Interplay Between Endocrine and Genetic Disorders: Insights from Cushing's Syndrome and MODY3 Co-occurrence

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Abstract

In clinical endocrinology, the co-occurrence of Cushing's syndrome and Maturity-Onset Diabetes of the Young 3 (MODY3) poses a special problem. While MODY3, which is caused by mutations in the HNF1A gene, results in decreased insulin secretion without compromising insulin sensitivity, Cushing's syndrome, which is characterized by chronic hypercortisolism, causes insulin resistance and metabolic abnormalities. Even though they have different pathophysiologies, diagnosing both conditions at the same time is challenging because they both cause hyperglycemia in different ways. The molecular, genetic, and clinical interactions between Cushing's syndrome and MODY3 are examined in this review, with an emphasis on the similarities and differences in the pathways affecting glucose metabolism. Diagnostic problems are discussed, with a focus on the use of imaging tools, genetic screening, and biochemical tests to differentiate between the main metabolic impacts of each disorder.The review also offers management approaches that combine lifestyle, medication, and surgical changes to address the co-occurrence of these illnesses. It is suggested that future research focus on developing tailored medicines, improving diagnostic accuracy, and better understanding their molecular interactions. Clinicians can improve patient outcomes in this intricate overlap of endocrine and monogenic diabetes diseases by using endocrinological and genetic information to create more individualized treatment plans.

Keywords: Cushing’s Syndrome, Maturity-Onset Diabetes of the Young (MODY3), HNF1A mutation, Hypercortisolism, Insulin Resistance, Monogenic Diabetes.

1. Introduction

Cushing's syndrome is an endocrine disorder caused by adrenal insufficiency with consequent elevation of cortisol levels. In this disorder, insulin resistance arises which is a common metabolic disturbance seen in Cushing's syndrome that runs parallel with secondary diabetes mellitus [1][2]. The glucocorticoid-induced insulin resistance can disturb the glucose balance and-foster other metabolic problems such as hypertension, dyslipidemia, and obesity. Mainly if the condition remains untreated, complications such as cardiovascular disease and diabetic nephropathy may occur [3][4].

On the other hand, Maturity-onset diabetes of the young (MODY) is a rare monogenic form of diabetes resulting from mutations in specific genes, most prominently HNF1A, HNF4A, and GCK, which play an important role in insulin secretion [5]. In addition to having a positive family history of the condition, people with MODY frequently have non-insulin-dependent diabetes that was discovered earlier in life, frequently before the age of 25. This distinguishes it from type 1 and type 2 diabetes, which are more prevalent [6][7]. Although MODY is a disorder of insulin secretion, an important feature is the presence of normal insulin sensitivity differentiating it from the insulin resistance as seen in conditions like Cushing's syndrome [7][8].

The coexistence of Cushing's syndrome and MODY creates a particularly difficult clinical picture. Both conditions are known to affect glucose metabolism: Cushing's syndrome exercises its primarily cortisol-induced insulin resistance; MODY, on the other hand, does so through faulty secretion of insulin due to identified genetic mutations [9]. Significantly, clinicians know both the genetic information and the pathophysiology and clinical implications of both diseases to formulate effective treatment strategies [10]. The main aim of this review is to explore the genetic, molecular, and clinical interactions between Cushing’s syndrome and MODY, as well as management approaches that could optimize patient care in such complex cases [11] [12].

2. Pathophysiology and Genetic Insights

2.1 Cushing’s Syndrome

Cushing's Syndrome is defined by chronic hypercortisolism resulting from hypothalamic-pituitary-adrenal (HPA) axis dysfunction [13] . This condition usually arises from an excess of a hormone known as a, or by adrenal tumors that produce cortisol on their own. Cortisol stimulates hepatic gluconeogenesis, reduces glucose absorption in peripheral tissues, and promotes insulin resistance, all contributing to hyperglycemia and metabolic disorders. and [14]. It also promotes lipolysis and proteolysis, ultimately leading to muscular atrophy and central fat accumulation. These characteristics are been linked to obesity and a higher risk of cardiovascular disease. Hypercortisolism activates glucocorticoid receptors (GRs), leading to reduced β-cell function, oxidative stress, and disruption of transcriptional pathways. Genetic mutations, such as USP8 mutations in cor adenomas, increase ACTH release by influencing the ubiquitin-proteasome pathways. Furthermore, mutations in

CTNNB1 and NR3C1 in adrenal Cushing's disease induce carcinogenesis and interfere with cortisol release. Cortisol-induced epigenetic changes metabolic dysfunction by altering insulin sensitivity or gene expression [15].

2.2 Maturity-Onset Diabetes of the Young 3 (MODY3)

Mutations in the HNF1A gene, which codes for a transcription factor necessary for the formation of pancreatic β-cells and glucose-stimulated insulin production, result in MODY3. Reduced β-cell function results from these mutations, which interfere with the expression of genes such SLC2A2 that are important in glucose transport and glycolysis. Clinically, MODY3 differs from type 1 diabetes in that it is an autosomal dominant disorder that manifests early and lacks autoimmunity. Since patients usually have decreased β-cell activity, they respond very well to sulfonylurea therapy, which is a crucial tactic for increasing insulin release. Novel HNF1A mutations have been linked in studies to a variety of symptoms, such as dynamic hyperglycemia and reduced insulin secretion. Reduced glucose tolerance is the outcome of these mutations' effects on transcriptional regulation as well as other metabolic pathways [16].

2.3 Shared Molecular Pathway

The pathophysiology elements of Cushing's syndrome and MODY3 are similar, especially when it comes to insulin resistance and β-cell dysfunction. In Cushing's syndrome, chronic hypercortisolism worsens oxidative stress and inflammation, which further reduces β-cell survival and exacerbates the genetic abnormalities linked to MODY3. Glucocorticoids exacerbate metabolic disorders by interfering with insulin signaling pathways, including those impacted by mutations in the HNF1A gene. Furthermore, changes in transcriptional activity brought on by cortisol might impact the expression of important metabolic genes, resulting in a feedback loop that worsens insulin resistance and hyperglycemia. When Cushing's Syndrome and MODY3 coexist, the confluence of these molecular elements points to a synergistic impact that raises the metabolic burden and makes clinical management more difficult [17].

3. Clinical Manifestations and Diagnostic Challenges

Cushing's disease and MODY can be challenging to distinguish due to their similar clinical features. Despite differing causes, hyperglycemia is a common symptom in both disorders. In Cushing's syndrome, glucocorticoids lead to insulin resistance, which is worsened by raised cortisol levels, ultimately causing hyperglycemia [17]. Blood glucose levels rise as a result of elevated cortisol interacting with insulin's capacity to promote the absorption of glucose in peripheral tissues [1]. On the other hand, hyperglycemia in MODY is mostly caused by decreased insulin production as a result of mutations in genes like HNF1A or HNF4A that are linked to pancreatic beta-cell function. It is essential to comprehend the variations in the underlying causes of hyperglycemia in order to properly identify and treat it. Both Cushing's disease and Maturity-Onset Diabetes of the Young (MODY) frequently present with central obesity, albeit the traits and degree of the obesity can differ greatly between the two conditions. Elevated levels of cortisol in Cushing's syndrome encourage the buildup of

abdominal fat, leading to visceral obesity, which frequently shows up as muscle atrophy and a round face. Although it may not be as noticeable, obesity in MODY is typically caused by abnormal glucose metabolism. While MODY3 individuals may have substantial weight gain, this is usually less serious and less noticeable than the obesity linked to Cushing's disease [18].Hypertension is another common aspect of both illnesses. The main cause of hypertension in Cushing's syndrome is increased cortisol levels, which raise vascular resistance by encouraging salt and fluid retention, ultimately resulting in high blood pressure [19]. Vascular tone, blood flow, pressure regulation, and hypertension-which mostly results from aberrant glucose metabolism-can all be impacted by insulin resistance and blood glucose abnormalities in MODY [20].

4. Challenges in Distinguishing Primary from Secondary Metabolic Effects

It might be especially challenging to distinguish between primary and secondary metabolic abnormalities in patients who have both Cushing's syndrome and MODY. Although the underlying causes of both disorders are different, they can have comparable metabolic effects, including insulin resistance, dyslipidemia, and improper glucose control. The main abnormality in Cushing's syndrome is an overabundance of cortisol, which directly results in insulin resistance, elevated blood sugar, and fat storage [21]. MODY, on the other hand, is mostly an insulin secretion condition brought on by genetic abnormalities in particular genes, such as HNF1A, HNF4A, and GCK. Hyperglycemia and possible weight gain are caused by these mutations' decreased insulin production [22]. Therefore, a thorough diagnostic work-up is necessary to determine if metabolic dysfunction is caused by genetic abnormalities in insulin secretion or high cortisol.

The problem is made worse by the possibility that people with both disorders share characteristics of the metabolic syndrome, such as abdominal obesity, dyslipidemia, and hypertension. Because of this overlap, in order to properly differentiate between the primary and secondary metabolic consequences, doctors must take into account both the biochemical and genetic elements of the disorders [23]. When Cushing's syndrome and MODY coexist, doctors must treat the genetic abnormalities influencing insulin secretion and the excess cortisol at the same time, which might make treatment plans more difficult [24].

5. Biochemical Tests in Diagnosis

5.1 Diagnosis of Cushing’s Syndrome

The diagnosis of Cushing’s syndrome relies on biochemical testing to assess abnormal cortisol secretion patterns and elevated cortisol and adrenocorticotropic hormone (ACTH) levels. A common diagnostic approach involves a 24-hour urine free cortisol test, which helps confirm the diagnosis by detecting excessive cortisol production. Several other biochemical tests are necessary to detect hypercortisolism, a key feature of Cushing’s syndrome. These tests provide crucial information that differentiates Cushing’s syndrome from other endocrine disorders and allow clinicians to determine the most appropriate treatment approach [25].

5.2 Genetic Screening for MODY Diagnosis

Maturity-Onset Diabetes of the Young (MODY) is diagnosed primarily through genetic screening, which identifies mutations in key genes such as HNF1A, HNF4A, or GCK that regulate insulin secretion. Genetic testing plays an essential role in distinguishing MODY from type 1 and type 2 diabetes, both of which have distinct causes and physiological mechanisms. By identifying specific mutations, clinicians can implement targeted treatment strategies that improve patient outcomes. The ability to accurately diagnose MODY through genetic screening is essential for ensuring effective disease management and reducing the risk of unnecessary treatment with insulin or other therapies that may not be appropriate for MODY patients [26].

5.3 Imaging Techniques for Identifying Cushing's Syndrome

Imaging techniques are fundamental in identifying the underlying cause of hypercortisolism in Cushing's syndrome. Computed tomography (CT) and magnetic resonance imaging (MRI) are widely used to detect pituitary or adrenal tumors, which are the most common sources of excessive cortisol production. Identifying the tumor's location through imaging allows clinicians to determine the most appropriate course of treatment, which may include surgical removal, pharmacological therapy, or radiation-based interventions. These imaging modalities provide crucial information that guides decision-making and helps tailor treatment approaches to the patient's specific condition [27].

5.4 Genetic Counseling and Targeted Therapy for MODY

Genetic testing remains the most reliable method for diagnosing MODY3, a subtype primarily associated with mutations in the HNF1A gene. Early identification of these mutations allows for timely initiation of sulfonylurea therapy, which enhances insulin secretion and significantly improves glycemic control [28]. However, it is important to recognize that sulfonylureas are ineffective for managing hyperglycemia caused by Cushing's syndrome, highlighting the importance of differentiating between these conditions. Genetic counseling is highly recommended for patients and their families to provide guidance on treatment options, educate them on inheritance patterns, and facilitate early screening for at-risk family members [29].

6. Treatment Strategies and Management

6.1 Management of Cushing's Syndrome

The treatment of Cushing's syndrome requires a comprehensive approach involving surgical, pharmacological, and radiation-based interventions. The primary goal of treatment is to normalize cortisol levels and prevent the metabolic complications associated with hypercortisolism, such as insulin resistance, hypertension, and osteoporosis. The choice of treatment depends on the underlying cause of the disorder and the patient's overall health status [30].

6.1.1 Surgical Interventions

Surgical treatment is often the preferred approach when Cushing's syndrome is caused by a pituitary or adrenal tumor. Transsphenoidal adenoma resection is the first-line surgical

treatment for pituitary-dependent Cushing's disease, with success rates reaching up to 80% depending on tumor characteristics and surgical expertise. In cases of primary adrenal Cushing's syndrome, laparoscopic adrenalectomy is the preferred approach, particularly when adrenal adenomas or hyperplasia are present. When Cushing's syndrome is caused by ACTH-secreting tumors, such as those found in small-cell lung carcinoma, tumor resection is performed whenever feasible to address excess ACTH production [31].

6.1.2 Pharmacological Management

For patients who are not candidates for surgery or those with recurrent disease, pharmacological therapy is used to suppress cortisol production or block its effects. Steroidogenesis inhibitors, such as ketoconazole, metyrapone, and osilodrostat, inhibit cortisol biosynthesis and help reduce systemic hypercortisolism [32]. Glucocorticoid receptor antagonists, such as mifepristone, effectively block cortisol action and improve glucose metabolism and insulin sensitivity, making them particularly beneficial for patients with concurrent diabetes [33]. Pituitary-directed therapies, such as pasireotide, a somatostatin analog, have shown efficacy in suppressing ACTH secretion, particularly in patients with persistent or recurrent disease. Metformin has also been explored as an adjunct therapy to counteract glucocorticoid-induced insulin resistance and dyslipidemia, which are common metabolic complications in Cushing's syndrome [34].

6.1.3 Radiation-Based Interventions

Radiation therapy is considered in cases where surgery is not feasible or when tumors recur despite initial surgical intervention. Stereotactic radiosurgery, such as Gamma Knife and Cyber Knife, provides targeted therapy for persistent pituitary tumors and is particularly beneficial for patients who are not candidates for conventional surgery [35]. Conventional radiotherapy is another option for treating refractory Cushing's disease, but it has delayed therapeutic effects and carries the risk of hypopituitarism, which must be carefully managed [36].

6.2 Management of MODY3

6.2.1 Pharmacological Treatment

The management of MODY3 focuses on optimizing glycemic control through targeted pharmacological therapy. Sulfonylureas, such as gliclazide and glimepiride, are the first-line treatment for MODY3 patients due to their high sensitivity to insulin [37][38]. These medications enhance insulin secretion and provide long-term glycemic control, reducing the need for insulin therapy in most patients [39]. However, in cases where beta-cell function progressively declines and sulfonylureas become ineffective, insulin therapy is initiated to prevent long-term complications [40][41][42].

6.2.2 Lifestyle and Dietary Management

A carbohydrate-moderate diet is recommended for patients with MODY3 to prevent glucose fluctuations and postprandial spikes [43]. Unlike type 2 diabetes, MODY3 is not significantly influenced by lifestyle factors, but regular physical activity can enhance insulin secretion efficiency and contribute to overall metabolic health [44].

6.2.3 Genetic Counseling and Family Screening

Given that MODY3 follows an autosomal dominant inheritance pattern, genetic testing and counseling are essential for early diagnosis and screening of family members. Early identification of MODY3 in asymptomatic relatives allows for timely intervention and appropriate disease management, reducing the risk of complications [45].

7. Integrated Approach to Managing Cushing's Syndrome and MODY3

7.1 Challenges in Dual Management

Managing patients with both Cushing's syndrome and MODY3 presents unique challenges due to the contrasting metabolic effects of these conditions [46]. Cushing's syndrome induces insulin resistance due to hypercortisolism, whereas MODY3 is characterized by defective insulin secretion [47]. These opposing metabolic mechanisms complicate the clinical approach to diagnosis and treatment. Since both conditions can cause hyperglycemia, differentiating between cortisol-induced diabetes and MODY3 requires a combination of genetic screening and biochemical markers [48].

7.2 Optimized Treatment Strategy

An effective treatment strategy for patients with both conditions requires a multidisciplinary approach involving endocrinologists, geneticists, and diabetes specialists. Cortisol levels must be stabilized first through surgery, medication, or radiation therapy before addressing MODY3-related hyperglycemia with sulfonylureas. Long-term monitoring of cortisol levels, glucose metabolism, and genetic markers such as HNF1A mutations is essential for tracking disease progression and optimizing treatment strategies. An integrated, patient-centered approach ensures the best possible outcomes by stabilizing metabolic function and preventing long-term complications associated with both conditions [49][50].

8. Research Gaps and Future Directions

Despite advances in understanding Cushing's syndrome and MODY3, several key areas remain under-explored. First, while initial studies have shed light on how glucocorticoid signaling may influence pancreatic beta-cell function, the precise molecular mechanisms linking hypercortisolism to impaired insulin secretion are not yet fully understood [51][52]. In addition, long-term clinical outcomes following various treatment strategies remain poorly characterized. There is a need for robust longitudinal studies to determine how sustained cortisol excess affects metabolic, cardiovascular, and overall health over time [53] [54].

Equally important is the recognition of heterogeneity within patient populations. Emerging evidence suggests that genetic and epigenetic variations might contribute to differences in disease severity and treatment response, yet these factors have not been comprehensively mapped [55] [56].

The potential for personalized medicine is particularly promising. Enhanced genetic screening and biomarker discovery could soon allow clinicians to classify patients more accurately by risk profile and guide individualized treatment choices [57] [58]. Early

detection of specific genetic mutations associated with MODY3, combined with a detailed clinical phenotype, may facilitate more targeted therapeutic interventions and better predict complications [59]. In the long run, integrating molecular profiles with clinical data holds the promise of tailoring treatment regimens to individual needs, thereby improving outcomes and quality of life [60] [61].

Looking forward, future research should prioritize : Clarifying the molecular interactions between cortisol signaling and beta-cell dysfunction, including the role of novel genetic modifiers, remains a crucial area of research [62][63]. Additionally, conducting multicenter, long-term studies is essential to evaluate the impact of different treatment modalities on metabolic and cardiovascular outcomes [64][65]. The development and validation of integrated treatment algorithms that incorporate genetic, biochemical, and imaging data could pave the way for truly personalized care [66][67]. Further exploration of new therapeutic agents targeting specific molecular pathways involved in endocrine disorders may lead to more effective treatment options . Lastly, assessing the clinical and economic benefits of cascade genetic testing in broader patient populations could help optimize disease management and early intervention strategies [68].

By addressing these gaps, future work can not only refine our understanding of the underlying biology but also pave the way for more effective, individualised management strategies for patients with Cushing's syndrome and MODY3 [69].

9. Conclusions

This review dissects the intertwined roles of endocrine disruption and genetic mutations in shaping the clinical course of Cushing's syndrome and MODY3. The discussion from the molecular mechanisms of hypercortisolism to the specific genetic alterations in HNF1A demonstrates that these conditions are not isolated phenomena but interrelated facets of a broader metabolic challenge. By unraveling how cortisol excess drives insulin resistance and disrupts metabolic homeostasis-and contrasting that with the beta-cell dysfunction seen in MODY3-a clear picture emerges: integrating clinical, biochemical, and genetic insights can greatly enhance diagnostic precision and treatment outcomes. Endocrinologists can benefit from incorporating genetic testing into their standard evaluations, ensuring that patients receive an assessment that captures both hormonal imbalances and genetic predispositions. Meanwhile, geneticists are presented with the opportunity to contextualize molecular findings within clinical practice, paving the way for targeted therapies that are attuned to individual patient profiles.

Ultimately, this integrated perspective underscores that effective management of these complex disorders demands a collaborative approach. The convergence of endocrinology and genetics is not merely an academic exercise; it is a practical strategy for developing personalized interventions that address the unique challenges faced by patients with Cushing's syndrome and MODY3.

10. Abbreviation

ACTH - Adrenocorticotropic Hormone

CT - Computed Tomography

CTNNB1 - Catenin Beta 1
GCK – Glucokinase
GRs - Glucocorticoid Receptors
HNF1A - Hepatocyte Nuclear Factor 1 Alpha
HPA - Hypothalamic-Pituitary-Adrenal
MODY - Maturity-Onset Diabetes of the Young
MRI - Magnetic Resonance Imaging
NR3C1 - Nuclear Receptor Subfamily 3 Group C Member 1
SLC2A2 - Solute Carrier Family 2 Member 2
USP8 - Ubiquitin-Specific Peptidase 8

11. Conflict of Interest

There was no funding or conflict of interest related to this work.

12. Author Contribution

All the authors have played significant role in this work.

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