EPIDEMIOLOGICAL ASPECTS OF EUTHYROID DIFFUSE GOITER IN A GROUP OF ADULTS WITH THYROID DISEASES AND DIABETES MELLITUS AND OTHER CHANGES IN GLYCEMIC BALANCE

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Abstract

Background & aims: thyroid disorders are frequently associated with diabetes in clinical practice. The purpose of this study is to assess the prevalence of euthyroid diffuse goiter (edg) in a group of adults with diabetes mellitus (dm) and other changes in glycemic balance. **Methods:** the studied group was of 650 people with dm and other changes in glycemic balance, aged between 18 - 79 years. The methods of investigation were represented by clinical, imaging, biochemical, hormonal and immunological parameters. **Results:** the prevalence of edg in the study group was 37.84% (38.43% f and 32.25% m, $p = 0.34$, $x^2 = 0.91$). Edg prevalence in type 1 diabetic group was 1.66% (1.81% f and 0% m, $p = 0.76$, $x^2 = 0.09$), 43.1% in type 2 diabetic group (44.04% f and 36.84% m, $p = 0.4$, $x^2 = 0.7$), 44.26% in igt group (43.93% f and 50% m, $p = 0.7$, $x^2 = 0.14$), and 33.33% in ifg group (35.18% f and 11.11% m, $p = 0.14$, $x^2 = 2.17$). Significant differences regarding edg prevalence were found between the group with type 1 and type 2 diabetes and other changes in glycemic balance, but not between type 2 diabetes and other changes in glycemic control. **Conclusions:** there were not significant differences regarding gender in patients with edg and dm or other changer in glycemic balance. We noticed no association with type 1 diabetes (autoimmune disease), but only with dm type 2 and other changes in glycemic balance.

Keywords: Euthyroid diffuse goiter, diabetes mellitus, other changes in glycemic balance, prevalence, adults

Introduction:

Euthyroid goiter is defined as thyroid enlargement with normal thyroid function. There are three forms: diffuse goiter, multinodular goiter and a solitary thyroid nodule.

The diagnosis of euthyroid goiter is based on palpation of the thyroid and evaluation of thyroid function. If the thyroid is enlarged, the examiner should determine whether the enlargement is diffuse or multinodular, or whether a single nodule is palpable. (Clutter, 2013)

All three forms of euthyroid goiter are common, especially in women. Imaging studies, such as thyroid scans or ultrasonography, provide no useful additional information about goiters that are diffuse or multinodular by palpation and should not be performed in these patients. Furthermore, 20% to 60% of people have no palpable thyroid nodules that are detectable by ultrasound. These nodules rarely have any clinical importance, but their incidental discovery may lead to unnecessary diagnostic testing and treatment. (Clutter, 2013)

Almost all euthyroid diffuse goiters in iodine – sufficient regions such as united states are caused by chronic lymphocytic thyroiditis (hashimoto's thyroiditis). Iodine deficiency also causes diffuse colloid goiter in much of the world. Because hashimoto's thyroiditis may also cause hypothyroidism, plasma thyroid – stimulating hormone (tsh) should be measured even in patients who are clinically euthyroid. The presence of antithyroid antibodies confirms the diagnosis of hashimoto's disease, but this test is seldom needed. Thyroid imaging should not be performed. (Clutter, 2013)

Another causes of euthyroid diffuse goiter are: excess iodine (wolff-chaikoff effect) (Duarte et al, 2009) or lithium ingestion, which decrease release of thyroid hormone, goitrogens, stimulation of tsh receptors by tsh from pituitary tumours, pituitary thyroid hormone resistance, gonadotropins, and/or thyroid-stimulating immunoglobulins , inborn errors of metabolism causing defects in biosynthesis of thyroid hormones, exposure to radiation, deposition diseases, thyroid hormone resistance, subacute thyroiditis (de quervain thyroiditis), silent thyroiditis, riedel thyroiditis, infectious agents : acute suppurative – bacterial and chronic - mycobacteria, fungal, and parasitic, granulomatous disease, thyroid malignancy and low selenium levels. (Rasmussen et al, 2011)

The frequency of euthyroid diffuse goiter varies around the world. In united states, autopsy studies suggest a frequency of greater than 50% for thyroid nodules; with high-resolution ultrasonography, the value approaches 40% of patients with nonthyroidal illness. In the wickham study from the united kingdom, 16% of the population had a goiter. (tunbridge et al, 1977) in the framingham study, ultrasonography revealed that 3% of men older

than 60 years had thyroid nodules, while 36% of women aged 49-58 years had thyroid nodules. (Sawin et al, 1989) in the united states, most goiters are due to autoimmune thyroiditis (i.e., Hashimoto disease). (Clutter, 2013)

The incidence of thyroid cancer has been rising worldwide. The reasons are unclear, but this trend may be related to better detection and diagnostic methods. (Cossu et al, 2013)

Worldwide, the most common cause of goiter is iodine deficiency. (triggiani et al, 2009) it is estimated that goiters affect as many as 200 million of the 800 million people who have a diet deficient in iodine.

In a german study, 635 people underwent ultrasonographic thyroid screening, as well as basal tsh measurement, during preventive-health checkups. (Guth et al, 2009) thyroid nodules were detected in 432 (68%) of the persons screened; in a previous german study, ultrasonographic screening of more than 90,000 people detected thyroid nodules in 33% of the normal population. The authors of the latter report attributed this difference to the fact that patients in their study were screened using 13 mhz ultrasonographic scanners, which were more sensitive than the 7.5 mhz scanners used in the previous study. According to the investigators, their results indicated that the question of routine iodine supplementation requires renewed attention.

No racial predilection exists.

The female-to-male ratio is 4:1.

In the wickham study, 26% of women had a goiter, compared to 7% of men. (Tunbridge et al, 1977)

Thyroid nodules are less frequent in men than in women, but when found, they are more likely to be malignant.

Fine-needle aspiration biopsy is used for cytological diagnosis. (Bardin, 1997)

The frequency of goiters decreases with advancing age. The decrease in frequency differs from the incidence of thyroid nodules, which increases with advancing age.

Most goiters are benign, causing only cosmetic disfigurement. Morbidity or mortality may result from compression of surrounding structures, thyroid cancer, hyperthyroidism, or hypothyroidism.

Diffuse goiter is diagnosed by thyroid palpation. Imaging is not needed and often detects incidental, clinically unimportant nodules.

small diffuse goiters usually are asymptomatic, and therapy is seldom required. Large goiters may cause compressive symptoms such as dysphagia, dyspneea, or neck fullness.

Patients should be followed annually with thyroid palpation and measurement of plasma tsh to monitor for development of hypothyroidism. Most diffuse goiters do not progressively enlarge, but in a few,

thyroidectomy may be needed to relieve compressive symptoms or for cosmetic reasons.

I.
Material and methods
Investigated population

650 people with diabetes and other changes in glycemic balance (588 f and 62 m) aged between 18 and 79 years represented the study group.

Depending on glycemic balance the group was divided into:

- the group with dm type 1 - 60
- the group with dm type 2 - 290
- the group with igt - 183
- the group with ifg – 117

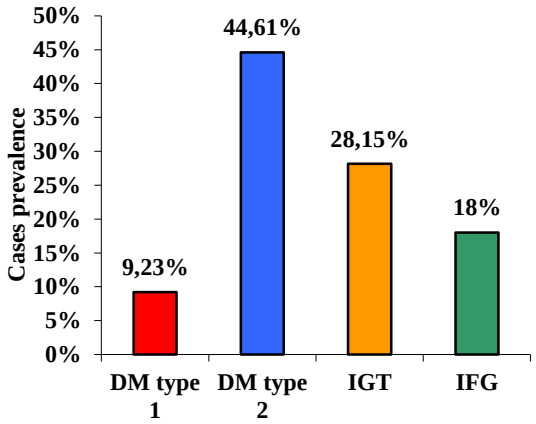


Fig. 1. Cases distribution according to the type of changes in glycemic balance

Methods of investigation

The methods of investigation were represented by clinical data - case history, current status, imagistic- thyroid ultrasound, biochemical - for glycemic balance: fasting blood glucose, glycosylated haemoglobin, investigation of the thyroid gland: tsh, ft4, ft3, thyroid antibodies.

Determination of plasma glucose was performed by enzyme technique with glucosooxidasis. Normal values were taken between 70 - 110 mg%; diabetes mellitus - values equal or over 126 mg%, impaired glucose tolerance - values between 110 - 125 mg% and the ogtt at 2 h between 140 - 200 mg% and impaired fasting glucose - values between 110 - 125 mg% and ogtt at 2 h under 140 mg%.

Determination of hba1c was achieved through the diastat for measuring hba1c reported to the total hba.

To determine the tsh level in plasma, the free fraction of triiodotironin (ft3), and the plasma free fraction of thyroxin (ft4) were

performed a quantitative method architect; witch is an immunological method, chemilumnescent micro particle immunoassay (cmia). Normal values were following: tsh = 0.465-4.68 miu/ml, ft3 = 3.69 -10.4 pmol/l, ft4 = 10-28.2 pmol/l.

The immunological parameters were represented by autoimmune thyroid markers - antibodies (antitpo and antitg antibodies).

To determine serum levels of antitpo antibodies it was used the kit axsym antitpo, an immunological method (micro particle enzyme immunoassay) (meia). Normal values: antitpo antibodies <35 iu/ml.

To determine serum levels of antitg antibodies it was used the kit axsym antitg, a meia method as well (micro particle enzyme immunoassay). Normal values: antitg antibodies <55 iu/ml.

Thyroid ultrasound was performed in all cases and allowed us to measure thyroid volume, thyroid study and the changes in parenchyma's density.

An increased density, uniform, characterizes normal thyroid parenchyma easily distinguished from the neck muscles that are hypo dens.

Inflammatory processes and autoimmune pathology appears hypo dens. The scale was assessed as being discreet +, moderate ++ and marked +++.

In the autoimmune thyroid disease the parenchyma of the gland appears hypo dens.

Chronic autoimmune thyroid disorder appears with a hypoecogenity of the parenchyma and normal or increased thyroid volume.

Statistical analysis

For statistical analysis we used microsoft excel and pop tools from microsoft office 2003 and epi 2000 program. To measure the quantitative variables were determined average and standard deviation, and to assess the gender differences and other differences we used the unpaired t test and anova test, considering statistically significant a $p < 0.05$.

Results and discussion

Adults group included 650 people, young adults, adults and the elderly, aged between 17 and 79 years. It consisted of subjects with diabetes which in time present thyroid diseases and subjects with thyroid disease who have developed glucose metabolism disorders or diabetes.

Adults group was subdivided according to the type of change in glycemic balance in four subgroups (fig. 1):

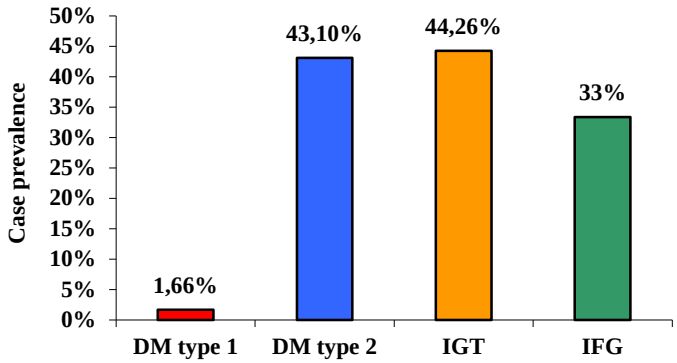
- group with dm type 1 with 60 cases (9.23%)
- group with dm type 2 with 290 cases (44.61%)
- igt group with 183 cases (28.15%)

- ifg group with 117 cases (18%)

Euthyroid diffuse goiter is characterized by overall increase in volume of the thyroid gland that is not attributable to inflammatory processes or neoplastic, being not associated with functional disturbances. In the general population, its prevalence is about 10% (Wartofski, 2001)

the prevalence of euthyroid diffuse goiter in the study group was 37.84% (38.43% f and 32.25% m, p = 0.34, x^2 = 0.91). Euthyroid diffuse goiter prevalence in type 1 diabetic group was 1.66% (1.81% f and 0% m, p = 0.76, x^2 = 0.09), 43.1% in type 2 diabetic group (44.04%f and 36.84% m, p = 0.4, x^2 = 0.7), 44.26% in igt group (43.93% f and 50% m, p = 0.7, x^2 = 0.14), and 33.33% in ifg group (35.18% f and 11.11% m, p = 0.14, x^2 = 2.17) (fig. 1 and fig. 2).

Fig. 2. The prevalence of euthyroid diffuse goiter in the study group



In the case of euthyroid diffuse goiter, f/m ratio was 1/0 for type 1 dm group, 7.9/1 in the case of the group with dm type 2, 15.2/1 for igt group and 38/1 in the ifg group. In literature f/m ratio is 1.2 to 4.3/1 (Lee et al, 2006).

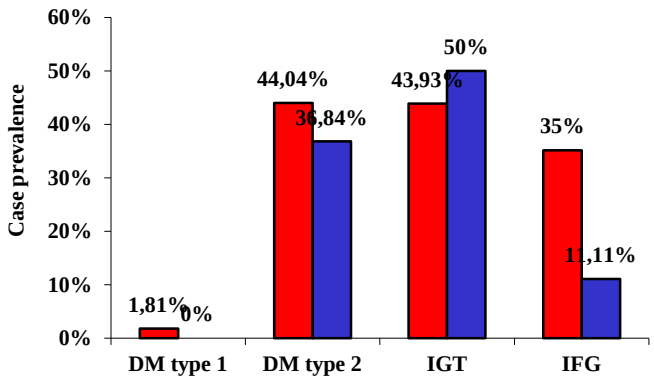


fig. 3. The prevalence of euthyroid diffuse goiter by gender in the study group

Significant differences regarding euthyroid diffuse goiter prevalence were found between the group with diabetes type 1 and type 2 diabetes and other changes in glycemic balance (1.66% vs. 43.1%, $p<0.001$, $x^2 = 37.05$ for diabetes type 1 and type 2 diabetes, 1.66% vs. 44.26%, $p<0.001$, $x^2 = 39.83$ for type 1 diabetes and igt, 1.66% vs. 33.33%, $p<0.001$, $x^2 = 22.74$ for type 1 diabetes and ifg), but not between type 2 diabetes and other changes in glycemic control (43.1% vs. 44.26%, $p = 0.8$, $x^2 = 0.06$ for type 2 diabetes and igt, 43.1% vs. 33.33%, $p = 0.06$, $x^2 = 3.31$ for type 2 diabetes and ifg, 44.26% vs. 33.33%, $p = 0.059$, $x^2 = 3.55$ for igt and ifg) (table i).

Table i. Differences regarding euthyroid diffuse goiter prevalence

		Dm type 1	**Dm type 2**	**Igt**	**Ifg**
Dm type 1	1.66%	-	P<0.001	P<0.001	P<0.001
Dm type 2	43.1%	P<0.001	-	0.8	0.06
Igt	44.26%	P<0.001	0.8	-	0.059
Ifg	33.33%	P<0.001	0.06	0.059	-

The average onset age and the medium duration of euthyroid diffuse goiter in adults with diabestes mellitus and other changes in glycemic balance are described in tables ii and iii. The average onset age for dm type 1 is 38 years and for dm type 2, igt and ifg is between 45 – 50 years. In the case of dm type 1 the thyroid disease appears after 18 years (this association is random) and for dm type 2, igt and ifg after 0.5 – 7 years (after administration of thyroid hormones).

Table ii. Average onset age of euthyroid diffuse goiter in adults with diabetes mellitus and other changes in glycemic balance

Type of changes in glycemic balance	Case number	Average	Standard deviation	Median
Dm type 1	1	38	-	38
Dm type 2	125	50.67	13.06	50
Igt	81	43.54	15	45
Ifg	39	46.64	14.51	47

Table iii. Medium duration of euthyroid diffuse goiter in adults with diabetes mellitus and other changes in glycemic balance

Type of changes in glycemic balance	Case number	Average	Standard deviation	Median	Minimum	Maximum
Dm type 1	1	18	-	18	18	18
Dm type 2	125	0.5	7.71	1	0	38
Igt	81	6.01	10.01	1	0	43
Ifg	39	7	9.99	2	0	42

In the case of euthyroid diffuse goiter, was absent symptoms, and diagnosis was based on clinical examination and ultrasound.

Table iv. Distribution after goiter stages of adult's patients with euthyroid diffuse goiter and diabetes mellitus and other changes in glycemic balance

Type of changes in glycemic balance	Goiter stages									
	0		1a		1b		2		3	
	n	%	n	%	n	%	n	%	n	%
Dm type 1	-	-	-	-	-	-	1	100	-	-
Dm type 2	51	40.8	43	34.4	12	9.6	12	9.6	7	5.6
Igt	28	34.57	34	41.97	10	12.34	9	11.11	-	-
Ifg	14	35.9	11	28.2	6	15.38	7	17.95	1	2.56

The most common cause of goiter developing is iodine deficiency. In patients who do not come from regions with iodine deficiency, the cause is obscure (Lee et al, 2006).

Sporadic goiter incidence in north america is estimated at 5%. Usually not appear before puberty and not shows a peak incidence. Generally goiter development increases with age. The prevalence of palpable nodules is approximately 5-6% in people aged 60 years, but at ultrasound examination, the incidence of impalpable nodules reach 50% in persons aged 60 years (lee et al, 2006).

Who, unicef and iccidd considers that in the absence of iodine deficiency goiter prevalence is below 5%, slightly iodine deficiency is associated with a prevalence of 5-20%, moderate iodine deficiency with a prevalence of 20-30% and severe iodine deficiency with a prevalence of 30% (Lee et al, 2006). Goiter is predominant in women, the ratio f/m being 1.2 to 4.3/1 (Lee et al, 2006). Some studies have shown that treatment at sporadic goiter with t4 decreased thyroid volume to 58% of patients compared to 4% of patients treated with placebo. When instituting therapy with t4 is should be considered sub clinical hyperthyroidism risks that are associated with various metabolic and visceral complications (Lee et al, 2006). Diffuse goiter, with hard consistency, fast growing, with compressive symptoms and regional lymphadenopathy are sometimes suspicious of malignancy.

Studies show variable correlation between physical exam findings and findings on imaging studies. In a retrospective chart review, ultrasound findings differed from clinical exam findings in 63% of cases. (Marqusee et al, 2000) thyroid ultrasound is less expensive and less invasive than other imaging modalities, provides excellent visualization of thyroid structure and the nature of cysts and nodules, and allows for estimation of thyroid size.

Computed tomography and magnetic resonance imaging perform better for visualization of extension of thyroid tissue substernally and are also preferred for evaluation of the neck in cases of severe local complications of goiter, such as compressive symptoms. (hurley et al, 1996)

The malignant potential in multinodular goiter (2%–4%) is similar to that of solitary nodules (4%–6%). (hurley et al, 1996) therefore, any dominant nodule in a multinodular goiter should be evaluated the same way one would evaluate a solitary nodule.

Thyroid ultrasound allows accurate assessment of thyroid volume and appreciation of thyroid parenchyma aspect.

After the study of iodine intake in banat plain, especially in the area of timisoara, the normal thyroid volumes were within the following values: women - 10.27 ± 2.09 ml and in men - 12.18 ± 2.52 ml.

In our case, the goiter has been diagnosed at thyroid volume that exceeded 3 sd (females > 16.54 ml and in men > 19.74 ml).

Table v. Cases classification in function of tv and thyroid parenchyma hypoecogenicity type

Type of changes in glycemic balance	Tv type				Hypoecognicity type					
	Normal		Increase		Mild		Medium		Intense	
	n	%	n	%	n	%	n	%	n	%
Dm type 1	-	-	1	100	1	100	-	-	-	-
Dm type 2	44	35.2	81	64.8	95	76	-	30	24	-
Igt	17	20.99	64	79.01	66	81.48	15	18.52	-	-
Ifg	9	23.07	30	76.92	28	71.79	11	28.21	-	-

Euthyroid diffuse goiter was encountered in 1 patient with type 1 diabetes, at 125 patients with type 2 diabetes, at 81 patients with igt and at 39 patients with ifg. In all these, hormonal functional parameters were within normal limits.

Table vi. Tsh and ft4 values in patients with euthyroid diffuse goiter

Parameters	**Dm type 1 (n = 1)**	**Dm type 2 (n = 125)**	**Igt (n = 81)**	**Ifg (n = 39)**
Tsh (miu/ml)	1.14	1.82 ± 1.14	2.17 ± 1.21	2.83 ± 1.15
Ft4 (pmol/l)	15	14.96 ± 4.49	14.5 ± 3.71	16.1 ± 3.76

Depending on the value of tsh was performed functional classification of cases. All cases with diffuse goiter functionally were euthyroid.

Patients with a reassuring initial workup can be followed clinically and should be assessed with serial clinical evaluations. No evidence could be found regarding optimal intervals for examination and testing; yearly exams

and tsh testing are considered adequate by some experts. (Berghout et al, 1990).

Because a few non-benign conditions such as thyroiditis and neoplasm can sometimes present in a euthyroid state, the clinician should be alert for any physical exam or laboratory changes. If any changes occur, then further workup is indicated.

Suppressive therapy with thyroxin is an option for decreasing thyroid size in euthyroid goiter, but this therapy remains controversial. One placebo controlled trial of thyroid suppression in non-toxic multinodular goiter showed regression of thyroid size with suppressive therapy (58% reduction in size in treatment group vs. 5% reduction in control group). However, not all goiters responded to this therapy, and the thyroid size returned to pre-treatment size within 9 months of discontinuation of suppressive therapy. (Berghout et al, 1990).

Many experts argue against the use of suppressive therapy in long-standing goiters, citing less response from these patients, along with concern about side effects and possible over suppression, but the evidence in this area is limited. Patients who are treated with thyroxin should be followed for possible side effects of the medication, including arrhythmia and osteopenia, particularly in elderly patients and those who take the medication for long periods.

Guidelines from the american association of clinical endocrinology's task force on thyroid nodules, released in 2006, recommends ultrasound be used routinely in the case of multinodular goiter to assist with diagnosis, detect suspicious nodules that may require biopsy, and to serve as an objective baseline measure. This group recommends against use of suppression therapy in long-standing goiters. (aace/ame, 2006)

Table vii. Distribution of cases by thyroid disease treatment

Type of changes in glycemic balance	Treatment type							
	None		Suppression		Inhibition		Surgery	
	n	%	n	%	n	%	n	%
Dm type 1	-	-	1	100	-	-	-	-
Dm type 2	28	22.4	87	69.6	-	-	10	8
Igt	10	12.34	61	75.3	-	-	10	12.34
Ifg	4	10.25	30	76.92	-	-	5	12.82

In the case of euthyroid diffuse goiter and dm type 1 all cases receiving suppression treatment with thyroid hormone.

In the case of euthyroid diffuse goiter and dm type 2, 22.4% of the cases did not require any treatment. A percentage of 69.6% of patients receiving suppression treatment with thyroid hormone and 8% cases required

surgical intervention due to the presence of higher goiter, with compression phenomena.

In the case of euthyroid diffuse goiter and igt, 12.34% of the cases did not require any treatment, a percentage of 75.3% of patients have received suppression treatment with thyroid hormone and 12.34% of patients had required surgical intervention due to the presence of a higher goiter, with compression phenomena.

In the case of euthyroid diffuse goiter and ifg, 10.25% of the cases did not require any treatment. A percentage of 76.92% of patients receiving suppression treatment with thyroid hormone and 12.82% cases required surgical intervention due to the presence of higher goiter, with compression phenomena.

If thyroid disorder was the first appearance, the administrations of excess thyroid hormone or thyroid hormone imbalance led to an unbalance of a pre-existing type 2 diabetes or to the unmasking of latent one, and the appearance of igt and ifg. Type 2 diabetes that appeared was mild, requiring only dietary treatment.

Conclusion

There were not significant differences regarding gender in patients with euthyroid diffuse goiter and diabetes mellitus or other changer in glycemic balance.

We noticed no association with type 1 diabetes (autoimmune disease), but only with diabetes mellitus type 2 and other changes in glycemic balance.

In the case of dm type 1 the association was random, and on the case of dm type 2, igt and ifg, these appear in the first 10 years after thyroid disease, due to the administration of thyroid hormones.

In all patients with euthyroid diffuse goiter, hormonal functional parameters were within normal limits. Some of them receive suppression treatment with thyroid hormones and some of the patients had required surgical intervention due to the presence of a higher goiter, with compression phenomena.

If thyroid disorder was the first appearance, the administrations of excess thyroid hormone or thyroid hormone imbalance led to an unbalance of a pre-existing type 2 diabetes or to the unmasking of latent one, and the appearance of igt and ifg. Type 2 diabetes that appeared was mild, requiring only dietary treatment.

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