**Cellular Senescence: A Cellular Decline and Its Correlation to Orthodontics**

**Abstract**

Cellular senescence is often characterized as having a dual nature, with both beneficial and detrimental aspects in various physiological processes. On one hand, it serves as a protective mechanism against cancer by suppressing the growth of damaged or pre-cancerous cells. The dual nature of cellular senescence, with both beneficial and detrimental aspects, underscores the complexity of its influence on health and disease. While it serves as a critical safeguard against cancer by suppressing the proliferation of damaged or pre-cancerous cells, the accumulation of senescent cells has also been implicated in the aging process and the development of age-related disorders. the role of cellular senescence in orthodontic treatment outcomes has been increasingly recognized. Aging of periodontal tissue cells, influenced by cellular senescence, can affect the success and stability of orthodontic interventions. The study highlights the need for personalized treatment strategies, especially for older patients, considering their age, overall health, and the degree of cellular senescence in their periodontal tissues. Further research is crucial to develop targeted interventions that mitigate the adverse effects of senescence on orthodontic treatment, potentially by modulating senescent cell behaviour or employing senotherapies.

Keywords: Cellular senescence, age-related disorders, functional transformations, homeostasis

## **Introduction**

Cellular senescence represents the irreversible decline in a cell's ability to divide and proliferate, accompanied by distinct morphological and functional transformations. This state arises as a natural consequence of the aging process, characterized by the gradual accumulation of damage to cellular components such as DNA, proteins, and organelles. As cells age, they undergo a series of alterations that ultimately result in their inability to continue dividing, a process known as replicative senescence. This phenomenon plays a crucial role in maintaining tissue homeostasis and preventing the uncontrolled growth of damaged or dysfunctional cells, which could otherwise contribute to the development of cancer.

## **Cellular Senescence : The Double Edged sword**

Cellular senescence is often characterized as having a dual nature, with both beneficial and detrimental aspects in various physiological processes. On one hand, it serves as a protective mechanism against cancer by suppressing the growth of damaged or pre-cancerous cells. However, the accumulation of senescent cells is also implicated in the aging process and the development of age-related disorders.

Cellular senescence is a biological response characterized by a permanent state of cell cycle arrest, often associated with age-related changes in cell structure and function [(Abiko et al., 1998a)](#ac2610181f3c76e7029a6f499ff93374). This process can be triggered by several factors, including DNA damage, telomere attrition, oncogenic stress, and oxidative stress [(Kirkland & Tchkonia, 2020a)](#5ace0f3097f90e2496f8b53de97214bb). Excessive hypoxia may cause significant and detrimental destruction of tooth-supporting tissues (Younis et al., 2019). Senescent cells exhibit a distinct phenotype, such as increased expression of cell cycle inhibitors like p16 and p21, and the secretion of a pro-inflammatory mix of cytokines, chemokines, and proteases, known as the senescence-associated secretory phenotype [(Zhu et al., 2014)](#e1565eba075b92ab3b8bf5552dc29d84)[(Deursen, 2014)](#1d188de1b4cf12bfe02e81bfe9e14b76). The accumulation of senescent cells in tissues can have detrimental effects, contributing to age-related diseases and the overall decline in tissue homeostasis and regenerative capacity [(Lopes-Paciência et al., 2019)](#10161733c6710f15cd93274da107eac7). In the context of dentistry and orthodontics, cellular senescence of dental pulp cells has been a subject of increasing interest, as it may play a significant role in the aging process of the oral cavity and the associated challenges faced in maintaining dental health, particularly among older individuals [(Ou et al., 2018)](#2c24fdd0c0c6b5fbd7caea63ed0176f5).

Beneficial effects:

* **Tumour suppression:** Senescence acts as a potent barrier against cancer development by preventing the proliferation of damaged or pre-cancerous cells. [(Rodier & Campisi, 2011)](#ff71428090ffa365eacc2b43257a47d9)[(Herranz & Gil, 2018a)](#b93a8905fdc6bf5c9fb82e6a53248eb4). The cell cycle arrest that characterizes senescence prevents these cells from developing into tumours.
* **Wound healing:** Senescent cells can promote tissue repair by secreting factors that attract immune cells and stimulate tissue regeneration. [(Deursen, 2014)](#1d188de1b4cf12bfe02e81bfe9e14b76) The senescence-associated secretory phenotype plays a crucial role in this process. [(Lopes-Paciência et al., 2019)](#10161733c6710f15cd93274da107eac7) elaborates on the SASP and its regulation.
* **Embryonic development:** Senescence plays a role in tissue remodelling during embryonic development. [(Deursen, 2014)](#1d188de1b4cf12bfe02e81bfe9e14b76) The temporary presence of senescent cells helps shape developing tissues and organs.

Detrimental effects:

* **Aging:** The accumulation of senescent cells with age contributes to tissue dysfunction and the development of age-related diseases. [(Deursen, 2014)](#1d188de1b4cf12bfe02e81bfe9e14b76)[(Fafián‐Labora et al., 2019)](#dc6dfe5adca4adb608968e6a2f9dd035) The SASP, while beneficial in some contexts, can also drive chronic inflammation and damage surrounding tissues. [(Kumari & Jat, 2021a)](#e37c976547a59bdbb8717c72dba70953)[(Kamal et al., 2020)](#9d134c2a6ca0670d43d57a0c9b873fda)
* **Age-related diseases:** Senescent cells are implicated in various age-related diseases, including osteoarthritis, cardiovascular disease, and neurodegenerative disorders. [(Deursen, 2014)](#1d188de1b4cf12bfe02e81bfe9e14b76)[(Fafián‐Labora et al., 2019)](#dc6dfe5adca4adb608968e6a2f9dd035) The chronic inflammation and tissue damage caused by the SASP contribute to the pathogenesis of these conditions.
* **Cancer progression:** Paradoxically, while senescence suppresses tumour formation, it can also promote cancer progression in certain contexts. [(Yang et al., 2021a)](#f4622f0713d46199d348b51b1e730956)[(Rodier & Campisi, 2011)](#ff71428090ffa365eacc2b43257a47d9) The SASP can create a pro-tumorigenic microenvironment, stimulating the growth and metastasis of existing tumours.
* **Impaired tissue regeneration:** While senescence can initially promote tissue repair, the persistence of senescent cells can hinder regeneration and lead to fibrosis. [(Lopes-Paciência et al., 2019)](#10161733c6710f15cd93274da107eac7) The SASP can disrupt tissue architecture and impair the function of stem cells.

The dual nature of cellular senescence, with both beneficial and detrimental aspects, underscores the complexity of its influence on health and disease. While it serves as a critical safeguard against cancer by suppressing the proliferation of damaged or pre-cancerous cells, the accumulation of senescent cells has also been implicated in the aging process and the development of age-related disorders (Sun et al., 2022). This highlights the need for further research to identify strategies that can mitigate the harmful effects associated with cellular senescence.

## **Biological Response and Cell Structure Alteration**

Cellular senescence is a fundamental biological response that occurs as cells age or encounter various stressors [(Lamster et al., 2016)](#5286029456ebfe71f18a8a6fa7d7995c). This process is characterized by a permanent cell cycle arrest, often accompanied by changes in cell structure, metabolism, and secretory profile [(Byun et al., 2015)](#ba491541bedaec4b41fe26a9af5c21b2).

Senescent cells undergo distinct morphological changes, including an enlarged and flattened cell shape, increased granularity, and the formation of senescence-associated heterochromatin foci. These alterations are accompanied by a shift in gene expression patterns, with the upregulation of cell cycle inhibitors, such as p16INK4a and p21CIP1, and the activation of the p53 and p16-Rb pathways. Senescent cells also involves the release of various inflammatory cytokines, chemokines, growth factors, and proteases. The regulation of cellular senescence involves complex signalling pathways, with the tumour suppressor p53 playing a central role. p53 acts as a "guardian of the genome," responding to various cellular stressors, such as DNA damage, oncogene activation, and oxidative stress, by initiating cell cycle arrest, senescence or apoptosis [(Morsczeck, 2019)](#03fa0d43abb142d282d157d55ff9a674).

Cellular senescence is a state of irreversible cell cycle arrest. While it can be triggered by various factors, including telomere shortening (replicative senescence) and DNA damage (stress-induced senescence), the outcome is a cell that can no longer divide [(Gorgoulis](#c3943c89017168f2f73b655964416dfc) et al., 2019)[(Yang et al., 2021b)](#bd3bf93e22bb8f589c2bc9e7694773b7)[(Kumari & Jat, 2021b)](#d79bf91db1d6bfc4320bc34a4c15bc04).

Although senescent cells can no longer proliferate, they remain metabolically active and undergo distinct phenotypic changes. These include:

* **Morphological changes:** Enlarged and flattened cell shape.
* **Expression of senescence-associated β-galactosidase:** A commonly used marker for identifying senescent cells.
* **Senescence-associated secretory phenotype:** Senescent cells secrete a variety of factors, including cytokines, chemokines, and growth factors, which can impact the surrounding tissue microenvironment divide [(Gorgoulis](#c3943c89017168f2f73b655964416dfc) et al., 2019)

Telomeres are repetitive DNA sequences at the ends of linear chromosomes, acting as protective caps. [(Oeseburg et al., 2009)](#099e3beb6a7a0b06413190e4bb2c5b66) [(Fathi et al., 2019)](#bf8dd33f83fe1dd58b3d90392732cdd6) [(Bernadotte et al., 2016)](#35cafa59197673c7f609c7ab0041ff4f) They prevent the recognition of chromosome ends as DNA breaks, which would otherwise trigger DNA damage responses and potentially lead to genomic instability.

With each cell division, telomeres shorten due to the "end replication problem," where DNA polymerase cannot fully replicate the lagging strand. [(Oeseburg et al., 2009)](#099e3beb6a7a0b06413190e4bb2c5b66) [(Fathi et al., 2019)](#bf8dd33f83fe1dd58b3d90392732cdd6) This progressive shortening eventually triggers a DNA damage response, leading to cell cycle arrest and senescence. [(Bernadotte et al., 2016)](#35cafa59197673c7f609c7ab0041ff4f) [(Telomeres in the Cell Cycle, 2023)](#07ccda9cb992f77a1a05235b3a8e43e4) This type of senescence is known as replicative senescence. [(Mijit et al., 2020)](#558aecee45362b2dd70b948cf4b02f95)

The shortest telomere, rather than the average telomere length, is critical for cell viability and chromosome stability. [(Bernadotte et al., 2016)](#35cafa59197673c7f609c7ab0041ff4f) When telomeres become critically short, they can no longer protect chromosome ends, leading to genomic instability and senescence.

Chromatin, the complex of DNA and proteins that makes up chromosomes, undergoes significant structural changes during senescence. [(Gonzalo, 2010)](#285f20cf128ca4ff23f7dfcb68cdbbe4) [(Sen et al., 2016)](#7224db445c91628e7b6454c754e7455c) One prominent change is the formation of senescence-associated heterochromatin foci. [(Yang et al., 2021a)](#f4622f0713d46199d348b51b1e730956) [(P. L. Patel et al., 2016)](#7b77984712b997b78b577a72b415cc38) These are regions of condensed chromatin that contribute to the stable cell cycle arrest observed in senescent cells.

SAHF formation involves the recruitment of heterochromatin proteins, such as HP1, to specific regions of the genome. [(Kamal et al., 2020)](#9d134c2a6ca0670d43d57a0c9b873fda) [(Yang et al., 2021a)](#f4622f0713d46199d348b51b1e730956) This leads to the silencing of genes involved in cell cycle progression, further reinforcing the senescent phenotype. [(P. L. Patel et al., 2016)](#7b77984712b997b78b577a72b415cc38)

The loss of linker histone H1, a protein that helps organize chromatin structure, also contributes to chromatin changes in senescence. [(P. L. Patel et al., 2016)](#7b77984712b997b78b577a72b415cc38) This loss can further promote chromatin condensation and contribute to the altered gene expression patterns observed in senescent cells.

While telomere shortening can initiate senescence, the resulting DNA damage response can also trigger chromatin changes. [(Gonzalo, 2010)](#285f20cf128ca4ff23f7dfcb68cdbbe4) [(Sen et al., 2016)](#7224db445c91628e7b6454c754e7455c) For example, DNA damage foci, such as telomere dysfunction-induced foci, can recruit chromatin-modifying proteins and contribute to SAHF formation. [(Yang et al., 2021a)](#f4622f0713d46199d348b51b1e730956)

The interplay between telomere shortening, DNA damage responses, and chromatin condensation ensures the stable cell cycle arrest characteristic of cellular senescence. These changes, while contributing to tumour suppression, can also have detrimental effects in the context of aging and age-related diseases.



*Figure 1 : Evolution of Cellular Senescence Modified from: (Kowald et al., 2020)*

The biological mechanisms underlying cellular senescence involve complex signalling cascades that converge on key regulators, such as the p53 tumour suppressor protein. The activation of these pathways leads to the induction of cell cycle arrest, ultimately preventing the cell from undergoing further divisions. Interestingly, senescent cells do not simply cease to function; instead, they acquire a distinct secretory phenotype, releasing a variety of factors that can influence the surrounding microenvironment, potentially contributing to both beneficial and detrimental effects on tissue homeostasis [(Kuwano et al., 2016)](#b9329db5224b18316eb1cb1bac97d4b1).

## **Observation Of Senescence In Human Periodontal Ligament Fibroblasts And Its Implications In Dentistry**

Periodontal ligament fibroblasts are a key cell type involved in the process of cellular senescence. These cells, which play a crucial role in the maintenance and remodelling of the periodontal tissues, also undergo age-related changes that contribute to the overall process of cellular senescence.

As periodontal ligament fibroblasts age, they exhibit distinct morphological and functional alterations. These include an increase in cell size, a flattened and enlarged appearance, and the accumulation of intracellular damage, such as DNA lesions and organelle dysfunction. The activation of senescence pathways, mediated by key regulators like the p53 tumour suppressor protein, leads to cell cycle arrest, preventing further cell division.

Interestingly, senescent periodontal ligament fibroblasts do not simply cease to function. Instead, they acquire a secretory phenotype, releasing a variety of factors that can influence the surrounding microenvironment. This secretome can have both beneficial and detrimental effects on the maintenance of periodontal tissue homeostasis, depending on the specific factors released and the overall balance within the local environment[(Kirschneck et al., 2020)](#50ed29c4fbc373a505cbaa09bf9ba037).

Periodontal ligament fibroblasts, essential for maintaining and remodelling periodontal tissues, are subject to cellular senescence like other cell types. As these cells age, they undergo characteristic changes:

* **Morphological alterations:** Senescent PDLFs become enlarged and flattened. [(Mohanakumar et al., 2021a)](#53c26c9f768d6502bbe6b7abd102fbe4)
* **Impaired function:** They lose their capacity for division and proliferation, impacting tissue regeneration and repair. [(Mohanakumar et al., 2021a)](#53c26c9f768d6502bbe6b7abd102fbe4)[(Sawa et al., 2000c)](#6beb15d20580b3bc5f16e5178816a3f7)
* **Osteocalcin production impairment:** Senescent PDLFs exhibit reduced production of osteocalcin, a protein important for bone formation. [(Sawa et al., 2000a)](#f2a85dc874e6b6f5511346a8f3e0ccd9)
* **Senescence-associated secretory phenotype:** They secrete a variety of factors that can influence the surrounding tissue microenvironment, contributing to both beneficial and detrimental effects. [(Mohanakumar et al., 2021a)](#53c26c9f768d6502bbe6b7abd102fbe4)[(Zhou et al., 2023a)](#66166e12e5c4fc963d4dca7e82026c72) For example, the SASP can promote inflammation and impair tissue homeostasis, potentially increasing susceptibility to periodontal diseases. [(Wiley et al., 2019)](#ff3845a67240be9f16a7b1d8de726b40) However, the SASP can also play a role in tissue repair. [(Menéndez & Alarcón, 2017)](#d85bb603fc4776896f576f1f09790e14)

Mechanical stress, such as that experienced during orthodontic treatment, can also induce senescence in PDLFs and cementoblasts. [(Zhou et al., 2023a)](#66166e12e5c4fc963d4dca7e82026c72) This stress-induced senescence can contribute to orthodontic root resorption. Stress-induced premature senescence is a key factor in orthodontic root resorption. Mechanical stress from orthodontic forces can trigger cellular senescence in periodontal ligament fibroblasts and cementoblasts. [(Zhou et al., 2023b)](#617874474f9297d8a79f53b7f9b25ad8)

Here's a breakdown of the process:

1. **Mechanical stress:** Orthodontic forces place stress on the teeth and surrounding periodontal tissues.
2. **Cellular senescence:** This mechanical stress can induce SIPS in PDLFs and cementoblasts. These cells exhibit characteristic features of senescence, including cell cycle arrest and altered morphology. [(Zhou et al., 2023b)](#617874474f9297d8a79f53b7f9b25ad8)
3. **RANKL expression:** Senescent PDLFs and cementoblasts upregulate the expression of Receptor Activator of Nuclear Factor Kappa-B Ligand. [(Zhou et al., 2023b)](#617874474f9297d8a79f53b7f9b25ad8) RANKL is a critical factor in osteoclastogenesis, the process of bone resorption.
4. **Odontoclast activation:** RANKL binds to its receptor RANK on pre-osteoclasts, promoting their differentiation into mature, bone-resorbing odontoclasts.
5. **Root resorption:** Activated odontoclasts resorb the root structure, leading to shortening and blunting of the roots. [(Zhou et al., 2023b)](#617874474f9297d8a79f53b7f9b25ad8)

The severity of root resorption varies among individuals and is influenced by factors such as force magnitude, duration, and direction. The presence of senescent cells expressing RANKL in the periapical tissues under mechanical stress contributes significantly to this process. [(Zhou et al., 2023b)](#617874474f9297d8a79f53b7f9b25ad8)

Research suggests that targeting senescent cells with senolytics, drugs that selectively eliminate senescent cells, may be a potential therapeutic strategy for preventing or mitigating orthodontic root resorption. [(Zhou et al., 2023b)](#617874474f9297d8a79f53b7f9b25ad8) Further investigation is needed to fully elucidate the complex interplay between mechanical stress, cellular senescence, and root resorption.

While senescence-associated beta-galactosidase activity is a widely used marker for senescence, it's not suitable for fixed tissues. Immunofluorescence, however, isapplicable to fixed tissues and can be used to detect several senescence markers:

* **p16:** A cyclin-dependent kinase inhibitor, p16 is often upregulated in senescent cells. Antibodies against p16 can be used in immunofluorescence to identify senescent cells. [(Kohli et al., 2021)](#785c903383816667c2f46cdb7a5b71a1) (Gorgoulis et al., 2019)
* **p21:** Another cell cycle inhibitor associated with senescence. Similar to p16, antibodies against p21 can be used in immunofluorescence. [(Kohli et al., 2021)](#785c903383816667c2f46cdb7a5b71a1) (Gorgoulis et al., 2019)
* **γH2AX:** A marker of DNA damage, γH2AX foci are often observed in senescent cells due to persistent DNA damage responses. Immunofluorescence with antibodies against γH2AX can reveal these foci (Gorgoulis et al., 2019)
* **Senescence-associated heterochromatin foci:** These condensed chromatin regions are characteristic of senescent cells. Antibodies against heterochromatin proteins, such as HP1, can be used to visualize SAHF in immunofluorescence (Gorgoulis et al., 2019)
* **Lipofuscin:** This age-related pigment accumulates in lysosomes of senescent cells. While not strictly a senescence marker, lipofuscin can be detected using autofluorescence or specific dyes like Sudan Black B (Gorgoulis et al., 2019).
* **GL13:** A recently developed reagent suitable for immunohistochemistry and immunofluorescence, GL13 can identify senescent cells in fixed tissues(Gorgoulis et al., 2019).

Using a combination of these markers in immunofluorescence can increase the specificity and reliability of senescence detection. [(Kohli et al., 2021)](#785c903383816667c2f46cdb7a5b71a1) (Gorgoulis et al., 2019). For example, co-staining for p16 and SAHF can provide strong evidence of senescence. Additionally, flow cytometry can be used to analyse immunostained cells, providing quantitative data on the proportion of senescent cells in a population.

The accumulation of senescent PDLFs with age is thought to contribute to the increased prevalence of periodontal diseases in older individuals [(Abiko et al., 1998a)](#ac2610181f3c76e7029a6f499ff93374). This is due in part to the impaired regenerative capacity of the tissue and the pro-inflammatory effects of the SASP. Understanding the mechanisms of cellular senescence in PDLFs is crucial for developing strategies to maintain periodontal tissue homeostasis and prevent age-related periodontal diseases. The gradual accumulation of senescent cells in periodontal tissues, as a result of aging, is thought to contribute to the increased susceptibility to periodontal diseases observed in older individuals. This is due to the impaired regenerative capacity of the tissue, as well as the potential pro-inflammatory effects of the senescence-associated secretory phenotype. Detecting cellular senescence through fluorescence staining can provide valuable insights into the underlying mechanisms and potential therapeutic interventions.

Targeting senescent cells with senolytics, drugs that selectively eliminate these cells, represents a promising approach for mitigating and managing age-related periodontal diseases and mitigating orthodontic root resorption. It was found that by administering a senolytic treatment comprising of dasatinib and quercetin can reduce the number of RANKL-positive senescent cells in a rat model of orthodontic tooth movement, ultimately leading to a decrease in the extent of root resorption [(Zhou et al., 2023a)](#66166e12e5c4fc963d4dca7e82026c72). It was reported, there is evidence of senolytics' effectiveness in decreasing senescent cells in humans [(Ellison, 2020b)](#82e29e4f83639c46fd8bb03f37e0a496).

In the context of human periodontal ligament fibroblasts, senescent cells demonstrate changes in their gene expression patterns, elevated secretion of inflammatory mediators, and diminished regenerative potential. In summary, the biology of cellular senescence is a complex process that involves the gradual accumulation of cellular damage, leading to irreversible cell cycle arrest and distinct morphological and functional changes in the affected cells.

## **Cellular Senescence And Its Correlation To Orthodontics : Treatment Approaches And Outcomes**

Cellular senescence is often accompanied by a distinct secretory phenotype known as the senescence-associated secretory phenotype [(Herranz & Gil, 2018b)](#2b338a1ac3b985fc03db1e51455b717b). This process has been linked to various age-related diseases, including those affecting the oral cavity[(Mijit et al., 2020)](#558aecee45362b2dd70b948cf4b02f95) [(Martin & Bernard, 2017)](#12776e0ca40d854dbb61483130eb324e) [(Abiko et al., 1998a)](#ac2610181f3c76e7029a6f499ff93374).

Furthermore, the role of cellular senescence in orthodontic treatment outcomes has been increasingly recognized. Aging of periodontal tissue cells, influenced by cellular senescence, can affect the success and stability of orthodontic interventions. [(Abiko et al., 1998a)](#ac2610181f3c76e7029a6f499ff93374). Factors such as the severity of periodontal disease, the responsiveness of periodontal cells to orthodontic forces, and the rate of tissue remodelling can all be impacted by the cellular senescence process. The compromised bone remodelling associated with cellular senescence can also exacerbate issues like root resorption, dental caries, and gingival recession during prolonged orthodontic treatment. Senescent osteoblasts and osteoclasts may have diminished ability to maintain the dynamic balance between bone formation and resorption, leading to greater risk of undesirable side effects. Understanding these mechanisms is crucial for developing more effective and personalized orthodontic treatment approaches to address the unique challenges posed by cellular senescence.

The rate of tissue remodelling plays a crucial role in the success and efficiency of orthodontic treatment. Orthodontic tooth movement relies on the controlled remodelling of alveolar bone and periodontal ligament in response to applied forces. Rate of remodelling influences treatment by few factors:

* **Treatment duration:** A faster rate of remodelling allows for quicker tooth movement, shortening the overall treatment time. A study concluded that average treatment takes 18-24 months and there's an interest amongst orthodontic practitioners to accelerate tooth movement [(Huang et al., 2018)](#52553a674ff119e2d528167eb6c01811)Increased remodelling rate expands the envelope of tooth movement, allowing for more complex tooth movements and improvements in treatment outcomes [(Huang et al., 2014)](#9d8dc67b94453420c71ce6c8ed029c33). Reduced side effects: Faster tooth movement can reduce the risk of side effects such as root resorption, which is a common concern in orthodontic treatment. [(Zhou et al., 2023a)](#66166e12e5c4fc963d4dca7e82026c72). Therefore, understanding the role of cellular senescence in the context of orthodontics is essential for developing more effective and personalized treatment strategies. In contrast, a slower rate of tissue remodelling can prolong treatment duration and increase the likelihood of adverse outcomes, such as root resorption, dental caries, and gingival inflammation. It has been proposed that utilizing lighter, continuous orthodontic forces may be beneficial, as this approach may allow for improved cell formation, particularly in adult patients who exhibit a slower initial tissue response to treatment [(Reitan, 1967a)](#7d90e1d5b70c1046cbfbf537c07559dd).
* **Treatment outcome:** Optimal remodelling ensures predictable and stable tooth movement which involves the mechanical and biological processes during tooth movement, including remodelling of the periodontal ligament and alveolar bone [(Henneman et al., 2008)](#b00ec6b386b744701f26414e2e95f973). A balanced rate of bone formation and resorption is essential for achieving the desired tooth position and maintaining long-term stability.
* **Patient age:** remodelling rates vary with age, generally being faster in younger individuals and slower in adults. [(Li et al., 2018a)](#e517b4d380eacfa52c9afe987f3971c7) highlights the increasing number of adult patients seeking treatment and their slower tissue metabolism and regeneration rates. [(Reitan, 1967a)](#7d90e1d5b70c1046cbfbf537c07559dd) discusses the slower initial tissue response in adults due to the tissue being in a static phase prior to treatment. This necessitates adjustments in treatment planning and force application for different age groups. Determining the "best" or "worst" age for orthodontic treatment is complex, varying with the malocclusion, individual factors, and goals. However, according to (Fleming et al., 2023) we can make some general observations:
1. Children (mixed dentition stage 7-10 years of age : Early intervention is beneficial for addressing developing orthodontic issues. Treatment focuses on guiding jaw growth, creating space for permanent teeth, and correcting harmful habits, potentially reducing the need for extensive future treatment.
2. Adolescents (permanent dentition stage 11-18 years of age) : Often an optimal time for comprehensive orthodontics as permanent teeth have mostly erupted, growth facilitates tooth movement, and tissues respond well to orthodontic forces.
3. Adults (18 years of age or more) : Orthodontic treatment is possible, but completed growth limits skeletal changes, potentially requiring surgery. Slower bone remodelling and periodontal health require careful consideration; however, many adults achieve excellent results.
* **Individual variation:** Genetic factors, systemic health, and local conditions can influence individual remodelling rates. [(Heidary et al., 2017)](#96cdcf16487c974e3067192f70911ebb) mentions that clinical orthodontic treatment can become inefficient due to several physiological and practical factors. [(Huang et al., 2014)](#9d8dc67b94453420c71ce6c8ed029c33) notes that biochemical and mechanical factors regulate the rates of bone modelling and remodelling. This underscores the importance of personalized treatment approaches.
* **Orthodontic force application:** The type, magnitude, and duration of orthodontic forces can affect the rate of remodelling [(Henneman et al., 2008)](#b00ec6b386b744701f26414e2e95f973) introduces a theoretical model to describe the events after orthodontic force application. [(Heidary et al., 2017)](#96cdcf16487c974e3067192f70911ebb) discusses temperature rise as a potential indicator of the orthodontic process. Excessive force can lead to undesirable effects like root resorption and pain, while insufficient force may not induce adequate tooth movement. Excessive force compresses blood vessels in the PDL, restricting blood flow and leading to localized ischemia (lack of oxygen). [(Minato et al., 2018a)](#5de7d74bb01a675d24769930db8ae3f0) This can cause cell death and the formation of hyalinized zones within the PDL[(Li et al., 2018b)](#2f8dec7bd240cfcc12f0b1952dc84155).
* **Cellular senescence:** The accumulation of senescent cells in periodontal tissues can impair remodelling and compromise treatment outcomes. A study examines the effect of aging on periodontal tissue cells. Senescent cells exhibit reduced proliferative capacity and altered secretory profiles, affecting bone turnover and responsiveness to orthodontic forces [(Abiko et al., 1998a)](#ac2610181f3c76e7029a6f499ff93374). Recent studies investigates aging changes in human-derived periodontal ligament cells before and after orthodontic force application [(George et al., 2020)](#b3e3d3fd494cae7d2227290994a1b46b)[(Mohanakumar et al., 2021b)](#52deb1ccb2ab19eba760b9b4c164a586). To date, there has not been any study which investigates the direct link between cellular senescence and orthodontic tooth movement.



*Figure 2 : Orthodontic Force Application and Tissue Responses Modified from* (Kharbanda et al., 2013)

Understanding the factors that influence tissue remodelling is crucial for optimizing orthodontic treatment. Tailored treatment in orthodontics, also known as personalised orthodontics, customises treatment plans for each patient. It involves: Thorough Assessment, Digital Technology, Individualised Mechanics, Interdisciplinary Approach and Patient Education (Giuntini et al., 2023). By tailoring treatment strategies to individual patient characteristics and biological responses, clinicians can achieve more efficient and predictable outcomes while minimizing the risk of complications [(Jheon et al., 2017)](#2ad363a46da3a289b4ecb7d3d56bd6e5).

Examining the effects of cellular senescence on the cellular and molecular mechanisms involved in orthodontic tooth movement is essential for developing more effective and personalized treatment approaches, particularly for older patients who may experience slower or less favourable responses to such interventions [(Huang et al., 2014)](#9d8dc67b94453420c71ce6c8ed029c33).

Consideration of craniofacial growth and development is also crucial when initiating orthodontic treatment, as these factors can significantly influence the outcomes of such procedures [(Buschang et al., 2017)](#ed9f79abe29ab60bd6f144360c4a21da). Practitioners must have a comprehensive understanding not only of tooth development but also of the dynamics of growth and development within the craniofacial complex. This knowledge allows clinicians to anticipate the potential outcomes of orthodontic treatment and tailor their approaches accordingly, particularly in cases requiring orthopaedic or functional appliances to address maxillofacial imbalances and dentoskeletal disorders [(Padalino et al., 2014)](#93a250115c7fa38ca06581cec3cdb120).

These complications are particularly relevant in the context of cellular senescence, as the compromised regenerative capacity of senescent cells may exacerbate these issues [(Xu et al., 2018)](#f7697cba16c2cafa3012a24efb9a47ae). Various strategies have been explored to accelerate orthodontic tooth movement and reduce treatment duration, including the use of biologically active substances, the application of cyclic mechanical and electric forces, and the development of surgically-facilitated orthodontics [(Nimeri et al., 2013)](#01179d9792cd148a986619a41fb603a8). Advances in orthodontic treatment have included the development of surgically facilitated techniques, such as corticotomy-facilitated orthodontics, which aim to accelerate tooth movement and reduce treatment duration [(N. Patel et al., 2013)](#6e07acdb9bfdddb801da4afabd050337). However, the impact of cellular senescence on the success and longevity of these techniques remains an area that requires further investigation. Senescence may lead to :

* **Impaired Tissue Regeneration:** Senescent cells exhibit reduced proliferative capacity and altered secretory profiles, impacting tissue regeneration and bone remodelling crucial for orthodontic tooth movement [(Abiko et al., 1998b)](#ca0b3a00f8ea4d7d082bc03770722b3f)[(Mohanakumar et al., 2021b)](#52deb1ccb2ab19eba760b9b4c164a586)[(Parkinson & Prime, 2022)](#bf75202afb2caea4a61def1540937931). This can lead to slower and less predictable tooth movement in older patients [(Li et al., 2018b)](#2f8dec7bd240cfcc12f0b1952dc84155)[(Reitan, 1967b)](#fb9f5a258d4ec57f0d421652e538807c).
* **Compromised Bone Remodelling:** Senescent cells contribute to impaired bone turnover and decreased responsiveness to orthodontic forces [(Sawa et al., 2000b)](#11f62197ad567bb945ea698271ebd836)[(Parkinson & Prime, 2022)](#bf75202afb2caea4a61def1540937931). The accumulation of senescent cells in periodontal tissues can compromise treatment outcomes by affecting the delicate balance of bone formation and resorption necessary for successful tooth movement [(Li et al., 2018b)](#2f8dec7bd240cfcc12f0b1952dc84155)[(Reitan, 1967b)](#fb9f5a258d4ec57f0d421652e538807c).
* **Increased Risk of Complications:** Longer treatment durations, often necessary due to slower remodelling in the presence of senescent cells, increase the risk of complications like root resorption, dental caries, and gingival recession [(Li et al., 2018b)](#2f8dec7bd240cfcc12f0b1952dc84155)[(Minato et al., 2018b)](#96f9a316196dda8f6b619011cbf647f5)[(Di̇ndaroğlu & Doğan, 2017)](#ab95829ed54ca4af7489ce9a89556aa1). The compromised regenerative capacity of senescent cells may exacerbate these issues.
* **Influence on Treatment Outcomes:** Cellular senescence can influence the severity of periodontal disease, the responsiveness of periodontal cells to orthodontic forces, and the rate of tissue remodelling, all of which are critical factors in determining the success and stability of orthodontic interventions [(Parkinson & Prime, 2022)](#bf75202afb2caea4a61def1540937931)[(Abiko et al., 1998b)](#ca0b3a00f8ea4d7d082bc03770722b3f).
* **Need for Personalized Approaches:** The impact of cellular senescence underscores the need for personalized treatment approaches, especially for older patients. Factors such as the patient's age, overall health, and the extent of cellular senescence in periodontal tissues should be considered when planning and executing orthodontic treatment [(Li et al., 2018b)](#2f8dec7bd240cfcc12f0b1952dc84155)[(Reitan, 1967b)](#fb9f5a258d4ec57f0d421652e538807c).

While the precise mechanisms linking cellular senescence and orthodontic tooth movement remain under investigation, current research indicates that this cellular phenomenon exerts a significant influence on treatment outcomes.

It is essential to increase our knowledge of how orthodontic treatments and cellular senescence interact since doing so will make it easier to create focused methods to lessen the negative consequences of this process. Possible strategies could involve investigating ways to modify the secretory patterns of senescent cells inside the periodontal tissues or to eradicate them specifically [(Kirkland & Tchkonia, 2020b)](#33b610ccbfa14f98985924cceb58d77d)[(Ellison, 2020a)](#4af625c9cc73aad62afff9ab18d8115b). The use of senotherapies, such as senolytic agents or interventions that target the mechanisms driving cellular senescence, may prove beneficial in improving the success and predictability of orthodontic treatment, particularly in older patients [(Baima et al., 2021)](#af40cec3e7e3871e2b2a90f736d23b83). (Zhou et al., 2023) indicates that senescent cells play a role in root resorption during orthodontic treatment and 2023 has found that dasatinib and quercetin (D+Q), selectively eliminate senescent cells on mouse models. Senolytics could potentially mitigate this by eliminating senescent cells in the periodontal ligament. The absence of clinical trials indicates that the translation of this research to orthodontic practice represents a key area for future investigation.

## **Conclusion**

Cellular senescence significantly influences orthodontic treatment outcomes, particularly in adults. The decreased regenerative capacity, impaired bone remodelling, and altered cell behaviour associated with senescence can lead to slower, less predictable tooth movement and a heightened risk of complications like root resorption and gingival recession. This highlights the need for personalized treatment strategies, especially for older patients, considering their age, overall health, and the degree of cellular senescence in their periodontal tissues. Further research is crucial to develop targeted interventions that mitigate the adverse effects of senescence on orthodontic treatment, potentially by modulating senescent cell behaviour or employing senotherapies.

Disclaimer (Artificial intelligence)

Option 1:

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image generators have been used during the writing or editing of this manuscript.

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