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A Review on 5-Hydroxyindoleacetic acid (5-HIAA) in Urine: Diagnostic and Therapeutic Implications for Carcinoid Tumours

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ABSTRACT

5-Hydroxyindoleacetic acid (5-HIAA), the main urinary metabolite of serotonin, is a key biomarker in diagnosing and managing carcinoid tumours. These neuroendocrine tumours, often originating from enterochromaffin cells in the gastrointestinal tract, frequently secrete excess serotonin. After hepatic metabolism, serotonin converts to 5-HIAA, which is excreted in urine. Measuring urinary 5-HIAA provides a non-invasive, cost-effective, and reliable method for detecting functional carcinoid tumours and monitoring disease progression or response to therapy. This review discusses the clinical significance of 5-HIAA, its application in routine monitoring, and factors affecting test accuracy, including diet, medications, renal function, and tumour burden. It also highlights improved detection techniques like high-performance liquid chromatography and LC-MS. Case studies illustrate 5-HIAA's practical clinical value, while alternative biomarkers such as chromogranin A and pancreatic polypeptide are explored. The article concludes by addressing diagnostic challenges and future directions in neuroendocrine tumour biomarker research and clinical practice.

Keywords: 5-Hydroxyindoleacetic acid (5-HIAA), Carcinoid tumours, Serotonin, Neuroendocrine.

INTRODUCTION

Carcinoid tumours, a subset of neuroendocrine neoplasms, are characteristically slow-growing but clinically significant due to their potential for hormone secretion and metastatic behaviour. Among the bioactive substances released by these tumours, serotonin (5-hydroxytryptamine, 5-HT) plays a pivotal role in the manifestation of carcinoid syndrome, a complex of symptoms including flushing, diarrhoea, and bronchospasm[1]. The primary metabolite of serotonin, 5-hydroxyindoleacetic acid (5-HIAA), is excreted in the urine and serves as a crucial biomarker for both the diagnosis and

monitoring of carcinoid tumours, particularly those of midgut origin.

The quantification of urinary 5-HIAA offers a non-invasive, reliable means of assessing serotonin production and tumour burden[2]. Elevated levels of 5-HIAA are often indicative of functioning carcinoid tumours and are frequently correlated with the severity of carcinoid syndrome. As such, 5-HIAA testing holds significant value in the initial workup, longitudinal disease monitoring, and assessment of therapeutic efficacy in patients undergoing treatment for neuroendocrine tumours (NETS)[3]. While it has proven clinical utility, the interpretation of 5-HIAA results requires strong consideration of dietary influence, drug interference and renal function, which can confound the accuracy of the diagnostic test[4]. This review aims to precisely dig into biochemical rationale, methodological features and clinical significance of urinary 5-HIAA determinations in carcinoid tumours. It further reviews recent developments in analytical methodologies, the function of 5-HIAA in informing decisions regarding treatment options, and new strategies to integrate biochemical markers with imaging and histopathology for improving diagnostic accuracy and treatment success in neuroendocrine cancer.

Biochemistry and Metabolism of 5-hiaa

5-Hydroxyindoleacetic acid (5-HIAA) is the primary urinary metabolite of serotonin, a prominent neurotransmitter and vasoactive amine involved in diverse physiological processes, including mood regulation, gastrointestinal motility and vascular homeostasis[5]. The synthesis of 5-HIAA starts with the essential amino acid tryptophan, which is converted to 5-hydroxytryptophan (5-HTP) by the enzyme tryptophan hydroxylase (TPH). This intermediate is then decarboxylated by aromatic L-amino acid decarboxylase (AAAD) to generate serotonin (5-HT)[6].

In carcinoid tumours, especially those arising from the gastrointestinal tract's enterochromaffin cells, serotonin is overproduction due to dysregulated expression of TPH and other enzymes involved in the serotonin biosynthetic pathway. Unlike normal physiology, where most serotonin is metabolised locally, in carcinoid tumours, large amounts of serotonin can spill into the systemic circulation, especially in cases with liver metastases that bypass hepatic first-pass metabolism[7]. Serotonin is subsequently inactivated in the liver, lungs, and other tissues through oxidative deamination by monoamine oxidase (MAO) to produce 5-hydroxyindoleacetaldehyde, which is further oxidised by aldehyde dehydrogenase (ALDH) to form 5-HIAA. This water-soluble compound is then excreted in the urine[8].

The rate of 5-HIAA excretion reflects the systemic serotonin load and is typically measured over a 24-h urine collection. Under normal conditions, urinary 5-HIAA levels remain low (typically less than 8 mg/24 h in adults). However, in patients with functioning carcinoid tumours, these levels can be significantly elevated, often exceeding 25–50 mg/24 hours[9].

For the clinical application of these, it is crucial to understand the metabolic pathway of 5-HIAA. Changes due to hepatic function, monoamine oxidase activity, and dietary intake of serotonin-rich foods (e.g., bananas, avocados, and walnuts) can affect 5-HIAA levels and should be considered in the context of test results. Several drugs may also impact the metabolism of serotonin or the accuracy of the urinary assay, including drugs to treat depression (e.g., SSRIS, MAO inhibitors), acetaminophen, and cough syrups[10]. Biochemical underpinnings of serotonin metabolism to 5-HIAA explain the basis of using this metabolite as a diagnostic and prognostic biomarker in carcinoid tumours[11]. For 5-HIAA to be used clinically effectively, it is important to have a clear understanding of the enzymatic pathways and physiological variables that cause variations in 5-HIAA levels. Serotonin (5-hydroxytryptamine, 5-HT) is produced in enterochromaffin cells from the amino acid tryptophan. When secreted into the bloodstream, serotonin is quickly catabolized in the liver through the action of monoamine oxidase (MAO) to give rise to 5-hydroxyindoleacetaldehyde, which is oxidised by aldehyde dehydrogenase to give 5-HIAA[12]. The kidneys eliminate 5-HIAA, and its urinary measurement serves as an accurate measurement of serotonin metabolism.

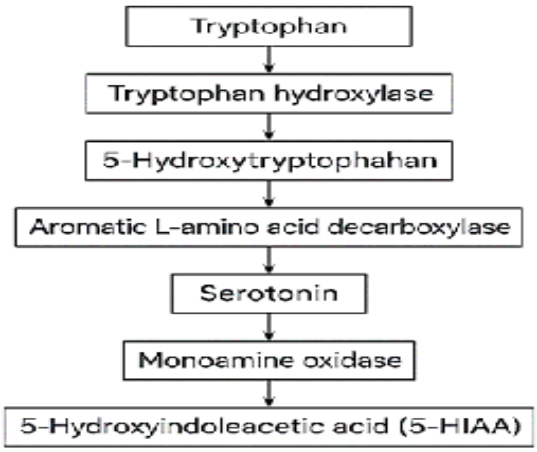

Fig. 1. Pathway of serotonin metabolism leading to 5-HIAA formation[13]

Diagnostic Utility of 5-HIAA measurement

The measurement of 5-hydroxyindoleacetic acid (5-HIAA), a major metabolite of serotonin, is of quintessential importance in the diagnostic workup of neuroendocrine tumours, especially as it relates to carcinoid tumours. Being a relatively stable and quantifiable biomarker, 5-hydroxyindole acetic acid acts as a non-invasive marker for serotonin overproduction, a hallmark of many carcinoid tumours[14]. Increased urinary excretion of 5-HIAA can offer robust biochemical confirmation for the clinical suspicion of the presence of a carcinoid and direct further imaging or histological evaluation. In addition, the specificity of this marker for serotonin-producing endogenous tumours makes it particularly useful in distinguishing between these and other gastrointestinal or endocrine conditions that can present with indistinguishable symptoms[15].

Screening and Early Detection

Urinary 5-HIAA measurement is also commonly used as a first-line screening test in patients reporting symptoms compatible with carcinoid syndrome (flushing, diarrhoea, bronchospasm). Very high levels of 5-HIAA, typically > 25 mg/24 h, are strongly suggestive of serotonin-secreting carcinoid tumours (s). If counselled as part of this test, early detection can lead to early intervention, significantly improving prognosis. In patients with metastatic neuroendocrine tumours, when early biochemistry confirmation can lead to faster imaging studies and therapeutic planning, it is particularly useful. Elevations of 5-HIAA may also assist in routine post-operative screening for recurrence or progression in high-risk patients[16].

Differentiation from Other Conditions

Several gastrointestinal and endocrine conditions, including inflammatory bowel disease, irritable bowel syndrome, and pheochromocytomas, can share clinical findings, with similarities including abdominal pain, diarrhoea, and episodic flushing. Yet these conditions usually don't lead to increased 5-HIAA levels. Thus, 5-HIAA measurement can also be a useful means of differentiating carcinoid tumours from these mimicking conditions. Although dietary influences or specific drugs can yield a false positive, the test is highly specific when appropriately controlled. This allows clinicians to avoid misdiagnosis and to make sure that patients receive the appropriate diagnostic work-up and treatment[17-18].

Testing Methodology

The 5-HIAA test must be performed following specific guidelines to ensure accuracy. The gold standard consists of 24 h urine collection, which offers a cumulative assessment of 5-HIAA excretion over time, thus improving reliability and reducing the effect of diurnal variation[19]. Patients should not consume foods high in serotonin (bananas, walnuts, avocados and tomatoes) or take certain medications (acetaminophen or cough suppressants) for a minimum of 72 h before and throughout the collection period to avoid false-positive results. Due to the sensitivity and specificity required for quantification, analytical methods such as HPLC and LC-MS are the preferred measures. Accurate determination of 5-HIAA versus potentially cross-reacting examinations can be achieved by these specialised analytical techniques, thus minimising analytical errors, ensuring a reliable diagnosis[20].

Factors Influencing 5-HIAA Levels

5-HIAA is, however, not without its limitations as a biomarker to detect serotonin-secreting tumours, and the diagnostic accuracy can be prone to variation from physiological, pharmacological, and pathological interference. It is important to know how to describe these influences to avoid false positives and negatives when testing[21]. The interpretation of elevated or borderline 5-HIAA levels should include consideration of clinical variables, including diet, medications, renal function, and tumour biology. Without that kind of context, there's a danger of misdiagnosis or unnecessary additional testing. In those with neuroendocrine tumours, it is imperative to ensure that proper patient

preparation has taken place and a complete clinical history has been obtained to indicate the reliability of 5-HIAA as a diagnostic and monitoring tool[22].

Several physiological and external factors can impact 5-HIAA concentrations.

Dietary Influences

Certain foods are naturally high in serotonin and can significantly elevate urinary 5-HIAA levels, leading to false-positive results. Examples include bananas, pineapples, avocados, eggplants, tomatoes, and walnuts. These foods contain either serotonin or its precursors, which can be metabolised into 5-HIAA and excreted in urine. For accurate testing, patients are advised to follow dietary restrictions and avoid these serotonin-rich items for at least 72 h before and during the urine collection period. Failure to adhere to dietary recommendations can obscure the true clinical picture and lead to incorrect assumptions about the presence of a carcinoid tumour[23].

Medications

Numerous medications can interfere with serotonin metabolism and, consequently, affect 5-HIAA levels. Selective serotonin reuptake inhibitors (SSRIS), used to treat depression and anxiety, increase serotonin availability and can elevate 5-HIAA excretion. Monoamine oxidase inhibitors (MAOIS) and certain over-the-counter cough medications (like those containing dextromethorphan) may also alter serotonin dynamics. These pharmacologic agents can either mimic the biochemical effects of carcinoid tumours or interfere with analytical detection, compromising the specificity of the test. A thorough review of the patient's medication history is essential, and in some cases, temporary discontinuation may be recommended under medical supervision to obtain valid test results[24].

Renal Function

Renal impairment, especially in chronic kidney disease (CKD), can lead to reduced excretion of 5-HIAA, resulting in falsely low urinary levels. Since 5-HIAA is primarily cleared through the kidneys, compromised renal function may mask elevated systemic serotonin turnover in patients with carcinoid tumours. This can be particularly problematic in patients with both CKD and suspected neuroendocrine neoplasms, as underestimation of tumour activity may delay diagnosis or affect treatment planning. Interpretation of 5-HIAA results in such patients should be approached cautiously, with renal function tests considered alongside biomarker levels. Alternative or adjunctive testing may be required for accurate assessment[25].

Tumour Differentiation

The degree of tumour differentiation significantly influences serotonin production and, by extension, 5-HIAA levels. Well-differentiated carcinoid tumours often produce large quantities of serotonin, leading to markedly elevated 5-HIAA excretion. In contrast, poorly differentiated or non-functioning neuroendocrine tumours may produce little to no serotonin, resulting in normal or only slightly elevated levels. Therefore, a normal 5-HIAA test does not exclude the presence of a neuroendocrine tumour, especially in atypical or aggressive subtypes. Clinicians must integrate 5-HIAA results with histopathology, imaging, and other tumour markers to achieve a comprehensive and accurate diagnosis[26].

5-HIAA in therapy monitoring

In addition to its diagnostic role, 5-HIAA is used for therapeutic monitoring. 5-Hydroxyl indole acetic acid (5-HIAA) is a composite measure of the 4 molecules associated with serotonin metabolism (5-Hydroxytryptophan, 5-HIAA, serotonin, and tryptophan) and, therefore, can provide insight into the biochemical response to treatment over time in patients with serotonin-secreting carcinoid tumours. 5-HIAA levels decreasing is suggestive of effective tumour suppression, while persistently elevated or increasing levels could represent resistance to treatment or tumour recurrence. As such, 5-HIAA is not only a static diagnostic marker but also a dynamic measure of treatment effectiveness that can inform continuing clinical management. 5-HIAA is also addressed via monitoring over time to ensure modification of treatment strategies, leading to improved patient outcomes[27].

Assessing Treatment Response

Monitoring 5-HIAA levels is important in assessing a patient's response to several therapeutic options, such as surgical resection, somatostatin analogues (octreotide or lanreotide), chemotherapy, and peptide receptor radionuclide therapy (PRRT). The decrease of 5-HIAA correlates with decreased

tumour burden and symptomatic relief, especially in carcinoid syndrome, and after treatment, can be significant. In surgical patients, the normalisation of 5-HIAA level after resection is associated with a favourable prognosis, while post-resection re-elevation of 5-HIAA may suggest persistence or recurrence of the disease. Therefore, fluctuations in 5-HIAA are an excellent and sensitive biochemical indicator of treatment response, frequently preceding changes apparent on imaging studies[28].

Prognostic Value

A consistent elevation of 5-HIAA, despite the start of therapy, may indicate a poor prognosis. These findings can reflect persistent tumour biology, metastatic disease, or the emergence of resistance to standard treatment approaches, such as somatostatin analogues. That allows clinicians to predict disease progression and devise more aggressive or alternative interventions. 5-Hydroxyindole Acetic acid Deficiency. Sustained high 5-HIAA levels are found in typical carcinoid syndrome, and they have been associated with the risk of complications, including carcinoid heart disease. As such, 5-HIAA becomes not only a tool to monitor response but also a vital biomarker for long-term prognostication and monitoring planning[29].

Emerging Therapeutic Approaches

More recently, emerging therapies, like the peptide receptor radionuclide therapy (PRRT) using targeting agents like Lutetium-177 DOTATATE, exhibit promising results in lowering 5-HIAA levels among advanced neuroendocrine tumour patients. PRRT, which targets somatostatin receptors on tumour cells, can decrease serotonin production, leading to improved symptom control. Biochemical and radiologic responses have been shown in clinical trials of PRRT, which is an important addition to the therapeutic toolbox. Now, the current open studies are aimed at combining PRRT with immunotherapies and molecular-targeted agents, which will make the role of 5-HIAA as a biomarker for assessment of the treatment response on multi-modality even more prominent[30].

Advances in 5-HIAA detection

With clinical and technological advancements, 5-HIAA testing has become much more accurate, reliable, and accessible. The old methods, although effective, took time and were susceptible to analytical variation. The newer platforms allow for rapid, highly sensitive, and specific detection of 5-HIAA in biological fluids[31]. Key innovations, including automated high-performance liquid chromatography (HPLC) and liquid chromatography-mass spectrometry (LC-MS), have simplified lab workflows and reduced pre-analytical errors. So, also point-of-care (POC) testing and dare biomarker multiplex panels research intend to make diagnosing neuroendocrine tumours easier, thus making biochemical surveillance easier for the patient[32].

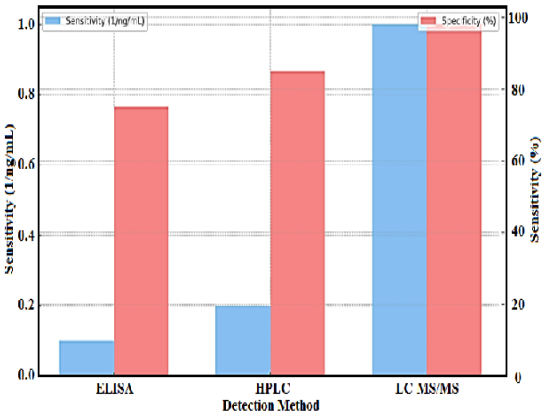

Fig. 2. Comparing the sensitivity and specificity of ELISA, HPLC, and LC-MS/MS for 5-HIAA detection

Automated HPLC and LC-MS Techniques

In general, automated HPLC and LC-MS/MS systems are an important advancement in 5-HIAA quantification. Compared to older colourimetric assays, these methods provide improved analytical performance, such as elevated resolution, low detection limits, and lower cross-reactivity. Automation of the sample preparation and analysis steps minimises the possibility of manual errors and improves the throughput, which is crucial for high-volume clinical laboratories[33]. LC-MS, specifically, can distinguish 5-HIAA from similarly structured substances with a very high level of specificity. Consequently, such approaches are now ubiquitous in reference laboratories and clinical practice and have become the new gold standard for 5-HIAA testing.

Point-of-care testing Developments

Emerging point-of-care (POC) technologies aim to provide rapid and reliable 5-HIAA results in outpatient or bedside settings. Though not yet widely implemented, prototype devices based on immunoassays or biosensor platforms are being

laboratory-based diagnostics for more streamlined patient care[34].

Alternative Biomarkers

While 5-HIAA remains the most established marker for serotonin-producing tumours, alternative and complementary biomarkers are being explored to improve diagnostic and prognostic accuracy. Chromogranin A (Cga) is frequently elevated in various neuroendocrine tumours and offers broader diagnostic utility, though its specificity is limited[35]. Neurokinin A has shown promise in assessing tumour progression, particularly in midgut carcinoids. Combining these markers with 5-HIAA may enhance sensitivity and provide a more comprehensive biochemical profile. Ongoing research is focused on validating these biomarkers in large patient cohorts and integrating them into multimodal diagnostic algorithms[36].

CONCLUSION

Urinary 5-HIAA measurement remains a cornerstone in the diagnosis, monitoring, and management of carcinoid tumours, particularly those associated with serotonin overproduction. Its high specificity makes it a reliable biomarker for confirming serotonin-secreting neuroendocrine tumours and tracking disease progression. Nonetheless, as its diagnostic utility can be affected by various environmental factors, such as diet and drugs, the specimen collection should be undertaken with the utmost care, and correct interpretation should consider lifestyle considerations. Improvements in analytical methods with high-performance liquid chromatography and liquid chromatography-mass spectrometry have improved the detection of 5-HIAA. New treatments such as peptide receptor radionuclide therapy (PRRT) have emerged and have shown substantial decreases in 5-HIAA levels correlating with therapeutic response. Although these treatment options did exist, there remains a need for further research to refine the prognostic value of 5-HIAA during long-term therapy, as well as to validate emerging biomarkers like chromogranin A and neurokinin A for a more holistic approach to the management of neuroendocrine tumours. A multimodal approach encompassing biochemical, imaging, and clinical data will be fundamental in optimising outcomes for patients with carcinoid tumours.

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Conflict of Interest: None

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