

The nail as an investigative tool in medicine: What a dermatologist ought to know

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Abstract

The nail is an important skin appendage, but not many dermatologists are aware of the importance it receives outside our specialty. This article focuses on the nail in non-dermatological contexts. The nail is a keratinized matrix capable of continuous growth with the ability to incorporate various compounds within its structure. Therefore it can be used to monitor long-term consumption of drugs. It is also an excellent source of germ-line DNA for genetic analyses. With an increased understanding of nail physiology, there is now a better understanding of its connection to various pathologies as well. Nails, being peripherally placed, are easy to sample without significant discomfort to the patient, making them a valuable diagnostic tool. For this narrative review, we carried out a PubMed search using the key words "nail clipping," "nail DNA," "nail diabetes mellitus," "nail clipping oncology," and "nail forensics". Retrieved articles were searched for information pertaining to non-dermatologic uses of nail for evaluation, which is presented in a narrative fashion. It is clear from recent literature that the nail is not just an inert skin appendage, but a dynamic window into the ever-changing metabolic and genetic milieu. We highlight the numerous roles of nail specimens, as well as point towards future research needed therein.

Key words: Biometrics, DNA, forensic science, forensic toxicology, nail clipping, oncology, selenium

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Introduction

Over the years, there is increasing interest in the study of the nail in health and disease. We know of its special structure and biological uses. It is also useful in diagnosis and as a marker of systemic disease. However, not many dermatologists know the amount of attention it receives outside our specialty.

This article focuses on the non dermatological relevance of this appendage. With developments in molecular biology and genetics, the nail is increasingly being seen as an ideal source of obtaining human specimens. It has attained the status of "a true window", not just to disease, but also to the health status of an individual.

Methods and Results

For this review, information was collected by a PubMed search of articles published regarding the nondermatological uses of nail

specimens. We used the key-words "nail clipping," "nail DNA," "nail diabetes mellitus," "nail clipping oncology," "nail forensic," and "nail biometrics." The searches yielded 82, 685, 437, 8, 122, and 2 indexed articles respectively, in English. These articles were retrieved and classified as case reports, review articles, and clinical trials. Information pertaining to nondermatologic applications of nails was collected. The final data was analyzed and is presented in a narrative fashion.

Why Use the Nail?

With the increasing popularity of screening programs, the need for appropriate human tissue specimens has increased. The specimen should afford adequate sensitivity and specificity in detecting what it is supposed to detect; it should involve low costs, collection should cause minimal discomfort to both patients and practitioners,

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and it should be easy to store and transport.¹ The nail satisfies most of these criteria.

Conventionally, human blood and serum are commonly used for diagnosis; however, the importance of alternative tissue sources has increased over the years due to various reasons. Venous blood collection may prove difficult, especially in special populations, for large-scale programs, or for international collaborative investigations.² Alternative tissue sources include card-based blood spots, buccal scrapes, hair samples and nail clippings as these are uniquely accessible as well as capable of delivering host DNA and other details. Nail as an alternative tissue sources has been found useful for genetic diagnosis as a part of screening procedures,³ diagnostic procedures,^{4,5} assessment of adverse reactions,⁶ familial and population genetic profiling,⁷ and molecular autopsy studies.^{8,9} In fact, for molecular autopsy studies, nail may be the only specimen which can be used for defining the cause of death or for clinical genetic information important for the surviving family.² In addition to the advantages of adequate sensitivity and specificity, low cost, ease of retrieval, minimal discomfort upon retrieval, and acceptability to both patients and practitioners, nail specimens are also easy to collect, store, and transport.¹

However, because of a lack of awareness and proper processing techniques in routine laboratories, nail samples have not widely been used as diagnostic tools.

Nail as a keratinized matrix

Both nail and hair are keratinized matrices capable of continuous growth, and incorporate compounds within their structure. This property can be utilized in monitoring long-term consumption of alcohol or drugs.¹⁰ Nail specimens are found useful in toxicology and especially as an alternative to hair specimens.¹⁰ Hair analysis has been an established tool for drug testing, driving ability examination, detection of gestational drug exposure, criminal assault, and post-mortem toxicology.¹¹ Correspondingly, our understanding of the mechanisms of incorporation of drugs into the hair matrix is advanced.^{12,13} In contrast, literature on incorporation mechanisms in nails is sparse;¹¹ nevertheless, we know the following mechanisms of drug incorporation in nails:¹

- a. *Nail matrix incorporation* occurs during the formation of the nail plate via matrix blood flow. Thus, an incorporated drug would be detectable only when the nail grows enough to reach the free edge (10–18 weeks based on average nail growth rate)
- b. *Nail bed incorporation* occurs during nail thickening. The nail bed contributes 21% of the nail thickness.¹⁴ A drug incorporated in this manner would be detectable in distal nail clippings much earlier (as early as 2–3 weeks)^{15–17}
- c. *Environmental contamination* occurs mostly in the distal part, which explains the presence of materials, mostly xenobiotics, in the distal nail¹⁸
- d. *Sweat-mediated transport* is responsible for rapid initial incorporation (within 24 hours) of drugs such as zolpidem.¹ Drugs are eliminated through sweat channels depending on their molecular weight and hydrophilicity.¹⁹ Nails have a water content of 9–10% and drug diffusion through the nail bed can lead to early detection at the free edge.^{14,20} Laufen *et al.* reported an uptake of fluconazole as early as 8 hours after intake.¹⁷ Similar diffusion for topically applied terbinafine has also been studied.²¹

The kinetics of drug incorporation in the nails have been especially well worked out for zolpidem, a drug used for drug-facilitated sexual assault.¹⁰ A single dose administered has been found to be detectable in all fingernail clippings from as early as 24 h to as late as 3.5 months. In fact, even the time of intake can be inferred from the analysis of single fingernail clippings. Nail analysis could thus be an alternative as well as a complement to hair analysis in cases of suspected drug-facilitated sexual assault, and for monitoring of consumption behaviour.

Table 1 summarizes drugs routinely and reliably tested for, in nail specimens. This “nail biologic monitor” has been found useful in monitoring long-term exposure to drugs, micronutrients and xenobiotics; it can even help in temporal correlation with the supposed period of exposure.²²

Nail as a source of DNA

Fingernail material is an excellent source of germline DNA for genetic analyses in almost all clinical settings.³⁷ Although the use of hair for this indication is well-known, there are practical problems, with hair specimens often being reported inferior for diagnostic use due to poorly detectable DNA. The Baylor SUDEP Tissue Donation Program (STOP) reported that hair samples were often received without follicles or that their integrity may be compromised by prior chemical processing with hair-care products.² Fingernails are a more reliable source of autologous DNA of high-quality.³⁷

The specialized structure of fingernails (embodying DNA in keratinized cells) makes DNA extraction more complex than with fresh somatic cells; hence, well-defined protocols and reagents have been designed for lysing keratin.³⁸ These protocols optimize the yield and quality of pure, intact DNA which has been found good enough even for demanding techniques such as next-generation sequencing for HLA typing.³⁷ Advanced techniques such as the Prepfilers Forensic DNA Extraction kit can yield a mean of 1 mg high-quality DNA (range, 0.5 to 2.3 mg) from 20 mg nail material (1 to 10 pieces of fingernail clippings, a few millimetres wide only).³⁷ DNA extracted from toenails³⁹ or fingernails⁴⁰ has been used for genotyping and identification of individuals in genetic epidemiology and forensic studies. Some of the indications for nail plate-derived DNA are summarized in Table 2.

How to Collect Nail Specimens

Collection of nail specimens is as simple as collection of fingernail trimmings or overhang of nail plates.² Specimens can be collected on a plain sheet of paper (as done for mycology) or in sterile 1.5 mL microcentrifuge tubes for more demanding DNA analyses. An adequate sample consists of at least 1 week of untampered fingernail growth (assuming an average growth rate of 3 mm/month).^{2,66} Except for daily hygiene, no additional nail cosmetic or nail treatment should have been done. Hands are thoroughly washed with soap and warm water and allowed to dry. Sterilized conventional metal nail clippers are used and whole nail trimmings are transferred into pre-labelled tubes or containers for transportation. These can easily be stored at room temperature until use. Depending on the analyses required, only one nail clipping may be collected (for serial detection of drugs)¹⁰ or ten nails (for DNA analyses) may be collected. For serial detection of drugs, ring fingernails are preferred (because of their medium growth rate) and serial collection from the same nail is advised.⁶⁷

Tables 3 and 4 summarize the advantages and disadvantages of using nails as a specimen.

Table 1: Various drugs incorporated in nail

Drug/chemical	Applications/potential applications of nail clippings
Amphetamine-type stimulants and phenyl-alkylamine derivatives ²³	Nail is used for detection and quantification of phenylalkylamines in possible drug abusers
Methadone ²⁴	Nail useful for monitoring of patient compliance to methadone-maintenance programs
Cocaine analytes	Detection of this drug of abuse in nail specimens
Cannabinoids ²⁵	Detected in nail specimens of drug-abusers
EtG alcohol ²⁶	New biomarker in nails for monitoring alcohol consumption behavior. Nail EtG levels in a social drinker are much higher than hair, suggesting a higher sensitivity. Used for evaluating both chronic excessive alcohol consumption as well as binge drinking habits
Antimycotics-terbinafine, ²⁷ itraconazole	Can be detected in distal nail clippings as early as 3 weeks and 1 month after starting therapy, respectively. Average nail concentrations are within fungicidal range for dermatophytes
Detection of <i>in utero</i> drug exposure ²⁸	Nails are formed during the second trimester. Thus they can indicate <i>in-utero</i> exposure to drugs like cocaine, morphine, methadone, caffeine, nicotine.
Trace elements and heavy metals ²⁹	Nail used for monitoring occupational or environmental exposure
Zolpidem ³⁰	This drug is used for drug-facilitated sexual assault or for regular consumption behavior. Nail analysis is an alternative as well as a complement to hair analysis
Selective serotonin reuptake inhibitors (fluoxetine and paroxetine) and serotonin-norepinephrine reuptake inhibitors (venlafaxine and duloxetine) ³¹	Nail clippings can be useful for monitoring drug intake in patients on fluoxetine treatment
Triclosan and triclocarban ³²	Nail specimens used for rapid detection of these contaminants in nails
Selenium ²²	Toe nail and fingernail Selenium levels are used as surrogate markers of selenium status in epidemiological studies is well established. ³³⁻³⁵ Blood selenium levels reflect recent exposures only (over weeks) whereas toenail selenium reflects exposures over 6-12 months, making the latter ideal for monitoring long-term exposure. Nail clippings have also been used for monitoring an outbreak of "selenosis" due to a mis-formulated dietary supplement ²²
Arsenic ³⁶	Nail analysis can indicate chronic exposure, which cannot be evaluated by conventional blood and urine analysis. Postmortem nail analysis is useful in determining past exposure, but may not reliably conclude arsenic as cause of death as there is no correlation between blood and nail concentrations

EtG: Ethyl glucuronide

Techniques Used to Examine Nail

As the nail has a unique structure, specialized techniques are required to examine and quantify specific components. Some such techniques used for nail analysis are summarized below.

- *Laser-induced breakdown spectroscopy* is used for the analysis of varied biological substrates such as bacteria,^{77,78} teeth,^{29,79} hair,⁸⁰ bones⁸¹ and fingernails.⁸² It employs a focused high-power, short-pulsed laser beam directed onto the nail surface.¹ Based on the analysis of emission spectra from the surface, varying elements can be analyzed.
- *High-performance liquid chromatography* has been used for determination of drugs such as selective serotonin-reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors in nail clippings.⁶⁸ It has also been used as a speedy, simple and accurate technique in forensic toxicology for elucidating the cause of death or drug abuse
- *Ultrapformance liquid chromatography-tandem mass spectrometry* has been used to detect triclosan and triclocarban in nails.⁸³ The collected nail clippings are digested with sodium hydroxide and chromatographic separation is performed with methanol. Target compounds are then determined by mass spectrometry
- *Micro-PIXE (particle-induced X-ray emission)* and *micro-RBS (Rutherford back-scattering spectrometry)* have been used to determine three-dimensional concentration maps of 18 elements in the human nail viz., major elements (C, N, and O), minor elements (P, S, Cl, K, and Ca), and trace elements (Fe, Mn, Zn, Ti, Na, Mg, Rb, Br, Sr, and Se)⁸⁴

- *Hard X-ray micro-analysis* has been used to examine arsenic distribution in nail-clippings.³⁶ Nail clippings embedded in polyester resin and cut in cross-sectional slices are analyzed for arsenic concentration in different areas
- *Synchrotron-based XRF (X-ray fluorescence) mapping* has also been used to evaluate arsenic micro-distribution in toenail clippings.^{2,85}

Clinical Indications for Use of Nail Specimens

The diagnostic use of nail specimens is well established for the following indications:

Nail in diabetes mellitus

Diabetes mellitus is a metabolic disease characterized by high blood sugar either due to insufficient insulin production or poor responsiveness.⁸⁶ Various systemic pathologic alterations and metabolic events in diabetes mellitus are known to affect the nail unit structure and composition, and a nail sample can be a useful for clinical investigations.⁸⁷⁻⁸⁹ Documented techniques for the detection and monitoring of diabetes in the nail unit include:

- Estimation of glycated nail proteins has been found to reflect average blood glucose control over the previous 6–9 months.^{90,91} An analysis is possible even on a 10 mg sample. The normal reference range for glycated nail protein is 0.55–3.60 μmol/g nail. In diabetics, the values are significantly higher (median, 4.07 μmol/g nail). Nail analysis could therefore be a simple alternative for diagnosing diabetes in persons from remote areas

Table 2: Applications of nail plate-derived DNA

Indication	Technique used/remarks
High-resolution HLA Class II genotyping in transplant recipients ^{37,41}	Next-generation DNA sequencing is the technique used for this indication and nail samples have been found adequate for this application ^{37,41}
Genotype analysis ⁴²⁻⁴⁴ for assessing patient/donor chimerism in patients who have received allogeneic stem cell transplantation	Nail has been a DNA source for genotyping ^{45,46} DNA extraction from nails can be of special relevance when the patient's pretransplant recipient material (e.g., peripheral blood) is not available. In such a setting, nails serves as a reliable source of pure autologous DNA for genotyping, because other specimens like oral mucosal swabs and skin scrapings are likely to have already been invaded by donor leukocytes (from the previous transplantation) and are thus contaminated with nonautologous cells. ³⁷ Patients undergoing such procedures are likely to have already lost hair which could have been an alternative source of autologous DNA. It has been shown that even a single nail clipping can provide an adequate quantity and quality of recipient DNA for genotyping ³⁷
Epidemiological studies ⁴⁵	DNA extracted from toenails or fingernails has been used for genotyping and identification of individuals for the purpose of genetic epidemiology and forensic science ⁴⁶
Investigation of specific biomarkers ⁴⁶	Nail samples are useful for monitoring <i>intra-individual biomarkers</i> ⁴⁶ which are basically cell-free (circulating) DNA, ^{44,47-50} proteins ⁵¹⁻⁵³ or RNA, acting as indicators of underlying disease processes including cancers. Cellular necrosis and apoptosis induced by various insults, release significant amounts of such DNA into body fluids which can be used for tracking these pathologies. ⁵⁴⁻⁵⁸ Nails, can sensitively reflect the status of these biomarkers, enabling noninvasive monitoring using RT-PCR and immune-blotting. Important nail biomarkers include circulatory xenobiotic DNA like hepatitis B virus DNA, ⁵⁹ detection and monitoring of tumors, diabetes mellitus, trauma, stroke, ⁶⁰⁻⁶² endometriosis ⁶³ and multimodal therapy effect ⁶⁴
Assessment of germline sequences (as control) for investigating cancer-specific clonal alterations ⁶⁵	DNA isolated from fingernails is a reliable source of germline DNA needed as a control while evaluating cancer-specific clonal alterations in malignant haematological neoplasms
Single nucleotide polymorphism (SNP) genotyping ⁴⁶	SNP genotyping for analysing genetic variation in specimens can be done on nail specimens by phenol/chloroform extraction ⁴⁶

RT-PCR: Reverse transcription polymerase chain reaction, mtDNA: Mitochondrial DNA

Table 3: Advantages of using nail as a specimen

- The nail unit is very vascular, hence serum concentrations of metabolites (including xenobiotic biomolecules and trace elements) is reliably reflected in nail specimens⁴⁶
 - Nail clippings can be obtained noninvasively in contrast to drawing peripheral blood.⁶⁸ There is no harm and no pain, ensuring high compliance⁴⁶
 - Being noninvasive and easy, even self-collection is easily possible. This is especially useful when serial monitoring of biomarkers is required.⁴⁶ Self-collection requires minimal instructions and ensures prolonged follow-up
 - Storage at room temperature is possible and no cold chain needs to be maintained⁴⁶ even in tropical countries. There is no risk of samples getting spoilt and no special preservation is required
 - Cost-effectiveness is high. All steps including collection method, manpower requirement, storage and transport costs are low.^{2,46} Nail samples can also be easily transported over long distances. This is especially important for large-scale, national or international population screening programs.⁴⁷ For international collaborations, the exchange of nail clippings is easier as compared to blood
 - Even onycholysed nails or nails which are being shed off can be useful for analysis⁴⁶
 - Nails are formed continuously and permanently. They do not undergo any resting or growth stages, unlike hair
 - Fingernails are versatile specimens, useful for the constantly increasing genetic and genomic applications ranging from population-based screening, diagnostics, molecular autopsy, medico-legal investigations, or multi-organ surveys of suspected mosaicism²
 - Nail specimens can be used both as stand-alone samples or to complement other specimens that may be limited in terms of their quality,^{69,70} scope^{71,72} or yield^{73,74}
 - Good quality studies are available providing reliable means of extraction from nail specimens as well as comparative nail levels in normal populations. A lack of reliable data was an initial drawback which has been successfully overcome, especially in the field of nail-based forensic toxicology¹⁰
 - The hardness of nail specimens and a layered structure are advantageous in preventing damage to samples in the preanalytic phase. Preservation of integrity of biomolecules prevents major errors in interpretation downstream⁴⁶
 - Due to the time lag inherent between formation of nail at the matrix and its growth up to the nail edge, nail specimens offer a wide diagnostic window (extending over weeks, months or even years).⁶⁸ This is in contrast to serum or urine samples, which can reflect only the present exposure or burden of xenobiotic.⁴⁶ Analysis of nail clippings can indicate chronic exposure, which cannot be evaluated by conventional blood and urine analysis.⁶⁹⁻⁷³
 - Nail clippings can be obtained and used as a source of pure autologous DNA in practically any situation. This may not be possible with other specimens like hair (which may fall off), peripheral blood, oral mucosal epithelium, or epidermal cells (may not be suitable posttransplant or posttransfusion)³⁷
- Changes in the molecular structure of human fingernail proteins in diabetic and nondiabetic specimens have been documented on the basis of their Fourier transform infrared spectroscopy spectra.⁹¹ It has been concluded that nail proteins of diabetics contain α -helical structure (including the presence of amide II bonds), whereas nails of nondiabetic patients do not have the amide II structures
 - The dielectric properties of keratin–water system in diabetic

Table 4: Disadvantages of nail specimens

Disadvantage	Remarks
Fingernail samples may not be optimal for PCR-based assays	<ul style="list-style-type: none"> • PCR-based amplification of DNA derived from nails has been found to be poor, especially for larger amplicons. This suggests potential DNA degradation or fragmentation occurring within the keratin matrix²
Current paucity of data about consistent baseline levels for some biomarkers in nails ⁴⁶	<ul style="list-style-type: none"> • This is an essential prerequisite for monitoring the levels of individual biomarkers in health and disease. Expected levels and their correlations should be known across various specimens like serum, body fluids and nails. Effective monitoring of biomarkers is dependent on differentiating the disease from normal background variation⁷⁵
Postmortem nail analysis may not be useful in determining cause of death	<ul style="list-style-type: none"> • Postmortem nail analysis is useful in determining past drug administration. However, due to varying dynamics, there is generally no correlation between blood and nail concentrations.⁶⁸ Hence determining cause of death may be tricky in some situations
Risk of contamination, especially with respect to analysis of xenobiotics in nail specimens	<ul style="list-style-type: none"> • Xenobiotic RNA e.g., dermatophyte mRNA has been shown to exist in infected nails.⁷⁶ Similarly, small internal proteins may also exist in nails and such things can confound expected outcomes⁵¹

PCR: Polymerase chain reaction

and healthy fingernails have also been evaluated.⁹² It was reported that the dielectric measurements of human nail could be used for the detection of diabetes

- Nasli-Esfahani *et al.* carried out elemental analysis of nail as well as other biological samples (serum, scalp hair, urine and other body fluids) in diabetic patients.⁹³ They concluded that scalp hair and nail are the best biological samples for trace element analysis in diabetics (especially Cr, Se, and Mn)
- Laser-induced breakdown spectroscopy (LIBS) has been used for analyzing diabetic and nondiabetic nails.¹ It was concluded that LIBS spectra of fingernail can be a valid screening tool for diabetics in a large population with the advantages of quick measurement, broad elemental coverage, and low cost¹
- Nail fold capillaroscopic (NFC) images were evaluated quantitatively as well as qualitatively in 145 children with Type 1 diabetes mellitus.⁹⁰ Increases in the number as well as length of capillaries, presence of mega-capillaries and Raynaud's loops, and intense red background (possible neoangiogenesis) were the recorded findings. Longer disease duration correlated with an increase in the number of capillaries, disturbances in distribution, as well as the presence of abnormal capillaries. NFC is a noninvasive, painless and easily repeatable test allowing digital storage of images; it can be used as an effective monitoring tool in diabetics.⁹⁰

Role of nail clippings in oncology

Recent oncological research has focused on the primary prevention of cancer and identifying individuals at risk. It is known that trace elements have inhibitory as well as causative roles in oncogenesis. In addition, exposure to trace elements can be predetermined (e.g. arsenic) and may also be a modifiable risk-factor.⁹¹ Nail-clippings are therefore regarded as valuable biomarkers for such exposures.^{93,94}

The FINBAR (Factors Influencing Barrett's Adenocarcinoma Relationship) study group attempted to correlate trace element status in toenails with the risk of Barrett's oesophagus and oesophageal adenocarcinoma.⁹¹ Toenail clippings from 638 participants and healthy controls were analyzed for eight trace elements. There was a two-fold higher risk of Barrett's oesophagus with high toenail zinc, a borderline significant, increased risk with higher cobalt levels, and no association with levels of chromium, cerium, mercury, and selenium.

The nail has been proposed as a more reliable biological meter for arsenic than serum because elevated levels would be maintained in the former for a longer time. Further, external contamination of nails with arsenic is much less extensive compared to that of hair.⁹⁴ Long-term exposure to arsenic can lead to adverse health effects^{95,96} Lu *et al.* concluded that high arsenic exposure in humans promotes cancer initiation,⁹⁷ though the exact mechanism of arsenic's role in carcinogenesis remains unknown.^{98,99} Mechanisms responsible for arsenic accumulation in nails are poorly understood. The affinity of arsenic to sulphhydryl groups of nail keratins may be responsible.¹⁰⁰

Forensic importance of nails

The nail plate is an important substrate for diagnosis in forensic science.¹⁰¹ Forensic casework routinely involves examination of fingernail scrapings and clippings for foreign DNA. In this scenario, both *in-vivo* and *in-vitro* analysis of nail specimens assumes significance. Though finger-nails may not be as useful as fingerprints for identification, in many cases broken fingernail plates have been used to associate a suspect with the victim by comparing nail ridge patterns.¹⁰²

Matte *et al.* reported that up to 19% of the general population may have foreign DNA beneath their fingernails, whereas foreign DNA may be detected in 33% of forensic fingernail samples.¹⁰³ The normally present foreign DNA also tends not to persist for long. This needs to be taken into account by forensic analysts when providing an opinion on the relevance of foreign DNA under fingernails.

In forensic toxicology, reports abound on the usefulness of detecting drugs of abuse in nails. Brown *et al.* reported the utility of fingernail clippings in testing for levels of anabolic steroids in sportspersons with doping charges.¹⁰⁴ Other reports include amphetamine-type stimulants, methadone, cocaine breakdown products, phenylalkylamine derivatives, and cannabinoids being detected.¹⁰⁵⁻¹¹³ Further, ethyl glucuronide (EtG) has been put forward as a new biomarker in nails for alcohol consumption behavior.¹¹⁴

Miscellaneous medical disorders

Apart from the diseases discussed above, nail clippings/biopsies have been useful in other diseases. The utility of the "nail window" into systemic diseases cannot be undermined.¹¹⁵

Nail biopsies have been found useful in gout to detect urate crystals in subungual horn.¹¹⁶ Tirado-González *et al.* described subungual urate crystals extruded subclinically in some cases of gout.¹¹⁶ Nail biopsies taken to evaluate fungal elements showed urate crystals instead and the history subsequently confirmed gout. It was reported that there were no tophi noted in or near the nail field. Such crystals probably occur via exudation/transudation of fluids into the nail structure, offering a “nail window” into haematic or metabolic abnormalities. The authors concluded that the cytological and histological findings in nail specimens could be used to evaluate nail diseases as well as systemic diseases.¹¹⁶

Similarly, toenail nicotine levels have been used as biomarkers to predict the risk of coronary heart disease (CHD). In a nested case-control study involving 62,641 women followed up over 16 years,¹¹⁷ a statistically significant, dose-response association was seen between increased toenail nicotine levels and risk of CHD. The authors concluded that toenail nicotine levels are predictive of CHD among women independent of other risk factors.

Nails for biometrics

With advances in information technology, security aspects have become paramount. Authentication is a prerequisite for security with biometric authentication being an important mode. This involves automated recognition of individuals based on their physiological characteristics, identifying a person based on “who she/he is” rather than “what she/he has” (card, token, key); or “what she/he knows” (password, pin).¹¹⁹ Common characteristics used for biometrics include face recognition, fingerprints, handwriting, hand geometry, iris, vein, voice or retinal scan. The use of fingernail patterns as biometric markers has been evaluated and found to be useful.¹¹⁸ Herein, authentication is based on unique individual ridge patterns of the nail bed reflected on the nail plate surface, which can be evaluated by computational analysis even in low-resolution images.¹²⁰ This has proved to be a very unique and stable biometric identifier, good enough for forensic as well as civilian applications.¹²⁰ Extensive experimentation has validated its use.

The low-resolution nail plate images are acquired with a contactless, unconstrained imaging setup analyzing texture-based feature descriptors. Then, computational analysis is used for integrating nail plates from three fingers. Outcomes of rigorous experimental analysis on 2700 nail plate images found this to be a promising biometric modality.¹²¹ Nail bed pattern can also be analyzed with a laser-based broadband interferometer technique.¹²² Another system measuring spacing of the capillary loops with highly monochromatic light has also been evolved.¹²³

Hand-based biometrics has high user acceptance and reliability. Of these, the fingernail plate is characterized by high individuality,^{124,125} with a high degree of distinctiveness, even among identical twins.¹²⁶ Moreover, the hardened nail resists environmental effects, barring changes caused by nail diseases/disorders and malnutrition.¹²⁷ This ensures high reproducibility as well.

Radiation dosimetry

Rapid and accurate determination of individual radiation exposure would be needed to screen exposed populations in case of a radiological/nuclear event. It has been seen that estimating the chemical or physical alterations produced in biomaterials can

be used to determine the level of exposure. Radiation sensitivity of nails is relatively high and changes produced in nails exposed to radiation have been found to be a useful biodosimetry method. In addition, the radicals generated in condensed nail protein are stable over time.^{128,129} An *ex-vivo* estimation of severity of radiation exposure based on the electron paramagnetic resonance nail dosimetry was evaluated by He *et al.*¹²⁸ Human nail clippings were used to evaluate stable radiation-induced signal. It was found that a reliable triage based on radiation dosage was possible.¹³⁰ The technique also ensured immediate and rapid dose assessment.

This review has some limitations. The topic being vast, we may have missed additional diagnostic applications of the nail unit not adequately represented in the indexed literature. In addition, with expanding developments in the field, a compendium such as this may fall short of the latest information at times despite our efforts to make it up-to-date.

Conclusion

It is clear from the recent growth in literature that the nail is not just an inert skin appendage, but a dynamic part of the human body, reflective of the changes in the metabolic and genetic milieu. Nail specimens are a valuable diagnostic tool as they are easy to retrieve, without causing significant discomfort. The coming years are likely to see more research and expansion of knowledge in this field.

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Conflicts of interest

There are no conflicts of interest.

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