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Insights of Metabolomics in Human Calcium Metabolism Disorders

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Abstract

Calcium is involved in many physiological processes, including intracellular signalling, metabolism regulation, muscle contraction, and gene expression. The majority of calcium in the human body (up to 99%) is found in bones as calcium hydroxyapatite [$Ca_{10}(PO_4)6(OH)_2$], with less than 1% found in extracellular fluids. The most active form of calcium in extracellular fluids is the free ionised fraction, which directly interacts with calcium channels, calcium-sensing receptors (CaSRs), and cell membranes. The gastrointestinal tract, bones, and kidneys are primarily responsible for the physiological maintenance of calcium levels. The parathyroid gland produces parathormone (PTH), which regulates calcium within narrow limits by increasing calcium absorption in the intestine, bone-calcium mobilisation, and calcium reabsorption by the kidneys. Calcium ions are thought to be the primary physiological regulators of PTH secretion through CaSRs. As a result, patients with hyperparathyroidism and hypercalcemia have lower CaSR expression in parathyroid gland tissue. However, the effect of other factors, such as L-amino acids, on CaSRs was also observed. Calcium concentration deviations above or below the normal range are now more frequently diagnosed than in the past, owing primarily to increased access to laboratory tests in developed countries. Calcium disorders are classified as hypocalcemia or hypercalcemia, and they frequently coexist with other serum biochemical abnormalities such as phosphate, alkaline phosphatase (ALP), PTH, fibroblast growth factor 23, and vitamin D levels.

Keywords: Calcium ions • Hypercalcemia • Hyperparathyroidism

Introduction

Hypercalcemia is commonly caused by cancer and primary hyperparathyroidism (PHPT). PHPT is a common endocrine neoplastic disorder characterised by autonomous PTH production and a wide range of pathophysiological consequences. It can occur sporadically or as a hereditary familial abnormality. The phenotypic diversity of PHPT clinical presentation may be due to parathyroid tumour subclasses with distinct molecular profiles. Familial hypocalciuric hypercalcemia (FHH), like PHPT, is a condition that causes hypercalcemia and PTH elevation. Nonetheless, FHH is a rare inherited disorder caused by a CaSRs mutation. Hypocalcemia occurs in vitamin D deficiency and hypoparathyroidism due to irreversible parathyroidectomy, congenital disabilities, or radiation damage.Changes in calcium levels can cause a wide range of symptoms, including skeletal anomalies, nephrolithiasis, and muscle spasms. This frequently has an impact on patients' quality of life, and despite the high demand for novel methods of diagnosis and treatment, medical approaches to calcium metabolism disorders frequently pose a significant diagnostic challenge. Functional analyses are becoming more popular. Among these is metabolomics, which is the comprehensive examination of the entire metabolome. Using modern analytical chemistry techniques, this discipline enables high-throughput analysis of metabolites from cells, tissues, organs, and biofluids. Metabolomics is a critical'omic' approach. Metabolites, or small molecules, are biomarkers for a variety of biological processes. Metabolomics is gaining popularity, and metabolites' ability to serve as sources of novel potential biomarkers used in disease screening and efficient therapies is being observed in a variety of medical disciplines. The metabolome can be studied in two ways: untargeted analysis of a large number of unknown metabolites or targeted quantification of pre-defined known metabolites.Metabolomics is a relatively new field of science that connects cellular phenotypes to genotypes and provides biochemical information about the regulation of specific gene transcripts. Environmental influences can also cause metabolic changes [1-3]. As a result, their analysis may aid in understanding disease pathogenesis and the discovery of new biomarkers in simple biological samples such as urine and plasma. Cancer tissue samples can also be examined for in-situ metabolic changes.

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Literature Review

Following a review of the literature on the application of metabolomics in calcium metabolism disorders, several publications were chosen and classified into five major categories: PHPT, SHPT, osteopenia and osteoporosis, calcium and vitamin D3 deficiency. Only four publications described the targeted approach, while 78% of these studies used untargeted metabolomics. These analyses were carried out on a variety of biospecimens. Serum was the most commonly used type of sample (57% of the time). Surprisingly, only two studies used plasma samples. Four studies used urine samples, and two used parathyroid tissue. Furthermore, only a few studies examined combined serum, urine, and faecal samples. Further investigation revealed that 79% of analyses were carried out using MS, while only 21% used NMR. This is not surprising given that MS has dominated the field of metabolomics due to its exceptional sensitivity [4,5]. MS is typically used in conjunction with another separation technique: LC was used in ten publications, while GC and CE were used in two. Surprisingly, there are only two studies that used more than one technique. Because of its metabolite coverage, LC is the most widely used separation technique, particularly in untargeted studies. Changing the chromatographic column type, mobile phases, or modifiers allows separation of different groups of metabolites, providing a more complete picture of metabolic changes occurring under specific conditions.

All LC/MS analyses were carried out using RP-chromatography with C18 columns in this case. At this point, it is critical to emphasise that all of these summaries were created using the information that was available.

Unfortunately, the publications do not include a large number of analytical details [6-8]. The lack of even the most basic information prevents deep data synthesis and comparison, and, more importantly, prevents similar studies from being conducted and the results from being replicated. This is especially important in metabolomics studies, where even minor changes in analytical conditions or data analysis settings can result in drastically different results. As a result, even if the profile of a particular journal is not analytical, a community should make an effort to report all conditions.

Discussion

Nuclear magnetic resonance (NMR) spectroscopy and mass spectrometry (MS) are currently used in metabolomics, and they are combined with various separation methods such as (high-/ultra-pressure) liquid chromatography (LC-MS), gas chromatography (GC-MS), and capillary electrophoresis (CE-MS). The combination of these analytical platforms allows for the quantification of metabolites with low molecular weight. Because of their higher sensitivity, GC-MS and LC-MS are the most popular technical platforms for metabolomics. However, LC-MS is regarded as the best tool for precise metabolomics because it can quickly separate and identify individual metabolites with the highest clinical sample throughput and sensitivity. Metabolomics has provided important new insights into a variety of critical biological and physiological processes. In medicine, metabolic profiling can be used to develop new diagnostic algorithms or to uncover phenotypic differences in various disorders, which can then be used to guide personalized therapy. A number of metabolic pathways involved in calcium metabolism diseases have yet to be identified. Given the versatility and importance of metabolomics, this review focuses on metabolomics research on human calcium metabolism disorders. PHPT, secondary hyperparathyroidism (SHPT), calcium deficiency, osteoporosis, and vitamin D supplementation, in particular. The pathogenesis of calcium metabolism disorders is not fully understood. This review looks at the studies that used metabolomics in this field. Indeed, metabolomics has the potential to play a critical role in the discovery of biomarkers and the elucidation of pathological mechanisms. Despite a limited bibliography, the current review emphasises the potential of metabolomics in identifying biomarkers for some of the most common endocrine disorders, including primary hyperparathyroidism (PHPT), secondary hyperparathyroidism (SHPT), calcium deficiency, osteoporosis, and vitamin D supplementation. Metabolites associated with the aforementioned disorders were classified and mapped into metabolic pathways. Furthermore, disrupted metabolic pathways can lead to new avenues of investigation into the fundamental mechanisms of these diseases at the molecular level.

Conclusion

Hyperparathyroidism is a common condition characterised by excessive PTH secretion. PHPT is a common endocrine disease in Western countries caused by an abnormal proliferation of tumour parathyroid cells. Parathyroid tumours are classified as a genetically heterogeneous group with significant variation in clinical features. Hereditary forms of PHPT affect both sexes almost equally. Women, on the other hand, are far more commonly affected in sporadic cases. The incidence of PHPT is increasing among women in their sixth decade of life. Because of advances in diagnostics, the clinical presentation of PHPT in developed countries has changed from symptomatic to incidentally discovered and asymptomatic. Excess PTH secretion in normocalcemic PHPT, the first subclinical phase of PHPT, may cause metabolic disturbances and increase the risk of cardiovascular disease and tissue dysfunction, according to recent observational studies.

SHPT is one of the earliest clinical manifestations of chronic kidney disease (CKD). SHPT is caused by parathyroid hyperplasia, which is triggered by factors such as low serum calcium levels associated with renal failure or a decrease in active vitamin D concentration. One of the pathogenic factors of SHPT is a decrease in CaSRs in the parathyroid glands. Patients with SHPT typically have hyperphosphatemia, hypocalcemia, and elevated PTH levels in their serum. The increase in PTH is caused by abnormal calcium homeostasis, a decrease in glomerular filtration rate, and a decrease in the metabolically active form of vitamin D, 1, 25-dihydroxycholecalciferol (1,25(OH) 2D)—the main mediator of calcium absorption in the gastrointestinal tract. THPT occurs when the enlarged parathyroid gland fails to resolve and continues to oversecrete PTH despite successful kidney function.untargeted metabolomic study involving 35 patients successfully demonstrated serum metabolites correlated with PTH in SHPT. With an area under the curve (AUC) of 0.947, allyl isothiocyanate, indoleacetaldehyde, L-phenylalanine, D-aspartic acid and D-galactose form a group of biomarkers that could be used to distinguish patients with SHPT from healthy controls. Following parathyroid surgery, these metabolite concentrations were restored or tended to be normal.

In physiological concentrations, L-amino acids, particularly aromatic and aliphatic L-amino acids, are known to be strong regulators of PTH secretion and thus whole-body calcium metabolism. L-phenylalanine is an allosteric activator of CaSRs that inhibits PTH secretion. Shen's reported increase was thought to be the result of negative feedback to increased PTH levels. Wu's study, on the other hand, did not confirm this finding, presenting a decreased expression in patients with high PTH levels. The inconsistency of this result across studies could be attributed to the small sample sizes and various types of control groups used in the analyses. Furthermore, because the researchers used different methods, the data they provided may have been difficult to compare.

Conflict of Interest

None.

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