

Metabolic abnormalities in pituitary adenoma patients: a novel therapeutic target and prognostic factor

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Abstract: Metabolic abnormalities are common in cancers, and targeting metabolism is emerging as a novel therapeutic approach to cancer management. Pituitary adenoma (PA) is a type of benign tumor. Impairment of tumor cells' metabolism in PA seems not to be as apparent as that of other malignant tumor cells; however, aberrant hormone secretion is conspicuous in most PAs. Hormones have direct impacts on systemic metabolism, which in turn, may affect the progression of PA. Nowadays, conventional therapeutic strategies for PA do not include modalities of adjusting whole-body metabolism, which is most likely due to the current consideration of the aberrant whole-body metabolism of PA patients as a passive associated symptom and not involved in PA progression. Because systemic metabolic abnormalities are presented by 22.3%–52.5% PA patients and are closely correlated with disease progression and prognosis, we propose that assessment of metabolic status should be emphasized during the treatment of PA and that control of metabolic abnormalities should be added into the current therapies for PA.

Keywords: metabolic abnormalities, pituitary adenoma, therapeutic target, prognostic factor

Introduction and background

Tumor cross talks with its environment, macroenvironment, and microenvironment. The macroenvironment of tumors is a concept relative to that of tumor microenvironment. Al-Zhoughbi et al¹ defined “tumor macroenvironment” as the pathological interaction between the tumor cells, as well as the tumor microenvironment, with other organs and systems of the body, which emphasizes the influence of tumors on the whole body. A number of studies have been done to understand the role of tumor microenvironment in tumor progression. Changes in microenvironment such as inflammatory cytokines, angiogenic factors, integrins, matrix metalloproteinases, and hypoxia are known to play important roles in tumor growth.² Cytokines released by tumor cells can, on the one hand, remodel the microenvironment, and, on the other hand, also influence the homeostasis of the whole body. One of the most consequential changes of the whole body in response to impacts originating from tumors is the metabolic imbalance in tumor patients.

Alterations in metabolisms of protein, lipid, and carbohydrate are often associated with tumor progression. Fearon et al³ found that in lung or colorectal cancer patients, the whole-body protein synthesis was decreased. Increase of muscle protein degradation was observed in noncachectic sarcoma patients, and leucine metabolic abnormalities are specific to tumor growth in humans with high-grade sarcomas.⁴ Tumor can also directly affect the profile of plasma-free amino acids. Studies on different types of cancers such as breast cancer and non-small cell lung cancer have shown that each type of these

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cancers has its specific plasma-free amino acid profiles.^{5,6} Lipid is another important dysregulated metabolite in cancer patients. Dysregulated lipid metabolism is considered a hallmark of cancer.⁷ Cancer cells can use exogenous fatty acids for membrane synthesis and oncogenic signaling, which can ultimately influence the plasma lipid profile.⁸ Compared with body mass index (BMI)-matched healthy controls, hematological neoplasia patients exhibit lower concentrations of plasma cholesterol, high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), and higher concentrations of triglyceride (TG).⁹ These observations confirm the influence of tumor on the whole-body metabolism.

The whole-body metabolic imbalance may affect the progression of cancer. Progression of cancer is also found to be associated with the so-called metabolic syndrome, which is defined as a syndrome composed of obesity, dyslipidemia, hyperglycemia associated with insulin resistance, and development of diabetes mellitus.¹⁰ Obesity has been reported as a cancer risk in colon cancer and rectal cancer,¹¹ pancreatic cancer,¹² ovarian cancer,¹³ breast cancer,¹⁴ and liver cancer.¹⁵ Recently, Bhaskaran et al¹⁶ conducted a population-based cohort study on 5.24 million adults in the United Kingdom, and found that BMI was associated with 17 most common cancers, although the effects varied substantially by tumor site. Hyperglycemia is also linked to cancers independent of BMI. Levine et al's¹⁷ study in 1990 revealed the relationship of postload plasma glucose and 12-year cancer mortality, and the conclusion was that hyperglycemia was related to cancer mortality in men, but not in women. A significantly increased risk of pancreatic cancer and malignant melanoma was found in both male and female hyperglycemia patients.¹⁸ Dyslipidemia is another metabolic factor associated with risks of several cancers. Dyslipidemia presents low HDL-C, high LDL-C, and high serum TG levels. Low HDL-C level was associated with non-Hodgkin lymphoma,¹⁹ lung cancer,²⁰ prostate cancer,²¹ and breast cancer.²² High serum TG was associated with postmenopausal breast and prostate cancer in a few studies.^{23,24} The pathophysiological mechanisms by which metabolic abnormalities participate in tumor progression is complicated. Braun et al²⁵ summarized the potential causal factors. The key factors include insulin and insulin-like growth factor (IGF) system; inflammatory factors such as IL-6, TNF- α , and C-reactive protein; transcription factors such as NF- κ B, HIF-1 α , PPARs; and other factors such as COX-2, leptin, and adiponectin.²⁵ In general, these observations indicate that tumor-associated whole-body metabolic alterations are not a passive element, but an active participant

in tumor progression. Thus, correcting the whole-body imbalance of metabolism may be an effective approach for tumor management.

Pituitary adenoma (PA) is known to be often associated with whole-body imbalance of metabolism due to its aberrant secretion of hormones. In addition to the mass effects, the oversecretion of pituitary hormones is another key clinical manifestation. Even though 39% of PA are hormone silent, namely the nonfunctioning pituitary adenomas (NFPAs),²⁶ yet because of the mass effects of NFPAs, the portal vessels and pituitary stalk can be compressed, which can lead to a decrease in dopamine delivery that can cause hyperprolactinemia in nearly 35% of NFPA patients.²⁷

Pituitary hormones can affect whole-body metabolism directly or indirectly. The most common hormone-secreting pituitary tumors are prolactinomas (40%),²⁸ and 63% of prolactinoma patients have weight gain.²⁹ Prolactin can affect whole-body metabolism by regulating key enzymes and transporters that are associated with lipid and glucose metabolism. Prolactin can act as an autocrine or paracrine factor in human adipose tissue. Prolactin can either bind to its receptor, which induces the activation of the downstream pathways such as dimerization and phosphorylation of JAK2, recruitment of STAT 5a/b, finally alters the transcription of lipid-metabolism-related genes and the secretion of IL-6, adiponectin, and leptin.³⁰ In addition, prolactin can also reduce the excretions of water, sodium, and potassium from the kidney.³¹ Growth hormone (GH) is another hormone that can significantly affect the whole-body metabolism. The predominant effect of GH is to stimulate lipid oxidation and lipolysis, switching energetic substrate from glucose and protein to lipid.³² In acromegaly patients, hyperinsulinemia and impaired glucose tolerance are quite common. In an acromegaly registry clinical study conducted in France, the prevalence of diabetes in these patients was 22.3%,³³ and another study reported a 52.5% prevalence of diabetes in acromegaly patients.³⁴ Additionally, impaired glucose metabolism was also found in 66% of acromegaly patients.³⁵ GH acts through two pathways: one is to bind to GH receptors and then activate JAK2, MAPK, and STATs;³⁶ the other is to induce the production of IGFs that can stimulate proteoglycan, glycosaminoglycan and protein synthesis.³⁷ Adrenal corticosteroid is closely related to whole-body metabolic imbalance. Adrenocorticotrophic hormone (ACTH) regulates the secretion of adrenal gland hormones directly. Glucocorticoids can increase blood glucose concentration by affecting glycogen, protein, and lipid metabolisms. Cortisol can stimulate glycogen deposition in the

liver, inhibit glucose uptake and use in peripheral tissues, and activate lipolysis in adipose tissue, leading to the release of free fatty acids into circulation. High cortisol levels are thought to be related to the pathogenesis of metabolic syndrome.³⁸ A high prevalence of metabolic syndrome exists in Cushing's syndrome patients.³⁹ 95% of patients have obesity, 75% have hypertension, and 60% have glucose intolerance.⁴⁰ Prolonged and excessive glucocorticoid exposure and activation of the hypothalamic–pituitary–adrenal axis are involved in the pathogenesis of metabolic syndrome.⁴¹ Polymorphisms of human glucocorticoid receptor gene are found to be associated with hypertension and obesity.⁴² Metabolic syndrome is even considered to be a mild form of Cushing's syndrome.⁴³ Interestingly, the prevalence of metabolic syndrome in NFPAs is up to 44.7%.³⁹ In a cross-sectional study, TSH in the upper normal range was found to be related to more obese, higher TGs, and increased likelihood of the metabolic syndrome.⁴⁴ And the thyroid hormone can bind to high-affinity thyroid hormone receptors, which can activate pathways such as NcoR/SMRT, MEK/STATs, ANT, UCPs, and Raf1/MEK/MAPK, thus affecting the synthesis, mobilization, and degradation of protein, carbohydrate, and lipid metabolism.^{45,46} Leptin is thought to play a role in the regulation of food intake and metabolism. A recent study shows that leptin-treated females and males had significantly elevated serum levels

of luteinizing hormone and follicle-stimulating hormone, respectively (Figure 1).⁴⁷

Currently, the first-line therapy for PA is surgery, which can be conducted transsphenoidally, transcranially, or in a combination of both. But prolactinomas are an exception.⁴⁸ Surgery can achieve local control completely or partly by releasing the compression of vital structures. Owing to infiltration to the adjacent structures, tumor tissues can be residual, which may elevate hormone levels and lead to a need for repetitive surgeries or pharmacological treatment. Dopamine agonists and somatostatin analogs are the most widely used medications to treat PA. But some patients with invasive PA are resistant at the beginning or develop resistance to these drugs.²⁸ When surgery and pharmacotherapy have failed, radiotherapy is the third-line therapy.⁴⁸ With the current procedures of managing PA, the recurrence rate is still not ideal, which is often related to tumor size and cavernous sinus extension.⁴⁹ In NFPA, the recurrence rate from nondetectable residual tumor is approximately 12%, and from the detectable tumor residuals is approximately 46%.⁵⁰ With successful surgeries, hormonal control cannot be achieved in every case. In Wang et al's⁵¹ study, the hormonal control rate was 69% of ACTH adenomas, 66% of GH adenomas, 85% of PRL adenomas, and 86% of TSH adenomas.

Imbalance of body metabolism can affect the prognosis of PA. A high rate of postoperative or postmedical therapy

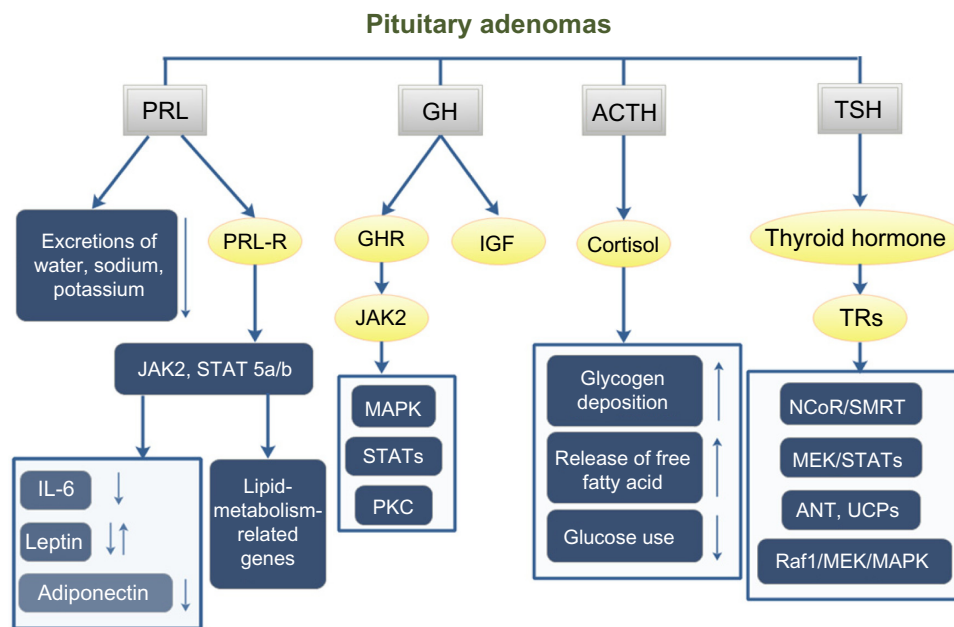


Figure 1 PA affects the whole-body metabolism through the pituitary hormones.

Notes: The molecular mechanisms of pituitary hormones involve specific receptors and transcription factors. NFPAs are hormone silent, but some of them can cause hyperprolactinemia. The FSH/LH PA affects the whole-body metabolism indirectly; the mechanism is not shown in Figure because of limited data.

Abbreviations: GH, growth hormone; ACTH, adrenocorticotropic hormone; TSH, thyroid-stimulating hormone; GHR, growth hormone receptor; IGF, insulin-like growth factor; TRs, thyroid hormone receptors; PA, pituitary adenoma; NFPAs, nonfunctioning pituitary adenomas; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

imbalance of body metabolism exists. Often, after 6 months of treatment with dopamine agonists, the BMI of prolactinoma patients does not change at all.⁵² Acromegaly patients with abnormal glucose metabolism need more combined medical therapies than surgery alone.⁵³

Hypothesis

Based on the close association between PA and whole-body metabolic alterations, we propose that it is necessary to assess the status of whole-body metabolism and monitor the metabolic abnormalities before and after surgical or medical therapies, and control of imbalance of body metabolism should be added to the current procedures of treating PA.

Prospects

The metabolic abnormalities of PA patients should not be ignored or just considered as an associated symptom. The effect of pituitary hormones on body metabolism is apparent. But the relationship between the imbalance of whole-body metabolism and prognosis of PA has not gained enough attention. In fact, the prevalence rate of metabolic abnormalities in PA is high. Current therapies cannot relieve the metabolic abnormalities completely, and assessing the changes of metabolic status before and after therapies is not a standard practice. The change of metabolic indexes is a chronic process. Only after 12 months of treatment by dopamine agonists do the prolactinoma patients tend to lose weight, and can cabergoline induce weight loss.⁵² In the treatment of acromegaly, different drugs affect the body metabolism to different degrees. Somatostatin analog Octreotide failed to change glucose tolerance significantly even though the insulin levels tended to be decreased by the treatment. Pegvisomant, a GH analog and functioning as a specific GH receptor antagonist, can effectively reduce plasma glucose concentrations.⁵⁴

Metabolic syndrome is a complicated disease. Treatment of metabolic syndrome-associated PA is not simple. Grundy has reviewed the therapies of metabolic syndrome.⁵⁵ Effective lifestyle therapies, including weight reduction, increasing physical activity, and antiatherogenic diet composition, are the first recommended way to control or slow down the progression of metabolic syndrome. Postponing the initiation of drug therapy as long as possible is preferred.

PA is benign, but has severe clinical complications. The mass effects of tumors can be severe or even fatal such as PA apoplexy, but they can always be remitted immediately by surgeries. Compared with its other life-threatening complications, hormonal disorders seem to be moderate. But even after

surgeries, many patients will still suffer endocrine disorders. Postsurgery medical treatments are needed. As metabolic abnormalities are involved in all stages of PA development, the assessment and interference of whole-body metabolism before and after surgery should be considered in order to bring about better outcomes of PA patients.

Disclosure

The authors report no conflicts of interest in this work.

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