Metabolic complications of nonfunctioning pituitary macroadenomas: a mini review

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Abstract
Nonfunctioning pituitary macroadenomas (NFMA) make up 20% of pituitary adenomas. Previous studies have shown that patients treated for NFMA have disturbances in sleep characteristics, circadian movement rhythm, subjective sleep quality, and decreased quality of life. Furthermore, studies have shown that NFMA patients have an increased risk for the metabolic syndrome and insulin resistance. Despite these findings, long-term studies on the metabolic outcomes of NFMA patients are scarce. The purpose of this review is to familiarize clinicians with the potential metabolic complications of nonfunctioning pituitary adenomas, with an emphasis on pituitary macroadenomas. Patients with NFMA have an increased risk for developing the metabolic syndrome and have adverse metabolic outcomes, but the exact mechanisms involved remain unknown. The adverse metabolic profile of these patients could be the result of hypothalamic damage or intrinsic imperfections in hormone replacement therapy. However, because the optimal doses of levothyroxine, hydrocortisone and rhGH are not known and are variable between patients, and because the effects of these hormones are difficult to quantify at the tissue level, the metabolic effects of these replacement strategies are difficult to determine. This represents a limiting factor in designing studies to determine the metabolic complications of individual hormone deficiencies in patients with NFMA. From a clinical perspective, this represents a challenge in the outpatient management NFMA patients as the notion of adequate and stable hormone replacement is frequently challenged. Furthermore, the benefits of long-term rhGH therapy are still unknown, and it is still unclear which patients should receive rhGH substitution therapy. Despite these uncertainties, it is evident that patients treated for nonfunctioning pituitary adenomas should receive proper follow-up that includes cardiovascular risk assessment and treatment of metabolic complications as they arise. Patients should be informed of this potential complication so that lifestyle modifications can be made early in the course of their treatment.

Keywords: nonfunctioning pituitary adenomas, metabolic complications
1. Introduction

Nonfunctioning pituitary macroadenomas (NFMA) make up 20% of pituitary adenomas [1]. Patients often present with signs and symptoms of pituitary insufficiency or compressive symptoms such as headaches and visual field defects. Transsphenoidal surgery is the preferred treatment of choice with postoperative radiotherapy given as needed [2,3]. Even after surgery, patients have a high prevalence of hypopituitarism and may require lifelong substitution therapy [4].

Previous studies have shown that patients treated for NFMA have disturbances in sleep characteristics, circadian movement rhythm, and subjective sleep quality [5]. NFMA patients also report decreased quality of life. These findings have been explained by the impaired functioning of the suprachiasmatic nucleus (SCN) of the hypothalamus, which is the main director of circadian rhythmicity. Due to the close proximity of the optic chiasm and hypothalamus, pituitary macroadenomas may cause hypothalamic damage. The hypothalamus is the main regulator of energy homeostasis, and patients with structural damage to the hypothalamus due to a pituitary macroadenoma can develop hypothalamic obesity (HyOb), a syndrome characterized by polyphagia and weight gain [6]. Therefore, circadian dysregulation may be associated with the metabolic syndrome directly through HyOb and indirectly through decreased sleep duration and quality [4]. Furthermore, intrinsic imperfections in hormone replacement therapy may lead to metabolic derangements in NFMA patients.

Despite this intriguing data, long-term studies on the metabolic outcomes of NFMA patients are scarce. In fact, most studies on metabolic features in pituitary diseases have been performed in heterogeneous patient groups with hormone excess syndromes or growth hormone (GH) deficiency, which makes it difficult to ascertain the potential hypothalamic effects of pituitary tumors [4]. One mortality study on 192 adequately substituted NFMA patients did not find increased cardiovascular or cerebrovascular mortality [7], while another study on 573 NFMA patients with variable adequacy of replacement therapy found increased mortality due to cardiovascular and respiratory diseases [8]. A recent study on NFMA patients with adequate hormone replacement demonstrated an increased risk for the metabolic syndrome, mainly due to reduced high-density lipoprotein (HDL) cholesterol and increased triglycerides [4]. Another study found that patients with clinically nonfunctioning pituitary adenomas have high atherosclerotic risk markers such as insulin resistance and hyperandrogenemia.

From these findings it is evident that metabolic risk factor assessment should be an integral part of NFMA follow-up. However, these potential metabolic derangements are often overlooked and not routinely assessed in NFMA patients. The purpose of this review is to familiarize clinicians with the potential metabolic complications of nonfunctioning pituitary adenomas, with an emphasis on pituitary macroadenomas.

2. Pathogenesis of structural hypothalamic obesity

Approximately 25% of patients with structural hypothalamic damage display hyperphagia and obesity [9,10]. The hypothalamus is the main regulator of energy homeostasis, and the main hypothalamic areas that cause HyOb when damaged are: the ventromedial hypothalamus, paraventricular nuclei, arcuate nucleus (ARC), and the lateral hypothalamic area [6]. The ARC plays an important role in the integration of feeding signals and energy reserves from the periphery [11]. Two populations of neurons are found in the ARC. One inhibits food intake via the expression of neuropeptides proopiomelanocortin and cocaine and amphetamine-regulated transcript, and the other stimulates food intake via neuropeptide Y and agouti-related peptide. Second-order neuronal populations including the paraventricular nuclei, dorsomedial nucleus, ventromedial nucleus, and lateral hypothalamic area, project from the ARC and activate downstream pathways that control appetite and energy expenditure. Peripheral circulating markers including leptin, adiponectin, and insulin, and markers from the gastrointestinal tract (ghrelin, peptide YY, glucagon-like peptide 1, cholecystokinin, oxyntomodulin, and pancreatic polypeptide) relay information regarding the body’s energy status to the hypothalamus and brainstem [11].
Structural hypothalamic damage may occur as a result of tumors, including macroadenomas, inflammatory diseases, head injury, or cranial radiotherapy [6]. Common clinical findings of patients with HyOb include hyperphagia, reduced physical activity, somnolence, and secondary pituitary deficiencies. The pathophysiology of HyOb involves the loss of sensitivity to afferent peripheral signals such as leptin and dysfunctional afferent signaling. HyOb may result from hypersecretion of insulin and leptin, high 11β-hydroxysteroid dehydrogenase 1 activity (the enzyme that catalyzes the conversion of inactive cortisone to active cortisol), decreased sympathetic nervous system activity, and decreased basal metabolic rate. Melatonin may also play a role in its development [6]. This complex signaling pathway is delicately coordinated and is beyond the scope of this review.

3. Unfavorable metabolic parameters in patients with NFMA

Although several studies have investigated metabolic derangements in pituitary somatotropinomas, prolactinomas and corticotropinomas, studies on nonfunctioning adenomas are scare [12–16].

The metabolic syndrome is comprised of a constellation of interrelated risk factors that promote the development of atherosclerotic cardiovascular disease and type 2 diabetes mellitus [17]. The metabolic syndrome is diagnosed when any of the 3 criteria are present: increased waist circumference, reduced HDL cholesterol, elevated blood pressure, or elevated fasting glucose.

Recently, Sjoerd et al. [4] performed a study on the metabolic syndrome in 145 NFMA patients in long-term remission, receiving adequate stable hormone replacement therapy and compared this cohort to a population of Dutch inhabitants (data derived from the Lifelines cohort study) [18]. Criteria for the metabolic syndrome was derived from the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III), last updated by the American Heart association in 2005 [17]. In comparison to the Dutch cohort, NFMA patients had decreased HDL-cholesterol and increased triglyceride levels, resulting in a 60% increased risk for the metabolic syndrome. Blood pressure was not increased in NFMA patients compared to the control group, nor was waist circumference or hyperglycemia. However, preoperative visual field defects (indicating compression of the optic chiasm) independently affected the risk for increased blood pressure, and hypopituitarism was associated with a body mass index-dependent risk for increased waist circumference. Even though visual field defects were not associated with central obesity or the metabolic syndrome, the duration of compression cannot be accurately evaluated and it is not known whether visual field defects per se, or just radiological evaluation is sufficient to evaluate hypothalamic compression [4]. As one might expect, the number of deficient pituitary axes was associated with an increased odd for abdominal obesity and the metabolic syndrome, which was mostly attributed to GHD but this association was dependent on body mass index, visual field defects, radiotherapy and other hormone deficiencies. Interestingly, GHD did not affect the level of triglycerides; therefore, GHD cannot explain all the metabolic derangements in NFMA patients.

In addition to these known metabolic risk factors, studies have shown that there is a close relationship between mean platelet volume (MPV) and cardiovascular risk factors [19]. Furthermore, hyperandrogenism could be the progenitor of inflammation and a risk factor for atherosclerosis in PCOS [20]. A recent retrospective study examined atherosclerotic risk markers including lipid parameters, MPV, total testosterone, androstenedione, dehydroepiandrosterone sulfate, and insulin (calculated using the homeostatic model assessment-insulin resistance, HOMA-IR) in 47 women with nonfunctioning pituitary adenomas (45 with microadenomas and 2 with macroadenomas) and 73 healthy controls [21]. In comparison to the healthy control group, women with nonfunctioning pituitary adenomas had higher HOMA-IR and androstenedione levels (p = 0.003, p = 0.021, respectively). There was also a positive association between androstenedione and insulin/HOMA-IR in patients with nonfunctioning pituitary adenomas.
4. Intrinsic imperfections in hormone replacement therapy

Many patients with hypopituitarism receiving adequate and stable hormone replacement therapy still report vague complaints that are difficult to assess objectively. These patients may also have a decreased quality of life. Although these complaints are difficult to assess by biochemical tests, they should not be overlooked because hormonal substitution therapy does not reproduce the normal plasma hormone profiles of healthy individuals. As previously mentioned, intrinsic imperfections of hormone replacement therapy might increase the risk for the metabolic syndrome in NFMA patients [22].

Although previous studies found associations between untreated GHD and hypertension, abdominal obesity and the metabolic syndrome [23–25], supporting the benefits of recombinant growth hormone therapy (rhGH), a recent study called to question the long-term benefits of rhGH [26]. The study compared the proportion of the metabolic syndrome and its individual components in 161 middle-aged GHD patients with heterogeneous causes of GHD before the start of rhGH and after 5 years of treatment compared to 1671 subjects of the general population. Before rhGH replacement, 41.0% of GHD (37.1% in males and 45.8% in females) patients fulfilled the criteria for the metabolic syndrome as defined by the NCEP-ATP III criteria, and after 5 years of therapy, the proportion of the metabolic syndrome increased to 53.4%. This rise was attributed to a higher proportion of hyperglycemia, whereas the lipid profile was not affected. In contrast, the metabolic syndrome was identified in 30.3% of the general population, and even after chronic substitution therapy, GHD patients still had a 1.3 times increased proportion of the metabolic syndrome compared with the general population independent of age, sex, and body mass index (BMI). Furthermore, GHD patients still had a different metabolic profile than the general population, with a lower prevalence of insulin resistance, but an adverse lipid profile. The study demonstrated that the metabolic profile after chronic rhGH replacement is similar to an untreated GHD patient, suggesting that the metabolic profile of these patients is not significantly influenced by long-term rhGH replacement. The study questioned whether circulating total insulin like growth factor 1 (IGF1) levels truly reflects peripheral IGF1 activity, and pointed out that there is a fine line between rhGH replacement and insulin resistance, suggesting further lowering of the GH doses. The authors concluded that further studies are needed to determine whether rhGH replacement is beneficial in the long-term, taking into account cost-effectiveness, quality of life, and the potential negative effects of growth hormone therapy on cancer, longevity, and cardiovascular risk [27].

Because most patients treated for NFMA have multiple pituitary hormone deficiencies, the metabolic effects of individual hormone deficiencies is difficult to assess, as this effect may be contributed to GHD or rhGH replacement, suboptimal or supraphysiological replacement of other hormones, or a result of hypothalamic damage and subsequent hypothalamic obesity. As an example, higher glucocorticoid replacement doses are associated with increased overall mortality and the metabolic syndrome in patients with nonfunctioning pituitary adenomas [27].

5. Conclusion

Patients with NFMA have an increased risk for developing the metabolic syndrome and have adverse metabolic outcomes, but the exact mechanisms involved remain unknown. The adverse metabolic profile of these patients could be the result of hypothalamic damage or intrinsic imperfections in hormone replacement therapy. However, because the optimal doses of levothyroxine, hydrocortisone and rhGH are not known and are variable between patients, and because the effects of these hormones are difficult to quantify at the tissue level, the metabolic effects of these replacement strategies are difficult to determine. This represents a limiting factor in designing studies to determine the metabolic complications of individual hormone deficiencies in patients with NFMA. From a clinical perspective, this represents a challenge in the outpatient management NFMA patients as the notion of adequate and stable hormone replacement is frequently challenged. Furthermore, the benefits of long-term rhGH therapy are still unknown, and it is still unclear which patients should receive rhGH substitution therapy. Despite these uncertainties, it is evident that patients treated for nonfunctioning pituitary adenomas should receive proper
follow-up that includes cardiovascular risk assessment and treatment of metabolic complications as they arise. Patients should be informed of this potential complication so that lifestyle modifications can be made early in the course of their treatment.

Author contributions

LSKB performed literature review, wrote the article and gave the final approval. MV gave the idea for the article, critically revised the manuscript, gave suggestions regarding data presentation and gave the final approval.

References


