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**Medical Science**

# Ultrashort pulse lasers in medicine, current applications and prospects for future advances

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**To Cite:**
Filipek K, Pisklak A, Behrendt H, Głód M, Węgrzynek M. Ultrashort pulse lasers in medicine, current applications and prospects for future advances. *Medical Science* 2024; 28: e130ms3422
doi: https://doi.org/10.54905/disssi.v28i152.e130ms3422

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**Peer-Review History**
Received: 09 July 2024
Reviewed & Revised: 13/July/2024 to 01/October/2024
Accepted: 05 October 2024
Published: 09 October 2024

**Peer-review Method**
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

**DISCOVERY**
SCIENTIFIC SOCIETY

## ABSTRACT

Femtosecond laser which is an ultra-short pulse found applications in novel technologies that have been used in medicine. Femtosecond lasts 10-15 of a second. Femtosecond lasers were used to create new technologies that have been explored in medicine. Dermatology and ophthalmology are fields of medicine in which femtosecond laser gained most popularity. Future research may result in the creation of new clinical applications for ultrashort pulse lasers. Lasers wit even shorter pulse duration called attosecond lasers (attosecond lasts 10-18 of a second) enable research at the molecular level. In the future this innovative technology may be used to study complex biological processes, contributing to the development of medicine. Further development of research into the use of ultra-short lasers may result in their use to create new solutions that could find application in clinical practice. The aim of this publication is to review the literature on ultra-short pulse lasers and identify areas for further research.

**Keywords:** Ultra-short pulse lasers, Femtosecond laser, Attosecond laser, Medical diagnostics, Medical technologies

## 1. INTRODUCTION

Ultra-short pulse lasers have found many interesting applications in medicine. Thanks to their ultra-short pulse duration, they deliver extremely high energy and what more provide precision. Ultra-short lasers are used to develop promising diagnostic tools (e.g. imaging techniques) (Meijer et al., 2002). The femtosecond laser with pulses lasting only a few quadrillionths of a second, is revolutionary thanks to its precision in various fields including medicine. A femtosecond lasts 10-15 or 1⁄1,000,000,000,000,000 of a second. The mechanism of action of the femtosecond laser consist of delivering intense pulses of energy over a short period of time. Femtosecond laser technologies allow precise results without thermal damage to surrounding tissue, which has led to numerous applications for this laser in the development of technologies where precision is crucial (Zewail, 2000).

In recent years, attosecond technologies have been explored. Attosecond is a unit of time equal to 10-18 or 1⁄1,000,000,000,000,000 000 (one quintillion) of a second (Agostini and DiMauro, 2004). The first reports of obtaining pulses of light with attosecond duration are from 2001 and it initiated further research about attosecond pulses (Hentschel et al., 2001). The purpose of this publication is to provide an overview of the opportunities that ultrashort pulse lasers offer in medicine. It reviews recent reports on technology concepts using femto- and attosecond lasers, which may represent solutions that have the potential for future clinical application.

## 2. REVIEW METHODS

The review consisted of a collection of reports from recent years (we paid particular attention to include publications from the last 5 years). We used the PubMed and Google Scholar platforms, where scientific reports were searched using keywords such as femtosecond laser in medicine, dermatology, ophtalmology or neurology, attosecondlaser, ultrashort pulse lasers in medicine, dermatology, ophtalmology or neurology. Studies that made a significant contribution to science were included in the review. The review ultimately included a total of 24 studies.

## 3. RESULTS AND DISCUSSION

### Application of femtosecond laser in dermatology

#### *The multiphoton tomographs*

A femtosecond laser was used to create a multiphoton tomograph, skin diagnostic device which enables to perform noninvasively skin biopsy in vivo (Schenke-Layland et al., 2006; König, 2008). Similar to optical biopsy, high-resolution microscopic information was obtained noninvasively on living skin using multimodal multiphoton imaging. Possible imaging included cell morphology, mitochondrial distribution and depth of epidermal-dermal junction, measurement of 780 nm beam-excited autofluorescence of intradermal melanin, keratin, elastin and the coenzymes NADH and flavin using time correlated single photon counting. An unquestionable advantage of skin imaging diagnostics using multiphoton tomography is the incredible resolution, unattainable by other technologies such as OTC.

Another advantage is the in vivo performance of the examination (König et al., 2020; König, 2023). The technology has clinical applications in skin diseases such as atopic dermatitis and psoriasis and allows early diagnosis of melanoma and detection of initial focal points of malignant transformation with high diagnostic sensitivity and accuracy (Leupold et al., 2011). The benefit of in vivo diagnostics is the immediate imaging of abnormal cells. In the future, compact multiphoton tomographs have the potential to replace conventional skin histology, emerging as clinical tools for diagnosing skin lesions. Multiphoton tomographs may also serve for long-term follow-up of skin lesions and prevent unnecessary removals. However, despite the existence of commercial multimodal multiphoton tomographs with femtosecond laser such as DermaInspect, MPTflex further research and technology development is needed to become viable for widespread use in clinical practice (Meng et al., 2021; König and Riemann, 2003).

#### *Femtosecond laser applications: Skin Remodeling, wound healing, and antibacterial therapy*

Research on mouse skin using femtosecond laser micromachining has shown that femtosecond lasers can effectively activate skin remodeling through upregulation of matrix metalloproteinases 3 and 9, which are involved in extracellular matrix degradation and synthesis. Low levels of cytokines such as IL-6, IL-17 and TGF-β and no involvement of T cells was also observed, indicating a minimal inflammatory response. These findings indicate the possible future potential of using focused femtosecond laser micromachining for skin repair and photo rejuvenation without causing inflammation in the skin (Wang et al., 2021). Application of femtosecond laser in wound healing was investigated. Transient photoactivation of epidermal stem cells, which have significant potential in wound healing, was applied. Activation of epidermal stem cells in vivo was observed by significantly increased stem cell density and stemness for at least 60 hours after a single transient photoactivation.

The results obtained on the mouse model may provide a basis for further research into the potential of applying the femtosecond laser to wound healing (Hu et al., 2022). Recent findings present properties of femtosecond lasers in antibacterial therapy. The use of different parameters of the femtosecond laser against S. aureus was evaluated. A reduction in bacterial viability was observed. It was determined that the optimal parameters were 390 nm and 400 nm wavelengths, an average power of 50 mW, and a duration of 15 minutes. Further studies may result in the discovery of new m (Ahmed et al., 2021). In addition, another study evaluated exposure to femtosecond laser radiation comprising ultraviolet to blue light for more than 20 minutes and a power density of ≈ 0.063 W/cm2. This demonstrated efficacy in inhibiting bacterial pathogens, with lasting effects observed up to a week after irradiation, a promising result considering the treatment of chronic wounds (Ahmed et al., 2021).

## Application of femtosecond laser in ophthalmology

### *Refractive surgery*

Femtosecond lasers are used in ophthalmology in refractive surgery for more than 20 years, and its due to high precision and minimal damage to the surrounding tissue (Soong and Malta, 2009). In 2002 one of the first reported corneal procedures were performed with the use of a commercial femtosecond laser device in a clinical setting (Juhasz et al., 2002). Since then, commercial femtosecond laser devices have been used for laser vision correction world vide. Precision and safety of this technology contributed to the extensive use of femtosecond lasers in ophthalmology (Sugar, 2002; Kymionis et al., 2012).

### *Pterygium surgery*

Pterygium surgery is a procedure that demands extreme precision. Preparation of the conjunctival autografts (CAG) without tenons was performed with femtosecond laser technology. Visual and refractive results are comparable to the manual technique with a low recurrence rate and shows the potential to overcome the learning curve associated with manual CAG preparation (Fuest et al., 2017; Liu et al., 2020).

### *Ocular melanoma*

A recent novel discovery opens a new perspective to a minimally invasive approach to treating ocular melanomas, using photodynamic therapy with femtosecond (fs) laser technology for precise targeting with reduced damage to surrounding ocular structures. In addition, the immunomodulatory effects of photodynamic therapy offer prospects for reducing metastasis in ocular tumours, underscoring the importance of further research in this area to improve patient outcomes (Pires et al., 2024).

### *Cataract surgery*

Femtosecond laser found another clinical application in cataract surgery, which is a procedure quite often performed in ophthalmology (Nagy et al., 2009). The following years resulted in further advances in research on cataract surgery using the femtosecond laser, and analyses of the benefits or possible advantages of this method over phacoemulsification. Benefit-cost analysis of the technology showed no advantage of the femtosecond laser over phacoemulsification, indicating comparable outcomes at significantly higher costs that can place a significant burden on healthcare systems (Schweitzer et al., 2020; Narayan et al., 2023; Day et al., 2020).

The femtosecond laser has gained wide recognition in ophthalmology for its precision. Areas of medicine beyond ophthalmology are also being explored where clinical application of the femtosecond laser might be possible. The advantage of this technology over conventional techniques is its precision and minimal damage to surrounding tissues. The precision of ablation is at the level of single cells. Despite its relatively slow ablation rate, the femtosecond laser can be used in ablation of sensitive tissues where precision is paramount (Calvarese et al., 2023).

## Application of femtosecond laser in neurosciences

Research in neurosciences might bring other clinical applications of femtosecond lasers in technologies that enable advances in diagnosing and investigating neurodegenerative disorders (Hanczyc et al., 2013). A recently conducted study showed a technique for the detection of amyloids in brain tissue using a femtosecond laser. Two-photon excitation, together with the effect of light amplification, showed a favorable outcome in amyloid identification with satisfactory sensitivity, demonstrating its potential application in neurodegenerative disorders. Detection, differentiation, and imaging of amyloids may contribute to advances in research conducted on neurodegeneration (Hanczyc et al., 2022).

Those advances may contribute in developing diagnostic tool for the early detection of neurodegenerative diseases before clinical symptoms appear which is of importance in clinical practice (Hanczyc and Fita, 2021). Moreover, imaging techniques using ultra-short pulse lasers ensure safety even with prolonged tissue exposure without causing damage, which is of great clinical importance (Sibai et al., 2018). More research is needed to develop diagnostic techniques and targeted therapies for neurodegenerative diseases and to determine their safety using femtosecond leser technologies (Zongyue et al., 2021). Femtosecond laser technology has found its way into various medical fields, particularly dermatology, ophthalmology and neurology. Table 1 sums up the possible applications of the femtosecond laser in various medical fields, provides details of the new possibilities and their safety.

**Table 1** Applications and specific details of femtosecond laser use in dermatology, ophthalmology, and neurosciences.

| Field | Application | Details |
|---|---|---|
| Dermatology | Multiphoton Tomographs | Noninvasive in vivo skin biopsy (Schenke-Layland et al., 2006; König, 2008). High-resolution microscopic imaging of living skin. Imaging of cell morphology, mitochondrial distribution, epidermal-dermal junction. Measurement of autofluorescence of melanin, keratin, elastin, NADH, flavin (König et al., 2020; König, 2023). Clinical applications in skin diseases like atopic dermatitis, psoriasis, early melanoma diagnosis (Leupold et al., 2011). Potential to replace conventional skin histology (Meng et al., 2021; König and Riemann, 2003). |
| | Skin Remodeling | Activation of skin remodeling via upregulation of matrix metalloproteinases 3 and 9. Low inflammatory response (Wang et al., 2021). |
| | Wound Healing | Transient photoactivation of epidermal stem cells, increasing stem cell density and stemness (Hu et al., 2022). |
| | Antibacterial Therapy | Optimal parameters against S. aureus: 390 nm and 400 nm wavelengths, 50 mW power, 15 minutes duration (Ahmed et al., 2021). Effective in inhibiting bacterial pathogens with sustained effects for up to a week (Ahmed et al., 2021). |
| Ophthalmology | Refractive Surgery | Precision and minimal tissue impact (Soong and Malta, 2009; Juhasz et al., 2002). Common tool for laser vision correction (Sugar, 2002; Kymionis et al., 2012). |
| | Pterygium Surgery | Precise and consistent preparation of conjunctival autografts (Fuest et al., 2017; Liu et al., 2020). |
| | Ocular Melanoma | Photodynamic therapy with femtosecond laser for precise targeting. Reduced damage to ocular structures and potential reduction in metastasis (Pires et al., 2024). |
| | Cataract Surgery | Higher precision of capsulorhexis and lower power of phacoemulsification (Nagy et al., 2009). Comparable outcomes to phacoemulsification but at higher costs (Schweitzer et al., 2020; Narayan et al., 2023; Day et al., 2020). |
| | General Ophthalmic Surgery | Utilized for precision in ablation at the level of single cells (Calvarese et al., 2023). |
| Neurosciences | Neurodegenerative Disorders | Detection of amyloids using two-photon excitation (Hanczyc et al., 2022). Differentiation of protein oligomers in nucleation phase for early detection of neurodegenerative diseases (Hanczyc and Fita, 2021). |
| | Safe Neuroimaging | Shorter laser pulses improve neuroimaging without causing tissue damage (Sibai et al., 2018). |
| | Future Research | Promising potential for enhanced diagnostic techniques and targeted therapies (Zongyue et al., 2021). |

**Exploring attosecond technology, future prospects.**

Lasers with pulses lasting attoseconds are used to study processes at the molecular level, allowing the study of chemical reactions and their dynamics (Guo et al., 2024). This could have significant use in the biological sciences in conducting studies of biological molecules such as DNA and proteins in their natural environment. Studying biological processes at the molecular level opens up possibilities that were not previously available (Biegert et al., 2021). The application of attosecond technology is still an object of research and development that might result in novel findings in medicine, biomedical engineering, and other fields (Krausz and Stockman, 2014).

Femtosecond lasers have been used to create technologies used in medicine in many fields. Their ultra-short pulse duration allows for high precision which reduces the risk to surrounding tissues. Particularly treatments that require precision due to anatomical conditions benefit from femtosecond lasers, for example in ophthalmology.

In dermatology femtosecond lasers were used in developing multiphoton tomography. This technologi allows for non-invasive skin imaging. This technology provides a diagnostic option for patients with a many skin diseases and is already commercially available but more research is needed to make it common in clinical practice. Technology that explores femtosecond laser properties is being used in research in many areas of medicine. There are several research with femtosecond lasers being utilised in neurobiological sciences, creating new possibilities in the future for diagnostic of neurodegenerative conditions. In addition, it is worth noting the emergence of attosecond technology, which makes it possible to observe movements at the level of atoms in molecules. This technology may enable us to make breakthroughs in complex biological processes at the molecular level which may have future implications in medicine.

## 4. CONCLUSIONS

In summary, ultrafast lasers are widely used in medicine being part of advanced technologies that may become common tools in clinical work in the future. Undoubtedly, their precision at the cellular level, has resulted in their widespread use in ophthalmology. Further research is needed to fully understand and optimize their medical applications. In addition, attosecond lasers have the potential to make significant contributions in the future, particularly in the field of pharmacology. As research progresses, new and ever more innovative technological solutions with medical applications are being developed.

**Acknowledgments**

No acknowledgments.

**Author’s Contributions**

Kinga Filipek: Conceptualization; writing - rough preparation; supervision
Agata Pisklak: Writing - rough preparation
Hanna Behrendt: Writing - rough preparation; writing - review and editing
Marcin Głód: Writing - rough preparation
Marta Węgrzynek: Writing - review and editing

**Ethical approval**

Not applicable.

**Informed consent**

Not applicable.

**Funding**

This study has not received any external funding.

**Conflict of interest**

The authors declare that there is no conflict of interests.

**Data and materials availability**

All data sets collected during this study are available upon reasonable request from the corresponding author.

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