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Thyroid lesions in patients with acromegaly — case-control study and update to the meta-analysis

Zmiany ogniskowe w tarczycy u pacjentów z akromegalią — badanie kliniczno-kontrolne oraz aktualizacja metaanalizy

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Abstract

Introduction: Acromegaly results from oversecretion of growth hormone and subsequently insulin growth factor-1. According to some authors, the disease can cause increased prevalence of nodular goitre and thyroid cancer (TC). However, the number of studies comparing acromegalic patients with control groups is low. We aimed to assess the prevalence of thyroid lesions in patients with acromegaly in comparison to an age- and sex-matched control group and to update the meta-analysis previously performed in our department by the same authors.

Material and methods: We searched medical documentation of patients with acromegaly treated in our department between 2003 and 2013. The prevalence of thyroid abnormalities was compared with the group of patients with hormonally inactive adrenal *incidentalomas*. To perform the meta-analytic part of the paper we also searched ten databases to find relevant papers.

Results: Two hundred and five patients with acromegaly and 184 patients with *incidentalomas* were included. Any thyroid lesions were present in 77.6% of patients with acromegaly *vs.* 63.0% with *incidentalomas* (p = 0.002), multinodular goitre — 66.8% *vs.* 47.8% (p = 0.0002), and TC- 5.4% *vs.* 2.7% (p = 0.21) respectively. For thyroid lesions the pooled odds ratio (OR) was 3.1 (95% confidence interval [CI] 1.8–5.5), and for TCs the OR was 4.5 (95% CI 1.9–10.3).

Conclusions: According to our results thyroid lesions were significantly more common in patients with acromegaly; in case of TC the difference was not significant. The updated meta-analysis showed significantly increased prevalence of both disorders. In conclusion, systematic thyroid examination should be an important part of follow-up in case of acromegalic patients. **(Endokrynol Pol 2017; 68 (1): 2–6)**

Key words: *thyroid; thyroid cancer; acromegaly; meta-analysis; pituitary*

Streszczenie

Wstęp: Akromegalia jest skutkiem nadmiernego wydzielania hormonu wzrostu i w konsekwencji insulinopodobnego czynnika wzrostu 1. Według części autorów choroba ta może skutkować zwiększoną częstością występowania wola guzkowego i raka tarczycy (TC). Jednakże liczba prac porównujących pacjentów z akromegalią z grupą kontrolną jest niewielka. Celem pracy była ocena częstości występowania zmian ogniskowych u pacjentów z akromegalią w porównaniu z grupą kontrolną dopasowaną pod względem płci i wieku, a także aktualizacja metaanalizy wykonanej wcześniej w naszej Klinice przez tych samych autorów.

Materiał i metody: Przeszukano dokumentację medyczną pacjentów chorujących na akromegalię, leczonych w naszej Klinice pomiędzy 2003 i 2013 rokiem. Częstość występowania nieprawidłowości w tarczycy porównano z grupą pacjentów z hormonalnie nieczynnymi przypadkowiakami nadnercza. W celu wykonania metaanalizy przeszukano osiem różnych baz danych w celu odnalezienia adekwatnych publikacji.

Wyniki: Włączono 205 pacjentów z akromegalią i 184 z przypadkowiakami nadnercza. Jakiekolwiek zmiany ogniskowe były obecne u 77,6% pacjentów z akromegalią i 63,0% pacjentów z przypadkowiakami (p = 0,002), wole wieloguzkowe — 66,8% *vs.* 47,8% (p = 0,0002), RT — odpowiednio u 5,4% *vs.* 2,4% (p = 0,21). Dla zmian ogniskowych w tarczycy łączony iloraz szans (OR) wyniósł 3,1 (95% przedział ufności [CI] 1,8–5,5), dla RT OR wyniósł 4,5 (95% CI 1,9–10,3).

Wnioski: Na podstawie opisanych wyników zmiany ogniskowe tarczycy występowały istotnie częściej u pacjentów z akromegalią; w przypadku TC różnica nie była istotna. Uaktualniona metaanaliza wykazała znamiennie podwyższoną częstość występowania obu nieprawidłowości. Podsumowując, regularne badania tarczycy powinny być istotnym elementem monitorowania pacjentów z akromegalią. **(Endokrynol Pol 2017; 68 (1): 2–6)**

Słowa kluczowe: *tarczyca; rak tarczycy; akromegalia; metaanaliza; przysadka*

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Introduction

Increased growth hormone (GH) secretion and subsequently IGF-1 (Insulin-like growth factor 1) secretion output results in clinical manifestation of acromegaly. This rare chronic disorder, when untreated, leads to severe complications and reduces the patient's life expectancy [1]. Mortality is increased mostly due to cardiovascular problems, but also because of carcinogenesis. Although the issue of higher incidence of neoplasms in the course of prolonged exposition to an excess of GH and IGF-1 is still a matter of debate, many authors suggest a link between the illness and colorectal, breast, prostatic, or lung cancers [2, 3]. Also, a large meta-analysis revealed higher frequency of thyroid nodular disease and thyroid cancer among acromegalic patients. Thyroid cancer is suggested to be even more prevalent than colorectal carcinoma [4, 5]; however, the amount of case-control studies on this topic remains unsatisfactory [4].

The main possible explanation of an increased risk of nodular goitre and thyroid cancer (TC) is the proliferative and anti-apoptotic effect of IGF-1 on thyrocytes, probably mediated through IGF-1 receptors [3, 6, 7]. The relative risk (RR) of developing TC among subjects diagnosed with acromegaly is calculated to be 2.5–4.3 in comparison to the general population [4, 8, 9]. Nevertheless, the increased prevalence of thyroid abnormabilities in patients with acromegaly remains the issue of debate.

The goal of our research was to estimate the incidence of thyroid nodular disease and thyroid malignancy among acromegalic patients treated in our clinic in comparison to the control group. We also aimed to update the meta-analysis performed in our department with current results and eventual outcomes of other recently published studies.

Material and methods

Patients

We reviewed the medical documentation of patients with acromegaly treated in a single endocrine department in the years 2003–2013. Written informed consent was given by all participants, and the study was approved by the Poznan University of Medical Sciences Ethical Committee. The prevalence of thyroid lesions was compared with the group of patients with incidentally detected adrenal lesions, so-called *incidentalomas*. Only patients with small, benign, and hormonally inactive nodules were included. Exclusion criteria were: maximal diameter over 4 cm, any hormonal activity, and malignant character. Diagnosis of acromegaly was based on clinical signs and symptoms, increased GH levels, lack of GH suppression under 1 ng/ml during an oral glucose tolerance test (with 75 g of glucose), and IGF-1 levels over reference values for age and gender.

Thyroid ultrasonography

Thyroid ultrasonography is a routine procedure performed in every patient hospitalised in our department. All examinations were conducted with the use of an AIXPLORER system by Supersonic Imagine and an ALOKA alpha-7 with 2–10 MHz linear transducers. Thyroid volume was measured using ultrasonography; normal values — up to 18 cm^3 for women and 25 cm^3 for men.

Statistical analysis

All calculations were performed using Statistica v.10 software with the medical package (from StatSoft). A p-value less than 0.05 was considered statistically significant.

Meta-analytic part

We searched the following: PubMed/MEDLINE, Cochrane Library, Scopus, Cinahl, Academic Search Complete, Web of Knowledge, PubMed Central, PubMed Central Canada, and Clinical Key databases from May 2013 to November 2014 using same methodology as in a meta-analysis previously published by the same authors [4]. Briefly — we used the search term "acromegaly and (thyroid or "thyroid cancer" or "thyroid nodules" or goitre)". Two researchers (K.W., A.S.) independently searched all included databases. Only studies including sex- and age-matched control groups were selected. We meta-analysed odds ratios (OR) as well as risk ratios (RR) using a random-effect model. The risk of publication bias was assessed using Kendall's tau.

Results

Research part

Two hundred and five patients with acromegaly (including 86 patients described in our previous publication in 2009 [10]) and 184 patients with *incidentalomas* were included. The mean age was 52.6 and 53.9 years, respectively ($p = 0.44$), percentage of women was 60.5 and 65.2%, respectively ($p = 0.35$). Any thyroid lesions were present in 77.6% of patients with acromegaly and 63.0% with *incidentalomas* ($p = 0.002$), multinodular goitre in 66.8% *vs.* 47.8% ($p = 0.0002$), thyroid cancer in 5.4% of acromegalic patients - 10 papillary thyroid cancers (PTCs) and one follicular thyroid cancer (FTC) were diagnosed and in 2.7% (all PTCs) of patients from the control group, respectively ($p = 0.21$). ORs were 2.0 (95% CI 1.3–3.2), 2.2 (95% CI 1.5–3.3), and 2.0 (0.7–6.0), respectively. RRs were 1.2 (95% CI 1.1–1.4),

Table I. *Summarisation of results — comparison between acromegalic patients and control group. SD — standard deviation*
Tabela I. *Podsumowania wyników — porównanie pacjentów z akromegalią i grupą kontrolną. SD — odchylenie standardowe*

	Acromegalic patients (n = 205)	Control group (n = 184)	p-value
Age (mean ± SD)	52.6 ± 12.3	53.9 ± 12.7	0.44
Gender	124 F/ 81 M	120 F/ 64 M	0.35
Thyroid lesions (%)	77.6	63.0	0.002
Multinodular goitre (%)	66.8	47.8	0.0002
Thyroid cancer (%)	5.4	2.7	0.21
Mean thyroid volume [cm^3]	35.7*	18.1**	< 0.0001
Patients with enlarged thyroid (%)	62.2*	22.5**	< 0.0001

*Patients with prior history of thyroid surgery or radioiodine treatment have been excluded from calculations — results based on the group of 165 patients; **Patients with prior history of thyroid surgery or radioiodine treatment have been excluded from calculations — results based on the group of 171 patients

1.3 (1.1–1.6), and 2.0 (95% CI 0.7–5.6), respectively. In case of subjects with at least one thyroid lesion, maximal diameter of the biggest thyroid lesion was significantly higher in patients with acromegaly than in the control group — mean 15.3 *vs.* 10.6 mm, median 13.0 *vs.* 9.0 mm (p = 0.0008). Among women any thyroid lesions were present in 84.6% of acromegalic and 73.7% of control-group patients (p = 0.04); multinodular goitre was present in 77.8% and 55.9%, respectively (p = 0.0003). Thyroid cancer was present in eight women with acromegaly (6.4%) and four subjects from the control group (3.3%, p = 0.38). Among men, any thyroid lesions were present in 67.9% of patients and 45.3% of subjects from the control group (p = 0.007); multinodular goitre (MNG) was seen in 52.5% and 34.4%, respectively (p = 0.04), and TC in 3.7% and 1.6%, respectively (p = 0.63).

Forty patients with acromegaly and 13 subjects from the control group had prior history of thyroid surgery or radioiodine treatment. These patients were not included in calculations concerning thyroid volume.

Mean thyroid volume was 35.7 ± 36.5 (1 standard deviation) cm^3 in acromegalic patients and 18.1 ± 11.1 cm^3 in the control group; medians were 26.1 *vs.* 15.1 cm^3 (p < 0.0001), respectively. Thyroid was enlarged (over 18 cm^3 in women and 25 cm^3 in men) in 65.5% of patients and in 24.2% of subjects from the control group (p < 0.0001). In the case of patients without any thyroid lesions, diffused goitre was present in 21 of 45 acromegalic (46.7%) and 9 of 62 (14.5%) patients from the control group (p = 0.0004); mean thyroid volume was 25.3 *vs.* 16.1 cm^3, medians – 19.6 and 14.4 cm^3, respectively (p = 0.001).

Among women the mean thyroid volume was 32.8 ± 29.8 *vs.* 15.9 ± 10.6 cm^3, median — 22.0 *vs.* 12.1 cm^3 (p < 0.0001), respectively; in the case of patients without thyroid lesions the mean volume was 21.8 ± 16.4 *vs.* 12.6 ± 6.9 cm^3, median — 16.4 *vs.* 11.3 cm^3 (p = 0.009), respectively. In general, 58.3% of women with acromegaly and 20.6% of women in the control group had enlarged thyroid (> 18 cm^3, p < 0.0001).

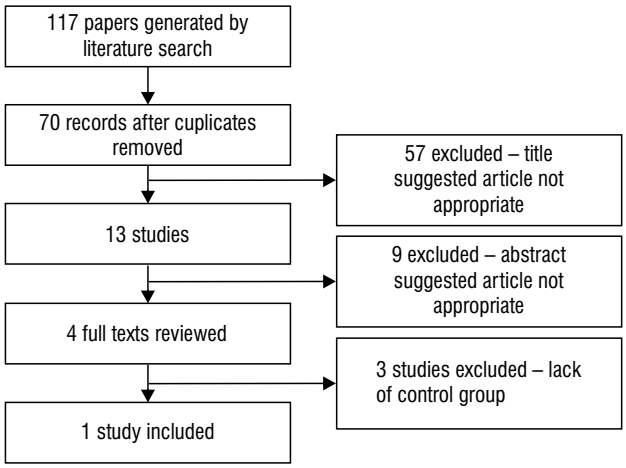

Figure 1. *Flowchart presenting steps of literature search and selection*
Rycina 1. *Diagram pokazujący etapy selekcji prac*

Among 19 patients without thyroid lesions five had diffused goitre (26.3%), and in the case of the control group — three of 28 patients (10.7%, p = 0.24).

Among men the mean thyroid volume was 39.4 ± ± 43.6 *vs.* 21.7 ± 11.1 cm^3 (in acromegalic *vs.* control group), median — 31.1 *vs.* 19.9 cm^3 (p < 0.0001), 68.0% *vs.* 25.8% (p < 0.0001), respectively, had enlarged thyroid (> 25.0 cm^3). In the case of patients without thyroid lesions the mean thyroid volume was 27.7 ± 15.6 *vs.* 19.0 ± 11.6 cm^3, median — 26.4 *vs.* 17.0 cm^3, respectively, 14 of 26 patients with acromegaly (53.8%), and four of 34 subjects from the control group (11.8%) had enlarged thyroid (p = 0.0006).

The results of our study are summarised in Table I.

Meta-analytic part

The search results and steps of selection are shown on the flowchart (Fig. 1). Finally, there was one new case-control study [11] on the topic since the previous meta-analysis [4] was published. The results presented in the current study were also included.

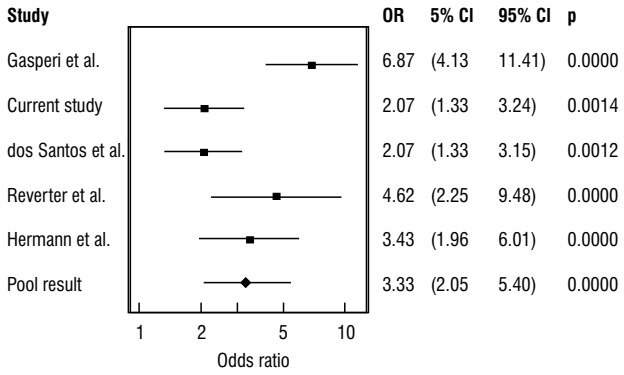

Figure 2. *Forrest plot showing individual ORs and pooled outcome with 95% confidence intervals and p-values for studies comparina the prevalence of thyroid lesions beetwen patients with acromegaly and control groups. OR — odds ratio*

Rycina 2. *Wykres pokazujący ilorazy szans wraz z 95% przedziałem ufności oraz wartości p dla indywidualnych prac porównujących częstość zmian ogniskowych w tarczycy u pacjentów z akromegalią i w grupie kontrolnej oraz wynik łączony*

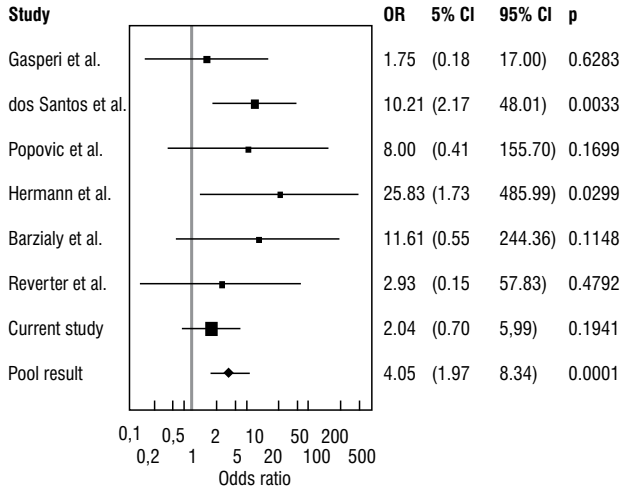

Figure 3. *Forrest plot showing individual ORs and pooled outcome with 95% confidence intervals and p-values for studies comparina the prevalence of thyroid cancer in acromegalic patinets and control groups. OR — odds ratio*

Rycina 3. *Wykres pokazujący ilorazy szans wraz z 95% przedziałem ufności oraz wartości p dla indywidualnych prac porównujących częstość występowania raka tarczycy u pacjentów z akromegalią i w grupie kontrolnej oraz wynik łączony*

For thyroid lesions the pooled odds ratio (OR) was 3.3 (95% CI 2.1–5.4), and the risk ratio (RR) was 1.9 (95% CI 1.4–2.6), $p < 0.0001$. There is no evidence for publication bias (Kendall's tau = 0.60, two-tailed p value = 0.14). Particular and pooled results are shown in Figure 2.

For thyroid cancers the pooled OR was 4.1 (95% CI 2.0–8.3), and RR was 3.9 (95% CI 1.9–7.8), $p = 0.0001$). There is no evidence for publication bias (Kendall's tau = 0.14, two-tailed p value = 0.65). Particular and pooled results are shown in Figure 3.

We also updated calculations about the malignancy rate in thyroid lesions. Pooled RR was 2.3 (95% CI 0.9–6.1), $p = 0.08$.

Discussion

According to our results, thyroid lesions and MNG turned out to be significantly more common in patients with acromegaly than in the control group; lesions in acromegalic patients were also significantly larger. TC was also more frequent; however, the difference was not statistically significant. Patients with acromegaly had also significantly higher volume of the thyroid, and the percentage of patients with enlarged thyroid was significantly higher in this group. In general, thyroid abnormalities were very common in patients with acromegaly — among 204 patients 40 had thyroid surgery or radioiodine treatment in anamnesis, 119 — thyroid lesions, 19 — diffused goitre; only 26 patients — less than 15% — had no structural thyroid abnormalities.

Increased risk of thyroid diseases in acromegaly remains a matter of debate, and it has been the topic of numerous studies. According to the meta-analysis performed in our department and published in 2014, thyroid lesions as well as thyroid cancer were significantly more common in patients with acromegaly — RR 2.1 and 7.6, respectively [4]. However, the amount of studies including control groups was quite small — only three studies concerning thyroid lesions and five concerning thyroid cancer (a few further studies had control groups excluded due to methodological reasons, e.g. groups not matched by age). In this context, the recent study comprises valuable data on this important but poorly explored topic. Among previously published studies containing data on both thyroid lesions and thyroid cancer, only Gasperi et al. [12] described a slightly larger studied group.

The mentioned meta-analysis [4] combined also data about the prevalence of nodular goitre and thyroid cancer from available studies — according to 13 studies on thyroid lesions in US examination including 1125 patients, the pooled prevalence was 59.2%; in the case of thyroid cancer there were 13 papers containing data on 1372 patients — the pooled prevalence was 4.3%. Our study brought even higher prevalence of both abnormalities — 77.6 and 5.4%, respectively; thyroid lesions were also very common in patients with *incidentalomas* (63.0%). This can be partially explained by the fact that the Polish population was iodine deficient until 1997, when obligatory household salt iodisation started [13, 14]. A previous study on the topic of nodular goitre in patients with acromegaly performed in another Polish endocrine department also showed very high prevalence of this abnormality [15]. Altogether, the

amount of patients with nodular and diffused goitre was significantly higher in acromegalic patients than in the control population; this fact indicates a causative role of acromegaly in the development of thyroid pathologies.

Most previously published studies on the topic of thyroid disorders in patients with acromegaly compared the prevalence of particular pathologies with volunteers [11, 16] or subjects suffering from pituitary microadenomas — hormonally inactive or secreting prolactin [17]. However, we were not able to collect an acceptably large sex- and age-matched control group among those patients because most them were quite young women hospitalised due to problems with conception or irregular menstruation. On the other hand, we were afraid that a control group composed of volunteers could be biased by patients with previously diagnosed thyroid disease, family history of thyroid disorders, etc. We decided to select patients with incidentally detected benign and hormonally inactive adrenal nodules, so-called *incidentalomas*. First of all, there are no data about common pathogenesis or increased frequency of co-morbidity of these disorders. Secondly, all patients hospitalised in our department undergo thyroid ultrasonography routinely, so there was no risk of preselection of patients with previously diagnosed thyroid disorders etc. Finally, it was possible to achieve a large sex- and age-matched control group because the amount of these patients is very high.

The second aim of our study was to update the meta-analysis performed in our department [4] with current data and possibly with the results of other, recently published studies. We found one paper meeting the inclusion criteria [11]; our current results were also added. In general, the ORs and RRs described in our study were lower than pooled results of the meta-analysis. Partially it can be caused by the fact that thyroid abnormalities were also very common in the control group because the Polish population was iodine deficient for a long period of time, as mentioned above. Over 60% of subjects in the control group had thyroid lesions; in this situation, even if all patients with acromegaly had such disorders, RR would be slightly over 1.5. Inclusion of our outcomes slightly lowers the effect size values, e.g. OR for thyroid nodular disease (TND) decreased from 3.6 to 3.1, OR for TC — from 7.9 to 4.5. However, the results after the update gained lower p-values and more accurate confidence intervals; e.g. for OR of thyroid malignancies 95% CI was 2.8–22.0, after update it was 2.1–5.4. Another issue is the risk of malignancy in thyroid lesions. The question is if the risk of TC is elevated proportionally to the increased prevalence of thyroid lesions or nodules in this group of patients are at higher risk of malignancy. However RR was over two, the result is of borderline statistical significance. Further case-control studies are strongly indicated.

In conclusion, structural thyroid abnormalities are significantly more common in patients with acromegaly. Our study, performed on one of the largest described groups of acromegalic patients, as well as the results of updated meta-analysis, confirm that systematic thyroid examination should be important part of follow-up in patients with acromegaly. However, more case-control studies are indicated to establish the precise effect-size and consequently clinical importance of this co-morbidity.

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