TOURO COLLEGE & UNIVERSITY SYSTEM

The Science Journal of the Lander College of Arts and Sciences

Volume 17
Number 2 *Spring 2024*

-

2024

Full Issue: Volume 17, Number 2, Spring 2024

The Science Journal
of The Lander College of Arts and Sciences
1602 Avenue J Brooklyn, NY 11230
718-252-7800 • las.touro.edu

LANDER COLLEGE
OF ARTS & SCIENCES
TOURO UNIVERSITY

The Science Journal of the Lander College of Arts and Sciences-Flatbush

Vol. XVII • Number II • Spring 2024

The Science Journal

LANDER COLLEGE
OF ARTS & SCIENCES
TOURO UNIVERSITY

Volume XVII • Number II • Spring 2024

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 celebrated its 50th anniversary at a dinner on December 4, 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-Presbyterian 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.

TOURO UNIVERSITY

The Science Journal

LANDER COLLEGE
OF ARTS & SCIENCES
TOURO UNIVERSITY

Vol. XVII · Number II · Spring 2024

Table of Contents

The Cover Picture: The cover illustration, created with AI and laid out by Professor Antony O'Hara of the Digital Multimedia Design Program, pertains to the paper. "What are the best Treatment Options for Infantile Cataracts?" by Breindy Hecht

How does Marijuana Affect Reproductive Health?

Miriam Blatner

Miriam Blatner will graduate in September 2024 with a Bachelor of Science degree in Honors Biology.

Abstract

Marijuana use has become prevalent worldwide, especially amongst men and women of reproductive age. Marijuana acts on Cannabinoid receptors, which are a part of the Endocannabinoid system. CB1 and CB2 receptors are most found in humans. Activation of Cannabinoid receptors in males cause a reduction in healthy sperm parameters and inhibits the acrosomal reaction, and therefore minimizes fertility potential. Researchers have not yet discovered any significant interactions between marijuana and the female reproductive system. There has also been limited evidence displaying the effects that marijuana has on pregnancy and breastfeeding of infants. Nevertheless, physicians have recommended against marijuana use while trying to conceive and while pregnant. Researchers continue to search for evidence linking the adverse effects that marijuana has on the female reproductive system and on the offspring of chronic marijuana users.

Introduction

Approximately 1 in 6 couples globally have trouble conceiving. In recent years, researchers have discovered that unhealthy lifestyle factors can contribute to fertility issues. Alcohol and tobacco use have been widely studied and it has been proved that excessive consumption causes a moderate reduction in healthy sperm parameters (Joo et al, 2012). The recent legislative changes have brought a new focus on the role of marijuana and fertility potential. Marijuana is one of the most used drugs worldwide, due to its recent increased availability. Use is especially prevalent amongst men and women of reproductive age. Research shows that marijuana use adversely affects both male and female reproductive health. Additionally, there is limited evidence associating marijuana use during pregnancy and increased risk for preterm birth and small for gestational age infants. The purpose in this review is to analyze the effects that marijuana has on both male and female reproductive systems, as well as pregnancy outcomes amongst marijuana users.

Methods

Data was retrieved from PubMed and other sources, such as ProQuest and NIH, with access granted through Touro University Library. This comprehensive review and critical analysis on marijuana and how it affects reproductive health is based on the interpretation of various medical research papers. Key words used to retrieve data were "marijuana and reproductive health, "cannabis and reproductive health", "drug use", "male infertility" and "marijuana and pregnancy".

Discussion

Effects of Marijuana Use on Male Fertility

Marijuana is a product of the dried leaves and flowers of the plant Cannabis sativa. Marijuana contains several cannabinoids, such as cannabidiol and cannabinol, but the main psychoactive compound is called tetrahydrocannabinol (THC), with delta 9-tetrahydrocannabinol being the most active isomer. Upon consumption, it acts via release of cannabinoid compounds which bond to cannabinoid receptors, part of the endocannabinoid system (ECS). Numerous biological roles have been linked to the ECS, including inflammation reduction and post synaptic signaling. Studies have shown linkage to the ECS and functions of male reproduction. Cannabinoids are found in two categories, exogenous and endogenous. Endogenous cannabinoids are synthesized by various tissues in the human body, while exogenous cannabinoids, like THC, are plant based.

There are four endogenous substances characterized as endocannabinoids: N-arachidonoylethanolamine (AEA), 2-arachidonoylglycerol (2-AG), 2- arachidonoylglycerol ether, and virodhamine. AEA and 2-AG have been the most studied. They act on the cannabinoid receptors, CB1 and CB2, and perform biologically similar actions as THC (Du Plessis et al, 2015).

CB1 and CB2 are both G-coupled receptor proteins (GCPRs) (Howlett et al, 2002). CB1 is found mainly in the central nervous system (CNS) and have been found on the acrosomal region, midpiece and tail of spermatozoa (Cacciola et al, 2008). In the brain, they are found in the preoptic area of the hypothalamus, which stimulates the release of luteinizing hormone releasing hormone (LHRH). CB2 receptors are mainly linked to the immune system and cells within the peripheral nervous system but have also been found on Sertoli cells and in the post acrosomal region of spermatozoa (Agirregoita et al, 2010).

The Endocannabinoid System and the Hypothalamic-Pituitary-Gonadal-Axis

The hypothalamus-pituitary-gonadal axis is a major component in maintaining the reproductive functions in both males and females. In males, Gonadotropin-releasing hormone (GnRH) is released by the hypothalamus and stimulates the adenohypophysis to secrete two hormones, follicle stimulating hormone (FSH) and luteinizing hormone (LH). FSH stimulates Sertoli cells, which are involved in spermatogenesis, while LH stimulates Leydig cells to release testosterone.

The endocannabinoid system and hypothalamus-pituitary- gonadal axis are closely linked, due to the presence of CB1 and CB2 receptors found throughout the axis. Activation of these receptors, whether by endogenous endocannabinoids such as AEA or 2-AG, or exogenous

cannabis consumption, negatively affects the functioning of the hypothalamus-pituitary-gonadal axis. In the adenohypophysis, CB1 receptor activation leads to the inhibition of spontaneous release of gamma aminobutyric acid (GABA). Post synaptic GABA receptors, located on GnRH neurons are not activated, and consequently, GnRH is not released. Additionally, when the CB1 receptors located in the preoptic nucleus of the hypothalamus are activated, serum LH levels decrease. CB1 receptor expression is more prominent in males, making them more sensitive to cannabinoid induced changes.

CB1 receptor activation on spermatozoa causes a decrease in motility and viability. Additionally, it inhibits the acrosomal reaction. CB2 receptor activation has also been linked to decreased motility. A decrease in sperm concentrations have been found in both humans and animals who are regularly exposed to cannabis (Du Plessis et al, 2015).

A cross-sectional study analyzed semen samples of 229 men ages 23-72. Forty seven percent of the group admitted to chronic marijuana use, and 21% reported recent use. Regression analysis showed that frequent and recent users were 2.6-4.3 times more likely to have sperm with abnormal morphology and motility parameters (Carrol et al, 2019). A second study assessed both urine and semen from 62 participants. The study found 25% of the urine samples contained THC, the active compound found in marijuana. Semen analysis performed on the THC positive samples showed a large percentage of sperm with abnormal morphology. A third study performed a laboratory analysis on morphology and spontaneous acrosomal reactions after exposing 78 healthy sperm samples to THC. The researchers conducting the study separated the sperm into subgroups by the sperm fertilizing potential, 90% potential and 45% potential. The samples were incubated with recreational doses of THC for 3 hours. The acrosome reaction was artificially induced in vitro by incubating the sperm with a Ca2+/ H+ ionophore. A moderate decrease of normal morphology and spontaneous acrosomal reaction was found in the 90% potential group. In the 45% group, THC caused a significant decline in normal morphology and spontaneous acrosomal reaction (Whan et al, 2004).

Implications for Further Research

The studies performed highlight the effects that marijuana consumption has on sperm parameters. THC directly affects sperm parameters, likely by activating CB1 and CB2 receptors which negatively affect the function of the hypothalamic- pituitary-gonadal- axis and the function of the sperm itself. However, some of the studies were performed on small groups and were not controlled trials. More extensive research, such as expanded, controlled trials would be stronger evidence.

The Female Reproductive System

In contrast to males, where spermatogenesis only begins at puberty, formation of gametes in the ovaries begins in females before they are born. During early fetal development, primordial germ cells migrate from the yolk sac to the ovaries where they differentiate into oogonia. Oogonia are diploid stem cells which divide mitotically to produce millions of germ cells. Even before birth, many oogonia degenerate, while the remaining oogonia develop into primary oocytes which complete prophase of meiosis I. During the reproductive years, some will complete meiosis to form a haploid oocyte. In the interim, the primary oocyte is surrounded by follicular cells in a primordial follicle. Beginning at puberty, the menstrual cycle occurs each month, in which one oocyte completes meiosis, matures within its follicle, and gets released into the fallopian tubes. The menstrual cycle has two aspects, the ovarian cycle, and the uterine cycle (Tortora and Derrickson, 2017)

The Ovarian Cycle

At the beginning of the month, the hypothalamus releases GnRH. GnRH stimulates the release of FSH by the adenohypophysis. FSH stimulates follicular growth in the ovary. As the follicle reaches maturation, it releases estrogen. When maturation is reached, estrogen reaches peak levels, initiating a feedback response inhibiting the release of FSH. Peak levels also trigger a surge in LH to be released from the adenohypophysis. The LH surge causes the mature follicle to release an oocyte into the fallopian tubes. The remaining follicular tissue becomes a corpus luteum, which secretes estrogens and progesterone (Tortora and Derrickson, 2017).

The Uterine Cycle

The uterus closely parallels the events occurring in the ovaries.

The inner lining of the uterus, the endometrium, also undergoes cyclic events every month. Menses marks the beginning of the cycle, when levels of progesterone become insufficient, and the endometrial tissue sloughs off. As estrogen levels increase due to follicular activity, the proliferative phase begins, and the uterine epithelium is restored. Around the time of ovulation, the secretory phase begins. Endometrial glands increase secretions, and the endometrium reaches maximum thickness and maturity. If fertilization occurs and the embryo successfully implants in

the uterine wall, Human Chorionic Gonadotropin (hCG) hormone is released. HCG signals the corpus luteum to continuously release progesterone, which maintains the endometrial lining and the pregnancy, until the placenta forms and takes over progesterone secretion. If fertilization does not occur, the corpus luteum aborts progesterone secretion about 14 days post ovulation. Progesterone withdrawal stimulates menses, and the cycle restarts (Tortora and Derrickson, 2017)

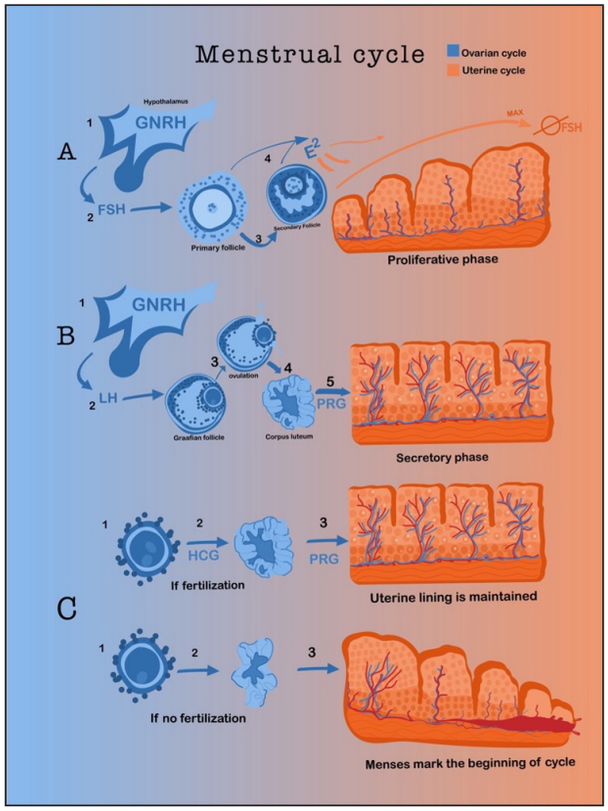

Figure 1: Correlation of the ovarian and uterine cycles

Marijuana's effect on the Menstrual Cycle

Endocannabinoid receptors are found throughout the female reproductive tract, including the ovaries, fallopian tubes, myometrium, and endometrium, and throughout the hypothalamus. Activation of these receptors may cause disruption of the menstrual cycle and implantation. One of the mechanisms in which marijuana disrupts the menstrual cycle is by suppressing GnRH from the hypothalamus. GnRH suppression prevents the secretion of cyclical female hormones which regulate the menstrual cycle. Several animal studies have suggested that marijuana use causes prolonged and anovulatory menstrual cycles which decrease fertility potential (Brents, 2016).

Studies were conducted on rhesus monkeys since their reproductive cycle closely mimics the human female reproductive cycle. Rhesus monkeys' menstrual cycles are also 28 days long and are regulated by mechanisms similar to humans. Two studies analyzed the effects of daily THC exposure on menstrual cycle length and ovulation. Daily THC injections during the follicular phase caused lengthy and anovulatory cycles. THC injections during the luteal phase did not have any profound effects on the menstrual cycle. (Asch et al., 1981). A study performed on ovariectomized female rhesus monkeys found decreases in serum LH and FSH levels shortly after marijuana administration. A final study analyzed female rhesus monkeys who were given marijuana 3 times per week beginning on cycle day 1 for about 230 days or until at least two anovulatory cycles occurred. Results showed decreased serum LH, estrogen, and prolactin levels for greater than 100 days since treatment began (Smith et al., 1979). However, two studies from the 1980s examined a small group of self-reported human marijuana smokers during the follicular phase of the menstrual cycle and found no significant changes to their hormones (Mendelson et al., 1985) Another human study performed on marijuana users during the luteal phase resulted in a decrease in serum LH and prolactin hormones within the first 1-2 hours after the dose. (Mendelson, et al., 1986). LH is involved in maintaining progesterone secretion during the luteal phase, and a decrease in LH serum concentrations can disrupt the endometrial lining and shorten cycle length.

Implications for Further Research

Although several animal studies showed findings indicating the effect of marijuana on reproductive hormones, most of the human studies did not show any clinically significant results. More research is necessary to determine the effects that marijuana has on the menstrual cycle. The studies were performed several years ago, before marijuana was popular and use was prevalent amongst reproductive age women. Additionally, sample sizes were small and largely relied on self-report. Larger and more robust trials would need to be performed in order to yield significant evidence.

Cannabis Impact on Pregnancy

Maternal cannabis use during pregnancy has been associated with small for gestational age infants, preterm birth, and impaired behavioral and cognitive development. Women who use cannabis often use other substances such as alcohol or tobacco, which cause a synergistic affect and increases the danger for the fetus. Cannabis is often used by pregnant women to minimize nausea during the first trimester. The first trimester is the most

vulnerable time for a fetus since most of the organ development occurs during that time. Fetal exposure to harmful substances during the first trimester can cause serious birth defects or developmental delays.

In the 1950s, a drug called Thalidomide became popular in many countries in Europe. It was used to treat morning sickness and nausea in early pregnancy. However, it soon became apparent that the children born to mothers who used Thalidomide during their first trimester were born with Phocomelia, a congenital deformity in which the child's hands and feet are connected to their trunk instead of their limbs. Researchers later discovered that the clinical trials of the drug were performed using only the R- enantiomer of the molecule. They marketed the drug, however, as a racemic mixture, not realizing the harmful effects that the other enantiomer would have on the fetus. This incident further proves the vulnerability of the fetus during early pregnancy.

Maternal cannabis consumption is harmful for the fetus since expression of Endocannabinoid receptors has been found in the fetus as early as 5 weeks of gestation. The main psychoactive compound in Marijuana, THC, can cross the placenta and activate receptors in the fetal brain and placenta, and cause adverse effects. Researchers have suggested that cannabinoid receptor activation in the placenta may cause stillbirth and miscarriages.

A study analyzed 12,000 women with singleton pregnancies between 18 to 20 weeks of gestation. Five precent self- reported marijuana use before or during pregnancy. Results showed that women who had chronically used marijuana before and throughout pregnancy had offspring with smaller head circumference and shorter birth length than offspring of non- users. (Fergusson et al., 2003)
Another study analyzed 5588 participants. The proportion of women who used marijuana during or before pregnancy was 5.6%, while tobacco use was 24%. Small for Gestational Age infants were born to the marijuana and tobacco users. There were also minimal findings of Spontaneous Preterm Birth and Preeclampsia amongst marijuana users. (Leemaqz, et al., 2016)

A third study involved 3164 participants. Participants self- reported marijuana, alcohol, cocaine, and tobacco use before or during pregnancy. Heavy use of all four substances decreased birth weight by 26%. (Janisse, et al., 2014)

Several studies suggested that marijuana use is associated with stillbirth and early miscarriage. However, no statistically significant findings were reported with marijuana use alone. The largest study performed was conducted by Stillbirth Collaborative Research Network, which studied the impact of drug use and smoking on stillbirth. The study included 663 stillbirth deliveries from 5 different clinical locations over 2 years. The researchers performed cord homogenate toxicology and maternal cotinine assays at the time of delivery. Marijuana use was detected through tetrahydrocannabinolic acid (THC-COOH). There were significant findings of concurrent marijuana and tobacco use associated with stillbirth, but no significant findings with marijuana alone (Varner, et al., 2014).

Implications for Further Research

Although there is a correlation seen between marijuana and negative effects on birth weight and on time delivery, most of the existing research regarding pregnancy and marijuana dates to an era when marijuana use was far less prevalent than it is currently. Additionally, most of the studies relied on self-report and contained relatively small sample sizes. Women may have inaccurately reported their use and there is no biological validation for self-report. Thirdly, many of the studies analyzed the effects of marijuana as well as other substances. The effects cannot be sourced to marijuana alone. More up to date trials with better methodology would be needed to yield significant results.

Marijuana and Lactation

Tetrahydrocannabinol (THC) is 99% protein bound, highly lipid soluble and has low molecular weight. Therefore, it easily travels into human breastmilk. The THC can then activate receptors in the breastfeeding infant's brain or reproductive tract and cause adverse effects. A Non-human primate study recorded that .2% of THC ingested by the mother was found in breastmilk. If a mother uses marijuana 1-2 times per day, the breastfeeding infant may ingest several milligrams of THC daily. However, there is not much significant research that proves the direct effects of marijuana on a breastfeeding infant's development. Several studies were conducted without proper long term follow up. Since there is little evidence, the American College of Obstetricians and Gynecologists (ACOG) recommended Ob/Gyn providers to counsel breastfeeding women against marijuana consumption until future studies can delineate proper clinical guidance. ACOG also recommended that women trying to conceive, and pregnant women should refrain from marijuana consumption.

Conclusion

In conclusion, cannabis disrupts the reproductive system by activating CB1 and CB2 which are present throughout the hypothalamic-pituitary-gonadal axis. In males, significant evidence has proved that Tetrahydrocannabinol, the main psychoactive component in cannabis negatively

affects semen parameters. THC affects sperm production and thereby reduces sperm concentration and quality. It also activates receptors on the sperm, which causes a reduction in motility and normal morphology. CB1 receptor activation on spermatozoa can also inhibit the acrosome reaction and disables fertilization of an oocyte. THC has not been proven to interfere with the functioning of the female menstrual cycle. Although evidence has shown that THC may impact some animal serum hormone concentrations, the human studies did not yield positive results. Weak evidence has been found regarding the effects of marijuana on pregnancy and lactation. Studies show that THC can cross the placenta and breastmilk and can therefore harm the fetus or breastfeeding infant. However, the direct effects in either case have not been researched enough. Despite the inconclusive results, ACOG has recommended against the use of maternal marijuana consumption until studies prove that marijuana is deemed safe enough to use while breastfeeding. Similarly, the American Academy of Pediatrics has also recommended against marijuana use during pregnancy and lactation. Additionally, the American Society for Reproductive Medicine (ASRM) states that a prospective gestational carrier and their partner may not be marijuana users. Emphasis should be placed on educating patients and their partners in the preconception and early pregnancy period about the risks associated with fertility and fetal development when consuming marijuana.

References

Agirregoitia, E., Carracedo, A., Subirá, N., Valdivia, A., Agirregoitia, N., Peralta, L., . . . Irazusta, J. (2010). The CB(2) cannabinoid receptor regulates human sperm cell motility. Retrieved from Fertility and Sterility PMID: 19328464 DOI: 10.1016/j.fertnstert.2009.01.153

Asch, R. H., Smith, C. G., Siler-Khodr, T. M., & Pauerstein, C. J. (1981). Effects of delta 9-tetrahydrocannabinol during the follicular phase of the rhesus monkey . PMID: 6256405 https://doi.org/10.1210/jcem-52-1-50

Brents, L. K. (2016). Marijuana, the Endocannabinoid System and the Female Reproductive System. The Yale Journal of Biology and Medicine 89(2), 175–191.

Cacciola, G., Chioccarelli, T., Ricci, G., Meccariello, R., & Fasano, S. (2008). The endocannabinoid system in vertebrate male reproduction: A comparative overview. PMID: 18342433 DOI: 10.1016/j.mce.2008.01.004

Carroll, K., Pottinger, A. M., Wynter, S., & DaCosta, V. (2019). Marijuana use and its influence on sperm morphology and motility: identified risk for fertility among Jamaican men. Retrieved from Wiley Online Library: onlinelibrary.wiley.com/doi/full/10.1111/andr.12670

Du Plessis, S. S., Agarwal, A., & Syriac, A. (2015). Marijuana, phytocannabinoids, the endocannabinoid system, and male fertility. Journal of assisted reproduction and genetics, 32(11), 1575–1588. https://doi.org/10.1007/s10815-015-0553-8

Fergusson, D. M., Horwood, L. J., & Northstone, K. (2003). Maternal use of cannabis and pregnancy outcome. BJOG international journal of obstectrics and gynecology PMID: 11843371 DOI: 10.1111/j.1471-0528.2002.01020.x

Howlett, A. C., Barth, F., Bonner, T. I., Cabral, G., Casellas, P., Devane, W. A., Felder, C. C., Herkenham, M., Mackie, K., Martin, B. R., Mechoulam, R., & Pertwee, R. G. (2002). International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. Pharmacological reviews, 54(2), 161–202. https://doi.org/10.1124/pr.54.2.161

Janisse, J., Bailey, B., Ager, J., & Sokol, R. (2014). Alcohol, tobacco, cocaine, and marijuana use: relative contributions to preterm delivery and fetal growth restriction. Sage Pub PMID: 24588295 DOI: 10.1080/08897077.2013.804483

Joo K, Kwon Y, Myung S, Kim T. The Effects of Smoking and Alcohol Intake on Sperm Quality: Light and Transmission Electron Microscopy Findings. Journal of International Medical Research. 2012;40(6):2327-2335. doi:10.1177/030006051204000631

Leemaqz, S. Y., Dekker, G. A., McCowanc, L. M., Kenny, L. C., Myers, J. E., Simpson, N. A., . . . Roberts, C. T. (2016). Maternal marijuana use has independent effects on risk for spontaneous preterm birth but not other common late pregnancy complications S. Reproductive Toxicology. PMID: 2714218 DOI: 10.1016/j.reprotox.2016.04.021

Mendelson, J. H., Mello, N. K., & Ellingboe, J. (1985). Acute effects of marihuana smoking on prolactin levels in human females. PMID: 3965692

Mendelson, J. H., Mello, N. K., Ellingboe, J., Skupny, A. S., Lex, B. W., & Griffin, M. (1986). Marihuana smoking suppresses luteinizing hormone in women. PMID: 3012072

Smith, C. G., Besch, N. F., Smith, R. G., & Besch, P. K. (1979). Effect of tetrahydrocannabinol on the hypothalamic-pituitary axis in the ovariectomized rhesus monkey. Doi: 10.1016/s0015-0282(16)43885-9. PMID: 108139.

Tortora, G., & Derrickson, B. (2017). Principles of

Anatomy and Physiology, 15th Edition.

Varner, M. W., Silver, R. M., Rowland Hogue, C. J., Willinger, M. P., Parker, C. B., Thorsten, V. R., . . . Stoll, B. M. (2014). Cite Share Favorites Permissions CONTENTS: ORIGINAL RESEARCH Association Between Stillbirth and Illicit Drug Use and Smoking During Pregnancy. ACOG, 113-125.

Whan, L. B., West, M. C., McClure, N., & Lewis, S. E. (2004). Effects of delta-9-tetrahydrocannabinol, the primary psychoactive cannabinoid in marijuana, on human sperm function in vitro. Retrieved from Fertillity and Sterility: https://doi.org/10.1016/j.fertnstert.2005.08.027.

What are the best Treatment Options for Infantile Cataracts?

Breindy Hecht

Breindy Hecht will graduate with a Bachelor of Science degree in Biology in June 2024.

Abstract

Congenital and infantile cataracts are characterized by opacity of the ocular lens, causing decreased visual acuity and inducing amblyopia. Treatment of pediatric patients is complicated because the eye is still growing during childhood, and the mind-eye connection is developing during this time. Anything that obstructs visual input from the eye to the brain raises risks of permanent visual deficit. Treatment includes immediate cataract extraction; this is sometimes followed by intraocular implantation of an artificial lens. After surgery, treatment continues in the form of occlusive patching therapy, corrective spectacles, or cycloplegic eye drops. Oftentimes, several methods are used simultaneously for maximal outcomes. This literature review discusses treatment options for infantile and congenital cataracts, analyzes the risks and benefits of the available options, and evaluates which options have the most successful long-term outcomes.

Introduction

Although cataracts are common in adults over fifty, their appearance in the pediatric population is rare. Cataracts are a condition that affects the ocular lens, causing it to be cloudy instead of clear. This results in visual impairments or blindness if left untreated. This condition is a leading cause of monocular vision loss in infants and children and is the cause of more visual disability than any other form of treatable blindness (Wang et al., 2021; Wilson, 2015).

The first phase of treatment is to surgically remove and replace the cloudy lens. When this procedure is done for adults, normal vision is restored, and no follow-up treatment is required. However, several unique obstacles arise in the next steps of treating congenital/infantile cataracts. Childhood years are critical for the development of a proper mind-eye connection. Therefore, every moment of obstructed vision interferes with visual development and induces amblyopia (Wang et al., 2021).

Amblyopia, often referred to as a "lazy eye," is a condition caused when a child's eye has a disparate visual ability compared to the fellow eye. This causes the brain to turn off nerve signaling from the weaker eye, relying solely on the stronger eye for visual input. If left untreated, amblyopia can cause lifelong vision impairment, as treatment is largely ineffective once a person reaches adulthood due to decreased neuroplasticity at that stage (Boyd, 2023).

Additionally, a child's eyes are rapidly growing during the first few years of life, which shifts the ocular focus and, over time, alters vision. Because these changes are unpredictable, evaluating a suitable lens power for an intraocular lens replacement in a child is difficult (VanderVeen et al., 2012).

Treating and managing pediatric cataracts is challenging and involves years of collaboration between parents, primary care pediatricians, surgeons, orthoptists, and community health workers to achieve successful outcomes (Wilson, 2015). Although technological advances have allowed for better treatment, further research is ongoing to assess the effectiveness of the available treatment options and their potential challenges/complications. This review aims to examine and determine which treatment options best serve the growing child's long-term vision and binocularity.

Methods

The studies reviewed and analyzed in this paper were accessed from the databases of Google Scholar, PubMed, and JAMA Ophthalmology. Keywords included congenital cataracts, aphakia, pseudophakia, intraocular lens, amblyopia, glaucoma, and occlusive patching.

Discussion

Cataract Surgery

Childhood cataracts must be removed in a timely manner, or the child will be left with permanent visual deficits. The surgery itself consists of a lensectomy to remove the clouded lens and leaves behind a clear visual axis (Yorston, 2004).

Aphakia versus Pseudophakia

Prior to surgery, the parents and medical team decide if the child should receive a replacement lens intraocularly or not. When cataract surgery is performed, and the patient does not receive an intraocular lens (IOL) implantation, the child is considered aphakic (i.e., lacking a lens in the eye). An aphakic child is typically prescribed a corrective contact lens after surgical treatment. Alternatively, some children have an artificial lens permanently implanted during surgery. Such a child is said to have pseudophakia, literally defined as a "fake lens." The decision is complex and requires case-by-case evaluation.

Several studies compare vision outcomes in infants with aphakia versus those with pseudophakia. A crucial factor in reestablishing normal vision of the eye post-cataract surgery is compliance with the prescribed refractive correction. One study performed by the Infant Aphakia Treatment Study (IATS) demonstrated a marked difference in compliance with refractive correction of aphakic versus pseudophakic patients. Caregivers of aphakic infants reported that the prescribed optical correction (corrective contact lenses and spectacles as indicated) was worn by the child at least 95% of waking hours. In contrast, the pseudophakic infants had only a 50% median use of spectacles during waking hours. However, the pseudophakic group was at an advantage because the intraocular lens was always in place and never falls out

or needs to be changed. This increased compliance was found to be correlated with superior visual outcomes (Drews-Botsch et al., 2012). These findings correlate ease of treatment with treatment outcomes. When a patient receives an IOL, it is implanted permanently and does not require handling on an ongoing basis. Conversely, a patient who had a lens removed but not intraocularly replaced requires more ongoing intervention. This intervention includes routinely removing and replacing the press-on contact lens and ensuring that the lens remains properly placed on the eye.

Another study trended the same factors in a similar study performed on 60 infants. The infants were randomly assigned to group A, IOL implantation with corrective spectacles as needed, or group B, press-on spherical lens and spectacles. Although both groups had significantly improved visual acuity one year after surgery, subjects in group A had visual outcomes that were greater than those in group B. Similar to the previous study, adherence was greater in group A, the IOL group (Li et al., 2014). These findings are significant because refractive correction alone has been found to improve visual acuity. In some cases, this can be enough to lead to the resolution of amblyopia in children (Cotter, 2006). It is apparent from these studies that the increased adherence to prescribed treatment of the IOL group contributed to their enhanced visual outcomes at the one-year post-surgery mark.

Predictability of Intraocular Lens Power

A child's eyes are still growing, which shifts the focus of the lens and causes changes in the prescription of the eye. Because the growth of a child's eye is not predictable, evaluating the correct power lens to implant in a child's eye permanently is a complex task. Precise and consistent biometric data for IOL power is difficult to obtain. This is due to the poor cooperation of young patients and the limitations of the available equipment used to measure the eyes (VanderVeen et al., 2012).

Additional factors that complicate eye measurement include short axial length, steep cornea, shallow anterior chamber depth, dense cataracts, and dense vitreous. These conditions are particularly prevalent among pediatric patients, and all contribute to biometry errors. Additionally, the formulas to measure refractive error and predict lens power use data from adult eyes. There are several structural differences in pediatric eyes; therefore, using the adult formula results in inaccurate measurements in children. These inaccuracies may be insignificant after surgery; however, as the infantile eye matures, the refractive error grows. Ultimately, this results in a large disparate error by the time the patient reaches adulthood. Therefore, a patient given an inaccurate IOL implantation as a child will be wearing thick, heavy glasses by the time s/he reaches adulthood to compensate for the error (Shuaib et al., 2021).

Another study was conducted on 40 children who underwent successful cataract extraction and IOL implantation. Biometric and refractive data analysis revealed that children under 36 months of age or with exceptionally small axial lengths (< 20 mm) still had significant refractive errors after surgery. These errors, averaging greater than one diopter, demonstrate the great need for an IOL prediction formula specifically designed for infants and children (Tromans et al., 2001).

An additional study analyzed the accuracy of predicted refraction compared to actual post-op measures. When refractive measurements were taken two months after surgery, there was already a notable error averaging 1.2 to 1.4 diopters (Andreo & Wilson, 1997). These studies highlight an important question: Is IOL implantation the best option for the treatment of infantile cataracts, given the high degree of refractive error that remains?

Surgical Complications

Surgical treatment decisions need to be considered in relation to the relative complexity of the surgery. A lensectomy followed by IOL implantation is a more complex surgery, and therefore has increased risks of complications. Common complications after cataract surgery include visual axis opacification and glaucoma.

Visual axis opacification occurs when epithelial cells on the lens capsule continue to rapidly divide. These divisions, caused by increased mitotic activity in children, result in lens opacification and the formation of a membrane across the pupil. This opacification occurs in an estimated 40% of IOL patients. It causes continued visual obstruction and decreased optical image quality. Visual axis opacification disrupts the mind-eye connection and causes persistent amblyopia even after cataract extraction (Shrestha & Shrestha, 2014).

This complication was investigated in a study of 144 infants, that evaluated the incidence of visual axis opacifications and pupillary membrane formation after pediatric cataract surgery. Included in the study were 68 pseudophakic infants and 76 aphakic infants. The rate of pupillary membrane formation in the pseudophakic group was found to be significantly higher than in the aphakic group. Forty percent of the pseudophakic group were diagnosed with pupillary membrane formation, of which 72% required a second surgery for correction. Conversely, only 7% of the aphakic eyes had pupillary membrane formation. Of that small percentage, only 16%

required secondary surgery for visual axis opacification (Hložánek et al., 2023).

A similar study performed several years earlier supports these findings. It was noted that 12.1% of the aphakic group required a second procedure for visual axis opacification, compared to 80.0% in the pseudophakic group (Plager et al., 2002). These studies reflect the need for careful consideration before deciding to implant an IOL in a child.

Another common postoperative complication is the development of glaucoma, an eye disease that damages the optic nerve and causes permanent vision loss. Glaucoma-related adverse effects often develop 1-2 years following cataract surgery (Wang et al., 2020). Studies have been performed with a focus on the rate of post-op glaucoma development.

In the first study, The Pediatric Eye Disease Investigator Group collected data from 810 children. It assessed the correlation between IOL implantation and the development of glaucoma post-lensectomy. Data collected within five years after surgery found that 29% of pseudophakic eyes and only 7% of aphakic eyes developed glaucoma. Furthermore, glaucoma surgery was necessary for 7% of pseudophakic eyes and only 0.5% of aphakic eyes (Bothun et al., 2023).

These findings are reflected in another study, which included 368 children who underwent cataract surgery. Two hundred and seventy-seven patients were treated with IOL implantations, and the remaining 148 patients had cataract surgery without intraocular lens replacement. In the pseudophakic group, there were no signs of glaucoma development within 16 months after surgery. Conversely, the aphakic group had a 4.8% incidence of glaucoma development within the same timeframe. (Sahin et al., 2023). This study showed a relatively higher incidence of glaucoma-related adverse events in aphakic patients. Limited conclusions can be made based on this, because the experiment was done on a small scale and does not include long-term treatment results. However, glaucoma development is a significant risk, and the likelihood of development must be accounted for when evaluating the treatment of pediatric cataracts.

Treatment of Amblyopia

Following a successful cataract extraction, a significant barrier to visual rehabilitation is amblyopia. Treatment of amblyopia involves forcing the use of the weaker eye by covering or temporarily blurring vision in the dominant eye.

The first line of treatment for amblyopia is the use of an eye patch to occlude the non-amblyopic eye. This serves to reestablish the mind-eye connection (Von Noorden, 1974). A frequent issue is that children demonstrate poor adherence and remove the patch earlier than recommended, leading to suboptimal treatment results. This issue is the factor most strongly associated with poor visual acuity in children following treatment for unilateral cataracts (Drews-Botsch et al., 2012; Wallace et al., 2018).

A study that illustrates this was conducted by the IATS on 114 infants, all of whom had unilateral cataract surgery performed between the ages of 1-6 months. A daily patching regimen was prescribed, beginning two weeks after cataract surgery and extending until 12 months of age. During this time, caregivers reported data on their compliance with the prescribed therapy. All infants had regular examinations by certified IATS investigators to assess optical correction and visual acuity. Infants who had better adherence had visual outcomes that were notably superior at 12 months than those with poorer compliance. The statistical data showed that those who reported at least 75% compliance had the best visual outcomes (Drews-Botsch et al., 2012). These findings support patching therapy as a safe, non-invasive, and effective treatment of amblyopia.

In cases of poor compliance, a pharmacological agent can be used to prevent accommodation of the non-amblyopic eye. This involves instilling a cycloplegic agent, which temporarily blurs vision. Typically, ophthalmic Atropine Sulfate 1% solution is instilled into the non-amblyopic eye, which relaxes the eye muscles (Repka et al., 1985).

The efficacy of this treatment was evaluated in a randomized study that compared visual outcomes of patching versus ophthalmic atropine. In one group, participants were prescribed an occlusive patching regimen with a personalized protocol for patching based on the child's age and the severity of amblyopia present. In the second group, participants were treated with one drop of atropine 1% in the conjunctival fornix of the non-amblyopic eye each morning. Parents of participants in both groups were asked to rate compliance, and providers assessed visual acuity at regular intervals. Following treatment, both groups showed statistically significant improved vision. Even though treatment compliance was higher in the atropine group, the patching group scored notably higher on visual acuity testing. It is believed that the lower success rate of the atropine group was caused by insufficient blurring of the non-amblyopic eye. Ultimately, in cases where conventional occlusion therapy is not feasible due to skin sensitivity, emotional issues, or lack of cooperation, blurring the dominant eye is a somewhat effective alternative treatment (Foley-Nolan et al., 1997).

Another treatment protocol combining atropine and patching therapy (CAPT) was evaluated for effectiveness

in cases of severe amblyopia. This solves the problem of treatment failure due to poor patching adherence without the concern of insufficient blurring by atropine. To this end, 108 amblyopic children were randomly assigned to either receive a daily regimen of patching and atropine therapy or patching therapy alone. Participants of both groups received patching therapy for six continuous hours per day. In the CAPT group, ophthalmic atropine 1% was administered on a daily schedule. All participants had examinations for baseline measurements and follow-up examinations at regular intervals. The results of this study found greater improvements in the CAPT group. However, both groups showed significant improvement, with only a small difference between them (Wang et al., 2021). These findings are in line with previous studies that demonstrate the efficacy of patching therapy.

Conclusion

Based on the above research, it is clear that cataract surgery without IOL implantation is the preferable treatment. This is due to the high rate of complications associated with IOL implantation and the incidence of inaccurate IOL power predictions. Although pseudophakia seems better for the treatment of amblyopia, experimental data has not found this to be a significant factor contributing to superior vision outcomes. The risk of surgical complications is greater with IOL placement, and in many cases, IOL placement alone is not sufficient treatment to restore binocular vision. Therefore, it is better to leave a child aphakic and use a press-on contact lens and/or prescription spectacles after surgery. This provides the child with proper refractive correction while eliminating the risks associated with IOL implantation.

Regardless of whether or not an IOL is implanted, prompt and consistent treatment of amblyopia is of utmost importance for optimal visual outcomes. To best achieve these results, occlusive patching is the first line of treatment. The use of blurring eye drops is less effective. It can be used in conjunction with patching therapy but is insufficient as a stand-alone treatment. Cataract treatment by lensectomy without IOL implantation, followed by patching therapy, is adequately supported as the most effective treatment for infantile cataracts.

References

Andreo, L., & Wilson, E. (1997). Predictive value of regression and theoretical IOL formulas in pediatric intraocular lens implantation - PubMed. PubMed. http://pubmed.ncbi.nlm.nih.gov/9253739/

Bothun, E., Repka, M., Kraker, R., Wu, R., Leske, D., Hatt, S., Li, Z., Freedman, S., Astle, W., Cotter, S., & Holmes, J. (2023, February 16). Incidence of Glaucoma-Related Adverse Events in the First 5 Years After Pediatric Lensectomy. JAMA Network; JAMA Network. https://jamanetwork.com/journals/jamaophthalmology/fullarticle/2801365

Boyd, K. (2023, November 11). Amblyopia: What Is Lazy Eye? - American Academy of Ophthalmology. American Academy of Ophthalmology. https://www.aao.org/eye-health/diseases/amblyopia-lazy-eye

Cotter, S. (2006, June). Treatment of Anisometropic Amblyopia in Children with Refractive Correction. American Academy of Ophthalmology. https://doi.org/10.1016/j.ophtha.2006.01.068

Drews-Botsch, C. D., Celano, M., Kruger, S., & Hartmann, E. E. (2012). Adherence to Occlusion Therapy in the First Six Months of Follow-Up and Visual Acuity among Participants in the Infant Aphakia Treatment Study (IATS). Investigative Ophthalmology & Visual Science, 7, 3368. https://doi.org/10.1167/iovs.11-8457

Foley-Nolan, A., McCann, A., & O'Keefe, M. (1997). Atropine penalisation versus occlusion as the primary treatment for amblyopia. British Journal of Ophthalmology. https://doi.org/10.1136/bjo.81.1.54

Hložánek, M., Cilečková, L., Alió, J., Autrata, R., Zelenayová, N., Komínek, M., Cendelín, J., & Mahelkova, G. (2023, June). Risk of visual axis opacification in infants with and without primary IOL implantation after congenital cataract surgery performed during the first 4 months of age - PMC. PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10667373/

Li, Q., Fu, T., Li, Z.-E., Bi, H.-S., Wang, X.-R., Dong, M., & Xin, T. (2014, December). Optical correction of aphakia following unilateral infantile cataract removal. PubMed. https://pubmed.ncbi.nlm.nih.gov/24930475/

Plager, D., Yang, S., Neely, D., Sprunger, D., & Sundhi, N. (2002, September). Complications in the first year following cataract surgery with and without IOL in infants and older children. PubMed; JAAPOS. https://pubmed.ncbi.nlm.nih.gov/11907473/

Repka, M. X., Gallin, P. F., Scholz, R. T., & Guyton, D. L. (1985, November). Determination of optical penalization by vectographic fixation reversal . PubMed. https://pubmed.ncbi.nlm.nih.gov/4080330/

Sahin, A., Caca, I., Kürşat Cingü, A., Mehmet Türkcü, F., Yüksel, H., Sahin, M., Cinar, Y., & Ari, S. (2023, April 18). Secondary glaucoma after pediatric cataract surgery. PubMed. https://pubmed.ncbi.nlm.nih.gov/23638427/

Shrestha, U. D., & Shrestha, M. K. (2014). Visual Axis Opacification in Children Following Paediatric Cataract Surgery. PubMed; Journal of Nepal Medial Association. https://pubmed.ncbi.nlm.nih.gov/26982905/

Shuaib, A. M., Elhusseiny, A. M., Hassanein, D. H., Zedan, R., & Elhilali, H. M. (2021, June 17). Predictive Value of Intraocular Lens Power Calculation Formulae in Children . PubMed Central (PMC). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8216728/

Tromans, C., Haigh, P. M., Biswas, S., & Lloyd, C. (2001, August). Accuracy of intraocular lens power calculation in paediatric cataract surgery. PubMed. https://pubmed.ncbi.nlm.nih.gov/11466250/

VanderVeen, D., Nizam, A., Lynn, M., Bothun, E., McClatchey, S., Weakley, D., Dubois, L., & Lambert, S. (2012, March 1). Predictability of Intraocular Lens Calculation and Early Refractive Status: The Infant Aphakia Treatment Study | Ophthalmology | JAMA Ophthalmology | JAMA Network. JAMA Network; JAMA Network. https://jamanetwork.com/journals/jamaophthalmology/fullarticle/1148428

VonNoorden, G. (1974). Factors involved in the production of amblyopia. Europe PMC; Europe PMC. https://europepmc.org/article/PMC/1214727

Wallace, D. K., Repka, M. X., Lee, K., Melia, M., Christiansen, S. P., Morse, C. L., & Sprunger, D. (2018, January). Amblyopia Preferred Practice Pattern. PubMed. https://pubmed.ncbi.nlm.nih.gov/29108744/

Wang, J., Chen, J., Chen, W., Wang, Q., Zhao, L., Wang, R., Liu, Z., Chen, H., Cao, Q., Tan, X., Lin, Z., Li, X., Li, J., Lai, W., Zhu, Y., Chen, C., Zheng, D., Wu, M., Han, Y., … Lin, H. (2020, January). Incidence of and Risk Factors for Suspected Glaucoma and Glaucoma After Congenital and Infantile Cataract Surgery: A Longitudinal Study in China. PubMed. https://pubmed.ncbi.nlm.nih.gov/31688374/

Wang, S., Wen, W., Zhu, W., Liu, Y., Zou, L., Tian, T., Lin, J., Tech, J., Liu, R., & Liu, H. (2021, July 1). Effect of Combined Atropine and Patching vs Patching Alone for Treatment of Severe Amblyopia in Children Aged 3 to 12 Years: A Randomized Clinical Trial. JAMA Network; JAMA Network. https://jamanetwork.com/journals/jamaophthalmology/fullarticle/2781899

Wilson, M. E. (2015, November 11). Pediatric Cataracts: Overview. American Academy of Ophthalmology; American Academy of Ophthalmology. https://www.aao.org/education/disease-review/pediatric-cataracts-overview

Yorston, D. (2004). Surgery for Congenital Cataract. PubMed Central. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1705722/

What is Aphthous Stomatitis? What are the Possible Causes and Treatments?

Shirah Balakhane

Shirah Balakhane will graduate in June 2024 with a Bachelor of Science degree in Biology and a minor in Psychology and is accepted to Touro College of Dental Medicine.

Abstract

The historical understanding of Recurrent Aphthous Stomatitis (RAS), also known as canker sores, has evolved. This paper aims to collect data that determines the underlying factors that can cause RAS and highlights treatments or preventive measures one should take. RAS is a common mucosal disease of the mouth that affects healthy people and presents atypically in immunocompromised people. Geographical, age, and gender-related factors can all affect the prevalence. RAS still has no known cause; however, several systemic, local, immunologic, genetic, dietary, allergy, and microbiological factors—including immunosuppressive medications and stress—have been suggested as potential culprits. Using topical and systemic medicines, the clinical therapy of RAS is based on the number, size, frequency, and severity of lesions. Reduction of pain and ulcer size, promotion of healing, and reduction in recurrence frequency are the objectives of these therapies.

Introduction

The most prevalent ulcerative illness of the oral mucosa is recurrent aphthous stomatitis (RAS), which manifests as painful, shallow, circular ulcers with a precisely outlined erythematous border and a yellowish-gray pseudomembranous core, usually measuring 3 to 5 mm and displaying a centrally adhering yellowish exudate along with an erythematous peripheral rim. Before an ulcer forms, RAS is characterized by a distinctive prodromal burning feeling that lasts for two to forty-eight hours (Akintoye & Greenberg, 2014). RAS is defined by the recurrent formation of one or more distinct, painful ulcers, which heal in 7–14 days on average. Individuals may either report occasional lesions or experience such frequent occurrences that the ulcers are practically always active. Usually found on the tongue, buccal, and labial mucosa, it occurs in otherwise healthy people. It less frequently involves the highly keratinized mucosa of the gingiva and palate (Akintoye & Greenberg, 2014).

Background

RAS is a common oral lesion, affecting approximately 10-20% of the population. A population-based study found that 13.2% of participants had RAS. Risk factors associated with RAS include being female, history of rheumatic diseases, joint swelling and lower back pain are (Kiraz et al., 2015). A variety of autoimmune and inflammatory disorders as well as mucosal damage are recognized as causes of mouth ulcers. For instance, mouth ulcers are frequently seen in people with systemic lupus erythematosus, ulcerative colitis, and Crohn's disease. They are also thought to be a diagnostic characteristic of Behçet's disease, an inflammatory blood vessel illness that results in ulceration of the mouth, eyes, and genitalia (Dudding et al., 2019).

Immunological modulation is essential for mediating tissue damage and the clinical manifestation of RAS, regardless of the original trigger. In those who are susceptible, there is a proliferative healing phase and the loss of surface mucosa after a localized infiltration of monocytes and T lymphocytes into the oral mucosa that extends deep below the basal membrane. T-cell modulation may contribute to the etiology, as suggested by in-silico functional analysis, by examining genetic variants and gene expression (Dudding et al., 2019). There is also a suggestion that the T-cell-mediated response observed in RAS is a result of Streptococcus sanguinis antigens damaging the oral mucosa through a cross-reaction with mitochondrial heat shock proteins (Plewa & Chatterjee, 2021).

Part of the reason there is a lack of adequate treatment is due to the uncertainty of the cause (Al-Maweri et al., 2020). Causes for aphthous stomatitis ulcer can be very different for each individual. When it comes to finding the factors that can extend from "stress and trauma to strawberries and toothpaste with sodium lauryl sulfate. Even stopping smoking can cause lesions to occur (DDS, 2019)."

Etiology

Family-based studies tend to back up the hypothesis that RAS to some extent has some genetic predisposition, however, RAS's etiology is still not fully known (Dudding et al., 2019). It is thought that a combination of a genetic predisposition and a cell-mediated immune response are the causes. Changes in histology are visible before ulceration. The oral epithelium is invaded by lymphocytes; this results in edema, vacuolization, and vasculitis of the keratinocytes. This causes the epithelium to enlarge locally before eventually becoming ulcerated. Before the epithelium heals and regenerates, neutrophils, lymphocytes, and plasma cells infiltrate the area. Tumor necrosis factor-alpha, an inflammatory cytokine, is involved in the T-cell-mediated immunological response that provides the pathophysiology of RAS. Major Histocompatibility Complex (MHC) expression and an initial inflammatory response are caused by TNF-α activating neutrophil chemotaxis. As a result, the CD8+ T lymphocytes target the epithelial cells for destruction (Plewa & Chatterjee, 2021).

With varying degrees of success, earlier candidate gene association studies have looked into variations in the regions of genes producing important cytokines TNF-α, IL-1α, IL-1β, IL-6, IL-10, and IL-12. Gene variations linked

to sensitivity to early triggers and the immune response that causes tissue damage and ulcer formation may be found by genome-wide association studies (GWAS). In a recent study, a collection of cases of patients with systemic lupus erythematosus were examined to find correlations between gene pathways and particular sub-phenotypic traits, such as oral ulcers, using genome-wide data. The study discovered a few findings linking the oral ulcer sub-phenotype to the vascular endothelial growth factor (VEGF) pathway (Dudding et al., 2019).

There are no prior traditional genome-wide association studies for RAS or mouth ulcers, and it is unclear how these findings apply to the broader population. Consequently, a genome-wide investigation for RAS is necessary, yet big cohorts lack particular measures. Using large databases to find and reproduce linked genetic variants in a "well-powered GWAS of self-reported non-specific mouth ulcers" is the most appropriate approach, considering the data available. The effects of these variants can then be validated in smaller collections using more clinically relevant RAS-specific measures. This genome-wide association study reproduces its findings in a separate cohort and reveals 97 variations that change the risk of getting non-specific mouth ulcers (Dudding et al., 2019).

According to Audrey L Boros (2019), " There's no age, gender, or race predilection, but there is a familial tendency based on human leukocyte antigen (HLA) types (DDS, 2019)." RAS has a hereditary propensity; between 24 and 46 percent of patients have a family history of the illness. Typically, ulceration occurs more quickly and severely in these people. There is a known connection between HLA-B51 and the genes that regulate heat shock proteins or cytokines (Plewa & Chatterjee, 2021). The most established primary trigger for RAS is genetics. The existence of RAS in one or both parents greatly increases predisposition to it. Research on identical twins has also shown that this condition is inherited. People who have a positive family history of RAS are more likely to experience RAS early in life. Children born to two RAS-positive parents are 90% more likely to acquire RAS, which is characterized by severe signs and more frequent recurrences. RAS patients have been found to carry certain genetic variants of the HLAs HLA-A2, HLA-B5, HLA-B12, HLA-B44, HLA-B51, HLA-B52, HLA-DR2, HLA-DR7, and HLA-DQ series. The fact that several ethnic groups have been linked to distinct HLA alleles or haplotypes without any HLA that is consistently linked to RAS is a confusing discovery (Akintoye & Greenberg, 2014). These findings offer a fresh understanding of the pathophysiology of a prevalent and significant ailment.

Predisposing Factors

Older individuals are less likely to develop RAS. Alcohol consumption and smoking may reduce RAS. The exact cause of RAS remains unclear and is considered multifactorial. Some causes may be: immune system dysregulation, allergic reactions triggering RAS, diet and nutrient deficiencies, infections or microbial imbalances, and certain drugs may influence RAS occurrence (Kiraz et al., 2015). Trauma to certain parts of the oral mucosa can also increase the likelihood of developing recurrent aphthous ulcers (Plewa & Chatterjee, 2021). In those who are vulnerable to stress, local trauma is thought to be the cause of RAS. Trauma causes edema and early cellular inflammation linked to an increase in the viscosity of the extracellular matrix in the oral submucosa, which predisposes to RAS. Denture wearers do not have a high prevalence of RAS, while being three times more sensitive to oral mucosal ulceration, suggesting that not all oral trauma results in RAS (Akintoye & Greenberg, 2014).

Furthermore, persistent smokers who expose their oral mucosa to nicotine regularly have shown a negative correlation between smoking and RAS. Therefore, it appears that only people with a genetic predisposition to the disease are at risk for developing RAS due to local stress (Akintoye & Greenberg, 2014). Some individuals may be more prone to developing recurrent aphthous stomatitis due to either their susceptibility or a genetic predisposition inherited from their family. Recurrent aphthous stomatitis tends to occur less frequently in areas of the mouth where the tissue is keratinized, therefore tobacco smokers are less likely to experience RAS (Plewa & Chatterjee, 2021). Certain patients with recurrent aphthous stomatitis have been shown to have hematinic deficiencies, a deficiency in zinc, iron, folic acid, or vitamin B12. Patients with hematinic deficiencies will have RAS twice as frequently. Low hematinic acid levels can lead to anemia, which in turn can reduce the blood's ability to deliver oxygen to the cells in the oral mucosa, potentially causing atrophy or degeneration of the oral epithelial cells. However, iron or vitamin supplements don't always make lesions go away. RAS may indicate the presence of bowel diseases such as ulcerative colitis, gluten-sensitive enteropathy, and Crohn's disease. On the other hand, hematinic malabsorption defects may be the cause of the ulcerations. Human Immunodeficiency Virus (HIV) patients are more susceptible to RAS due to decreased CD4 lymphocyte levels and increased CD8 lymphocyte levels (Plewa & Chatterjee, 2021).

Epidemiology

RAS frequency, amongst communities, ranges from 5% to 25%. Depending on the study's design and methodology,

as well as the origins of the individuals and groups under investigation, these kinds of notable variances have been documented (Ślebioda et al., 2013). RAS affects 20% of the population in general, however, the incidence varies from 5% to 50% according to the socioeconomic and ethnic groups that are researched. Environmental factors, diagnostic standards, and the population under study all have an impact on the occurrence of RAS. The presence of RAS in one or both parents can have an impact on the prevalence of RAS in children, which can reach 39%. Compared to 20% of children with RAS-negative parents, those with RAS-positive parents had a 90% risk of acquiring RAS. RAS is five times more common and accounts for 50% of oral mucosal lesions in children from high socioeconomic backgrounds (Akintoye & Greenberg, 2014).

Usually, it first manifests throughout adolescence or childhood. It could manifest as a standalone ailment or as a component of a larger illness, such as Behçet disease (Plewa & Chatterjee, 2021). A cross-sectional study that was performed in the Health Management Center, Xiangya Hospital, Central South University in Changsha city, Hunan province, showed that the physician population has a higher prevalence of RAS due to inadequate sleep and stress (Liu et al., 2022). When comparing RAS prevalence among professional school students to the same subjects 12 years later, after they had entered the workforce, it was discovered that the male had a higher prevalence (male, 48.3%; female, 57.2%). This result led some researchers to hypothesize that stress experienced by a student is a significant contributor to RAS, although age-related variations should also be taken into account. RAS seems to peak between the ages of 10 and 19 and then becomes less common as one ages or moves to a different location. If RAS develops during the third decade and continues to worsen well into adulthood, there should be more reason to suspect that an underlying medical problem, such as connective tissue disease, hematologic illness, or immunologic dysfunction, may be the cause of the syndrome (Akintoye & Greenberg, 2014).

Types of Aphthous Stomatitis

All the different types of aphthous stomatitis will be on moveable mucosa and typically will have an erythematous halo around the ulcer (DDS, 2019). "Moveable Mucosa" refers to the flexible and mobile lining inside the oral cavity, also known as the oral mucosa. Persistently painful mouth ulcers that continue for days to months are a hallmark of recurrent aphthous stomatitis (Plewa & Chatterjee, 2021). RAS is further divided into three subgroups: Minor Aphthous Ulcers, Major Aphthous Ulcers, and Herpetiform Aphthous Ulcers.

Minor Aphthous Ulcers

Roughly 80% of RAS patients have minor aphthous ulcers, which are the most prevalent kind of the condition. They happen again every one to four months. The lesions are round or oval in shape, typically smaller than 5 mm in diameter, and manifest as one to six ulcers at a time. The lesions are coated in a gray white pseudomembrane and have an erythematous halo surrounding them. Minor RAS primarily affects non-keratinized mucosa, particularly the floor of the mouth, buccal, and labial mucosa. It heals completely within two weeks. The aphthous lesions may be preceded by oral pain (Plewa & Chatterjee, 2021).

Major Aphthous Ulcers

Major aphthous stomatitis, alternatively named Sutton's disease or Periadenitis Mucosa Necrotica recurrens, affects roughly 10% of RAS patients (Akintoye & Greenberg, 2014). These ulcers are a more severe form of the condition. The ulcers are larger (>10 mm), typically leave scars, and last for 5 to 10 weeks. Any part of the mouth, including the oropharynx, could be impacted. The most common form of RAS in AIDS patients is major aphthous ulcers, and there is a stronger correlation between these lesions and hematological and gastrointestinal issues. These ulcers typically don't adhere to a predictable pattern (Plewa & Chatterjee, 2021). Additionally, they are found to be deeper than minor aphthous ulcers, while typically being rounded with well-defined boundaries, but when they are very big, they might have uneven edges (Mayo Clinic, 2018). Major aphthous ulcer can be seen on the lower lip, the maxillary unattached gingiva, and the anterior tongue. All of the ulcers will have a distinctive feature of an erythematous halo with a central yellowish gray pseudomembrane (Akintoye & Greenberg, 2014).

Herpetiform Aphthous Ulcers

The least prevalent kind of RAS, herpetiform ulceration, affects 1% to 10% of patients. There is no relationship to herpes viruses; rather, the name comes from the similarity to primary herpetic stomatitis. Compared to other types of recurrent aphthous stomatitis, they most often affect women and manifest at a later age (Akintoye & Greenberg, 2014). The lesions look like countless, tiny, painful ulcers. Up to 100 ulcers may appear at once, each with a diameter of 2 to 3 mm for a duration of one to two weeks. The tongue's tip and lateral edges, as well as the floor of the mouth, are the most common locations. They could show up on mucosa that is keratinized or not. Occasionally, the little ulcers may merge to form a larger, uneven ulcer that leaves scars behind (Plewa & Chatterjee, 2021). Herpetiform aphthous ulcer can be seen on the mandibular buccal fold (Shah et al., 2016).

Herpes

Herpes simplex viruses can cause sores on the skin or mucous membranes, including but not limited to the areas around the mouth, lips, genitalia, and rectum. Usually, the sores start as blisters that burst and leave tender sores behind. Both nonprofessionals and doctors frequently mistake RAS for herpes simplex virus (HSV) infection, even though multiple research studies have not shown an etiological association between RAS and the virus. Neither HSV virus nor antigens have been found in aphthous lesions nor have they been effectively separated from RAS biopsy tissues. There is a suggestion that the reactivation of certain viruses (varicella-zoster virus and human cytomegalovirus) might be linked to the frequent recurrence of aphthous ulcers. To explore this association, researchers conducted evaluations of biopsy tissue from individuals with RAS. The researchers used a technique called polymerase chain reaction (PCR) to check for the presence of viruses (HV6, CMV, VZV, EBV) in the biopsy samples. Despite the suggestion of an association, the PCR analysis did not detect the presence of these viruses as causative factors for recurrent aphthous ulcers. Given the lack of evidence for a viral cause, it is the responsibility of medical professionals to distinguish RAS from herpes infections. Medical professionals should reassure RAS patients that they do not have an infectious disease and that antiviral therapy is not necessary nor effective for RAS (Akintoye & Greenberg, 2014). To tell the difference between herpes and aphthous stomatitis in a healthy patient, one must know that aphthous stomatitis is only seen on moveable mucosa. However, herpes is only found on attached mucosa (DDS, 2019).

Behçet Disease

To diagnose someone with Behçet disease the patient will have recurrent aphthous stomatitis. Behçet illness is a chronic inflammatory ailment affecting the genitalia, eyes, skin, joints, and mucosa of the mouth that has an unclear cause. The condition's defining feature, mucocutaneous lesions, typically manifest first. Behçet disease should be suspected if oral aphthous ulcerations appear along with ulcers in other body areas (Plewa & Chatterjee, 2021).

Evaluation

When taking a biopsy of an aphthous ulcer, no report will be given because the findings are nonspecific. The tissue has a hyperkeratotic outer layer and the inner layer, towards the middle, proves that it's nonspecific. To achieve the diagnosis of aphthous ulcers, a clinical diagnosis must be done (DDS, 2019). However, when RAS occurs suddenly in an adult patient, it is important to rule out other possible reasons for recurrent aphthous ulcers in the mouth, such as Behçet disease, nutritional deficits, or inflammatory bowel disease, and doing additional testing as necessary (Plewa & Chatterjee, 2021).

Treatment

Recurrent aphthous stomatitis (RAS) has no established cure; instead, treatment aims to keep the lesions under control as long as possible with the least number of adverse effects. The degree of pain, the frequency of ulcers, the patient's medical history, and their medication tolerance all have an impact on the treatment plan. It is imperative to identify and manage any contributing factors that might be causing aphthous ulcers before starting focused treatment. The principal aims during treatment are to mitigate symptoms, lessen the intensity of ulcers (both in quantity and dimensions), encourage recovery, and prolong the times without illness (Plewa & Chatterjee, 2021). Topical corticosteroids and non-steroidal anti-inflammatory drugs (NSAIDs) are typically used to treat milder episodes of RAS (Lau & Smith, 2022). Mouthwash with chlorhexidine and benzydamine is an example of a topical corticosteroid. This method aids in preventing further bacterial infections. In certain situations, a topical tetracycline plus steroid combination may be taken into consideration (Plewa & Chatterjee, 2021) .

In cases of extreme severity, particularly when significant aphthous ulcers are involved, a brief course of systemic steroids, like prednisone, may be recommended (Lau & Smith, 2022). Systemic steroid use should be discouraged for an extended period due to serious side effects. Herpetiform ulceration is typically treated in the same way as small aphthous ulcers. Topical corticosteroids and mouthwash containing chlorhexidine gluconate have been demonstrated to lessen the intensity and length of aphthous ulcers. They are beneficial in curing and relieving symptoms, but they don't always reduce the frequency of breakouts. Applying topical corticosteroids during the prodromal phase, the initial stage before an episode of aphthous ulcers manifests as tingling or burning sensations in the patient, may prove to be most beneficial (Plewa & Chatterjee, 2021). It has been suggested that doxycycline, a more recent semisynthetic tetracycline, possesses stronger anti-inflammatory and anti-collagenase qualities than other tetracyclines. More precisely, it efficiently inhibits the gelatinolytic effects of collagenases, suppresses leukocyte activity and prostaglandin production, and downregulates matrix metalloproteinase collagenase, an interstitial collagenase that is believed to be crucial for tissue destruction events in RAS. Based on the current systematic review and meta-analysis, we can conclude that, in patients with RAS, a single topical application of doxycycline shows promise in

lowering discomfort and speeding up the healing process, within the constraints of the evidence currently available (Al-Maweri et al., 2020).

Conclusion

Recurrent aphthous stomatitis (RAS) is a complicated and multidimensional oral mucosal disease with a wide range of clinical symptoms. The precise cause of RAS is still unknown after a great deal of research. However, the causes seem to be a result of a mix of environmental influences, immune system dysregulation, and genetic predisposition. Different demographics have different rates of RAS depending on characteristics related to geography, age, and gender. The presentation of RAS is made more complex by the division of the condition into minor, major, and herpetiform subtypes, each of which has unique traits and clinical symptoms. Accurate diagnosis and effective care depend on the lesion being distinguished from other oral lesions, such as herpes simplex virus infections, Behçet's illness, and nutritional deficiencies.

Family-based research has demonstrated the hereditary predisposition of RAS, which highlights the significance of genetics in its pathogenesis. Finding certain genetic variants, especially in the HLA system, sheds light on the heritability of RAS and how it is connected to various ethnic groups. Even though treatment options try to lessen symptoms, encourage healing, and lower the frequency of recurrences, the fact that there isn't a permanent cure emphasizes the need for more investigation into the underlying causes of RAS. Targeted therapeutics may become possible as a result of new insights into the genetic basis of RAS provided by genome-wide association studies and molecular biology advancements. In addition to looking for efficient treatments, researchers are also working to gain a better understanding of the genetic, immunologic, and environmental factors that contribute to RAS. With more research, a more thorough and sophisticated method of treating RAS might become apparent, offering comfort to individuals afflicted by this common yet mysterious oral mucosal ailment.

References

Akintoye, S. O., & Greenberg, M. S. (2014). Recurrent Aphthous Stomatitis. Dental Clinics of North America, 58(2), 281–297. https://doi.org/10.1016/j.cden.2013.12.002

Al-Maweri, S. A., Halboub, E., Ashraf, S., Alqutaibi, A. Y., Qaid, N. M., Yahya, K., & Alhajj, M. N. (2020). Single application of topical doxycycline in management of recurrent aphthous stomatitis: a systematic review and meta-analysis of the available evidence. BMC Oral Health, 20(1). https://doi.org/10.1186/s12903-020-01220-5

DDS, A. L. B. Ms. (2019, May 1). Aphthous Stomatitis: Treatment, Diagnosis, and Clinical Pictures. Online Dental Programs. https://ostrowonline.usc.edu/aphthous-stomatitis-treatment-and-diagnosis/

Dudding, T., Haworth, S., Lind, P. A., Sathirapongsasuti, J. F., Tung, J. Y., Mitchell, R., Colodro-Conde, L., Medland, S. E., Gordon, S., Elsworth, B., Paternoster, L., Franks, P. W., Thomas, S. J., Martin, N. G., & Timpson, N. J. (2019). Genome-wide analysis for mouth ulcers identifies associations at immune regulatory loci. Nature Communications, 10(1). https://doi.org/10.1038/s41467-019-08923-6

Kiraz, S., Akdogan, A., Karadag, O., Erden, A., Kilic, L., Kalyoncu, U., Bilgen, S. A., & Ertenli, I. (2015). AB1173 Prevalence of Recurrent Aphthous Stomatitis and Related Factors: Outcomes of Cappadocia Chronic Diseases Epidemiological Study. Annals of the Rheumatic Diseases, 74(Suppl 2), 1295–1295. https://doi.org/10.1136/annrheumdis-2015-eular.5581

Lau, C. B., & Smith, G. P. (2022). Recurrent aphthous stomatitis: A comprehensive review and recommendations on therapeutic options. Dermatologic Therapy, 35(6). https://doi.org/10.1111/dth.15500

Liu, Y., He, M., Yin, T., Zheng, Z., Fang, C., & Peng, S. (2022b). Prevalence of recurrent aphthous stomatitis, oral submucosal fibrosis and oral leukoplakia in doctor/nurse and police officer population. BMC Oral Health, 22(1). https://doi.org/10.1186/s12903-022-02382-0

MAYO CLINIC. (2018). Canker sore - Symptoms and causes. Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/canker-sore/symptoms-causes/syc-20370615

Plewa, M. C., & Chatterjee, K. (2021). Aphthous Stomatitis. PubMed; StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK431059/

Shah, K., Guarderas, J., & Krishnaswamy, G. (2016). Aphthous stomatitis. Annals of Allergy, Asthma & Immunology, 117(4), 341–343. https://doi.org/10.1016/j.anai.2016.07.005

Ślebioda, Z., Szponar, E., & Kowalska, A. (2013). Etiopathogenesis of Recurrent Aphthous Stomatitis and the Role of Immunologic Aspects: Literature Review. Archivum Immunologiae et Therapiae Experimentalis, 62(3), 205–215. https://doi.org/10.1007/s00005-013-0261-y

Targeting vs. Modulating: How to Confront Variation in Cystic Fibrosis?

Yechiel Muller

Yechiel Muller will graduate with a Bachelor of Science degree in Honors Biology in June 2024.

Abstract

Cystic fibrosis is a genetic disease with over 2,000 reported mutation varieties. It affects a chloride channel called CFTR, which by the transmembrane transport of chlorine, maintains an apical membrane electrolyte equilibrium in luminal epithelial cells. Its malfunction results in cystic fibrosis which causes excess mucus in various organs and is associated with respiratory complications and salty sweat. Treatment of cystic fibrosis has primarily taken two approaches: a mutation-specific method, targeted at a particular mutation to restore its function, and a mutation-non-specific method, which modulates intracellular barriers to CFTR trafficking or cellular repression of mutant protein function. This paper presents a review of the literature on the strengths and weaknesses of the most prevalent therapies for cystic fibrosis. It seeks to assess whether either approach, targeting or modulating, holds more significance and should therefore be emphasized in future research. The review concludes that despite the recent advancement and success of targeted therapies, there is good reason to continue research in both targeting and modulating therapies because they can complement each other and help increase availability while also lowering drug costs.

Introduction

Cystic fibrosis8 (CF) is a genetic, autosomal recessive disease that affects an estimated 100,000 people worldwide (Regard et al., 2022). It targets the lungs, pancreas, intestinal tract, liver, and reproductive organs by filling them with mucus and congesting them. Though once considered a pediatric condition with a life expectancy of around six months, people with CF now have a median life expectancy of over 50 years and can lead fairly normal lives (Bell et al., 2019). This is largely due to the development of medications and the improvement of healthcare. However, continuous research is needed since CF is a complicated condition that affects individuals differently. There are many CF mutation variants and a range of phenotypes because of them (Cutting, 2015). This greatly complicates care since treatment options can be exclusive to specific CF cohorts and incompatible with others.

CF was first defined in 1938 as a condition of excess mucus clogging various organs (Davis, 2006). Then, during a heat wave in 1948, New York pediatrician Pual di Sant'Agnese, observed many infants with CF come to the emergency room with abnormal sweating and correlated the two. He discovered that CF patients had sweat chloride concentrations fivefold that of normal people and thus rendered the sweat test the method for diagnosing CF (di Sant'Agnese et al., 1953). His discovery of "salty sweat" in CF patients dispelled the presumption that CF was primarily about mucus. It established the perspective that electrolyte transport in cells was at the heart of the issue.

Further research confirmed that chloride transport was the primary defect in CF. In 1989, the gene that codes for a cAMP-regulated apical membrane chloride channel protein called CF transmembrane conductance regulator (CFTR), was found to be the CF mutant gene. Its discovery led to a flurry of research into the CF mutation's effects and to the eventual development of treatments and therapies.

The CFTR protein is primarily found on the apical membrane of secretory epithelial cells (Lukasiak, Zajac, 2021). Its function is to transport chlorine into or out of a lumen via an electrochemical gradient. It is present in cells of the lungs, pancreas, GI tract, vas deferens, and sweat glands. In patients with CF, the absence or malfunction of CFTR at the plasma membrane blocks the reabsorption or release of chlorine by cells. This causes a chemical imbalance and the buildup of viscous mucus, which in turn causes inflammation, infection, and various organ pathologies. It is also the reason why sweat glands don't reabsorb chlorine and produce salty sweat.

The CFTR protein is structured as an ATP-gated ion channel. It has two cytosolic nucleotide-binding sites (NBDs) and a regulatory R-domain. The phosphorylation of the R-domain by kinases determines the affinity of CFTR for phosphorylating ATP and its permeability to chlorine. Notably, some CF mutations are seen at the ATP binding sites.

The production, trafficking, and maintenance of CFTR are important processes to understand for treating CF (fig. 1). On chromosome seven, the CFTR gene encodes its 1,480 amino-acid protein. Normally, the nascent CFTR protein follows a path to the plasma membrane beginning in the endoplasmic reticulum (ER). In the ER, core sugars are attached to stabilize the molecule. Also hosted by the ER are proteases, waiting to destroy any misfolded proteins (Ameen et al., 2007). The protein is then trafficked to the Golgi apparatus where the sugars are modified. The CFTR protein is then sent to the plasma membrane to function. Even at the plasma membrane, unstable CFTRs are not safe since they will have shorter half-lives and can be degraded in endocytic recycling. Because of the cell's rigorous checks on CFTR, mutant versions have a slim chance of surviving to functionally transport chlorine through the plasma membrane. Some popular CF drugs have tried to circumvent these issues, as we will now describe.

It is critical to understand that CF is a disease that has many variations. Over 2,000 different mutations have been reported for the CFTR gene (Cystic Fibrosis Mutation Database, 2011). To categorize the numerous versions of CF, scientists have sorted them into six classes

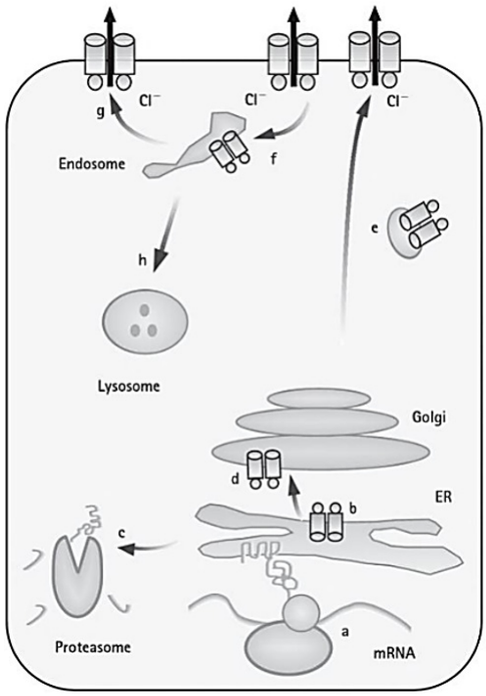

Figure 1: Schematic diagram of CFTR processing. (a) Translation.(b) Post-translational folding in the ER. (c)ER-associated degradation. (d) Acquirement of cell type-specific carbohydrates in the Golgi. (e) CFTR trafficking. (f) Endocytosis. (g) Recycling.(h) Degradation. Reproduced from Cystic Fibrosis, Third Edition, Hodson et al., Page 51, Figure 3.2, Copyright (2007), with permission from Taylor & Francis.

of functional impact (Ratjen et al., 2015). It has been found that nearly 90% of all CF cases contain at least a single copy of the Phe508del CFTR mutation, a class II mutation (Cystic Fibrosis Foundation Report, 2021). Because of the Phe508del CFTR mutation's prevalence, it has been the focus of CF drug therapies for many years.

Class II mutations are CFTR trafficking defects (fig. 2). When they are present, the manufactured CFTR protein is misfolded. Because of this, it cannot traffic past the ER and is degraded by proteases. Because the proteins are degraded at the ER, very few CFTR molecules make it to the plasma membrane. If any CFTR molecules do manage to travel through the cell, they are unstable and not fully functional. The lack of functioning CFTR channels at the plasma membrane makes it impermeable to chlorine and creates the transmembrane electrolyte imbalance typical of CF.

Originally, to combat the CFTR mutation, two types of drugs were contemplated: correctors and potentiators. These drugs are targeted at specific mutations of the CFTR gene and therefore are only effective in certain cohorts. To improve and expand their effectiveness, combinations of these drugs have been used with added success. Still, the scope of patients who are eligible to benefit from these drugs is limited.

Correctors and potentiators work in different ways to help patients with CF. Correctors are a class of drugs that, as their name implies - correct mutations. Correctors need to be tailored to a specific mutation so that they can repair it. For example, a corrector targeted at Phe508del enables the protein to fold properly so it can proceed past the ER and travel to the cell surface.

Potentiators, on the other hand, work to increase the efficiency of the rare mutant CFTR proteins that make it to the plasma membrane. Because it is difficult for a mutant protein to arrive at the plasma membrane and because those that do are often functionally deficient, improving their ability and giving them more potential can minimize the negative effects. Since different mutations affect different parts of the CFTR protein, potentiators also need to be tailored to a specific mutation. Drugs like Ivacaftor, Lumacaftor, and recently Elexacaftor and Tezacaftor, all fall into the corrector/potentiator classes of drugs.

More recently, a new methodology for treatment has emerged. These are so-called modulator therapies.

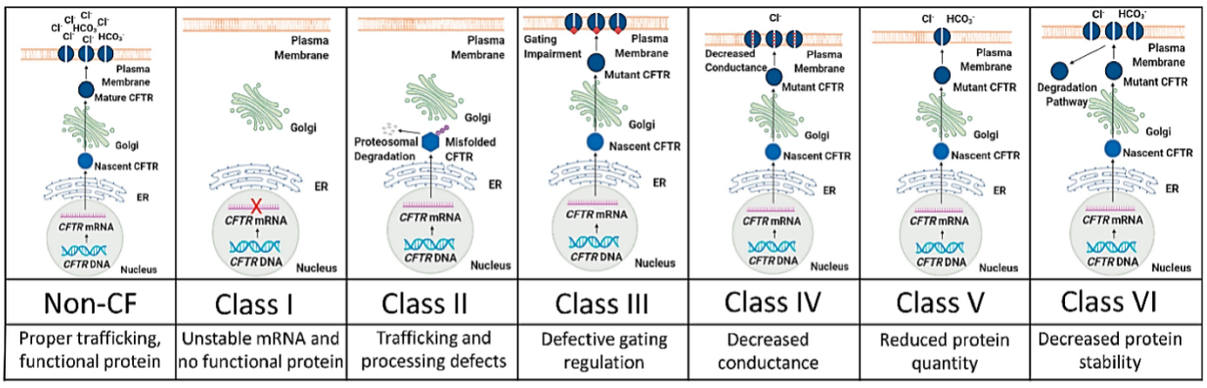

Figure 2: Schematic representation of CFTR (CF transmembrane conductance regulator) mutation classes. Reproduced from open access (Strub, McCray, 2020).

Modulators are different from correctors or potentiators as they are not specific to any single gene mutation. This is because modulators work by altering the cell environment as opposed to trying to fix or enhance the protein itself. By altering the cell environment, modulators effectively make the cell more friendly towards trafficking imperfect proteins. In this way, mutant proteins that typically might get stuck or destroyed before making it to the cell surface can now arrive there and function to some degree.

In this paper, we will examine the effectiveness of the more common corrector and potentiator drugs and compare them with modulator therapies that have been theorized. By weighing the pros and cons of each type of therapy we will determine what to emphasize in further research.

Methods

PubMed and Google Scholar search engines were used to research scientific literature for this paper. All literature referenced is from acknowledged scientific sources including prevalent science organizations and journals. Keywords used: cystic fibrosis, CFTR, correctors, potentiators, modulators.

Discussion

Ivacaftor

No discussion on CF therapies would be complete without talking about Ivacaftor - the first major drug approved for treating CF (Cystic Fibrosis Foundation, 2020). Ivacaftor is a potentiator designed for CF patients with at least one copy of the missense gating mutation G551D. Although only about 4-5% of cases of CF have this mutation (Cystic Fibrosis Foundation Report, 2020), ivacaftor is perhaps the most ubiquitous drug on the market due to its combination with other drugs and its use in patients with other gating mutations dol lll).

The CFTR protein is a channel with two nucleotide-binding domains (NBD1 and NBD2) that control channel gating (fig. 3). This is accomplished through the binding and hydrolysis of ATP. The CFTR molecule's two NBDs fold into ATP binding pockets (ABP1 and ABP2) and sandwich the ATP molecules. It has been shown that the two ABPs have different roles (Zhou et al., 2006). While ABP2 allows for the opening of the CFTR channel, ABP1 stabilizes the channel gate when it is already open.

Research done in 2007 determined that the G551D mutation affects the ABP2 site, making it virtually unresponsive to ATP (Bompadre et al., 2007). In the presence of ATP, G551D-CFTR has about a 100-fold lower probability of opening, compared with WT-CFTR (wild type). However, experiments showed that there was still some minimal channel gating activity observed in G551D-CFTR. This was hypothesized to be due to random, ATP-independent openings, which were also observed in WT-CFTR in the absence of ATP.

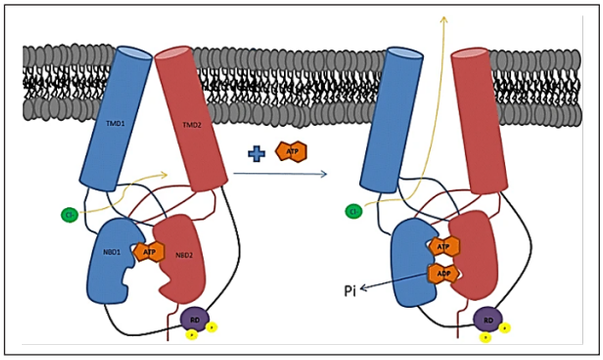

Figure 3: Cartoon illustrating how ATP binding and subsequent hydrolysis could lead to channel opening and flux of chloride ions. Reproduced from open access (Meng et al., 2017).

Because of this observation, it was thought that if ABP1 alone bound ATP, even when the ABP2 site was non-functioning, it would stabilize the channel gate during ATP-independent openings and increase the time open for chlorine flow through the channel. A study using P-ATP (analog ATP: N6 -(2-phenylethyl)-ATP) then confirmed that indeed, ABP1, on its own, increased the channel gate open time (Bompadre et al., 2008). In turn, this confirmation indicated that the ABP1 site was the perfect target for a CFTR potentiator for the G551D-CFTR defective gating mutation.

The drug ivacaftor was designed as a potentiator that targets the G551D-CFTR gating mutation. In a study conducted in 2011, the drug was tested in a phase 3 trial with people who had at least one G551D-CFTR mutation (Ramsey et al., 2011). In addition to sweat chloride, the results were measured by the change in predicted forced expiratory volume (FEV) in one second, which is the amount of breath one can exhale in that amount of time. Since CF greatly affects the lungs, an increase in predicted FEV would indicate a successful drug. The study found that after taking ivacaftor for 48 weeks, the G551D cohort saw a 10.5% increase from the baseline FEV, with the first effects being seen on day 12. Additionally, sweat chloride levels decreased from the baseline to -48.1 mmol/liter. It was also reported that CF patients gained weight during this period and that there was an overall decrease in respiratory symptoms which are generally common in CF.

Although ivacaftor was designed for G551D-CFTR, other studies have shown that it can work for other gating mutations (class lll) as well. One study tested the in vitro effects of ivacaftor on different gating mutations including

G178R, S549N, S549R, G551S, G970R, G1244E, S1251N, S1255P, and G1349D. Incredibly, in all these mutations, ivacaftor had a similar positive effect as compared with G551D (Yu et al., 2012). Comparable results were shown in other studies (De Boek et al., 2014; Rosenfeld et al., 2018; Rowe et al., 2014). This study showed that ivacaftor did not need to be restricted to one mutation and that it could be effective for an entire class of CF. This later translated into ivacaftor being used in combination with other drugs for mutations that are even more common, such as in Phe508del, an entirely different class of CF (class II).

Although ivacaftor was a significant step forward in CF drug therapies, it had a very limited impact when used as an isolated drug. Foremost, class III mutations (gating mutations) only account for about 6% of CF incidence (Cystic Fibrosis Foundation, 2017). Though considerable in terms of the thousands of possible CF mutations, it is a very small proportion overall. Indeed, only 2,600 patients globally were eligible for ivacaftor treatment when it was first approved (Hollis et al., 2019). Furthermore, the drug is prohibitively expensive, costing close to $300,000 annually for treatment - something quite common for drugs with such limited eligibility.

Lumacaftor

Lumacaftor is a drug that acts as a corrector. It is often paired with ivacaftor in treatment and is rarely studied as an independent drug. Unlike potentiators which strengthen CFTR channels already at the plasma membrane, correctors work to repair CFTR molecules so that they aren't degraded before reaching the plasma membrane or discarded in endocytic recycling. An inherent characteristic of a corrector drug is that it is specific to a mutation because every mutation has a unique molecular phenotype. While there are many CF mutations a drug might attempt to target, lumacaftor is a corrector for the Phe508del mutation, which is easily the most common cause of CF.

The Phe508del mutation is a class II mutation that is characterized by improper folding of the CFTR protein. Improper folding results in the protein being degraded at the ER, resulting in a diminishment of CFTR at the plasma membrane. Even though Phe508del-CFTR is a class II mutation, sparing amounts of the mutant channels make it to the plasma membrane. However, once at the membrane, these few survivors exhibit gating malfunctions, something characteristic of class III mutations (Dalemans et al., 1991).

The misfolding seen in Phe508del-CFTR is due to a defect in the NBD1 segment of the molecule. The defect in NBD1 somehow causes the molecule to be kinetically, and at normal body temperature, thermodynamically unstable which results in faulty folding (Rabeh et al., 2012). It is unclear how Phen508del causes NBD1 to become destabilized. Also uncertain, is precisely how corrector drugs like lumacaftor help the mutant proteins. A key question is whether lumacaftor (and other correctors) restore the misfolded protein to their normal structure or rather stabilize the misfolded protein in its faulty configuration. Research seems to suggest the latter (Fiedorczuk, Chen, 2022). It was found that lumacaftor (and tezacaftor – discussed next) did not alter the overall structure of the CFTR molecule and seemed to only interact with TMD1, the transmembrane segment near NBD1.

Most studies pair lumacaftor with ivacaftor and examine their effects together. In a study with a population of more than 1,000 and over the span of one year, lumacaftor/ivacaftor was shown to have significant results for various clinical endpoints (Wainwright et al., 2015). Improved FEV was seen in as little as 15 days and was maintained throughout the study (24 weeks). The results showed a mean absolute change of FEV between 2.6 to 4.0 percentage points compared to the placebo. The lumacaftor/ivacaftor groups also saw significantly fewer pulmonary exacerbations with a 30-39% decrease. The study showed that overall hospitalizations and the administration of intravenous medications were reduced and that BMI steadily increased as well. Similar rates of adverse effects were seen in the placebo and study groups.

Although the lumacaftor/ivacaftor findings were significant, they were still not as impressive as the numbers seen in ivacaftor monotherapy for G551. This can possibly be attributed to the fact that ivacaftor potentiates G551D-CFTR that already exists at the plasma membrane, while lumacaftor must first work to traffic the Phe508del-CFTR to the membrane before the CFTR can even attempt to function. Though lumacaftor/ivacaftor is available to a much larger group than ivacaftor alone, it remains well on par regarding cost, with a year of treatment of lumacaftor/ivacaftor priced at approximately $379,000.

Notably, although we have said that lumacaftor is a corrector, some studies have suggested that lumacaftor also exhibits potentiator characteristics. In a study, it was found that in addition to aiding in the proper folding of mutant-CFTR, some correctors like lumacaftor also bound rescued Phe508del-CFTR and increased their function (Eckford et al., 2014).

Trikafta

In October of 2019, a new combination of drugs came to market with better results than lumacaftor/ivacaftor therapy (Comegna et al., 2021). Trikafta combines ivacaftor,

tezacaftor (an improved version of lumacaftor), and elexacaftor (another corrector) in a drug that treats people with at least one Phe508del-CFTR mutation. This drug is monumental in terms of its widespread applicability. This new triple combo is open to variations of CF, including heterozygous for Phe508del with another minimal function mutation, or homozygous Phe508del-CFTR. The introduction of Trikafta means that now approximately 90% of CF cases are candidates to benefit from some kind of drug therapy (Ridley et al., 2020).

A study with close to 500 participants, over a follow-up period of six months, looked at the effects of Trikafta for different sub-cohorts including those that previously took ivacaftor, the lumacaftor/ivacaftor combination, or neither (these sub-cohorts were a result of different gene mutations) (Nichols et al., 2022). The study found that overall, across all subgroups, the change in FEV was an average of 9.8% - a much greater result than the lumacaftor/ivacaftor combination. For those who had not previously been using any drug therapy, the difference was 10.8% from baseline. In addition to FEV, a positive change was seen in sweat chloride levels as well as BMI. The study mentions that the sub-cohort that had previously been taking ivacaftor monotherapy (meaning for the G551D mutation) saw a smaller, though still substantial, change than the other sub-cohorts.

The Trikafta drug is certainly a large step forward for many cases of CF. Perhaps its most significant attribute is that it has been approved for patients who are heterozygous for Phe508del (ivacaftor/lumacaftor was only approved for homozygous Phe508del). However, despite the wider eligibility for Trikafta, the price remains high at over $250,000 (Tice et al., 2020). This high price limits its availability, and according to a report from The Journal of Cystic Fibrosis, just 12% of eligible CF patients receive it (Guo et al., 2022a). Though the price of manufacturing the drug has been estimated at around $5,700 (Guo et al., 2022b), the huge markup is typical of the pricing trend for personalized medication for unique genetic diseases (Balfour-Lynn, 2014).

Modulators

Because modulators do not constitute any major drug currently in use, we can only review the fundamental attributes of modulators and the types that are being proposed. For clarification, some research studies refer to correctors and potentiators (such as ivacaftor and lumacaftor) as "modulators". However, in the context of this paper, "modulators" refer to drug therapies that are unspecific to a gene mutation and focus on modulating the cell environment.

The idea of a modulator is to bypass the issue of variation between the thousands of genotype mutations for a disease. This is done by modulating a stage in a cellular pathway that influences more than one phenotype of a disease with the aim of it being a more universal solution. Approaches to modulating the cellular environment include remedying the protease pathway, the use of alternative ion channels, and tempering endocytic recycling. All of these are points within a cell that will affect many CFTR phenotypes.

While doing research for this paper it became clear that unfortunately, very few ideas meet the criteria for modulators as described above. Virtually every point throughout the cellular environment is more specific than one might expect.

The Protease Pathway

A protease pathway that has been shown to prevent CFTR trafficking is a system called endoplasmic reticulum-associated degradation (ERAD) (Estabrooks, Brodsky, 2020). This system functions at the ER to degrade misfolded proteins. In theory, a modulator would attempt to suppress this system and allow for minimally functional mutant-CFTR to continue trafficking to the permeable membrane (El Khouri et al., 2013; McKelvey et al., 2020). Unfortunately, however, carrying this out is not so straightforward.

The way premature CFTR passes through the ER is complex. When the nascent CFTR molecule comes to the ER it is an unstable and partially folded protein. Upon arrival, the molecule must be monitored by protein quality control (PQC) factors which decide whether to allow the unfinished CFTR protein passage or send it for degradation. This is accomplished by numerous molecular chaperones conjugating to different regions of the unstable CFTR protein. These different chaperones all stabilize the CFTR molecule. However, some of them promote folding and maturation while others recruit additional molecular add-ons that mark the molecule for degradation. Essentially, the net effect of the different types of chaperones determines the molecule's fate.

The complexity of this system is significant since there are many different chaperones and PQC machinery that interact with the molecule in different stages. While the process begins with heat shock proteins attaching to the CFTR, it then binds more chaperones when some of the heat shock proteins prompt the molecule into new folding conformations. At each level, there are PQC proteins that are pro-folding and pro-degradation and sometimes one can inhibit the other. Critically, for each CFTR variant, the varieties of chaperones that bind to the molecule may

be unique. Essentially, trying to suppress ERAD for CF might be as specific a task as some of the correctors and potentiators drugs attempt.

Alternative Ion Transport Pathways

Another idea for modulating is the use of alternative pathways for chloride transport through the permeable membrane. With this strategy, even CF cases with CFTR mutations that are not currently amenable to specific drugs can be treated. One idea on how to achieve this is to use a calcium-activated chloride channel called TMEM16A (Mall, Galietta, 2015).

The TMEM16A channel has been shown to express in the mucus-secreting goblet cells and cells in the bronchi. They appear to function as rapid adaption channels that are stimulated for a few minutes by high levels of calcium (Li et al., 2017). Conveniently, these channels are found in mucus-secreting cells which are a major source of difficulty in CF. They provide an opportunity for induced chlorine transport with a drug that targets TMEM16A. By overcoming some of the chlorine/electrolyte imbalance typical of CF, we can reduce the amount of mucus secreted and prevent infection and respiratory issues.

A different alternative chloride transport pathway for consideration is the use of ionophores (Quesada, Dutzler, 2020). Ionophores work by creating supramolecular lipophilic structures around an ion allowing it to diffuse across a cell's lipid membrane. Very few ionophores (or anionophores in the case of anions) are produced in nature, necessitating synthetic ionophores to be developed. In the case of CF, ionophores can potentially aid trapped chlorine molecules to cross through the membrane and restore some electrolyte balance. Unlike the TMEM16A channel, using ionophores evades the use of a channel altogether and can potentially be a source of therapy for CF patients who are unresponsive to other CF drugs.

Endocytic Recycling

Endocytic recycling is a key process in ensuring that damaged or malfunctioning cellular machinery is disposed of. It is also a major reason why mutant CFTR, even when they succeed in arriving at the cell surface, are mostly ineffective. The endocytic recycling pathway works using ubiquitination. Ubiquitination is a state where a protein has a ubiquitin marker conjugated to it. The endocytic recycling pathway uses ubiquitin to mark a molecule for destruction. Unless a molecule is deubiquitinated by a deubiquitinating enzyme (DUB) it will be sent to a lysosome for degradation (Sharma et al., 2004). For healthy cells, more than 75% of wild-type CFTR is deubiquitinated by DUBs and recycled back to the plasma membrane (Bomberger et al., 2010). However, mutant proteins are often not deubiquitinated and are therefore not recycled.

Research into the DUB specific for CFTR yielded a protein called USP10, indicating that USP10 is a significant determinant in the degradation process of CFTR. One study has shown that vasopressin, an anti-diuretic, can upregulate USP10 in the cortical kidney (Boulkroun et al., 2008). Another study found that CFTR channel secretion was increased in mice given vasopressin (Chang et al., 2005). Taken together, these studies indicate that vasopressin may be upregulating USP10 and that USP10 may be a suitable target to help recycle more CFTR which will be favorable in CF (Bhattacharya et al., 2020).

Analysis

In writing this paper, it was purported that either targeting or modulating drugs should be emphasized in CF research. However, after a review of the literature, it seems that neither of the two approaches is superior.

Foremost, we must recognize that most research covering potential therapies for CF is relatively current. This is the case for the newly approved mutation-specific correctors and potentiators like ivacaftor, lumacaftor, and trikafta. While there has been considerable success in large studies over periods as long as one year, it remains to be seen how patients who take these medications for years on end will fare. It is projected that they will indeed enable CF patients to live longer, healthier lives, but this has not yet been experienced and we do not know what new complications may arise for CF patients who live longer.

As mentioned earlier, trikafta truly seems to be the miracle drug that many waited for. Yet its high price makes it controversial. Though its cost may eventually go down, it is clear that the current lack of alternative options permits its exorbitant cost. For this reason, it would seem that modulators have a void to fill in providing relief to a larger group of CF patients and helping drive down the price of drugs like trikafta.

Unfortunately, research into modulating therapies seems more theoretical than practical. There is currently no modulator therapy approved for use. With the debut of trikafta in 2019, it appeared that the crux of the CF issue has been solved with this mutation-specific drug. However, this is not the case a) because of the numerous other CF mutations that remain untreatable and b) because the price of this exclusive drug makes it unattainable for many.

Modulators are ideal because they are intended to be a universally applicable treatment. Theoretically, because they are not mutation-specific and instead inhibit or upregulate certain cellular machinery or pathways, they can be used to treat the cellular barriers encountered by mutant CFTR

rather than repairing mutations themselves. Because they are a more general form of treatment, they should cost less and should be available to a larger cohort of patients.

The reality is, however, that some modulator therapies turn out to be highly specific themselves. For example, in the protease pathway, depending on the mutation, different chaperones conjugate themselves to CFTR to promote folding or degradation. This means that suppressing this process can require a different drug for different CFTR mutations.

While current considerations indicate that for now CF will remain an expensive disease to treat, there are good reasons for continued research in both targeting and modulating therapies.

At present, mutation-specific therapies, even when economical to manufacture, run exorbitant prices due to their small market and the enormous investments required to develop them. However, as pharmaceutical technology evolves, developing mutation-specific therapy will be more streamlined and efficient, and therefore cheaper. The eligibility of trikafta for many CF patients indicates that mutation-targeted drugs are effective and should continue to be pursued and improved. Though prohibitive costs make it unattainable for many, the success of the drug cannot be ignored, and with time it will hopefully become more available.

Nonetheless, modulators should not be overlooked. Their availability would likely help decrease the cost of mutation-specific therapies and would affect a wider cohort of CF patients. An advantage of modulators, even those that may be specific to certain CF mutations, is that they can potentially be used outside of CF for other diseases, broadening their market and making them cheaper. Furthermore, as stated earlier, we have not yet seen what complications may arise with the long-term use of targeted drugs like trikafta. The supplementation of these targeted drugs with other modulators may turn out to be a preferable route or they may serve as an enhancement to these therapies.

Conclusion

In conclusion, there is good reason to say that both targeting and modulating therapies have a place in CF treatment. Research should not be hindered by the success of current drugs like ivacaftor or trikafta since there is more to be achieved in treatment efficacy, in reducing costs, and in increasing availability. With the help of G-d and diligent scientific research, CF patients will have a variety of therapy options available, enabling them to live reasonably healthy and overall normal lives.

References

Ameen, N., Silvis, M., & Bradbury, N. A. (2007). Endocytic trafficking of CFTR in health and disease. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 6(1), 1–14. https://doi.org/10.1016/j.jcf.2006.09.002

Balfour-Lynn I. M. (2014). Personalised medicine in cystic fibrosis is unaffordable. Paediatric respiratory reviews, 15 Suppl 1, 2–5. https://doi.org/10.1016/j.prrv.2014.04.003

Bell, S. C., Mall, M. A., Gutierrez, H., Macek, M., Madge, S., Davies, J. C., Burgel, P. R., Tullis, E., Castaños, C., Castellani, C., Byrnes, C. A., Cathcart, F., Chotirmall, S. H., Cosgriff, R., Eichler, I., Fajac, I., Goss, C. H., Drevinek, P., Farrell, P. M., Gravelle, A. M., … Ratjen, F. (2020). The future of cystic fibrosis care: a global perspective. The Lancet. Respiratory medicine, 8(1), 65–124. https://doi.org/10.1016/S2213-2600(19)30337-6

Bhattacharya, U., Neizer-Ashun, F., Mukherjee, P., & Bhattacharya, R. (2020). When the chains do not break: the role of USP10 in physiology and pathology. Cell death & disease, 11(12), 1033. https://doi.org/10.1038/s41419-020-03246-7

Bomberger, J. M., Barnaby, R. L., & Stanton, B. A. (2010). The deubiquitinating enzyme USP10 regulates the endocytic recycling of CFTR in airway epithelial cells. Channels (Austin, Tex.), 4(3), 150–154. https://doi.org/10.4161/chan.4.3.11223

Bompadre, S. G., Li, M., & Hwang, T. C. (2008). Mechanism of G551D-CFTR (cystic fibrosis transmembrane conductance regulator) potentiation by a high affinity ATP analog. The Journal of biological chemistry, 283(9), 5364–5369. https://doi.org/10.1074/jbc.M709417200

Bompadre, S. G., Sohma, Y., Li, M., & Hwang, T. C. (2007). G551D and G1349D, two CF-associated mutations in the signature sequences of CFTR, exhibit distinct gating defects. The Journal of general physiology, 129(4), 285–298. https://doi.org/10.1085/jgp.200609667

Boulkroun, S., Ruffieux-Daidié, D., Vitagliano, J. J., Poirot, O., Charles, R. P., Lagnaz, D., Firsov, D., Kellenberger, S., & Staub, O. (2008). Vasopressin-inducible ubiquitin-specific protease 10 increases ENaC cell surface expression by deubiquitylating and stabilizing sorting nexin 3. American journal of physiology. Renal physiology, 295(4), F889–F900. https://doi.org/10.1152/ajprenal.00001.2008

Chang, C. T., Bens, M., Hummler, E., Boulkroun, S., Schild, L., Teulon, J., Rossier, B. C., & Vandewalle, A. (2005). Vasopressin-stimulated CFTR Cl- currents are increased

in the renal collecting duct cells of a mouse model of Liddle's syndrome. The Journal of physiology, 562(Pt 1), 271–284. https://doi.org/10.1113/jphysiol.2004.077933

Comegna, M., Terlizzi, V., Salvatore, D., Colangelo, C., Di Lullo, A. M., Zollo, I., Taccetti, G., Castaldo, G., & Amato, F. (2021). Elexacaftor-Tezacaftor-Ivacaftor Therapy for Cystic Fibrosis Patients with The F508del/Unknown Genotype. Antibiotics (Basel, Switzerland), 10(7), 828. https://doi.org/10.3390/antibiotics10070828

Cutting G. R. (2015). Cystic fibrosis genetics: from molecular understanding to clinical application. Nature reviews. Genetics, 16(1), 45–56. https://doi.org/10.1038/nrg3849

Cystic Fibrosis Foundation. Know Your Mutations Infographic. (2017, July) https://www.cff.org/sites/default/files/2021-12/Know-Your-CFTR-Mutations-Infographic.pdf.

Cystic Fibrosis Foundation. (2020). Our history. https://www.cff.org/about-us/our-history#:~:text=2006%3A%20Supported%20by%20the%20Foundation,as%20ivacaftor%20(Kalydeco%C2%AE).

Cystic Fibrosis Foundation Patient Registry 2020 Annual Data Report Bethesda, Maryland ©2021 Cystic Fibrosis Foundation. https://www.cff.org/sites/default/files/2021-10/2019-Patient-Registry-Annual-Data-Report.pdf

Cystic Fibrosis Foundation Patient Registry 2021 Annual Data Report Bethesda, Maryland ©2022 Cystic Fibrosis Foundation. Pg 19. https://www.cff.org/sites/default/files/2021-11/Patient-Registry-Annual-Data-Report.pdf

Cystic Fibrosis Mutation Database. (2011, April). http://www.genet.sickkids.on.ca/StatisticsPage.html

Dalemans, W., Barbry, P., Champigny, G., Jallat, S., Dott, K., Dreyer, D., Crystal, R. G., Pavirani, A., Lecocq, J. P., & Lazdunski, M. (1991). Altered chloride ion channel kinetics associated with the delta F508 cystic fibrosis mutation. Nature, 354(6354), 526–528. https://doi.org/10.1038/354526a0

Davis P. B. (2006). Cystic fibrosis since 1938. American journal of respiratory and critical care medicine, 173(5), 475–482. https://doi.org/10.1164/rccm.200505-840OE

De Boeck, K., Munck, A., Walker, S., Faro, A., Hiatt, P., Gilmartin, G., & Higgins, M. (2014). Efficacy and safety of ivacaftor in patients with cystic fibrosis and a non-G551D gating mutation. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 13(6), 674–680. https://doi.org/10.1016/j.jcf.2014.09.005

di Sant'Agnese, P. A., Darling, R. C., Perera, G. A., & Shea, E. (1953). Abnormal electrolyte composition of sweat in cystic fibrosis of the pancreas; clinical significance and relationship to the disease. Pediatrics, 12(5), 549–563.

Eckford, P. D., Ramjeesingh, M., Molinski, S., Pasyk, S., Dekkers, J. F., Li, C., Ahmadi, S., Ip, W., Chung, T. E., Du, K., Yeger, H., Beekman, J., Gonska, T., & Bear, C. E. (2014). VX-809 and related corrector compounds exhibit secondary activity stabilizing active F508del-CFTR after its partial rescue to the cell surface. Chemistry & biology, 21(5), 666–678. https://doi.org/10.1016/j.chembiol.2014.02.021

El Khouri, E., Le Pavec, G., Toledano, M. B., & Delaunay-Moisan, A. (2013). RNF185 is a novel E3 ligase of endoplasmic reticulum-associated degradation (ERAD) that targets cystic fibrosis transmembrane conductance regulator (CFTR). The Journal of biological chemistry, 288(43), 31177–31191. https://doi.org/10.1074/jbc.M113.470500

Estabrooks, S., & Brodsky, J. L. (2020). Regulation of CFTR Biogenesis by the Proteostatic Network and Pharmacological Modulators. International journal of molecular sciences, 21(2), 452. https://doi.org/10.3390/ijms21020452

Fiedorczuk, K., & Chen, J. (2022). Mechanism of CFTR correction by type I folding correctors. Cell, 185(1), 158–168.e11. https://doi.org/10.1016/j.cell.2021.12.009

Guo, J., Garratt, A., & Hill, A. (2022). Worldwide rates of diagnosis and effective treatment for cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 21(3), 456–462. https://doi.org/10.1016/j.jcf.2022.01.009

Guo, J., Wang, J., Zhang, J., Fortunak, J., & Hill, A. (2022). Current prices versus minimum costs of production for CFTR modulators. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 21(5), 866–872. https://doi.org/10.1016/j.jcf.2022.04.007

Hodson M., Geddes D., Bush A. (2007) Chapter 3: Molecular biology of cystic fibrosis: CFTR processing and function, and classes of mutations. Cystic Fibrosis. Third Edition. United Kingdom: Taylor & Francis. Page 51

Hollis A. (2019). Orphan Drug Pricing and Costs: A Case Study of Kalydeco and Orkambi. Healthcare policy = Politiques de sante, 15(1), 70–80. https://doi.org/10.12927/hcpol.2019.25937

Li, H., Salomon, J. J., Sheppard, D. N., Mall, M. A., & Galietta, L. J. (2017). Bypassing CFTR dysfunction in cystic fibrosis with alternative pathways for anion transport.

Current opinion in pharmacology, 34, 91–97. https://doi.org/10.1016/j.coph.2017.10.002

Lukasiak, A., & Zajac, M. (2021). The Distribution and Role of the CFTR Protein in the Intracellular Compartments. Membranes, 11(11), 804. https://doi.org/10.3390/membranes11110804

Mall, M. A., & Galietta, L. J. (2015). Targeting ion channels in cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 14(5), 561–570. https://doi.org/10.1016/j.jcf.2015.06.002

McKelvey, M. C., Weldon, S., McAuley, D. F., Mall, M. A., & Taggart, C. C. (2020). Targeting Proteases in Cystic Fibrosis Lung Disease. Paradigms, Progress, and Potential. American journal of respiratory and critical care medicine, 201(2), 141–147. https://doi.org/10.1164/rccm.201906-1190PP

Meng, X., Clews, J., Kargas, V., Wang, X., & Ford, R. C. (2017). The cystic fibrosis transmembrane conductance regulator (CFTR) and its stability. Cellular and molecular life sciences : CMLS, 74(1), 23–38. https://doi.org/10.1007/s00018-016-2386-8

Nichols, D. P., Paynter, A. C., Heltshe, S. L., Donaldson, S. H., Frederick, C. A., Freedman, S. D., Gelfond, D., Hoffman, L. R., Kelly, A., Narkewicz, M. R., Pittman, J. E., Ratjen, F., Rosenfeld, M., Sagel, S. D., Schwarzenberg, S. J., Singh, P. K., Solomon, G. M., Stalvey, M. S., Clancy, J. P., Kirby, S., … PROMISE Study group (2022). Clinical Effectiveness of Elexacaftor/Tezacaftor/Ivacaftor in People with Cystic Fibrosis: A Clinical Trial. American journal of respiratory and critical care medicine, 205(5), 529–539. https://doi.org/10.1164/rccm.202108-1986OC

Quesada, R., & Dutzler, R. (2020). Alternative chloride transport pathways as pharmacological targets for the treatment of cystic fibrosis. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 19 Suppl 1, S37–S41. https://doi.org/10.1016/j.jcf.2019.10.020

Rabeh, W. M., Bossard, F., Xu, H., Okiyoneda, T., Bagdany, M., Mulvihill, C. M., Du, K., di Bernardo, S., Liu, Y., Konermann, L., Roldan, A., & Lukacs, G. L. (2012). Correction of both NBD1 energetics and domain interface is required to restore ΔF508 CFTR folding and function. Cell, 148(1-2), 150–163. https://doi.org/10.1016/j.cell.2011.11.024

Ramsey, B. W., Davies, J., McElvaney, N. G., Tullis, E., Bell, S. C., Dřevínek, P., Griese, M., McKone, E. F., Wainwright, C. E., Konstan, M. W., Moss, R., Ratjen, F., Sermet-Gaudelus, I., Rowe, S. M., Dong, Q., Rodriguez, S., Yen, K., Ordoñez, C., Elborn, J. S., & VX08-770-102 Study Group (2011). A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. The New England journal of medicine, 365(18), 1663–1672. https://doi.org/10.1056/NEJMoa1105185

Ratjen, F., Bell, S. C., Rowe, S. M., Goss, C. H., Quittner, A. L., & Bush, A. (2015). Cystic fibrosis. Nature reviews. Disease primers, 1, 15010. https://doi.org/10.1038/nrdp.2015.10

Regard, L., Martin, C., Burnet, E., Da Silva, J., & Burgel, P. R. (2022). CFTR Modulators in People with Cystic Fibrosis: Real-World Evidence in France. Cells, 11(11), 1769. https://doi.org/10.3390/cells11111769

Ridley, K., & Condren, M. (2020). Elexacaftor-Tezacaftor-Ivacaftor: The First Triple-Combination Cystic Fibrosis Transmembrane Conductance Regulator Modulating Therapy. The journal of pediatric pharmacology and therapeutics : JPPT : the official journal of PPAG, 25(3), 192–197. https://doi.org/10.5863/1551-6776-25.3.192

Rosenfeld, M., Wainwright, C. E., Higgins, M., Wang, L. T., McKee, C., Campbell, D., Tian, S., Schneider, J., Cunningham, S., Davies, J. C., & ARRIVAL study group (2018). Ivacaftor treatment of cystic fibrosis in children aged 12 to <24 months and with a CFTR gating mutation (ARRIVAL): a phase 3 single-arm study. The Lancet. Respiratory medicine, 6(7), 545–553. https://doi.org/10.1016/S2213-2600(18)30202-9

Rowe, S. M., Heltshe, S. L., Gonska, T., Donaldson, S. H., Borowitz, D., Gelfond, D., Sagel, S. D., Khan, U., Mayer-Hamblett, N., Van Dalfsen, J. M., Joseloff, E., Ramsey, B. W., & GOAL Investigators of the Cystic Fibrosis Foundation Therapeutics Development Network (2014). Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. American journal of respiratory and critical care medicine, 190(2), 175–184. https://doi.org/10.1164/rccm.201404-0703OC

Sharma, M., Pampinella, F., Nemes, C., Benharouga, M., So, J., Du, K., Bache, K. G., Papsin, B., Zerangue, N., Stenmark, H., & Lukacs, G. L. (2004). Misfolding diverts CFTR from recycling to degradation: quality control at early endosomes. The Journal of cell biology, 164(6), 923–933. https://doi.org/10.1083/jcb.200312018

Strub, M. D., & McCray, P. B., Jr (2020). Transcriptomic and Proteostasis Networks of CFTR and the Development of Small Molecule Modulators for the Treatment of Cystic Fibrosis Lung Disease. Genes, 11(5), 546. https://doi.org/10.3390/genes11050546

Tice J.A., Kuntz K.M., Wherry K., Chapman R., Seidner M., Pearson S.D., Rind D.M. (2020, September) Modulator Treatments for Cystic Fibrosis: Effectiveness and Value; Final Evidence Report and Meeting Summary. Institute for Clinical and Economic Review, https://icer.org/wp-content/uploads/2020/08/ICER_CF_Final_Report_092320.pdf

Wainwright, C. E., Elborn, J. S., Ramsey, B. W., Marigowda, G., Huang, X., Cipolli, M., Colombo, C., Davies, J. C., De Boeck, K., Flume, P. A., Konstan, M. W., McColley, S. A., McCoy, K., McKone, E. F., Munck, A., Ratjen, F., Rowe, S. M., Waltz, D., Boyle, M. P., TRAFFIC Study Group, … TRANSPORT Study Group (2015). Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. The New England journal of medicine, 373(3), 220–231. https://doi.org/10.1056/NEJMoa1409547

Yu, H., Burton, B., Huang, C. J., Worley, J., Cao, D., Johnson, J. P., Jr, Urrutia, A., Joubran, J., Seepersaud, S., Sussky, K., Hoffman, B. J., & Van Goor, F. (2012). Ivacaftor potentiation of multiple CFTR channels with gating mutations. Journal of cystic fibrosis : official journal of the European Cystic Fibrosis Society, 11(3), 237–245. https://doi.org/10.1016/j.jcf.2011.12.005

Zhou, Z., Wang, X., Liu, H. Y., Zou, X., Li, M., & Hwang, T. C. (2006). The two ATP binding sites of cystic fibrosis transmembrane conductance regulator (CFTR) play distinct roles in gating kinetics and energetics. The Journal of general physiology, 128(4), 413–422. https://doi.org/10.1085/jgp.200609622

The Effects of Electronic Cigarettes on the Oral Cavity

Batsheva Saposh

Batsheva Saposh will graduate in June 2024 with a Bachelor of Science degree in Biology and will be attending Touro University College of Dentistry beginning in July 2024.

Abstract

Electronic cigarettes, which became available for purchase in the United States in 2007, were initially touted as a harmless aid for smoking cessation. However, recent research into the impact of electronic cigarettes on the human body has shown potential deleterious effects. This paper aims to examine the effects electronic cigarette usage has on the oral cavity. The methods to compile research involved reading through many peer-reviewed articles to analyze the most current information on the topic. The findings indicate several potentially adverse effects on the oral cavity including oral cancer, periodontitis, dental caries, xerostomia, facial fractures, failed dental implants, and oral lesions. The research was highly suggestive, and additional time will be needed to form definite conclusions.

Introduction

Electronic cigarettes (EC) are perceived as less harmful and toxic than conventional cigarettes. People use them as an electronic nicotine delivery system to wean off their addiction to conventional cigarettes. Nevertheless, recent studies have focused on the fact that ECs have toxic effects on the body including specific effects on the oral cavity. Research has shown a causal relationship between the use of ECs and dental caries, periodontitis, oral cancer, and other problems. While ECs may arguably offer certain benefits as a temporary smoking cessation device, vaping certainly should not be viewed as a harmless recreational indulgence.

Electronic cigarettes, which became available for purchase in 2005, are handheld devices composed of a container filled with a highly volatile liquid that is connected to a battery. When the battery is powered, an electric current is generated heating the container causing a vapor to form which is then inhaled by the user. Components of these liquids often include nicotine, flavorings, propylene glycols, and vegetable glycerin.

E-cigarettes are gaining popularity amongst all ages in America. In 2014 the Federal Emergency Management Agency reported that there were over 2.5 million users in the United States and as of 2023, 4.5% of America's adult population consumed ECs. The lack of research on the negative effects that ECs have on the body, and the general perception that they are safe, contributed to the rise in popularity.

Methods

This review of the effects that ECs have on the oral cavity is based on peer-reviewed papers found in the Touro University's Library database, EBSCO, PubMed database, and Google Scholar as well as additional sources. Key search terms included "effects of electronic cigarettes on the oral cavity", "prevalence of electronic cigarette usage", and "comparison of electronic cigarettes to conventional cigarettes".

Discussion

Prevalence and Usage

ECs are popular amongst many different populations and ages. According to the CDC, about 4.5% of the American population ages 18 and above are EC users with the highest prevalence being among adults between the ages of 18-24 (Kramarow and Elgaddal, 2023). The National Youth Tobacco Survey from 2022-2023 found that 10% (1.56 million) of high school students and 4.6% (550,000) of middle school students were currently using ECs. More than 25% of youth consumers reported EC usage as a daily occurrence.

Conventional Cigarettes

The negative effects of conventional cigarettes on the oral cavity are well-known and documented. Conventional cigarette smokers were found to have an increased presence of precancerous oral lesions and are at a greater risk of developing a variety of oral cancers such as tongue, lip, gingiva, and alveolar ridge. Furthermore, conventional cigarette smokers are likely to develop some form of periodontitis, infected root canals, dental caries, halitosis, and peri-implantitis. Additionally, conventional cigarette smoking is highly addictive due to the presence of tobacco therefore making it difficult for smokers to quit even if they are beginning to experience harmful effects (Ozturk, et. al. 2017).

E-cigarettes

Toxic Chemicals

As of 2018, there were over 10,000 e-liquid formulations available on the market (Zhu, et. al. 2014). All these formulations contain numerous chemicals including carcinogens such as formaldehyde, acetaldehydes, and nitrosamines (Goniewicz, et al. 2013). Diacetyl and acetyl propionyl are added to many EC liquids as well. These chemicals are known to cause bronchiolitis obliterans also known as 'popcorn lung' disease, which causes obstructions in the small airways of the lungs (Allen, et. al. 2016). Acrolein, another component of EC liquid, has been proven to be involved in the cross-linking of DNA and has also been shown to inhibit cytochrome P450 enzymes, which play a crucial role in cellular metabolism and the detoxification of xenobiotics (Park, et. al 2018, Ebersole et al., 2020).

Flavorings are one of the more appealing characteristics of ECs, and on the surface are seemingly innocent. Nevertheless, they too can cause damage. One flavoring

that was found to be particularly harmful to the body is cinnamon. Cinnamaldehyde has been found to act as an immunosuppressant. Instances of oxidative stress, cytotoxicity, and inflammation linked to the use of cinnamaldehyde have been documented as well (Ebersole et al., 2020).

In addition to the harmful chemicals found in e-liquids, there are toxic compounds that can form during EC use. These compounds include metals, carbonyls, and reactive oxidative species(ROS) (Olmedo, et. al. 2018). During the vaping process, the heating element of the EC can reach temperatures anywhere between 100 to 300 degrees Celsius. These high temperatures can facilitate the transfer of heavy metals such as nickel, chromium, cadmium, and lead from the device to the liquid (Gaur and Agnihorti, 2018). Carbonyls, such as α, and β-unsaturated aldehydes have been shown to induce oxidative stress, which may lead to pulmonary, cardiovascular, and oral diseases. Hydroxyl radicals, a very destructive ROS given off by an EC, can cause damage to DNA, proteins, and lipids (Ebersole et al., 2020). Furthermore, the breakdown of the wick material in the EC can lead to the presence of arsenic and silica which are known to have both carcinogenic and non-carcinogenic effects on many of the body's systems (Hong et al., 2014, Bishop et al., 2019, Williams, Monique, et al., 2013).

The direct effects on the oral cavity come from numerous chemicals. Studies on rats have demonstrated that formaldehyde disrupted the functions of the periodontium, including the alveolar bone, leading to collagen fiber degeneration (Laçin et al., 2018). Menthol has been found to have a negative impact on periodontal ligament fibroblasts (Willershausen et al., 2013). Damage to both the alveolar bone and periodontal ligaments will loosen the support for the teeth, causing potential tooth loss. Heavy metals can cause periodontitis, oral cancer, and inflammation (Bishop et al., 2019).

Nicotine content in ECs can vary greatly; one e-liquid cartridge can contain anywhere from 3 to 36 mg/ml. For comparative purposes smoking one conventional cigarette is comparable to approximately fifteen puffs of an EC. Those fifteen puffs of an average EC will release 0.025 – 0.77 mg of nicotine. This is lower than the average nicotine consumption from one CC which can range between 1.54 – 2.60 mg. Despite the fact that the nicotine levels are significantly lower in an EC, they can still have harmful effects on the body. In addition, it is worth pointing out that testing done on several e-liquid brands showed traces of nicotine in EC cartridges that claimed to have no nicotine in the liquid (Goniewicz et al., 2012, Kesimer, 2019). Nicotine is an addictive and carcinogenic substance. When introduced to the body it reacts with acetylcholine receptors and stimulates the release of dopamine. Dopamine when released alters an individual's mood and produces a temporary good feeling. After this feeling wears off, many are tempted to inhale more of this nicotine, which leads to an addiction to this substance. Nicotine acts on many of the body's systems. It causes emphysema, and gastric ulcers and poses an increased risk of macular degeneration (Trybek et al., 2018).

Nicotine also affects the oral cavity in a variety of ways, all problematic. It causes caries, discoloration, and tooth loss as well as halitosis, stomatitis, candidiasis, and oral cancer. Specifically, in the periodontium, it can lead to loss of the connective tissue attachment to the alveolar bone resulting in periodontal disease (Trybek et al., 2018).

Oral Cancer

Both nicotine-free and nicotine-containing formulas of ECs were tested on the normal epithelial cell line HaCaT and two head and neck squamous cell carcinoma cell lines, to determine the ability of ECs to induce DNA strand breaks. Repeated DNA strand breaks due to long-term EC exposure and dysfunctional repair will generate accumulated mutations, and other genomic alterations will lead to the development of cancer. The results indicated a significant increase in DNA strand breaks, even in the cells induced with nicotine-free EC vapor. DNA strand breaks began to appear after a mere one week of EC treatment. Cell lines treated with EC vapor extract were suspended in the G1 and G2 phases of mitosis and showed increased apoptosis and necrosis (Yu et al., 2016).

Another study showed that ECs induced behavioral and morphological changes in healthy oral keratinocytes. Using a variety of normal and tumor cell lines of oral squamous cell carcinoma, researchers demonstrated that ECs mediated tumor progression and metastasis by inducing epithelial-to-mesenchymal cell transition, thus enhancing the invasive abilities of this particular kind of cancer. Furthermore, ROS are known to promote DNA mutations, which can contribute to the survival, proliferation, angiogenesis, invasion, and metastasis of cancer cells. This is all consistent with the epithelial-to-mesenchymal transition phenotype and may indeed be its cause (Muniz et al., 2023).

The nickel contained in the nickel-chromium heating filaments of ECs can also potentially cause oral cancer. Studies done on the effect of nickel in metal dental crowns in the mouth showed induced genotoxicity in buccal epithelial cells in children (Morán-Martínez et al., 2013). In addition, a study showed a positive correlation between farm soil that contained nickel and an increased prevalence of oral cancer in nearby communities (Su et al., 2010)

Periodontitis

Periodontitis is a bacterial infection resulting from an excessive inflammatory response. It begins with gingivitis, the mild inflammation of the soft tissue that surrounds the teeth. It then develops further into periodontitis when the condition turns chronic and results in irreversible gum inflammation. At this stage, bacteria can penetrate deeper into the periodontium. This triggers an immune response, and in the process of protecting itself the periodontium can get damaged. This disease, if left untreated, will lead to the loss of attachment of the periodontium, subsequently leading to alveolar bone loss and potential tooth loss. Furthermore, people with periodontitis are at a higher risk of developing cardiovascular disease and stroke(Gasner and Schure, 2023).

In an attempt to determine the effects of EC aerosols on oral epithelial cells, researchers generated nanoparticles from EC aerosols using a variety of advanced technologies. The results of cytotoxicity assays and quantitative PCR suggested that these aerosols have components that can cause oxidative stress in the oral cavity (Ji et al., 2016). In response to the inflammation in the gums, ROS such as hydrogen peroxide and superoxide are released from neutrophils. This results in oxidative stress, an imbalance between the accumulation of ROS in tissues and cells, and the ability of the body to detoxify these products by producing antioxidants. Excessive ROS can induce cytotoxic effects on cells by interfering with the cell cycle, cause oxidative damage to proteins and DNA, and induce apoptosis of gingival fibroblasts. All of this enables the ROS to directly cause periodontal tissue damage. ROS can also indirectly cause periodontal tissue destruction because the species play a role as intracellular signaling molecules in the osteoclast activity pathway. Excessive osteoclast activity is a typical pathology of periodontitis (Kanzaki et al., 2017).

One study on rats showed that formaldehyde disrupts the periodontal membrane by reacting with collagen and forming toxic hydroxymethyl compounds. These compounds can cause the degradation of collagen fibers that surround the alveolar bone, potentially leading to periodontitis (Laçin et al., 2018).

Dental Caries

Dental caries affects 97% of the world population making it one of the most infectious diseases in humans. It is a complex disease with many different factors that contribute to it including host genetics, oral microbiome, immune system, diet, oral hygiene, and water fluoridation. One way it progresses is due to pathogenic oral bacteria such as Streptococcus mutans (S. mutans). These bacteria metabolize fermentable carbohydrates (glucose, fructose, maltose, sucrose) to produce lactic acid and other organic acids. The acid diffuses into the tooth enamel and dentine, causing demineralization and enamel lesions. The saliva acts as a pH buffer system, by providing calcium and phosphate ions to aid in the remineralization of these lesions. An increased intake of carbohydrates disturbs the mouth's homeostasis and leads to an acidic environment beyond the normal saliva buffering capacity, preventing it from remineralization of enamel, and thereby causing caries (Featherstone, 2008).

Like conventional cigarette smokers, people who smoke ECs seem to be at a greater risk of dental caries. The esters in e-liquid flavors including ethyl butyrate, triacetin, and hexyl acetate provide an additional food source for S. mutans to flourish in the oral environment. Other ingredients in e-liquids interact with enamel and dentine in a manner that strongly resembles the effects caused by high sucrose candies and highly acidic drinks (Kim et al., 2018).

The viscosity of e-liquid aerosol can cause the enamel surface of the teeth to change which can lead to increased adhesion of S. mutans. Surface characteristics such as tackiness, roughness, and charge can impact the way bacterial cells adhere to enamel, forming a biofilm. S. mutans in biofilm can rapidly metabolize carbohydrates leading to an increase in enamel demineralization (Kim et al., 2018), (Ebersole et al., 2020).

Xerostomia

Xerostomia, also known as dry mouth, is a condition in which the salivary glands cannot produce enough saliva to keep the mouth wet. The lack of saliva can lead to discomfort while swallowing, chewing, and speaking. In addition, it can lead to oral candidiasis, gingivitis, and dental caries (Sapru et al., 2020). The prevalence of this condition was found to be about 11% higher in EC users than in conventional cigarette consumers (Guo et al., 2023), probably due to the propylene glycol found in the e-liquid. Propylene glycol is a humectant that utilizes the moisture from the oral environment to convert it into vapor, leaving the user with a dryer mouth.

Facial Fractures

Although rare, ECs have been known to explode because of the proximity of the heating elements to an improperly insulated lithium-ion battery and the highly volatile liquid. This can cause facial fractures, especially in the oral cavity. In one case in Canada, an 18-year-old had oral burns, oral lacerations, tooth fractures, and tooth avulsion from an EC explosion (Rogér et al., 2016). Fifteen adolescents in

the western United States sustained similar traumatic injuries which included the loss of multiple teeth, mandible fractures, and incisor fractures (Russell et al., 2022).

Dental Implants

When a person loses a tooth to injury or disease, in addition to the aesthetic implications, he or she can experience complications such as defective speech and rapid bone loss. Implant dentistry offers solutions to these problems; the implant can replace a missing tooth or entire arches. The implant consists of an implant body made from titanium, an abutment, and a crown. The implant body is surgically inserted into the jawbone and the abutment extends through the gums and into the mouth to support the crown. Once the implant is placed in the jawbone, osseointegration occurs, as the jawbone fuses with the surface of the dental implant. This process takes several months and creates a solid foundation for the new artificial tooth. Stress factors such as osteoporosis, radiation, and conventional cigarette smoking can weaken implant functions and stability. There is evidence suggesting that ECs have adverse effects on implant sustainability as well, due to nicotine and other compounds found in them. The vapor can affect osteoblast behavior and can potentially dysregulate bone-tissue interaction with the implant. This is supported by the fact that when vapor was introduced to a titanium dental implant osteoblasts showed reduced attachment to it. This was due to the lack of focal adhesion proteins such as F-actin. Cell adhesion is critical for both the interaction of cells with material and cell survival and differentiation. The inhibition of osteoblast growth and decreased osteogenic activity was found in both cultures treated with nicotine-containing and nicotine-free EC vapor. In addition to decreased osteoblast adhesion and growth, EC vapor increased the degradation of mineralized bone tissue around the implant. All of this would contribute to implant failure (Rouabhia et al., 2019).

Oral Lesions

An increased prevalence of various oral mucosal lesions was found in EC consumers. Three specific types of inflammatory lesions were found to be more common among EC users than in conventional smokers. These include nicotine stomatitis, black hairy tongue, and hyperplastic candidiasis (Bardellini et al., 2017).

Nicotine stomatitis is an irritation of the oral mucosa and presents itself clinically as a gray or white color change to the hard palate. Exposure to heat on the hard palate can be one cause of this disease (Andamuthu Yamunadevi et al., 2023). Nicotine and the chemical compounds found in flavorings can be a factor as well, although further research is required to clarify this pathophysiology (Bardellini et al., 2017).

Black hairy tongue is a benign and asymptomatic condition that gives the tongue a dark and hairy appearance. Filiform papillae on the tongue collect food, bacteria, and dead skin cells which provide the tongue with its color. These papillae usually go through a process of desquamation in which the skin layer sheds. If desquamation does not occur, these papillae will elongate and give this distinct appearance. Why this condition results from EC consumption is unknown. Speculation as to possible causes includes an altered pH change, high intraoral mucosal dryness, and altered immune responses (Bardellini et al., 2017).

An overgrowth of Candida species in the oral cavity is known as hyperplastic candidiasis. It usually presents itself as white patches on oral mucosa commissures and can be associated with diseases such as diabetes mellitus and immunosuppression. The condition is probably due to the pH alteration from the flavorings found in ECs (Bardellini et al., 2017).

Conclusions

In contrast to conventional cigarettes, which have a history dating back to the 1800's, ECs represent a relatively recent addition to the market. Although they were initially promoted as a benign alternative to traditional smoking and a tool for smoking cessation, recent research paints a more nuanced and concerning picture. That is particularly alarming given the fact that EC users may be even younger than conventional cigarette smokers because of the misconception that ECs are harmless. The findings presented in this article suggest that ECs may have the potential for adverse effects on the oral cavity.

Admittedly, research is new, and further research is needed before these findings can be considered conclusive. In addition, as with all medical research into risk factors, an increased risk of a medical condition does not imply that it is inevitable. However, the evidence is mounting and the risks are severe enough to suggest that dentists would be well advised to ask about EC use, and to alert those who use ECs to the dangers.

References

Allen, Joseph G., et al. "Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes." Environmental Health Perspectives, vol. 124, no. 6, June 2016, pp. 733–739, https://doi.org/10.1289/ehp.1510185.

Andamuthu Yamunadevi, et al. "Nicotina Stomatitis – a

Report of Two Cases." Journal of Pharmacy and Bioallied Sciences, vol. 15, no. Suppl 1, 1 July 2023, pp. S799–S801, www.ncbi.nlm.nih.gov/pmc/articles/PMC10466508/, https://doi.org/10.4103/jpbs.jpbs_17_23. Accessed 26 Oct. 2023.

Bardellini, Elena, et al. "Oral Mucosal Lesions in Electronic Cigarettes Consumers versus Former Smokers." Acta Odontologica Scandinavica, vol. 76, no. 3, 21 Nov. 2017, pp. 226–228, https://doi.org/10.1080/00016357.2017.1406613.

Bishop, E., et al. "An Approach to Testing Undiluted E-Cigarette Aerosol in Vitro Using 3D Reconstituted Human Airway Epithelium." Toxicology in Vitro, vol. 54, Feb. 2019, pp. 391–401, https://doi.org/10.1016/j.tiv.2018.01.010. Accessed 15 Nov. 2019.

Ebersole, Jeffrey, et al. "Harmful Chemicals Emitted from Electronic Cigarettes and Potential Deleterious Effects in the Oral Cavity." Tobacco Induced Diseases, vol. 18, no. 18, 8 May 2020, www.ncbi.nlm.nih.gov/pmc/articles/PMC7233525/, https://doi.org/10.18332/tid/116988.

Featherstone, JDB. "Dental Caries: A Dynamic Disease Process." Australian Dental Journal, vol. 53, no. 3, Sept. 2008, pp. 286–291, https://doi.org/10.1111/j.1834-7819.2008.00064.x.

Gasner, Noah S., and Ryan S. Schure. "Periodontal Disease." PubMed, StatPearls Publishing, 10 Apr. 2023, www.ncbi.nlm.nih.gov/books/NBK554590/.

Gaur, Sumit, and Rupali Agnihotri. "Health Effects of Trace Metals in Electronic Cigarette Aerosols—a Systematic Review." Biological Trace Element Research, vol. 188, no. 2, 4 July 2018, pp. 295–315, link.springer.com/article/10.1007/s12011-018-1423-x, https://doi.org/10.1007/s12011-018-1423-x.

Goniewicz, et al. "Nicotine Levels in Electronic Cigarettes." Academic.oup.com, 22 Apr. 2012, academic.oup.com/ntr/article/15/1/158/1105400.

Goniewicz, Maciej Lukasz, et al. "Levels of Selected Carcinogens and Toxicants in Vapour from Electronic Cigarettes." Tobacco Control, vol. 23, no. 2, 6 Mar. 2013, pp. 133–139, www.ncbi.nlm.nih.gov/pmc/articles/PMC4154473/?report=classic, https://doi.org/10.1136/tobaccocontrol-2012-050859.

Guo, Xingtong, et al. "The Prevalence of Xerostomia among E-Cigarette or Combustible Tobacco Users: A Systematic Review and Meta-Analysis." Tobacco Induced Diseases, vol. 21, no. February, 9 Feb. 2023, pp. 1–11, https://doi.org/10.18332/tid/156676. Accessed 27 Feb. 2023.

Hong, Young-Seoub, et al. "Health Effects of Chronic Arsenic Exposure." Journal of Preventive Medicine and Public Health, vol. 47, no. 5, 11 Sept. 2014, pp. 245–252, www.ncbi.nlm.nih.gov/pmc/articles/PMC4186552/, https://doi.org/10.3961/jpmph.14.035.

Ji, Eoon Hye, et al. "Characterization of Electronic Cigarette Aerosol and Its Induction of Oxidative Stress Response in Oral Keratinocytes." PLOS ONE, vol. 11, no. 5, 25 May 2016, p. e0154447, https://doi.org/10.1371/journal.pone.0154447. Accessed 1 Mar. 2023.

Kanzaki, Hiroyuki, et al. "Pathways That Regulate ROS Scavenging Enzymes, and Their Role in Defense against Tissue Destruction in Periodontitis." Frontiers in Physiology, vol. 8, 30 May 2017, https://doi.org/10.3389/fphys.2017.00351. Accessed 12 Apr. 2022.

Kesimer, Mehmet. "Another Warning Sign: High Nicotine Content in Electronic Cigarettes Disrupts Mucociliary Clearance, the Essential Defense Mechanism of the Lung." American Journal of Respiratory and Critical Care Medicine, vol. 200, no. 9, 1 Nov. 2019, pp. 1082–1084, https://doi.org/10.1164/rccm.201905-1080ed.

Kim, Shin Ae, et al. "Cariogenic Potential of Sweet Flavors in Electronic-Cigarette Liquids." PLOS ONE, vol. 13, no. 9, 7 Sept. 2018, p. e0203717, https://doi.org/10.1371/journal.pone.0203717.

Kramarow, Ellen, and Nazik Elgaddal. Current Electronic Cigarette Use among Adults Aged 18 and Over: United States, 2021 Key Findings Data from the National Health Interview Survey. 2023.

Laçin, et al. " Effects of Formaldehyde on VEGF, MMP2, and Osteonectin Levels in Periodontal Membrane and Alveolar Bone in the Rats." Https://Www.researchgate.net/Profile/Ebru-Gokalp-Ozkorkmaz/Publication/329577863_Effects_of_formaldehyde_on_VEGF_MMP2_and_Osteonectin_levels_in_periodontal_membrane_and_alveolar_bone_in_the_rats/Links/5cef9890a6fdcc8475f6e267/Effects-of-Formaldehyde-On-VEGF-MMP2-And-Osteonectin-Levels-In-Periodontal-Membrane-And-Alveolar-Bone-In-The-Rats.pdf, 5 Dec. 2018.

Morán-Martínez, Javier, et al. "Genotoxicity in Oral Epithelial Cells in Children Caused by Nickel in Metal Crowns." Genetics and Molecular Research, vol. 12, no. 3, 1 Jan. 2013, pp. 3178–3185, https://doi.org/10.4238/2013.august.29.1. Accessed 1 Oct. 2023.

Muniz, Jefferson, et al. "E-Liquid Alters Oral Epithelial Cell Function to Promote Epithelial to Mesenchymal Transition and Invasiveness in Preclinical Oral Squamous Cell Carcinoma." Scientific Reports, vol. 13, no. 1, 27 Feb.

2023, https://doi.org/10.1038/s41598-023-30016-0.

Olmedo, Pablo, et al. "Metal Concentrations in E-Cigarette Liquid and Aerosol Samples: The Contribution of Metallic Coils." Environmental Health Perspectives, vol. 126, no. 2, Feb. 2018, p. 027010, www.ncbi.nlm.nih.gov/pmc/articles/PMC6066345/, https://doi.org/10.1289/ehp2175.

Ozturk, Onur, et al. "Effects of Smoking on Oral Cavity." Clin. Med, vol. 34, no. 1, 2017, pp. 3–7, dergipark.org.tr/en/download/article-file/333028, https://doi.org/10.5835/jecm.omu.34.01.002. Accessed 27 Jan. 2022.

Park, Jung Hyun, et al. "Hesperetin Mitigates Acrolein-Induced Apoptosis in Lung Cells in Vitro and in Vivo." Redox Report, vol. 23, no. 1, 1 Jan. 2018, pp. 188–193, https://doi.org/10.1080/13510002.2018.1535640. Accessed 10 May 2022.

Products, Center for Tobacco. "Results from the Annual National Youth Tobacco Survey." FDA, 2 Nov. 2023, www.fda.gov/tobacco-products/youth-and-tobacco/results-annual-national-youth-tobacco-survey#Findings%20on%20Youth%20Use%20for%20E-Cigarette%20Products.

Rogér, et al. Oral Trauma and Tooth Avulsion Following Explosion of E-Cigarette. 7 Jan. 2016, www.joms.org/article/S0278-2391(16)00009-4/fulltext#%20.

Rouabhia, Mahmoud, et al. "Cigarette Smoke and E-Cigarette Vapor Dysregulate Osteoblast Interaction with Titanium Dental Implant Surface." The Journal of Oral Implantology, vol. 45, no. 1, 1 Feb. 2019, pp. 2–11, pubmed.ncbi.nlm.nih.gov/30160606/, https://doi.org/10.1563/aaid-joi-D-18-00009.

Russell, Katie W., et al. "Adolescent Vaping-Associated Trauma in the Western United States." Journal of Surgical Research, vol. 276, 1 Aug. 2022, pp. 251–255, www.sciencedirect.com/science/article/pii/S0022480422000956, https://doi.org/10.1016/j.jss.2022.02.026. Accessed 29 Nov. 2022.

Sapru, Sakshi, et al. "E-Cigarettes Use in the United States: Reasons for Use, Perceptions, and Effects on Health." BMC Public Health, vol. 20, no. 1, 9 Oct. 2020, bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-020-09572-x, https://doi.org/10.1186/s12889-020-09572-x.

Su, Che-Chun, et al. "Incidence of Oral Cancer in Relation to Nickel and Arsenic Concentrations in Farm Soils of Patients' Residential Areas in Taiwan." BMC Public Health, vol. 10, no. 1, 12 Feb. 2010, https://doi.org/10.1186/1471-2458-10-67. Accessed 18 Nov. 2021.

Trybek, Grzegorz, et al. "The Effect of Nicotine on Oral Health." Baltic Journal of Health and Physical Activity, vol. 10, no. 2, 30 June 2018, pp. 7–13, www.balticsportscience.com/cgi/viewcontent.cgi?article=1580&context=journal, https://doi.org/10.29359/bjhpa.10.2.01.

Willershausen, Ines, et al. "Influence of E-Smoking Liquids on Human Periodontal Ligament Fibroblasts." Head & Face Medicine, vol. 10, no. 1, 15 Sept. 2014, https://doi.org/10.1186/1746-160x-10-39. Accessed 13 Feb. 2021.

Williams, Monique, et al. "Metal and Silicate Particles Including Nanoparticles Are Present in Electronic Cigarette Cartomizer Fluid and Aerosol." PloS One, vol. 8, no. 3, 2013, p. e57987, www.ncbi.nlm.nih.gov/pubmed/23526962, https://doi.org/10.1371/journal.pone.0057987.

Yu, Vicky, et al. "Electronic Cigarettes Induce DNA Strand Breaks and Cell Death Independently of Nicotine in Cell Lines." Oral Oncology, vol. 52, Jan. 2016, pp. 58–65, www.sciencedirect.com/science/article/pii/S1368837515003620?via%3Dihub, https://doi.org/10.1016/j.oraloncology.2015.10.018.

Zhu, Shu-Hong, et al. "Four Hundred and Sixty Brands of E-Cigarettes and Counting: Implications for Product Regulation." Tobacco Control, vol. 23, no. suppl 3, 16 June 2014, pp. iii3–iii9, https://doi.org/10.1136/tobaccocontrol-2014-051670.

SIBO and the Effectiveness of Treatment via Diet and Medication

Elizabeth C. Hersko

Elizabeth C. Hersko graduated cum laude in January 2024 with a Bachelor of Science degree in Biology and is currently attending the Touro University Physicians Assistance program in Middletown NY.

Abstract

This study delves into small intestinal bacterial overgrowth (SIBO), exploring its origins, diagnosis, and treatment methods. The research illuminates the complexities of SIBO, a condition characterized by an abnormal surge of bacteria in the small intestine. Factors contributing to SIBO include impaired motility, anatomical abnormalities, and digestive system dysfunctions. Diagnosing SIBO proves challenging due to its nonspecific symptoms which often overlap with other conditions like irritable bowel syndrome (IBS). Various diagnostic approaches, including lactulose breath testing, blood tests, stool analysis, and imaging, aim to identify SIBO and its underlying causes. Treatment involves dietary modifications—such as low FODMAP, biphasic, or fast track diets—antibiotics like rifaximin, and herbal therapies. However, concerns arise regarding extreme dietary restrictions causing potential malnutrition and eating disorders. This study highlights qualitative insights from women diagnosed with SIBO, revealing diverse treatment experiences. Understanding this connection empowers women to manage symptoms by adapting diets and stress management strategies. Overall, this comprehensive review unveils the intricate nature of SIBO, urging personalized approaches to its treatment and management.

Keywords:

Small intestinal bacterial overgrowth, SIBO, low FODMAP diet, antibiotics, rifaximin

Introduction

Small intestinal bacterial overgrowth, or SIBO, causes pain and ultimately lowers vitamin and mineral levels in the body, causing lasting damage to the bones and nervous systems. Many of those who suffer from SIBO are prescribed heavy doses of antibiotics and/or diet management, while others have utilized a functional medicine approach consisting of diet, physical therapy and natural supplements. This review will explore the effects of increased bacteria in the small intestine on individuals in an attempt to gather the information researchers have found. It will aim to answer the question "Can medication alone benefit patients with SIBO?" It will also include a qualitative research study conducted by the author which included a survey of four people suffering from SIBO. The primary purpose of the review of extant literature and the gathering of further research on the topic of SIBO is to determine the multiple ways people deal with their SIBO and how it is currently managed by healthcare professionals.

Methods of Research

Through Touro University, information and data has been collected from NIH, Pubmed, The Cleveland Clinic, The Mayo Clinic and other credible institutions. Data was also retrieved from four individuals who suffer from SIBO using methods from a qualitative research study. This is critical analysis and comprehensive review of SIBO and the Effectiveness of Treatment via Diet and Medication. Key terms used when researching were "the effectiveness of antibiotics as treatment for SIBO," "homeopathic remedies for SIBO," "Small Intestinal Bacterial

Overgrowth," "FODMAP diet," "rifaximin," "the gastrointestinal tract," "chinese herbal medication," "causes of SIBO," "IBS and its relation to SIBO," "gut flora," and "SIBO treatment."

Discussion

How Does SIBO Occur?

SIBO occurs when there's an abnormal increase in the population of bacteria in the small intestine (Cleveland Clinic, 2021). Normally, the small intestine contains a relatively low number of bacteria compared to the large intestine. Several factors can contribute to SIBO. Impaired motility or movement of the small intestine, due to conditions like intestinal obstructions or muscular issues, can lead to stagnant areas where bacteria can overgrow. Anatomical abnormalities or surgeries, like gastric bypass, which alters the structure of the small intestine, might also disrupt the natural flow of digestive contents, allowing bacteria to accumulate. Additionally, conditions that affect the normal functioning of the digestive system, like low stomach acid, pancreatic insufficiency, or immune system disorders, can create an environment conducive to bacterial overgrowth in the small intestine. These factors collectively contribute to the disruption of the delicate balance of gut bacteria, leading to the symptoms associated with SIBO, such as bloating, abdominal pain, diarrhea, and nutrient malabsorption (Dukowicz, et al., 2007).

A healthy gut is composed of numerous microorganisms depending on age, environmental reasons, antibiotic use and infant transitional stages. The human microbiota diversity changes as one ages until they reach three years of age. At age three, a child's gut microbiota is similar to most adults: firmicutes (lachnospiraceae and ruminococcaceae), bacteroidetes (bacteroidaceae, prevotellaceae, and rikenellaceae), and cctinobacteria (bifidobacteriaceae and coriobacteriaceae). A healthy gut can handle diverse foods, does not have digestive discomfort, reduces inflammation, and aids in maintaining good energy levels together with a healthy immune system. Factors like diet, stress levels, medications, and underlying health conditions can greatly impact gut health. Maintaining a healthy gut involves consuming a

balanced diet rich in fiber, prebiotics, and probiotics, managing stress levels, getting enough sleep, staying hydrated, and avoiding excessive use of antibiotics or unnecessary medications that can disrupt the gut microbiome. Taking care of gut health can significantly impact overall well-being and quality of life (Rinninella et al., 2019).

There is a delicate balance of flora in the small intestine. This is maintained through multiple factors: peristalsis, bile and enzymes, stomach acid, and mucosal immunity. Peristalsis is the typical contractions and movements of the small intestine which aids in flushing out bacteria in order to prevent overgrowth and limit bacterial buildup. The liver and the pancreas release substances, such as bile and digestive enzymes in order to aid digestion and help control bacterial growth. The stomach is an extremely acidic environment which helps keep bacterial levels low in the upper digestive tract. The acid in the stomach also kills a significant portion of ingested bacteria. The small intestine has a protective mucosal lining that functions to prevent the overgrowth of bacteria by recognizing and eliminating potential threats like bacteria, parasites, and viruses. These mechanisms collectively create an environment that limits bacterial colonization and ensures a balanced microbial population within the small intestine (Gorbach, 1996). Disruptions in these factors due to various conditions can lead to an imbalance, contributing to conditions like SIBO (Wilkinson, 2022).

When there is an issue with the emptying of food contents from the small intestine into the large intestine, an environment where bacteria from the small intestine proliferate excessively may be created. The small intestine typically has a relatively low bacterial count compared to the large intestine. However, if this mechanism is slowed or impaired anatomically, the bacteria in the small intestine have more time to breed, and the bacteria in the large intestine may begin to creep upward. This may lead to an overgrowth of bacteria in the small intestine. The bacteria in the small intestine are responsible for breaking down carbohydrates by converting them into gas and short-chain fatty acids. If there is an increase of bacteria in the small intestine there will be more gas in the small intestine, which causes bloating and diarrhea. The bacteria also absorb vitamins, bile salts, and proteins that the body needs in order to function; as a result the digestive system does not absorb important nutrients, leading to poor digestion specifically for fats, calcium, and fat-soluble vitamins. This causes vitamin and mineral deficiencies and can lead to further damage in the future (Cleveland Clinic, 2021). Consequently, the bacteria in the small intestine might ferment undigested food, causing abdominal pain, bloating, diarrhea, and malabsorption of nutrients (Ren et al., 2022).

Some studies indicate that up to 80% of people with irritable bowel syndrome (IBS) have SIBO. The prevalence among healthy people is unknown. Doctors assume that SIBO is generally underdiagnosed, since mild cases may be asymptomatic, while moderate cases feature many non-specific symptoms that overlap with other conditions, such as IBS. SIBO is not often directly tested for, and even when it is, the tests available are not always accurate (SIBO, 2021). Often, a healthy body strives to rectify imbalances naturally. However, bacterial imbalances can lead to various illnesses. Some examples include clostridioides difficilem (C. diff): an overgrowth can result in multiple green, foul-smelling, watery stools, accompanied by abdominal pain and tenderness. Enterococcus faecalis is a bacterium that contributes to post-surgical infections in the abdomen and urinary tract infections. Escherichia coli (E. coli) resides in the colon of most healthy adults helping the body digest foods. Certain strains of E. coli are infectious and are commonly responsible for adult diarrhea, it is the main cause of the common stomach virus. Bacteroides overgrowth is linked to colitis, a painful inflammation of the colon. These imbalances pose a challenge in accurately diagnosing patients, adding complexity to medical assessments (Zhang et al., 2015).

Diagnosing SIBO

The Cleveland Clinic proposes that there are other factors that contribute to diagnosis of SIBO, such as age, or illnesses that affect motility—like diabetes, lupus, celiac disease, inflammation and irritable bowel syndrome, inflammatory bowel disease, pancreatitis, colon cancer, scleroderma, chronic renal failure, cirrhosis—immunodeficiency orders, abdominal surgery, or radiation exposure (Cleveland Clinic 2021). It is extremely difficult to diagnose SIBO due to the fact that symptoms of SIBO are nonspecific, and vary from mild to severe. Bloating, stomach pain and distension, nutrient deficiency, specifically vitamin B12 and vitamin D, weight loss,

chronic diarrhea and fatigue are all possible SIBO symptoms (Ahuja, 2019). Diagnosing SIBO is complex and requires multiple examinations, tests, and time to truly determine. Responses from the qualitative study of women between ages 20-45 shows that 75% of respondents only had a definitive diagnosis after 120+ days. Proving how complex and difficult it is to diagnose SIBO.

There are several diagnostic tests that can be employed to identify potential issues such as bacterial overgrowth in the small intestine or poor fat absorption, which may underlie symptoms (Mayo Foundation, 2022). These tests encompass a range of methods. The gold standard diagnostic test is a small intestine aspirate

and fluid culture that requires an endoscopic procedure to obtain a sample of intestinal fluid. This sample is cultured in a lab to determine the presence of bacterial overgrowth. Lactulose breath testing or hydrogen breath testing involves a noninvasive assessment where the patient drinks a glucose-water mixture, and the subsequent measurement of exhaled hydrogen or methane levels. While it is widely available, this method lacks specificity compared to other tests for diagnosing bacterial overgrowth. Blood testing, although less common, can provide valuable insights. Elevated C-reactive protein levels might signal inflammation, while a complete blood work count (CBC) assesses white blood cell count and screens for vitamin deficiencies associated with small intestinal bacterial overgrowth (SIBO, 2021). Stool tests evaluate fat absorption and help rule out other gastrointestinal conditions. Imaging tests, including X-rays, CT scans, or MRIs, are occasionally recommended to identify structural abnormalities, intestinal blockages, or motility issues within the intestine (Dukowicz et al., 2007).

Treatment

There are multiple dietary restrictions that advertise as gut healing remedies. The low FODMAP diet (Fermentable Oligosaccharides, Disaccharides, Monosaccharides, and Polyols) is a diet that generally involves strict elimination of foods followed by systematic reintroduction to identify specific trigger foods. This attempts to allow for a more personalized and sustainable approach to managing digestive health. FODMAP is a dietary approach that is often recommended for those attempting to manage symptoms of many gastrointestinal issues. It is not a SIBO specific diet. FODMAPS are types of carbohydrates that can ferment in the gut, leading to bloating, gas, abdominal pain, and other discomforts in those with gastrointestinal issues. This diet involves avoiding foods high in these fermentable compounds, such as certain fruits (like apples and cherries), vegetables (such as onions and garlic), dairy products, wheat-based items, and certain sweeteners (Veloso, 2021). SIBO is when there is an excessive number of bacteria in the small intestine, leading to various digestive symptoms. The connection between a low FODMAP diet and SIBO lies in the fermentable nature of certain carbohydrates. FODMAPs are fermentable carbohydrates that can exacerbate symptoms in individuals with SIBO. When these carbohydrates are consumed, they can ferment in the small intestine, causing gas production, bloating, and discomfort due to the extreme overgrowth of bacteria (de Roest et al., 2013). By reducing intake of these FODMAP-rich foods, individuals may experience relief from their SIBO symptoms such as decreased gas production, less stomach discomfort and bloating. A low FODMAP diet requires significant restriction of various foods, many of which are primary sources of essential nutrients and vitamins that are crucial for maintaining overall health . This restriction can pose challenges as these foods provide necessary elements vital for proper bodily functions. Hence, it is important to note that FODMAP is not a sustainable lifestyle and can lead to extreme vitamin and mineral deficiencies due to the restrictive nature of the diet (Bascuñán et al., 2019).

Similar to FODMAP, the bi-phasic and fast tract diets severely limit multiple categories of food during each week of the cycle. These diets claim to be designed to enhance gut health and motility among patients suffering with gut related symptoms. The biphasic diet involves two phases. The first phase, often called the "SIBO-specific" phase, restricts fermentable carbohydrates like certain fruits, vegetables, processed grains and sugars, and some dairy products. This phase aims to starve or reduce the food source for bacteria in the small intestine. After a specified period, individuals transition to the second phase, which involves reintroducing restricted foods gradually to determine which foods trigger which symptoms. This is a more simplified version of the diet, focusing on reducing fermentable carbohydrates known as FODMAPs. It involves avoiding or limiting certain foods high in these compounds that can contribute to bacterial overgrowth and related symptoms. The Fast Track Diet simplifies the initial phase of dietary restriction without the gradual reintroduction phase seen in the biphasic diet (Veloso, 2021). These diets aim to alleviate symptoms associated with SIBO by reducing the intake of carbohydrates that can potentially feed the bacteria in the small intestine. However, there is much concern for patients who restrict their diets too much, causing eating disorders and/or malnutrition. Categorizing nutritious and healthy foods into categories that limit a person from specific vitamins can harm the body and alter the way the person views food in the long run, possibly causing more harm than the SIBO.

In addition to dietary approaches, medications such as rifaximin are often used to help combat SIBO. Rifaximin, an antibiotic that is primarily used to treat gastric infections, holds significant promise in SIBO treatment due to its unique characteristics. Its primary active ingredient is rifaximin, a semi-synthetic derivative of rifamycin. This is due to the fact that rifaximin, unlike other antibiotics that may foster bacterial resistance over time, operates in a way that discourages such adaptation; this characteristic lies in its mechanism of action and pharmacokinetics and enhances its effectiveness in combating SIBO while mitigating concerns regarding bacterial resistance (Pimentel,

2009). When taken orally, rifaximin remains largely within the gastrointestinal tract without significantly entering the bloodstream. It exerts its antimicrobial effects predominantly within the gut, targeting and acting against gram-positive and gram-negative bacteria. The low systemic absorption reduces its exposure to bacteria outside the gastrointestinal tract, minimizing the opportunity for widespread resistance development in other parts of the body. Additionally, rifaximin has a broad spectrum of activity against a range of bacteria without fostering resistance. Its mode of action involves inhibiting bacterial RNA synthesis, which contributes to its effectiveness against various bacterial strains while limiting the development of resistance. These combined factors make rifaximin less prone to fostering bacterial resistance compared to some other antibiotics (Koo, 2010).

Although antibiotics may seem like a simple cure for SIBO, there has been a lot of research done in order to examine the effectiveness of antibiotics as a treatment for SIBO. In order to determine the effectiveness of Rifaxamin, studies have been conducted with SIBO patients who have been diagnosed through Lactulose Breath Testing (LBT). The researchers offered patients 1200 mg of Rifaxamin daily for 10-14 days or four weeks of herbal therapy in order to combat their SIBO. Patients choose their method of treatment and after four weeks were reassessed for SIBO through LBT. The conclusion was that herbal therapies are as effective as rifaximin, if not more when it comes to treating SIBO. The study also found that patients that did not respond to the antibiotics did respond to the chinese herbal therapy (Chedid et al., 2014).

There are recent studies that have found that Chinese herbal medicine, or CHM, has been able to aid those with Small Intestinal Bacterial Overgrowth. These studies have highlighted the efficacy of herbal treatments in alleviating SIBO symptoms, offering promising alternatives to conventional therapies. Herbs like oregano oil, berberine, garlic, and neem have antimicrobial properties that can help reduce bacterial overgrowth in the small intestine. When used in specific doses and combinations these herbs may help rebalance the gut microbiota. Herbal teas such as chamomile and ginger are known to have mild anti-inflammatory properties and have been proven to decrease inflammation levels, a major symptom of SIBO (Ren et al., 2020).

Qualitative Study

The author asked four women, between the ages of 20-45, who have been diagnosed with SIBO, what methods of treatment they used after they were diagnosed with SIBO (see APPENDIX). Subjects A and B took rifaximin twice without any reprieve. Subject A, who tested positive for SIBO through LBT and blood work, had a regimen of herbal supplements that have helped alleviate her symptoms. The protocol prescribed by a homeopathic nutritionist was as follows: take ADP, allicidin, and berberine three times a day; mid morning, take S. boulardii and propbiospore; be careful to take it at least two hours apart from the herbs. Subject A found that the herbal supplements had an immensely positive effect on her gut health. Subject B, who tested positive for SIBO through Lactulose breath testing, has found that Magnesium, a low FODMAP diet and stool softeners has helped alleviate her symptoms. Subject C, who tested positive for SIBO through Lactulose breath testing, is currently taking rifaximin and has changed her diet in order to alleviate her symptoms. Subject C is working with a licensed nutritionist that specializes in chronic and gastrointestinal issues, keeping a food diary, monitoring stomach pain and symptoms in order to target problem foods and eliminate them from her diet. Subject D, who tested positive for SIBO through LBT, initially started on a low FODMAP diet and saw no results; she then took rifaximin and felt immediate reprieve from her symptoms.

Conclusion

Treating SIBO is like navigating a strategic board game where the goal is to restore balance and harmony within the gut. Picture it as a multi-level quest with various challenges to overcome and different strategies to employ. At the start of the game, you are presented with a complex maze representing the digestive system, with its twists and turns symbolizing the intricate pathways of the small intestine. The enemy, represented by an overgrowth of bacteria, is lurking in certain areas of the maze, causing chaos and disrupting the balance. Players begin by selecting their team of strategies and treatments, each represented by different pieces on the board. Antibiotics or herbal remedies act as warriors, fighting against the invading bacteria. Diet modifications and lifestyle changes such as a low FODMAP diet function as shields, providing protection and support. Probiotics and digestive enzymes become allies, aiding in the restoration of balance. As the game progresses, players strategically move their pieces through the maze, carefully selecting the right combination of treatments to target the enemy bacteria while maintaining and supporting a healthy gut. Each move made by the player represents a treatment decision, considering factors like effectiveness, side effects, and individual tolerance. Throughout the game, players encounter challenges and obstacles, represented by symptoms such as bloating, discomfort, and digestive distress. The key

is to adapt and adjust strategies accordingly, fine-tuning the approach to find the most effective combination for each player's unique gut landscape. Successful navigation through the maze requires patience, persistence, and a keen understanding of the game's mechanics. Players must be vigilant, constantly monitoring their progress and adjusting their tactics to overcome setbacks and reach the ultimate goal: a harmonious, balanced gut environment. Ultimately, winning the game involves restoring equilibrium within the digestive system, defeating the bacterial overgrowth, and allowing the gut to function optimally once again. While SIBO has no cure, each move, decision, and adjustment made by the patient, or player, contributes to this overarching goal of achieving digestive wellness. This is what treating SIBO is all about. Medication, dietary changes, and herbal supplements are all tools that aid in the treatment of SIBO. You win the game by delicately rebalancing the bacteria in the gut regardless of the methodology. Unfortunately, there is no definitive "one size fits all" treatment for SIBO but there are definitely options. Trial and error is the only way to combat each individual's case of SIBO.

References

Ahuja, A., & Ahuja, N. K. (2019). Conventional, complementary, and controversial approaches to small intestinal bacterial overgrowth. Practical Gastro.

https://practicalgastro.com/2018/10/31/conventional-complementary-and-controversial-a pproaches-to-small-intestinal-bacterial-overgrowth/.

Bascuñán, K. A., Elli, L., Pellegrini, N., Scricciolo, A., Lombardo, V., Doneda, L., Vecchi, M., Scarpa, C., Araya, M., & Roncoroni, L. (2019). Impact of FODMAP content restrictions on the quality of diet for patients with celiac disease on a gluten-free diet. Nutrients,

11(9), 2220. https://doi.org/10.3390/nu11092220

Chedid, V., Dhalla, S., Clarke, J. O., Roland, B. C., Dunbar, K. B., Koh, J., Justino, E., Rn, E. T., & Mullin, G. E. (2014). Herbal therapy is equivalent to Rifaximin for the treatment of small intestinal bacterial overgrowth. Global Advances in Health and Medicine, 3(3), 16–24. https://doi.org/10.7453/gahmj.2014.019.

Cleveland Clinic SIBO (small intestinal bacterial overgrowth): Symptoms, diet, causes & what it is.. (2021). https://my.clevelandclinic.org/health/diseases/21820-small-intestinalbacterial-overgrowth-sibo.

de Roest, R. H., Dobbs, B. R., Chapman, B. A., Batman, B., O'Brien, L. A., Leeper, J. A., Hebblethwaite, C. R., & Gearry, R. B. (2013). The low fodmap diet improves gastrointestinal symptoms in patients with irritable bowel syndrome: A prospective study.

International Journal of Clinical Practice, 67(9), 895–903.

https://doi.org/10.1111/ijcp.12128.

Dukowicz, A. C., Lacy, B. E., & Levine, G. M. (2007). Small intestinal bacterial overgrowth: a comprehensive review. Gastroenterology & hepatology, 3(2), 112–122.

Gorbach, S. L. (1996). Microbiology of the gastrointestinal tract. National Library of Medicine. https://www.ncbi.nlm.nih.gov/books/NBK7670/.

Koo, H. L., & DuPont, H. L. (2010). Rifaximin: A unique gastrointestinal-selective antibiotic for enteric diseases. Current Opinion in Gastroenterology, 26(1), 17–25. https://doi.org/10.1097/mog.0b013e328333dc8d.

Mayo Foundation for Medical Education and Research. (2022). Small intestinal bacterial overgrowth (SIBO). Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/ small-intestinal-bacterial-overgrowth/ diagnosis-treatment/drc-20370172.

Pimentel, M. (2009). Review of Rifaximin as treatment for SIBO and IBS. Expert Opinion on

Investigational Drugs, 18(3), 349–358. https://doi.org/10.1517/13543780902780175.

Rusev, Alex. (2022). The Complete Guide to SIBO and how to restore digestive balance. Living

Nutrition. https://livingnutrition.co.uk/ the-complete-guide-to-sibo/.

Ren, X., Di, Z., Zhang, Z., Fu, B., Wang, Y., Huang, C., & Du, Y. (2020). Chinese herbal medicine for the treatment of small intestinal bacterial overgrowth (SIBO). Medicine, 99(51). https://doi.org/10.1097/md.0000000000023737.

Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G., Gasbarrini, A., & Mele, M. (2019). What is the healthy gut microbiota composition? A changing ecosystem across age, environment, diet, and diseases. Microorganisms, 7(1), 14.

https://doi.org/10.3390/microorganisms7010014.

Veloso, H. G. (2021). FODMAP diet: What you need to know. Johns Hopkins

Medicine. https://www.hopkinsmedicine.org/ health/wellness-and-prevention/fodmapdiet-what-you-need-to-know#:~:text=When%20 people%20say%20%E2%80%9CFODM

AP%20diet,and%20which%20foods%20reduce%20 symptoms.

Wilkinson, J. (2022). Discover the real difference between good and bad gut flora.

Verywell Health. https://www.verywellhealth.com/what-are-gut-flora-797425.

Zhang, Y. J., Li, S., Gan, R. Y., Zhou, T., Xu, D. P., & Li, H. B. (2015). Impacts of gut bacteria on human health and diseases. International journal of molecular sciences, 16(4),

7493–7519. https://doi.org/10.3390/ijms16047493.

Non-surgical Treatment Options for Male-Pattern Baldness

Robert Schiffer

Robert Schiffer will graduate in September 2024 with a Bachelor of Science Degree in Biology

Abstract

Male pattern baldness affects nearly 50% of the world's male population. It is associated with physiological conditions such as cardiovascular disease as well as psychological issues with self-image and self-esteem. Although surgical treatments exist, they are associated with risks and complications. Various non-surgical treatment modalities for male pattern baldness are available for patients. Topical and oral formulations of minoxidil, finasteride, and dutasteride can be used, in addition to low level light therapy (LLLT) and platelet rich plasma (PRP) therapy. As many treatment options exist, it may be challenging for patients to decide which to choose. Although there have been few studies within the literature on the topic, there has been no consensus as to which non-surgical treatment is the most effective option. Although all the aforementioned treatment have been shown to be effective, more studies are needed to definitively conclude whether there is one that is superior to the others.

Introduction

Male pattern baldness is a genetic condition in which hair loss results as an excessive response to physiological androgens, or hormones that direct and regulate male characteristics. It is quite prevalent within the general population, affecting nearly half of all males worldwide. Physiologically, when androgen receptors are activated, the growth phase of hair follicles shortens. Therefore, when there is an excessive response to androgens, there is less growth of hair follicles, and they weaken, thin out, shorten, and die, leading to baldness (Katzer, 2019).

Although male pattern baldness is not deadly, it can still come with adverse effects. For example, hair loss can have a great effect on individual self-image and self-esteem. Studies have shown that those with alopecia report less self-esteem than those who don't have hair loss. Additionally, there are many studies within the literature demonstrating a clear association between male pattern baldness and cardiovascular diseases such as diabetes, myocardial infarction, or hypertension (Fattah & Darwish, 2011).

Therefore, for the psychological well being of patients, it is imperative that treatments for male pattern baldness are effective and readily available for those that are affected. Although surgical hair transplantation is an option for patients, many patients may be hesitant to undergo the procedure due to its association with complications such as bleeding, swelling, folliculitis, scalp numbness, epidermal cysts, and infection (Garg & Garg, 2021). Many patients opt for non-surgical procedures or medications to control their baldness. To treat male pattern baldness and control its negative outcomes and associations, it is essential to identify the optimal and most effective treatment and management.

Male pattern baldness can be addressed with a variety of non-invasive treatments; Minoxidil, oral and topical, Finasteride, Dutasteride. platelet rich plasma (PRP), and low level light therapy LLLT) will be compared, both individually or in conjunction with each other, to determine the most effective treatment plan.

Methods

To investigate the optimal non-surgical management of androgenetic alopecia, a comprehensive literature review was conducted. The online scientific database, PubMed, was used as a means to collect previous studies on the topic. The search engine of PubMed was used, and relevant literature was identified by searching with the following keywords: "androgenetic alopecia treatment", "androgenetic alopecia management", and "male baldness medication". Articles were excluded if they included surgical treatments, if they were only abstracts without full articles, if they were in a language other than English, and if they were purely review articles. After the exclusion criteria was applied, the relevant articles identified from the search were all reviewed and the data within each of them was collected and analyzed.

Discussion

There are a variety of non-surgical treatments for male-pattern baldness. Each class of treatment has a different mechanism of effectively increasing hair growth. Hair growth occurs continuously within a cycle of four distinct stages. The anagen stage is characterized by growth; it is where the hair follicle undergoes several rounds of mitotic activity to produce a hair shaft. Next, the catagen phase is characterized by regression, where follicles may detach from the dermal papilla resulting in loss of the hair shaft. The telogen phase is essentially a resting stage where there is no further growth or maturation of hair follicles. Finally, the exogen phase is the stage of shedding, when a hair follicle is pushed out of the telogen phase and into the anagen phase, thereby shedding old hair in preparation for the growth of new hair (Natarelli et. al., 2023). While natural bodily processes such as the increase in androgen activity, tends to keep hair follicles in the catagen and telogen phases, all the medications and non-surgical treatments of male pattern-baldness seek to push follicles out of the catagen and telogen phases and into the anagen phase.

Medication Description

Minoxidil

Minoxidil, one of the most commonly utilized medications for hair loss, comes in both topical as well as oral formulations. Although only the topical drug is FDA approved for androgenetic alopecia, oral minoxidil is currently used by

many as an alternative, as it has shown to be effective as well (Randolph & Tosti , 2021). The mechanism of action of minoxidil involves the drug binding to and opening ATP sensitive potassium channels, which leads to membrane hyperpolarization. This directly leads to relaxation of vascular smooth muscle cells, which causes vasodilation of arterioles. As more blood flows through vessels, more nutrients and oxygen are delivered to hair follicles, which then facilitates their growth and sustenance (Keerti et. al, 2023).

5-alpha-reducatse inhibitors

Another class of medications used to treat androgenetic alopecia are the 5-alpha-reductase inhibitors, which also come in both topical and oral formulations. Unlike minoxidil, only the oral formulations of the 5-alpha-reducatse inhibitors are FDA approved for androgenetic alopecia, even though the topical formulations are utilized by the general population as well. This class of medications include finasteride and dutasteride. Their mechanism of action involves the inhibition of the conversion of testosterone into dihydrotestosterone (DHT). DHT, a more potent androgen, binds to receptors located on or near scalp hair follicles, inhibiting follicle growth and maturation, and causing shrinking and early death of the follicles (Ustuner, 2013). By inhibiting the formation of DHT, the 5-alpha-reductase inhibitors allow for less binding of androgen receptors on the scalp hair follicles, which permits them to continue growing and maturing instead of shrinking. The difference in finasteride and dutasteride is that while finasteride only inhibits one isoenzyme of 5-alpha-reductase, dutasteride inhibits both isoenzymes (Nickel, 2004).

Platelet Rich Plasma

Platelet rich plasma (PRP) injections are another nonsurgical modality of treatment for androgenetic alopecia. This process involves extensive preparation as blood must be extracted from the patient themselves and be centrifuged down to remove other components such as red blood cells. After centrifugation and extraction of unnecessary components, what is left is plasma that is rich in platelets as well as platelet activating factors. This platelet rich plasma has many uses in medicine outside of androgenetic alopecia; it is often used to treat torn muscles and tendons as well as arthritis and joint injuries (Everts et. al, 2020). Its mechanism of action involves the activated platelets and platelet activating factors within the plasma releasing many different growth factors including molecules such as vascular endothelial growth factor (VEG-F), epidermal growth factor (EGF), and insulin-like growth factor (IGF-1) (Stevens & Khetarpal, 2018). All of these growth factors stimulate cell growth, proliferation, maturation, as well as growth of new blood vessels. In androgenetic alopecia, PRP is injected into the scalp where all of the growth factors contribute to an environment where hair follicles are encouraged to grow, mature, proliferate, and thrive.

Low Level Laser Therapy

Another non-surgical treatment modality is low-level laser therapy (LLLT). LLLT utilizes a range of wavelengths of light on the spectrum from red to infrared. The laser light penetrates through the skin, and acts upon hair follicles. In general, hair follicles can be in the anagen, or growth phase, catagen, or regressing phase, or the telogen, or resting phase. When LLLT reaches the hair follicles, it acts upon telogen follicles to stimulate them to re-enter the anagen phase. Additionally, LLLT acts upon anagen hair follicles to prolong the duration of anagen, allowing more time for the follicle to grow, mature, and proliferate. With more hair follicles spending more time in a longer anagen phase, this fosters an environment conducive for greater hair growth, thereby combating androgenetic alopecia.

Review of all Treatments

There have been several studies comparing the efficacy of the various non-surgical treatments of androgenetic alopecia to elucidate the most optimal management. In one comprehensive systematic review and meta-analysis, Gupta et al., the relative efficacies of oral finasteride and dutasteride, topical minoxidil 2% and 5%, LLLT, and PRP were all compared to one another. This systematic review was quite extensive and all encompassing as it included seventy-eight full studies with a total of 15,888 study participants. All studies that were included were required to report the mean change in hair count from before starting the therapy compared to after the therapeutic intervention. All studies regarding one specific intervention had their mean change in hair count averaged out, and at the end, therapeutic interventions were ranked from greatest mean change in hair count to least mean change in hair count.

Based on assessments of individual studies with data regarding treatments compared to placebo as well as comparing two treatments with each other, this systematic review concluded that LLLT resulted in the largest increase in hair count. Additionally, although all treatments resulted in increased hair count, there was no significant difference in hair count between PRP, finasteride, minoxidil 2%, minoxidil 5%, and dutasteride. Also, minoxidil 2% and 5% resulted in the largest number of adverse events including dermatological and cardiovascular side effects. All in all, based on the data provided by Gupta et al., it

seems that LLLT is superior to other non-surgical treatments, and that Minoxidil is inferior as it provides no advantage over other treatments, but comes with the most potential adverse events (Gupta et. al , 2018).

Although the systematic review by Gupta et al. is quite comprehensive and offers invaluable information on the topic, it is not without its flaws. Firstly, the study mentions that 88.1% of all participants in all of the studies that were included in the review were male. This means that approximately 1,900 individuals included in the study were females. This is a major source for bias within the study, because while the main focus was on male pattern baldness, a significant amount of data is coming from females. Another limitation of this systematic review is the fact that it only included studies that reported on mean change in hair counts. However, there are many studies within the literature on nonsurgical management of androgenetic alopecia that report their results through other modalities such as physical images or hair density. By limiting the systematic review only to studies that report on mean change in hair count, the review is shutting out a massive amount of potentially useful data. Nevertheless, even with all its limitations, Gupta et al. provided an enormous amount of valuable information on the topic. Because it compared all therapeutic interventions by a single factor, mean change in hair count, and included seventy-eight studies with over 15,000 participants, the conclusions that they drew from their data was valid and based on well-proven evidence.

In a different systematic review 2% minoxidil, 5% minoxidil, 1mg finasteride, and LLLT were all compared to each other as well as to placebo. After comparing all the studies that were included in the review, none of the four therapeutic interventions were found to significantly better than another. However, all four therapeutic interventions were found to result in significantly more hair growth than placebo. Therefore, although it could not be said which is the more effective therapy, there is definitely sufficient evidence that minoxidil at varying dosages, finasteride and LLLT all improve hair growth in androgenetic alopecia (Adil & Goodwin, 2017).

Finasteride vs Dutasteride

A review by Zhou et al. studied the difference in efficacy specifically between finasteride and dutasteride. As mentioned earlier, dutasteride inhibits both isoenzymes of 5-alpha reductase while finasteride only inhibits one isoenzyme. Therefore, theoretically it would make sense for dutasteride to be more effective. However, clinical evidence is needed before making recommendations to patients. Zhou et al. studied these two medications and provided clinical evidence comparing their efficacies. Three studies with a total of 576 participants were all included in the review. Firstly, dutasteride resulted in a greater mean change in hair count than finasteride. Secondly, when a third party analyzed before and after treatment photographs of study participants' scalps, the dutasteride patients were assessed to have better looking scalps with more hair than the finasteride patients. Lastly, when patients themselves were asked to subjectively assess their satisfaction with hair growth following treatment, the dutasteride patients were significantly more satisfied than the finasteride patients. For all these reasons, Zhou et al. concluded that although both treatments can improve hair growth in androgenetic alopecia, there is sufficient evidence to conclude that dutasteride is more effective than finasteride (Zhou, 2019).

Minoxidil vs Finasteride

A study sought to compare the efficacy of topical minoxidil with the efficacy of oral finasteride, two of the most commonly used treatments of androgenetic alopecia. Study participants were divided into two groups with each group taking either minoxidil or finasteride. The participants were subsequently followed over a period of two years, with their scalps and hair counts being assessed every three to six months. After the two-year period, there were no significant differences in the results between the two treatments, as 82% of minoxidil users reported no further hair loss while 85% of finasteride users reported no further hair loss. However, at the three month mark, a significantly greater percentage of minoxidil users reported increased hair growth than finasteride users, and this subjective reporting was confirmed by analysis of thick hair counts, as the minoxidil group saw a 43% increase compared to only a 25% increase in the finasteride group at the three month mark. However, as time went on until the final two year mark, the differences between the finasteride and minoxidil groups evened out, and they produced similar results at the end of the two year mark, as mentioned earlier (Saraswat, 2003). From this data, it can be concluded that although topical minoxidil may produce faster results than oral finasteride, both treatments have similar long-term results. Although this study provided important data with a comparison of two of the most popular treatments for androgenetic alopecia, it only included approximately 100 study participants, and so any conclusions drawn by a relatively small-scale study such as this one, may not necessarily be the most definitive or decisive.

Based on these studies, although definitive conclusions may not be drawn without further, more comprehensive

studies, important inferences and understandings can be made. For example, Zhou et al. concluded that dutasteride is more effective than finasteride. Saraswat et al. found that although topical minoxidil works faster than oral finasteride, there is no significant difference in the overall effectiveness in the two. From these two studies, it is impossible to answer whether dutasteride or minoxidil achieves more rapid results. However, if oral finasteride is on equal footing as topical minoxidil as per Saraswat et al, and oral dutasteride is more effective than oral finasteride as per Zhou et al., then it would be reasonable to deduce that oral dutasteride may be more effective overall than topical minoxidil.

LLLT vs Minoxidil

A study compared the use of LLLT with minoxidil and the use of minoxidil alone. Although improvement in hair loss was seen in both study groups, the LLLT with the minoxidil group resulted in better outcomes than the minoxidil group alone (Mokhtari et. al , 2023). Although this study shows that LLLT enhances the efficacy of minoxidil and supports the use of combination treatment, it does not strictly compare one treatment against the other, and so no conclusions can be drawn regarding which one treatment may be better than the other. In contrast to that, a different study did compare the two individual treatments. This study separated participants into three different groups; one group was treated with LLLT alone, one group was treated with 5% minoxidil alone, and one group was treated with the combination of LLLT and 5% minoxidil. The data showed that all three groups resulted in the treatments producing decreased hair loss. However, there was no significant difference between the minoxidil group and the LLLT group. However, the minoxidil and LLLT combination group resulted in the best outcomes including the greatest increase in the number of regrowing hair follicles, and the greatest percentage of patient satisfaction (Esmat, 2017et. al, 2017). This study also presents valuable data showing once again the superiority of the combination of treatments to either individual treatment, as well as the important finding of no significant difference between either individual treatment. However, this study was conducted with only forty-five study participants, and all the study participants were female. This limits the relevance of its findings toward men with androgenetic alopecia, but as it is one of very few studies within the literature directly comparing the individual treatments of LLLT and minoxidil, it is nonetheless useful information.

Although no definitive conclusions can be drawn when comparing LLLT to oral medications such as finasteride or dutasteride, reasonable inferences may be deduced. Esmat et al. concluded that there was no difference between LLLT treatment and topical minoxidil. Since Saraswat et al. found no significant difference between topical minoxidil and oral finasteride, it is reasonable to infer that there may also be no significant difference between LLLT and oral finasteride. However, as both Mokhtari et al. and Esmat et al. concluded that combination treatment of LLLT and minoxidil is more effective than minoxidil alone, it is also reasonable to infer that the combination of LLLT and minoxidil would be more effective than oral finasteride alone as well.

PRP vs Minoxidil

PRP is a more recently popular treatment that is being utilized by an increasing number of people affected by androgenetic alopecia, but it has yet to obtain the FDA approval that topical minoxidil and oral finasteride have already had for years. In another study, participants were separated into two different groups. One group received PRP therapy alone, while one group received minoxidil alone. The PRP group resulted in better outcomes across the board. PRP resulted in better before and after photographs, higher patient satisfaction score, higher scores on hair growth questionnaires, and better results on hair pull tests. Although this study was also done on a relatively smaller scale with only forty patients, the data seems to point to PRP being more effective than topical minoxidil.

That showed PRP to be more effective than topical minoxidil and Saraswat et al. found no difference between oral finasteride and topical minoxidil, it would be reasonable to infer that PRP is more effective than oral finasteride as well. Esmat et al. found no significant difference between LLLT therapy and topical minoxidil and so if Verma et al. is showing PRP to be superior to topical minoxidil, then PRP may be more effective than LLLT as well. However, there is insufficient evidence to draw any inferences or conclusions in regard to the comparison of PRP and combination LLLT and minoxidil or the comparison of PRP and dutasteride (Verma et al).

Conclusion

Male pattern baldness is a serious condition affecting nearly half the male population on the globe. Although there are surgical options for treatment, a variety of non-surgical medications and procedures are available for patients, each of which works in different ways. Oral and topical 5-alphad reductase inhibitors, oral and topical Minoxidil, LLLT, and PRP are all viable non-surgical treatment modalities that have shown to be effective in treating male-pattern baldness. Based on the review of the

literature, Dutasteride has been shown to be somewhat more effective than Finasteride, and combination therapies have been shown to be more effective than individual treatments alone. However, other than that, there is not sufficient evidence to definitively conclude whether there is one treatment that is superior to all others. Further research is certainly warranted to help elucidate whether one of the non-surgical treatments is superior to all the others, in an effort to help patients treat their male-pattern baldness more effectively.

References

Abdel Fattah, N. S., & Darwish, Y. W. (2011). Androgenetic alopecia and insulin resistance: are they truly associated?. International journal of dermatology, 50(4), 417–422. https://doi.org/10.1111/j.1365-4632.2010.04677.x

Adil, A., & Godwin, M. (2017). The effectiveness of treatments for androgenetic alopecia: A systematic review and meta-analysis. Journal of the American Academy of Dermatology, 77(1), 136–141.e5. https://doi.org/10.1016/j.jaad.2017.02.054

Esmat, S. M., Hegazy, R. A., Gawdat, H. I., Abdel Hay, R. M., Allam, R. S., El Naggar, R., & Moneib, H. (2017). Low level light-minoxidil 5% combination versus either therapeutic modality alone in management of female patterned hair loss: A randomized controlled study. Lasers in surgery and medicine, 49(9), 835–843. https://doi.org/10.1002/lsm.22684

Everts, P., Onishi, K., Jayaram, P., Lana, J. F., & Mautner, K. (2020). Platelet-Rich Plasma: New Performance Understandings and Therapeutic Considerations in 2020. International journal of molecular sciences, 21(20), 7794. https://doi.org/10.3390/ijms21207794

Garg, A. K., & Garg, S. (2021). Complications of Hair Transplant Procedures-Causes and Management. Indian journal of plastic surgery : official publication of the Association of Plastic Surgeons of India, 54(4), 477–482. https://doi.org/10.1055/s-0041-1739255

Katzer, T., Leite Junior, A., Beck, R., & da Silva, C. (2019). Physiopathology and current treatments of androgenetic alopecia: Going beyond androgens and anti-androgens. Dermatologic therapy, 32(5), e13059. https://doi.org/10.1111/dth.13059

Keerti, A., Madke, B., Keerti, A., Lopez, M. J. C., & Lirio, F. S. (2023). Topical Finasteride: A Comprehensive Review of Androgenetic Alopecia Management for Men and Women. Cureus, 15(9), e44949. https://doi.org/10.7759/cureus.44949

Mokhtari, F., Zavare, Z., & Iraji, F. (2023). Topical 5% minoxidil versus combined erbium YAG laser and topical 5% minoxidil in androgenetic alopecia: A randomized controlled trial. Journal of cosmetic dermatology, 22(10), 2737–2743. https://doi.org/10.1111/jocd.15955

Natarelli, N., Gahoonia, N., & Sivamani, R. K. (2023). Integrative and Mechanistic Approach to the Hair Growth Cycle and Hair Loss. Journal of clinical medicine, 12(3), 893. https://doi.org/10.3390/jcm12030893

Nickel J. C. (2004). Comparison of clinical trials with finasteride and dutasteride. Reviews in urology, 6 Suppl 9(Suppl 9), S31–S39.

Randolph, M., & Tosti, A. (2021). Oral minoxidil treatment for hair loss: A review of efficacy and safety. Journal of the American Academy of Dermatology, 84(3), 737–746. https://doi.org/10.1016/j.jaad.2020.06.1009

Saraswat, A., & Kumar, B. (2003). Minoxidil vs finasteride in the treatment of men with androgenetic alopecia. Archives of dermatology, 139(9), 1219–1221. https://doi.org/10.1001/archderm.139.9.1219-b

Stevens, J., & Khetarpal, S. (2018). Platelet-rich plasma for androgenetic alopecia: A review of the literature and proposed treatment protocol. International journal of women's dermatology, 5(1), 46–51. https://doi.org/10.1016/j.ijwd.2018.08.004

Ustuner E. T. (2013). Cause of androgenic alopecia: crux of the matter. Plastic and reconstructive surgery. Global open, 1(7), e64. https://doi.org/10.1097/GOX.0000000000000005

Verma, K., Tegta, G. R., Verma, G., Gupta, M., Negi, A., & Sharma, R. (2019). A Study to Compare the Efficacy of Platelet-rich Plasma and Minoxidil Therapy for the Treatment of Androgenetic Alopecia. International journal of trichology, 11(2), 68–79. https://doi.org/10.4103/ijt.ijt_64_18

Zhou, Z., Song, S., Gao, Z., Wu, J., Ma, J., & Cui, Y. (2019). The efficacy and safety of dutasteride compared with finasteride in treating men with androgenetic alopecia: a systematic review and meta-analysis. Clinical interventions in aging, 14, 399–406. https://doi.org/10.2147/CIA.S192435