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The impact of transsphenoidal surgery on glucose homeostasis and insulin resistance in acromegaly

Wpływ przezklinowej resekcji gruczolaka przysadki na gospodarkę węglowodanową i insulinooporność w akromegalii

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Abstract

Background and purpose: Impaired glucose tolerance and overt diabetes mellitus are frequently associated with acromegaly. The aim of this study was to find out whether these alterations could be reversed after transsphenoidal surgery.
Material and methods: Two hundred and thirty-nine acromegalic patients were studied before and 6-12 months after transsphenoidal surgery. Diagnosis of active acromegaly was established on the basis of widely recognized criteria. In each patient, glucose and insulin concentrations were assessed during the 75 g oral glucose tolerance test (OGTT). To estimate insulin resistance, we used homeostasis model assessment (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI).
Results: At the moment of diagnosis, diabetes mellitus was present in 25% of the acromegalic patients. After surgery, the prevalence of diabetes mellitus normalized to the level present in the general Polish population. We found a statistically significant reduction after surgery in plasma glucose levels both fasting (89.45 ± 13.92 mg/dL vs. 99.12 ± 17.33 mg/dL, $p < 0.001$) and during OGTT. Similarly, a prominent reduction in insulin secretion was found after surgery compared to the moment of diagnosis (15.44 ± 8.80 mIU/mL vs. 23.40 ± 10.24 mIU/mL, $p < 0.001$).

Streszczenie

Wstęp i cel pracy: Nietolerancja glukozy oraz cukrzyca często współwystępują z akromegalią. Celem badania była ocena wpływu przezklinowego wycięcia gruczolaka przysadki na zaburzenia gospodarki węglowodanowej i insulinooporność u chorych na akromegalię.
Materiał i metody: Kolejnych 239 chorych na akromegalię zostało ocenionych przed operacją oraz 6–12 miesięcy po przezklinowym wycięciu gruczolaka przysadki. Rozpoznanie akromegalii potwierdzono na podstawie powszechnie uznanych kryteriów. U każdego pacjenta oznaczono glukozę i insulinę na czczo oraz w teście doustnego obciążenia glukozą (*oral glucose tolerance test* – OGTT). Insulinooporność oceniono, wyliczając wskaźniki: HOMA-IR (*homeostasis model assessment*) oraz QUICKI (*quantitative insulin sensitivity check index*).
Wyniki: W momencie rozpoznania choroby cukrzyca była obecna u 25% osób z akromegalią. Po przezklinowej resekcji gruczolaka częstość występowania cukrzycy istotnie się zmniejszyła, osiągając częstość występowania cukrzycy w ogólnej populacji polskiej. U pacjentów po operacji stwierdzono istotne zmniejszenie glikemii na czczo oraz w OGTT (89,45 ± 13,92 mg/dl *vs* 99,12 ± 17,33 mg/dl; $p < 0{,}001$). Obserwowano również znaczące zmniejszenie

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After transsphenoidal surgery, there was a significant reduction in HOMA-IR (3.08 vs. 6.76, $p < 0.0001$) and a significant increase in QUICKI (0.32 vs. 0.29, $p < 0.001$). There were no statistically significant differences after surgery in fasting glucose and insulin levels between patients with controlled and inadequately controlled disease.

Conclusions: We conclude that in acromegalic patients glucose homeostasis alterations and insulin sensitivity can be normalized after transsphenoidal surgery, even if strict biochemical cure criteria are not fulfilled.

Key words: acromegaly, insulin resistance, impaired fasting glucose, impaired glucose tolerance, diabetes mellitus, transsphenoidal surgery.

wydzielania insuliny na czczo (15,44 ± 8,80 mIU/ml *vs* 23,40 ± 10,24 mIU/ml; $p < 0,001$) i w OGTT. U pacjentów po przezklinowym wycięciu gruczolaka przysadki wskaźnik insulinooporności HOMA-IR był istotnie mniejszy (3,08 *vs* 6,76; $p < 0,0001$), natomiast wskaźnik insulinowrażliwości QUICKI znacząco większy (0,32 *vs* 0,29; $p < 0,001$) w porównaniu z momentem rozpoznania choroby. Nie zaobserwowano istotnej różnicy w stężeniu glukozy i insuliny na czczo u pacjentów po doszczętnej i niedoszczętnej operacji gruczolaka przysadki.

Wnioski: W badaniu stwierdzono, że po przezklinowej resekcji somatotropowego gruczolaka przysadki zaburzenia tolerancji glukozy ulegają normalizacji nawet u pacjentów, którzy nie spełniają biochemicznych kryteriów wyleczenia z choroby.

Słowa kluczowe: akromegalia, insulinooporność, nieprawidłowa glikemia na czczo, nieprawidłowa tolerancja glukozy, cukrzyca, przezklinowa resekcja gruczolaka.

Introduction

Acromegaly is a rare and insidious disease caused by growth hormone (GH) and insulin-like growth factor 1 (IGF-1) hypersecretion and is characterized by disabling symptoms and relevant comorbidities that contribute to premature death observed in this condition [1-5]. Increased mortality is mainly due to a specific cardiomyopathy [6] that is worsened by the coexistence of several cardiovascular risk factors, such as abnormal glucose metabolism [7], insulin resistance [8], systemic hypertension [9], and abnormal lipid profile [10]. It is well established that GH plays an important role in the regulation of metabolism and body composition and that excessive secretion of GH may cause insulin resistance [8]. The increased cardiovascular morbidity and mortality associated with acromegaly may be partly a consequence of increased insulin resistance that frequently accompanies GH excess. In recent years, it has been reported that patients with acromegaly and coexisting hypertension and diabetes mellitus have the most severe alteration of cardiac function [11]. The prevalence of diabetes mellitus in acromegaly ranges from 19% to 56% in different series. Similarly, the prevalence of the most well-known intermediate form of altered glucose metabolism, referred to as impaired glucose tolerance (IGT), ranges from 16% to 46% [12-15].

The objectives of treatment include the normalization of GH/IGF-1 secretion and the control of pituitary tumour growth and acromegaly-related comorbidities to improve quality of life and reduce mortality from acromegaly to the level in the general population [16]. To date, among available management options, transsphenoidal surgery is the first-line treatment in most cases of acromegaly [17]. It is still uncertain whether surgical treatment can reverse acromegalic comorbidities such as glucose homeostasis abnormalities and insulin resistance.

The aim of the present study was to assess the effect of surgical treatment on glucose metabolism and insulin resistance in acromegalic patients.

Material and methods

In this retrospective study, 239 consecutive acromegalic patients (age range: 22-79 years) who were diagnosed at our department between 1995 and 2008 were studied before and 6-12 months after surgical treatment of somatotropinoma. All patients were operated on by two neurosurgeons from the same medical centre. The diagnosis of active acromegaly was established on the basis of elevated plasma GH above 1 μg/L during the 75 g oral glucose tolerance test (OGTT) and elevated plasma IGF-1 above the normal range for age and gender. According to Melmed and others, acromegaly is considered to be controlled after surgery if random GH concentrations are no greater than 2.5 μg/L in the presence of normal IGF-1 levels for age and gender [17]. According to the Acromegaly Consensus Statement, nadir GH during OGTT no greater than 1 μg/L is also an option to evaluate disease control [16]. Inadequately con-

trolled disease after surgery was defined when nonsuppressible GH during the oral glucose load and/or elevated IGF-1 levels were found. All patients with persistent hypopituitarism received appropriate adrenal, thyroidal, and gonadal hormonal replacement therapy, if necessary.

In each patient, glucose and insulin concentrations were assessed fasting and after 30, 60, 90, and 120 min of the 75 g OGTT at diagnosis and after surgery. The abnormalities in plasma glucose concentrations were categorized according to recent WHO criteria [18]. Diabetes mellitus (DM) was diagnosed when fasting glucose was above 126 mg/dL at two consecutive measurements or when glucose concentration was at least 200 mg/dL two hours after OGTT. Impaired glucose tolerance (IGT) was diagnosed when fasting glucose was less than 126 mg/dL and was at least 140 mg/dL and below 200 mg/dL two hours after OGTT. Impaired fasting glucose (IFG) was diagnosed when fasting glucose levels were between 100 and 126 mg/dL.

Insulin resistance was investigated on the basis of simple indices derived from fasting insulin and glucose values; i.e., the homeostasis model assessment (HOMA-IR) = fasting insulin (μIU/mL) × fasting glucose (mmol/L)/22.5 [19] and the quantitative insulin sensitivity check index (QUICKI) = 1/[log (fasting insulin, μIU/mL) + log (fasting glucose, mg/dL)] [20].

Statistical analysis

The assumption of normality was verified using the Shapiro-Wilk test. Variables are presented as mean ± standard deviation or median (and range) if not normally distributed. One-sample Student's t-test was used to compare examined parameters before and after surgery in acromegalic patients. The marginal homogeneity test was used to determine differences in distribution of categorical variables before and after surgery. The areas under the response curve (AUC) for glucose and insulin during OGTT were estimated according to the trapezoidal method. Differences were considered statistically significant at $p < 0.05$. Statistical analysis was performed using Stata 9.0 software.

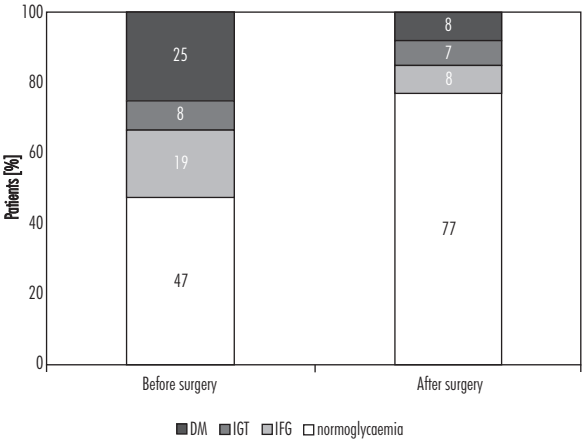

Fig. 1. Prevalence of impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and diabetes mellitus (DM) in acromegaly before and after surgery

Results

Women constituted the majority (65%) of the studied group. The female to male ratio was nearly 2 to 1. The mean age at the moment of diagnosis was 44.75 (SD 13.95) years. The duration of the disease since the onset of the first symptoms was 7.61 (SD 4.98) years. Normoglycaemia existed in 47% of acromegalic patients. Most of the patients (53%) had glucose metabolism alterations. Among these glucose tolerance abnormalities, we found IFG in 19%, IGT in 9%, and overt DM in 25% of the cases (Fig. 1). There was no statistically significant difference in gender, duration of the disease, basal plasma GH, IGF-1, or fasting insulin concentrations between normoglycaemic patients and those with glucose tolerance impairments. As we proved recently, the best predictor of glucose homeostasis impairments was the age of the patients [21].

Glucose metabolism and prevalence of glucose homeostasis abnormalities after surgery

After transsphenoidal surgery, 57% of patients had biochemically controlled disease and 43% of the cohort had either inadequately controlled disease or discrepancies between GH and IGF-1 levels. We found a statistically significant decrease in fasting plasma glucose in patients after surgery (89.45 ± 13.92 mg/dL vs. 99.12 ± 17.33 mg/dL, $p < 0.001$). Glucose levels in patients after surgical treatment were also significantly reduced during OGTT compared to the baseline ($p < 0.05$) (Fig. 2). The entire glucose response curve during OGTT showed a significant decrease in surgically treated patients ($p < 0.001$) (Fig. 3).

Fasting plasma glucose was slightly lower in the group of patients completely cured after surgery compared to the group of patients that did not meet the cure cri-

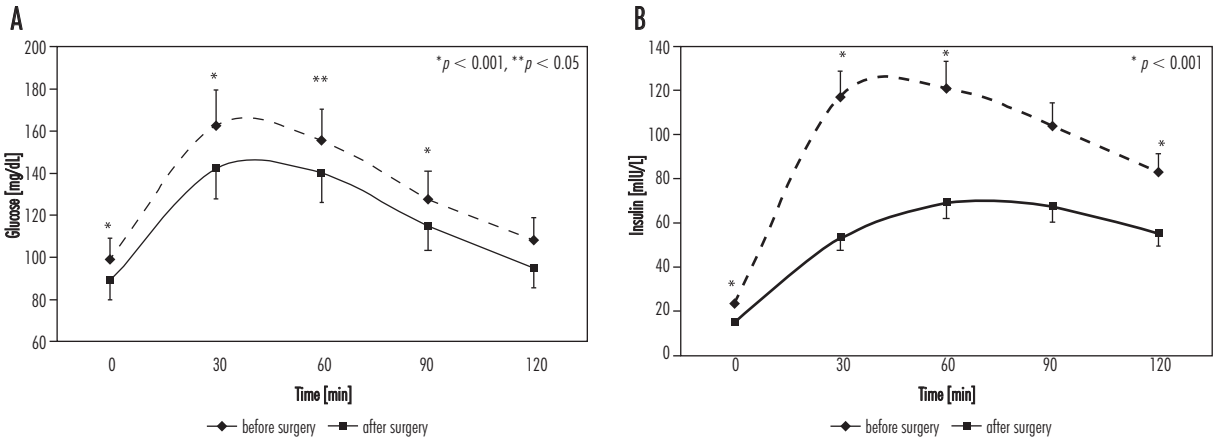

Fig. 2. Effect of transsphenoidal surgery on plasma glucose and insulin concentrations in patients with acromegaly. (A) Plasma glucose and (B) insulin concentrations fasting and during oral glucose tolerance test (OGTT) before and 6-12 months after surgery. Values are expressed as means ± standard deviations

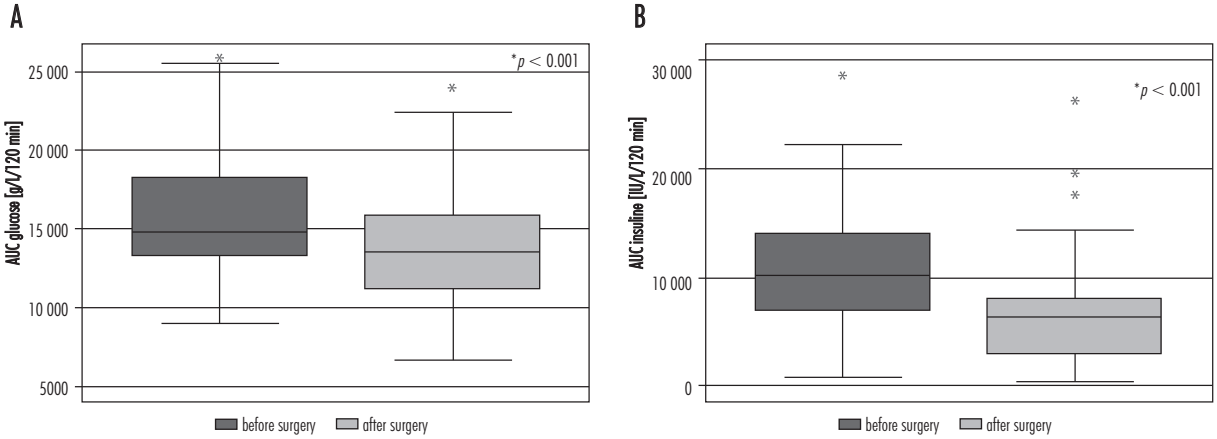

Fig. 3. Effect of transsphenoidal surgery on area under the curve (AUC) for (A) glucose and (B) insulin in acromegalic patients before and 6-12 months after surgery. Values are expressed as means ± standard deviations

teria; however, there was no statistically significant difference ($p = 0.056$) (Fig. 4).

The percentage of patients with normoglycaemia was greater after surgery (77% vs. 47%, $p < 0.001$). Among the glucose homeostasis abnormalities, we found fewer patients with IFG (8% vs. 19%), IGT (7% vs. 9%), and DM (8% vs. 25%) ($p < 0.001$) (Fig. 1).

Insulin secretion and sensitivity after surgery

As we suspected, fasting plasma insulin levels decreased significantly and similarly to fasting glucose levels in patients after surgery (15.44 ± 8.80 mIU/L vs. 23.40 ± 10.24 mIU/L, $p < 0.001$) (Fig. 2). After surgery, there was no statistically significant difference in fasting insulin levels between patients with completely and inadequately controlled disease (Fig. 4). There was a statistically significant decline in insulin secretion after the oral glucose load ($p < 0.001$) (Fig. 2), which was also confirmed when the total area under the insulin response curve was calculated ($p < 0.001$) (Fig. 3). Compared to the baseline, the insulin resistance index HOMA-IR was significantly lower (3.08 vs. 6.76, $p < 0.0001$) and the insulin sensitivity index QUICKI was significantly higher (0.32 vs. 0.29, $p < 0.001$) in patients after surgical treatment (Fig. 5).

Discussion

This study investigated the metabolic effects of neurosurgical treatment in acromegalic subjects. Transsphenoidal surgery is the treatment of choice in most

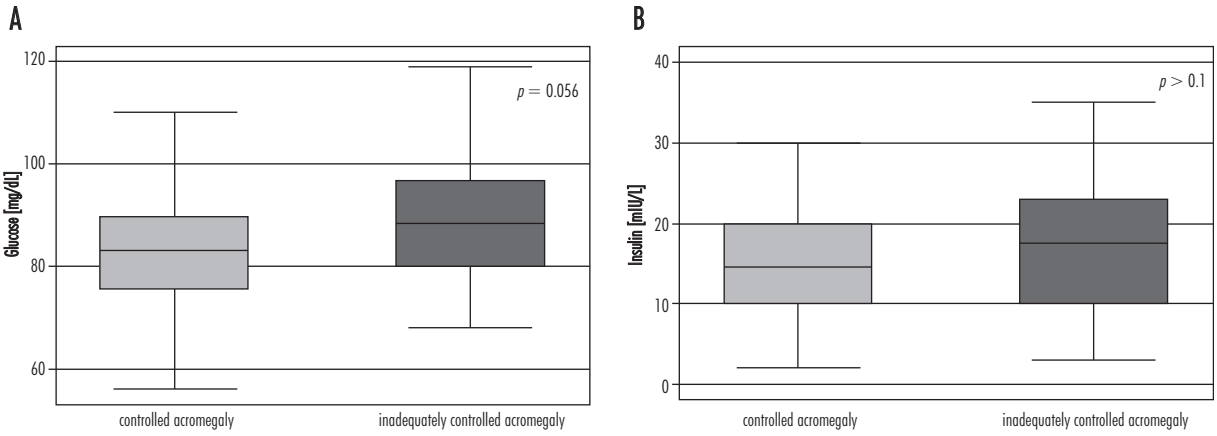

Fig. 4. (A) Fasting glucose and (B) insulin concentration in patients with acromegaly after surgery with controlled and inadequately controlled disease. Values are expressed as means ± standard deviations

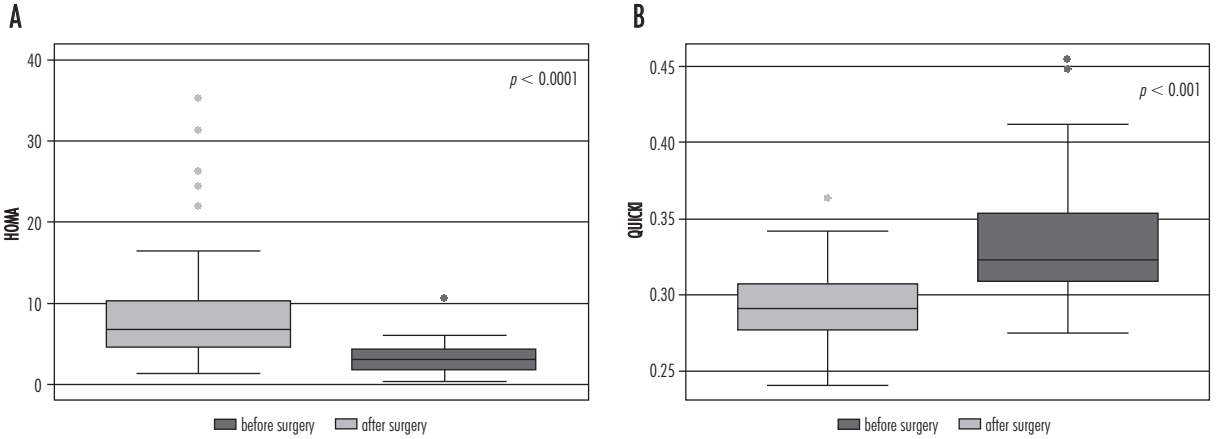

Fig. 5. Effect of transsphenoidal surgery on insulin resistance in patients with acromegaly. (A) HOMA-IR and (B) QUICKI indices in acromegalic patients before and 6-12 months after surgery. Values are expressed as means ± standard deviations

cases of somatotropinomas [16,17]. Determinants of surgical remission include the experience of the neurosurgeon, tumour size, and degree of invasiveness. In patients with intrasellar microadenomas, surgical removal provides biochemical control in 75-95% of patients. Control rates are lower in patients with macroadenomas, but even in these cases surgical removal provides biochemical control in 40-68% of patients [17]. In our cohort, 57% of patients were biochemically controlled after transsphenoidal surgery.

Many studies have shown increased mortality of acromegalic patients compared to the general population [2-4, 22]. The latest metaanalysis estimated an overall 72% increase in mortality in acromegaly compared to the general population. It should be emphasized that the major cause of early mortality in acromegaly is cardiovascular disease [4,23], which is also the major cause of mortality in patients with insulin resistance and diabetes mellitus [24,25]. Insulin resistance that leads to glucose intolerance is one of the most important contributory factors to cardiovascular diseases in acromegaly [8]. It is known that patients with acromegaly and coexisting hypertension and diabetes mellitus have the most severe alterations of cardiac function [11]. Therefore, investigation of a possible reversible impact of surgery on glucose tolerance and insulin resistance has major clinical implications.

To date, very few reports exist on the effects of neurosurgery on glucose metabolism and the results have been conflicting [26-29]. Our study revealed that glucose homeostasis alterations are present in 53% of the cases at the moment of diagnosis. Among these abnor-

malities, diabetes mellitus was diagnosed in 25% of the patients, which is almost three-fold higher than in the general Polish population. According to the International Diabetes Atlas, diabetes mellitus is present in around 9% of the Polish population between 20 and 79 years of age [30]. After surgery, most patients were normoglycaemic (77% vs. 47%). Diabetes mellitus after surgery was found in a significantly lower percentage of patients (8%), which is similar to the prevalence in the general Polish population. The incidence of pre-diabetic conditions was also significantly lower compared to the moment of diagnosis (IFG: 8% vs. 19%, IGT: 7% vs. 9%). In this study, we observed a statistically significant reduction in plasma fasting glucose 6-12 months after surgery, which was accompanied by a decrease in insulin secretion both fasting and during OGTT. This is in agreement with the results of the study by Jaffrain-Rea and others who found normalization of glucose abnormalities in all cases among 31 patients with acromegaly who were assessed before and six months after successful transsphenoidal surgery [26]. Consistently with this investigation, we also observed a significant reduction in insulin levels both fasting and after the glucose load as well as a prominent improvement in insulin sensitivity evaluated by the HOMA-IR and QUICKI indices. Similar results were obtained by Ronchi and others, who compared a group of acromegalics treated with long-acting somatostatin analogues to those who were cured by surgery. In a group of surgically treated patients, they found a significant reduction in plasma glucose and insulin levels and improvement in insulin sensitivity after a median observation time of 80 months compared to the baseline [28].

The above-mentioned results are in contrast to what Colao and others found in a five-year observational study in which the long-term effects of different therapeutic modalities on glucose homeostasis were investigated [27]. In a group of 30 acromegalic patients who were successfully treated with surgery, they found a reduction only in fasting insulin levels and the HOMA-IR insulin resistance index, but no significant reduction in fasting glucose levels. Improvement in insulin sensitivity was also reported in past research using the 'gold standard method', i.e., the euglycaemic hyperinsulinaemic clamp, but the results were based only on a very small number of patients [29].

What is of great clinical interest is that we did not observe any statistically significant difference in fasting glucose and insulin levels between patients with complete biochemical remission and those who did not meet the cure criteria after transsphenoidal surgery. This is in agreement with what was previously described by Damjanovic and others that even incomplete disease control after surgery can result in improvement of the insulin resistance and cardiac indices assessed by echocardiography [31].

Conclusions

We concluded that in acromegalic patients glucose homeostasis alterations and insulin sensitivity can be normalized after transsphenoidal surgery of somatotropinoma even if strict biochemical cure criteria are not fulfilled.

Disclosure

The authors report no conflict of interest.

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