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Review Article

Pineal Gland Calcification and its Long-Term Effects: A Contemporary Review

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ABSTRACT

The pineal gland exhibits a high propensity for physiological calcification that increases with age. Pineal gland calcification (PGC) has been postulated to reduce endogenous melatonin production and to associate with sleep disturbance, neurodegeneration, psychiatric disorders, vascular disease and altered endocrine function. This review synthesizes literature published between 2018 and 2025, focusing on epidemiology, putative mechanisms, clinical associations, imaging methods for quantification, and therapeutic implications. We analysed contemporary systematic reviews, histomorphological studies, neuroimaging reports, mechanistic animal studies, and clinical association studies to provide an integrated appraisal and to highlight key gaps for future research.

INTRODUCTION

The pineal gland is a neuroendocrine structure primarily responsible for the synthesis and nocturnal secretion of melatonin, a regulator of circadian rhythms with antioxidant, anti-inflammatory and neuroprotective properties. Pineal gland calcification (PGC), colloquially referred to as 'brain sand' or corpora arenacea, is common on neuroimaging and histology and increases with advancing age. Recent research has focused on understanding whether PGC is purely a benign, age-related phenomenon or whether it contributes to clinically relevant declines in melatonin output with downstream effects on cognition, mood, sleep and vascular health. This review summarizes contemporary evidence (2018–2025) regarding PGC and its potential long-term consequences.

METHODS

A narrative review was conducted by searching PubMed, Europe PMC and Google Scholar for articles published from 2018 through 2025 using combinations of terms: 'pineal gland calcification', 'pineal calcification', 'melatonin', 'pineal volume', 'pineal imaging', 'corpora arenacea', and clinical

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terms (Alzheimer's disease, schizophrenia, stroke, sleep, ageing). Priority was given to systematic reviews, cohort studies, neuroimaging reports and mechanistic studies. Reference lists of retrieved articles were scanned to identify additional reports. At least 30 references published between 2018 and 2025 were included and are presented in Vancouver format.

PINEAL ANATOMY AND CALCIFICATION:

COMPOSITION AND HISTOLOGY

The pineal gland comprises pinealocytes, interstitial (glial) cells, and a connective tissue capsule. Calcified deposits—corpora arenacea—are complex microliths that contain calcium and magnesium salts, organic matrix components, and sometimes cellular remnants. Micromorphological analyses show heterogeneity in intrapineal and extrapineal acervuli and evidence that some calcified deposits can undergo partial destruction or remodeling with age and disease. These structural transformations likely influence residual secretory tissue volume and therefore functional melatonin output. (See histomorphology and micromorphology studies for detailed descriptions.)

EPIDEMIOLOGY AND PREVALENCE

Several recent population- and imaging-based studies report a high prevalence of radiologically detectable PGC in adults, with pooled prevalence estimates indicating that approximately 60–65% of adults show some degree of calcification on CT-based detection. Prevalence increases with age and shows geographic and methodological heterogeneity, driven by imaging modality (CT vs CBCT vs MRI), population demographics and criteria for ‘clinically significant’ calcification.

MECHANISTIC CONSIDERATIONS LINKING CALCIFICATION TO FUNCTION

The principal proposed mechanism by which PGC may affect long-term physiology is via reduction of functional, uncalcified pineal tissue leading to decreased melatonin synthesis. Additional hypotheses include local inflammatory changes, altered calcium metabolism within the gland, deposition of matrix proteins that sequester ions, and genetic or molecular contributors to acervulus formation. Recent animal studies implicate proteins (e.g., retinoschisin) and molecular pathways that regulate deposition and maintenance of acervuli; transcriptomic studies further suggest that inflammatory and transport pathways are altered in disease models.

CLINICAL ASSOCIATIONS AND LONG-TERM EFFECTS

1. Sleep and circadian disruption: Reduced endogenous melatonin—whether age-related or due to PGC—has been associated with sleep fragmentation, decreased sleep efficiency and altered circadian amplitude. The causal chain remains incompletely resolved because melatonin levels are influenced by multiple central and peripheral factors beyond calcification.

2. Neurodegenerative disease: Multiple imaging studies report smaller pineal volumes and greater calcification in patients with mild cognitive impairment and Alzheimer disease compared with controls. A reduction in uncalcified pineal tissue has been proposed as a biomarker for decreased melatonin output and a possible contributor to neurodegenerative processes through loss of antioxidant and anti-amyloidogenic actions.

3. Psychiatric disorders: Structural changes of the pineal gland, including increased calcification and reduced volume, have been reported in

schizophrenia and in subjects at clinical high risk for psychosis. The directionality and causality remain debated; some hypothesize that developmental perturbations of the gland or chronobiological dysregulation contribute to illness vulnerability.

4. Vascular disease and stroke: Several cross-sectional studies have described associations between greater PGC and markers of small vessel disease, aortic atherosclerosis and stroke in some cohorts; proposed mediators include chronodisruption, systemic calcium metabolism and shared ageing-related pathologies.

5. Endocrine and oncologic implications: Pineal dysfunction by calcification or atrophy has been discussed in relation to pediatric brain tumors, reproductive endocrine timing, and altered melatonin-mediated cancer suppression in animal models, though human causal data are limited.

IMAGING, QUANTIFICATION AND BIOMARKERS

CT remains the most sensitive modality for detecting calcified corpora arenacea; cone-beam CT has also been used in dental and head-imaging cohorts to report prevalence. MRI has lower sensitivity for calcification but allows volumetric assessments of uncalcified pineal tissue. Methods such as degree of calcification (DOC) scoring on CT, volumetry of uncalcified tissue, and correlation with urinary aMT6s (6-sulfatoxymelatonin) have been used to estimate functional melatonin output. Standardization of imaging protocols and reporting is necessary to improve comparability across studies.

THERAPEUTIC IMPLICATIONS AND TRANSLATIONAL CONSIDERATIONS

If PGC contributes materially to reduced melatonin production and downstream pathology, then melatonin supplementation offers a pragmatic intervention; several trials of melatonin in sleep disturbance and neurodegenerative disease suggest symptomatic benefit though disease-modifying effects remain unproven. Other speculative strategies include preventing or modifying calcification through manipulation of calcium handling, matrix turnover, or inflammatory pathways—approaches that currently lack clinical validation.

GAPS IN KNOWLEDGE AND FUTURE DIRECTIONS

Key unanswered questions include: (i) the causal contribution of PGC to reduced melatonin and to clinical endpoints (sleep, cognition, psychiatric morbidity, vascular disease); (ii) the molecular drivers of calcification in humans and potential modifiable pathways; (iii) longitudinal imaging–biomarker studies correlating calcification progression, melatonin secretion (aMT6s), and clinical outcomes; and (iv) standardized imaging and quantification methods to harmonize research. High-quality prospective cohorts and mechanistic human studies linking imaging-derived measures with serial melatonin assays and clinical phenotyping are priorities.

CONCLUSION

Pineal gland calcification is common and increases with age. Contemporary evidence (2018–2025) supports biologic plausibility for functional consequences mediated by loss of secretory pineal tissue and reduced melatonin synthesis, with reported associations across sleep, neurodegeneration, psychiatric and vascular domains. However, causality remains unproven and key mechanistic and longitudinal data are needed. Clinicians should interpret incidental PGC

on imaging in the individual clinical context; researchers should prioritize longitudinal imaging–biomarker correlation studies and interventional trials where appropriate.

PINEAL GLAND AND CIRCADIAN RHYTHM REGULATION

INTRODUCTION

Circadian rhythms are ~24-hour biological cycles that orchestrate physiology and behavior. The pineal gland, via nocturnal secretion of melatonin, is a pivotal humoral output of the circadian system, translating environmental light cues into hormonal signals that synchronize peripheral clocks. Recent literature (2018–2025) has expanded understanding of melatonin's roles beyond sleep regulation, highlighting antioxidant, immune-modulatory, and chronobiotic functions.

ANATOMY AND PHYSIOLOGY OF THE PINEAL GLAND

The pineal gland lies in the dorsal diencephalon between the superior colliculi. In humans, it is supplied by posterior choroidal branches of the posterior cerebral artery and contains pinealocytes (melatonin-producing cells) and interstitial glia. The gland receives circadian information indirectly via the retina → retinohypothalamic tract → suprachiasmatic nucleus (SCN) → paraventricular nucleus → intermediolateral cell column → superior cervical ganglion → pineal.

MELATONIN SYNTHESIS AND CIRCADIAN REGULATION

Melatonin is synthesized from serotonin within pinealocytes. Key enzymatic steps include serotonin N-acetyltransferase (AANAT) and hydroxyindole O-methyltransferase (HIOMT/ASMT). AANAT activity is rhythmically regulated by the SCN through sympathetic noradrenergic signaling, leading to high melatonin synthesis at night and low synthesis during daytime.

LIGHT INPUT, BLUE LIGHT, AND MELATONIN SUPPRESSION

Intrinsically photosensitive retinal ganglion cells (ipRGCs) containing melanopsin detect environmental light—particularly short-wavelength blue light (~460–480 nm)—and project to the SCN. Evening exposure to blue-enriched light suppresses nocturnal melatonin, shifts circadian phase, and impairs sleep onset. Modern sources (LED screens, smartphones) emit wavelengths that strongly affect melatonin timing, with clinical relevance for sleep and metabolic health.

PINEAL CALCIFICATION AND AGING

Human pineal glands frequently show age-related calcification (corpora arenacea). Several studies link greater calcification with reduced melatonin metabolites and potential associations with neurodegenerative diseases and sleep disturbances, although causality remains debated.

CLINICAL IMPLICATIONS AND THERAPEUTIC USE OF MELATONIN

Melatonin and melatonergic agonists are used to treat circadian rhythm sleep disorders, jet lag, and some sleep disorders in older adults and in shift workers. Evidence supports timed, low-dose melatonin for circadian phase advancement in delayed sleep phase disorder and for reducing jet lag when timed appropriately. Recent work also highlights melatonin's pleiotropic protective actions (antioxidant, anti-inflammatory) that may have broader clinical implications.

RESEARCH GAPS AND FUTURE DIRECTIONS

Open questions include the impact of chronic low-level night-time light exposure on long-term health, the functional consequences of pineal calcification, the relative roles of pineal versus extrapineal melatonin, and optimized chronotherapeutic strategies. High-quality longitudinal human studies are needed.

CONCLUSION

The pineal gland, through nocturnal melatonin secretion, remains central to circadian regulation. Understanding how environmental lighting, aging, and disease alter pineal function will improve strategies to treat circadian disorders and mitigate health risks associated with circadian disruption.

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