

Selenium Supplementation in Obese Patients with Subclinical Hypothyroidism and Type 2 Diabetes

Guarino G¹, Ragozzino G¹, Della Corte T¹, Fontana S¹, Strollo F², Cecaro M³, and Gentile S^{*1}

¹Department of Experimental and Clinical Medicine, University of Campania “Luigi Vanvitelli”, Naples, Italy

²Department of Pharmacology and Biomolecular Sciences, University of Milan, Italy

³Register of Biologist, Salerno, Italy

*Corresponding author: Gentile S (2018) Department of Experimental and Clinical Medicine, University of Campania “Luigi Vanvitelli”, Naples, Italy, E-mail: s.gentile1949@gmail.com

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Abstract

Selenium (Se) is a trace element present in many foods. Selenium-protein co-factor plays a critical anti-oxidant and anti-inflammatory role in thyroid function, but quite recently its ability to prevent adipocyte hypertrophy and adipogenesis has also been evaluated. The aim of our study was to assess whether thyroid function, as well as, body mass index (BMI) and body composition might improve in Se-treated obese patients as compared to those getting placebo (P). 50 obese patients (BMI \geq 30 kg/m²) with non-autoimmune subclinical hypothyroidism participated in the study. They were randomized to either Se (Se Group, SG, L-seleno-methionine 83 mcg/day) or P (P Group, PG) and underwent a low-calorie diet. BMI, homeostatic model assessment-based insulin resistance (HOMA-IR), TSH, FT4, as well as, Vi-SCAN bioimpedance assessed waist circumference (WC) and % visceral fat (%VF) were evaluated both at baseline and 6 plus 12 months after treatment start. The SG showed a significant decrease in TSH at 6 and 12 months as compared to the PG, might be through the well-known selenium ability to modulate thyroid hormone synthesis. The SG also displayed a significant decrease in BMI, WC and %VF in support to our original hypothesis of a strong association of visceral obesity with low Se intake rates.

Keywords: Type 2 Diabetes; Subclinical Hypothyroidism; Selenium Supplementation; Obese Patients

Introduction

Morbid obesity is associated with multiple co-morbidities, such as type 2 diabetes mellitus (T2DM), hypertension (HT), dyslipidemia (DL), and obstructive sleep apnea syndrome [1]. It is not commonly appreciated that morbid obesity is also associated with an increased prevalence of subclinical hypothyroidism (SH). The underlying pathophysiology of obesity related SH is not completely understood. High leptin levels and insulin-resistance appear to play a role, possibly by inducing a reset of the central thyrostat [2]. In the general population SH is diagnosed 3–4 times more frequently in women than in men and its prevalence varies from 4 to 9%, and it [3,4]. SH is associated with an increased risk of death from all causes as well as from cardiovascular diseases (CVD) [3]. The prevalence of hypothyroidism appears to be higher in morbidly obese than in not obese patients [3]. SH-related hypercholesterolemia (HC), impaired left ventricular diastolic function, endothelial dysfunction and increased C-reactive protein levels have been proposed as etiologic factors [5]. Consideration of thyroid hormone treatment for SH in the general population is gaining in strength [3] and in obese patients with additional risks of CVD the indication for SH treatment may even be stronger.

The relationship between weight loss and serum TSH levels is well documented. In SH patients bariatric surgery dependent percent excess weight loss (%EWL) - defined as weight loss divided by excess weight as referred to 25 kg/m² BMI - was associated to decreased serum TSH levels from 5.82 \pm 2.05 mU/L preoperatively to 2.78 \pm 1.31 mU/L at 12 months (P<0.001). A subset of morbidly obese patients may thus display transient hypothyroidism vanishing after major weight loss. Moreover a weak positive correlation is found between BMI and TSH, suggesting that the prevalence of SH is BMI dependent [6].

The exact mechanism leading to elevated TSH levels in obesity is not known. TSH secretion is also affected by other endocrine factors including leptin, dopamine and serotonin [7]. Most evidences suggest that leptin plays a major role: it has been reported to enhance TSH production and its levels not only increase in morbid obesity but also positively correlate with mean 24-hour TSH levels [8]. In contrast, dopamine and serotonin exert suppressive effects on TSH secretion and brain reduced dopaminergic and serotonergic tone has been suggested as a further TSH increasing factor in obesity [7,8]. However, the high prevalence of elevated TSH levels in obesity might also be due to SH as a result of an increased prevalence of Hashimoto disease. This hypothesis was tested by Rotondi *et al.* who measured circulating antibodies against thyroglobulin (anti-Tg) and thyro-peroxidase (anti-

TPO) in a group of 350 obese patients with a mean BMI of 48.8 ± 6.7 kg/m² [9]. In fact they found their prevalence (11%) was similar to that found in the general population and, in case of associated SH, was even 50% lower in obese than in normal weight patients. Both findings indicate that morbid obesity is not associated with increased thyroid autoimmunity.

On the other hand, T4 and T3 thyroid hormones exert their effects through the regulation of genes involved in the differentiation of many organs, including brain, muscle, heart, liver, adipose tissue and skin, and controlling carbohydrate / lipid metabolism, protein transcription and basal metabolism [10]. Their plasma concentrations not only depend on direct thyroid output but are also on peripheral tissue concentrations of Selenium (Se) a trace element playing a major role in thyroid hormone metabolism, as well as, in protection from oxidative stress and inflammation after being incorporated into type 1 and type 2 seleno-protein enzymes including glutathione peroxidase [11,12].

Moreover, as suggested by several studies, Se might also exert an inhibiting effect on adipocyte hypertrophy and adipogenesis, and obesity has been reported to be inversely associated with circulating Se and tissue glutathione peroxidase levels [13-15]. A possible underlying mechanism might be Se insulin-mimicking properties through protein kinase activation and by Se-deficiency association with insulin resistance [16-18]

When taking together all of the above, we decided to analyze the effects of Se administration upon obese subjects with SH. The primary endpoint of our study was Se-dependent weight loss; the secondary endpoints were eventually occurring (i) TSH decrease, and (ii) body composition improvement as assessed by bioimpedance analysis.

Materials and Methods

Patients, diet, and measures

This was a double-blind, placebo-controlled study conducted in accordance with the Helsinki Declaration. The study was formally approved by the Ethics Committee of the University of Campania "Luigi Vanvitelli", Naples, Italy.

Inclusion criteria were: age between 18 and 70 years; obesity (body mass index (BMI) >30 kg/m²); type 2 diabetes mellitus under oral hypoglycemic agents and HbA1c between 6.5% and 7.5%; insulin resistance index according to the Homeostatic Model Assessment (HOMA-IR) >2.5 [19].

Exclusion criteria were: evidence of thyroid autoimmunity (high Anti-thyroglobulin antibodies [Ab-TG] and Anti-peroxidase antibodies [Ab-TPO] titers); type 1 diabetes; known Se hypersensitivity / intolerance; previous cardiovascular events; pregnancy; lactation; hypoglycemic or cholesterol-lowering or contraceptive treatment; previous bariatric surgery; history of severe hepatic, renal or cardiac diseases; any malignancies.

The estimated sample size expected to yield a statistically significant result for this study calculated on the basis of the primary outcome endpoint to have a power of 90% with an alpha error of 0.02 was 40 paired subjects. One hundred and twenty-two patients meeting the enrollment criteria and giving their informed consent were selected to take into account the presence of secondary outcomes and expected eventually occurring dropouts. They were randomized to receive either treatment or placebo. 16 did not show up on the starting day, 4 did not complete the full study period, and 2 discontinued treatment spontaneously after a few weeks despite no side effects. As a result 50 pairs of subjects were finally involved in the 52 week study, randomized to take each day after lunch either L-selenio-methionine 83 mcg (Se Group, SG) or placebo (Placebo Group, PG) through size, shape, color, smell, and taste matched tablets (Figure 1).

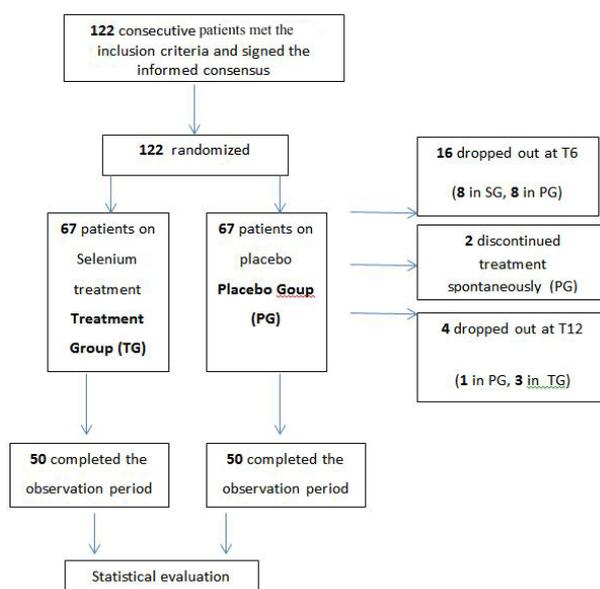


Figure 1: Flow chart depicting patients enrollment procedure

In greater detail, both medication and placebo packaging intended to couples of paired subjects were prepared by the hospital pharmacy and to each box of pills a serial number was attributed as supplied by a generator of pairs of random numbers corresponding to a specific package of drug and placebo. This way each component of each pair of matched subjects was blindly administered either drug or placebo.

During the study all patients received a low-calorie diet (20–25% less than the amount of calories required to maintain current weight) characterized by low glycemic index foods and based on a variable percentage of proteins (10–20%), fat (20–30% with less than 10% as saturated fat), and carbohydrates (50–60% with less than 5% as sucrose). Individual diet regimens were prepared to try and satisfy participant tastes and wishes as much as possible. Favorite carbohydrate sources were starches with a low glycemic index and high soluble fiber content (35 g/day). All subjects reported to perform at least 30 min a day of predominantly aerobic physical exercise as prescribed.

The following parameters were evaluated at baseline (T_0) and after 6 (T_6) and 12 months (T_{12}): fasting blood glucose, fasting serum insulin, HOMA-IR, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides, uric acid, TSH, FT3, FT4, anthropometric measures including weight, height, BMI, and bio-impedance analysis results as reported below.

Serum selenium was estimated by inductively coupled plasma-mass spectrometry as previously described [20]

Bio-impedance analysis (BIA) Abdominal fat was measured using an innovative bio-impedance device (Bia-TANITA AB140 ViScan, BIO) [21] which we also found to be a useful tool in our hands [22]. It consists of a band with four electrodes placed directly on the abdomen, with the subject lying supine. The position of the band was guided by a laser beam from the base unit indicating the navel. Thanks to its high accuracy and repeatability, rather than using any hand-held measuring tape we preferred to have waist circumference (WC) recorded by the base unit itself according to the infrared system [23] along with trunk fat (TF), and percent visceral fat (VF) [24-27].

Safety parameters: AST, ALT, total bilirubin, serum albumin, γ -glutamyl-transferase, alkaline phosphatase, blood urea nitrogen, serum creatinine, red and white blood cell and platelet count, as well as, all the above mentioned blood parameters were measured using a high performance autoanalyzer (*Automatic biochemistry analyzer with integrated system Selectra Pro XL, Elitech, USA*) and an automated blood cell counter (*Countess II Automated Cell Counter, Thermo Fisher, USA*) at baseline and after 6 and 12 months. Side effects were also recorded at baseline and after 6 and 12 months, using a semi-quantitative scale.

Diet adherence: All subjects completed a questionnaire (Q) to evaluate diet adherence during the treatment period. Q consisted of five questions including the frequency of breaches of nutritional advice and the type and amount of food eaten outside the recommended value. Were considered variations from the recommended diet to be acceptable when \leq four per week and within 250 calories each. The questionnaire was previously tested for validity and reliability in a sample of 10 health care workers, verifying the concordance of the answers by the same subjects to whom Q was administered three times in a two-week period (mean concordance degree of 95+5 %).

Statistics: Results were expressed as means \pm SD or %. Observed treatment and differences were tested by the repeated measures analysis of variance (rANOVA) integrated by two-tailed paired Student's t-test with 95% Confidence Intervals (CI) for parametric variables and Mann-Whitney's U test for non-parametric ones. The χ^2 test with Yates correction or Fisher Exact test was used to compare categorical variables. A $p < 0.05$ was chosen as the least accepted statistical significance level. All the evaluations were performed using IBM SPSS Statistics Version 25 software.

Results

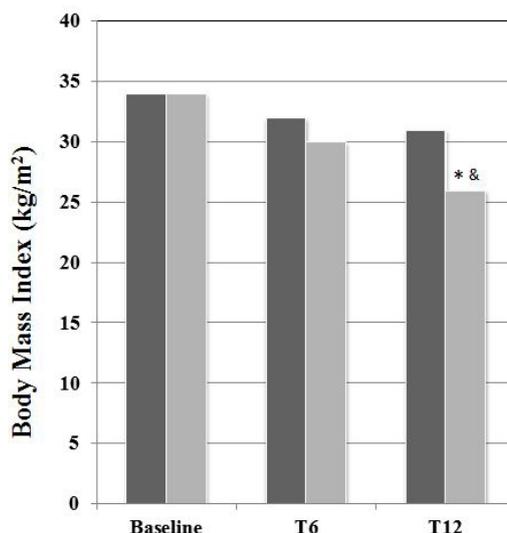
No significant differences were found between the two treatment groups at baseline, as described in Table I. Good diet and exercise adherence was observed in both groups (88% vs 91% and 85% vs 84% in SG and PG, respectively; p n.s.). Reported side effects were low and quite similar in both groups. In greater detail, transient abdominal distension was reported during the first two weeks by 1 subject in the SG and 2 subjects in the PG, which in fact spontaneously vanished thereafter. No significant changes in safety parameters occurred until T_{12} , nor were observed significant changes in HbA1c in both groups ($< 2\%$).

	Control Group	Selenium Group
Subjects (n)	50	50
Male (n)	12	13
Age (year)	58 \pm 9	57 \pm 8
BMI (kg/m ²)	34 \pm 2	34 \pm 4
Smoking habits (n.)	3	5
Systolic BP (mm Hg, M+DS)	136 \pm 15	137 \pm 13
Diastolic BP (mm Hg, M+DS)	82 \pm 9	83 \pm 9
Fasting Glycemia (mg/dl)	92 \pm 10	90 \pm 12

	Control Group	Selenium Group
HbA1c (%)	7+03	7+04
HOMA-IR	4.5±0,8	4.6±1.0
Creatinine (mg/dl)	0.8±0.2	0.8±0.3
AST (IU/l)	27±9	25±9
ALS (IU/l)	28±8	29±8
Y-GT (IU/l)	18±7	20±5
Total cholesterol (mg/dl)	198±10	200±13
HDL-Cholesterol (mg/dl)	38±8	40±6
LDL-Cholesterol (mg/dl)	107±6	105±10
TSH (µU/ml)	6.8±2.4	7.0±2.1
FT ₄ (pmol/l)	15.1±2	14.9±1.9
FT ₃ (pmol/l)	4.1±1.0	4.2±0.9
Selenium (µg/L)	83±10	82±13
Waist circumference (cm)	120±7	118±9
Trunk fat level (%)	48±6	46±7
Visceral fat level (%)	24±7	24±5
24(OH)Vitamin-D mmol/l)	15±6	14±6

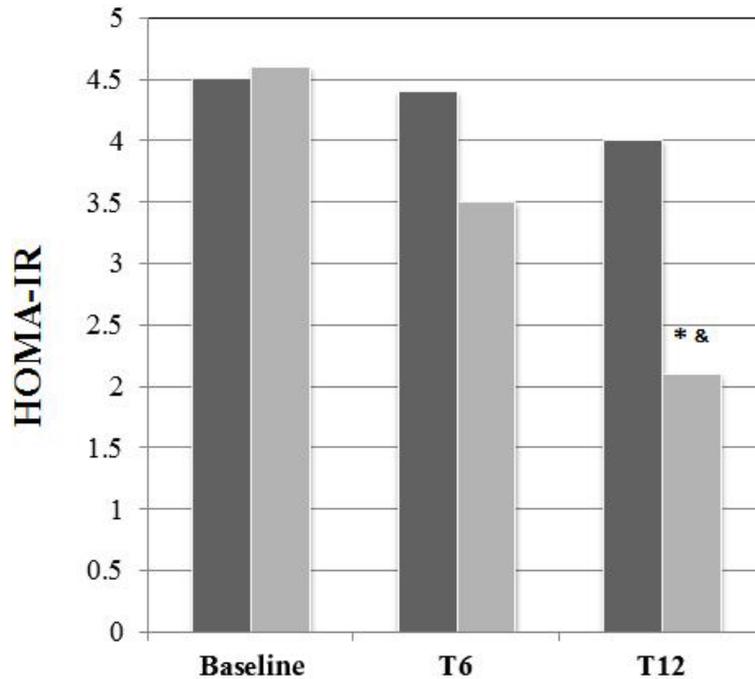
Table 1: General parameters of patients enrolled at baseline; data are given as n. or Mean±SD. Between the two groups no statistically significant differences were found

At T₁₂ Se plasma concentrations were quite similar to baseline in the PG (84±12 vs 83±10 µg/L, p n.s.), and significantly higher than baseline in the SG (101±10 vs 82±13; (p>0.01). The main results observed after 52 weeks are shown in Figures 2 and 3. In greater detail, a significantly lower BMI (difference from baseline 24.1% vs -8.5%, respectively; p<0.001) and HOMA-IR (difference from baseline -54.4% vs -11%, respectively; p<0.0001) was observed in the SG than in the PG. The decrease in BMI was significantly associated with decreased TSH (Figure 2), implying a difference from baseline of -42.8% in the SG vs -11% in the PG, respectively (p<001). Conversely, no FT₄ changes were found either in the PG (15.1±2.0 pmol/l at T₀ vs 14.6±2.0 pmol/l at T₁₂, p n.s.) or in SG (14.9±1.9 pmol/l at T₀ vs 14.7±2.2 pmol/l at T₁₂, p n.s.) and, similarly, no FT₃ changes were found either in the PG (4.1±1.0 pmol/l at T₀ vs 4.3±1.0 pmol/l at T₁₂, p n.s.) or in SG (4.2±0.9 pmol/l at T₀ vs 4.5±0.9 pmol/l at T₁₂, p n.s.). The Figure 4 depicts the % effect of Se on WC, TF and VF in both SG and PG. All the above mentioned parameters, despite significantly decreasing in both groups, did so more prominently in the SG. TSH kept stable in the CG but significantly decreased after treatment in the SG only (Figure 5).



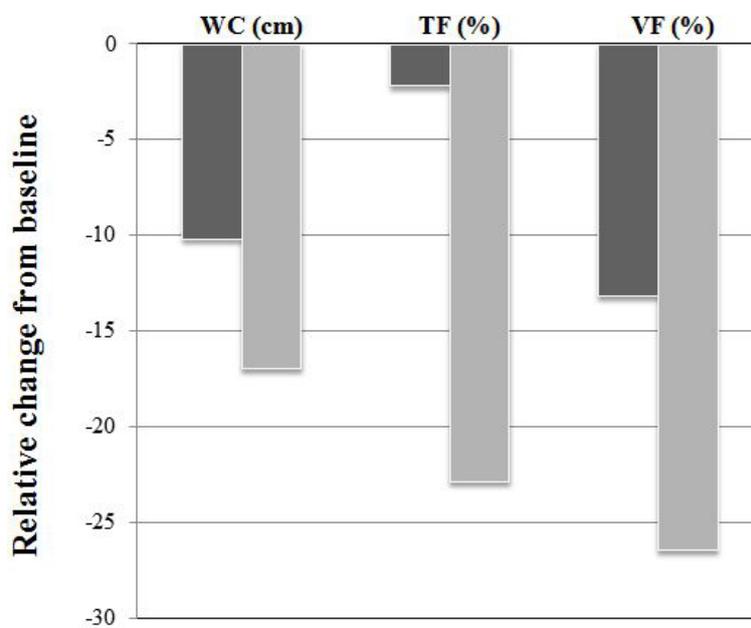
	Baseline	T6	T12
Control Group	34.2±2.1	32.0±2.2	31.3±2.4
Selenium Group	34.4±1.9	30.2±1.8	26.1±1.8* [§]

Figure 2: BMI (kg/m²; M±SD): comparison between Placebo and Selenium Groups during the 12-months treatment period (*p<0.01 vs Baseline; [§]p<0.01 vs Controls; Dark Bars = Control Group, Light Bars = selenium Group)



	Baseline	T6	T12
Control Group	4.5±0.8	4.4±1.0	4.0±0.6
Seleniun Group	4.6±1.0	3.5±1.0	2.1±0.5 ^{* &}

Figure 3: HOMA-IR (M±SD): comparison between Placebo and Seleniun Groups during the 12-months treatment period (^{*}p<0.01 vs Baseline; [&]p<0.01 vs Controls; Dark Bars = Control Group, Light Bars = seleniun Group)



	WC (cm)	within-group P	TF (%)	within-group P	VF (%)	within-group P
Control Group	- 10.2	<0.05	-2.2	n.s.	-13.2	<0.05
Seleniun Group	-17.0	<0.001	-22.9	<0.001	-26.5	<0.001
Between- group p	<0.05		<0.001		<0.001	

Figure 4: T12 Changes from baseline (%) as for waist circumference (WC, cm), trunk fat (TF, %) and visceral fat (VF, %) in Seleniun Group (Dark Bars) vs Placebo Group (Light Bars)

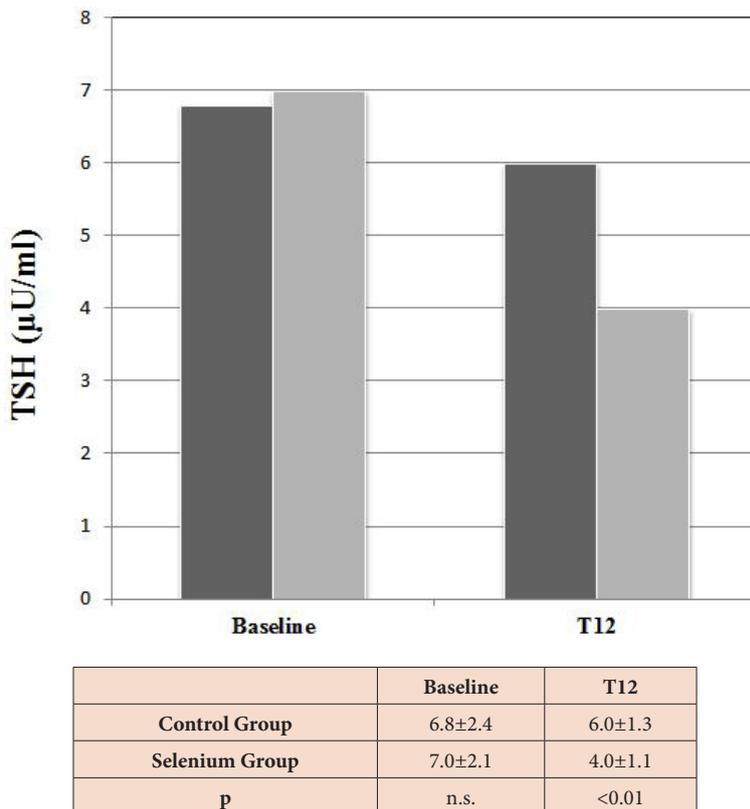
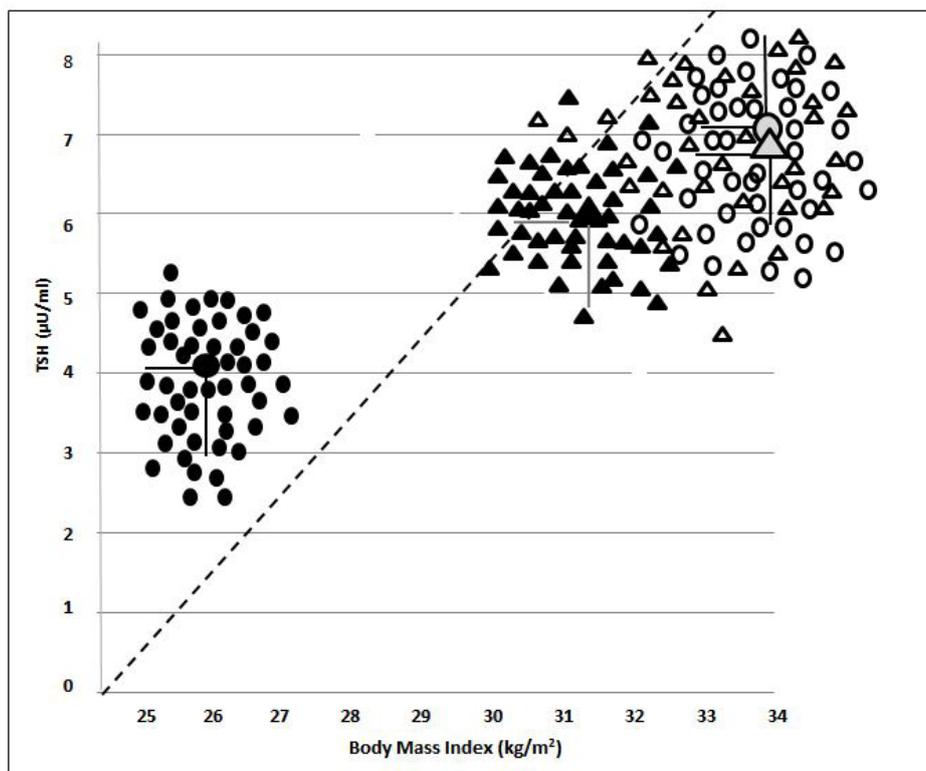
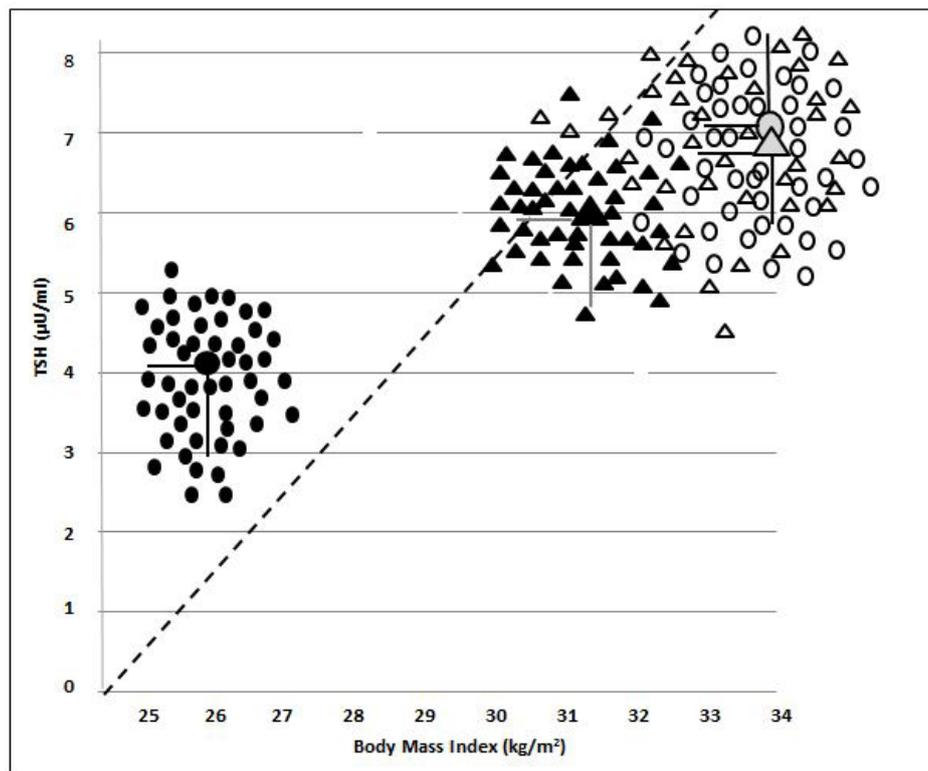


Figure 5: TSH (µU/ml; M±SD): group comparison during the 12-month treatment period (Dark Bars = Placebo Group, Light Bars = Selenium Group)

A significant correlation was found between TSH and BMI decrease rate in all patients participating in the study ($r=0.847, p<0.01$), being those from the SG contributing to the greatest decrease of both BMI and TSH at T₁₂ (Figure 6). A similar significant correlation was observed between HOMA-IR and TSH decrease rates ($r=0.921, p<0.01$) (Figure 7).



Controls Group at baseline=open circle; at end of follow-up black circle, $p<0.001$; Selenium Group at baseline=open triangle; open circle; at end of follow-up black triangle, $p<0.05$. Horizontal and vertical bars=half of SD
Figure 6: Correlation between mean values (+SD) of thyroid-stimulating hormone (TSH) and body mass index (BMI) in 100 patients with subclinical hypothyroidism (SH) and obesity



Placebo Group: at baseline = open circle; at end of follow-up = black circle, $p < 0.001$; Selenium Group: at baseline = open triangle; at end of follow-up = black triangle, $p < 0.05$. Horizontal and vertical bars = single SDs.

Figure 7: Correlation between mean values (\pm SD) of thyroid-stimulating hormone (TSH) and HOMA-IR index in 100 patients with subclinical hypothyroidism (SH) and obesity

Conclusion

In our study, selenium supplementation inversely associated with anthropometric (BMI, WC) and metabolic (HOMA-IR) indexes. These results provide indirect support to the fact that insulin resistance and visceral adiposity may induce selenium deficiency [28-29] as well as, that insulin resistance might indeed depend on it [18,30,31]. In fact, observational studies meant at assessing any eventually occurring association of Se concentrations with central obesity or insulin resistance provided inconsistent results. Conversely, two relatively short duration (6-8 weeks) intervention studies reported on significantly reduced fasting blood insulin levels and HOMA-IR after Se supplementation [32].

What is really new in our study is the observed visceral fat decrease after Se supplementation, strongly supporting our original hypothesis that visceral adiposity might depend on Se deficiency.

Selenium is present in seleno-proteins, which play a vital role for antioxidant and anti-inflammatory activities and contribute to anti-diabetic activity [33]. Selenium supplementation improves blood glucose and blood insulin levels, and inhibits gluconeogenesis in diabetic rats [33,34]. The Se concentration expected to maximize seleno-enzyme antioxidant activity has been determined to be 95 mg/L on average (range 89-114 mg/L) [36-38], i.e. very similar to the level attained in our study experiment. Therefore, we can conclude that at physiological concentrations selenium is involved in the metabolic activities responsible for maintaining blood glucose compensation opposite to what observed at higher concentrations, associating with an increase in diabetes prevalence according the results of a post-hoc analysis of the National Health and Nutrition Examination Survey (NHANES) [38]. In addition, 1999 to 2004 NHANES data demonstrated that people on a selenium-deficient diet were at higher risk of overweight [39]; lastly, a positive correlation was described between Se concentrations and BMI, as well as an inverse association between anthropometric indexes and serum/plasma selenium [39-42]. In our study, the efficacy of Se supplementation can be detected in its primary action on the conversion metabolism (de-iodination) of the pro-hormone thyroxine to the active form tri-iodo-thyronine, supporting the theory that an adequate plasma selenium concentration is useful to prevent excessive weight. This theory is reinforced by the consideration that, in obese patients, (reduced) plasma selenium concentrations could be due to habitual and excessive consumption of high-fat and high-sugar foods, as well as high-sugar drinks [43,44].

Although the effects of Se on body fat metabolism have not been fully elucidated yet, there is evidence relating Se to adipogenesis, i.e. the trace element is thought to be able to inhibit adipogenesis by reducing the expression of m-RNA encoding for PPAR and fatty acid synthase, while stimulating the activation of tissue growth factor (TGF) [45,46].

Limitations

On the basis of speculative observations, it is essential to highlight the presence of limitations of our work. First, given the design of the study, we did not establish a causal relationship between selenium concentration and visceral fat; second, although the results were adjusted for the most likely confounding factors, we might have ignored further potentially involved additional factors; third, we reduced the study costs by assessing insulin resistance through HOMA-IR, a widely used, low accuracy parameter, rather than the gold standard method represented by the dynamic euglycemic-hyperinsulinemic clamp.

Our study confirmed previously reported association between Se treatment and TSH level normalization in the absence of any changes in circulating FT4 concentrations. The latter results agree with those coming from other studies on Se-related enhanced T4 to T3 de-iodination [11] and on thyroid hormone effects in obese patients with moderate hypothyroidism [44].

The most relevant outcome of our study, however, was the first evidence that selenium supplementation per se decreases % abdominal fat depots as reflected both by waist circumference, its widely used surrogate marker, and by bio-impedance derived %VF measurements.

Compliance with ethical standards

Ours was a spontaneous, unconditioned study organized and supported by a special research grant of University of Campania "Luigi Vanvitelli", Naples, Italy.

Ethical standard

This study was conducted in conformance with good clinical practice standards. The study was led in accordance with the Declaration of Helsinki 1975, as revised in 2008, and was approved all the Ethics Committees of the Centers participating in the study.

Human and animal rights

All followed procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national).

Informed consent

Written informed consent was obtained from all participants before enrollment.

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