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CLINICAL ARTICLE

Placental tissue iodine level and blood magnesium concentration in pre-eclamptic and normal pregnancy

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Abstract

Objective: To assess iodine concentration in the placental tissue and magnesium concentration in the blood of women with severe pre-eclampsia in northeast Anatolia and compare these values with those of healthy pregnant women from the same region. *Methods*: Placental tissue and blood specimens were obtained from 20 severely pre-eclamptic and 15 healthy pregnant women. Iodine levels in placental tissue were determined by the Foss method based on the Sandell–Kolthoff reaction. *Results*: Placental tissue iodine levels were lower in women with severe pre-eclampsia than in healthy pregnant women (4.30 ± 1.36 ng of iodine/mg protein vs. 7.71 ± 2.84 ng of iodine/mg tissue protein; $P < 0.001$), as were blood magnesium levels (1.63 ± 0.05 mg/dL vs. 1.87 ± 0.05 mg/dL; $P < 0.001$). There was a positive correlation between placental tissue iodine levels and blood magnesium levels in women with severe pre-eclampsia ($r = 0.55$, $P < 0.05$), but no such correlation was observed in healthy pregnant women ($r = 0.23$, $P = 0.41$). *Conclusion*: Magnesium assimilation is known to be defective when iodine levels are insufficient. In northeast Anatolia, where iodine deficiency is common, clinical trials of iodine supplementation should be considered for pre-eclamptic therapy.

1. Introduction

Pre-eclampsia occurs in 7% to 10% of pregnancies and remains a leading cause of maternal and neonatal mortality and morbidity. It is usually diagnosed in late pregnancy, in women with increased blood pressure and proteinuria, and these symptoms disappear shortly after delivery of the placenta. Although the causes of these symptoms are still unknown, studies have shown that pre-eclampsia is a multisystemic disease affecting the placental endothelium, with an unidentified circulating factor, or factors, causing alterations in the vascular function [1]. Morikawa and Yoshida [2] has reported that pre-eclamptic women have pathologically low levels of circulating magnesium compared with healthy pregnant women [2]. Moreover, it is known that magnesium assimilation is defective when iodine is missing [3].

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Iodine is an essential component of the thyroid hormones [4]. The thyroid gland shares its capacity to actively accumulate iodine with several other tissues such as the stomach, the salivary glands, and the lactating mammary glands. The amount of iodine in the human body ranges between about 30 and 50 mg, and less than 30% is present in the thyroid gland. About 60% to 80% of the total iodine is non-hormonal and concentrated in tissues other than the thyroid gland, but the biologic role of non-hormonal iodine is unknown. Venturi et al. [4] have hypothesized that iodide may have an ancient antioxidant role in extra-thyroidal iodine-concentrating cells.

Geographic differences in the rates of breast, endometrial, and ovarian cancer appear to be inversely correlated with dietary iodine intake [5]. Endocrinologic considerations suggest that a low dietary iodine intake may increase effective gonadotropin stimulation, which in turn may produce a hyperestrogenic state characterized by a relatively high production of estrone and estradiol and a relatively low estriol to estrone-plus-estradiol ratio. This altered endocrine state may increase the risk of breast, endometrial, and ovarian cancer. Increasing dietary iodine intake may reduce the risk of these cancers [5].

Turkey has been included in the countries with endemic goiter. Akarsu et al. [6] have reported a goiter prevalence of 5.6% in Erzurum, a city in northeastern Anatolia. These authors estimated at 37.6% the prevalence of persons with urinary iodine concentration less than 5 μg/dL, indicating that iodine deficiency is endemic in this region, where Dundar reported a 7.2% rate of pre-eclamptic pregnancies [7].

The aim of this study was to investigate the differences in blood magnesium concentration and placental tissue iodine concentration in women with severe pre-eclampsia and healthy pregnant women in Erzurum, Turkey.

2. Patients and methods

After giving informed consent, 20 women with severe pre-eclampsia and 15 healthy pregnant women seen at the Obstetrics and Gynecology Department of the Medical Faculty of Ataturk University were included in the study. The women's ages ranged between 19 and 44 years (mean age, 32.9 years) in the study group and between 19 and 39 years (mean age, 27.9 years) in the control group. Pregnancy duration was similar in the 2 groups (Table 1). Severe pre-eclampsia was diagnosed when the following criteria were present: (A) A systolic blood pressure of 160 mm Hg or greater or a diastolic blood pressure of 110 mm Hg or greater on 2 occasions at least 6 h apart, with the patients resting in bed; and (B) a proteinuria of 5 g or greater in a 24-hour urine collection or of 3+ or greater on a dipstick in at least 2 random clean-catch samples at least 4 h apart.

Table 1 Characteristics of the study participants

	Patients with pre-eclampsia ($n=20$)	Controls ($n=15$)
Age, year	32.90 ± 8.23	27.93 ± 5.79
Gestational age, week	34.32 ± 1.25	33.94 ± 1.65
Height, m	1.60 ± 0.03	1.61 ± 0.05
Body weight, kg	73.55 ± 4.92	74.47 ± 4.75

Values are given as mean ± SD.

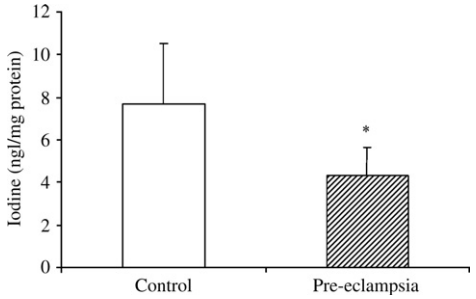

Figure 1 Iodine levels in placenta of patients with pre-eclampsia and control group. *: $P<0.001$, unpaired t test.

All chemicals used in this study were obtained from Sigma-Aldrich Co., St. Louis, MO, USA.

2.1. Determination of tissue iodine level

Placental tissue was gently separated by sterile dissection and washed repeatedly in a normal saline solution and the specimens were stored at −80 °C until homogenization. After thawing, they were homogenized at 0 °C in a 0.05 mol/L solution of potassium phosphate containing 10 M potassium hydroxide. The homogenates were incubated at 115 °C overnight and incinerated in a muffle furnace at 600 °C for 180 min [8]. The ash was dissolved in 10 mL of double distilled water and quantified spectrophotometrically at 420 nm using the Sandell–Kolthoff reaction [9]. Protein concentration in the supernatant was measured by the Bradford method [10]. To account for differences in tissue cellularity, results were expressed as nanograms of iodine/mg of protein. Two surgical specimens of thyroid tissue served as positive controls.

2.2. Determination of blood magnesium concentration

An Olympus kit was used to measure magnesium levels (Olympus America, Center Valley, PA, USA). Blood samples were collected into tubes after an overnight fast of 12 or a fast up to 24 h and serum samples were obtained by blood centrifugation. Determination of magnesium concentration in these samples was carried out with an AU 2700 auto-analyzer (Olympus America).

2.3. Statistical analysis

The results are given as mean ± SD. The unpaired t test was used to compare group means of iodine placental concentration. The Pearson correlation coefficient was used to assess relationships.

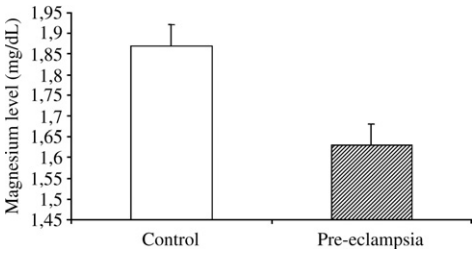

Figure 2 Magnesium in blood of patients with pre-eclampsia and control group. *: $P<0.001$, unpaired t test.

3. Results

Iodine levels in placental tissue are shown in Fig. 1. The level was 4.30 ± 1.36 ng of iodine/mg tissue protein (range, 2.5–7.4) for women with severe pre-eclampsia, lower than 7.71 ± 2.84 ng of iodine/mg tissue protein (range, 4.5–14.4) for healthy pregnant women ($P<0.001$) (Fig. 1).

In all placental tissue specimens, iodine concentration was lower than in 2 healthy thyroid tissue specimens, in which iodine concentration was 566 and 611 ng of iodine/mg of tissue protein, respectively (mean ± SD, 588.5 ± 22.5).

Blood magnesium concentration was 1.63 ± 0.05 mg/dL (range, 1.6–1.7), lower in women with severe pre-eclampsia than in healthy pregnant women 1.87 ± 0.05 mg/dL (range, 1.8–1.9 mg/dL) ($P<0.001$) (Fig. 2).

There was a positive correlation between iodine levels in placental tissue and blood magnesium concentration in women with severe pre-eclampsia ($r=0.55$, $P<0.05$). There was no correlation between the iodine levels in placental tissues and blood magnesium concentration in healthy pregnant women ($r=0.23$, $P=0.41$).

There were no statistically significant differences in age, height, and body weight between women with severe pre-eclampsia and healthy pregnant women (Table 1). There was also no difference in thyroid hormone levels between women with severe pre-eclampsia and healthy pregnant women (Table 2).

4. Discussion

To the authors' knowledge, this study is the first to report lower placental tissue iodine levels in women with severe pre-eclampsia than in healthy pregnant women. A lower blood magnesium level was also noted in women with severe pre-eclampsia than in healthy pregnant women, and there was a positive correlation in women with pre-eclampsia between iodine levels in placental tissue and magnesium level in blood. However, there was no such correlation in healthy pregnant women.

Pre-eclampsia is a pregnancy disorder of unknown origin characterized by vasospasm, elevated blood pressure, and increased neuromuscular irritability—all features common to syndromes of magnesium deficiency. Disturbances in serum and ionized magnesium metabolism have been observed in women with pre-eclampsia. Cellular magnesium depletion is characteristic in healthy pregnancy and may be a factor contributing to the pathophysiology of pre-eclampsia. Furthermore, the influence of central nervous system factors on blood pressure may be mediated, at least in part, by ambient intracellular magnesium levels [11].

Table 2 Thyroid hormone levels in the study participants

Hormone	Patients with pre-eclampsia ($n=20$)	Controls ($n=15$)
T3, μg/dL	1.43 ± 0.44	1.57 ± 0.33
T4, μg/dL	9.91 ± 2.50	10.98 ± 2.28
TSH, μIU/mL	2.54 ± 1.73	2.64 ± 1.99
FT3, pg/mL	2.34 ± 0.61	2.51 ± 0.67
FT4, ng/dL	1.03 ± 0.22	1.04 ± 0.23

Abbreviations: FT, free thyroxine; T, thyroxine; TSH, thyroid-stimulating hormone.
Values are given as mean ± SD.

Magnesium sulfate is widely used parenterally to treat severe pre-eclampsia and prevent recurrent seizures in eclampsia, and for tocolysis in preterm labor. In addition, magnesium sulfate is known to decrease blood pressure [11]. Although magnesium sulfate has been used for a long time in pre-eclamptic and eclamptic pregnant women, its mechanism of action at the molecular level remains an enigma. When initially administered, it has a mild vasodilatory effect in the maternal circulation. This vasodilation may improve feto-placental perfusion, which is known to be diminished in pre-eclampsia. Antenatal use of magnesium sulfate in pre-eclamptic women decreases the incidence of intraventricular hemorrhage in the newborn [12] and thus protects the fetus [13]. Other studies have also shown decreased neonatal mortality rates when magnesium is used in pre-eclampsia or preterm labor [11]. However, recent studies have warned that high, tocolytic doses of magnesium sulfate can be toxic in pregnant women and sometimes lethal to the newborn [14]. It has been suggested that magnesium sulfate may interfere with calcium channels in vascular smooth muscle and endothelial cells [15]. On the other hand, total serum calcium, magnesium, and phosphorus are all significantly elevated in the maternal serum at the end of the third trimester of pregnancy [16].

The thyroid gland shares its capacity to actively accumulate iodide (I^-) with several other tissues, including the gastric mucosa and the lactating mammary gland. Venturi et al. [4] have hypothesized that a deficiency or an excess in dietary iodine is associated not only with thyroid cancer but also with the development of some gastric and mammary cancers.

Venturi et al. [4] have shown the atrophic action of iodine on the gastric mucosa, a regulating action similar to the one exerted on the thyroid, and have found relationships among iodine deficiency, goiter, and atrophic gastritis. These authors found that the gastric mucosa contains more iodine when it is healthy than when it is affected with atrophic gastritis, and in their study the prevalence of atrophic gastritis was correlated to the degree of iodine deficiency and goiter [4]. Similarly, the authors of the present study have previously shown that iodine levels were decreased in gastric cancer tissue compared with surrounding healthy tissue [17].

A relatively low dietary intake of iodine may increase the risk of breast, endometrial, and ovarian cancers [5]. Relatively low levels of thyroid hormone do not appear to increase gonadotropin levels but may potentiate gonadotropin activity. Thus, the level of effective gonadotropin stimulation in affected women may be relatively high. This relatively high level of stimulation may reasonably be expected to increase the likelihood that an ovarian malignancy will emerge [5].

Kilbane et al. [8] demonstrated that iodide content was significantly lower in the tissue of breast carcinomas than in healthy tissue from the tumor-bearing breast or in fibroadenomas [8]. It has therefore been proposed that an iodide uptake disorder may be involved in the development of breast cancer, which might also involve the inhibition of sodium iodide symporter (NIS) antibodies [18].

Teas et al. [19] have shown that a diet supplemented with seaweed (*Laminaria*) significantly delayed the occurrence of tumors in animals treated with the chemical carcinogen 7,12-dimethylbenzanthracene [19]. The enhancement of iodine uptake by progesterone has been observed in other hormone-dependent tissues, including the uterus and ovary [20].

It has recently been hypothesized that iodide might have an ancient antioxidant function in all iodide-concentrating cells [4]. In these cells, iodide acts as an electron donor in the presence of hydrogen peroxide and peroxidase, and the remaining iodine atom readily iodinates tyrosine or certain specific lipids. Iodine can exchange electrons with the double bonds of some polyunsaturated fatty acids in cellular membranes, making them less reactive to free oxygen radicals [21].

Iodine has different ways of action in vertebrates [22]. As an antioxidant, it competes with free radicals for membrane lipids, membrane proteins, and DNA to stabilize the cells (oxidized iodine species obtained from the diet or local deiodination may be responsible for this antioxidant action). Iodine may also induce anti-proliferative and apoptotic mechanisms through the formation of iodolactones, and it is a constitutive part of thyroid hormones [22].

On the other hand, the synthesis of glutathione, an important antioxidant of the cells as well as the substrate of glutathione peroxidase, is magnesium dependent. In this regard, the anti-peroxidant effect of intravenous magnesium sulfate has been observed in patients with acute aluminum phosphide poisoning [23], an effect probably due to its capacity to increase glutathione levels [13]. Considering that serum magnesium concentration appears to be reduced in pre-eclamptic women [11], magnesium sulfate administration, by increasing the magnesium serum concentration, could increase the synthesis and hence the serum level of glutathione, contributing to an increase in the antioxidant capacity of the organism [13]. Magnesium assimilation is also defective in cases of iodine deficiency [3].

Some studies have found that levels of reactive oxygen species (ROS) were increased and levels of antioxidants were decreased in the placentas of pre-eclamptic women [24]. Possible causes of oxidative stress in pre-eclampsia may be increased mitochondrial activity, reduced antioxidant scavenging potential, and the occurrence of ischemia and reperfusion events in the placenta [25].

In conclusion, this study identified a positive correlation between iodine levels in placental tissues and magnesium levels in the blood of women with severe pre-eclampsia. However, there was no such correlation in healthy pregnant women. These findings indicate that decreased iodine and magnesium levels are associated with pre-eclampsia. And since decreased magnesium and iodine levels may increase placental ROS levels, increased placental ROS levels may play an important role in the pathogenesis of pre-eclampsia.

The iodine deficiency seen in northeast Anatolia may be one of the factors responsible for the high numbers of the pre-eclamptic pregnancies in this region. And since magnesium sulfate administered at high doses can be toxic to pregnant women, and sometimes lethal to the newborn [14], clinical trials of iodine supplementation should be considered for pre-eclamptic treatment.

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