as recovery tracers during plasma and tissue extractions and [^{125}I]-T4, [^{125}I]-T3 and [^{125}I]-rT3 were used as substrates for deiodinase determinations.

Analytical procedures

Kinetic analysis: The kinetic characteristics of DIO1 and DIO2 in human WAT was determined as described for rat [7].

Determination of Deiodinase activities: Iodothyronine Deiodinase activities (D1, D2 and D3) were assayed in tissue homogenates prepared (1:8, weight/ volume) in 0.32 M sucrose, 10 mM Hepes and DTT (1 mM for D1 and 10 mM for D2). Homogenates were centrifuged at 1500 rpm to separate the lipid cake as an upper phase, the infranatant being used for the deiodinase assay.

For the determination of D1 in WAT: [^{125}I]-rT3 (60.000 cpm/ tube) was used, 100 nMrT3 and 2 mM DTT, during 1 h at 37°C using 20-30 µg protein/ 100 µl. For kinetic analysis, 2-500 nM rT3 and 2 mM DTT was used during 0.5 h at 37°C.

D2 activity was assayed using 100.000 cpm of [^{125}I]-T4, 2 nM T4+ 1 µM T3, 20 mM DTT and 1 mM PTU during 1 hour at 37°C, using 150-200 µg protein /100µl.

D3 activity was measured using 100.000 cpm of [^{125}I]-T3, 2 nM T3, 20 mM DTT and 1 mM PTU during 1 hour at 37°C, using 40-50 µg protein /50µl, as described [16].

Before each assay [^{125}I]-rT3, [^{125}I]-T4 or [^{125}I]-T3 were purified by paper electrophoresis to separate the contaminating iodide. The [^{125}I] - released was separated by ion-exchange chromatography on Dowex-50W-X2 columns equilibrated in 10% acetic acid. The production of equal amounts of iodide and 3', 3 -T2 was checked in preliminary tests. The protein content was determined by the method of Lowry et al., after precipitation of the homogenates with 10% TCA to avoid interferences from

Table 1: Clinical characteristics of the obese patients used.

GROUP	Obese (men)	Obese (women)
age	42.86±14.44	40.88±11.38
n	6	6
BW	143.6±21.9	116.8±21.24
BMI	47.4±2,37	49.3±7.70
Glucose (60-115)	104.0±13.57	109.5±34.56
Cholesterol (120-240)	189.0±21.92	190.7±28.22
LDL (230-460)	338 ±39.87	293.5 ±92.47

Mean ± SD. n.s. between obese men and women
Abbreviations: BW: Body weight; BMI: Body mass index; LDL: Low density lipoprotein

Table 2: Clinical characteristics of the lean and obese patients without and with insulin resistance (IR).

GROUP	LEAN	OBESE (non IR)	OBESE IR
age	47.6±11.9	44.1±9.5	37.0±10.0
sex (W/M)	7/5	13/6	5/2
BW	64.0± 13.5	132.0±24.6*	134.1±17.9*
BMI	22.8± 2.0	49.1±7.8*	49.1±5.7*
Glucose	82.6± 10.1	102.6±24.9*	103.5±14.0*
Insulin	5.8± 2.3	19.0±6.5*	36.3±12.6*,#
HOMA-IR	1.1± 0.5	4.8±1.8*	9.1±2.4*,#
TG	66.3±19.3	96.5±26.3	139.4±65.0*
Cholesterol	198.7± 26.4	177.5±31.3	206±43.7

Mean ± SD, *p < 0.05 *vs* Lean, # p < 0.05 *vs* Obese (non IR)
Abbreviations: IR: insulin resistance; W: women; M: men or male; BW: Body weight; BMI: Body mass index; HOMA-IR: Homeostatic model assessment of Insulin resistance; TG: triglycerides

DTT in the colorimetric reaction. The values shown are the mean of at least 5-6 samples, using duplicates. Units are: pmols per min / mg protein for D1 and fmols per h / mg protein for D2 and D3 activities.

DIO1, DIO2 and DIO3 mRNA

Total RNA was extracted using the RNeasy lipid tissue mini kit from Quiagen, specific for adipose tissue (Quiagen Sciences, Maryland). This purification method was chosen because of the high purity of the RNA obtained after testing other methods that gave some interference in the Taqman quantitative RT-PCR (qRT-PCR). Human DIO1, DIO2 and DIO3 mRNAs were measured by qRT-PCR, using specific Taqman probes and Gene expression assays from AP Biosystems (Hs00174944_m1, Hs00255341_m1, Hs00956431s1). Results were normalized using IPO8 as internal control [17]. Results were expressed as $^{-\Delta\Delta}$Ct. *vs* controls.

Floating adipocytes (F) and stromal-vascular-fraction (SVF) were isolated from fresh WAT and RNA extracted [18].

Determination of thyroid hormone concentrations in plasma and tissues

Thyroid hormone concentrations were determined by specific RIAs, as previously described [15] after extraction and extensive purification of the tissues. The limits of detection are 2.5 pg T4 and 0.7 pg T3 / tube. Cross-reactivity for the T4 and T3 RIA were reported [19].

Statistical analysis

Mean values (± SD) are given. One-way analysis of variance (ANOVA) was done, after homogeneity of variance was ensured using square roots or logarithmic transformations, if not found with the raw data. Significance of differences between groups was assessed using the protected least significant difference test. All the calculations were done as described in Snedecor and Cochran [20]. Asterisks in Figures (*or #) indicate statistical significant differences (P< 0.05) among groups.

RESULTS AND DISCUSSION

Clinical data of the obese patients

Table 1 shows the biochemical characteristics of the obese patients used. All the patients had morbid obesity (BMI > 40). Most biochemical parameters fell within the normal ranges. The same patients and paired samples of OM and SC were selected for the determination of thyroid hormones concentrations, deiodinase activities and mRNA levels.

Characterization of D1 and D2 activities in human adipose tissue

We did kinetic studies comparing rat and human WAT: D1 and D2 activities are higher in human WAT than in rat WAT [7]. We did kinetic studies for both deiodinases and its kinetic characteristics are: D2 Km = 30 nM T4 in human and rat WAT, Vmax = 3 and 7 pmols/h/mg p, for rat and human WAT, respectively. For D1: Km= 0.35 µM rT3 in human and rat WAT and Vmax = 6-18 and 24-60 pmols/h/mg p, for rat and human, respectively. DIO1 and DIO2 mRNA are present in human white adipose tissue, as confirmed by Taqman qRT PCR.

Thyroid hormone concentrations in human WAT in obesity

Thyroid hormone concentrations (T4 and T3) were determined in human WAT from obese patients, using paired samples from SC and OM WAT from 12 obese patients. WAT samples from OM and SC depots were purified from lipids. T4 concentrations were about 8 times higher than those of T3. As shown in Figure (1A), WAT T4 was lower only in SC WAT from obese men. T3 was lower in OM and SC WAT from obese women, although SC WAT in obese men showed a tendency to decrease (20%, n.s.) *vs* men OM WAT. Protein concentrations were only somewhat lower in SC WAT from obese women, thus not explaining the changes we found. Thyroid hormones have not been previously reported in WAT from obese patients, though T3 is required for the proper function of WAT [5]. So, we checked for the enzymes that produce or degrade T3, the deiodinases.

D1, D2 and D3 activities in SC and OM WAT from obese patients. Effect of gender and anatomical depot

D1, D2 and D3 activities are present in human white adipose tissue from obese patients. We find gender differences in D1, D2

and D3 activities (Figure 1B): DIO2 activity was lower in SC WAT from obese women, while D3 tended to be higher in women both in OM and SC (n.s.). In summary, the lower D2 activities found in SC WAT from obese women together with increases in D3 activities are in agreement with the lower T3 concentration found in WAT from women. The highest T3 was found in OM WAT from obese men together with the lowest D3 activity. We found no correlation between D2 or D3 activities and T3 in SC WAT from obese women. Differences due to gender have not been reported before in human fat, but there is a clear regulation of the location and function of WAT by sexual steroids. Differences by gender have been described in liver, pituitary and other tissues [21,22].

DIO1 and DIO2 mRNA in SC and OM human WAT in obese patients

In the same samples (Figure 1C), *DIO1* and *DIO2* mRNA were higher in SC WAT from both women and especially in men. We found no changes in *DIO3* mRNA, which tended to be lower in WAT from obese women.

Comparison between WAT from lean and obese subjects

We compared *DIO1, DIO2* and *DIO3* mRNA from lean, obese and obese with insulin resistance (ObIR). The clinical data from those patients are given in Table 2.

DIO1 and *DIO3* mRNA were increased in obese both in OM and SC samples (Figure 2). *DIO2* mRNA is higher only in OM from ObIR, and was higher in all SC WAT from lean, Ob and ObIR. *DIO1* mRNA has been reported to increase in SC and OM WAT in obesity [13]. But there are no reports for changes in *DIO3* and *DIO2* mRNAs in obesity.

Unfortunately we did not have enough amounts of WAT from lean patients without pathology to measure D1, D2 and D3 activities and to compare with obese patients.

Subcellular location of DIO2 and DIO3 mRNA

DIO2 and *DIO3* mRNA were measured in the stromal vascular fraction (SVF) and the floating adipocytes from SC and OM WAT from obese patients. *DIO2* mRNA is higher in floating adipocytes from OM WAT, while *DIO3* mRNA is higher (n.s.) in the SVF both from the OM and SC WAT (Figure 3).

CONCLUSION

In conclusion, deiodinases regulate the amount of T3 present in the cells, as well as the amounts of T4 and other thyroid metabolites, and contribute to a fine and individualized tune-up of T3 in each tissue. We find that D1, D2 and D3 activities and *DIO1, DIO2* and *DIO3* mRNAs are present in human WAT in obese patients. We find differences in OM and SC fat due to gender, obesity and anatomical depot. In obese patients T3 is lower in

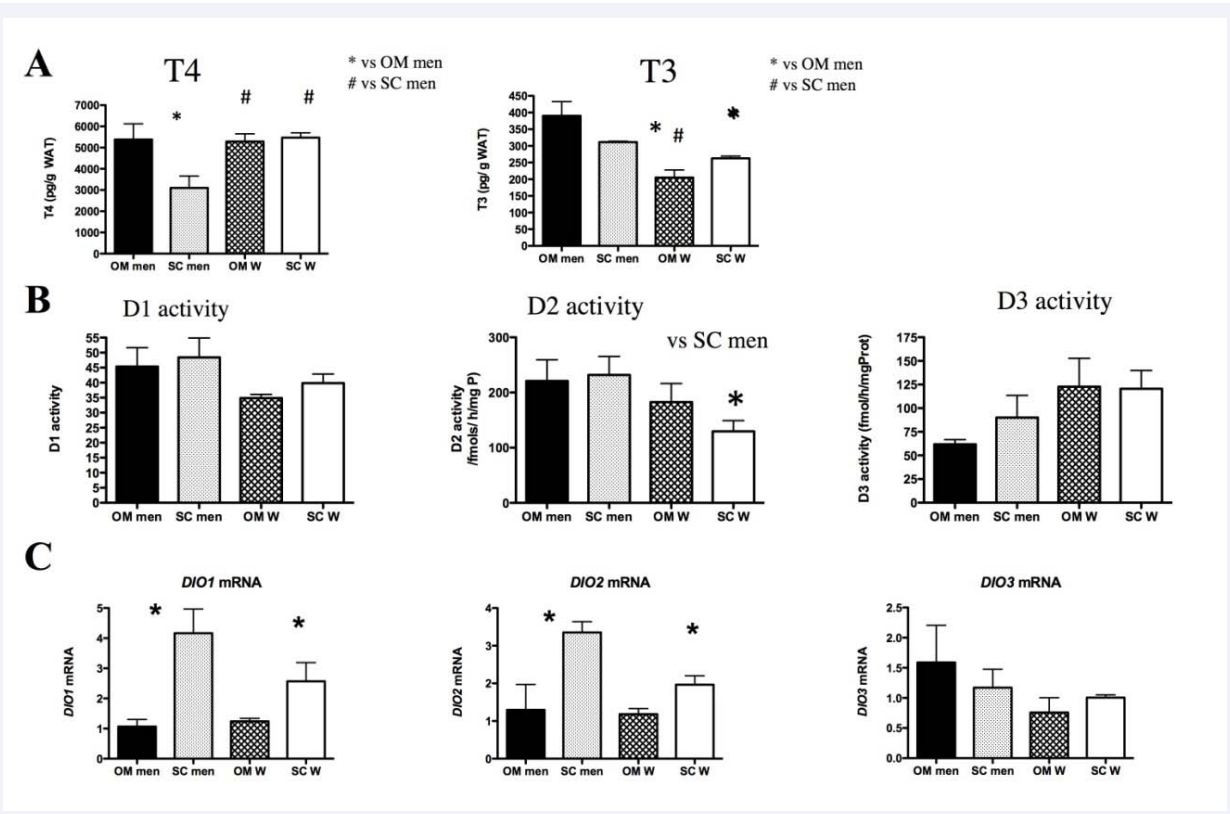

Figure 1 Obese patients: Differences due to gender and anatomical depot in OM and SC human WAT from obese Men (M) and Women (W). Figure 1A: T4 and T3 concentrations (pg / g) in OM and SC human WAT from M and W. Mean ± SEM, (n=6/group), *$P< 0.05$ *vs* OM, #$P< 0.05$ *vs* SC M. OM crossed bars. SC empty bars. Figure 1B: D1, D2 and D3 activities in OM and SC human WAT from M and W (same samples as above). Mean ± SEM, (n=6/group), *$P< 0.05$ *vs* SC M. Figure 1C: *DIO1, DIO2* and *DIO3* mRNA in OM and SC human WAT from M and W (same samples as in A and B). Mean ± SEM, (n=6/group), *$P< 0.05$ *vs* its respective OM.

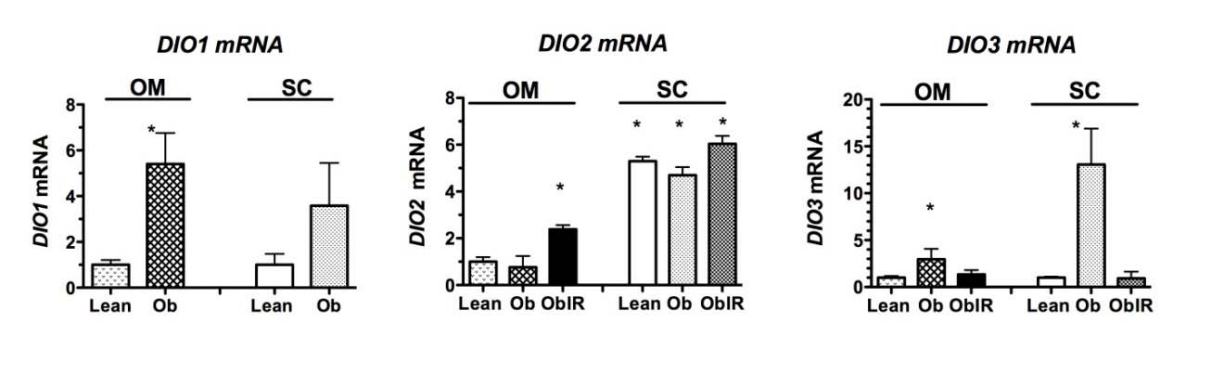

Figure 2 Lean and Obese patients: Effect of obesity and anatomical depot on *DIO1, DIO2* and *DIO3* mRNA in OM and SC in human WAT from lean, obese (Ob) and obese with insulin resistance (Ob-IR). Mean ± SEM, (n=12, 19 or 7/group), *$P<0.05$ *vs* lean.

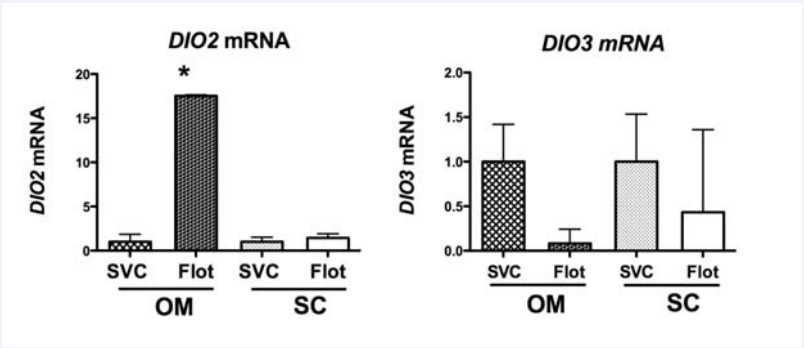

Figure 3 *DIO2* and *DIO3* mRNAs in stromal-vascular cells (SVC) and floating adipocytes from OM and SC human WAT from Obese patients. Mean ± SEM, (n=5/group).

OM and SC fat from women, together with lower D2 and higher D3 activities.

Obesity increases *DIO1* and *DIO3* mRNA in OM and SC WAT, while *DIO2* mRNA increases only in OM from OB-IR. The increase of the *DIO1* mRNA in obesity suggests the requirement of T3 for the proper functioning of WAT, although we did not found correlative increases in D1 activities. The decrease in T3 in SC WAT from obese women suggests deficits that might interfere with its normal function. It is not clear the biological processes regulated by the decrease of T3 in WAT, but likely could affect lipogenesis, lipolysis, glucose uptake or lipid metabolism and transport. The metabolic processes regulated by the deiodinases in WAT and specifically in obesity remain unknown.

We are aware that our study is a first approximation to understand the role of deiodinases in WAT from obese patients. More studies are required to assess the positive role of deiodinases for T3 regulation. But even so, and with a small number of samples our study reproduces the findings on D1 in obese patients from other studies [13].

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