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Evaluation of glucose tolerance in methimazole and radioiodine treated Graves' patients

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ABSTRACT

Background: One of the major concerns of the administration of radioiodine is its complications. The pancreas has sodium iodine symporter and may concentrate radioiodine.
Objectives: This study compared glucose tolerance in Graves' disease patients on continuous treatment with methimazole to radioiodine-treated hypothyroid patients on levothyroxine.
Materials and Methods: In this study 132 patients with Graves' disease who had relapsed after drug therapy were studied. Fifty-nine were on long term treatment with methimazole, and 73 were radioiodine treated hypothyroid patients on levothyroxine. In each group the glucose tolerance test was performed, and serum lipid profiles and glucose, TSH, insulin concentrations, and HOMA-IR and HOMA-B values were measured.
Results: No significant differences were observed in age, sex, BMI, and BP between the two groups. Mean FBS and HOMA-IR in the radioactive iodine group were higher than in the methimazole group: 94 mg/dl versus 90 mg/dl, P = 0.019 and 1.5 (1.2-2.3) versus 1.3 (0.8-2.1), P = 0.045, respectively. After controlling for family history of diabetes and total cholesterol, the two groups were not significantly different on any of the dependent variables. No significant differences were found between the two groups on the HOMA-B, median 2-hour blood glucose, and serum-insulin levels.
Conclusions: The results of this study indicate that radioiodine treatment had no adverse effects on glucose tolerance and insulin resistance.

Implication for health policy/practice/research/medical education:
Radioiodine and methimazole therapy of Graves' patients have no adverse effect on glucose hemostasis.

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1. Background

Radioactive iodine is an isotope that emits gamma and beta rays (1) and, since its identification in 1940, is used largely for the treatment of patients with hyperthyroidism due to Graves' disease (2). Although the response to the effect of this method is slower than drug therapy, it is still in all other respects an ideal method for treatment. Radioactive iodine is orally administrated and is excreted through the kidneys. The effects and complications resulting from administration of radioactive iodine on various tissues and organs have always been of some concern. Complications such as carcinogenesis teratogenicity and increased mortality have been suggested in the literature (3, 4).

Several studies have shown leukocyte chromosomal abnormalities in patients treated with therapeutic doses

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of radioactive iodine (5, 6), and carcinogenesis and increased mortality are among the major concerns (7-9). Initially, radioactive iodine causes cell necrosis that results in an inflammatory response (10).

Following administration, radioiodine may be found in many tissues, such as the salivary glands, gastric mucosa, lactating mammary glands, ovaries, placenta, choroid plexus, pancreas, and thymus (11, 12). Because the iodine concentration in plasma is very low, a mechanism is needed to concentrate this element in the thyroid; this process, called iodide trapping, is mediated by a membrane protein known as sodium iodide symporter (NIS; [13]). Although the transfer of iodine in such tissues is not dependent on TSH, numerous studies have shown that iodine organification is done by some tissues outside the thyroid. Several studies have found NIS in the pancreatic gland (14, 15) and other studies have shown localization of radioactive iodine in the pancreas (16, 17). Therefore, the accumulation of radioactive iodine in the pancreas can have harmful effects on the function of beta cells and impair glucose tolerance in such patients.

2. Objectives

This study was designed to investigate the effects of radioactive iodine on glucose tolerance. We aimed to compare glucose tolerance in hyperthyroid patients who received radioactive iodine and developed hypothyroidism and were euthyroid on levothyroxine with the glucose tolerance of patients on continuous methimazole treatment.

3. Materials and methods

Between 1983 and 1989, 576 patients with a clinical and laboratory diagnosis of diffuse toxic goiter were treated with methimazole; of these, 51 cases did not return during treatment or preferred to have radioactive iodine treatment. Twelve patients who relapsed during treatment were treated with radioactive iodine. Of the remaining 513 patients, 104 experienced a recurrence of hyperthyroidism. Nineteen patients wanted treatment options other than those offered by random allocation and were excluded from the study, so remained 85 patients. Additionally, 47 patients with a recurrence of hyperthyroidism were added to these 85 patients. Relapse of hyperthyroidism was confirmed in all of 132 of these patients by their high T3 and T4 levels and low TSH levels; These 132 patients were divided into two groups of continuous methimazole or radioiodine treatment, one and half year after discontinuing the drug either randomly or by patient preference. All of the patients in the methimazole group (n = 59) were euthyroid and received methimazole at a dosis of 20 mg daily in the first month, 10 mg daily in the second month, and 2.5 to 10 mg in the following months. The average dose of radioactive iodine was 7.9 ± 5.1 mci with a range of 5-13 mci. The second group of patients was followed for at least 10 years after taking radioactive iodine. If hyperthyroidism relapsed, radioactive iodine therapy was administered. If TSH levels exceeded 10 mU/l, treatment with levothyroxine was begun, and dosis was adjusted to maintain serum TSH levels between 0.3 and 3 mU/l. In both groups, patients were visited every 3 months in the first year and every 6 months in the second year. During each visit, patients were examined and clinical and laboratory statuses of thyroid were determined by measurements of serum T_4, T_3, T_3RU, and TSH.

Fifty-nine patients of the methimazole group and 73 of the radioiodine group who developed hypothyroidism, were euthyroid with levothyroxine, and were successfully followed up for at least 10 years. Physical and thyroid examinations were performed, and blood pressure, heart rate, height, weight, and body mass index (BMI) were calculated. A questionnaire for personal information and previous history of drug use and diseases was completed. Serum samples were obtained after a 12- to 14-hour fast to measure serum glucose, insulin, total cholesterol, triglycerides, and HDL cholesterol. Two hours after 75 g of glucose administration (equivalent to 82.5 g of glucose monohydrate) serum glucose was measured and HOMA- IR (Homeostasis Model Assessment-Insulin Resistance) and HOMA-B (Homeostasis Model Assessment-β cell function) were calculated; additionally, T3 by radioimmunoassay (RIA) and TSH by immunoradiometric assay (IRMA) were measured using the relevant commercial kits (Isotop, Budapest, Hungary). Free T_4 was measured with an enzyme-linked fluorescent immunoassay method (kit by Biomerieux, Marcy, France, and apparatus by Mini Vdas, Marcy, France). Insulin levels were measured with EIMA (Mercodia, Uppsala, Sweden) and Elisa (Sunrise,Tecan Co.Salzburg, Austria) methods. Serum glucose level was measured using enzymatic calorimeter with glucose oxidase. Total cholesterol was measured using an enzymatic calorimeter with cholesterol esterase and cholesterol oxidase, and LDL and HDL cholesterol were measured directly. Triglycerides were measured using enzymatic calorimetry with glycerol phosphate oxidase. For all these measurements the relevant commercial kits (Pars Azmoon, Tehran, Iran) and Autoanalyzer Selectra-2 (Vital Scientific Spankeren,The Netherlands) were used. Intra- and intercoefficients of variation for T3 were 3.3% and 3.6%, for free T4 were 4.6% and 4.9%, and for TSH were 5.5% and 8.5%, respectively. For biochemical parameters, coefficients of variation were 2.0% and 2.2% for glucose, 1.2% and 1.6% for LDL cholesterol, and 1.0% and 1.5% for HDL cholesterol, respectively. For triglycerides, the intra- and intercoefficients of variation were both 2.8%.

We used following formulas for HOMA-IR and HOMA- B calculations:

$$\text{HOMA-IR} = \frac{\text{Fasting glucose (mmol/L)} \times \text{fasting insulin (mU/L)}}{22.5}$$

$$\text{HOMA-B} = \frac{20 \times \text{Fasting insulin (mU/L)}}{3.5 - \text{Fasting glucose (mmol/L)}}$$

3.1. Data analysis

To determine the normality of the distribution of variables, the Kolmogrof Smirnof test was used. Data with normal distributions were expressed as means and standard deviations, and data without normal distributions were expressed as medians and interquartile ranges. For comparisons between two groups, *t*-tests were used for variables with normal distributions and for variables without normal distributions; the Mann-Whitney test was used. To compare qualitative variables between two groups, Chi square tests were used. SPSS 16 software was used to perform the statistical analyses. *P* values below 0. 05 were considered significant.

4. Results

Baseline characteristics including age, height, weight, BMI, waist circumference, smoking history, physical activity, and systolic and diastolic blood pressure in 132 patients are shown in *Table 1*. Of the 132 patients, 52 were in the methimazole group (MMI) and 73 in the radioiodine group (RAI). Age, weight, waist circumference, smoking history, and blood pressure were not significantly different between the two groups. The MMI group had a higher average height than the RAI group ($P = 0.001$), but the RAI group had a higher average BMI ($P = 0.039$). A greater percentage of patients in the RAI group had low physical activity levels ($P = 0.009$), whereas a greater percentage of patients in the MMI group had moderate levels of physical activity ($P = 0.006$). Of the 132 patients who entered the study, 4 were excluded due to lack of complete data or laboratory tests; therefore, analysis was performed on 128 patients (73 patients in the RAI group and 55 in the MMI group).

Table 2 shows the fasting and 2-hour blood glucose, insulin, HOMA-IR, HOMA-B, thyroid function tests, and lipid profiles for the RAI and MMI groups by gender. The median fasting blood-glucose levels were higher for the RAI group than the MMI group ($P = 0.035$ and 0.029, respectively). The median 2-hour glucose in women of the RAI group was higher than the MMI group ($P = 0.014$). The median insulin levels did not differ between the two groups ($P = 0.169$). HOMA-IR was higher in the RAI group ($P = 0.036$), but HOMA-B was not significantly different in the two groups. TSH and T_3 were higher in the MMI group ($P = 0.012$ and 0.008, respectively), and FT_4 was higher in the RAI group ($P = 0.001$). Total cholesterol, LDL cholesterol, and triglycerides were higher in the RAI group ($P = 0.011$, 0.019 and 0.001, respectively). HDL cholesterol was lower in the RAI group than in the MMI group ($P = 0.005$).

These results led to an additional exclusion of 19 patients for the next round of analyses. Specifically, of the 128 cases, 15 patients were excluded due to a previous history of diabetes mellitus, and 4 patients were excluded due to overt hyperthyroidism ($FT_4 > 25$ or $T_3 > 180$ and TSH < 0.2), leaving a final sample of 109 patients. The mean age in the two groups was not significantly different ($P = 0.35$); 81.7% of patients in the RAI group and 73.5% of patients in the MMI group were women ($P = 0.35$). BMI and systolic and diastolic blood pressures were not significantly different in the two groups ($P = 0.14$, 0.91, and 0.82, respectively). Serum total cholesterol, LDL, and triglycerides were significantly higher in the RAI group ($P = 0.006$, 0.005, and < 0.001, respectively); HDL was lower in the RAI group ($P = 0.006$), whereas FT_4 in the RAI group and T_3 and TSH in the MMI were higher ($P < 0.001$, 0.009, and 0.039 respectively).

Table 3 shows the median fasting and 2-hour blood-

Table 1. General characteristics of the methimazole (MMI) and radioiodine (RAI) treated patients

Variable	Males			Females			Total		
	MMI, n=18	**RAI,** n=11	***P* value**	**MMI,** n=41	**RAI,** n=62	***P* value**	**MMI,** n=59	**RAI,** n=73	***P* value**
Age, y	60.9 ± 13.5*	52.5 ± 9.5	0.08	47.3 ± 15.4	53.2 ± 11.8	0.052	51.4 ± 16.1	53.1 ± 11.4	0.525
Height, cm	170 ± 9.6	169 ± 6.6	0.653	162 ± 6	157 ± 5	0.001	165 ± 8	160 ± 7	0.001
Weight, kg	80.2 ± 13.8	80.4 ± 12.9	0.931	67.8 ± 9.8	68.5 ± 11.2	0.748	71.6 ± 12.4	70.3 ± 12.1	0.555
BMI, kg/m^2	27.5 ± 4.1*	28 ± 4.1	0.675	26.2 ± 3.5	27.7 ± 4.6	0.021	26.2 ± 3.5	27.8 ± 4.5	0.039
Wc, cm	98 ± 10	103 ± 9	0.252	87 ± 9	89 ± 15	0.334	90 ±10	91 ± 15	0.441
Smoking, NO. (%)	7 (38.9)	6 (54.5)	0.446	4 (9.8)	4 (6.5)	0.71	11 (18.6)	10 (13.7)	0.296
Physical activity, NO. (%)									
Low	8 (47.1)	9 (81.8)	0.115	23 (56.1)	47 (75.8)	0.052	31 (53.4)	56 (76.7)	0.009
Moderate	10 (52.9)	2 (18.2)	0.115	18 (43.9)	15 (24.2)	0.052	28 (46.6)	17 (3.23)	0.006
SBP, mm Hg	140 (120-150)†	120 (110-140)	0.052	120 (110-140)	120 (110-140)	0.641	120 (110-140)	120 (110-140)	0.225
DBP, mm Hg	90 (80-95)	80 (80-85)	0.225	80 (80-85)	80 (80-90)	0.5	80 (80-90)	80 (80-90)	0.251
BSA, m^2	1.8 ± 0.22	1.92 ± 0.197	0.553	1.71 ± 0.124	1.7 ± 0.14	0.805	1.76 ± 0.17	1.74 ± 0.177	0.611

* Mean ± SD
† Range

Table 2. Laboratory variables in the two study groups

Variables	Males			Females			Total		
	MMI, n=15	**RAI**, n=11	***P* value**	**MMI**, n=40	**RAI**, n=62	***P* value**	**MMI**, n=55	**RAI**, n=73	***P* value**
FBS, mg/dL	95 (87-111)[a]	105 (88-119)	0.384	90 (81-96)	95 (86-108)	0.029	91 (84-105)	97 (87-108)	0.035
2hpp, mg/dL	120 (81-242)[a]	113 (69-194)	0.674	96 (80-130)	124 (96-150)	0.014	105 (81-134)	124 (92-153)	0.095
Insulin, mU/L	7.3 (3.1-8.6)[a]	7.4 (6.2-12.5)	0.169	6 (4-10)	7 (5-10)	0.478	6 (4-10)	7 (5-10)	0.169
HOMA-IR	1.3 (0.62-2.2)[a]	1.4 (1.6-1.3)	0.102	1.3 (0.68-2.1)	1.2 (1.7-2.4)	0.126	1.3 (0.836-2.1)	1.7 (1.3-2.5)	0.036
HOMA-B	62.2 (28.5-107)[a]	98.9 (60.4-126.5)	0.264	92 (56.3-145.2)	76.4 (47.1-128.2)	0.212	85.4 (50.3-136.9)	77.7 (47.3-126.9)	0.716
TSH, μU/ml	4.0 (2.5-5.8)[a]	2.9 (0.63-4.1)	0.164	2.8 (1.4-4.1)	1.4 (0.3-4.1)	0.051	3.1 (1.06-5.1)	1.73 (0.36-4.1)	0.012
FT4, pmol	11.9 (10.9-13.3)[a]	14.9 (12.4-18.5)	0.008	11.8 (10.1-13.1)	14.8 (12.5-19.6)	0.001	11.9 (11.4-13.3)	14.4 (12.8-19.1)	0.001
T3,ng/dL	145 ± 38	118 ± 32	0.069	148 ± 40	129 ± 45	0.035	147 ± 40	124 ± 43	0.008
Cholesterol mg/dL	198 ± 34	216 ± 55	0.305	190 ± 37	207 ± 29	0.011	192 ± 36	209 ± 34	0.011
TG, mg/dL	139 (103-161)[a]	167 (162-183)	0.008	109 (86-133)	163 (113-205)	0.008	115 (90-152)	167 (120-212)	0.001
LDL-C, mg/dL	106 ± 24	117 ± 38	0.425	101 ± 23	111±18	0.015	101 ± 23	1.2 ± 22	0.019

[a] Median and interquartile range. Others as mean ± SD

Table 3. Laboratory variables in the two groups after exclusion of patients with diabetes and overt hyperthyroidism by sex

Variables	Males			Females			Total		
	MMI, n=15	**RAI**, n=11	***P* value**	**MMI**, n=55	**RAI**, n=62	***P* value**	**MMI**, n=55	**RAI**, n=73	***P* value**
FBS mg/dL	93 (84-103)[a]	105 (88-119)	0.134	88 (79-96)	94 (85-107)	0.036	90 (80-96)	94 (86-107)	0.019
2hpp mg/dL	113 (77-191)[a]	113 (69-194)	0.928	95 (78-130)	117 (90-136)	0.070	98 (78-131)	115 (85-137)	0.168
Insulin mU/L	4 (3-9)	7.4 (6.2-12.5)	0.082	6.4 (4-9.4)	7.1 (5.5-8.9)	0.873	5.6 (3.8-9.2)	7.1 (5.5-9.2)	0.268
HOMA-IR	0.9 (0.6-1.9)	1.6 (1.4-3.3)	0.03	1.3 (0.8-2.1)	1.5 (1.2-2.1)	0.284	1.3 (0.8-2.1)	1.5 (1.2-2.3)	0.045
HOMA-B	62.2 (30.8-108.4)	98.9 (60.4-126.5)	0.311	101.7 (60.4-154.9)	77.4 (47.3-129.1)	0.107	91.4 (55.2-142.7)	78.6 (47.5-127.1)	0.446

[a] Median and interquartile range

glucose, insulin, HOMA-IR, and HOMA-B levels in the RAI and MMI groups after excluding diabetes and overt hyperthyroidism. The median fasting blood glucose in the RAI group was higher than in the MMI group (94 vs. 90 mg/dl, $P = 0.019$), a difference that was maintained after adjusting for family history of diabetes ($P = 0.016$) but disappeared after adjusting for family history of diabetes and total cholesterol ($P = 0.079$). After adjusting for family history of diabetes, total cholesterol, and T_3, this difference was lower ($P = 0.198$). HOMA-IR was higher in the RAI group (1.5 vs. 1.3, $P = 0.045$), but after adjusting for serum triglycerides, this difference disappeared ($P = 0.509$). Although 2-hour blood glucose and insulin were higher in the RAI group, these differences were not statistically significant ($P = 0.168$ and $P = 0.268$, respectively). HOMA-B did not differ between the two groups. To evaluate the relationship between dose of radioiodine and median fasting and 2-hour blood glucose, the dose of radioiodine was divided into two groups: ≤ 10 mci and > 10 mci. Median fasting blood glucose was higher in the group that received > 10 mci radioiodine compared to the group that received ≤ 10 mci radioiodine, but this difference was not statistically significant for fasting blood glucose (100 [87–107] vs. 90 [84–107] mg/dl, $P = 0.289$) or 2-hour blood glucose (125 [90–153] vs. 102 [84–135] mg/dl, $P = 0.328$).

The coefficient for the correlation between fasting blood glucose and radioiodine dose was 0.25 ($P = 0.053$), and the coefficient for the correlation between 2-hour blood glucose and radioiodine dose was 0.27 ($P = 0.035$).

To evaluate the relationship between time elapsed from the date of radioiodine and median fasting and 2-hour blood glucose, the time period was divided into two groups: < 14 years and ≥ 14 years. The median fasting and 2-hour blood glucose in the two groups did not differ significantly for fasting blood glucose (95 [84–116] vs. 94 [87–106] mg/dl, $P = 0.970$) or 2-hour blood glucose (117 [92–137] vs. 106 [84–142] mg/dl, $P = 0.911$). The coefficients for the correlations between time elapsed after radioiodine and fasting blood glucose was -0.017 ($P = 0.89$) and between time elapsed after radioiodine and 2-hour blood glucose was -0.023 ($P = 0.86$).

5. Discussion

The results of this study showed that the median fasting blood-glucose and HOMA-IR levels in patients with Graves' disease were higher in patients who received radioactive iodine than in patients who received methimazole. This difference, however, disappeared after adjusting for other factors. Two-hour blood-glucose and insulin levels were higher in the RAI group, although the difference was not statistically significant. HOMA-B was higher in the MMI group, although this difference was not statistically significant. The median fasting and 2-hour blood-glucose levels were not significantly different among those who received ≤ 10 mci RAI and those who received > mci RAI; however, the correlations between radioiodine dosage and median fasting and 2-hour blood glucose were significant, whereas the correlations between median fasting and 2-hour blood glucose and time elapsed after the radioactive iodine were not. High doses of radioactive iodine have short-term complications such as anorexia, taste changes, nausea, sialadenitis, neck swelling, inhibition of hematopoiesis, and headache and long-term complications such as decreased saliva secretion, decreased tear secretion, radiation-induced pneumonitis, ovarian and testicular dysfunction, and increased risk of secondary tumors. One of the likely complications is the possible effect of radioactive iodine on the endocrine part of the pancreas, especially the beta cells that can cause impaired glucose tolerance and diabetes mellitus. Indeed, no study has specifically addressed this subject in the past. Because the transfer of iodine into the cells is dependent on the existence of NIS, organs with NIS will be able to transfer iodine into the cell. Therefore, the possibility of each organ's iodine uptake can be studied by NIS existence, which can be investigated by immunohistochemical or genetic methods. Two studies conducted by Spitzweg and colleagues (14, 15), using immunohistochemical and genetic methods, showed the existence of NIS in the pancreas. Therefore, based on these two studies, iodine uptake by the pancreas should be expected, and administration of different radioiodine doses can be absorbed by the pancreas and can have adverse effects on this organ.

Uptake and concentration of radioiodine by the pancreas could damage the beta cells, which can be evaluated by assessing blood glucose, glucose-tolerance tests, insulin levels, and insulin resistance. This study included a total of 109 patients (after excluding patients with diabetes and overt hyperthyroidism): 60 in the RAI group and 49 in the MMI group. The mean age and sex distributions, BMI, and blood pressure in both groups were similar. Evaluation of lipid profiles showed that total cholesterol, LDL, and triglycerides were higher and HDL was lower in the RAI group, indicating a possible effect of radioactive iodine on the metabolism of lipoproteins. This effect and its consequences need to be confirmed by more studies. The median fasting blood-glucose and HOMA-IR levels were higher in the RAI group but disappeared after adjusting for other factors, and the median 2-hour blood-glucose and insulin levels were not significantly different between the two groups. The results showed that the radioactive iodine dose had a significant relationship with median fasting and 2-hour blood glucose levels. In one study investigating islet cell antibodies and anti-GAD in hyperthyroid patients before and after treatment, HbA1c before and after iodine were not significantly different in 78 patients (18); of course, this requires studies of longer duration that also investigate long-term effects.

The overall results of this study show the possible effects of radioactive iodine on glucose tolerance, effects that disappeared after adjusting for confounding variables such as family history of diabetes and total cholesterol. The main limitation of this study is that this is not a prospective study. It is better that patients be identified first, then followed up with at intervals, and then compared. The other limitation of this study is the limited doses of radioactive iodine that could be resolved by enrolling patients who received high doses of radioactive iodine, such as thyroid-cancer patients. Another drawback is the lack of laboratory data for patients before receiving radioactive iodine. Therefore, discussions on the effects of radioactive iodine on glucose tolerance require further studies on larger samples that investiage different doses of radioactive iodine and the effects before and after iodine. In conclusion, the findings of this research could not prove the probable effect of radioactive iodine on glucose tolerance and lipoprotein metabolism. A similar study with higher doses of radioactive iodine is recommended.

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Conflict of interest

None declared.

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