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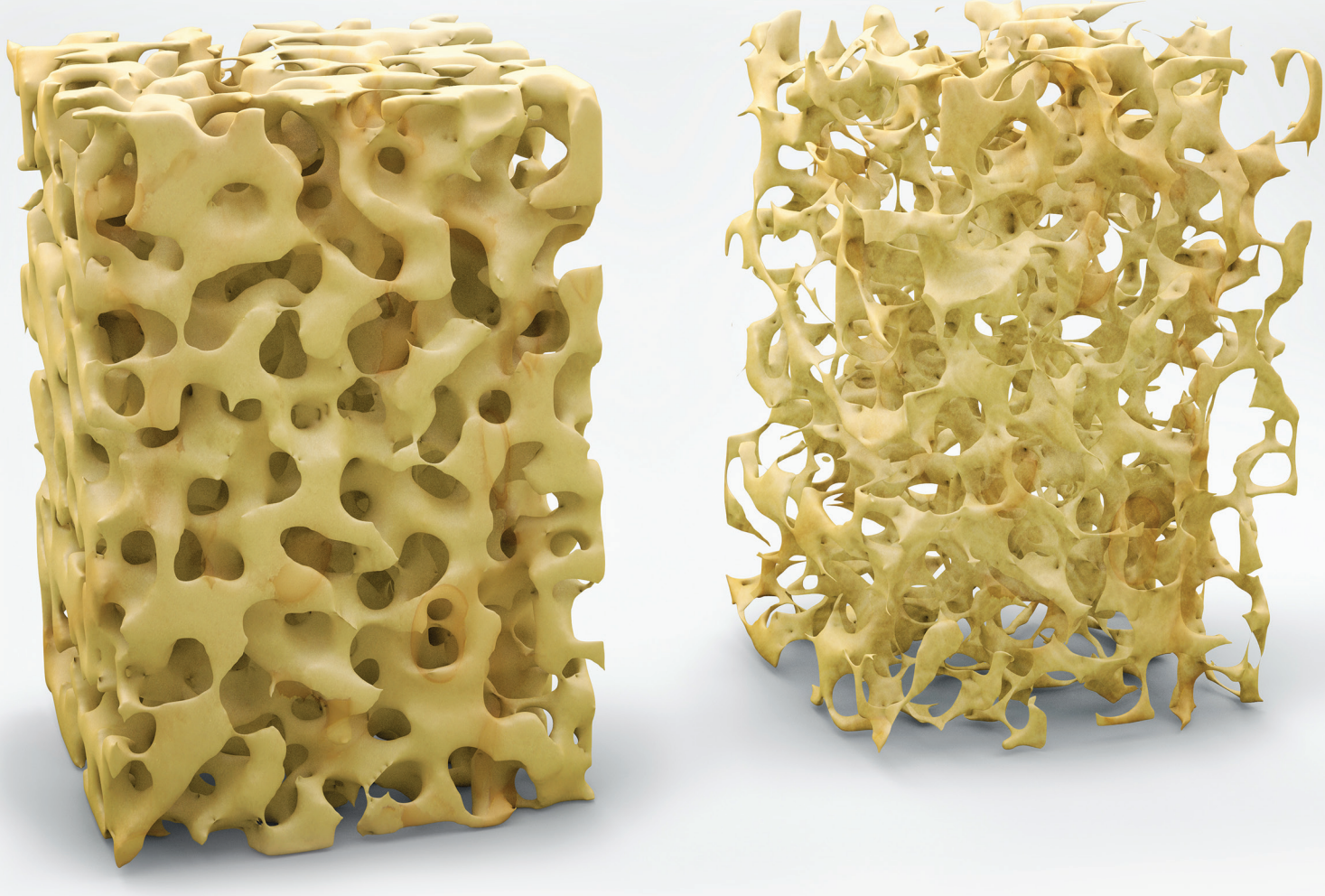
A DIVISION OF TOURO UNIVERSITY IN FLATBUSH
Where Knowledge and Values Meet



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The Lander College of Arts and Sciences at Touro University in Flatbush

Over forty-five years, Touro's Lander College of Arts and Sciences in Flatbush (with separate Schools for Men and for Women) has provided thousands of aspiring high school graduates from yeshivas and seminaries with a foundation of academic excellence for professional advancement and career growth, in an environment that is supportive of the students' religious values and perspectives. Our graduates have assumed leadership roles in various professions and have strengthened Jewish communities in the United States and in Israel.

In February 2022, Touro College was granted university status by the Board of Regents of the State of New York. Touro University will celebrate its 50th anniversary at a dinner in December 2022.

The Lander College of Arts and Sciences in Flatbush offers more than 20 majors and pre-professional options, including the Flatbush Honors Program, the Medical Honors Pathway with New York Medical College, the Integrated Honors Tracks in Health Sciences (OT, PT, PA, Pharmacy, SLP), the Fast Track Program with the Touro College of Pharmacy, the accelerated Nursing (BSN) Pathway Program, and the accelerated Accounting CPA Honors program. Additionally, students may choose Honors Majors in biology, political science and psychology. Five majors are available for students interested in accounting and business, including a top-rated CPA program.

Faculty members have earned recognition for outstanding achievements, including Dr. John Loike, Professor of Biology, who has published widely in the fields of bioethics and genetics; Joshua November, Assistant Professor of Languages and Literature, who was selected as a finalist for the Los Angeles Times Poetry Book of the Year Prize in 2011 and was a National Jewish Book Award finalist in 2016 in the poetry category; Thomas Rozinski, Assistant Professor of Political Science, and Pre-Law Advisor who served, in 2018-2019, as Vice President of the Northeast Association of Pre-Law Advisors, and who presented several times at the Annual Meeting of the American Political Science Association; and Atara Grenadir, Assistant Professor of Art, whose work was displayed at the Architectural Digest Home Design 2016 Show in New York City.

Distinguished alumni of Touro's Lander College of Arts and Sciences in Flatbush include: Dr. Israel Deutsch (MD, Einstein), Director of Brachytherapy at New York-Pres¬byterian Hospital/Columbia University; David Greenfield (JD, Georgetown), Executive Director of the Metropolitan Council on Jewish Poverty; Yossi N. Heber (MBA, Wharton), President, Oxford Hill Partners; Dr. Haim Mozes (PhD, NYU), Chair of Business and Professor, Graduate School of Business, Fordham University; Sharona Noe-Sharfman, Vice President and Officer, the Federal Reserve Bank of New York; Samuel Lowenthal, CPA, Partner, DeLoitte; Mindi Lowy, CPA, Partner, PwC; Joel Krasnow, JD, Partner, Milbank; Kalman Yeger, Member, New York City Council; and Simcha Felder, CPA, member of the New York State Senate.

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Osteoporosis: A Comprehensive Review

Eliyahu Greenberg

Eliyahu Greenberg will graduate with a Bachelor of Science degree in Biology in May 2022.

Abstract

Osteoporosis is a disease of the skeleton that becomes more common with advanced age, especially in postmenopausal women. Osteoporosis increases the risk of fractures, thereby reducing the quality of life for those who suffer from it. Due to the aging population, direct costs resulting from osteoporosis are projected to reach upward of $25 billion per year by 2025. The main pharmaceuticals primarily target osteoclasts. Exercise may be an effective method of preventing osteoporosis, although more research needs to be done. More research should be conducted to explore potential ways to enhance osteoblastic activity as a method to treat and/or reverse osteoporosis. This review compares the pros and cons of major methods to treat osteoporosis.

Introduction

Osteoporosis is a disease of the skeleton that becomes more common with advanced age, especially in postmenopausal women. The CDC reported based on the data from the NHANES (National Health and Nutrition Examination Survey) that 10.2 million adults had osteoporosis and 43.4 million had low bone mass, as of 2010 (Looker, 2015). Osteoporosis leads to an increased risk of fractures, reducing quality of life for those who suffer from it. Due to the aging population, direct costs resulting from osteoporosis are projected to swell upward of $25 billion by the year 2025 (Dempster, 2011). The goal of this review is to present the causes of osteoporosis, explain the current treatments, and weigh the pros and cons of the various therapeutics. Can osteoporosis be prevented, treated, or perhaps even reversed?

Bones are not inanimate objects that the body produces, rather bone is living tissue that continually undergoes a process called remodeling, i.e. the continuous degradation and rebuilding of the bone tissue.

Bones are composed of cells connected through a large extracellular matrix, which is comprised of 15 percent water, 20 percent collagen fibers, and 55 percent mineralized salts. The main salt is calcium phosphate, which combines with calcium hydroxide to form crystals of hydroxyapatite. These crystals continue to combine with other mineral salts to form a hardened tissue. This process, referred to as calcification, is initiated by cells called osteoblasts. Mineral salts crystallize in between and then around collagen fibers. The mixture of stiff crystalized minerals and flexible collagen provides bones with both strength and flexibility. Bone tissue is often compared to reinforced concrete. Collagen is analogous to flexible metal rods that provide support for the concrete-like mineral component (Totora & Derrickson, 2014).

There are many reasons for remodeling. Bones can buffer the amount of calcium in the blood by building more bone mass to use up excess calcium or degrade existing bone to release calcium when needed. The proper concentration of calcium must be maintained in the body, as too much calcium can cause a heart attack while too little can cause breathing to stop. There are two hormones regulating this process. PTH promotes the degradation of bone, releasing calcium, while Calcitonin promotes the deposition of bone, storing calcium.

Other factors that may affect remodeling and the rate of bone deposition include the availability of minerals that make up the bone, especially calcium and phosphorus. Vitamins, particularly Vitamin A which stimulate osteoblasts (the cells that build new bone), and Vitamin C, used in collagen production, are needed as well. Thyroid hormones (T3 and T4) from the thyroid gland promote bone growth by stimulating osteoblasts. In addition, the hormone insulin from the pancreas promotes bone growth by increasing the synthesis of bone proteins (Totora & Derrickson, 2014).

Sex hormones, including estrogen and testosterone, also affect bone growth. They are responsible for increased osteoblast activity, which is why post puberty, many teenagers experience growth spurts. As the level of sex hormones diminishes during middle age, especially estrogen in women after menopause, a decrease in bone mass occurs because bone resorption by osteoclasts outpaces bone deposition by osteoblasts. Estrogen can contribute to bone growth by promoting the death of osteoclasts. In addition, women who have smaller bones with less mass than those of men run a high risk of developing osteoporosis (Totora & Derrickson, 2014).

Bone remodeling happens in two stages. First, old bone tissue is broken down and reabsorbed into the blood via cells called osteoclasts. Then, bone deposition occurs, whereby osteoblasts deposit collagen fibers and minerals. Aside from calcium concentrations, remodeling may also be triggered by factors such as exercise, sedentary lifestyle, and changes in diet. Remodeling helps to fix injured bone and strengthen areas of bone subject to high stress. Newer bone is also more fracture-resistant than older bone (Totora & Derrickson, 2014). If the rate of degradation is higher than the rate of deposition, loss of bone mass will occur and result in osteoporosis.

Methods

The Touro library's database and Google were used to find peer-reviewed articles and papers. Search terms used included "prevention of osteoporosis", "treatment of osteoporosis", "adverse effects of osteoporosis treatments", etc. The Principles of Anatomy and Physiology 14th edition was used as well.

Discussion: Prevention

Although there are several pharmaceuticals that treat osteoporosis, treatments regimens are often poorly followed. A study of 178 patients on a course of treatment for osteoporosis found that 23% of patients did not stick to the prescribed treatment and dropped out. The study reported a number of reasons for noncompliance, ranging from expense, inconvenience of use, and fear of side effects (Segal, Tamir, & al, 2003). A large review of 24 studies on osteoporosis treatments found that "One-third to half of patients do not take their medication as directed. Nonadherence occurs shortly after treatment initiation" (Kothawala, Badamgarav, & al, 2007). As mentioned, bone is living tissue which respond to stress by strengthening itself. Therefore, applying stress through weight-bearing exercises could help to stimulate bone strengthening. A study showed that postmenopausal women who underwent back-muscle training for two years had a higher bone density than that of a control group. Interestingly, the effects were not immediately apparent, and were only evident when measured 8 years after the exercise regimen stopped. Apparently, exercise has long term, but not immediate effects (M. Sinaki, 2002). Aside from increased bone health, the impact of stronger muscles results in enhanced balance, which contributes to fewer falls and fractures. Conversely, an experiment was conducted to determine bone loss due to lack of physical stress. Ninety healthy men were placed on bed rest for 36 weeks and urine calcium concentration was measured to determine bone loss. The study found that urine calcium concentrations became elevated to 100 mg a day, showing demineralization of bone. This elevated excretion of calcium in urine continued for 36 weeks (Schneider, 1984).

How do bones react to physical stress? Bones react to physical stress through biochemical reaction resulting from mechanical stimulus. Bones contain cells called osteocytes, osteoblasts that have matured and reside within bone. Osteocytes are positioned in a way that the deformation of bone tissue is amplified by 20-100 times on its cell membrane. The deformation on the cell membrane signals that the bone is undergoing stress. This is thought to trigger a host of processes within the cell, resulting in osteogenesis. The process by which osteocytes signal is extremely complex and still not fully understood (Gusmão & Belangero, 2015). One way osteocytes can signal is through a chemical known as sclerostin, which promotes bone degradation and is coded for by the gene SOST. Mice with SOST gene deletion and humans with mutations on this gene have higher bone density. Mechanical loading has been reported to reduce sclerostin expression as well. New research is being conducted for an antibody against sclerostin to treat osteoporosis (Bonewald, 2011).

Treatments

The first line of treatment for osteoporosis is currently Bisphosphonates (BP), which disrupts osteoclastic activity. Because osteoclast are the cells responsible for bone degradation, many treatments seek to inhibit osteoclast activity. Osteoclasts degrade bone by releasing hydrogen ions, thereby creating a acidic environment. They use a ruffled border that attaches to the bone's surface. The ruffled border has crevices created by its protrusions which act as containers for the acid secreted by the osteoclast. The acid remains in these crevices, which form small pockets known as sub-osteoclastic compartments when sealing onto bone. The acidic environment causes the mineral component of bone to become more soluble, allowing bone's minerals to be absorbed by the osteoclasts.

BP has a strong affinity for calcium ions, which are found in bone, due to the presence of two phosphate groups, this results in the rapid localization of BP to bone material. Experiments using radio labeled BP has shown that BP are taken up and adsorbed in to bone primarily (Xiao-Long Xu, 2013).

When osteoclasts attach to bone that contains BP the acidic environment protonates the BP. Protonated BP has a lowered affinity for calcium ions, allowing for the release of BP into the sub osteoclastic compartment where BP is taken up by the osteoclast.

BP disrupts cell functions in the osteoclast, BP have a similar chemical structure to that of pyrophosphate. Pyrophosphate is involved in many cell processes in the osteoclast. Due to its similarity to pyrophosphate, BP is likely to interfere with any of the processes that involve pyrophosphate. It is thought that the BP inhibits prenylation of protein to the cell membrane, the lack of these proteins at the membrane results in loss of the ruffled border and prevents the osteoclast from being able to degrade the bone. This is shown as bisphosphonate-treated osteoclasts lack a ruffled border (Russell & Rogers, 1999).

Side Effects of BP

Doctors I have spoken with report that patients reported gastrointestinal (GI) discomfort while taking oral BP, and an NCBI continuing education paper for doctors states " All oral bisphosphonates have correlations with upper gastrointestinal adverse effects, including gastrointestinal reflux, esophagitis, esophageal/gastric ulcers, and gastritis. Gastrointestinal side effects are the most common

reason for discontinuation of oral bisphosphonates." The article recommends avoiding BP in patient that are at a higher risk of gastrointestinal distress (Ganesan K, 2021). A study conducted to determine the compliance of patient to osteoporosis treatment found that the major reason reported by patients for discontinuation of alendronate (a BP) was indeed GI side effects. Counter to this, a study conducted to determine if there is any correlation between alendronate (a BP) use and GI problems found no correlation of BP use and GI issues. The experiment was a randomized, double-blind, placebo-controlled trial with a mean follow-up of 3.8 years. Women were initially randomized to receive alendronate sodium, 5 mg/d, or placebo. After 2 years, the alendronate sodium dose was increased to 10 mg/d. The study did not find any significant correlation between BP use and GI problems. "The overall incidence of upper GI tract events was similar in the alendronate and placebo groups". The study goes on to suggest that GI side effects reported may be due to the higher age of osteoporotic patients (Bauer DC, 2000). The study that found that noncompliance in BP-taking patients also tracked patient adherence to Raloxifene (a different class of treatment known as a SERM), none of the Raloxifene-taking patients attributed the reason of their discontinuation of treatment due to gastrointestinal issues (Segal, Tamir, & al, 2003). This would call into question the suggestion that the gastrointestinal affects attributed to BP are really age related and not resultant of BP. Both groups were of the same population yet only the BP-taking group reported gastrointestinal issues. The study cited as well as other studies I came across that showed no correlation with oral BP use and upper GI issues were sponsored by pharmaceutical companies that produce oral BPs. These conflicting reports of gastrointestinal distress due raise eyebrows as to the potential biases in studies. Patients given intravenous BP do not report GI issues and the intravenous BPs need to be administered far less often. (Papapetrou, 2009) Both reasons make it more likely that a patient will maintain their intravenous treatment over an oral one and seem to make intravenous BP optimal.

Another method of treatment for osteoporosis is monoclonal antibodies. Osteoclasts originate from macrophages. The macrophage precursor cells have a receptor called RANK which binds to RANK ligand (RANKL) to differentiate into osteoclastic cells. Antibodies can bind to a ligand to prevent it from binding to its receptor. The antibodies bind to RANKL inhibiting their ability to bind with the RANK receptor on the macrophage precursor cells. As a result of the rate at which osteoclasts differentiate is decreases resulting in less osteoclastic cells that break up bone. (D. A. Hanley, 2012)

Antibody treatment, which circulate in the blood, can reach all skeletal sites. However, unlike BP which bind to bones and can have affects after cessation of treatment, antibodies lose their affect soon after cessation of treatment. Adverse events are rarely associated with denosumab. (Harshika Awasthi, 2018)

Calcium concentration is regulated by hormones PTH, and calcitonin. Calcitonin is produced in the thyroid gland and causes lower serum calcium concentration by acting on the renal tubules, causing them to excrete more calcium, and on osteoclasts, causing them to contract (temporarily), reducing their motility and ability to resorb bone. It also causes inhibition of carbonic anhydrase II, which disrupts the acidic environment that is optimal for osteoclast activity. Calcitonin also prevents osteoclast precursors from differentiating into their mature form. The ultimobranchial gland of salmon produces calcitonin with a different makeup of amino acids. Salmon calcitonin is a 32 amino acid, alpha-helical polypeptide that differs significantly from human calcitonin along amino acids 10-27. Salmon calcitonin is more potent then endogenous calcitonin due its difference in amino acids (Felsenfeld AJ, 2015)

Adverse Side Effects of Calcitonin

Adverse effects of calcitonin can include hypocalcemia, a dangerous condition. Since the calcitonin used to treat osteoporosis is sourced from salmon, patients who are allergic to fish can have an allergic reaction. Ten percent of patients taking calcitonin experience mild nausea that subsides as therapy continues. A meta-analysis of 21 randomized, controlled clinical trials with calcitonin-salmon (nasal spray and investigational oral forms) suggests an increased risk of malignancies in calcitonin-salmon-treated patients (4.1%) compared to placebo-treated patients (2.9%). A definitive causal relationship between the calcitonin-salmon use and malignancies cannot be established from this meta-analysis, the benefits for the individual patient should be carefully evaluated against all possible risks. (F. Cosman, 2014)

Further studies point to the questionable efficacy of calcitonin overall and show a definitive lack of efficacy in nonvertebrate fractures. This contrasts with both bisphosphonates and denosumab which both demonstrated a lowered fracture risk in vertebral, hip, and other nonvertebral fractures. (Overman RA, 2013)

Calcitonin has been shown to reduce fracture pain. The exact mechanism for its analgesic effects, is not known. There is a hypothesis that calcitonin may act on the central nervous system, and it has been used with some success in patients with migraine pain, phantom limb

pain, malignancy, Paget's disease, and other pathologies. It, however, has not been compared directly to NSAIDs in terms of effectiveness of pain relief. Regardless, Calcitonin may be helpful for pain in patients that cannot tolerate NSAIDS. (Linsey A Blau, 2016)

Post-menopausal women have low levels of estrogen, an essential hormone for bone remodeling. Osteoporosis is attributed to the diminished estrogen levels of post-menopausal women. Estrogen can inhibit osteoclasts from forming, cause osteoclastic apoptosis, as well as increase osteoblasts by inhibiting osteoblastic apoptosis (Sundeep Khosla, 2012) . An obvious therapeutic approach would be to provide hormone replacement therapy. However, hormone therapy is found to increase the risk of breast cancer (Beral, 2003) , and is therefore not widely used . Raloxifene, a drug that is an estrogen antagonist and agonist is promising drug, in bone, it behaves as an estrogen antagonist, increasing bone density, in reproductive and breast tissue it acts as an estrogen agonist. Thus, raloxifene both increases bone density and reduces risk of cancer. Raloxifene has not been shown to reduce non-vertebrate fractions and more research is necessary to determine its efficacy in non-vertebrate fractures. A meta-analysis found that "In comparison to other osteoporosis therapies, raloxifene has a lesser impact on bone mineral density, a similar effect on the occurrence of vertebral fractures, but no effect on the frequency of non-vertebral fractures. Raloxifene can be recommended for the prevention of vertebral fractures in women with osteopenia/osteoporosis who are not at high risk of non-vertebral fractures and who do not have a past history of venous thromboembolism" (Ann Cranney, 2005)

Conclusion

The most effective current method of treatment are bisphosphonates, which accumulate in bone and inhibit osteoclasts from functioning. However, many patients suffer gastrointestinal pain as a side effect. For those patients an antibody (denosumab) that prevent RANKL from signaling the osteoclastic precursor cells to mature, has also proven to be relatively effective. Other methods of treatment such as calcitonin and raloxifene while in theory look promising, proved to not be very effective in clinical trials. Calcitonin, while not necessarily very effective at reducing bone loss, may still play an important role in treating pain, especially in patients where NSAIDS aren't well tolerated. More research is needed to determine how effective exercise can be in the prevention of osteoporosis and what specific exercises, if any, would be most effective. Regardless, patients should be advised to exercise, as there is some evidence that links mechanical stress on bones to lasting improved bone mass., and stronger muscles can improve balance to further help reduce the risk of falls and fractures. Further research should be conducted to determine how it might be possible to enhance bone-building osteoblasts.

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An Analysis on Various Treatment Options for Triple-Negative Breast Cancer

Elisheva Dusowitz

Elisheva Dusowitz will graduate with a Bachelor of Science degree in Biology Honors in June 2022.

Abstract

Triple-Negative Breast Cancer (TNBC) is a highly invasive, under-researched subtype of Breast Cancer. Patients lack receptors for the protein Human Epidermal Growth Factor, and both estrogen and progesterone. This negatively impacts treatment by making all hormone-sensitive treatments unavailable to TNBC patients. Since the effectiveness of various options has remained understudied, the prognosis remains poor. This paper attempts to analyze and compare the effectiveness of various treatment options. Because TNBC is very aggressive, the standard approach is to jump in with harsh surgical procedures, including mastectomies and lumpectomies. This analysis finds that more aggressive treatment may not be necessary to treat all TNBC patients. The addition of immuno and platinum therapies to traditional chemotherapy appears to increase survival to the same extent as that of mastectomies and lumpectomies. It also appears that radiation therapy greatly enhances treatment and may be an option to avoid a full radical mastectomy as the survival rates proved to be higher in patients with radiation therapy in conjunction with lumpectomies. More research is needed; however, aggressive therapies do not need to be the first choice as the other options appear to provide just as high, if not higher survival rates.

Introduction

Breast cancer is the second leading cause of cancer deaths and the most common cancer among women. There are an estimated 281,000 cases of breast cancer amongst women in 2021. In their lifetime, 1/8 (13%) women will develop breast cancer, with an estimated 43,000 expected deaths per year. In contrast, only 1/833 males will develop it over their lifetime (BreastCancer.org, 2021B, Siegal et al., 2021).

Breast cancer has several different classifications with regard to the various receptors present on the cells for hormones that promote their growth, e.g., estrogen and progesterone.

In healthy breast tissue, these hormones bind to their receptors and in turn activate and contribute towards breast tissue formation and growth. In hormone-sensitive breast cancer patients, activation of those receptors initiates and contributes towards the cancer's growth. Treatment options in these patients generally block those receptors to slow and/or stop the tumor's growth (National Cancer Institute, 2021).

Triple-Negative Breast Cancer (TNBC) is a Breast Cancer subtype in which the patient lacks estrogen, progesterone, and Human Epidermal Growth Factor 2 receptors. This causes treatment options for TNBC patients to be more limited because hormone therapy generally targets and blocks those receptors to inhibit cancer growth. Treatment options are generally narrowed down to surgery, radiation therapy, and chemotherapy. (Center for Disease Control and Prevention, 2021) This paper will analyze various available treatments for TNBC and seek to explore the most effective options.

Methods

This comprehensive review of treatment options for TNBC was conducted based on the critical analysis of data collected from PubMed and other databases accessed through Touro College and University System's library including ProQuest and EBSCO. Among the keywords and phrases used to retrieve data included "TNBC treatment options," "TNBC meta-analysis," and "TNBC survival rates."

Genetic Component of TNBC

It has been established that the prognosis of TNBC is unfavorable due to the lack of treatment options and low survival rates. A study was aimed to identify the key genes that could be recognized as biomarkers for TNBC. Perhaps these biomarkers could promote early identification and potential treatment options for TNBC. The study identified 194 genes that were actively transcribed in TNBC patients and repressed in non-TNBC genes/patients. Gene Ontology and Kyoto Encyclopedia of Genes and Genomes pathway were both used to discover the biological functions of these genes. The clinical significance of the genes was then examined using the Kaplan-Meier and Receiver operating characteristic analysis. The top 20 upregulated and downregulated genes were found to be expressed consistently in all TNBC vs non-TNBC patients. Of the identified genes associated with TNBC, they were all found to be involved in negative regulation of apoptotic processes, response to drugs, and estradiol. Randomized gene samples were collected from the cell lines and revealed that the genes ART3, FABP7, and HORMAD1 were all upregulated in TNBC compared to non-TNBC tissue. In contrast, TFF1, AGR2, and FOXA1 were downregulated. These genes may serve as key biomarkers and regulators of TNBC (Zhong et al., 2020).

Correlation between TNBC and age:

Studies have found that TNBC is more prevalent amongst younger patients. In one of them it was found that of 216 Breast Cancer patients, 52% were ≤ 35, and of those 19% had TNBC, which consisted of the highest proportion of the group. Because young women diagnosed with Breast Cancer have a higher correlation to TNBC, they have a poorer prognosis. Expression of Ki-67, a protein associated with cell proliferation was also found

to be higher in the TNBC age ≤ 35 group (Ozisik et al., 2021). This may help understand why young breast cancer patients have significantly lower survival rates. One issue with this study, however, was that there was no statistical significance found between molecular breast cancer subtypes. This may either be due to their small sample size or could indicate that age is an independent prognostic factor in TNBC diagnosis and treatment.

Time Correlation

One study followed TNBC patients over 10 years, and interestingly enough found that risk and recurrence rates were not the same throughout the study. In the first five years following diagnosis, the patients had much higher death rates, 70% during that time frame. Additionally, the first five years showed a greater likelihood of recurrence, whereas those rates were significantly lower in the second five years. No recurrence was found after 8 years. These results suggest that TNBC patients who survive longer may have lower risks of death as they age (Dent et al., 2007). Additionally, these results show us the ambiguity of TNBC. Much research on illness impact, treatment, and survival is needed to further broaden the approach towards TNBC.

What is Fueling TNBC Growth

If progesterone, estrogen, and the protein HER-2 are not fueling TNBC growth, what is? One study found that phosphatase PTP4A3 was required for TNBC growth in vitro and in vivo, indicating its role in TNBC development (Hollander et al., 2016). It has also been found that the transcription factor c-Myc drives glucose metabolism in TNBC cells, involving the repression of thioredoxin interacting protein (TXNIP). This protein is a negative regulator of glucose uptake and aerobic glycolysis; so, its repression provides cells methods by which to metabolically fuel themselves and bypass apoptosis. The Mychigh/TXNIPlow ratio gene signature is correlated with overall decreased survival and metastatic-free survival in TNBC patients (Shen et al., 2015).

Treatment Options:
Hormone Receptor-Positive Breast Cancer

Traditional hormone therapy, which is not available for TNBC patients, works via several methods in which the interactions between hormone and receptor are blocked. These include blocking the production of hormones and blocking hormonal action on tumor cells. Tamoxifen therapy is one such example that acts as an estrogen antagonist in estrogen receptor-positive breast cancer cells. One study revealed that Tamoxifen treatment for 5 years decreased recurrence and death by 41% and 34%, respectively (Drãgãnescu and Carmocan, 2017). Another traditional method in treating hormone receptor-positive breast cancer patients is the use of aromatase inhibitors. This class of medication blocks the production of the enzyme aromatase, which turns androgenic hormones into estrogen. This treatment option is used in postmenopausal women because estrogen is primarily inhibited from being formed from the adrenal glands and other organs in the body. A study evaluating the impacts of aromatase inhibitor treatment found that median free survival was 23.8 months for these patients (Tripathy et al., 2018, Khanna, 2020).

Treatment options for hormone receptor-positive breast cancer have shown meaningful results. Significant amounts of patients showed a decreased recurrence, death, and progression-free survival. In contrast, one study that followed 1600 patients over a span of 10 years found that patients with TNBC were more likely to have died (42 vs 28%) compared to those with other cancers. Additionally, all deaths of TNBC patients were within 10 years of diagnosis whereas with other cancers patients lived up to 18 years post-diagnosis. (Dent et al., 2007). It is apparent that TNBC patients are at a disadvantage concerning survival rate and prognosis.

Triple-Negative Breast Cancer
Radiation Therapy Combinations

Whole breast radiotherapy and breast-conserving surgery have reduced recurrence rates from 10 to 2%. Postoperative radiation therapy has been shown to drastically minimize recurrence. A study found that patients who are treated with a radical mastectomy without radiation therapy had a significant risk of recurrence compared to those who received the mastectomy followed by adjuvant radiation therapy. The study followed 768 patients for over 7.2 years. They were split into 3 groups: Patients receiving Breast-Conserving therapy (lumpectomy and radiation therapy), Modified radical Mastectomy, and Modified mastectomy with radiation therapy. These groups had five-year recurrence-free survival of 94%, 85%, and 87% ($P < 0.001$). Five-year overall survival was also measured and was found to be 87%, 82%, and 68% ($P = 0.002$). The higher percentage of overall survival in the Breast-conserving therapy group and modified radical mastectomy + Radiation therapy group show promising treatment methods for TNBC patients. Various factors also impact survival, this includes tumor grade, size, and status (Abdulkarim et al., 2011).

Discussions regarding radiation treatment post radical mastectomy have been controversial. However, several

studies have found that postoperative radiation therapy following a radical mastectomy, in comparison to patients only receiving mastectomies, was significantly more efficient with lower recurrence and higher survival rates. One study found that the recurrence rate for patients treated with radiation after their mastectomy vs no post-operative radiation was 11.7% and 25.4%, respectively. The use of radiation therapy significantly lowers recurrence (Abdulkarim et al., 2011). Another study aimed to compare the effects of both chemotherapy in conjunction with radiation therapy vs chemotherapy alone. The study involved 681 TNBC patients all of whom received a mastectomy. The five-year recurrence-free survival rates were found to be 13.7% higher in the group treated with both treatments (88.3% vs 74.6%). Additionally, five-year overall survival was also higher in the group treated with both (90.4% as opposed to 78.7%) (Wang et al., 2011). It appears that there is increased improvement in patients receiving radiation therapy after mastectomy and even more so with chemotherapy.

Breast Conservation Options

Due to the high-risk, aggressive features of TNBC, concerns regarding surgical approaches to treatment have been raised. Harsher procedures such as mastectomies may appear to be a more effective treatment option; however, several studies analyzed this approach in comparison to those receiving other, less-aggressive operations, such as lumpectomies, which are done to conserve breast tissue.

One study analyzed TNBC patients who received a lumpectomy that was followed by reemission, and they found that of 46 of those patients, 51% subsequentially had residual invasive disease (Sioshansi et al., 2012). These rates show that following lumpectomy, TNBC patients have an elevated risk of residual invasiveness compared to those with other breast cancer subtypes. The study suggested that this may be due to the increased tumor burden associated with TNBC. Lumpectomies alone therefore do not appear to be as effective.

Researchers have investigated whether a lumpectomy is as effective as mastectomy in TNBC patients. In another study of 288 TNBC patients, 111 TNBC patients received lumpectomy to reserve breast tissue while the rest had a total mastectomy. The patients in the lumpectomy group were found to have increased overall survival, (85% vs 81%) after a 102-month follow-up (P=0.56). These patients also had an increased rate of disease-free survival at 10 years (P=0.42) (De-la-Cruz-Ku et al., 2020). These results indicate that lumpectomy may be more effective in the treatment of early-stage TNBC; however, more research is needed due to the lack of statistical significance in these results.

A meta-analysis of twenty-two studies further followed whether breast conservation therapy is as effective as a total mastectomy for treating TNBC patients. This study found that the TNBC patients who received breast-conserving therapy had lower recurrence and metastasis rates, as well as a more favorable prognosis (Wang et al., 2013).

Another study compared survival rates of TNBC patients in 2 groups: Lumpectomy patients with radiation therapy, and mastectomy patients without radiation therapy. The study intended to see if radiation therapy following a lumpectomy could have comparable results to the mastectomy group. Results were analyzed by comparing the amount of stromal tumor-infiltrating lymphocytes (TILs) post-treatment. Higher TILs correspond to greater amounts of helper and cytotoxic T cells that are present to fight and destroy tumor cells. In this study of hormone receptor-positive and negative patients, 46% had TNBC. In the group with high TILs, the patients who received lumpectomy followed by radiation therapy had an overall 5-year survival of 100% in comparison to 86% in the mastectomy group (P = 0.028). This indicates that radiation therapy in conjunction with a lumpectomy may be a good treatment option for some patients. The groups with lower TILs however did not have statistically significant survival differences, with survival at 5 years being 86% in the mastectomy and 81% in the lumpectomy with radiation therapy group (P= 0.241). Although these results show promising options for patients, they cannot be generalized to all TNBC patients because the study population had a mixture of various breast cancer subtypes (Mouabbi et al., 2021).

Androgen Receptor Inhibition

A subtype of TNBC has been found and classified to express an androgen receptor. Patients in this group were found to develop androgen receptor tumors that contribute to their illness. This serves as an additional option for treatment- including blocking and inactivating the receptors to reduce cancer growth. In a study aimed to test the use of androgen receptor antagonists/inhibitors, patients were treated with enzalutamide. The results found that progression-free and overall survivals were 2.9 and 12.7 months respectively (Traina et al., 2018). The treatment was tolerated, and this suggests that it may be useful in patients with this TNBC subtype. It was also found that patients in this subtype express high levels of PIK3CA (phosphatidylinositol-4,5-bisphosphate 3-kinase), catalytic alpha mutations and the use of PI3K inhibitors may enhance treatment and survival; however, more research is needed to explore this potential option (Lehmann et al., 2014).

Immunotherapy Option

Immunotherapies with various synthetic treatments aim to enhance the immune system's ability to fight the disease. The use of immunotherapy for TNBC has been largely analyzed. Tecentriq is one immunotherapeutic that acts as an "immune checkpoint inhibitor." Immune checkpoints serve as regulatory mechanisms in the immune system to prevent immune responses from being too strong and inadvertently destroying healthy tissue. Cancer cells often utilize immune checkpoints to their advantage by shielding them and overcoming identification and destruction by the immune system. This treatment method utilizes inhibitors that serve to target the checkpoint proteins, enhance the immune systems' ability to kill cancer cells, and prevent the metastasis of the cancer cells (BreastCancer.org, 2021A). A study analyzed the impacts of Tecentriq along with another traditional chemotherapy, Abraxane, which is often administered to impede the cancer cells' ability to grow and divide. (BreastCancer.org, 2020). This study split the patients into 2 groups; 50% were treated with Abraxane and Tecentriq whereas the other 50% were administered Abraxane and a placebo. The patients were followed up for 12.9 months, and it was found that progression-free survival was greater for patients treated with the combination (7.2 vs. 5.5 months). Overall survival was also improved in these patients (21.3 vs 17.6 months) (DePolo, J., 2018). This suggests that treatment and survival may be enhanced with the use of immunotherapy in addition to standard chemotherapy drugs.

Platinum-Based Chemotherapy

Platinum-based chemotherapy is a form of treatment that utilizes the metallic properties of platinum to destroy rapidly multiplying cells, including cancer cells. These drugs work by attaching to the DNA of cancer cells. The cell then works to remove the drug from the DNA; however, the cell is unable to do so which causes cell death and prevents the cancer's growth (University of Nottingham, 2020). Platinum-based treatments appear to be controversial due to their high toxicity rates; however, some studies have analyzed the implications of platinum-based chemotherapy in the treatment of TNBC patients. One study compared and analyzed the impacts of platinum vs non-platinum-based chemotherapy in TNBC patients. 70% of 495 patients received platinum-based chemotherapy, and of that group, 71% received it as their initial treatment. The overall survival was 19.2 vs 16.8 months for platinum vs. non-platinum-based treatment ($P = 0.439$). These results show that platinum-based chemotherapy may be impactful in treating TNBC patients; however, the small sample size and lack of statistical significance suggest a need for further research.

A meta-analysis (with 2946 patients) of 11 studies sought to discover platinum implications of patients with different stages of TNBC. Three of the studies utilized a platinum drug in combination with the Taxane regimen. It was found that the patients receiving both platinum chemotherapy and Taxane responded better compared to those only receiving Taxane (45 vs 38%, $P < 1x10\text{-}4$). Another 2 subgroups were compared, with and without the addition of platinum chemotherapy to the anthracycline regimen, a chemotherapy regimen that includes usage of compounds that aid in damaging cancer cells' DNA and preventing their reproduction (BreastCancer.org, 2012). Here, platinum chemotherapy did not show any additional benefits in addition to the anthracyclines. Finally, another 3 studies from the meta-analysis evaluated how platinum chemotherapy impacts the progression-free survival of metastatic TNBC patients. The different rates between the addition of platinum chemotherapy to the non-platinum were not statistically significant ($P = 0.24$), suggesting that platinum drugs may not impact survival upon metastasis (Pandy et al., 2019). Overall, it can be concluded that platinum drugs in addition to standard chemotherapy are not one-size-fits-all. Its addition to some standard chemotherapy regimens has shown to improve response and survival; however, because several studies had statistically insignificant results, more research is needed.

An additional study aimed to compare the impacts of platinum-based chemotherapy on TNBC patients that had lung metastasis. The patients in the platinum group had sufficiently longer median free survival (10 months vs 6 months), and also a higher overall survival (32 vs 22 months), with both of these tests giving statistically significant results (P for both tests < 0.05) (Hong et al., 2014). This suggests that even patients whose cancer has metastasized (due to TNBC) can benefit more from the addition of this treatment.

A major dilemma may be faced by TNBC patients and oncologists. Is it necessary to approach this disease with surgical treatments when other options such as immunotherapy and platinum-based chemotherapy appear to be effective? The answer is complex and would need to be determined on a patient-by-patient level; however, the results given above provide evidence that surgical methods in the treatment of TNBC are not necessarily more effective, and other less invasive/aggressive methods may be just as promising. The regimens appear to produce a more favorable prognosis when chemotherapy is used in conjunction with immuno- and platinum therapy as opposed to the use of chemotherapy alone.

Conclusion

Treatment options for TNBC patients are limited and require more research. Many oncologists believe that because TNBC is such an aggressive cancer, harsher treatment options are necessary to remove it, such as surgeries (eg. Mastectomies). As the first line of treatment, this may not be necessary, because other options including immuno and platinum chemotherapies are proving to be as effective. If taking the surgery route, a complete radical mastectomy is not always needed, because lumpectomies in conjunction with radiation therapy prove to have very effective outcomes. The immuno and platinum treatments with chemotherapy are also showing relatively high survival rates and are comparable to those of surgical approaches. This suggests that TNBC patients may do just as well with less aggressive treatment options; however, more research is needed to evaluate the effectiveness and efficiency of all currently available possibilities.

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The Development and Future of Prosthetics Controlled by Myoelectrical Impulses

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Abstract

Objective: To document the developmental history of prostheses to better understand the circumstances that led to enabling amputees to experience touch through sensory reinnervation surgery in conjunction with an innovative bionic arm; and to prove that sensory reinnervation is the key to further progress. Methods: The topic was researched extensively using scholarly databases and read relevant accounts of experimental studies and outcomes. Results: By examining the progress made in the field of prostheses, it has been determined that a sensory reinnervation technique is at the forefront of bionic limb technology and predict that it will continue to be utilized and perfected in the future.

List of Acronyms:
TMR- Targeted Muscle Reinnervation
MPL- Modular Prosthetic Limb

A prosthesis is a device that replaces a biological component of one's body. A.B. Kinnier wrote, "the objective is to make the prosthesis as nearly possible an extension of the wearer's will rather than am external power tool" (Parry, 1968). Scientists have been striving to create a prosthetic that can replace the function of the invalid component indistinguishably. This is the highest level of prosthetic aspiration (Craver, 2010). Through harnessing the brain's bioelectrical impulses with electrodes, scientists began tinkering with the idea of a mind-controlled prosthetic. Through many experiments, engineers worked to refine this method and used peripheral nerves attached to healthy muscles to collect directional input, resulting in myoelectrical control of bionic attachments without the need for electrode implantation. Recently, researchers have found a way to use a prosthetic as a relay device between outside stimuli and the brain. Engineers have entered a phase of devices that, from a functional perspective, can almost compete with a biological limb. The use of myoelectrical impulses and sensory reinnervation methods to control bionic limbs is redefining the field by yielding prosthetics that can receive input in addition to formulating output.

Methods

Various peer reviewed sources were gathered predominantly through JSTOR along with a plethora of electronic sources, such as research websites and lab produced videos, to collect data for this paper. I read papers recounting the results of relevant experimentation that were published throughout the decade to gain a sufficient comprehension of the topic and to produce a timeline of development.

Results

In examining the implications of a prosthetic which utilizes revolutionary technology, its developmental history must be examined. An early form of artificial limbs, known as body power prosthetics, works by harnessing the power of a joint to produce a small range of motion below the designated attachment site. While they were developed during the civil war, many people use them today as a cheaper alternative to the cutting-edge prosthetics. However, scientists and engineers have been working to find alternate methods of input to generate a more precise range of motion. As John T. Scales, Department of Biomechanics and Surgical Materials at the University of London, writes, the concept of an arm controlled by myoelectrical currents originated in Britain during the mid-1950's (Scales, 1965). A Science News article published in 1966 discusses research done at Litton Systems in Toronto regarding capturing lost motor impulses in otherwise idle muscles. While the concept of myoelectrical control is more than half a century old, it took decades to make real strides in harnessing the brain's neural signals, and eventually, adapting to those produced by the muscles (Society for Science & the Public, 1966).

In the past ten years, the development of prosthetics that respond to bioelectrical input has evolved through trial and error. In order to match neural firings to specific motor commands, scientists first had to discover which brain areas encode for each motion. Markus Hauschild, Grant H. Mulliken, Igor Fineman, Gerald E. Loeb, and Richard A. Andersen, a group of researchers involved in biology, neuroscience, and engineering, used two rhesus monkeys to map the brain's motor control areas. They did this in attempt to refine the motor control of those fitted with electrodes on their brains. The researchers discovered that while the motor cortex controls individual and immediate movement, the posterior parietal cortex gives rise to signals related to the goal and trajectory of a motion. After this breakthrough, researchers understood which areas of the brain could be targeted for the reading of neural impulses related to movement. Once scientists had made this discovery, the developmental stage of neural prosthetics began. These prosthetics are intended to record the brain's electrical signals from the sensorimotor pathway and project them to an external device (Hauschild, et al. 2012).

At the University of Pittsburgh, neurobiologist Andrew Schwartz developed a small electrode that is to be implanted into the brain in order to read its electrical impulses.

He detected patterns in neural firings and matched them with specific commands of motion. Schwartz succeeded in having patients move a robotic arm, though with a very limited range of motion (Gaidos, 2011).

J. Andrew Pruszynski and Jorn Diedrichsen predicted in 2015 that the future of prosthetics would revolve around improving the durability of electrode implants, developing stimulation protocols on the prosthetic to simulate touch, and working on isolating single nerve cells. They assumed that recording neural impulses directly from the brain would be the focus of researchers and engineers for years to come. Pruszynski and Diedrichsen expected patients to receive recording chips that would be implanted in the posterior parietal cortex and the motor cortex, allowing for precise movements and the ability to create an overarching goal for the movement (Pruszynski, Diedrichsen, 2015).

S. Musallam, B. D. Corneil, B. Greger, H. Scherberger, and R.A. Anderson conducted various experiments in the area of neural encoding for prosthetic use. They attempted to decode intended goals of trajectory and use their discovery to prove the viability of a prosthetic device which not only responds to a neural firing but anticipates subsequent ones. Using monkeys as tests subjects, the researchers placed electrodes on the simians' brains and mapped the various neurons which fire when an intended goal, such as reaching for an object, is actualized. They believe that this technology will make it easier for patients to acclimate to bionic limbs by expediting certain series of motion (Musallam, et al. 2004). Yet the drawback of having to permanently imbed electrodes into the brain has made their discovery worthwhile on concept though not in practical application.

However, this method of directly implanting electrodes and various other devices in the brain proved to be undesirable, since it requires the patient to undergo a complex surgery on multiple contact points of brain tissue. It would require hundreds of microscopic wires to identify input from microscopic individual nerves. Another issue present in this technique is that it renders the possibility of sending sensory feedback to the brain unreasonable, since it would be nearly impossible to convey an electrical signal of a specified magnitude to a particular neuron through an electrode. Due to the inconvenience inherent in this process, scientists began looking at alternate possibilities to harness the brain's signals.

While attaching electrodes to the brain may elicit satisfactory motor control, the process of doing so is incredibly complex and intricate. In response to this challenge, scientists began exploring other venues of collecting nerve impulses farther away from their site of generation. The concept is as follows: The body starts a command in the brain, then it travels down the spinal cord to nerves in the periphery, while sensation takes the same pathway but in the opposite direction. When a limb is lost, the neural signals are generated by the brain and travel down to the point where the prosthetic attachment site would be. Since muscles amplify nerve signals by about 1000 times, fewer sensors would be necessary to interpret signals and relay commands if electrodes would be attached to muscle nerves. This would be much safer and more practical than placing them directly onto the brain (Kuiken, 2011).

In response to this issue, scientists spent years perfecting a method of removing a nerve from the site of amputation and reinnervating it to a stronger muscle. Todd Kuiken and Gregory A. Dumanian, MD, of Northwestern Memorial Hospital, pioneered the development of a surgical procedure that would accomplish this feat (Barlow, Burt, 2021). Reinnervation works by taking a nerve that is at the site of amputation and relocating it. Therefore, a nerve that was part of a severed arm may be reattached to the chest, where a command to open a hand will cause a relaxation in the chest muscles (Kuiken, 2011). The contraction produces much larger signals and the electrical activity is then recognized by electrodes which translates the information into movement of the prosthetic (Bate, 2013). This provided a major step forward regarding the level of control awarded to amputees through their prosthetic. Targeted muscle reinnervation allows for more intuitive control of a prosthetic through creating additional control sites.

In further utilization of the muscle reinnervation technique, engineers began working on the next level of prostheses advancement: receiving outside sensory information. Since they were able to create a prosthetic capable of receiving information from the brain, they began to wonder if the reverse is possible as well.

The concept of prosthesis receiving stimuli and bypassing damaged organs to deliver an impetus to the brain has been achieved in various areas previously, which inspired scientists to achieve the same with mechanical limb prosthetics. In Europe, engineers have discovered a way to bypass an inferior retina to project images. Wires and coils are attached to chips that are placed in the back of the eye and participants wear goggles which are fitted with a miniature video camera to captures images that are projected into the eye via laser technology within the goggles. There, the photovoltaic chips send the signals to the visual cortex of the brain where a picture is produced and can be visualized (Ehrenberg, 2012). Another form of retinal prosthetics uses a sensor to translate

visual stimuli into a pattern of impulses that is akin to those produced by natural action potentials (Nirenberg, Pandarinath, 2012). Additionally, a vary common example of this phenomenon would be cochlear implants, which bypass damaged structures in the ear to directly stimulate the auditory nerve by collecting sounds and emitting impulses that mimic those typically experienced during hearing (Mayo Clinic, 2020).

Researchers Gregg A. Tabot, John F. Dammann, Joshua A. Berg, Francesco V. Tenore, Jessica L. Boback, R. Jacob Vogalstein, and Sliman J. Bensmaia, used Rhesus macaques to demonstrate how using intracortical microsimulation of the primary somatosensory cortex can give amputees a sense of touch. They did this by first locating the areas of the somatosensory cortex which respond to the various digits on each hand. After this was achieved, Tabot and his associates worked to produce sensations on the prosthetic limb that can be translated to the monkeys' brains though the electrodes. In this study they used to Modular Prosthetic Limb developed by The Johns Hopkin's Applied Physics Lab to detect these mechanical impulses (Tabot, et al. 2013).

Dr. Michael Mcloughlin, the chief engineer at the Physics lab, had been working on neural prosthetics for years when he finally succeeded in building the MPL, a machine capable of obtaining external impulses. Under the funding and auspices of the Defense Advanced Research Projects Agency, which started the Revolutionizing Prosthetics Program in 2005, Mcloughlin worked to achieve the organization's goal: to create the MPL, the world's most advanced prosthetic arm (Mcloughlin, 2016). When the Modular Prosthetic Limb interacts with an object, over 100 sensors, such as force, contact and temperature sensors, send information back to the brain, giving users the sensation of touch (The mind-controlled bionic arm with a sense of touch, 2016). With their trials, Tabot et al. were able to stimulate touch using the MLP with such accuracy that it was indistinguishable from the tactile sensation produced by the sensory nerves in the monkeys' paws. Although this was major progress in the area of sensation, engineers sought to find a method that avoided cranial electrode attachment (Tabot, et al. 2013).

Kuiken and his team conducted experiments which proved that the direct stimulation of a reinnervated nerve in the chest through pressure and temperature would produce a sensation that the patient would attribute to their phantom limb. He believed that eventually sensors would be placed on the prosthetic to accept sensory information and project it onto the reinnervated nerve (Kuiken, et al. 2007).

The assumption of Kuiken's team proved correct, for just a few years later, Dr. Ajay Smith, in conjunction with the Johns Hopkins' Applied Physics Lab, invented a surgical procedure that allows for the acceptance of sensation by the MPL through peripheral nerves. Smith invented a sensory reinnervation technique, wherein he locates the severed nerve which normally accepts tactile stimuli and implants it in an alternate area. Targeted sensory reinnervation gives them a sense of touch that isn't contingent upon electrodes being attached to the brain. Melissa Loomis, an amputee who underwent a sensory reinnervation procedure that remapped her nerves which respond to touch, became one of the first people in the world to acquire a sense of touch through her prosthetics. The sensors of the MPL then interact with those placed on the patient's reinnervated nerves that corresponded to the digits of the hand, allowing them to experience a form of touch (The mind-controlled bionic arm with a sense of touch, 2016).

Additional studies have been conducted in order to understand a patient's acclimation to highly sophisticated prostheses. Kelly L. Collins, Arvid Guterstam, Jeneva Cronin, Jared D. Olson, H. Henrik Ehrsson, and Jeffrey G. Ojemann conducted an experiment to see if "ownership" of an artificial limb can be achieved. Learning from the studies conducted on primates, these researchers already understood that a prosthetic can be supplanted with sensors to receive input directly from the primary somatosensory cortex. However, they wanted to see if the two human participants in their study would feel as though the prosthetic hand was their own by bypassing the peripheral nervous system. They found that the participants' brains fell for the illusion of ownership regarding their artificial limb (Collins, et al. 2017). This was a step forward in understanding how seamlessly amputees would be able to acclimate living with a bionic body part and how electrical stimulation of the somatosensory cortex can play a role in the illusion. However, regardless of how sophisticated the world of prosthetics will get, there will always be a need for adaption, which will vary by patient (Marks, Michael, 2001).

Discussion

As with any study attempting to showcase the forefront of technological development, those explored above run the risk of eventual obsoletion. The same way that attaching electrodes to read neural impulses was at some point a cutting-edge technique, sensory reinnervation may one day prove to be an inferior mode of prostheses control. The next step may be to increase the level of tactile sensor reception and one day have prosthetics distinguish between materials, which may require an alternate

method of sensory perception. However, as seen through the studies by Collins and associates19, patients already find a prosthetic indistinguishable from its biological counterpart, rendering future advancements open-ended. Since scientists have achieved their functional goals, they must now find a way to mass produce these prosthetics and increase their availability to all those in need.

Conclusion

By exploring the long chain of progress attached to the field of prosthetics, one can better understand and appreciate the dedication necessary to produce a bionic arm that is controlled through myoelectrical impulses. Additionally, we can predict that the future of development will probably revolve around integrating Smith's sensory reinnervation method on a larger scale and attempting to refine bionic limbs by equipping them with additional sensors above those for pressure and temperature. However, we must understand that science and engineering are ever-evolving disciplines. Just as cerebral electrode placement had been improved upon and later overshadowed, sensory reinnervation may one day be replaced by systems currently not within our realms of imagination.

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Effective Treatments for Onychomycosis

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Abstract

Background: Onychomycosis is a highly prevalent nail infective disorder. Many treatments, with varied success rates and side effects, are used.

Objectives:To assess the most recommended treatment for Onychomycosis with the optimal cure rate and least severe side effects. Search Methods: PubMed, ProQuest, EBSCO Multisearch, and Google Scholar were used to gather information. Search terms such as "Onychomycosis," and "Effective treatments for Onychomycosis" etc. were used.

Results: Effective treatments include oral, topical, nail avulsion, and laser treatments. Topical treatments have low cure rates and minimal side effects. Oral treatments have various side effects but the highest mycological and clinical cure rates. Laser treatments yield high cure rates and minimal to none side effects, but a small chance of recurrence of the Onychomycosis is possible.

Conclusion: For those who are not susceptible to adverse effects, Oral treatment is the recommended treatment. For individuals who have pre-existing conditions that may be harmed by adverse effects of medication, Laser should be the sought treatment. Topical treatments are not recommended due to its low efficacy rate.

Introduction

Onychomycosis, fungal infection, is the most ubiquitous nail infective disorder with a prevalence in males and elderly individuals. It is accountable for almost half of nail disorder consultations. Although traditionally harmless, Onychomycosis, if left untreated, can occasionally lead to more serious complications, especially in individuals with pre-disposing factors, such as diabetes, HIV- induced immunosuppression, and arterial disease (Piraccini, Alessandrini, 2015). Various researched treatments with high success rates are used to treat fungal nail infections. The Success of treatments is weighed by the clinical cure, which refers to the decreased deformity or discoloration of the nail, and mycological cure, which refers to the absence of fungus within the nail (Kreijkamp-Kaspers, Hawke, 2017). This study seeks to determine what is the most recommended treatment for Onychomycosis.

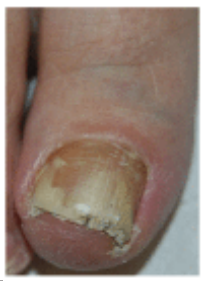
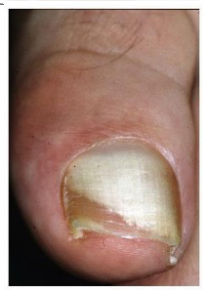
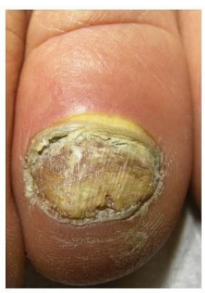
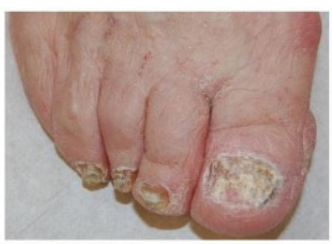
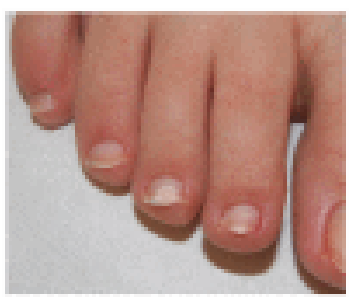
There are several forms of Onychomycosis. Distal and Lateral Subungual Onychomycosis (DLSO) is caused by fungus infecting the distal or lateral area of the nail (Kreijkamp-Kaspers, Hawke, 2017). It is characterized by a yellow-white detached nail plate and hardening of the skin, also known as hyperkeratosis. It is often associated with athletes' foot, and occasional brown, black, or orange discoloration (Figure 1). A detached nail from the nail bed or white streaks on the nail are also common (Kreijkamp-Kaspers, Hawke, 2017). Superficial Onychomycosis (SO) occurs when fungus enters the nail plate and forms white opaque colonies in the form of raised grooves that can be easily rubbed off (Figure 2). This form of Onychomycosis is also often associated with athlete's foot. The most basic form of SO happens because of dermatophytes colonizing the outer layers of the nail without penetrating it. Endonyx Onychomycosis (EO) occurs when the fungal hyphae in the distal nail plate is permeated by fungus. The nail appears to be split in half lengthwise with possible discoloration (Figure 3) (Kreijkamp-Kaspers, Hawke, 2017). Proximal Subungual Onychomycosis (PSO) is caused by fungus originating in the proximal nail fold and spreading to the upper portion of the nail (Kreijkamp-Kaspers, Hawke, 2017). It causes a white area to appear under the lunula area of the nail along with periungual inflammation. It also causes bacterial paronychia and nail pustular psoriasis (Figure 4) (Piraccini, Alessandrini, 2015). Mixed Pattern Onychomycosis (MPO) occurs when different forms of Onychomycosis are present in the same patient, and

	Fungal Location	Toe/Nail Features
Distal Lateral Subungual Onychomycosis (DLSO)	Distal or lateral area of the nail is infected	Hyperkeratosis Discoloration of the nail Onycholysis Streaking
Superficial Onychomycosis (SO)	Nail surface is infected but the surrounding area is not	Striae on the nail
Endonyx Onychomycosis (EO)	Fungus permeates the fungal hyphae of the nail	Nail split lengthwise Discolored nail
Proximal Subungual Onychomycosis (PSO)	Originates in the proximal nail and spreads upward	White area appears under the lunula area of the nail Periungual inflammation Bacterial paronychia Nail pustular psoriasis
Mixed Pattern Onychomycosis (MPO)	Different forms of onychomycosis occur in the same person, possibly in the same nail	Features associated with whichever form of onychomycosis is present
Total Dystrophic Onychomycosis (TDO)	Occurring following other forms of onychomycosis, it is caused by different organisms entering the nail plate	Crumbled nail Thick and ridged nailbed

possibly even in the same nail. The final form of fungal nail infection is Total Dystrophic Onychomycosis (TDO), which follows other forms of Onychomycosis and is characterized by a crumbled nail with a thickened nail bed (Figure 5) (Kreijkamp-Kaspers, Hawke, 2017)

Methods

PubMed, ProQuest, Ebsco Multisearch, and Google Scholar were used to extract information. Terms such as "Onychomycosis" and "Effective Treatment for Onychomycosis" etc. were used.

	**Figure 1** Distal Lateral Subungual Onychomycosis (DLSO). It is characterized by a yellow-white detached nail plate and hardening of the skin, also known as hyperkeratosis. It is often associated with discoloration of the nail and white streaks on the nailbed (Kreijkamp-Kaspers, Hawke, 2017).
	**Figure 2** Superficial Onychomycosis occurs when fungus enters the nail plate and forms white opaque colonies in the form of raised grooves that can be easily rubbed off (Kreijkamp-Kaspers, Hawke, 2017)..
	**Figure 3** Endonyx Onychomycosis- the nail appears to be split in half lengthwise with possible discoloration (Kreijkamp-Kaspers, Hawke, 2017)
	**Figure 4** Proximal Subungual Onychomycosis causes a white area to appear under the lunula area of the nail along with periungual inflammation. It also causes bacterial paronychia and nail pustular psoriasis (Piraccini, Alessandrini, 2015).
	**Figure 5** Total Dystrophic Onychomycosis is characterized by a crumbled nail with a thickened nail bed (Kreijkamp-Kaspers, Hawke, 2017).

Oral Treatment

One method currently used in treating fungal nails is an oral medication. The three most common ones prescribed are griseofulvin, terbinafine, and azoles. The drawback of this treatment method is that oral medications generally require long treatment periods and can cause various side effects. Because oral drugs can cause liver damage, patients must first undergo a liver function test to begin this form of treatment. Medication can be classified as fungistatic (inhibiting the growth of fungal cells), or fungicidal (directly causing cell death)(Kreijkamp-Kaspers, Hawke, 2017).

Griseofulvin, a fungistatic drug, was the first oral medication created to treat Onychomycosis. It disrupts the cell microtubules and is effective in fighting dermatophytes but ineffective at fighting yeast. The response rate of this drug is poor. Common side effects associated with Griseofulvin are allergic reactions, stomach disturbance, and nausea (Kreijkamp-Kaspers, Hawke, 2017).

The Azoles are a fungistatic class of medications. Common ones include Itraconazole and Ketoconazole, and they are given over the course of a few months. The growth of the fungus is halted by suppressing the synthesis of ergosterol in the cell membrane via the CYP51A1 enzyme. Side effects of the Azoles include nausea, bloating, diarrhea, and liver damage (Shirwaikar et. al. 2008).

Terbinafine, an allylamine drug, is the most recent oral medication created to treat Onychomycosis. As a fungicidal treatment, it acts as a non-competitive inhibitor for Squalene Epoxidase, the enzyme responsible for the conversion of Squalene to Eroserol in the fungal membrane. This causes toxic levels of Squalene that make holes in the membrane, eventually killing the fungus (Kreijkamp-Kaspers, Hawke, 2017). Terbinafine requires an 8–12-week daily dose and can cause headaches and diarrhea (Shirwaikar et. al. 2008). Terbinafine has been demonstrated multiple times to be the most effective oral medication with the least severe side effects (Kreijkamp-Kaspers, Hawke, 2017).

To determine the effects of oral treatment, a randomized double- blind study was done contrasting two oral medications, terbinafine and itraconazole. The Terbinafine group, consisting of 186 patients, received a daily dose of 250 mg/day for 12 weeks, while the itraconazole group, also consisting of 186 patients, received 200 mg/day for 12 weeks. Clinical and mycological cures were assessed at weeks 4, 8, 12, 24, 36, and 48. At 48 weeks, negative mycology was achieved by 73% of patients in the Terbinafine group and 45.8% in the Itraconazole group. Clinical cures were attained by 76.2% in the Terbinafine group and 58.1% in the Itraconazole group (De Backer Et al, 1998).

Based on this study, the oral treatment seems to be an effective cure for Onychomycosis as the rates of mycological cure and clinical cure are high. Of the three most common ones, Terbinafine is the most recommended due to its efficacy and lack of side effects, but the Azoles and Griseofulvin have a high cure rate as well. Oral medication may be safest with younger children, as the older population is often on other medications and drug-drug interactions may occur (Leung et. el., 2020). Additionally, because adverse effects of medication are common amongst the immunosuppressed population, who are prone to onychomycosis, oral treatments should be avoided to ensure an effective and safe treatment.

Topical Treatment

Another method used to treat fungal nail is topical therapy. Because toenails are generally non permeable, creams are not always effective because they are unable to get through the nail. Examples of commonly used creams include Efinaconazole and Tavaborole. A new topical method using nail lacquer has been recently introduced. The nail lacquers contain chemicals that aid the penetration of the nail and allow for more effective healing. The two main types of nail lacquers currently approved are ciclopirox and amorolfine. Ciclopirox lacquers disrupt the breakdown of toxic peroxides and the production of

	Classification	Method of Fungal	Side Effects
Griseofulvin	Fungistatic	Disrupts cell microtubules	Allergic reactions, stomach disturbance, and nausea
Azoles	Fungistatic	The synthesis of ergosterol is suppressed by CYP51A1 inhibition	Nausea, bloating, diarrhea, and liver damage
Terbinafine	Fungicidal	The synthesis of ergosterol is suppressed by squalene epoxidase inhibition	Headaches and Diarrhea

intracellular energy. It may also prevent nutrient uptake of the fungus which leads to fungal nutrient uptake resulting in exhaustion of amino acids and a reduction in protein synthesis. Side effects include rashes, nail irritation, discoloration, and ingrown toenail. On the other hand, an Amorolfine lacquer leads to cell death by inhibiting sterol biosynthesis. It is known to fight various forms of yeast, molds, and dermophytes. After the amorolfine is applied to the nail, it rests on the nail for seven days and slowly penetrates the nail to reach the nail bed and heal the fungal infection. This treatment requires constant application until the fungus is completely removed, which averages nine to 12 months for toenails. Side effects, though rare, include itching, burning, inflammation, and irritation (Shirwaikar et. al. 2008).

To assess the efficacy of topical treatments, a research study measured the success rate of efinaconazole, a topical antifungal treatment. There were 62 patients, ages six through 16 years, in the study. The cream was administered once a day for 48 weeks, and patients were re-evaluated at 4 weeks post-treatment. At 12 weeks following the onset of treatment, 36.7 % of patients received a complete mycologic cure, and 65.0% reached a complete cure by the post-treatment follow-up (Eichenfield et. al. 2020).

To determine the efficacy of topical treatment, a 36-week sequential treatment of chemical nail avulsion, RV104A ointment, Ciclopirox cream, and Ciclopirox nail lacquer was compared with a 36-week treatment of Amorolfine. At 48 weeks, the mycological cure rate was 36.6% for the combination treatment and 12.7% for the amorolfine treatment. Clinical cure at week 48 was achieved by 53.5% of the patients in the sequential treatment group and 17% in the nail lacquer group (Paul et. al., 2013).

Topical treatments such as creams and nail lacquers do not appear to be effective treatments for onychomycosis. Low cure and clinical rates are associated with these interventions, and it relies heavily on the patient to comply with directions and remember instructions.

Nail Avulsion Treatment

Nail avulsion, another treatment for Onychomycosis, involves removing part of the nail to access the infection site and treating the root, along with the nearby tissues with topical therapy. Chemical avulsion and surgical avulsion are two versions of this treatment. While surgical avulsion is more painful and is prone to risks such as hematomas and nail distortions, chemical avulsion is a highly tedious process. These treatments have high relapse rates and poor patient compliance, so they are generally not performed unless other treatments have failed (Nayak, 2021).

Forty patients were treated for onychomycosis using a combined treatment of nail avulsion and topical therapy. Following the removal of the fungal nail, or part of it, the creams were to be applied daily. There were many dropouts or cases of non-compliance in the study, but 15 (56%) of the 27 remaining patients received a complete cure. On a follow-up visit, recurrence was noted on two patients. No side effects were noted in the study (Grover et. al, 2007).

This study confirms prior research which suggests that nail avulsion is not an effective treatment for onychomycosis. A low cure rate is associated with this method of treatment, and painful side effects are common.

Device-Based Treatments

Device-based therapies are non-invasive treatments for Onychomycosis that have high success rates. One such treatment is Iontophoresis, which applies a current and a charged drug to the infected nail bed. The flux rate of the drug administered is controlled by the device, and this treatment is sought after because of its high rate of nail permeability. Another example of a device-based therapy is ultrasound, which uses soundwaves to deliver drugs to the infection. This also has a successful rate of permeability. Photodynamic therapy is a recent device-based therapy that has been introduced. It involves the excitation of photosensitizing agents which create singlet oxygen that is responsible for the death of fungal cells. Aminolevulinic acid and methyl ester are two photosensitizing agents used for this process (Nayak, 2021).

Laser therapy, another device-based treatment, was developed using the principle of photothermolysis by targeting tissue in a designated area. A device sends a pulse of radiation to the infected area and kills the fungi. There are a few drawbacks of laser therapy, for example possible damage to the tissue if used at an extreme level. Laser therapy can also decrease collagen production, which provides structure in the tissue (Kushwaha et. al. 2015). Finally, the devices used for laser therapy are very expensive and are not covered by many insurances (Liddell, Rosen, 2015). There are several types of FDA-approved laser treatments utilized by podiatrists today.

The efficacy of laser treatment is dependent on several factors. Firstly, the wavelength of the light must be capable of penetrating many layers, such as the nail plate and underlying tissues. Therefore, the near-infrared spectrum is used in laser treatments as this light is found to be the most piercing. The pulse duration is another factor that affects the treatment. The span of the pulse must

be less than the thermal relaxation time of the target (the infection), which requires the laser systems to use relatively short pulse systems. The success of the laser is also dependent on the repetition rate of the system, which refers to the rate of the delivery of the pulses. A higher repetition rate allows for an increased pulse rate, which can speed up the treatment process. The diameter of the laser beam, known as the spot size, varies in length from 1mm to1 10mm, and the size of the beam has different effects on the treatment. A smaller size beam will likely cause the laser to reach a greater surface area while the larger beams may speed up the treatment time. The fluence, which refers to the amount of energy pulsed into the target area, is the final factor affecting the laser treatment and it is generally an average calculated by the spot size and maximum pulse energy allowed (Gupta, Simpson, 2012).

There are several types of FDA-approved laser treatments utilized by podiatrists today. A long pulse laser system delivers long pulses to the infected area. The Fotona Dualis system is a long pulse laser system. In a clinical trial of this laser, 162 participants with confirmed onychomycosis were treated once a week for four consecutive weeks. At the follow up visits, which ranged from 12-18 months post-treatment, 100% of participants achieved mycological cures, and 93.5% reached clinical cures (Gupta, Simpson, 2012).

A short-pulse laser system is another form of laser treatment that delivers laser by the microsecond. The Pin-Pointe FootLaser, GenesisPlus, VARIA, and JOULE ClearSense are all examples that are on the market. There have been many studies done on these systems, which all yielded above 70% improvement of fungal nail. (Gupta, Simpson, 2012).

A study on short-pulse laser divided 21 subjects with Onychomycosis into three groups: 1319 nm laser light, 1064 nm laser light, and broadband light. Four treatments spaced one week apart were given, and cultures were taken at one, three, and six-months following treatment. Patients reported mild to moderate discomfort and no unpleasant effects occurred. Determined by the six-month culture, 20 of the 21 patients reached mycological cure (Waibel et. al. 2013). This study may be confounded due to bias because an author of the study expressed, via a disclosure, a benefit in the production and usage of the specific laser used in the study (Lidell, Rosen, 2015).

Long-pulse and short-pulse lasers were compared in a trial consisting of 10 toenails with Onychomycosis. Cultures were taken prior to treatment and at the nine-month follow-up, and two independent evaluators rated the fungus using the Onychomycosis Severity Index (OSI). Patients were also ordered to apply Ciclopirox daily to the infected area. Results showed no significant difference between the different laser systems and the lowest OSI level was seen at six months (Hees et. al. 2014). This study suggests a recurrence of the fungus at nine months.

The final form of laser systems used by current medical professionals is the Diode-laser system. This method can be done in a range of wavelengths and uses a semiconductor to deliver laser beams. The Noveon Laser uses a diode system and provides options of 870 and 930 nm (Gupta, Simpson, 2012). A clinical trial was performed on this system and measured the improvement of fungal nail in 26 infected toes. Treatment was administered on days 1, 14, 42, and 120, and follow up occurred on day 180. Results indicated that 85% of participants showed a decreased infection area, 65% displayed 3mm of clear nail growth, and 4 mm of clear nail growth was seen on 26% of the toes. This study provides objective proof of the improvement of the toenails, but the sample size is relatively small (Landsman et. al. 2010).

Jefferson et al., conducted a study that found diode laser therapy to be effective with little or no side effects. This study took samples of toenails from 3 independent clinical trials that used a dual-diode laser system. Results indicated that 67% of the toenails experienced more than 3mm of clear nail growth following the laser treatment, and 89% had increased clear nail growth at the six month follow up. No side effects were noted in any of the patients (Zang et. al. 2017).

Laser therapy demonstrates high cure rates for Onychomycosis. While all forms yield successful results, the long pulse laser seems to be the most effective in treating fungal nail. Although recurrence is a small possibility, laser treatment may be suggestable for patients with pre-existing conditions who cannot undergo other forms of Onychomycosis treatment due to its limited side effects.

Discussion

Onychomycosis is a prevalent nail disorder affecting many people daily. While various forms of treatment are used, their treatment lengths, cure rates, and side effects must be taken into account. Topical remedies such as ointments and lacquers do not achieve clinically significant cure rates. Nail avulsion is a painful process and does not have a high efficacy. Oral treatments have the highest cure rate, but the common side effects prevent many people from using this treatment. For those without pre-existing conditions whose safety will not be compromised by its use, oral medication is the optimal course of treatment. Laser therapy, because of its high cure rate and lack of

side effects, is recommended as the gold standard of treatment for Onychomycosis for those who cannot tolerate the adverse effects of oral medications.

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Can Androgenetic Alopecia be Reversed and What Are the Effective Treatments?

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Abstract

Androgenic alopecia (AGA), also known as male and female pattern baldness, is the loss of hair on the scalp for both men and women. The onset of hair loss for men suffering from this condition can occur as early as their teens or early 20s. Symptoms include a receding hairline and gradual disappearance of hair at the vertex and frontal scalp. When women have female pattern baldness (FPB), their hair doesn't appear thinning until they reach their 40s or older. Generally, women experience a thinning of the hair over the whole scalp, with the most extensive hair loss at the vertex. The FDA-approved hair loss treatments finasteride and minoxidil topical are often capable of halting and even reversing hair loss when examined over the course of many treatments. Other medications that have shown effectiveness in treating hair loss have yet to be approved by the FDA, either due to a lack of evidence showing their effectiveness or because of concerns about side effects. The main disadvantage of using hair loss drugs is having to take them continuously in order to maintain their benefits and the intake of finasteride causing sexual functional disorders. For those who want to avoid the risk of sexual function disorders, there are other alternatives to these two drugs, such as low-level light therapy, platelet-rich plasma therapy (PRP), and hair transplant. Even though there is no cure for hair loss, this study discusses a number of treatments that are invasive or non-invasive, and the patient should consult with their doctor before beginning any treatment.

Abbreviations

AGA: androgenetic alopecia

AR: androgen receptors

DHT: dihydrotestosterone

FDA: Food and Drug Administration

FPB: female pattern baldness

KCZ: ketoconazole

LLLT: low-level laser therapy

MAA: male androgenetic alopecia

MPB: male pattern baldness

MPHL: male pattern hair loss

MS: minoxidil solution

OTC: over-the-counter

PDGF: platelet-derived growth factor

PG: propylene glycol

PRP: platelet-rich plasma

5AR: 5-alpha-reductase/5α−reductase

Introduction

Many people experience hair loss, medically known as alopecia. Hair loss comes in a variety of forms. Androgenetic alopecia (AGA), also known as male pattern baldness (MPB), is characterized by a receding hairline (making an "M" shape), thinning at the crown of the head, and is caused by hormones. By the age of 50, roughly 30-50% of men experience this type of hair loss (Rafi & Katz, 2011). The trend of hair loss in women differs from that of males. Women's hair thins all over the head, but the hairline does not recede like the men. In women, androgenetic alopecia rarely results in complete baldness (Medline Plus, 2015). Alopecia has few physical side effects, but it can cause psychological problems, such as excessive levels of anxiety, depression, and can greatly affect self-esteem and self-image (Cranwell & Sinclair, 2016). Males are typically thought to suffer from androgenetic alopecia more often than females (Feinstein, 2020). This study will determine whether lost hair can be regrown and review the pharmacologic treatments of androgenetic alopecia. Hormonal hair loss is the most common and well-studied kind, therefore, androgenetic alopecia will be the subject of this research.

Objectives

- To understand what androgenetic alopecia is
- The causes of androgenetic alopecia
- Discuss medicinal treatments for hair loss.
- Explain the clinical studies and chemical aspects of prescribed drug use among patients struggling with male and female pattern baldness.
- Explore the probable health complications with prescribed drug intake by the patient with androgenetic alopecia.
- Discuss alternative methods to manage hair loss, like platelet-rich plasma, therapy (PRP), low-level light therapy, and hair transplant.

Methods

This comprehensive review was conducted using multiple databases available through Google Scholar, Medline Plus, Mayo Clinic, and WebMD. Additional resources were available via the website of the National Center for Biotechnology (NCBI). Additionally, filters were applied to retrieve relevant articles. The search for articles on the topic revealed articles describing the treatments used for hair loss and the adverse effects that come with taking them.

Signs and Symptoms

How does one know if they are experiencing androgenetic alopecia? On average, people lose 50 to 100 hairs every day. This frequently goes undetected because new

hair grows at the same time. One of the symptoms of alopecia is when the hair that has fallen out is not replaced by new hair (Mayo Clinic Staff, 2020). The affected areas progress from highly pigmented, thick, terminal hairs to thinner, shorter, indeterminate hairs (Feinstein, 2020).

The average male or female patient notices a thinning of their scalp hair as they age (Shapiro, 1998). The most common form of hair loss is male androgenetic alopecia (MAA), which affects 30-50% of men by 50 years of age (Cranwell & Sinclair, 2016). Usually, after puberty, some men notice scalp hair loss or a receding hairline. As opposed to men, women usually begin experiencing symptoms in their 50s or 60s. Women may experience androgenetic alopecia earlier, as early as their 30s or 40s. Male-pattern baldness and female-pattern baldness are both hereditary conditions that lead to more drastic hair loss than that which occurs with normal aging (Shapiro, 1998).

For male pattern baldness, there is a receding hairline and thinning hair on the crown of their heads. There are different stages for males depicted in figure 1. With female pattern baldness, thinning occurs on the top and crown of the head (Figure 2). Women commonly experience this thinning as a widening of the midline hairline that leaves their front hairline untouched (Feinstein, 2020).

The image shows the normal amount of hair on a woman in stage 1. In stage 2 the image shows signs of hair loss by the widening of the central part. By stage 3 there is widening of the central part of the scalp and there is loss of volume lateral to the part line. Stage 4 shows the development of a bald spot anteriorly. The hair loss at Stage 5 is advanced (Sinclair, et al., 2015).

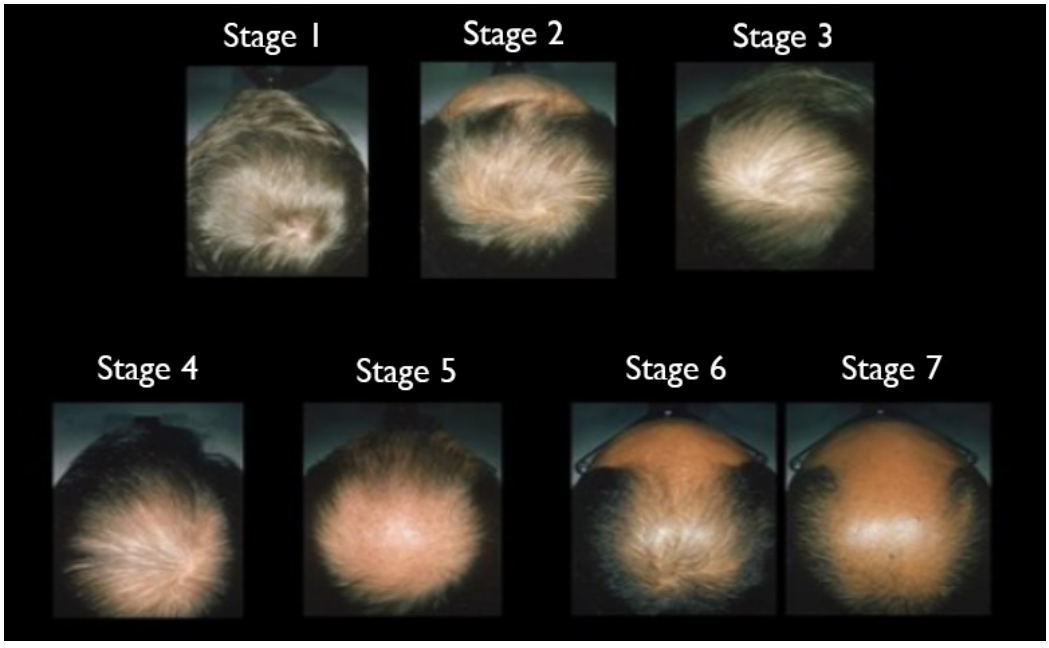

Figure 1: The Norwood- Hamilton Scale of male androgenetic alopecia (Cranwell, & Sinclair, 2016).

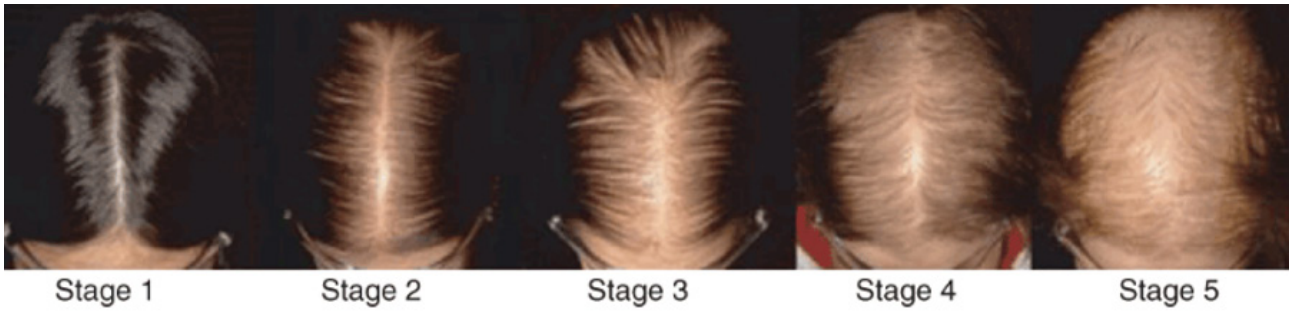

Figure 2: Sinclair Scale for female pattern baldness

Cause

Androgenetic alopecia is caused by both genetic and hormonal factors (Shapiro, 1998). Hair loss caused by androgenetic alopecia can be inherited from both the mother and the father. The disease tends to run in families with male androgenetic alopecia and having a close relative

with patterned hair loss appears to be a risk factor for developing the condition (Medline Plus, 2015). About 80% of the risk is inherited (Cranwell, & Sinclair, 2016). There are a number of genetic factors that influence male pattern baldness, but the main influencers are the body's production of androgens (Liang, et al., 2018). Androgens are the male sex hormones, which are responsible for various male characteristics such as body and beard hair, muscle mass, bone growth, fat distribution throughout the body, voice deepening, etc (Jewell, 2019). As the body tries to encourage the development of male sexual characteristics during puberty, significant amounts of androgens are produced (Liang, et al., 2018). Androgens in men are usually available in the form of testosterone, much of which is converted to dihydroxy testosterone (DHT). DHT is a naturally occurring by-product of testosterone. 5α–reductase, an enzyme in the hair follicle's sebaceous (oil) glands helps convert testosterone to DHT. This process happens in both men and women, even though women have less testosterone than men. In research studies, about 10% of testosterone molecules are converted to DHT by the enzyme 5α–reductase (Jewell, 2019). By DHT binding to the scalp hair follicle androgen receptors (AR), it causes androgenetic alopecia (Cranwell, & Sinclair, 2016). DHT is a far more potent hormone for hair growth than testosterone due to its higher binding affinity and lower dissociation constant with the androgen receptor (French, et al., 1990). As DHT travels through your bloodstream, it can then bind to receptors on hair follicles on your scalp, causing them to shrink and become less able to support a healthy head of hair (Jewell, 2019).

A significant pathophysiological feature of androgenetic alopecia is the alteration of hair cycle development and the miniaturization of the hair follicle (Cranwell & Sinclair, 2016). Understanding the hair growth cycle helps understand how DHT causes hair loss. The cycle includes four phases: growing (anagen), transitional (catagen), resting (telogen) and shedding (exogen). Over time, DHT accumulates in hair follicles, interfering with its growth cycle. Known as miniaturization, DHT shrinks hair follicles, slowing the rate at which hair strands reproduce by either shortening the growing phase or lengthening the resting phase. With each subsequent life cycle, AGA advances along with the destruction of follicles by DHT, which causes hair to become thinner, brittle, and lighter in color. A follicular pore ultimately remains empty because the hair will not grow long enough to reach the surface of the skin during the anagen phase. Eventually, the follicles shut down and will no longer produce hair (Cranwell & Sinclair, 2016).

Gene Factor of MPB

The main cause of male pattern hair loss is DHT. DHT affects both the natural genetic predisposition to hair loss as well as natural processes in your body that lead to hair loss as you age. Proteins called androgen receptors allow hormones such as testosterone and DHT to bind to them. As a result, normal hormonal processes such as hair growth occur. Depending on how the androgen receptor gene (AR) is configured, some individuals are more susceptible to the effects of DHT on scalp hair. Therefore, having variations in the AR gene increases the chances of experiencing MPHL (Jewell, 2019).

Treatments

Alopecia androgenetic is an androgen-dependent trait determined primarily by genetics (Redler, et al., 2017). It is characterized by the gradual conversion of terminal hairs into indeterminate, with the help of the DHT hormone. Both men and women are affected by this disease. In order to treat androgenetic alopecia, there are only two drugs that have been approved by the US Food and Drug Administration (FDA) (Feinstein, 2020). The two drugs increase hair length and diameter by modulating the hair-growth cycle, although their mechanisms of action are different. Both medications slow the rate of hair loss but only partially reverse baldness, and must be taken continuously to maintain their effectiveness. AGA can also be treated with oral dutasteride, ketoconazole, platelet-rich plasma (PRP), low-level laser therapy, and hair transplantation (Dabek, et al., 2019).

Minoxidil

In today's technologically advanced world, minoxidil can be found as an oral drug, a topical cream, and a foam. Minoxidil is used both by men and women who suffer from pattern hair loss. It is a non-androgen hair-growth stimulator, it promotes new hair growth by allowing blood vessels in the scalp to carry nutrients to the affected hair follicles. Minoxidil does not stop DHT from reaching the follicles. It is effective for many men because it encourages hair growth and makes areas of the scalp with thin hair look thicker, fuller, and less affected by hair loss (Suchonwanit, et al., 2019).

Minoxidil was first introduced in the 1970s as an oral medication to treat severe hypertension (Campese, 1981). A topical minoxidil formulation was developed as a result of physicians observing hair growth in balding patients and generalized hypertrichosis in women after they observed hair regrowth in male patients (Suchonwanit, et al., 2019). According to Suchonwanit, the minoxidil 2% solution was first made available to the public in 1986,

followed by its 5% version in 1993. The US FDA approved minoxidil brand-name Rogaine, at a maximum concentration of 5%, for over-the-counter use in 1996 (Goren & Naccarato, 2018). A generic version is available by prescription in the form of oral tablets and over the counter in the form of a topical liquid or foam.

Many studies have shown that minoxidil has been widely used since the early 1980s; however, the mechanisms by which it promotes hair growth are not completely understood (Suchonwanit, et al., 2019). The hair growth that is caused by minoxidil has been attributed to various theories. This molecule opens potassium channels, which induces hyperpolarization of cellular membranes, as well as acting as a vasodilator; it is hypothesized that by widening blood vessels and opening potassium channels, it allows more oxygen, blood, and nutrients to pass to the follicles. In addition, in the telogen phase, hair follicles can shed, usually shortly before they are replaced by new, thicker hair in the anagen phase (Rossi, et al., 2012)

The effectiveness of topical minoxidil was investigated in numerous clinical trials using different concentrations and preparations. For men with AGA, 5% MS increased the mean difference in hair density significantly compared to 2% MS or a placebo. Significantly more hair regrowth was noted in the 5% MS group than in the 2% MS group at week 48. FPHL results for both the 2% and the 5% MS groups were promising. There were, however, more side effects with 5% MS, including dermatitis, headaches, and hypertrichosis. Women are prescribed the 2% solution, while men receive the 5%. It is preferred for women to use 2% MS since hypertrichosis could be problematic for them, having unwanted hair growth that can occur, resulting in poor treatment compliance (Suchonwanit, et al., 2019).

Treatment of androgenetic alopecia with topical minoxidil has been demonstrated to be safe and effective. In order for the hair to be maintained consistently, it must be applied once or twice a day. (Rossi, et al., 2012). After 12 weeks of daily treatment, results should be visible, but hair loss will return within four to six months if treatment is discontinued (Dabek, et al., 2019). Usually, regrowth occurs at the vertex rather than in the frontal areas and it is not observable for at least 4 months (Feinstein, 2020). While complications are extremely rare, patients who use minoxidil may experience symptoms such as pruritus, scaling of the scalp, skin irritation, orthostatic hypotension, and erectile dysfunction (Dabek, et al., 2019). However, reports show that the most common adverse reactions of the topical formulation are irritant and allergic contact dermatitis on the scalp with symptoms like itching and scaling (Rossi, Mari, et al., 2012). According to studies, several topical solutions containing propylene glycol are known to cause allergic reactions, particularly if they contain galenic. When using 2% minoxidil, the incidence is lower than with 5% minoxidil. Propylene glycol (PG) or minoxidil itself can also cause allergic contact dermatitis. It is important to conduct a patch test to identify the cause. Minoxidil can cause an allergic reaction, but it is rare. It is recommended to substitute butylene glycol, glycerin, or polysorbate if the patient is allergic to PG. If the reaction does not resolve, minoxidil foam (MF), which is PG-free, should be prescribed. In such a circumstance, a minoxidil allergy should be suspected, and all minoxidil preparations should be discontinued (Friedman, et al., 2002).

Many patients who are prescribed topical minoxidil have difficulties adhering to the treatment plan because it requires two applications a day, it causes undesirable hair texture, and it causes scalp irritation (Randolph & Tosti, 2021). To address these concerns, a topical foam of minoxidil was developed that is free of propylene glycol. A study comparing a minoxidil solution and minoxidil foam was conducted. As a result, the US Food and Drug Administration (FDA) has approved 5% MF for the treatment of both men and women who have AGA due to its ability to deliver the active ingredient to the target site and penetrate the drug easily with less irritation. A major advantage of MF is that it dries quicker and spreads less to the peripheral region. (Campese, 1981).

As an alternative to topical MS, another study was conducted on oral minoxidil. This was found to be an effective, safe, and well-tolerated treatment option for healthy patients who had difficulty with topical formulations (Randolph & Tosti, 2021). The benefit of topical minoxidil is that it has greater patient compliance in addition to its therapeutic properties. Studies recommend that woman take less than 0.25 mg daily, while men should take at least 1.25 mg daily for maximum effect (Villani, et al., 2021).

In order to determine the most effective treatment protocol, including dosage and treatment duration, larger randomized comparative studies should be conducted. The evidence appears to suggest that minoxidil can be used effectively to treat male pattern baldness.

Finasteride

FDA has approved only two drugs to treat hair loss and finasteride is one of them. It is an inhibitor of the enzyme 5α–reductase that can potentially reduce male pattern baldness. The FDA approved finasteride for medical use in 1992 (Fischer & Ganellin, 2006). Patients with benign prostatic hyperplasia were initially prescribed finasteride at a dose of 5mg daily under the brand names Proscar and Propecia. In men, this medication is now used to treat benign prostatic hyperplasia and hair loss. (Cranwell & Sinclair, 2016).

Despite its name, finasteride is an antiandrogen because it inhibits 5α-reductase type II and III. As a result, dihydrotestosterone (DHT) production drops by about 70% in the prostate gland and on the scalp. This is accomplished by finasteride binding to the 5-AR proteins and preventing DHT from binding with them. Since DHT cannot bind to your hair follicles, your hair follicles will not shrink. (Cranwell & Sinclair, 2016).

An oral finasteride dose of 1 mg/day is recommended to treat male pattern hair loss (Gormley, et al., 1990). By taking this daily, it will reduce the scalp DHT by 64% and serum DHT by 68%. The efficacy of finasteride in patients with MAA was further demonstrated in a randomized, double-blind, placebo-controlled twin study. Four out of five subjects in the finasteride group had an increase in hair count by month 12, while 44% of the placebo group had decreased hair count. In the finasteride group, levels of serum DHT were significantly lower, while placebo levels did not change significantly. (Cranwell & Sinclair, 2016).

The hair on the bitemporal and vertex regions of the male scalp is particularly susceptible to high levels of circulating androgens, and it responds well to finasteride oral treatment (Dabek, et al., 2019). It was also clinically observed, that finasteride acts in both the front area and the vertex, (Rossi, Mari, et al., 2012). On the vertex and superior-frontal areas of the scalp, the finasteride group showed significant improvement in hair growth, whereas neither group showed improvements in hair growth on the temporal or anterior hairline areas. Compared to the minimal response over the temporal and anterior hairline regions, this study shows the relative efficacy of finasteride in protecting hair over the vertex and superior-frontal regions of the scalp (Cranwell & Sinclair, 2016).

A randomized controlled study using 5% topical minoxidil and 1 milligram of finasteride showed that finasteride increased hair growth dramatically. The effectiveness of finasteride is greater than that of minoxidil, but it comes with its own side effects (Cranwell & Sinclair, 2016). The tolerability of the placebo and finasteride receiving groups was similar overall. In the group receiving finasteride, the main difference between those who received finasteride and those who did not was a higher percentage of sexual function abnormalities (Waldstreicher, et al., 1997). The sexual function disorders include libido and impotence, and in severe cases, it may cause gynecomastia, pain in the testicles, and inability to urinate (WebMD, 2021). In both groups, there was a difference, but it was quite small, only 3.8% in the placebo group and 2.1% in the finasteride group. The majority of patients who reported sexual problems during treatment were able to resolve those problems despite continuing to take finasteride. Many of those who withdrew from the trial due to sexual disorders reported that the problems resolved after discontinuing the drug (Waldstreicher, et al., 1997). Based on these studies, it appears that men experience reduced hair loss when taking finasteride. From this study, we see that Finasteride causes hair regrowth by altering DHT levels, which lends credence to the DHT theory of baldness.

Along with knowing the side effects, it is essential not to use finasteride near pregnant or nursing women. Dermatologically, the drug can be absorbed. It is not recommended that pregnant or planning to become pregnant women handle a tablet if the film coating has been broken or if the tablet has been crushed. An infant exposed to finasteride may develop abnormalities of the genital area (WebMD, 2021).

In order to determine the most effective treatment protocol, including dosage and treatment duration, larger randomized comparative studies should be conducted. It is well known that minoxidil is an effective treatment for male pattern hair loss. However, it is less effective than finasteride, but the advantage of using a topical solution is that it is easily absorbed into the scalp. Since one needs to use finasteride continuously to prevent further hair loss, long-term studies of potential side effects are necessary.

Dutasteride

The FDA does not approve all drugs, but some of them are potentially helpful medications. Dutasteride 0.5mg dosage was approved by the FDA for the treatment of benign prostatic hyperplasia while MAA uses are off-label. The oral drug dutasteride may also be used for androgenetic alopecia, like finasteride. Approximately three times as potent as finasteride in inhibiting the type II enzyme, and 100 times as potent in inhibiting the type I enzyme, this drug inhibits both types I and II 5-a reductase isoenzymes (Feinstein, 2020). In comparison, dutasteride can decrease serum DHT by more than 90%, whereas finasteride decreases it by 70%. Due to these properties, dutasteride makes a more promising candidate for MPB treatment. Although dutasteride has more desirable properties, relatively little research has been conducted on its use in the treatment of MPB (Rafi & Katz, 2011).

During a phase II randomized placebo-controlled trial, it was determined dutasteride had a stronger effect than finasteride when it came to improving scalp hair growth in men between the ages of 21 and 45. An observational phase II randomized placebo-controlled trial of dutasteride and finasteride found that dutasteride was more effective than finasteride at increasing scalp hair growth, and 2.5mg dutasteride was more effective at enhancing growth in men aged 21 to 45. As compared to

finasteride, it also increased hair growth. Hair count data and clinical assessment data at 12 and 24 weeks were used to demonstrate this (Rafi & Katz, 2011).

According to another recent randomized, double-blind, placebo-controlled study, dutasteride 0.5mg/day significantly reduced hair loss progression in men with MAA. According to another recent randomized, double-blind, placebo-controlled study, dutasteride 0.5mg/day significantly reduced hair loss progression in men with MAA. In a case report a woman who had failed to show any response to finasteride had success with dutasteride 0.5mg (Cranwell & Sinclair, 2016).

Due to its ability to inhibit type I and type II five-alpha reductase, it may be superior to finasteride at promoting hair growth in young males. Nevertheless, finasteride is the preferred treatment for androgenetic alopecia. Dihydrotestosterone plays important physiological roles unrelated to androgenetic functions in finasteride, researchers stated. With dutasteride, side effects are more likely than with finasteride. Among the possible side effects are decreased libido, impotence, and gynecomastia (enlarged breasts). In patients treated with dutasteride, the sperm count, and volume were reduced (Cranwell & Sinclair, 2016).

Ketoconazole

Ketoconazole, pharmaceutically known as Nizoral, is an antifungal agent with anti-inflammatory and anti-androgenic properties. It is available as a cream, solution and shampoo for cutaneous fungal infections. It is commonly known to be used as an anti-fungal shampoo to treat seborrheic dermatitis, dandruff, caused by excess Malassezia. Besides KCZ treating fungus, there has been evidence accumulated that shows ketoconazole being an effective treatment for hair loss (Perez, 2004).

There is no clear explanation for why ketoconazole causes hair regrowth. It was found that Ketoconazole works by interfering with DHT production, the hormone responsible for hair loss in men. When it is used topically on hair, it works as a mild DHT antagonist compared to finasteride. However, KCZ works as well as the FDA-approved topical treatment minoxidil (Piérard-Franchimont, et al., 1998). It is also found effective when used either alone or when used with another FDA-approved hair loss treatment, like finasteride or minoxidil (Perez, 2004).

There are different postulated theories of how KCZ shampoo helps with hair loss It may be caused by an inflammatory reaction abutting the hair follicles (Piérard-Franchimont, et al., 1998). Fields explains that every individual's head contains a fungus called Malassezia. When there is too much buildup of Malassezia, it causes dandruff and it produces inflammation, resulting in flaking and itching and some hair loss (Fields, et al., 2020). Interestingly, researchers have found that men with male pattern baldness have more Malassezia on their heads than the general population (Perez, 2004).

The ketoconazole anti-fungal shampoo gives relief from dandruff and itching by killing the excess Malassezia (Huang, et al., 2019). Malassezia may contribute to the process of inflammation in androgenic alopecia, based on the data presently available. A study was conducted to determine how KCZ acted as an active against the microflora and showed intrinsic anti-inflammatory activity that improved alopecia. Researchers compared 2% KCZ shampoo to an unmedicated shampoo with or without 2% minoxidil therapy in a study. There was an almost similar improvement in hair density, size, and proportion of the anagen follicles by both KCZ and minoxidil regimens, and there was a significant decrease in sebum levels by KCZ. To assess the clinical significance of the results, a larger sample size is needed (Piérard-Franchimont, et al., 1998).

According to Cranwell, W., and Sinclair, R., a study was conducted showing that topical ketoconazole shampoo increased hair growth in both humans and rodents. Additionally, there was an increase in the diameter of hair shafts in association with the agents. Researchers found topical ketoconazole to be an effective adjunctive or alternative treatment for androgenetic alopecia (Cranwell & Sinclair, 2016). Another study, conducted in 1998, found that ketoconazole shampoo increased hair density as well as the proportion and size of hair follicles (Piérard-Franchimont, et al., 1998).

Ketoconazole may cause irregular hair texture, discoloration, irritation, or pimple-like bumps on the scalp. In addition, hair and scalp may be oily or dry. Ketoconazole shampoo is only approved for treating seborrheic dermatitis of the scalp and dandruff. As an anti-hair loss treatment, the product cannot be advertised or marketed to the general public. Further studies need to be conducted to show the effectiveness of KCZ. It is also worth noting that more research needs to be done on the mechanism behind how hair growth is caused. There also needs to be research to demonstrate whether taking ketoconazole for an extended period is safe.

PRP Treatment

The growth factors and stimulatory mediators naturally present in platelet-rich plasma (PRP) can be extracted from whole blood for use in medicine. PRP therapy has been used for decades for the stimulation of muscle, tendon, and ligament healing. A recent limited study suggests that PRP can also be used as a standalone treatment

for AGA with minimal side effects. This procedure uses platelet-rich plasma, which can be found in your blood, to promote hair growth on your scalp (Cranwell & Sinclair, 2016).

A study conducted in Spain in 2015 proved that plasma rich in growth factors, called PGRP, could be effective in treating androgenetic alopecia. In the study of over 100 patients, PGRF was administered intradermally twice a week for a total of four cycles. It was found that the anagen follicle count significantly increased by 6.2% compared with baseline, while telogen follicle count decreased by 5.1%. There were no adverse effects observed in any of the patients (Cranwell & Sinclair, 2016).

Low-level Light Therapy

As an over-the-counter hair growth method, laser light therapy, in particular a red-light hairbrush, is being marketed. The HairMax LaserComb® has been approved for medical use by the FDA as a medical device. In this approval, safety has been emphasized rather than effectiveness, and the data necessary to demonstrate the safety and effectiveness of medical devices differ considerably from those needed for drugs (Feinstein, 2020).

An extensive study was published in 2014, which had the largest sample size to date. The purpose of this double-blind, randomized, sham-controlled study was to examine 128 males and 141 females with pattern hair loss. Researchers randomized participants to either receive a sham or a real HairMax Lasercomb®. Over the course of 26 weeks, patients received three treatments per week, with varying treatment times per day depending on the model of Lasercomb®. This ensured that the total laser dose remained the same across all models. Based on the results, all LLLT-treated groups showed statistically significant improvement in hair density compared to their sham counterparts. Although not all patients experienced statistically significant results, most self-assessments of hair loss condition and thickness showed improvement after LLLT treatments. A number of adverse events have been reported, including dry skin, pruritus, a warm sensation, and scalp tenderness. The current study has several strengths, including the large sample size, sham device-controlled, double-blind design, as well as objective measurements and self-assessments by the subjects (Darwin, et al., 2018).

In the case of androgenic alopecia, LLLT is a safe and effective treatment option. In studies with similar treatment durations, oral finasteride and topical minoxidil appear to be comparable in their hair growth efficacy. In comparison with other AGA treatment options on the market, LLLT has been shown to have no significant side effects. The research suggests that the drug may be effective when combined with minoxidil and finasteride, as well as a primary treatment option. Patients who have not reacted to finasteride or minoxidil and do not want to undergo hair transplantation may benefit from the LLLT. The device is safe and easy to use, and it does not leave any residue on the scalp. In order to determine the optimal wavelength and intensity of LLLT as a treatment for androgenic alopecia, further research is needed. In addition, further study is required to understand the physiology and mechanism of LLLT for hair regrowth (Darwin, et al., 2018).

Hair transplant

Surgical hair transplants are reserved for individuals who do not respond to topical minoxidil and/or oral finasteride, or who cannot tolerate their risks. Individuals with very little hair may not be recommended to have a hair transplant. During a hair transplant, hair from the occipital scalp is removed and re-implanted into the bald vertex and frontal scalp. It has only been in the last few years that modern grafting techniques have permitted grafts to survive reliably with greater than 90% survival. The two prerequisites for the procedure are the stabilization of the hair loss with medical treatment as well as a healthy population of donor hair in the area of occipital hair (Cranwell & Sinclair, 2016).

Discussion

Based on the research, DHT is a major cause of male pattern hair loss, caused both by a genetic predisposition to hair loss as well as by natural changes in the body that causes hair loss as one ages. Plenty of hair loss treatments addressing DHT are available and reducing hair loss may make us feel more confident about our appearance in our everyday life. It is still best to consult a doctor before beginning any treatment, since not all treatments are safe or effective for everyone.

Conclusion

Having androgenetic alopecia is distressing for many men and women, and an increasing number of men and women are pursuing treatment to prevent and reverse the process. It has been found that there are medications that can slow or stop hair loss, and therefore, we may conclude that androgenetic alopecia can be managed. Additionally, it is concluded that drugs used to treat AGA are only effective for so long as they are administered. This means hair loss cannot be cured. In order to find a cure for hair loss, we need a comprehensive theory that explains the mechanism.

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Retinal Detachment: What are the Types and Potential Causes?

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Abstract

Retinal detachment is one of the few ocular emergencies. Depending on the extensiveness of the detachment, and whether it is macula on or macula off, will affect the patient's visual acuity after treatment. Therefore, it is vital that after experiencing any common retinal detachment symptoms, the patient sees an ophthalmologist immediately. High-risk factors for retinal detachment include aging, ocular trauma, high myopia, and prior eye surgery. Statistically, the cause of a given retinal detachment often determines the specific type of detachment that occurs. There are three forms of retinal detachment, categorized separately based on their anatomical characteristics.

Introduction

Everywhere we go, we are surrounded by the wondrous creations of G-d. Our eyes, a pair of those creations, are organs, each one intricately curated to provide us with vision. The structure of an eye is a formation of three layers of tissue surrounding a fluid-filled sphere. The sclera is the most external tissue, which transforms into the cornea at the front of the eye (Purves et al., 2001). This is where light initially enters and begins its pathway to be translated into the images we see. The light energy travels through the eye until it reaches the retina, the innermost layer of the eye, where it is converted into electrical energy. The electrical signals then travel through the remainder of the eye, reaching the optic nerve, where they will then continue onto the occipital lobe to be interpreted into vision. If anything along this path were to become damaged, it would result in reduced vision and sometimes even blindness (Rehman et al., 2021).

The retina is the site of conversion from light energy to electrical energy due to its neuronal makeup. Five major neuronal cell classes form the retina, along with Muller glial cells for support and protection. Two of these classes are photoreceptors, which can be further categorized into rods and cones. These photoreceptors are the ones that receive light energy and convert it into electrical energy, enabling the signals to be transmitted through the brain (Hoon et al., 2014).

The blood supply for the retina comes from multiple sources, including the central retinal artery (CRA) and the choroid, a rich capillary bed within the middle layer of the eye, which receives its blood supply from the posterior ciliary bodies (Purves et al., 2001). However, certain layers of the retina rely entirely on the choroid for their blood and oxygen supply, specifically the photoreceptor cells. Lying on the posterior portion of the retina is the macula lutea, the area responsible for central vision. The fovea centralis, which is the central portion of the macula, is densely packed with photoreceptor cells, primarily cones (Kolb, 2005). If the macula (inclusive with the fovea) becomes detached from the choroid, it would result in apoptosis of the photoreceptor cells and probable blindness (Ghazi, Green, 2002, & Kolb, 2005).

Retinal detachment (RD) is one of the few ocular emergencies; it occurs when the neurosensory retina (NSR) separates from its underlying membrane, the retinal pigment epithelium (RPE), and therefore, from the choroid as well (Ghazi, Green, 2002). Depending on the extensiveness of the detachment, and whether or not the macula is detached as well, will determine the chances of regaining decent vision post retinal detachment treatment. Therefore, it is a time-sensitive emergency, because although initially localized, it can progress and go from a partial to a complete retinal detachment.

Methods

Research for this paper was conducted with the use of databases available through Touro College Library, such as ProQuest and EBSCO, along with Google Scholar.

Discussion

To begin, we will discuss the different classifications of retinal detachment and then go on to discuss causes and the most likely type of retinal detachment that each corresponds to.

Types of Retinal Detachment

Retinal detachment is classified into three different types based on anatomical characteristics.

1. Rhegmatogenous retinal detachment (RRD)
2. Tractional retinal detachment (TRD)
3. Exudative retinal detachment

Rhegmatogenous retinal detachment is the most common type of retinal detachment, occurring in about 1 in 10,000 persons per year (Feltgen, Walter, 2014). This form of retinal detachment is a result of a retinal break, which can be seen in the name, "'rhegma,' meaning a rent or a fissure" (Jalali, 2003). Vitreous humor from the vitreous cavity seeps through the retinal break, pushing the neurosensory retina away from the underlying retinal pigment epithelium and choroid. Rhegmatogenous retinal detachment can occur at any age "but reaches peak prevalence in people aged 60 to 70 years" (Fraser, Steel, 2010).

Tractional retinal detachment is due to "pre-retinal membrane formation and scarring that pulls the retina from its

attachment" (Jalali, 2003). On the other hand, exudative retinal detachment develops due to fluid from the retina and/or choroidal vessels collecting in the subretinal space, which is the area between the photoreceptors (neurosensory retina) and the retinal pigment epithelium (Amer et al., 2017). Exudative retinal detachment occurs in the absence of retinal breaks or traction (Ghazi, Green, 2002).

The latter two classifications of retinal detachment, tractional and exudative, are far less common than the rhegmatogenous form. However, all causes of retinal detachment share one common characteristic: the accumulation of subretinal fluid (Ghazi, Green, 2002).

Symptoms

The most common symptom of retinal detachment is "sudden, painless loss of vision or blurring of vision in the affected eye." Some patients also undergo field loss, which they describe as a "veil or shadow in one area of their vision." Flashes or floaters may also occur "due to vitreous degeneration and its traction on the retina" (Jalali, 2003). It is the responsibility of the doctor to inform and educate high-risk patients of these symptoms and the importance of seeing an ophthalmologist immediately after experiencing any of the aforementioned signs.

Potential Causes

Risk factors, such as aging, ocular trauma, high myopia (nearsightedness greater than -6.00 diopters), or prior eye surgery can predispose a patient to retinal detachment (Kwok et al., 2020). However, these factors do not warrant that a patient will definitely experience retinal detachment, only that there is a greater incidence of it occurring than in those who do not possess any of these risk factors. Patients with any of the aforementioned conditions should have routine ophthalmic exams, allowing the doctor to perform dilated examinations and collect diagnostic imaging for future reference (Jalali, 2003). Such imaging tools can include optical coherence tomography (OCT) and fundus photographs, each providing different views of the retina. If somebody is experiencing retinal detachment symptoms, it is vital that they see an ophthalmologist immediately (Williams, Hammond, 2019). The sooner a patient sees an ophthalmologist to confirm or deny a retinal detachment will increase the chances of preserving visual acuity. Unfortunately, "it has been estimated that between 50% and 70% of patients present too late because they did not recognize the typical symptoms of detachments." It is, therefore, very important "to ensure that high-risk patients are informed accordingly" (Feltgen, Walter, 2014).

Aging

One of the most common risk factors of retinal detachment is aging. The type of retinal detachment that occurs due to aging is rhegmatogenous retinal detachment (Feltgen, Walter, 2014). Generally, "the annual incidence of RRD range[s] from 6.3 to 17.9 per 100,000 population globally, however, for those aged "70 to 79 years old, the incidences [of retinal detachment] vary from 15.21 to 50 per 100,000 worldwide" (Ma et al., 2014). The reason for this is that as people age, changes occur in the structure of their eyes, and complications can cause retinal issues (Salvi et al., 2006). One such change involves the vitreous humor, the gelatinous substance filling the space between the back of the lens of the eye and the surface of the retina (Purves et al., 2001). Initially, the vitreous humor has a gel-like consistency, made up of collagen fibers, hyaluronic acid, and water; it adheres most strongly to the retina "around the vitreous base (ora serrata), at the optic disc margins, at [the] macula, and around peripheral blood vessels" (Ramovecchi et al., 2021). However, as one ages, the vitreous begins to liquify, degenerating from its gel phase into a water phase and the adhesion to the retina begins to weaken (Bond-Taylor et al., 2017). The liquefication of the vitreous humor can result in posterior vitreous detachment (PVD), which is when the vitreous suddenly separates from the retina (Ramovecchi et al., 2021).

Posterior vitreous detachment is a normal and physiologic part of aging; however, complications can result in retinal damage, such as retinal tears and/or retinal detachment. As previously mentioned, the vitreous adheres to the retina, and over time, naturally, the adherence begins to weaken. However, if, when the vitreous humor begins to collapse, it is still strongly attached to the retina, its weight will exert traction and result in a retinal tear, which can potentially progress into retinal detachment (Feltgen, Walter, 2014). According to the report written by Drs. Feltgen and Walter, "every fifth patient with posterior vitreous detachment develops a retinal hole" (2014). Therefore, it is crucial to see an ophthalmologist after experiencing common posterior vitreous detachment symptoms, such as "photopsia (flashes) and myodesopsia (or floaters [aggregated collagen fibers])," especially if the symptoms begin to worsen, as it can be a sign of retinal damage (Ramovecchi et al., 2021).

Ocular Trauma

Trauma to the ocular region can cause retinal detachment. The forceful impact to the eye results in the sudden compression and indentation of the eyeball and, when strong enough, can cause retinal breaks and/or retinal detachment (Wilians, 2021). According to studies performed by

Drs. Ghazi and Green, "about 15% of all retinal detachments are traumatic" (2002). In a past study, "seventy-seven patients developed retinal breaks following an episode of ocular contusion, and 65 (84.4%) of these developed rhegmatogenous retinal detachment" (Johnston, 1991). The form of retinal detachment that occurs is dependent on the type of trauma that took place, either blunt or penetrating. Generally, blunt trauma results in rhegmatogenous retinal detachment, and penetrating trauma results in tractional retinal detachment, with "blunt trauma represent[ing] about 70-85% of all traumatic retinal detachments" (Ghazi, Green, 2002).

In general, retinal detachment is fairly uncommon amongst children; however, when it does occur, the majority of detachments are caused by ocular trauma (Yasa et al., 2018). In fact, traumatic retinal detachment is actually more common among young individuals than adults (Ghazi, Green, 2002). However, as mentioned previously, rhegmatogenous retinal detachment occurs when the vitreous humor seeps through a retinal tear, pushing the retina away from its supporting tissues. In young individuals, the vitreous is still intact in its original gel-phase and actually provides a "sealing effect on retinal breaks." For a retinal detachment to occur, the trauma would have to also induce a traumatic vitreous syneresis (degeneration of the vitreous humor from its gel-phase into the water phase), thereby allowing the fluid to seep into the subretinal space and develop into retinal detachment (Ghazi, Green, 2002).

Myopia

In order "to obtain clear vision, the eye must accurately focus an image in space on the retina" (Fredrick, 2002). Refractive error is when a pair of eyes are unable to focus an image on the retina due to the shape of the cornea, aging of the lens, or the length of the eye. Myopia (nearsightedness) is a type of refractive error that is caused by "the cornea or lens curvature [being] too strong" or the eye being too long (axial myopia) (Fredrick, 2002). In normal eyes, the image falls precisely on the retina. However, in myopic eyes, the image is focused in front of the retina, causing far objects to appear blurry while objects up close are clear.

Myopic patients have an "increased risk of sight-threatening diseases, including retinal tears which may lead to a retinal detachment." This is due to the anatomical structure of myopic eyes. As mentioned previously, one cause of myopia is that the length of the eyeball increased, which is known as axial elongation. This excessive growth stretches out the retina and therefore makes it more "prone to peripheral retinal tears." Additionally, in myopic eyes, the vitreous humor is already degenerating, so it is "more likely to collapse and separate from the retina," thereby also increasing the risk of retinal tears (Williams, Hammond, 2019). In various study groups, it was found that "50% of all patients with rhegmatogenous retinal detachment were myopic" (Feltgen, Walter, 2014).

The measurement term used for refractive errors is diopters (D), and when referring to myopia, it is designated with a minus sign. "Mild myopia is 0 D to −1.50 D, moderate −1.50 D to −6.00 D, and high myopia −6.00 D or more" (Fredrick, 2002). The stage of myopia, whether mild, moderate, or high affects the chances of retinal detachment occurring, as Drs. Feltgen and Walter explain, "shortsightedness of up to -3.00 diopters (D) quadruples the risk of retinal detachment, and myopia of more than -3.00 D increases the danger of detachment tenfold" (2014). Furthermore, "the prevalence of myopia is increasing globally," and it is predicted that "by the year 2050, high myopia will affect 9.8% of the global population; a total of 938 million people" (Williams, Hammond, 2019). Therefore, it is important to ensure that myopic patients are well-informed of the risks and symptoms of retinal detachment. It is incumbent on the doctor to emphasize the importance of myopic patients taking certain necessary precautions, such as wearing protective eyewear during contact sports (Kwok et al., 2020).

Prior Eye Surgery

Light is transmitted and focused on the retina with the assistance of structures within the eyes, including the crystalline lens (Hejtmancik, Shiels, 2015). The lens needs to be transparent for an image to be planted clearly on the retina. Therefore, when opacification of the lens occurs, known as a cataract, it causes visual impairment (Davis, 2016) and decreases the quality of life. So, in order to re-acquire decent visual acuity, the cataract must be removed. According to Vision 2020, every year, approximately ten million cataract surgeries are performed worldwide. The majority of cataract extractions occur without complication; however, surgery, no matter the type, always poses a risk to the patient. Cataract surgery can potentially cause retinal detachment, and the risk of it occurring, specifically rhegmatogenous retinal detachment, is approximately 1/1000 (Feltgen, Walter, 2014).

Cataract surgery, along with being one of the most common procedures performed, can also be traced back to the earliest. In 1747, "the first true cataract extraction" was performed in a manner of extracapsular cataract extraction (ECCE), meaning that the lens capsule was left in place. In 1753, a new approach to cataract surgery was taken, known as intracapsular cataract extraction (ICCE),

where the entire lens (including the capsule) was removed. The modern-day approach to cataract surgery is a form of ECCE, known as phacoemulsification, where the lens is emulsified and aspirated through an ultrasound-driven needle. However, although this procedure is considered the safest and most preferred method of cataract surgery, retinal detachment risks are still involved (Davis, 2016).

In a population-based study, it was found that cataract extraction increases the risk of posterior vitreous detachment (Erie et al., 2006). The surgery "accelerates the liquification of the vitreous humor," enabling it to collapse and exert traction on the retina with the potential to progress into a retinal detachment (Feltgen, Walter, 2014). The study also discovered that certain risk factors, such as "myopia, increased axial length, and posterior capsular tear at surgery significantly increased the risk of retinal detachment." Specifically, with regard to posterior capsular tears, it was found that "six of nine cataract extractions" that underwent this complication "had a retinal detachment within 1 year of surgery" (Erie et al., 2006). Furthermore, it was found that the danger of retinal detachment "grows as the postoperative interval increases" (Feltgen, Walter, 2014). The probability of retinal detachment occurring "increased from 0.27% at 1 year after cataract extraction to 1.79% at 20 years" (Erie et al., 2006).

Conclusion

Retinal detachment is considered an ocular emergency, and if not treated properly and immediately, can result in blindness. Patients who possess any high-risk factors for retinal detachment should routinely see an ophthalmologist. The doctor's responsibility is to inform these patients of the necessary precautions to take and the signs and symptoms of retinal detachment. It is also crucial to express the time-sensitive aspect of this emergency and how immediately after experiencing any symptoms, patients need to see their ophthalmologist.

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Is Deep Brain Stimulation a Desirable Therapy for Parkinson's Disease?

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Abstract

Parkinson's disease is a neurodegenerative disorder that currently impacts 6.1 million people globally. Although it has different presentations, its core features are tremors, postural instability, bradykinesia (slowing of movement), and psychological disabilities such as mood disorders and cognitive decline. A primary treatment is Levodopa, but it has limited success. A promising treatment called Deep Brain Stimulation (DBS) has been shown to induce significant improvements in motor skills where Levodopa has failed to help. Deep Brain Stimulation works via implanted electrodes. It has been used successfully in many studies to decrease motor issues associated with Parkinson's, but potential side effects pose a problem. Overall though, DBS is a promising field of study in the ongoing attempt to find treatments for Parkinson's disease, especially as we identify specific aspects of DBS that improve the risk to benefit ratio. This review of the current literature was conducted in order to determine the efficacy and safety of DBS as a treatment for PD.

Introduction

Parkinson's disease (PD) was first described medically by James Parkinson in 1817. Jean-Martin Charcot continued discovering more about Parkinson's disease in the mid 1800's and was instrumental in further developing the definition of Parkinson's by stating what made it a unique disorder (Goetz, 2011). Over the years, Parkinson's disease has been a subject of research, and although there is still no cure, there are many treatments aimed at relieving the symptoms. There are very effective pharmaceutical interventions available, such as the drug Levodopa. Other treatments range from traditional (lesioning of brain areas associated with PD symptoms) to new and experimental (implantation of human parthenogenetic stem cell-derived neural stem cells in animals with PD symptoms [Gonzalez, et al. 2016]). This paper will focus on discussing Parkinson Disease, and the use of deep brain stimulation to treat it. It will also seek to answer questions regarding the mechanisms, effectiveness, and drawbacks of DBS.

Methods

Available literature on the topics of Parkinson's Disease and Deep Brain Stimulation were reviewed using the search function on the Touro Library website, and by utilizing Google and Google Scholar.

Discussion

Parkinson's disease impacted 6.1 million people globally in 2016, and the rate keeps rising, as seen from the fact that only 2.5 million people had Parkinson's in 1990 (Dorsey, et al. 2018). Age is one of the most important risk factors, as more than 75% of people with Parkinson's developed it after the age of 65 (Bloem, et al. 2021), although people can develop it at a young age if they have a genetic predisposition. The main genes associated with Parkinson's disease are the SNCA, LRRK2, PRKN, PINK1, and GBA genes. Other risk factors associated with Parkinson's are head injuries and lifestyle factors, such as lack of exercise and exposure to toxins. Interestingly, smoking has been shown to be inversely related to developing Parkinson's disease, although it is unclear if the connection is correlational or causal (Bloem, et al 2021).

Parkinson's presents with many motor and non-motor symptoms. Prominent motor symptoms include bradykinesia, or slowness of movements, tremor, postural instability and rigidity. Dyskinesia, or impairment of movements, is another significant side effect that may develop with long-term treatment with Levodopa, and may cause involuntary movements that severely impact a person. There are also many non-motor symptoms associated with Parkinson's, such as dementia, depression, and dysregulation of a person's sleep cycle.

Buildup of α-synuclein in Lewy bodies and neurites is the pathological defining feature of Parkinson's disease. New studies suggest that a similar accumulation occurs in other tissues such as skin cells, which may be a helpful predictor of onset of Parkinson's as that tissue is much more accessible than brain tissue (Bloem, et al 2021). Currently PD is diagnosed clinically, based on symptoms. It may be difficult to diagnose, as the symptoms may be similar to other diseases.

Parkinson's is caused by a decrease of the neurotransmitter dopamine, which is caused by the death of cells in the substantia nigra. This is the source of dopamine production in the brain, and as cells die less dopamine is produced. Dopamine is integral in regulating movement. Loss of cells is normal with aging, but accelerated loss leads to Parkinson's; 50-60% loss indicates the onset of symptoms (Johns Hopkin's Medicine).

Replacing dopamine is not as simple as taking supplementary pills, as dopamine cannot enter the brain. Currently, a primary treatment for Parkinson's is levodopa, a drug that is converted to dopamine in the brain. However, some people don't respond to levodopa, or become resistant to it over time, or may experience fluctuations in their responses. For people who are not receiving optimal results with pharmaceutical therapies, neurosurgical treatments such as deep brain stimulation, or DBS, may be effective in controlling motor symptoms. (Bloem, et al 2021)

As explained by the Mayo Clinic, the surgical portion of DBS takes place in two parts; first, the brain is mapped out via screening tests such as an MRI, and electrodes are surgically implanted in the targeted areas. Later, in a different procedure, the battery source for the electrodes, the pulse generator, is implanted near the collarbone and connected to the electrodes via wires. In future doctor visits, the patient undergoes testing to determine the correct level of stimulation needed. Once all this is in place, ongoing supervision and tweaking of the signaling is done via a special remote control. A person may have ongoing stimulation, or it may be turned on and off via remote as needed. (Mayo Clinic, 2021).

Improvement times of symptoms vary, and are partly based on the area where the electrodes are located. For example, with subthalamic nucleus deep brain stimulation (STN DBS), tremors are relieved after seconds of DBS activation, rigidity and bradykinesia are relieved after minutes to hours, and axial symptoms may take days to be relieved. The return of symptoms once the electrode is deactivated mirrors the time of activation; for example, tremors return in minutes. This suggests that the improvements are due to different mechanisms. Quick relief of symptoms may be due to instant release of neurotransmitters, while long term relief may at least partly be due to plasticity or remodeling of the brain (Herrington, et al 2016)

DBS replaced lesioning operations, and in comparison, caused little or no tissue damage, and is therefore reversible (Groiss et al, 2009). In a postmortem case study done on the brain of a 21 year old patient who underwent DBS in the anterior thalamus for epilepsy, it was found that the DBS caused little tissue damage. The patient died unexpectedly 8 months after surgery, and an autopsy showed his death was an unexpected result of epilepsy. When studying his brain posthumously, it was found that DBD caused only mild tissue reaction and did not cause significant damage (Pilitsis, et. al. 2008)

The two primary target areas for DBS in people with PD are the subthalamic nucleus (STN) and globus pallidus interna (GPi). In a study, 299 patients were randomly assigned to either STN or GPi DBS. One hundred and fifty-two patients received GPi DBS, and 147 patients underwent STN DBS. The two groups started with similar baseline characteristics, except for minor differences in areas such as emotional well-being, social support, and cognition. Of the original group of patients, only 279 patients completed a 6-month evaluation.

At 24 months, it was found that there was no significant difference of motor symptom outcomes (based on the UPRDS III) between the two groups. There was a reduction of 11.8 in the group that received DBS-STN and a reduction of 10.7 points in the group that received STN-DBS. When the participants took the PDQ-39 (Parkinson daily questionnaire) to test quality of life, both study groups indicated improvement in 6 of the 8 subscales. Social support was slightly increased for the group with STN DBS, and decreased for GPi DBS, but no significant differences were found between the two groups. They also had similar results when testing for neurocognitive function and mood, but the group that received GPi DBS had slightly better scores on the Beck Depression Inventory, and the STN DBS group had a slight decline (P=.02).

Another finding from the study was that patients who received STN DBS were able to reduce their dopaminergic medication, as compared to patients who received GPi DBS. Additionally, STN DBS has lower amplitudes and pulse widths, which translates to lower power usage, and ultimately less frequent replacement of the pulse generator. This can contribute to lower therapy costs, and decreased risk from surgical replacement of the pulse generator (Follet, et al. 2010). This aspect is very important, as patients with Parkinson's often have a hard time with basic activities of daily living, and having to undergo surgery every couple of years is a real hardship. Anything that minimizes the amount of upkeep their hardware requires is an advantage.

In a study on the effect of STN DBS versus GPi DBS specifically on action and rest tremors in PD, 88 patients were studied in a final cohort; 57 patients underwent STN DBS, and 31 underwent GPi. They found that there was no significant difference in how the two forms of DBS treated tremors, but that STN DBS was effective more quickly. At 6 months post treatment, the patients who underwent STN DBS had more relief from tremor than the GPi DBS patients, but at the 12-month checkup the GPi group had caught up (Wong, et al. 2020).

Another study analyzed 25 patients who underwent either STN or GPi DBS. Both on and off medication, it was shown that there is not a significant difference in outcomes between the two groups. After 12 months, there was a 39 % improvement in motor scores in the GPi group, and a 48% improvement in the STN group (P<.001). Similar to results from the study above, after twelve months of DBS the STN group had a reduction in Levodopa of 38%, whereas the GPi group had a reduction of only 3%. Additionally, it was found that STN was more effective in reducing bradykinesia than GPi DBS, but GPi DBS may cause long term changes in dopaminergic systems (Anderson, et al. 2005).

Many studies have shown the positive effects of DBS on motor symptoms of PD. In a metanalysis done on 38

short term studies, STN DBS improved rigidity by 62% and bradykinesia by 52% after 12 months. GPi DBS had comparable results (Fasano, et al. 2012).

In a study done using the Deep Brain Stimulation for Parkinson's Disease Study Group on GPi DBS and STN DBS, 96 patients underwent STN DBS, and 91 underwent double blind evaluations and 6 months of follow up. It was found that there was a significant relationship between STN DBS therapeutic treatment and therapeutic effect ($p<.0001$), with treatment resulting in a 43% mean improvement in motor symptoms based on ratings from the UPDRS (Obeso, et al. 2001).

In the same study, forty-one patients received GPi DBS, 36 of whom underwent 6 months of follow up. Again, there were significant effects associated with the treatment, ($p<.0001$) with a mean improvement of motor symptoms based on the UPDRS of 32 percent. This suggests that STN DBS may be superior to GPi DBS, but both have been shown to significantly improve the motor symptoms of PD. Based on these results, it appears that DBS is an optimal therapy to treat PD, and patients who meet the criteria for it should be encouraged to explore this option. When a person experiences impaired functioning due to PD symptoms, it may be difficult to regain that functioning even if symptoms are reduced. We should be treating PD proactively, and offering treatments such as DBS as early as possible.

The previous studies discussed short term results of DBS on PD. Paul Krack et al conducted a 5 year follow up on 49 patients treated with STN DBS. When not taking medication, patients' motor symptoms improved (as rated by part III of the UPDRS) from the base line value by 66 percent after the first year, 59 percent after the third year and by 54 percent after 5 years. Additionally, before surgery 35 of the 49 patients had dystonia when not taking medication, and after a year of receiving DBS only 8 out of 43 had dystonia, and at 5 years only 14 out of 42 patients had it. However, when the patients were taking medication, there was no improvement. In fact 5 years post surgery the motor functions had decreased overall, with worsening of postural stability and freezing gait (Krack, et al. 2003). This study had no control group, but it would be interesting to see these results compared to results of patients treated only with pharmaceutical interventions.

There are a few accepted models to explain the pathophysiology of PD. One is the firing rate model. Dopamine triggers excitatory inputs to striatal direct pathway neurons projecting to the GPi, and inhibitory inputs to the indirect pathway neurons; loss of dopamine reduces both of these signals, increasing firing rates of the GPi and SNr (substantia nigra pars reticulata) neurons. Lesioning of the GPi or STN had beneficial effects on PD, backing up this theory. Alternatively, impaired functioning may due to firing patterns, or faulty oscillatory circuits, not disturbed firing rates (Chiken, Nambu, 2014). The brain is not composed of one complete oscillatory circuit; it is composed of many circuits, small and large, parallel and working together. When there is pathological oscillatory activity, especially beta band oscillations, in the circuit between the cortex, the basal ganglia, and the cerebellum, it may contribute to the motor symptoms of PD. A future area of focus therefore may be on DBS aimed specifically at disrupting these abnormal beta band oscillations, rather than general continuous DBS (Herrington, et al. 2020) When dopamine is low, as in PD, there is increased oscillatory movement in the basal ganglia. This in turn disables individual neurons, which can no longer properly process or pass on motor-related information.

Initially DBS was thought to inhibit neurons near the electrode. This theory was backed up by the fact that chemical inhibition of the STN or GPi also reduced Parkinson motor dysfunction, perhaps by release of the neurotransmitter GABA. However, currently there are many theories proposed for the exact mechanism of DBS. One that is supported by research is that DBS introduces a new electrical circuit that drowns out the faulty electrical signals in a PD patient's brain (Herrington, et al. 2020).

A study examined the impact of adaptive DBS (a form of DBS that utilizes feedback from neuronal activity to activate more selectively) on beta band bursts. The study was done on 13 patients who underwent adaptive DBS that broke up long beta bursts. The researchers found that Parkinson symptoms were relieved with short beta bursts, regardless of the frequency of the bursts, and intensified with long bursts. This effect occurs with conventional DBS as well, but with a different mechanism (Tinkhauser, et al. 2017).

Although DBS has been shown to improve motor symptoms in patients with Parkinson's disease, there is still concern regarding its effect on non-motor functions such as cognitive and psychiatric functioning. In a study, 60 patients were assigned to either SNT or GPi DBS, and 63 people were assigned to other types of treatment. The participants underwent cognitive and psychiatric assessment 6 months after the treatment. Criteria for participation were having a diagnosis of Parkinson's for at least 5 years, being below 75 years in age, having no prior or current psychiatric disorders, and being prepared to undergo neurosurgery. The participants who received DBS had bilateral stereotactic surgery, with a baseline pulse of 60 μs at 130 Hz with individualized adjustments.

The group who received alternate medical treatment received medication such as Levodopa. Cognitive tests were picked that focused on skills often affected by PD, such as cognitive skills, and had less motor skills aspects. Tests such as the Mattis dementia rating scale, the Wechsler adult intelligence test, and modified versions of the Stroop test were utilized. Participants' emotional states were measured by tests such as the Beck depression inventory and the Beck anxiety inventory. Quality of life was also assessed, with tests like the Parkinson's Disease questionnaire.

Results showed a significant improvement in motor skills and quality of life post DBS treatment, as compared to the group that received only medication. Overall cognitive functions were not impaired in participants who received DBS, but there were specific areas of decline. For example, based on the Mattis dementia rating scale, participants from both treatment plans had similar results when excluding verbal scoring, but when verbal scoring was factored in, the group who received DBS had worse results. Seven participants had reduction of more than 2 SD. By comparison, four participants from the other group had reduction of more than 2 SD. When excluding verbal fluency however, only 3 DBS participants were further away than 2 SD, as opposed to 4 participants from the other group. People from the DBS group also showed reduced performance in the Stroop tests.

The study demonstrated that people who received DBS exhibited no significant decline in cognitive or psychiatric functioning, with the possible exception of verbal fluency. They even experienced an improvement in areas such as anxiety, although that may be due to other factors such as the nature of the questions on the test (Witt, et al. 2008).

These results have also been shown in a review which analyzed studies published in England on patients with PD who underwent STN or GPi DBS. The studies included neuropsychological testing, and included at least 5 subjects who were followed for at least 3 months after their operations. The authors concluded that although different studies show different results, overall cognitive functioning decline is rare for patients that undergo DBS, and any change found is probably subtle. In addition, taking into account the significant improvements in motor function, even if DBS may be associated with decreased cognitive functions in some studies, it is still shown to improve overall quality of life (Mehanna, et al. 2017).

Another potential concern with DBS is the risk of hardware complications, or other risks associated with the surgery. In another study, 478 patients who had received DBS at a single medical center were retrospectively analyzed. Forty-one people had died. The biggest cause of death was pneumonia, with trouble swallowing being another leading cause of death. Two of the deaths were due to hemorrhaging the week following surgery. Only 22 people reported hardware troubles, including rejection, infection, and hardware failure. This study seems to indicate that hardware problems are not a significant issue in patients who undergo DBS, and other issues such as pneumonia and trouble swallowing are larger risk factors for patients with PD (Zhang, et al. 2017).

Conclusion

Parkinson's disease is a neurodegenerative disorder that impacts an increasing number of people. Although it can often be treated with medications such as Levodopa, there are times when medication alone is not effective. DBS can cause a significant improvement in motor symptoms over a long period of time. The side effects are found to be minimal. DBS is currently a very good treatment option for people struggling with PD symptoms that cannot be controlled by medication alone. As we do more research and improve DBS, it will become even more effective and safe.

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Are Clear Aligners Better than the Conventional Orthodontic Fixed Appliances?

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Abstract

Clear aligner therapy (CAT) has become an attractive alternative for orthodontic treatment as more adolescents and young adults pursue othodontic care. CAT is comprised of removable transparent appliances that offer a more aesthetic appearance to prospective patients. Recent studies have shown that CAT efficiency and efficacy for orthodontic procedures for cases of mild to moderate malocclusions are of equal or greater caliber to those of conventional fixed appliances. Clear aligners are also found to be less painful, better for periodontal health, and more accessible in comparison with fixed appliances. For those meeting the criteria for CAT, clear aligners may be a worthwhile course of treatment to explore.

Introduction

The pursuit of orthodontic treatment for adolescents and young adults has become a standard in regard to oral aesthetics and care. Conventional fixed appliances made from steel and ceramics are commonplace due to their years of applied practice and cost-effective treatment. However, along with the use of traditional orthodontic fixed appliances are shortcomings that impair the orthodontic experience. Clear aligners are a rather novel orthodontic device that are becoming attractive as an alternative for orthodontic procedure due to their aesthetics and accessibility.

In 1944, TP Orthodontics introduced the idea of removable orthodontic appliances meant for moderate cases of teeth repositioning. The approval for Align technology, the use of clear aligners in orthodontic treatment, by the FDA in 1998 spearheaded the popularity of CAT including Invisalign. CAT comprises of a variety of different orthodontic appliances which differ in their construction, duration of use, and effectiveness in treating oral malocclusions. The transparent plastic aligners offer diverse courses of treatment and with recent technology, can be employed to treat an assortment of problems in dental orthopedics.

Assessment of CAT applicability and its flaws is challenged by its rapid advancements in design and composition. Improvement of imaging technology and clear thermoplastic materials increases the comfort of wear while minimizing pain and duration of orthodontic treatment. More sophisticated CAT systems are available for increasingly complex oral malocclusions such as inter arch changes where additional attachments or alternative geometries are necessary. Using Invisalign or similar technologies provides patients a viable substitute to fixed braces. Essentially any form of dental malocclusion can now be successfully managed using clear aligner therapy (Weir, 2017).

Orthodontic treatments applied with standard fixed appliances, while effective, are uncomfortable and unsightly for the patient. Invisalign wearers perceived significantly lower pain levels than those being treated with metal appliances, particularly in the earlier stages of treatment (Cardoso, et al. 2020). It was also noted that fixed appliances may contribute to inflammation of the gums and aggravate periodontal health and gingivitis, a bacterial infection of the gums. CAT offers an appealing substitute in orthodontic therapy, although limited to mild to moderate malocclusion conditions. Is the treatment efficacy and safety of clear aligners better than the conventional orthodontic fixed appliances? This review is aimed at determining a better choice of orthodontic therapy to patients seeking dental orthopedic care.

Method

Peer reviewed academic journals and scientific articles were used to obtain research on Clear Aligner Therapy and fixed appliances in orthodontic procedures. Various data were used to review and provide evidence of the legitimacy of the research question. Proquest, Ebsco, and Medline databases were accessed through Touro College Library online and Pubmed.

Discussion:

Features, Materials, and Mechanics of Clear Aligners

The biomechanical characteristics of Clear Aligner Therapy are influenced by the various properties of its thermoplastic composition, texture, and fit. The series of aligner treatments can be fashioned to be constructed using one aligner material, or to be made from different aligner components as therapy progresses. Clear aligner formation can be vacuum or pressure modeled. Both methods rely on air pressure for the structure of the product. However, the pressure-based design involves higher pressures of up to 100 psi which is equated with enhanced precision of fit and force efficiency of the aligner around the tooth surface. Impressions, usually composed of polyvinyl siloxane, are taken by the clinician to send to a laboratory where 3D scanning technology is used to manufacture the appliances. CAD-CAM technology allows for the model to be adjusted for the individual stages of treatment. Accuracy of the model is critical for the efficacy of the subsequent tooth rearrangement. Some orthodontists will offer in-house 3D printing of the appliances, while others have them assembled and shipped from a specialized laboratory.

CAT is directed at maintaining proper adhesion of the

aligner to the teeth while transmitting sufficient force that allows for the movement of the teeth in a predictable trajectory. This is performed while attempting to minimize discomfort of the patient pursuing treatment. Commonly used materials for clear aligners are polyester, polyurethane, and polyethylene glycol terephthalate (PETG). Appliances composed of polyurethane tested to be of higher hardness and indentation modulus, measuring greater levels of elasticity than PETG-based products (Putrino, et al. 2021). Clinical behavior can be anticipated prior to treatment by analyzing the content and configuration of aligner appliances.

The thickness of the thermoplastic materials used in CAT can either be predetermined by manufacturers of the product or can be modified based on the course of treatment. Thickness can also be alternately modified in order to apply forces of fluctuating intensity during treatment. The width of the aligner, typically 0.5, 0.625, or 0.75mm, does not have a significant effect on general examined tooth movements. However, incrementing thickness does adversely impact more complex malocclusions.

The pressure exerted on the tooth by the material enables the aligner to stimulate movement. The presence of composite resin buttons placed on the buccal or palatal surface of one or more teeth guides the displacement of the bridgework. Specificity of the structure of the resin attachments depends on their function. Horizontal shaped attachments would be used to increase aligner stability of premolars and incisors while beveled rectangular attachments are used for aligners in cases of a deep bite. The interactions between the aligner, attachment, and the tooth necessitates precision to achieve effective movement. Aligner systems can also integrate auxiliary elements, such as mini-screws and elastics, for increased corrections and refinements.

Differentiation Among Clear Aligner Products

There are many different types of clear aligners now available that fall under the umbrella of CAT. For minor tooth movements (MTM), where clinical applicability is limited, orthodontic products such as MTM Clear Aligner, Originator, and Simpli 5 offer a less expensive and quicker substitute to other CAT appliances. Aligners from Suresmile, 3 Shape, and Orchestrate allow for completely in-house fabrication and production of the appliance using 3D treatment planning software. For more comprehensive systems, where 3D CAD-CAM treatment and bonded resin attachments are incorporated, popular companies like Invisalign, ClearCorrect, and eClinger are providing aligners for more complex tooth movement. Invisalign is the most intricate CAT appliance available, focusing on a high level of precision using 3D model manipulation and a sophisticated appliance design. Invisalign products have built in pressure points to aid tooth intrusion movements as well as detailed attachment types and precision cuts for ease of wear. Different brands of clear aligners have consistent differences between their products and will obtain diverse results. The strategy and design of a clear aligner product converge in determining the capability of a system of aligners for a specific treatment.

Fixed Appliances - Background and Categories

Fixed orthodontic appliances are the most widely used, producing precise tooth movements after 18-24 months of treatment. Following any fixed orthodontic therapy, the patient must participate in a retention system. Although there are multiple different brands of fixed appliances available, the function between the products don't really vary. Conventional metal fixed appliances, often termed "train tracks", are most popular among children and adolescents (British Orthodontic Society, 2014). The metal is typically composed of stainless steel and attached onto the teeth using a tooth-colored composite resin. An archwire is woven into the brackets using silver or colored elastic rings. The attachments are easily detached and therefore care must be taken to avoid consuming hard or sticky foods that can disrupt the treatment. As the tooth movement progresses, thicker wires are enforced to apply greater force onto the teeth and "tighten" the appliance. At the completion of treatment, the appliance is simply removed from the teeth of the patient.

Attachments may also be formed from a hard ceramic material, ceramic fixed appliances, as an alternative for a more aesthetic look for adults. The ceramic is designed to blend with the tooth color and the orthodontic wires can also be made to match the shade of the teeth, further improving the appearance. Although similar in function and effectiveness to fixed metal appliances, ceramic appliances are often discouraged from use on the lower teeth since the hard material can potentially damage opposing teeth contacting the attachments. Additionally, ceramic appliances are more challenging to remove, although unlikely to cause damage to the teeth.

Self-limiting appliances, whether produced from metal or ceramic, use an integral clip mechanism to hold the position of the wire of the appliance instead of the traditional elastics. The clip allows the wire to slide more freely and reduces the time necessary to change the wire. Lingual fixed appliances differ from other fixed appliances as they are attached to the inside surface of the teeth and are externally invisible. Despite them being adept at achieving high quality results, lingual appliances may

involve tongue soreness, difficulty speaking, and maintenance problems for the patient. Furthermore, there is a considerable increase in the cost of treatment due to the manufacturing and additional clinical time required.

Clear Aligner Efficacy and Outcome- Data and Case Reviews

The diversification of the primary characteristics of clear aligners has improved their indications and capabilities. Initially, clear aligners were limited to leveling and the alignment of arches. Today, even more intricate cases can be managed with clear aligners. Several factors must be considered in determining successful tooth movement when evaluating the results of CAT. The material and thickness of the aligner, the shape and position of the attachments, and the techniques used for the production of the aligner heavily influence the outcomes of treatment. Moreover, the individual patient's crown and root morphology as well as bone density affect the development of orthodontic therapy. Therefore, there is a variance among different clear aligner systems regarding their eligibility, efficacy, and predictability.

For oral malocclusions of greater complexity, CAT is coupled with additional orthodontic techniques such as additional attachments, auxiliary tools, and altered geometries to provide better control of movement and to improve treatment results. The use of fixed expanders, lingual buttons, intermaxillary elastics, power arms, and temporary anchorage devices can be integrated into more sophisticated aligner therapies for more difficult movements. CAT is relatively predictable for treatment of simple malocclusions such as cases of intrusion of the anterior teeth and for control of posterior buccolingual inclination, crossbite of the premolar and molar teeth (Buschang et al, 2014). However, areas of rotation and anterior buccolingual inclination are more problematic.

The efficacy of Clear Aligner Therapy in terms of alignment and straightening of the arches in cases of mild to moderate crowding is superior to the results obtained by fixed appliances. Additionally, levels of relapse are higher in fixed appliances than those treated with CAT. A study conducted on the Nuvola aligner system noted that although aligners aren't capable of significant root movement, they are useful for crown tilting movement of the tooth and for torque movements of canines and central and lateral incisors (Tepedino et al, 2018). A case series on preliminary treatment of anterior crossbite in young children observed that clear aligners were effective in treating the malocclusion, with little discomfort experienced by the patients in comparison to those of fixed appliances (Staderini et al, 2020). The Model Grading System (MGS) of the American Board of Orthodontics evaluated that Invisalign treatment was active in correcting tooth alignment and buccolingual inclination when used in less severe malocclusions (Kassas et al, 2013). Invisalign achieves this bodily movement through the use of Power Ridge, an oral attachment (Simon et al, 2014). Overall treatment efficacy is additionally influenced by the staging and total amount of planned movement of the aligner.

The effectiveness of clear aligners is expressed by the device's ability to perform complicated dental movement in a predictable fashion in equivalent or greater magnitude to the performance of fixed appliances. Progression of aligner and tooth cooperation is contingent upon the precision of the operative protocol. A clinical trial investigating CAT in controlling vertical buccal occlusion revealed that aligners were successful in regulating the tooth movement. The Orthodontics Objective Grading System (OGS) discovered similar average scores for CAT (-4.9) and fixed appliances (-4.5) for treating the malocclusion (Rossini et al. 2015). It was also reported that CAT and fixed appliances earned close OGS scores in regard to root angulation, the angle formed by the intersection of the tooth root and the long axes of the crown, at the end of treatment. The presence of an attachment on the tooth surface and aligner geometries also allows for more accurate bodily movement of the upper molars, specifically when a distalization movement of 1.5 mm is prescribed (Rossini et al, 2015). However, data shows that currently clear aligners are not recommended to treat an open bite, the inability to make contact with the upper and lower teeth, as well as for severe cases of extrusion.

Pain Level Comparisons Between Clear Aligners and Fixed Appliances- QoL

Orthodontic treatment involves a variable degree of pain. Pain is a subjective response that is dependent on multiple factors such as age, gender, stress, tolerance, and applied force. A patient's individual experience with pain during treatment has a significant impact on their quality of life. Pain directly influences the patient satisfaction of treatment and is often the cause for treatment discontinuation. Pain is felt to some extent by 95% of patients at individual stages of treatment. Additionally, fear of pain is a factor in preventing many from pursuing orthodontic treatment. Therefore, the assessment of the difference in pain levels between clear aligners and fixed appliances while undergoing orthodontic treatment is of immense importance.

Treatment with fixed appliances is commonly perceived as painful and uncomfortable, particularly during the twenty-four hours after arch insertion. Pain and discomfort experienced by CAT in the first week of therapy was perceived to be substantially reduced in comparison

to those of fixed appliances. After the first few months of treatment, as patients adjust, the considerable pain between modes of treatment become less disproportionate. However, quality of life for aligner patients estimates better results in regard to eating and chewing due to CAT's removable nature. Removable appliances generate intermittent forces, allowing the gum tissue to adapt before the compressive forces are reapplied. It is necessary to note that the type of appliance used within CAT will have its own specific force applied, impacting the discomfort experienced by patients.

A study evaluating pain levels in self-ligating appliances from the companies Speed and Damon with Invisalign reported that the group using fixed appliances presented increased levels of pain in comparison to the Invisalign group (Masi-Damois, 2015). A different study revealed that lingual appliances are associated with more severe pain than those using clear aligners. Although the CAT patients complained of elevated levels of pain for a few days after insertion, the oral symptoms and general disturbances felt throughout treatment were relatively low (Shalish et al, 2011). Analgesic consumption, which function as pain relievers, is also higher in patients with fixed appliances. The sensation of orthodontic pain is attributed to the changes in blood flow caused by the force of the appliance, compressing the periodontal ligament. During the first days of treatment, inflammatory mediators such as prostaglandins and interleukins are released. Analgesics reduce the inflammatory process, thereby reducing pain felt by patients. The pattern of pain observed is explained by the levels of the mediators in the gingival cervical fluid, with a peak twenty-four hours after insertion of the appliance and leveling off after seven days.

The search for more comfortable approaches to orthodontic treatment has led to increased CAT use and techniques. Patients treated with clear aligners reported an improved quality of life. Reinsertion of aligners usually occurs between every 15-30 days of treatment, and lower pain levels were experienced at each subsequent activation. Additionally, the aligners can be removed by the patients themselves for short-term pain relief. The type of malocclusion is relevant in estimating pain during treatment. The more serious the malocclusion, the higher the likelihood of pain and discomfort. Orthodontic professionals should guide and inform their patients on how to best manage and alleviate their pain depending on the course of treatment.

Aesthetics

The increase in adults pursuing orthodontic treatment has led to a corresponding rise in demand for dental appliances that are more aesthetic than the conventional fixed appliances. Many patients who specifically seek CAT for their orthodontic treatment have stated that the aesthetic of the appliance was their primary concern. Adults and adolescents alike are worried about their appearance and fixed appliances may evoke feelings of anxiety over one's dentofacial appearance. Therefore, providing more aesthetic alternatives for orthodontic treatment, such as CAT which blends with the crown anatomy, allows patients to improve their teeth and any malocclusions without the expense of their mental health.

In younger children and adolescents who require orthodontic treatment, where parents are the ones scheduling and determining the treatments, a main concern was that the effect of the appearance and speech impairment caused by fixed appliances would harm the self-confidence of the patient. Often, a young patient may experience teasing and embarrassment in public due to their image. The use of clear aligners in improving dentition should be taken into consideration as a viable and comfortable alternative for younger patients. CAT allows children and young adults to still participate in all social activities without any aesthetic restraints. However, discipline in wearing the removable device is important and should be discussed with the parent by the orthodontist before treatment.

The appliance brand and material composition affect the attractiveness of the appliance. Attractiveness ratings ranked clear aligners at the top of the hierarchy, followed by ceramic and self-ligating appliances and afterwards, fixed metal appliances (Rosvall et al, 2009). The increased willingness-to-pay value for CAT indicates that patients are willing to pay more money for more aesthetic orthodontic appliances. Accordingly, the aesthetics of clear aligners such as Invisalign are superior to conventional fixed appliances.

Oral and Periodontal Health-Associated Conditions

Orthodontic treatment can have a significant impact on periodontal and oral health. Periodontal diseases are serious gum infections that can cause damage to the bone and soft tissue surrounding the tooth. Gingivitis, bleeding, as well as alveolar bone loss are common periodontal related conditions. The main causative agent for periodontal diseases is the bacteria that accumulates in dental plaque. Fixed appliances activate an increase in plaque during treatment. Oral hygiene, such as daily brushing and flossing, is the primary defense in minimizing dental plaque and controlling gingival inflammation. Maintenance of a healthy periodontium is dependent upon good oral upkeep. However, fixed appliances and wires make oral

hygiene and plaque control difficult. Additionally, orthodontic treatment can stimulate periodontal disease by increasing bacterial aggregation due to plaque buildup. Patients with active periodontal issues pursuing orthodontic treatment with conventional fixed appliances are at risk for additional periodontal disruption.

Use of clear aligner therapies has increased as adults more frequently seek orthodontic treatment. An analysis on oral health in CAT reported that patients being treated with fixed appliances had substantially higher plaque index scores than those with clear aligners (Han, 2015). This may be a result of the aligners being removable, thus oral hygiene isn't restricted. Patients wearing traditional braces must meticulously brush each bracket and floss around the wires to prevent plaque accretion; this can be very difficult. The regular adjustments involved can create plaque retention sites and lead to white spot lesions and periodontitis. Growth of subgingival plaque greatly increases the discomfort of the patient. A twelve-month study associated CAT with decreased levels of periodontopathic bacteria and increased oral health in comparison to treatments with fixed appliances (Weir, 2017). Therefore, in order to inhibit periodontal complications, removable orthodontic therapies should be strongly considered.

Contemporary fixed appliances enforce a light but continuous force to the teeth to manage orthodontic movement. This mechanotherapy is characterized by the formation of new layers of bone in the soft tissue as movement progresses resulting in alveolar bone resorption. In comparison, CAT applies intermittent forces on the teeth, inducing activation of receptors. For example, kappa-B ligand activity through IL-1ß expression, reducing damage in periodontal ligament cells (Han, 2015). In cases of severely inclined teeth, where CAT is not a viable course of action, then fixed appliances can be coupled with clear aligners for orthodontic and periodontic treatment.

In a study evaluating periodontal health in those using the Invisalign system and those being treated with fixed lingual appliances, thirty patients were examined at three consecutive times for their oral health status. The patients' gingiva, papillary bleeding index, plaque, and sulcus probing depth were measured and compared. At the end of the evaluation, Invisalign patients demonstrated superior periodontal indices with exception to the sulcus probing depths which were similar in both groups. Despite the teeth and parts of the gingiva being covered with the clear aligner for around 20 hours a day, the periodontal risk is lower than those of fixed appliance due to CAT's removability (Miethke & Brauner, 2007).

Clear aligner therapy allows its patients to clean the appliance out of the mouth in addition to using dental floss, which improves dental hygiene. The CAT system can control the amount of force exerted on the tooth due to the aligner covering a large part of the crown. Supragingival plaque destroying periodontal tissue can thereby be avoided as the teeth undergo movement. Treatment using CAT is a safer and preferable method for periodontal tissues than the techniques of conventional fixed appliances.

Efficiency

As clear aligners and their features have evolved and diversified, their efficiency has increased. Treatment with CAT presents advantages such as decreased chair time and treatment duration for patients with mild to moderate malocclusions. In the occurrence of a lost or damaged aligner, replacement usually takes under 2 weeks while the patient continues to wear an old aligner in the meantime in order to avoid prolonging treatment. In addition, aside from misplacing an aligner, there are relatively few emergencies when being treated with clear aligners, unlike therapy with fixed appliances. Conventional appliances often experience a broken wire or removed bracket that can cause the patient discomfort or prevent them from eating.

Treatment with fixed appliances requires frequent visits to the clinician for adjustments and monitoring as tooth movement progresses. In contrast, patients using clear aligners such as Invisalign, are generally given a few sets of aligners at once, and only come in every few months to regulate the treatment. Reduced chair time with CAT over conventional appliances was confirmed in a study, promoting the efficiency of clear aligners (Buschang et al., 2014). The time period of therapy for CAT is generally either in-line with conventional approaches or shorter. It is important to recognize however that poor compliance in wearing the removable appliance, specifically in younger patients, can prolong treatment duration.

Ultimately, the effectiveness of the aligner to achieve dental torque movements with accuracy affects its efficiency in treatment. With CAT, the final aligner can be used as a retainer for the following months after orthodontic treatment, instead of using an additional retention appliance for the next couple of years. The short treatment time and comfortability is attractive to busy adults as well as for parents of young patients who seek rapid improvement in their tooth repositioning and movement. Clear aligners offer an efficient and accessible mode of treatment to its patients.

Clear Aligner Limitations and Deterioration

The force produced by CAT is dependent on the thermoplastic material's initial mechanical properties and

stiffness. The aligner material and its properties can therefore affect treatment outcomes. Intraoral aging can modify the mechanotherapy of the aligner and compromise the efficacy of treatment and the overall force delivery. Intraorally aged aligners have morphological modifications such as localized calcification, discoloration, and abrasion at cusp tips. There are no detectable chemical changes, however, the mechanical properties of CAT are adversely affected by intraoral aging.

There is a detrimental effect on the surface roughness of clear aligners due to the material composition of the appliance during the first week of treatment. The deterioration of the mechanical properties of Invisalign aligners is attributed to its polyurethane's inherent structural instability. Additionally, attachments introduced into the aligner system for increased control of tooth movements results in wear and surface alteration of the aligner. Although exerted aligner forces are decayed during treatment, there is no clinical evidence of it significantly impacting the efficacy of tooth movement.

Taking into account the device's mechanical properties, it was found that aligners with a 2-week activation period resulted in the best measures of tooth alignment improvement (Bradley et al., 2015). The abbreviated period for intraoral aging combined with high oral care minimizes CAT mechanical alterations. Therefore, patient compliance regarding oral hygiene and wear is critical for clear aligner efficacy. There are relatively few clinical studies on clear aligner systems, therefore there is a need for further experimental data and scientific research for a more comprehensive understanding of CAT and its limitations.

Tele Orthodontics/Covid-19

The Coronavirus pandemic required all non-emergency medical related appointments and procedures to be limited and/or postponed in order to avoid the possible spread of the infection. Orthodontic practices suspended patient visits as well as the management of orthodontic emergencies such as detachment of bands or brackets for fixed appliances. Orthodontists began to employ professional platforms for "tele-orthodontics" as a substitute for in-person regulation of their patients' orthodontic treatment. To conduct the remote visits, clinicians relied on video calls and mobile messaging to manage their patients' dental activity. COVID-19 highlighted the need for remote virtual dental care in cases of distance or minor emergencies. In times of crisis, mobile technology offers patients the ability to regulate their intra-oral development in a safe and effective manner. Tele-orthodontics can also be useful for when a patient would like to report an issue prior to the next visit or for questions in regard to treatment.

Treatment with fixed appliances necessitates frequent in-person visits for adjustments and assessment of pain and gingival health. In contrast, clear aligners, as a result of their efficient treatment period, minimal chair time, and rare emergencies, are optimal for tele-orthodontics. The tele-orthodontic system is a significant clinical advancement that would allow patients who are disabled, sick, or unable to travel to receive orthodontic care. In clinical cases eligible for CAT treatment, patients unavailable for regular visits should strongly consider treatments with clear aligners. Post-pandemic orthodontics via tele-orthodontic care grants reduced social contact and promotes safe dental treatment in a healthy and professional environment.

Conclusion

It is of immense value to search for alternatives in treatment of orthodontia in order to alleviate some of the current adverse effects of orthodontic practice. CAT may be a satisfactory option to explore if deemed tantamount in effectiveness or superior to standard orthodontic appliances due to their aesthetic look, comfortability, and oral health benefits. Clear aligners offer its patients a removable device that improves appearance without compromising periodontal health or comfort. CAT is therefore a better course of treatment for cases of mild to moderate malocclusion, however, other modes of treatment should be explored for more complex dental movements.

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Optimal Treatment of Osteoporosis

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Abstract

Osteoporosis affects tens of millions of people in America and is the most common disease of the bones. New treatments are constantly sought, as existing ones have documented side effects. This review seeks to pinpoint the most effective and safe treatment for osteoporosis by looking at head-to-head trials and research regarding combination therapies. This review also looks at the effectiveness of non-pharmacologic treatments and whether any options are beneficial. The importance of an open patient/provider relationship proves itself, as many medications and treatment plans depend on personal factors that need to be measured and weighed by a medical professional together with the patient.

Introduction

Osteoporosis is a condition in which the density of bones decreases and their overall quality deteriorates. Mainly affecting postmenopausal women and men over the age of 50, osteoporosis puts people at risk for fractures, disability, and in the case of hip fractures, even mortality (Panula et al., 2011).

Bones are dynamic and are constantly being remodeled. The remodeling process accomplishes two objectives: it repairs micro-cracks in bone that result from everyday use, and it also re-aligns and reshapes bone to better handle the stress put on it. The two main cells involved in this process are osteoblasts, responsible for building bone, and osteoclasts, responsible for removing old bone and the resorption of Ca2+ back into the bloodstream. Bones are extremely important for maintaining homeostasis because they are reservoirs of calcium. Muscles and the nervous system also use calcium ions in their basic functions, and when there is a shortage of calcium in the bloodstream, bone resorption is triggered. The thyroid and parathyroid glands control release of calcium from bone into the blood through endocrine signaling.

As we age, different factors increase the risk of osteoporosis. Vitamin and mineral deficiency, more commonly seen in those over 65 years old, contributes to bone loss as vitamin D3 and calcium are necessary for bone health. Stem cells differentiate into osteoblasts at a slower rate over time. Additionally, menopause leads to the decrease of estrogen, the sex hormone responsible for inhibiting osteoclast activity, thereby increasing the risk of osteoporosis in women over 45 years old.

There are numerous pharmacologic treatments approved by the FDA for both prevention and treatment of osteoporosis. These drugs vary greatly in their mechanisms and pathways but fall into two general categories. Some are anti-resorptive, preventing osteoclast activity, and others are anabolic, causing osteoblast activity. Unfortunately, these drugs come with side effects and health risks. The National Osteoporosis Foundation recommends clinicians to use the pharmacological approach only after attempting treatment through diet, exercise, physical therapy and fall prevention guidance. However, once a patient presents with a fracture, drugs are recommended immediately (Cosman et al., 2014).

The first line of treatment recommended are bisphosphonates, such as alendronate and zoledronic acid, which are anti-resorptive drugs that cause osteoclast apoptosis. A more expensive and effective drug is teriparatide (TPTD), the first anabolic drug for osteoporosis. It encourages osteoblast activity and results in greater bone density. Each of these treatments present with their own risks and cannot be used indefinitely, therefore there is a need to maximize the benefit of each treatment. This review is aimed at determining the best treatment of osteoporosis to date.

Methods

Articles were obtained using Touro College's online library and PubMed database using keywords such as "osteoporosis," "bisphosphonates," "teriparatide," and other key terms.

Diagnosis

There are a few major predictors of osteoporosis. The age of a patient is a factor, as most of those with osteoporosis are above the age of 50. A history of fractures and maternal history of fractures also provides a glimpse of future bone-related problems. The OFELY study identified left hand grip strength as an indicator, along with low physical activity and low bone mineral density (Albrand et al., 2003). Patients who have experienced a fracture or who are considered at risk for fracture are advised to have a dual energy x-ray absorptiometry (DEXA) test performed to measure their bone mineral density (BMD). A score is given based on comparison to DEXA results of 30-year-olds of the same race and gender. This frame of reference allows the clinician to assess whether medication is the correct approach to manage a patient's osteoporosis. A BMD T-score of ≤-1.0 in standard deviation indicates osteopenia, the stage of bone density decline that precedes osteoporosis. A score of ≤-2.5 is considered osteoporosis. Measures of the hip, femoral neck, and the vertebral column are taken, and their scores may be independent of each other. Using these numbers alone is not an appropriate way to gauge whether medication is correct. Patient lifestyle and diet should be considered,

as a sedentary individual or a patient who smokes is at risk for a sharper decline in bone density (Krall, Dawson-Hughes, 1999) and should be monitored more often than a physically active or non-smoking patient.

Pharmacologic Treatment

In the event medication is deemed appropriate, the numerous options available are both a blessing and a hurdle. No single medicine has proven completely effective or safe for long term use. As such, new remedies are constantly being sought and extensive research has been done to assess the efficacy of each drug and drug combination as well as the appropriate duration of treatment.

The drugs currently available fall into two main categories: anabolic and anti-resorptive. The anabolic drugs increase osteoblast activity, thereby directly building bone. The anti-resorptive drugs stop osteoclasts from destroying older bone by inducing apoptosis in osteoclasts.

In the category of anti-resorptive drugs are bisphosphonates. These drugs disrupt the resorptive action of osteoclasts by inducing osteoclast apoptosis. The osteoblasts will continue to build bone and that results in greater BMD. Alendronate (Fosamax) is usually the first medication given to an osteoporotic patient, and as Black et al. (2006) found, its effects continue even after discontinuation. Patients who took Alendronate for five years continued to have decreased markers for bone turnover for another five years. Taking bisphosphonates together with an anabolic drug, such as teriparatide (TPTD), a PTH analog, does not show any synergistic benefit, and using a bisphosphonate might even limit the anabolic effect of teriparatide (Black et al., 2003). However, Cosman et al. (2011) asserts that the combination of teriparatide and zoledronic acid (Reclast, a bisphosphonate) is better than either one alone. In a study done by Finkelstein et al. (2003), one group took only alendronate, and another group was given teriparatide 6 six months after starting alendronate. The results were in favor of alendronate monotherapy. Finkelstein comments that the study did not explore whether combination therapy would be better if the two drugs were started at the same time. Muschitz and colleagues researched what would happen if alendronate were given in conjunction with TPTD a few months after TPTD therapy was started, as opposed to TPTD monotherapy. The results showed that combination therapy was more effective (Muschitz et al., 2013). This would indicate that TPTD needs time to start building bone and only then will the combination of an anti-resorptive have an effect greater than TPTD alone. In Cosman's research the drug combination was started at the same time. One may explain such results by conjecturing that distribution of zoledronic acid inside the body works differently than alendronate and allows the TPTD to start building bone before the anti-resorptive starts working. However, this is not true because research has shown that zoledronic acid affects the body faster than alendronate does (Saag et al., 2007). It would seem that there is a benefit to taking zoledronic acid together with TPTD but not alendronate with TPTD.

The anabolic drugs available include teriparatide (Forteo) and abaloparatide (Tymlos). These drugs are recombinant parathyroid hormone, which stimulates the process of bone remodeling. Though continuous release of PTH in the body releases calcium from the bones, weakening them, spaced doses of these PTH analogs stimulate the entire bone remodeling unit. The result is increased bone formation. This is the basis for the hypothesis that bisphosphonates do not work together with anabolic drugs. Bisphosphonates inhibit osteoclasts, and anabolics might rely on osteoclasts as a part of the remodeling unit to result in a net gain of bone. Hagino et al. (2021) found a discrepancy between once-daily administered teriparatide and once-weekly administration. Hagino discovered that although once-daily increases bone formation, once-weekly also decreases bone resorption. We know that the amount of the drug given plays an important role, and a higher dose will result in greater bone formation but also greater bone resorption; at times leading to a net loss of bone density (Neer et al., 2001). The results of Hagino et al. indicate that even at high doses, a once weekly injection of teriparatide prevents bone resorption besides for increasing bone formation. Whether once daily or once weekly injections are more effective is a source of dispute between the results of different trials. The trial led by Hagino, called the JOINT-05 trial, indicated that once weekly is more effective as compared to the once daily VERO trial, led by Kendler. However, the VERO trial considered a patient who took 75% of the injections over the course of the study to be compliant (Kendler et al., 2017). In that case, once-daily administration may indeed be more effective if taken correctly. Additionally, only 29% of participants followed through in the JOINT-05 trial, and therefore the data is less reliable for comparison. In both trials teriparatide was proven to be more effective than bisphosphonates at preventing fractures. Both trials ended the treatment before 24 months because trials in animal models show a risk of osteosarcoma if teriparatide is taken for more than two years. No serious adverse effects were reported, making another case for the use of teriparatide over bisphosphonates.

Recently, Romosozumab (Evenity), a newcomer to the market, appeared to accomplish both goals of anabolism and anti-resorption. Romosozumab is a monoclonal

antibody that binds sclerostin, a protein produced by osteoclasts that inhibits bone growth. It too, was compared head-to-head with alendronate and increased bone mass more than alendronate (Saag, et al. 2017). In a study comparing it to teriparatide, Romosozumab performed better at increasing BMD and bone mineral content (Genant et al., 2017). That study was very small, so it is hard to consider the results as a final judgement. The authors attempt to justify their small numbers with the use of quantitative computed tomography (QCT) which is a more accurate way of imaging and might reflect the results of a larger trial. Romosozumab is administered once monthly as an injection and is to be used for only 12 months due to risk of cardiovascular issues.

Denosumab (Prolia), another monoclonal antibody, functions as an anti-resorptive by binding to receptor activator of nuclear factor-kappa B ligand (RANKL). This receptor normally activates its counter-protein RANK which in turn activates osteoclasts. By binding to RANKL, denosumab stops resorption and increases BMD at a rate similar to zoledronic acid. The two were compared head-to-head in a large trial by Choi et al. (2017). Both showed equal safety and positive effect on BMD and very few cardiovascular events. However, the mean age in the study was 63, and therefore would not reflect the safety of those substantially older and taking these drugs.

Denosumab can cause hypocalcemia and therefore must be taken with calcium and vitamin D3 supplements. Patients who discontinue denosumab lose BMD quickly and are at great risk for a rebound fracture. It is for this reason that those who stop taking denosumab are given a different osteoporotic drug (Cosman et al., 2014).

Denosumab and zoledronic acid are compared because of the frequency and route of administration: subcutaneous injection once or twice a year. Frequency and route of administration are important factors in treating osteoporosis because patient adherence is lower with oral bisphosphonates. They are not absorbed well and so must be taken on an empty stomach and the patient must not lie down for a period of time after taking them. They can cause esophageal ulcers and other GI ailments (Cosman et al, 2014). Denosumab and zoledronic acid are both injections which are absorbed much more efficiently. Their doses are spaced widely, so although they may cause a certain amount of discomfort, they are tolerated better than daily oral or subcutaneous administration.

One concern for all anti-resorptives is the risk for atypical femoral fractures (Shane et al., 2014). These fractures are caused by the decrease in bone remodeling. When osteoclasts are inhibited, they do not clear away old bone and the infrastructure upon which new bone is built can fracture even without trauma. However, these fractures are rare and the benefits of taking bisphosphonates or denosumab and preventing an osteoporotic related fracture outweighs the risk of an atypical femoral fracture. A summary of these drugs, their use, duration, and side effects is presented in Table 1.

Though the possible side effects for each drug might dissuade patients, most are relatively rare. It is notable that in every clinical trial there were those who discontinued the treatment simply due to the discomfort of taking the drug. Indeed, a drug such as zoledronic acid

Drug	Brand Name	Prevention or Treatment	Route of Administration/ Frequency	Type of Drug	Recommended Duration	Main Outcome	Side Effects
Alendronate	Fosamax	Prevention (lower dose) and treatment	Oral (IV not FDA approved) / Daily and weekly dosages available	Bisphosphonate	5-10 years	Anti-resorptive. Induces osteoclast apoptosis	GI perforation, ulcers, esophageal ulcers Rare: osteonecrosis of jaw, atypical femoral fracture
Teriparatide	Forteo	Treatment only	Subcutaneous / daily	Recombinant PTH analog	2 years	Builds bone by stimulating entire remodeling unit.	Hypercalcemia, nausea, pain Rare: osteosarcoma
Denosumab	Prolia	Treatment only	Subcutaneous / once every 6 months	Monoclonal antibody	Up to 10 years	Anti-resorptive, binds to RANKL, stops osteoclast formation	Hypocalcemia, Muscle and joint pain Rare: osteonecrosis of jaw
Romosozumab	Evenity	Treatment only	Subcutaneous / once a month	Monoclonal antibody	1 year	Binds sclerostin, anti-resorptive and anabolic.	Rare: cardiovascular events
Zoledronic Acid	Reclast	Prevention (lower dose) and treatment	IV / one time or once yearly (lower dose)	Bisphosphonate	2 years	Same as alendronate	Flu-like symptoms, muscle and joint pain

Table 1. Information based on National Osteoporosis Foundation's Clinician's Guide to Prevention and Treatment of Osteoporosis (Cosman et al., 2014). Denosumab was found to be safe for up to 10 years (Bone et al., 2017).

causes flu-like symptoms. To judge which drug is the best way to treat osteoporosis one might need to consider side effects that make it difficult to take the drug. The clinician should discuss the side effects with the patient and explain how the benefits outweigh the short-term discomfort.

Non-Pharmacologic Treatment

Osteocytes act as mechanoreceptors and signal bone modeling in areas of high stress. This greatly contributes to the thickness of cortical bone and the unique formation of trabecular bone each person may have. Exercise activates the osteocytes and builds bone. However, as a treatment for osteoporosis, it is difficult to prescribe exercise because of the numerous factors surrounding it. The intensity, type, and amount of each exercise and constitution of each individual plays a role in determining the efficacy of the exercise in building bone.

The LIFTMOR trial sought to demonstrate the effectiveness of high resistance training (HiRT) over a more aerobic, balance-focused exercise program. Using DEXA and a 3D imaging program, the authors verified that a high resistance training program, marked by higher loading and power lifting, will increase BMD significantly more than aerobic training (Watson et al., 2018). The LIFTMOR trial proved that with correct supervision, exercise could provide an increase in BMD and prevent fractures. However, the trial did not include those with cardiovascular problems, and the mean age was 65 ±5, leaving a large population for whom exercise may not be a solution. Additionally, the need for careful supervision during the program may explain why medicine is the first line of treatment for osteoporosis. It is of note that regarding the safety of this program only one out of a hundred and one participants suffered a minor injury that required only a week of rest from the program. Only 7 participants experienced a fall during the 8-month period; none of the falls resulted in a fracture. All the participants had low bone mass, so this indicates that all forms of exercise performed, both balance and HiRT, had a positive effect on fracture occurrences.

Besides for the benefit of high resistance exercise, a trial was done to ascertain whether the rate of mechanical loading also affected bone density. The participants were approximately 4.5 years post-menopause and were all accustomed to high resistance training. Two groups were formed: one performing exercise with a slower rate of loading and unloading, and another group performing the contraction part of each exercise as quickly as possible. Though an increase in BMD was noted in the second group, referred to as the power training (PT) group, it was only noted during the first year of the two-year trial, and only at the spine (von Stengel et al. 2007). Von Stengel hints that such results can be explained by the bones and muscles becoming accustomed to the rapid rate and the osteocytes no longer activating bone growth in response. If there had been a rest period and the exercise subsequently continued, it is possible there would have been an increase in BMD.

Fall prevention and balance training are always recommended (Cosman et al. 2014) and will have a positive effect for those with osteopenia and osteoporosis. Exercise as performed in the above trials is not an appropriate treatment for those with advanced osteoporosis or those who will not have supervision. But there remains an option for the elderly that does not involve medication – whole body vibration (WBV). Research into this technology shows that even the elderly can reap the benefits of mechanical stimulation using WBV. WBV involves a platform with a vibrating plate that delivers a low magnitude vibration that is barely felt yet causes anabolic growth via stimulating the bones (Rubin et al. 2001). A three-year study, however, did not show any benefit to using the WBV platform. The authors of that study conjecture that the large age range, a mean of 82.5 +/-8.1, might have interfered with their results. They also hypothesized that though the technology showed a benefit for younger patients at the same magnitude (Rajapakse et al, 2021), older individuals may require higher intensity (Kiel 2015). It seems that the study by Kiel et al. (2015) was done in a way to ensure safety, but the magnitude was much lower than the standard allowed. In addition, the participants only used the platform for ten minutes a day, whereas from a safety standpoint they could have used it for longer. Also, those who exercise spend more than ten minutes daily doing so, so if WBV can serve as a replacement it should be prescribed for longer durations. The study done by Rajapakse et al. (2021) holds a certain amount of weight over similar studies that did not show as much benefit in WBV because of the adherence level. In Rajapakse's study, the devices were fitted with a sensor that measured usage, supplying more accurate information than self-reporting.

Vitamins

The use of vitamins alone to prevent fractures serves the benefit, like exercise, of avoiding side effects from medication. Vitamin D3 is necessary for bone growth and is often given together with calcium, also a component of bone growth. In a three-year study in Denmark, where most people do not produce enough Vitamin D3 from sunlight alone, Vitamin D3 and calcium together showed

a 16% reduction in fractures (Larsen et al., 2004). In this study, and in another two that showed similar results, there was no use of BMD measurement. Instead, the researchers sent out questionnaires or followed patients through hospital registries to find out who suffered from a fracture. In one of those studies, it was demonstrated that daily administration of 800 IU cholecalciferol, an effective form of vitamin D3, together with calcium, significantly reduced fractures by 30% compared to a placebo (Chapuy et al., 1994). The participants all lived in nursing homes, so adherence was probably very high. The large group (over 870 participants per arm) and similar environment also gives weight to Chapuy's study. Trivedi et al. (2003) studied the effects of vitamin D3 given in large, spaced doses on fracture reduction. They gave a 100,000 IU pill once every four months over a five-year period. Adherence and collection of data was determined through a questionnaire sent with each pill. A 20% reduction in all fractures and 30% at major osteoporotic sites was found in the active group. These three studies imply that preventing fractures can be achieved in an economic fashion with vitamin D3. A difficulty with using fall data, as these three studies did (some via questionnaire), is the need to specify the type of fall, for example low or high impact, and which body parts were affected and whether there was a follow up by a doctor to see if the fall resulted in a fracture. Chapuy specifies whether there was a hip fracture or not and Larsen obtained fracture information from the Danish Hospital Registration Database. No sample of the questionnaires given out were provided, and there may have been cases of fractures that the patients did not report. In short, there is still a very strong case for prescribing medication and not relying on vitamins alone. Though the results are impressive at 30%, the remaining 70% (or a large portion) of participants who experienced fractures would have benefited from medication.

Conclusion

Though osteoporosis affects millions of Americans, there are many options to treat this disease. However, to ensure proper treatment, each case requires a thorough review of the patient's circumstances. This includes the progression of bone loss, patient's diet and lifestyle, and tolerance to drugs. For those with osteopenia or just meeting the threshold for osteoporosis it might be enough to engage in supervised resistance exercise and to take vitamin D3 and calcium. Those with fractures or advanced osteoporosis will require drugs in addition to balance therapy. Most clinicians will agree that the benefits of the current drugs available outweigh the risks of adverse effects. It is important to understand the risks of each drug to ensure that the more serious side effects, such as cardiovascular issues, will not be a concern with a particular patient. It is upon the clinician to have clear knowledge of the patient's health status and know which drug is most suitable. For example, though romosozumab causes the greatest bone growth, it is not suitable for a patient at risk for cardiovascular disease. Monitoring the progress of a treatment and discussing any side effects experienced will help the clinician further tailor the patient's regimen. As technology advances, we can look forward to new remedies in forms such as stem cell infusions and targeted gene therapy. Until then, treating osteoporosis is a lifelong process and patients can benefit from a combination of pharmacologic and non-pharmacologic treatments.

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Cardiovascular Disease - Is a Whole Food Plant-based Diet the Answer?

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Abstract

Objective: To determine if a whole food plant-based diet can prevent and cure cardiovascular disease.

Results: People on whole food plant-based diets exhibit extremely low levels of plasma LDL. Another risk factor for developing atherosclerosis, is inhibited production of nitric oxide, which is vital for healthy blood flow. One of the main inhibitors of nitric oxide production is asymmetric dimethyl-l-arginine (ADMA). An inverse relationship was found between dietary fat and ADMA levels. The diets with the best results were the diets where oil intake was reduced to a minimum. Clinically, people who went on whole food plant-based diets had their cardiovascular disease stabilized or improved. A possible difference was also found between a person already exhibiting symptoms of cardiovascular disease versus a healthy person. LDL only causes damage under oxidative stress and Dimethylarginine dimethylaminohydrolase, the enzyme that degrades ADMA, is also inhibited by oxidative stress. This would suggest that a diet high in antioxidants may have similar benefits.

Conclusion: A whole food plant-based diet is a good method for stabilizing and improving cardiovascular disease, especially if oil and processed foods are removed from a person's diet as much as possible. It may be possible to structure a diet based on antioxidant intake with similar effects.

Introduction

Based on the most recent data available, in 2018, the United States spent about $3.65 trillion or $11,172 per person on health care. It is estimated that by 2028 the United States will be spending $6.2 trillion or $17,611 per person on health care (Centers for Medicare & Medicaid Services, 2021). This would amount to close to 20 percent of the United States' GDP. When dividing this up by individual diseases, heart disease and stroke are responsible for more than 868,000 American deaths, which is one-third of all deaths. These diseases cost the health care system $214 billion in 2018, or 5.9 percent of the total US expenditure on health care (Benjamin et al., 2018). More than 34.2 million Americans have diabetes, and another 88 million Americans have prediabetes, which puts them at risk for type 2 diabetes. In 2017, the total estimated health care cost of diagnosed diabetes was $237 billion (American Diabetes Association, 2017). In 2017–2018, the age-adjusted prevalence of obesity in adults in the United States was 42.4% (Hales et al., 2020). It is estimated that the medical costs of obesity had risen to $147 billion per year in 2008 (Finkelstein et al., 2009). All this money is spent only after a person gets sick; to treat the symptoms. If the United States focused its efforts on the underlying causes of illness and not just the symptoms, a lot of this money wouldn't need to be spent. This paper will explore if following a whole food plant-based diet could be utilized to prevent cardiovascular disease and reverse its effects.

Methods

Data was found using google, google scholar and PubMed databases. Keywords used were whole-food plant based, WFPB, cardiovascular disease, atherosclerosis, LDL, vegan, vegan diet, ADMA, asymmetrical dimethylarginine, and antioxidant.

Discussion

What is a whole-food, plant-based (WFPB) diet, and how is it different from a vegan diet

The people who follow a vegan diet do so mostly for moral and ethical reasons, though health is also a significant factor (Janssen et al., 2016). It is worth noting that this study was done in Germany and may not apply to other countries. Those who follow a WFPB diet, the primary motivator is usually for health purposes (Wendel B., 2019). It is important to note the motivation for following a diet because that could indicate if the diet will be strictly adhered to and may help gauge how long a person would continue to follow it. The difference between the two is that someone following a vegan diet will not consume any animal products or derivatives, but any plant-based food is fine. A WFPB diet, on the other hand, is not as clear. However, the main goal is to eat plant-based (exclusively or small amounts of animal products will be allowed) and to refrain from overly processed foods. WFPB diets also recommend refraining from all processed and hydrogenated oils (Esselstyn, 2008 which does not allow any animal products). One of the most well-known benefits of plant-based diets is that they prevent and sometimes reverse cardiovascular disease.

Can a WFPB Diet Prevent and Reverse Cardiovascular Disease?

Esselstyn et al., 2014 performed a study that followed a cohort of 198 participants to determine if they could voluntarily adhere to the necessary dietary changes and to document their cardiovascular outcomes. The patients were self-selected after learning about the program through their own research. All the patients had cardiovascular disease. The participants were requested to follow a core diet consisting of whole grains, legumes, lentils, other vegetables, and fruit. They were also encouraged to take a multivitamin and vitamin B12 supplement

and to use flax seed meal, which served as an additional source of omega-6 and omega-3 essential fatty acids. They were asked to refrain from consuming all added oils and processed foods, fish, meat, fowl, eggs, dairy products, avocado, nuts, caffeine, and excess salt. Each patient was also told to avoid sugary foods (sucrose, fructose, and drinks containing them, refined carbohydrates, fruit juices, syrups, and molasses). Patients who avoided all meat, fish, dairy, and, knowingly, any added oils were considered adherent. The patients were followed for an average of 3.7 years. It is worth noting that there was no proper control group instead the non-compliant patients were used as the control group. Of the 198 participants, 177 remained compliant while 21 did not. Of the 177 compliant patients, a remarkable 90 percent remained stable or improved, while in the non-compliant group, only 38 percent remained stable while none improved. In Esselstyn, 2008, he similarly documents many personal experiences with individual patients showing similar results.

The limitation of these studies is the lack of random selection and proper control groups. Wright et al., 2017, on the other hand, performed a randomized controlled trial to assess the benefits of a WFPB diet with the same restrictions as Esselstyn et al., 2014. The limitations of this trial were that this trial only documented the risk factors for cardiovascular disease and not symptoms or clinical outcomes. Furthermore, the control versus the intervention group were only compared for the first six months. Nonetheless, the trial showed a statistically significant reduction in both the body mass index and cholesterol levels in the intervention group compared to the control group. Remarkably, the need for medications for the control group went up by 8 percent, while in the intervention group, it decreased by 21 percent in such a short period of time.

Ornish et al., 1998 conducted a randomized controlled trial from 1986 to 1992 to demonstrate the beneficial effects of a diet change on patients with cardiovascular disease. Patients were allowed fruits, vegetables, grains, legumes, and soybean products without caloric restriction. No animal products were allowed except egg white and one cup a day of non-fat milk or yogurt. Cholesterol intake was limited to 5 mg/day or less. Caffeine was eliminated, and alcohol was limited to a minimal amount. Vitamin B12 was a recommended supplement (Ornish et al., 1990). At the end of the study, there were about 0.95 cardiac events per patient in the control group as opposed to 0.50 cardiac events in the experimental group. While this is certainly a positive outcome, there was still a 50 percent chance of an adverse event per patient in the experimental group. Contrast this with Esselstyn et al., 2014, where there were only .023 events per patient in the compliant group; this number isn't great. The only difference between the two diets was that Esselstyn et al., 2014 required abstention from all animal products and oils while Ornish et al., 1998 allowed egg whites and one cup per day of non-fat milk or yogurt and didn't have any oil restrictions.

In a large prospective cohort study, it was found that even if a person is following a plant-based diet, if it is high in healthy plant foods (defined by the authors as whole grains, fruits/vegetables, nuts/legumes, oils, tea/coffee), there was a substantial reduction in coronary heart disease. However, if it is high in less-healthy plant foods (juices/sweetened beverages, refined grains, potatoes/fries, sweets), there was an increased risk of coronary heart disease (Satija et al., 2017). There are many other studies (De Lorgeril et al., 1999; Singh et al., 2002; Burr et al., 1989; Kappagoda et al., 2006; Baden et al., 2019) that investigated plant-based diets and their effects on cardiovascular disease, however, only a diet restricting all animal products and oils had an almost guaranteed positive outcome (as seen in Esselstyn et al., 2014) while the other diets, despite favorable outcomes, only had reduced risks. This suggests that eating only healthy plant-based foods is the most effective diet, as evidenced by Satija et al., 2017 and Esselstyn et al., 2014.

How does a WFPB diet help with cardiovascular disease, and what mechanisms does it target?

Cardiovascular disease is usually related to atherosclerosis (American Heart Association, 2017). Atherosclerosis is a disease where plaque gets deposited inside the lumen on the walls of arteries. The areas in the arteries that are vulnerable to atherosclerosis are where disturbed flow and consequently low endothelial shear stress (ESS) and oscillatory shear stress occur (Jolanda et al., 2012). ESS is the force per unit area exerted by blood flow on the vessel wall that depends on blood viscosity and flow velocity (fig. 1). These are usually near the branch points and along inner curvatures or regions where the uniformity of the blood flow is disturbed. The most common regions are the abdominal aorta, coronary arteries and

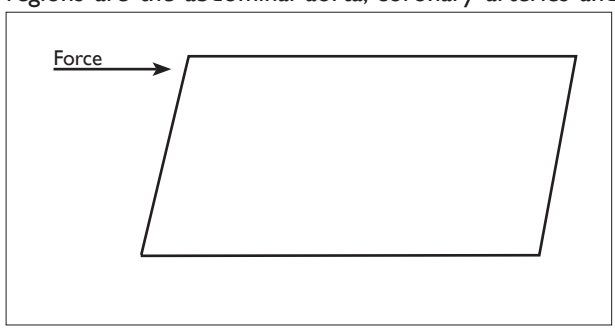

Figure 1: visual representation of shear stress

iliofemoral arteries (DeBakey et al., 1985). In contrast, arterial regions exposed to moderate physiological ESS are protected from atherosclerosis (Zarins et al.,1983). When endothelial cells are in a high ESS area (more than 15 dyne/cm¬2) they exist in an almost dormant state. They decrease their expression of vasoconstrictors, paracrine growth factors, inflammatory mediators, adhesion molecules, and oxidants while increasing their expression of vasodilators and anti-platelet factors (like nitric oxide), growth inhibitors, and antioxidants. This causes minimal proliferation and apoptosis of these cells.

Furthermore, these cells align in the direction of the blood flow. Nitric oxide (NO) is produced to maintain homeostasis because NO reduces the ESS by vasodilation and thus reduces the shear stress on the cells. On the other hand, when the endothelial cells are in a low ESS (less than 4 dyne/cm¬2) they have a greater vulnerability to factors that stimulate proliferation and apoptosis (such as oxidized low-density lipoproteins). They are in a persistent low antioxidant state and have a reduced expression of vasodilators, growth inhibitors, anti-platelet factors, and antioxidants. They increase their expression of vasoconstrictors, paracrine growth factors, inflammatory mediators, adhesion molecules, and oxidants. Furthermore, these cells present in an unorganized fashion ((Malek, 1999; Ziegler et al., 1998; Furchgott, Zawadzki, 1980). The endothelial cells attempt to maintain homeostasis and consequently a certain ideal rate of flow in the blood stream. Therefore, they will try to narrow the lumen through proliferation to raise the flow rate and consequently the shear stress to optimal levels.

Glycocalyx is a highly charged layer of membrane-bound macromolecules connected to a cell's apical membrane. This layer functions as a barrier between a cell and everything in the extracellular space. Glycocalyx also serves as a mediator for cell-to-cell interactions and protects the cell membrane from the actions of physical forces and stresses, allowing the membrane to maintain its integrity (Martinez-Seara Monne et al., 2013). Glycocalyx also behaves as a sort of lubrication layer, assisting in the movement of red blood cells through blood vessels and buffering the effect of fluid shear stress acting directly on the endothelial cell's membrane (Tarbell, Pahakis, 2006). When the endothelial cells are in a low ESS environment, the layer of glycocalyx starts to thin, thereby weakening the cells' ability to protect themselves. Furthermore, when the endothelial cells are in a low ESS environment, because of the high proliferation rate and disturbed blood flow, the cells have weaker tight junctions. They can be less functional, and thus, tend to favor the migration of lipids (specifically low-density lipoproteins (LDL)) into the subendothelial space. Furthermore, due to the thinning of the glycocalyx, the LDL begins to migrate through the endothelial cells into the subendothelial space though vesicular bodies that travel through the endothelial cells (Zmysłowski, Szterk, 2017).

After the LDL enters the subendothelial space, it begins to undergo oxidation, primarily from reactive oxygen species. First, the LDL forms minimally oxidized LDL, which has a pro-inflammatory effect on the arterial wall. The LDL is further oxidized to form moderately oxidized LDL particles, and then finally, they form aggregates of highly oxidized LDL (oxLDL). These oxidized LDL particles are recognized by macrophages that congregate around the aggregate (Zmysłowski, Szterk, 2017). These macrophages begin to break down the oxLDL into cholesterol and fatty acids. Some of the free cholesterol will be transported to the plasma membrane and then out of the cells while the rest will be re-esterified to cholesterol fatty acid esters which accumulate as a foam-like substance in the macrophages (and hence, those macrophages are called 'foam cells') (Brown et al., 1980) (Zmysłowski, Szterk, 2017). If there is a continuous supply of oxLDL, these foam cells keep ingesting it until cell death occurs. These dead foam cells form the inner lipid-rich core of the atherosclerotic lesion (Falk, 2006). It is worth noting that high-density lipoproteins (HDL) have the opposite effect and facilitate the removal of the free cholesterol from the cells and back out into the bloodstream and therefore, can reverse this process. This is the beginning of the atherosclerosis, and over time if left to progress, this plaque buildup leads to the narrowing in diameter of the lumen of blood vessels. Eventually, the lesion will attract platelets due to the roughness caused by the endothelial dysfunction. The aggregation of these platelets will cause a clot to begin to form, which can detach (thrombosis), leading to myocardial infarction, stroke, or sudden death (Khatana et al., 2020).

The Nitric Oxide Pathway and its Importance

As previously mentioned, nitric oxide acts as a vasodilator, and an anti-platelet factor. Additionally, it inhibits endothelial inflammation and inhibits smooth muscle cell proliferation (Lowenstein, 2006). The anti-platelet characteristic essentially keeps the blood flowing smoothly and aids in maintaining a stable blood pressure (Moncada, Higgs, 2006). Nitric oxide is synthesized in the endothelial cells from l-arginine by the enzyme endothelial nitric oxide synthase (eNOS). A competitor for the l-arginine binding site is asymmetric dimethyl-l-arginine (ADMA). There is another enzyme, dimethylarginine dimethylaminohydrolase (DDAH), that degrades ADMA (fig. 2). The ability of DDAH to degrade ADMA is diminished

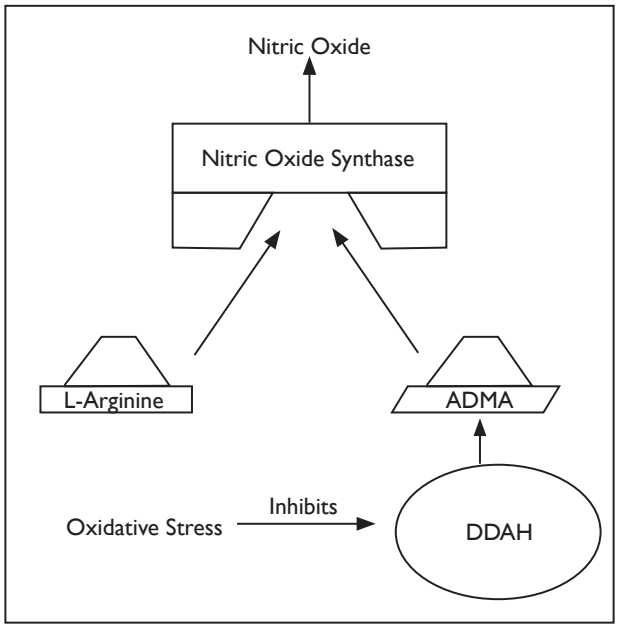

Figure 2: nitric oxide synthase and its inhibitor. (Adopted from Esselstyn C. B., 2008)

in the presence of reactive oxidizing agents, which incidentally is the same environment that LDL gets oxidized in (Förstermann, Sessa, 2012). It is no coincidence that in the presence of oxLDL plaque formation, weakened nitric oxide expression is also witnessed (Cooke 2004). Abnormally high levels of ADMA are seen in patients with cardiovascular disease (Schlesinger et al., 2016), congestive heart failure (Usui et al., 1998), hypercholesterolemia (Böger et al., 1998), hypertensive children and adolescence (Goonasekera et al., 1997), some cancers (Sulicka et al., 2012; Javadiyan et al., 2012), end-stage chronic renal failure (Vallance et al., 1992), schizophrenic patients (Das et al., 1996) and many other illnesses (Tain, Hsu, 2017).

Does a WFPB diet impact a person's ADMA levels?

Since nitric oxide is so important in maintaining proper blood flow and diminishing the risk of thrombosis by acting as an anti-platelet factor, if nitric oxide production could be improved, it would follow that the risk of thrombosis would also diminish. Furthermore, because a low ESS is an early risk factor for the formation of an atherosclerotic lesion, an increase in nitric oxide production would yield smoother flowing blood and a reduced number of low-ESS areas. Because ADMA is an inhibitor to eNOS and consequently the production of nitric oxide, it would be a reasonable target for measuring the effects of a diet that is trying to reduce the risk of atherosclerosis and subsequent thrombosis. It is also reasonable to assume that ADMA is in part responsible for these illnesses because it is well documented that abnormally high levels of ADMA are present in patients with cardiovascular disease (Schlesinger et al., 2016) (Bultink et al., 2005; Stühlinger et al., 2002; Meinitzer et al., 2007; Schnabel et al., 2005). If after following the diet, a patient's ADMA came down to normal levels, it would be reasonable to assume that this diet will help lower the risks of atherosclerosis and thrombosis. To the best of this author's knowledge, no study was performed on ADMA levels after a plant-based diet. However, in a study done on the effects of a high-fat meal (heavy cream, ice cream, safflower oil, a powdered whey protein, syrup, and Lactaid) on ADMA and vasodilation, an inverse relationship was found between the two. As ADMA levels increased (at about 5 hours after the meal), nitric oxide-mediated arterial vasodilation decreased. When a low-fat meal (whey protein, skim milk, evaporated skim milk, syrup, and granulated sugar) was given, no significant ADMA elevation was recorded (Fard et al., 2000). Even though the low-fat meal was not plant-based, it showed a direct correlation between fat consumption and ADMA levels. This would suggest that minimizing even plant-based fats would have a positive outcome. Another study was done over a 2-month period analyzing the effect of different diets on ADMA levels. What was found was that those diets high in carbohydrates caused a reduction in ADMA levels. This study also found that a change in ADMA levels did not associate with a change in the amount of fat consumed (Päivä et al., 2004). This would seem to conflict with Fard et al., 2000, who found that high-fat diets correlate with higher ADMA levels. However, regardless of this conflict, diet definitely influences ADMA levels, and more research must be done in this area to determine which foods affect ADMA levels.

A WFPB's Diets Effect on LDL Levels

It is well documented that elevated LDL levels are a major risk factor for cardiovascular disease (Castelli et al., 1977; Gordon et al., 1989; Duncan et al., 2019). Because oxLDL is a major contributing factor to the formation of atherosclerosis, lowering the levels of LDL in the blood would reduce the ability of an atherosclerotic lesion to form even if there is endothelial damage present. At current, it is recommended that total cholesterol levels should be less than 150 mg/dL and LDL levels should be less than 100 mg/dL (Grundy et al., 2018). It is worth noting that current literature suggests that dietary cholesterol does not impact a person's risk for cardiovascular disease. Rather, the dietary intake of fat (specifically saturated fats and trans-fats) is the primary cause of cardiovascular disease (Soliman 2018). This information fits with the current known mechanism of the formation of atherosclerotic lesions since it is the LDL that brings the cholesterol into the subendothelial space. This is shown by Esselstyn et al., 2014, that removing lipids from a person's

diet leads to the radically reduced risk of cardiovascular disease. Therefore, if a person has low levels of LDL, no lesion should form even if the endothelial cells were not performing optimally.

In a cross-sectional study that took place in six Slovenian regions, participants were placed into short-term (0.5–<2 years), medium-term (2–<5 years), and long-term (5–10 years) groups. Each group was instructed to follow a WFPB diet that consisted of whole grains, fruits, vegetables, and legumes, moderate intake of nuts, seeds, avocados, soy, wheat products, little or no added fats/oils (e.g., coconut, and palm fat/oil, olive oil), and the exclusion of all animal products. The participants were advised to consume a majority of starchy foods, such as whole grains, legumes, and potatoes, all prepared without oil or added fat. Participants were asked to limit portions of high fat plant foods. And it was suggested that consumption of high-fat foods be limited to 1–2 tablespoons of flax, 1–2 tablespoons of sesame seeds, 20–30 g of walnuts, hazelnuts or almonds a day. Occasionally pumpkin seeds (as part of salads, nut butters, or smoothies), and minor amounts of soy products were allowed up to 2–4 times a week (mostly as ingredients). Vitamin B12 and D3 were recommended to be taken as supplements. The mean LDL levels for groups one and two were 80 mg/dL, while group three had a mean LDL level of 70 mg/dL. Furthermore, the range was 54 mg/dL to 100 mg/dL for all participants, placing them at or below the recommended LDL levels. (Jakše et al., 2019). For all the participants, this was at, or better than, the current recommendation of 100 mg/dL. It is worth noting that the participant's LDL levels before the study began were not assessed, though, in Slovenia, where the study took place, the mean LDL level in 2018 was 140 mg/dL (NCD-RisC, 2021). It is rare to see an entire group of 154 people between 18 to 80 with optimal LDL levels.

It is important to note that not all the participants strictly followed the WFPB diet as recommended by Jakše et al., 2019. Some participants consumed fast food, sweet products, alcoholic drinks, vegetable fat, and some sweeteners, though in low quantities (mean: 6.5–0.2 g/day). Furthermore, some participants ate small amounts of food of animal origin (3–0.2 g/day for fish and meat; 0.1 g/day for milk and dairy products), though there was no consumption of eggs or added animal fat. Despite this, all the participants maintained optimal LDL levels. It is also worth noting that none of the participants were on any medications related to cardiovascular disease (in fact, none of the participants were on any medications except for 2 on thyroid medication, two on birth control, one taking medication for nausea, and 2 taking other medications). This contrasts with the previously mentioned distinction between Esselstyn et al., 2014 and Ornish et al., 1998, where removing egg whites, one cup per day of non-fat milk or yogurt, and oil reduced the chance of a reoccurring cardiac event by a factor of 22. Perhaps the distinction is that both Esselstyn et al., 2014 and Ornish et al., 1998 started with moderately to very sick patients while Jakše et al., 2019 started with healthy patients. This would suggest that if people were to adhere to a WFPB diet from a young age, before their arteries have suffered serious damage, the occasional (or minor) noncompliance wouldn't have any long-term effects. If a person's body is healthy, it can withstand and reverse small amounts of abuse. If, however, the abuse is constant and in large quantities, then the body won't be able to heal itself. These findings would suggest the need for more studies to be performed to figure out exactly how much 'small amounts of noncompliance' is.

Another Possible Approach to the Success of a WFPB Diet

As previously discussed, both the formation of atherosclerotic plaque from LDL and the inhibition of nitric oxide production is caused by oxidative agents. When the LDL gets oxidized, it can enter the subendothelial space, and it is oxidative stress that inhibits DDAH from degrading ADMA. If a person consumed foods with higher antioxidant levels, it would be reasonable to hypothesize that both these negative outcomes would be inhibited. In fact, if different food categories are analyzed based on their antioxidant content, the plant-based categories have significantly higher antioxidant levels. On the other hand, it is also possible that the antioxidant properties will be degraded during the digestive process and wouldn't affect antioxidant blood levels. A meta-analysis was done that studied the correlation between dietary intake of antioxidants and cardiovascular disease. It found a clear inverse relationship between antioxidant blood levels and cardiovascular disease. It also found a similar inverse relationship between fruit and vegetable consumption and cardiovascular disease. The higher levels of consumption of plant-based foods correlated with higher antioxidant levels. It is interesting to note that consuming antioxidant supplements did not correlate to an increase in antioxidant blood levels (Aune et al., 2018; (Aune, 2019). This would suggest that supplementation doesn't work, and more research needs to be done to discover why that is.

Conclusion

There is no question that a strict WFPB diet that restricts all added oil intake can be a lifesaver for someone who has already begun to exhibit symptoms of cardiovascular

disease. The necessity to follow the diet strictly, however, can be questioned in a healthy person. It is possible that as long as the majority of a healthy person's diet is WFPB, it would be enough. It is also possible that creating a high antioxidant diet (though not through supplementation) may have similar effects. Defining 'a healthy person' and 'mostly WFPB' would require future studies.

As an aside, although this research has focused on cardiovascular disease, many other illnesses such as diabetes, mental health, and cognitive decline have been shown to be less prevalent in people on a WFPB diet (Rajaram et al., 2019; Głąbska et al., 2020; Utami, Findyartini, 2018). Furthermore, a plant-based diet may have a greater impact on weight loss than other diets (Turner-McGrievy, et al., 2015).

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Does Exercise Make You Smarter?

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Abstract

Physical exercise has been applauded for its beneficial cardiovascular and mental effects for decades. Recently, researchers have begun to study exercise from a different perspective, focusing on the positive relationship between exercise and cognition. One area of cognition highlighted in association with exercise is its positive impact on executive function. Executive function refers to the collection of neurocognitive processes involved in goal-directed problem-solving. Improved levels of cognitive function have been found to impact significant achievements throughout life. Because of this, the development, improvement, and preservation of these functions are essential. While research has proven a correlation between exercise and improved cognition, the different aspects that might influence its effectiveness are currently unclear. This research paper comprehensively analyzes various factors such as type, intensity, and age groups that may modulate exercise's effect on cognitive and executive functions. Aerobic exercise was found to improve blood flow and increased transportation of nutrients and oxygen to areas in the central nervous system. While anaerobic exercise has also been shown to raise insulin-like growth factor-1 (IGF-1) concentrations, which enhances general cognitive function, lactic acid accumulation was found to have a negative effect on cognitive improvement. Exercises that include specific cognitive brain stimulation were found to directly improve that cognitive function. In terms of intensity, moderate exercise was shown to be the most effective overall. In some areas, High intensity interval training (HIIT) exercise matched moderate exercise's effect on cognitive function and outperformed it in others. These findings were shown to be true for all age groups, particularly among children, adolescents, and older adults. However, because the number of studies were limited, further research is needed to understand the exact influence exercise has on young to middle-aged adults. Furthermore, while the study did find that exercise can increase general cognition, it was unable to assess the exact impact of different types of exercise on specific cognitive processes.

Introduction

Hippocrates once said, "All parts of the body, if used in moderation and exercised in labors to which each is accustomed, become thereby healthy and well developed and age slowly; but if they are unused and left idle, they become liable to disease, defective in growth and age quickly." Physical exercise has long been associated with increased physical health and prevention of disease. Studies have associated exercise with preventing physical illnesses such as cardiovascular disease, (Agarwal, 2012) colon cancer, hypertension, and diabetes while improving mental health such as reduced anxiety, stress, and depression (Vina et al., 2012). Additionally, new research found that exercise may reduce the risk of acute respiratory distress syndrome (ARDS), a major cause of death in patients with the novel coronavirus (COVID-19) (COVID-19: Exercise May Help Prevent Deadly Complication, 2020). While the World Health Organization (WHO) recommends that adults should have at least 150–300 minutes of exercise per week, it estimates that 1 in every 4 adults and 4 out every 5 adolescents are insufficiently active (World Health Organization, 2020). Recently, researchers have begun studying the positive association between exercise and cognition. Cognition is broadly defined as the mental process of gaining information and understanding through intellect, observation, and sensation (Merriam-Webster, 2018). One area of cognition highlighted in association to exercise is executive function. Executive function refers to the collection of neurocognitive processes involved in goal-directed problem solving, which includes inhibitory control, cognitive flexibility, and working memory. These are basic skills that are used daily such as self-awareness, self-control, understanding different perspectives, organization, and completing tasks effectively (Carlson et al., 2013).

The development, enhancement, and preservation of cognitive processes is significant for all ages as they can play a major role in a variety of areas. For instance, studies have found that cognitive abilities are key factors of academic success (Rohde & Thompson, 2007) and school readiness (Welsh et al., 2010) among children. Furthermore, higher cognitive function is found to positively impact career success (Judge et al., 2010) and performance at work (Lang et al., 2010). Additionally, as life expectancy increases there's a rise of neurodegenerative diseases that cause cognitive decline in the elderly, which severely diminishes the quality of life (Batista & Pereira, 2016). Therefore, it is important to analyze how exercise can beneficially affect cognition. Besides for its well-established health benefits, exercise is cost-effective, non-pharmaceutical, and readily accessible. While the research linking exercise to improved cognition has been established, the various factors that can impact its effectiveness is still unclear. This review will first analyze several characteristics of exercise and discuss their underlying biological mechanisms in order to determine how to maximize exercise's benefits. Then, it will examine the pertinence of findings on various age groups and discuss recommended exercise regimens.

Method

Articles and studies for this paper were gathered using the EBSCO, PubMed, Google Scholar, and ProQuest databases, with access granted by the Touro College Library. The articles found discuss several elements that modulate exercise's effect on cognition and executive function. This

paper's analysis was formed after a thorough assessment of review articles, meta-analysis, case studies, and experimental investigations.

Results and Discussion:

Aerobic, Anaerobic, and Different Types of Exercise

Exercise can be differentiated into two general categories, aerobic and anaerobic. These differ in intensity and physical exertion and involve different muscle groups. Research has proven that both types of exercises benefit a variety of health issues, such as preventing cardiovascular disease and improving mental health. However, it remains to be seen if one specific type of workout is more effective in improving cognition than another.

Aerobic

Aerobic exercise is defined by the American College of Sports Medicine as any activity that engages large muscle groups, can be sustained continuously, and is rhythmic in character (Pescatello & American College Of Sports Medicine, 2014). Aerobic means "with oxygen". As the name implies, aerobic exercise relies on the body's ability to perform aerobic respiration to fuel these muscle groups. Biologically, this energy is produced when pyruvate can enter the citric acid cycle and undergo oxidative phosphorylation. However, this can only occur when there's oxygen present as the final electron acceptor of the cycle (Melkonian & Schury, 2019). Exercises that fall into this category include swimming, cycling, jogging, dancing, and hiking. All of these exercises are continuous exercises that require large muscle groups and rhythm to move. Research on aerobic exercise primarily revolves around its impact on the cardiovascular system as it is proven to help prevent heart attacks and coronary vascular diseases (Patel et al., 2017).

Recent studies have begun researching aerobic exercise's effect on cognition. A study analyzed aerobic exercise's effects on cognitive performance. Over a 10-week period, they studied 91 healthy adults split into 2 experimental groups and a control group. The control group exercised aerobically 0-2 times a week, while the experimental groups exercised aerobically 3-4 times a week, and 5-7 times a week, respectively. Many areas of cognitive function were tested using the Stroop test and various other tests. The study found considerable improvement in attention (rise of 33.7%) and cognitive flexibility (18.1%) in the experimental group compared to the control group (rise of 6.2% and 0.2%, respectively). The researchers also determined that as the frequency of exercises increased throughout the week, executive function increased. Since cognitive flexibility and attention are measures of executive functions, this indicates that aerobic exercise positively affects the prefrontal cortex which is associated largely with executive function (Masley et al., 2009). Similar results were found in a study that compared a control group to 66 subjects who exercised aerobically and found significant improvements in executive functions. Interestingly, they also found that exercise's effect on cognition increased as age increased. The best results were among 50-65-year-old group (Stern et al., 2019).

Researchers have proposed underlying mechanisms on how aerobic exercise affects cognition. One study has shown that aerobic exercise lowers blood viscosity which, in turn improves blood flow in the brain. This is due to hemodynamic changes, which consequently facilitates the transfer of nutrients and oxygen to essential central nervous system structures involved in learning and memory, thereby boosting cognitive performance (Cassilhas et al., 2007). They also set out to uncover a mechanism by analyzing aerobic exercise's positive effect on learning and spatial memory in rats. They found that aerobic exercise releases increased synapsin and synaptophysin in the hippocampus that are proven to improve spatial and learning memory (Cassilhas et al., 2012).

After researching various forms of aerobic workouts, specific cognitive benefits can be attributed to the specific forms of exercise. Dancing, for example was studied to determine its specific cognitive effects. The study was done over a 6-month period and compared a dancing experimental group to a non-dancing control group. The study found that in the dancing group there was significant improvement of cognition and attention compared to the control group, which found no change. They also noted that learning new and advanced dance-related motions has been shown to modify both functional and effective connections in the brain. This may suggest that if there's a cognitive aspect to the exercise it may provide an additional benefit, besides for the regular benefits generally associated with aerobic exercise (Kattenstroth et al., 2013). A review done by Yael Netz (2019) came to a similar conclusion. She found that motor-related exercises, such as ones that require coordination and balance, affect cognition directly. She hypothesized that how complex the motor-related task is determines the increase in neuroplasticity (Netz, 2019). Researchers suggested that this may be due to the increase in neurotrophic factors in the areas associated with those cognitive functions. They hypothesized a specific threshold may be required to facilitate lasting neural changes, and more cognitively challenging activities may help you get there more efficiently (Carey et al., 2005). It seems that overall aerobic exercise has a significant positive effect on cognitive functions, and it may be especially beneficial if there's a cognitive aspect to it.

Anaerobic

Anaerobic exercise is characterized by exercise that does not use oxygen and is often intense in a short duration of time (Patel et al., 2017). Without the presence of oxygen, our cells resort to glycolysis and fermentation to fuel the workout. This occurs when oxygen demand exceeds oxygen supply, and the muscles rely on anaerobic glycolysis for ATP synthesis. Under these circumstances, pyruvate is transformed into lactate, allowing glycolysis to occur (by regenerating NAD+) to create ATP as the energy source. A product of this process is the buildup of lactic acid (Melkonian & Schury, 2019). These exercises include sprinting, pushups, and powerlifting. Besides for building muscle mass, many positive effects are associated with resistance training as it is found to reduce fear of falling, depression, and anxiety. The elevation in mood and confidence causes an improved performance of day-to-day tasks that may indirectly help cognition.

A study conducted by Cassilhas et al., (2007) analyzed resistance training's effect on cognition. They followed 39 subjects who performed resistance training over a 6-week period compared to 23 non-exercisers. The volunteers were given various cognitive tests before and after the study to assess the outcome. It was discovered that following the period of the experiment, the subjects performed better in short and long-term memory tests as well as a considerable improvement in attention. This study suggests that anaerobic exercise seems to positively affect many executive functions. A meta-analysis conducted by Landrigan et al. (2019) found similar results. The analysis included 868 subjects from 24 studies on lifting and its effect on cognitive and executive functions. It was found that lifting has a beneficial influence on overall cognition and executive function. Interestingly, the study did not find much effect on working memory. However, it is unclear if this is due to the anaerobic aspect of the exercise or the cognitive aspect of resistance exercises. For instance, one must always pay attention to what they are doing during lifting so that they do not injure themselves or anyone around them. These periods of attentiveness may serve as a sort of attention training, explaining why there was a higher performance on executive function tests, since many of these tests assess an individual's capacity to focus on specific stimuli. In contrast, lifting doesn't activate memory performance, which may explain why memory wasn't so affected in the analysis. These findings are consistent with the aforementioned studies that found that task-specific exercises may affect the cognitive processes used in the exercise. (Landrigan et al., 2019)

Different theories were proposed in regard to the biological effect of anaerobic exercise on cognition. One proposed neurophysiological mechanism is the increase in IGF-1 concentrations. The IGF-1 hormone binds to receptors in the central nervous system, stimulating glial cell development, myelination, and neuron proliferation; an increase in its concentration is associated with greater cognitive and executive functions (Tsai et al., 2015). Multiple studies have found significantly higher levels of IGF-1 in people who performed resistance exercises compared to control groups (Cassilhas et al., 2007; Tsai et al., 2015).

While these studies imply that anaerobic exercise has a favorable effect on cognition, the impact of lactic acid production from these exercises' merits further examination. It remains to be determined whether these exercises are comparable or favored to aerobic exercise. Multiple studies were conducted to investigate the impact of the accumulation of lactic acid on cognitive functions compared to the lower levels of aerobic exercises. They found that levels of exercise that are high in lactic acid (in the anaerobic threshold) decrease the benefits of affected cognitive performances and executive functions such as attention skills. It has been suggested that this happens because high lactic acid conditions are associated with reduced pH levels and exhaustion of alkaline reserves. These states are known to affect voltage-gated channels that regulate neuronal excitability even with slight changes in pH levels (Córdova et al., 2009; Coco et al., 2019). While anaerobic exercises seem to beneficially impact cognitive functions, the proliferation of lactic acid seems to suggest aerobic exercises are more beneficial.

Intensity

One important factor that many studies research is which level of exercise intensity has the most beneficial effect on cognition. Understanding how different levels of exercise intensity affect various cognitive functions allows us to maximize the effects of our exercise regimen. While there are various ways to measure intensity, many studies categorize the three levels of intensity by percentages of maximum heart rate (% HR) a person reaches during the workout. Any exercise that causes between 40 and 50 % HR increase is referred to as low intensity, between 50 and 70 % is referred to as moderate, and above 70% is considered high (Mayo Clinic Staff, 2018). One of the early proposals hypothesized that the levels of intensity benefits are correlated as an inverted 'U.' They suggest that as the level of intensity increases, the greater the improvement of task performance is until a certain point, where then the task performance begins deteriorating (McMorris & Hale, 2012). The negative consequences of exhaustion may cancel out the beneficial effects of exercise. According to this proposition, moderate exercise is perceived as the optimal intensity of exercise. However, as recent studies begin to

analyze the effects of various intensities, a review of the results is required in order to compare the findings and ascertain the beneficial levels of intensity.

Researchers have used the inverted U theory as the baseline hypothesis for their studies. A study was done to measure the response rate of individuals after low, moderate, and high-intensity exercises. They proposed that the differences in intensity may affect different executive functions. Light and moderate intensity may benefit more response inhibition in executive function which requires less effort and demand, while more intense exercises may benefit more complex tasks. The study used the P3 component of an event-related brain potential to measure the interactions between the brain and exercise. The P3 component is believed to show how the brain distributes attentional resources and processes memory and is widely used as a measure for cognitive gains. Overall, it was measured that the P3 amplitude increases during the light and moderate exercise but not during intense exercise. According to this study, moderate exercise has a positive effect on executive functions, specifically allocating attention resources and memory processing. This seems to support the inverted U theory that the benefits may be diminished by the exhaustion associated with higher levels of intensity. However, the study did find a shortened response time amongst all intensities, which displays that intense exercise does have some positive effects (Kamijo et al., 2007)

In a different study, low and high-intensity exercise's cognitive effects were measured using an MRI to compare different cognitive effects on the brain. The MRI showed that low-intensity exercises increased resting-state functional connectivity (rs-FC) in the left and right frontoparietal networks. The frontal lobe in general is known to control executive function, and specifically the frontoparietal network areas are associated with cognitive functions and attentional control. In contrast, these areas were not highlighted during high-intensity exercises. The study aligns with the inverted U theory that proclaims that high-intensity exercise may deteriorate the positive effects of exercise. It supports that the greatest benefits of exercise are found between low and moderate intensities and decrease with further intensification. The study proposed that the post-exhaustive state after high-intensity exercises is what limits the positive cognitive aspects of exercise (Schmitt et al., 2019).

An interesting study was conducted to highlight the benefits of moderate exercise. The study began by researching whether a bout of moderate or high-intensity exercise increased cognitive function. They then proceeded to evaluate whether there was an effect on inhibitory control with food consumption. They found that there was a considerable improvement on the Stroop test following the moderate exercise, while there was negligible improvement following the high-intensity exercise. Similarly, while there was no correlation between the amount of food consumed and the intensity of exercise, the moderate exercisers selected the healthier choice. They exhibited an inhibitory response by selecting the healthier option rather than the unhealthy option. Again, this supports the previous theory that moderate exercise affects executive function, specifically response inhibition. Additionally, these benefits seem to deteriorate as the intensity increases (Lowe et al., 2014).

While the aforementioned studies seem to support the inverted U theory that higher levels of intensity may be detrimental, recently researchers have been studying how to utilize high-intensity exercise beneficially. Jiang et al. studied an MRI of the brain after extreme fatigue of the motor neurons. It was discovered that functional connectivity in subcortical nuclei, which are essential components of the motor control system, had increased significantly. These findings seem to indicate a stronger connection between the motor and interneurons after high-intensity exercise. This may suggest a bio-feedback system is regulating the motor neurons after fatigue to adjust optimally to accommodate the intense vigorous exercise. It may seem that high-intensity exercise helps the body adjust to accommodate higher motor performance and may build a tolerance to evade the detrimental effects (Jiang et al., 2016).

Furthermore, researchers may have devised a method to circumvent the possible cognitive deterioration caused by the exhaustion of high-intensity exercises. In a study, Alves et al., (2014) analyzed the use of HIIT as an alternative to traditional exercises. HIIT consists of a series of brief, intermittent bursts of intense exercise separated by intervals of rest or low-intensity exercise. HIIT can be extremely beneficial as studies have found people to enjoy it more than moderate exercise (Bartlett et al., 2011) and is considered to be time-efficient (this takes between 10-20 minutes). Alves et al. (2014) compared moderate exercise with HIIT by studying 22 subjects (9 men and 13 women). The results concluded that compared to moderate exercise, HIIT did indeed increase the cognitive function of selective attention tests, however, did not show improvement on short-term memory (Alves et al., 2014). According to this study, HIIT exercise enhances executive function just as much as moderate exercise and even exceeds it in terms of selective attention.

A similar study was conducted to analyze the effects of HIIT on executive function. They studied 12 male subjects

using the Stroop test. They discovered that both moderate and high-intensity exercise had an equivalent impact on executive function immediately following exercise. However, as opposed to the moderate workouts, the HIIT had a positive effect on executive function for a full 30 minutes post-workout. These findings show that HIIT may be a more effective technique for sustained improvement of executive function over time than moderate exercise (Tsukamoto et al., 2016).

Research seems to indicate that while all levels of intensities have some beneficial effect on cognition, there are preferred levels. Moderate exercise seems to be the optimal level while anything more intense seems to be detrimental, in line with the inverted U theory. However, researchers have identified a method to maximize higher intensity workouts, by incorporating breaks throughout the routine. These HIIT exercises were seen to match moderate exercise benefits in some executive functions while outperforming it in other ones.

Age Groups and Dose

One interesting component of exercise's effect on cognition is how the discussion varies between age groups. In children and adolescents, the studies analyze how exercise affects cognitive development and whether it should be implemented in the school curriculum. In adults, the discussion revolves around whether it improves cognitive function significantly enough to affect career development and job success. In the elderly, researchers investigate whether it can prevent cognitive decline and possibly even improve cognitive function. While exercise has been proven to help cognition overall, a review of the studies will help determine whether these findings hold true throughout different age groups, whether any group is favored, and the recommended exercise regimen.

Children and Adolescents

The primary goal of children and adolescents during their childhood years (ages 4-18) involve succeeding in school, creating social experiences, and progression of skills. Therefore, the development of cognitive and executive functions is crucial during this period. Memory, recall, concentration, and learning allows for better test-taking skills and higher academic achievements. Self-awareness and understanding other people's perspectives help foster social connections. A meta-analysis done by Alvarez-Bueno et al., (2017) on exercise's relationship with cognitive and executive functions in children and adolescents. They concluded that exercise has substantial beneficial effects on these functions including working memory, inhibition, and cognitive flexibility. In a cross-sectional study, Chaddock et al., (2010) discovered that active children have bigger hippocampus volumes than less active children. An increase in these areas has been associated with improved memory, which lends itself to the possibility that exercise throughout childhood may result in long-term changes in brain structure and function (Chaddock et al., 2010). Additionally, multiple studies have found that an increase in exercise has led to higher grades and academic success among children and adolescents (Brock et al., 2009; Ardoy et al., 2014; Donnelly & Lambourne, 2011). These findings seem to support that the findings of this paper pertain to children and adolescents. These positive associations strongly suggest that resources should be allocated on physical education in schools and be incorporated into the grade school curriculum (Álvarez-Bueno et al., 2017).

Young To Middle-Aged Adults

The application of the findings of this paper on young to middle-aged individuals (ages 18-50) is significant for a number of reasons. Besides for the fact that the bulk of the world's population is in this age group, adults are beginning, building, and establishing their careers and relationships during this stage. Cognitive improvement has been found to affect work accomplishment and career success (Judge et al., 2010; Lang et al., 2010) while providing a sense of fulfillment that creates an overall wellness to the individual. A systematic review looked at the relationship between physical activity and cognitive performance of adults in that age bracket (Cox et al., 2016). The review confirmed that exercise is positively associated with executive function. As for the frequency of exercise, researchers have not identified a specific amount that is beneficial, rather the magnitude of the effect rose as the intervention length increased (Ludyga et al., 2020). Interestingly, the review only discovered a limited collection of relevant literature (14 studies) exploring this association because the majority of the research focused on children and the elderly. Although a positive association was found, the small sample size disallows for any unequivocal conclusions. This age group represents a significant period of people's lives and it is imperative that more research is done to ascertain whether the findings of this paper are fully pertinent to them (Cox et al., 2016).

Elderly

In the elderly the focus hones in on whether exercise can prevent dementia, preserve cognition, and even improve cognitive processes. At the same time, the exercise has to be not too physically demanding in that the older adult can still be capable of executing the exercise without risking injury. Researchers have found that exercise benefits

healthy elderly adults in significantly improving both memory and executive functions. Additionally, exercise has been positively associated with helping elderly adults with cognitive impairments prevent decline and improve cognition in neurodegenerative diseases such as dementia and Alzheimer's (Blondell et al., 2014). To maximize the effects, the findings of this paper suggest a combination of aerobic and resistance exercises, as both have been linked to positive changes in neurobiological pathways, and they are likely to complement one another. Being that IGF-1 deficiency has been associated with cognitive decline, resistance exercise has been found to combat this by increasing IGF-1 concentrations (Tsai et al., 2015). Therefore, older adults should engage in a combination of aerobic and anaerobic workouts at least three times per week (45 min per session), on as many days of the week as possible (Sanders et al., 2019; Northey et al., 2017).

Summary and Further Research

In conclusion, while exercise has been found to overall benefit and improve cognitive and executive functions, several factors modulate how effective it is. Various elements of exercise stimulate different mechanisms which modifies their impact. Aerobic exercise has been found to significantly improve cognition by improving blood flow and increasing transportation of nutrients and oxygen to areas in the central nervous system. While anaerobic exercise has also been proven to increase IGF-1 which improves overall cognitive function, the buildup of lactic acid has a detrimental effect on cognition. Older adults though are still recommended to include anaerobic exercise as part of their regimen because it is the direct result of a lack of IGF-1 that causes their decline in cognitive function. Furthermore, exercises that include specific cognitive brain stimulation were found to directly improve that cognitive function. The greater the complexity of the task, the greater the impact on cognition. Following the inverted U hypothesis, moderate exercise was determined to be the overall optimal level of intensity. However, HIIT exercise matched moderate exercise's effect on cognitive function in some areas and even performed better in other areas. Therefore, it may be seen as an alternative as some people found HIIT more enjoyable and more time efficient. In regard to age, these findings are applicable to all age groups, particularly among children, adolescents, and older adults.

Further research is necessary to determine the exact magnitude of impact exercise had on young to middle-aged adults as the number of studies was limited. In addition, while overall cognition was found to be improved by exercise, the research was unable to determine the exact benefit of different modalities of exercise on specific cognitive functions. Therefore, in practice, it may be difficult to target a specific cognition function, such as attention or memory, with specific types of exercises in regard to intensity, type, and duration. Furthermore, as exercises' effect on cognition is a relativity new area of study, long-term studies are required to determine whether these effects are permanent or transient.

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Effective Treatments for Ductal Carcinoma In Situ

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Abstract

Ductal Carcinoma In Situ (DCIS) is the most common form of breast cancer wherein its progression interrupts the hormonal receptors and genetic variation of one's DNA. DCIS can be caused by hereditary means, or through mutations. Fortunately, due to the many different modes of contraction, there is a plethora of treatments available in the forms of mastectomy, radiation, chemotherapeutic drugs, and PARP inhibitors, each with their own mechanism of action to combat the tumor and any metastatic effects the cancer may have on the body. This paper analyzes the cancer's mechanism of action upon the body and the positive effects available treatments have to combat the disease.

Introduction

Breast cancer has been affecting 3.8 million women in just the United States alone, making it the most common cancer affecting women in said location. Breast cancer is commonly found in both men and women with an annual 42,500 deaths for women and 2,150 for men. Presuming a woman has not developed breast cancer before the age of 50, the percentage of susceptibility for it jumps up by 25%, resulting that 88 out of 100,000 women can develop ductal carcinoma in situ (DCIS) (Tomlinson-Hansen et al. , 2021). Furthermore, genetics is also a factor as they account for 25% of breast cancer in women under age 30, even though overall genetic mutations only account for 5-10% overall. Also, once a woman becomes post-menopausal there is a 17% increased risk of contraction every five years (Shah ,2014). Based on these jarring statistics, it is not surprising that the probability of a woman developing invasive breast cancer in her life is 12.3% or 1 in every 8 women. Despite these alarming numbers, there are a great deal of modalities to eradicate the cancer and increase life efficacy.

Methods

This comprehensive review is based on critical analyses of literature obtained using various databases available through The Touro College Library online, such as PubMed and ProQuest. The National Center for Biotechnology (NCBI) website was also useful in providing additional source material.

Ductal Carcinoma In Situ (DCIS)

DCIS (Ward et al., 2015), a cancer that occurs in the mammary ducts of the breast, causing the basal myoepithelial layer of the ducts to be filled with malignant cells, accounts for 83% of all cases of breast cancer. Normal breast ducts lead into lobules made of small glandular structures called acini, where there is a bilayer of cells lining this ductal lobular system. They consist of inner luminal epithelial cells and outer luminal myoepithelial cells, where the majority of breast lesions develop, whether benign or malignant. It is deduced that if the tumors remain at this basement membrane, the cancer is still in situ and not invasive (Ward, 2015).

In order to classify the intensity of cancer, five histological grades were established. They are compartmentalized as comedo, cribriform, micropapillary, papillary, and solid. In cribriforming DCIS, the tumor cells fill the duct and form lumen-like projections that appear as hollow protrusions. Micropapillary DCIS histology is characterized by the proliferated cells projecting into the lumen like a bunch of sticks but lack a fibrovascular core. Papillary DCIS, unlike micropapillary DCIS, does contain a fibrovascular core. Cribriform, micropapillary, and papillary in particular are all considered low grade lesions and the odds of developing into an invasive carcinoma are slim. On the other hand, tumor cells that have solid and comedo histological features, which are cells that divide aggressively and have an abnormal appearance, have a greater propensity to become invasive ductal carcinoma.

The spectrum of DCIS is wide with the many different hormone receptors, mitotic pathways, and/or genetic factors that are responsible for the proliferation of the cells, inhibition of tumor suppressor cells, and in some cases anti-apoptotic factors. However, if DCIS is left untreated from the moment of its inception, it would only take up to 2.5 years for it to progress into invasive ductal carcinoma (Tomlinson-Hansen et al., 2021).

Two elements that contribute to any cancer or tumor development are the loss of the TP53 gene and p53 proteins whose function is tumor suppression. If the DNA is not dividing properly, p53 would act against it, either by triggering apoptosis, or activating other genes for cell repair (Sever and Brugge, 2015), subsequently suppressing tumor development. The functionof the TP53 gene is to generate these p53 tumor suppression proteins. Should the TP53 gene be mutated, either through frameshift, missense, or nonsense mutations, it would not produce proper p53 proteins, and thus cell division would proliferate uncontrollably without proper borders (Olivier et al., 2010).

Being that breast tissue is constantly replenishing itself, there are hormone receptors running through it that activate cell division when hormones, namely estradiol-17β (estrogen) and progesterone, bind to their respective hormone receptors. The hormone of interest is then brought inside the nucleus by the hormone-bound receptor and binds to chromatin to initiate gene transcription and protein production. Of all DCIS cases, 75% have an ER (estrogen receptor) dysfunction, denoted as ER+, which

causes an overexpression of cell division, resulting in unregulated cancerous growth (Feng, 2018). Studies have shown that alterations to cyclin D-1, a cell cycle regulator that stimulates the proliferation of cells, is responsible for overexpression. In vitro experiments of breast cancer cells have shown that an influx of estrogen in the blood is clearly correlated with increased cyclin D-1 action or cyclin D-1 mRNA observed in the cell (Fernandez et al., 1998; Zwijsen et al., 1997). There comes a point where the mutant ER will still make cyclin D-1 without there being any estrogen there to activate its transcription (Zwijsen et al., 1997). In fact, the overexpression of cyclin D-1 is so ubiquitous that it is seen in 50-87% of ductal carcinoma cases (Fernandez et al., 1998).

Accordingly, a decrease of estrogen in blood or estrogen-receptor negativity has shown an expected decrease in cyclin D-1 activity in tumor cells. The same decrease in cyclin D-1 has been seen when anti-estrogens were found in the blood, further enhancing the notion that the steroid stimulates cell proliferation. Similar is the case for cyclin-dependent kinase inhibitors p21 and p27, whose job is to repair DNA when the cell cycle is arrested. They appear in abundance when anti-estrogens are counteracting the estrogen, expectantly limiting cyclin D-1 expression (Fernandez et al., 1998).

The important role of epigenetic changes such as aberrant DNA methylation and histone modification in cancer causation, progression, and treatment has been recognized in order to develop the proper therapeutic response to target the transcriptional abnormalities of the cancer. DNA methylation is commonly observed in the binding site at the enhancers of the transcriptional factor Erα in ER+ breast cancer, which would offer insight to the resistance of anti-estrogen chemotherapeutic agents to the binding site (Feng et al., 2018).

Along with the estrogen receptors are progesterone receptors in the breast that can dysregulate the cell cycle. There are progesterone receptors on the cell surface that allow for progesterone to interact with the cell and to partake in the proliferation of the cell with its cell processes and mitotic division. It's supposed to define gene expression, mainly chromatin and genome expression, when it binds to its steroid chemical progesterone. The defect occurs when the cell that produces the progesterone itself is the one that receives. In other words, it goes from paracrine signaling to autocrine signaling (Grimm, Hartig and Edwards , 2016). This may induce migration in early primary tumor cells and, in this way, activate mammary stem cells, thus resulting in uncontrolled cell division and dangerous proliferation (Feng et al., 2018).

Human epidermal growth factor receptor 2 (HER-2) is expressed in many cases of breast cancer. HER-2 expression is regulated by transcription factor AP-2gamma (TFAP2C). This transcription factor is one of the key regulators to hormonal responsiveness in the pathways utilized in breast carcinoma growth. High levels of TFAP2C have been associated with ER+ breast cancer (Wu et al. , 2020). DNA methylation or histone modification also affect this process of excess proliferation of cells, eventually leading to breast tumorigenesis (Feng et al., 2018). In breast cancer specifically, HER-2 is expressed in 50% of in situ carcinomas and eventually ends up in 20% of invasive carcinomas. It is a tyrosine kinase receptor that has an extracellular ligand-binding domain, a transmembrane domain, and an intracellular domain. HER-2 heterodimerizes with HER-3 since HER-3 doesn't have any tyrosine kinase activity. Cancer is formed when the HER-2 only homo and not heterodimerizes with HER-3. This affects many downstream signaling pathways associated with breast cancer such as the phosphatidylinositol 4,5-bidphosphate 3-kinase (PI3K)-AKT pathway (Albaghoush and Limaiem , 2020).

The PI3K-AKT pathway is a regulatory pathway for cell proliferation. PI3K is activated by G protein-coupled receptors which in turn translocates protein kinase B (AKT) to be phosphorylated by the plasma cell membrane. A conformational change happens, allowing for two phosphorylating sites to be opened. There is a threonine that is phosphorylated on the N-terminus and C-terminus to be fully active. It is unknown how, but the AKT is transferred to the plasma and nucleus where many of its substrates are located. There is negative regulator phosphatase and tensin homologue (PTEN) which inhibits the activation of AKT. It reduces the amount of PI(3,4,5)P3 produced by PI3K because the PTEN dephosphorylates the products of PI3K. Loss of PTEN either through inactivating mutation or a lack of PTEN in circulation causes more activation of AKT. From there the pathway enhances protein synthesis by phosphorylating mammalian target of rapamycin or mTOR, one of the body's protein synthesis regulators. Activated mTOR promotes cyclin D-1 mRNA production. Cancerous mTOR also inhibits anti-proliferative effects, so it's not only limited to increasing output, but also decreasing regulation as well (Osaki et al., 2004).

Whenever the cause for breast cancer is genetic alterations, it is most likely a mutation in the breast cancer gene, most commonly known as BRCA1 and BRCA2 (BReast CAncer). The genes themselves do not induce cancer, rather they act as tumor suppressor genes in the DNA repair processes such as chromatin remodeling, transcription control, and cell cycle regulation. Their tumor suppressive effects have been attributed mainly to cell cycle checkpoints and DNA repair management.

There are more than 1600 and 1800 known variants of BRCA1 and BRCA2 respectively, the majority of which induce frameshifts, leading to missense or non-functional proteins (Lee et al. , 2020). Thus, deletion mutations and/or loss of function in the BRCA genes lead to decreased DNA repair efficiency and possibly give rise to the expansion of cancerous cells, elevating the risk of developing breast cancer by five to six-fold. Lifelong risk of developing breast cancer through the BRCA1 gene is 65% and with BRCA2 is 45%. Even though BRCA1 or BRCA2 cause 5-10% of breast cancer, 75% of all DCIS cases are due to BRCA1 mutation (Feng et al., 2018).

Triple Negative Breast Cancer

The term triple negative breast cancer (TNBC) is due to the fact that it is ER-, PR-, HER-2-. TNBC accounts for 20% of all breast cancer cases and is most commonly found in women under 40 years old. The overall consensus is that TNBCs have a frequent occurrence of multiple copy-number aberrations involving genes that lead to alterations in multiple signal pathways, which include the mutations/deletions of BRCA1/2 in the DNA repair pathway (Bianchini et al. , 2016). TNBC occurs in 10-15% of sporadic, or non-genetic caused breast cancer, but 66-100% of pathogenic variant BRCA1 breast cancer. In contrast, 14-35% of TNBC cases carry BRCA2 pathogenic variant (Lee et al. , 2020). Breast tumors arising in patients who carry BRCA1 mutations have many molecular features of basal-like sporadic breast tumors, including a greater likelihood of being high-grade, ER/PgR-negative, HER2-negative, and a high frequency of TP53 mutations. The existence of a tight association between BRCA1 mutations, basal-like breast cancer and TNBC has raised the question as to whether BRCA1 loss of function through other mechanisms participates in the pathogenesis of sporadic basal-like breast cancer and TNBC; such an association could be exploited therapeutically with rational clinical trials exploring the role of chemotherapy and biological agents targeting defective DNA-repair pathways (Fernandez , 1998). High grade tissue is observed in TNBCs, with aggressive division and observed necrosis. Such a cancer would not be responsive to treatment used for receptor-positive cancers (Feng et al., 2018). As forkhead box O (FOXO) transcription factors have a recognized role in tumor development and progression, it was shown that FOXO3a expression was highly expressed in TNBC tumors with negative clinical and pathological features, including lymph node metastasis and perineural invasion, and correlated with poor disease-free survival. Due to the severity of TNBC, and limited treatments available for the cancer due to its negative receptor status, an accurate fluorescence in situ hybridization (FISH) assessment is taken so as to not falsely diagnose the cancer (Bianchini et al. 2016).

Risk Factors

Women are prone to breast cancer through certain risk factors. First off, one who has first degree relatives increases one's risk of developing breast cancer compared to those without a family history with a risk factor of 1.69 to 1.37, and the risk increases with the risk increases with the number of first-degree relatives a woman has that had or have breast cancer.

The onset of menarche also is a contributing factor to women developing breast cancer with those whose menarche comes early having a positive-receptor cancer risk by two-fold, while late menarche reduces the risk by 10%.

Early pregnancy has been noted to protect woman from breast cancer. Giving birth at the age of 20, 25,and 30 can reduce the risk of breast cancer by 20%, 10%, and 5% respectively. With breastfeeding, the risk of developing breast cancer is decreased by 4.3% per one year of breastfeeding due to the decrease in endogenous sex hormone levels, which play a role in receptor positive breast cancer (Shah, Rosso, & Nathanson , 2014).

Age at menopause also contributes to the increased possibility of developing breast cancer. The delay of menopause itself per year is a 3% increased risk and 17% every five years (Shah, Rosso, & Nathanson , 2014). (Feng et al., 2018)

Postmenopausal women on hormone replacement therapy exhibit a two to four-fold increase in breast cancer (Kinsinger et al. , 2002).

There are also lifestyle risk factors that increase one's susceptibility to contracting breast cancer such as alcohol, inactivity, and obesity. These risks account for 21% for all breast cancer deaths worldwide. Alcohol consumption of 5-9.9 grams a day has been proven to increase breast cancer risk. Physical, vigorous activity reduces risk by 5%.

If one has had cancer before, and has received radiation therapy for treatment, the previous exposure can eventually lead to DNA mutation leading to DCIS (Shah, Rosso, & Nathanson , 2014).

Testing

There are many tests that are performed to identify if a woman has breast cancer. Self-feeling of something that doesn't belong in the breast, as well as personal observations of how the breast looks can be clear indicators of breast cancer. Signs of breast cancer include finding a new lump in the breast or underarm (armpit); thickening or swelling of part of the breast; irritation or dimpling of

breast skin.; redness or flaky skin in the nipple area or the breast; pulling in the nipple or pain in the nipple area; nipple discharge other than breast milk, including blood; any change in the size or the shape of the breast, and pain in any area of the breast. Ductal Carcinoma In Situ (DCIS) is breast cancer that forms in the milk ducts and accounts for 75-80% of breast cancer found in patients (Memorial Sloan Kettering Cancer Center, 2021).

Close to 90% of breast cancer cases are found via mammogram. The mammogram looks for microcalcifications in the breast, or what is commonly known as dense breasts, mainly to clarify if the density in the breast is just the crowding of cells, or rather the start of a tumor. An MRI is also taken for equivocal findings where breast augmentation prevents effective screening mammography. MRI is also more specific for detecting high risk cancer at .77-.79 as compared to mammography which is only .33-.39 (Shah, Rosso, & Nathanson , 2014). The last test taken is core needle biopsy, to identify which hormone receptors the cancer is positive for, as well as if the cancer utilizes the PI3K-AKT pathway and HER-2 expression (Tomlinson-Hansen et al., 2021).

Surgery

Effective surgery for breast cancer is a mastectomy which is the removal of the full breast. This surgery is curative for 98% of cases and only leaves a 1-2% recurrence rate due to small negative margins or unseen invasive carcinomas. Breast-conserving surgery (BCS) is a surgery that conserves the breast and only removes the cancer within and 2mm of healthy surrounding tissue for negative margin (Tomlinson-Hansen et al. , 2021). The size of the tumor, the location of the tumor, and the quantity of tumors determines which excision the patient will receive. If tumor size is small, but there are many in the breast, it would call for a mastectomy, as well as large tumors would. A small tumor localized in one area would be a candidate for BCS (Ward et al., 2015).

After BCS, radiation therapy will follow to eliminate any residual disease. The NSABP B17 trial demonstrated that in patients who underwent breast-conserving surgery and followed by radiation, there was a 50% to 60% reduction in local recurrence with surgical excision and radiation therapy compared to surgical excision alone (Tomlinson-Hansen et al., 2021). No significant difference in survival rate has been seen down the line with BCS in conjunction radiation therapy at 91.7% when compared to a mastectomy at 92.8%, especially since radiation has its downside of mutating BRCA in DNA repair to alter its normal function (Lee et al. , 2020). The conventional dose of radiation to the whole breast is 45-50Gy (grey) followed by a boost to the lumpectomy bed for an additional 10-16Gy over a 6-week period. If the patient is older than 50, hypofractionation is the preferable treatment which entails less weeks of treatment but more intense waves of radiation that target the exposure of the radiation to normal tissue (Kim & Algan, 2021).

Radiation is significant in disease control. Although radiation therapy has its own drawbacks of possible recurrence, overall, those who had BCS in combination with radiation have only an 8% recurrence rate as opposed to those who had BCS without any radiation therapy whose recurrence rate is at 18.7% (Ward et al., 2015). After 10 years, those who had radiation treatment post-operation have shown a decrease in disease by at least 50% (Alkabban & Ferguson, 2021).

Chemotherapy for HR-positive Treatments

The general effect of chemotherapy treatment in patients post operation has been shown to reduce the risk of recurrence by 50% (Alkabban & Ferguson, 2021). In trials of 5 years of tamoxifen therapy versus no endocrine therapy, the recurrence rate in the tamoxifen group was approximately 50% lower than that in the control group during the first 5 years (the treatment period) and approximately 30% lower during the next 5 years (Pan , 2017). Those with DCIS whose status is hormone receptor positive have a plethora of treatments available for them. Selective estrogen receptor modulators (SERMs) act as agonists towards estrogen receptors in the breast. Though their structure is different than the regular steroidal structure since they have a tertiary structure, that's enough for them to bind to the ligand-binding domain. SERMs include tamoxifen, toremifene, and raloxifene (Adams and McCoy., 2010).

The use of tamoxifen is suggested for hormone positive premenopausal women due its selectivity towards estrogen. Recommended clinical treatment is to take tamoxifen for a 10-year period. Side effects include sexual dysfunction, irregular menstrual cycles, osteoporosis, endometrial cancer, stroke, deep vein thrombosis and pulmonary embolism (Tomlinson-Hansen et al. , 2021).

The outcome of utilizing aromatase inhibitors is to inhibit the cytochrome P-450 component of the aromatase enzyme complex, which is responsible for estrogen and progesterone biosynthesis. It prevents the conversion of androgens into estrogen. There are two types of aromatase inhibitors: Type I and Type II. A Type I aromatase inhibitor is exemestane, whose steroid structure is similar to the androgens and irreversibly inactivates the enzyme substrate binding site of estrogen. Type II aromatase inhibitors are anastrozole and letrozole whose functions

are the same as Type I, but are reversible because their structure is not steroidal. Side effects of aromatase inhibitors are similar to those of SERMs.

Selective estrogen receptor downregulators (SERDs) such as fulvestrant have a higher affinity for the ER than SERMs, but do not display any agonistic activities. It is a novel ER antagonist that binds to the ER to prevent dimerization leading to a rapid degradation and loss of cellular ER expression (Adams and McCoy., 2010).

Oophorectomy

Called a Prophylactic bilateral salpingo-oophorectomy, this surgery removes the ovaries, leading to a major decrease in estrogen produced in the body. It decreases the risks of ovarian cancer by 80% and breast cancer by 50%. This option is mainly considered for post-menopausal women since removal of the ovary would also remove all hormones coming from them which includes reproductive hormones (Kim & Algan, 2021).

Hormone Receptor Negative Treatment

As discussed earlier, the PI3K-AKT pathway's function is to regulate HER-2 to keep control of the cell cycle so that there isn't too much proliferation due to the suppression of tumor inhibitors. Trastuzumab, the first approved drug, is a monoclonal antibody that directly targets the HER-2 protein. It reduces the risk of recurrence and death by 52% and 33%, respectively, if combined with chemotherapy in HER2+ early breast cancer as compared to chemotherapy alone. The most common issue with infusion of cytotoxic chemicals in the blood is the pathway of delivery. The chemicals are delivered through a glomerular filtration, thus increasing the toxicity of the blood and weakening the kidneys (Alkabban and Ferguson , 2021).

After treatment of Trastuzumab, it is necessary to follow up with a combination of cytotoxic chemical agents that combine for a stronger effect. These chemicals provide the body with an ability to overcome the cancerous cells by disturbing the cancerous cell cycle (Carlson et al., 2009)

Doxorubicin is an anthracycline derived from the streptomycin bacteria which is from the group of polyketides (Ridley and Khosla , 2009). Anthracyclines function in halting protein synthesis by attaching to the 16s DNA chain of the smaller 30 chain polypeptide thus preventing anything else from attaching and arresting cell cycle function (Waters and Tadi, 2021).

Cyclophosphamide is a type of nitrogen mustard drug which exerts its effects through the alkylation of DNA. The drug is not cell-cycle phase-specific and metabolizes to an active form capable of inhibiting protein synthesis through DNA and RNA crosslinking. The majority of the antineoplastic effects of cyclophosphamide are due to the phosphoramide mustard formed from the metabolism of the drug by liver enzymes which hydroxylate, metabolize, and then cleave into alkylating agent phosphoramide mustard and acrolein. The phosphoramide metabolite forms cross-linkages within and between adjacent DNA strands. These modifications are permanent and eventually lead to programmed cell death (Ogino and Tadi , 2021).

Fluorouracil is an antimetabolite, acting as a competitive inhibitor towards DNA synthesis. It is a homologue that looks like the base uracil but has a fluoro group on its fifth carbon instead of a hydrogen. This prevents the conversion of deoxy-uridylic acid to thymidylic acid, halting DNA synthesis and cell division (National Center for Biotechnology Information , 2022). The main issue is that it does not differentiate between fast growing cells and cancerous cells, therefore it will attack all fast-dividing cells, such as hair follicles, blood cells ,mouth, stomach, and bowel cells (Mayo Clinic, 2021).

The Taxanes Docetaxel and paclitaxel, also known as Taxol, are mitotic inhibitors that act as a spindle poison to inhibit microtubule dynamics and arrest the cell cycle. Docetaxel exerts 1.2-2.6 stronger cytotoxicity than paclitaxel, and 1000 times greater than cisplatin (Katsumata , 2003).

Cisplatin is a platinum based chemotherapeutic agent that can form bonds with the polar ends of DNA due to platinum's positive charge. In particular, use of cisplatin therapy has been suggested for TNBC harboring a BRCA mutation. Cisplatin is a DNA-intercalating agent that cross-links DNA resulting in interference with RNA transcription and DNA replication activities. If the DNA lesions are not repaired, DNA-damage induced cell-cycle arrest and apoptosis are triggered. Cells can become resistant to cisplatin by several mechanisms including change in the accumulation of the drug in cells either by inhibited uptake or enhanced efflux, detoxification of the drug by redox mechanisms, repair of the DNA by excision repair mechanisms, or negative regulation of apoptotic mechanisms. Carboplatin was developed as a less toxic version of cisplatin, and also as a chemical with a longer half-life, but 90% would be excreted with urine (Hill et al., 2019).

Regarding the PI3K-AKT pathway, the initial treatment available was Wortmannin which inhibits the PI3K-AKT pathway thus promoting apoptosis. It was found that the main function of Wortmannin was that it prevented the phosphorylation of the AKT protein. But, due to its organic makeup which prevents is not soluble in water, Wortmannin was discontinued for clinical trials. LY294002, a water soluble Wortmannin, was developed but its PI3K inhibitive ability was reduced. LY294002,a

pro-apoptosis and anti-proliferative chemical reagent is a competitive and reversible inhibitor to the ATP binding sites of PI3K, as well as suppresser of tumor growth (Osaki et al., 2004).

One combination found to increase recovery after receiving treatment with trastuzumab is doxorubicin, cyclophosphamide, and either paclitaxel or docetaxel. Another is docetaxel and cisplatin (Carlson et al., 2009)

TNBC Treatment

For TNBC, the cancer is not generated through any hormonal response as its name suggests, therefore, it will require chemotherapy that will halt DNA replication. Poly (ADP-ribose) polymerases (PARPs) attach to single strand DNA breaks and intracellularly signals to nuclear repair proteins to fix the DNA. In cancerous cells, PARP reacts to repair a single stranded cell, but due to the inability of BRCA to heal double DNA strand breaks, the cell continues to divide damaged DNA. PARP inhibitors deactivate the PARP from reacting to the single strand breaks which would then lead to replication fork damage, thus causing the cell to program cell death (Lee et al. , 2020) (Feng et al., 2018).

Other forms of treatment for TNBCs include injection of the cytotoxic chemicals as mentioned by hormone-negative breast cancer. Surprisingly, although TNBC has the most limited options for treatment, it has the highest response rates to neoadjuvant chemotherapy. Approximately 30–40% of patients with early-stage TNBC treated with standard neoadjuvant anthracycline and taxane-based chemotherapy regimens achieve a pCR (pathogenic complete response) after treatment (Feng et al., 2018). A combination of a taxane and anthracyclines remain as important chemical agents needed for treatment. Adding carboplatin to paclitaxel followed by a dense dose of doxorubicin and cyclophosphamide has an increased pathogenic complete response from 46-60% due to the added cisplatin. Platinum based agents really help in BRCA1/2 mutations with a response rate of 75% (Feng et al., 2018).

Discussion and Conclusion

Due to the differences in the different cancer types, concocting a treatment utilizing each chemotherapeutic agent would not have the potency to effectively treat the patient. On the other hand, a PARP inhibitor would be something that all cancers whether hormone receptor positive or negative can benefit from. Even when the cancer is ER+ and/or PR+, the main result would still be a halting of DNA synthesis. The only issue is whether it would be effective for hormone receptor positive cancers. Hormone receptor positive breast cancers would prefer tamoxifen and AIs because they directly addresses the problem, and they will react swiftly and target the estrogen causing the issue. There is research that when insulin was pumped into MCF-7 breast cancer cells followed by a cytotoxic chemotherapeutic regimen, the pCR was higher because there was a greater absorbance of the chemicals, the cross-membrane channels have expanded permeability due to the GLUT 1 and 3 transporters. The pathway travelled is the PI3K-AKT pathway. Therefore, any injection of insulin can indeed enhance responsiveness to the chemotherapy treatment plan for whichever cancer is found while also reducing toxicity due to glomerular filtration(Agrawal et al., 2017). A way that usage of cytotoxic chemicals can be used even for HR+ breast cancer is to use a taxane pre-operation to shrink the size of the tumor before excision. This can further reduce the need for a mastectomy and instead one can proceed with a lumpectomy (National Cancer Institute, 2022).

Essentially, breast cancer is something that can affect one's life either through hormonal avenues, specific homeostatic pathways, or genetic aberrations. Conveniently, as many as there are variations of sickness there are as many methods of treatment, either through surgery, radiation, chemotherapeutic drugs, cytotoxic chemicals, or PARP inhibitors, each utilizing their own method of warfare to combat the body's ailments. Through our analysis of the disease and methods of treatment, we can provide treatment to aid in safe and healthy recovery.

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