About the Book

The "Archive of Human Health and Wellbeing" book appears to be an academic compilation that addresses a wide range of contemporary health issues. The book is divided into several sections covering various aspects of health and wellbeing, including mental health, the wellbeing of elderly and marginalized populations, the role of family and teachers, psycho-social support, the right to health, and strategies for future health challenges. One key feature of the book is its holistic approach to health, emphasizing both mental and physical health. It includes discussions on the impact of pandemics like COVID-19, examining both medical and psychological challenges. It also explores the need for multidisciplinary approaches in addressing health issues, making it a valuable resource for professionals in social sciences, public health, medicine, education, and environmental studies. The book also targets health policymakers, educators, law enforcement agencies, and health workers. The editors, Sibnath Deb and Brian A. Gerrard, bring extensive academic and professional experience to the book. Deb, with a background in applied psychology and social justice, and Gerrard, with a focus on clinical and educational settings, ensure the book is grounded in both theory and practical application.

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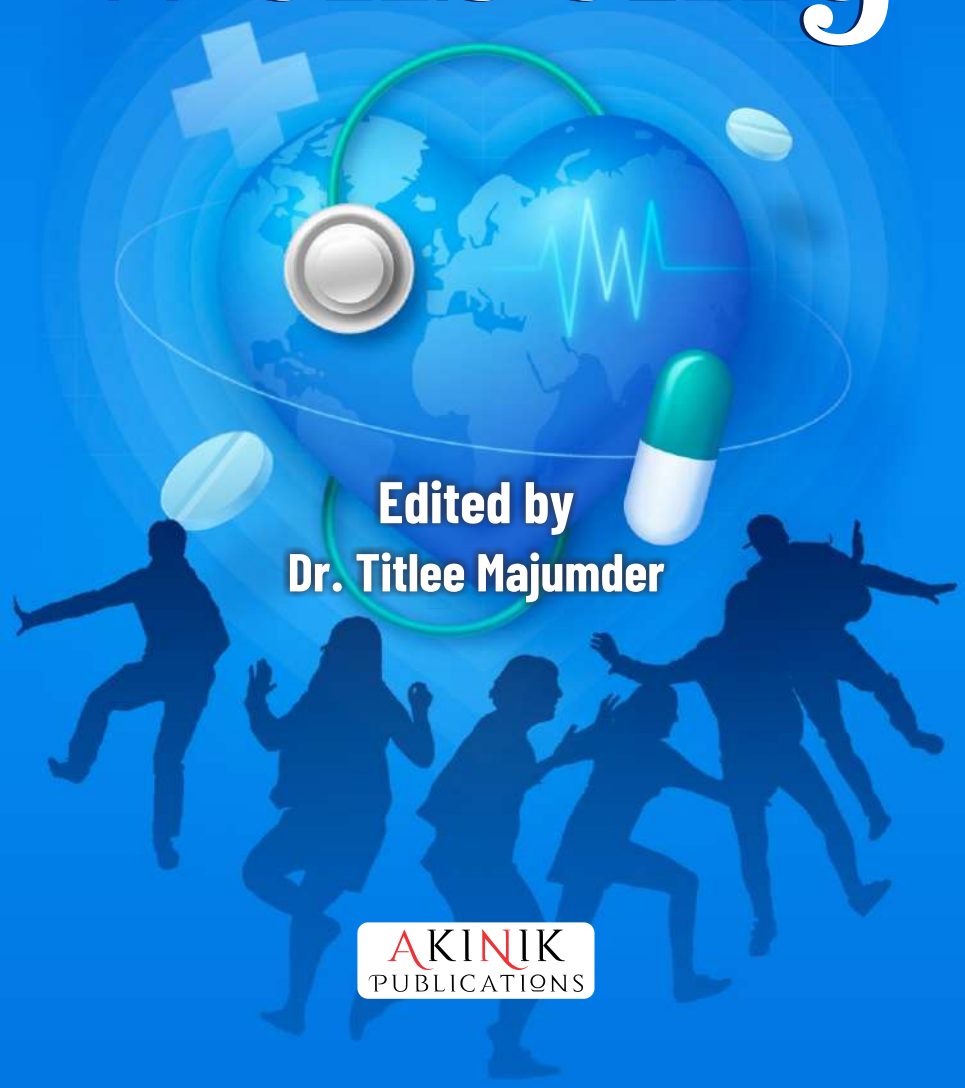

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Preface

The book entitled is a comprehensive overview which is an amalgamation of "various health aspects relating clinical manifestations", along with traditional aspects of hematology and other blood borne disease with recent dimensions of those same. The futuristic approaches relating conventional and newer frontiers are now considered as the most dominant vision for research. This field relates every part of the medical sciences like: physiology, pathophysiology, psychological health management, diagnostics and instruments followed by every even and odds.

The chapters given in the book are based upon the classical concepts of diseases based. The first volume of the book offers a comprehensive exploration into the intricate relationship between various disorders and its illustrative modes of therapeutic management shedding light on the fascinating interplay between these seemingly disparate medical fields

This book serves as a valuable resource offering a nuanced and integrated perspective that enriches clinical decision-making fosters interdisciplinary collaborations and stimulates further research endeavors. It aspires to be a cornerstone reference in the ever-evolving landscape of medical literature bridging gaps and fostering a holistic approach towards patient care

This will further help students to delve into the fundamental principles of allied health and the mechanisms by which infectious agents invade the body.

Different chapters in this book explore how infections influence hematological processes and engorge patho-physiological conditions might predispose individuals to infections which will further uncover the complex interdependencies and feedback loops between these two domains.

This book highlights the challenges and nuances in treating patients affected by concurrent physiological and therapeutic indices along with its regulatory conditions along with management including novel drug therapies and tailored approaches addressing both aspects simultaneously.

Thank you for embarking on this journey with us, and we hope you find this book both informative and inspiring.

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All authors declare that there are no conflicts of interest.

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No data was used for the research described in the article.

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Below named participated authors have contributed extensively in literature searches and extraction. Whereas students participation are also encouraged with their consent and considered for future academic endeavours.

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Content

Chapter - 1

Role of Vitamin B12 in Altering Von Willbrand Factor in India: A Review Based on Geographical Dimensions

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Chapter - 1

Role of Vitamin B12 in Altering Von Willbrand Factor in India: A Review Based on Geographical Dimensions

Dr. Titlee Majumder, Arghya Naskar and Dr. Chiranjeeb Dey

Process that stops bleeding at the site of injury. It is primarily produced and secreted by endothelial cells and megakaryocytes (platelet precursors) and circulates in the blood plasma. VITAMINamin B12 deficiency can affect the production of Von Willebrand factor (VWF) because VITAMINamin B12 is necessary for the proper functioning of the enzyme methionine synthase, which converts homocysteine to methionine. Without sufficient methionine, there can be impaired post-translational modification of VWF, leading to its abnormal structure and function. This can result in decreased levels of functional VWF and contribute to bleeding disorders like von Willebrand disease. VITAMINamin B12, is also known as cobalamin, which plays essential role in metabolism of sulpher containing amino acids. Many evidence suggest that, methionine synthase converts homocysteine to methionine, an essential amino acid. Methionine is then used in the synthesis of proteins, including Von Willebrand factor. In summary, VITAMINamin B12 deficiency can impact Von Willebrand factor by disrupting the synthesis of methionine, which is essential for the proper post-translational modification and function of VWF. This can have significant implications for hemostasis and contribute to bleeding disorders like von Willebrand disease.

Keywords: Pathophysiology, von will brand factor, von will brand disease. pathogen, hematology.

Introduction

The name Von Will brand factor (VWF) is a macromolecular glycol-protein, which has been synthesized from multiple resources namely megakaryocytes, endothelial cells. Whereas, the factor itself has been stored in the platelet alpha granules as well as a very small storage granules of the endothelial cells called as Weibel Palade granules [1]. The presence of this factor within the circulation assures the physiological homeostatis, though

the structure itself is multimeric and is ranging from 500-20000 kDA. The VWF gene is located on chromosome 12, and mutations in this gene can result in various types of VWD. The following factor is said as an antigen for the factor VIII, which is a very important factor in controlling the blood coagulation pathway and prevent faster degradation of this factor resulting in lowering the tendencies of Von Will brand Disease [2]. VWF levels and actiVITAMINy can be measured through laboratory tests, including VWF antigen levels, VWF actiVITAMINy, and factor VIII actiVITAMINy. Von Will Brand factor has been categorically divided into three sub types like (A) soluble plasma VWF, (B) sub-endothelial VWF, (C) cellular VWF. In many cross-sectional studies it have been said as lower levels of VWF leads to bleeding disorders and higher levels of VWF leads to thrombosis. Both are patho-physiological scenario and are influenced by the positive and negative regulatory pathways of VWF secretion [3]. VWF also acts as a carrier protein for factor VIII, extending its half-life and protecting it from degradation. The disorder relating Von Will Brand disease is associated with this factor or rather pre-pro form of the factor VWF leads to increase trauma relating an acute bleeding disorders. It refers to the quantitative deficiency [4]. Treatment for VWD may include desmopressin (DDAVP) therapy, plasma derived VWF concentrates, and recombinant VWF products. VWF also plays a role in non-hemostatic processes, such as angiogenesis and inflammation. Research continues to uncover the complexities of VWF's functions and its involvement in various physiological and pathological processes [5, 6].

VITAMINamin B12 most commonly called as cobalamin, has the potential in controlling the mechanism of DNA synthesis and also ensures energy production. VITAMINamin B 12 deficiency occurs due to dietary mis-management, aging, clinical and subclinical conditions. People with lower animal proteins or the vegetarians often face issues in VITAMINamin B12 absorption [7]. Many studies have evidenced that numerous hematologic disorders like very few types of leukemia, polycythemia vera and hyper-eosinophilic syndrome can be caused by elevated levels of VITAMINamin B12 [8]. Severe metabolic demotivation can be caused due to lack of VITAMINamin B12 deficiency, even the logic wheel persist like as it is extremely helpful in DNA synthesis so, may be protein translation enacts to synthesis VWF and its regulatory actions to be controlled accordingly [9]. Though the active cobalamin in circulation is found to be potential in controlling many of the hematologic and stomatologic disorders but those prays diagnostic indications or not required to be verified and assessed clinically [10].

Factors regulating the disease and vice versa

Von Willebrand disease (VWD) is primarily regulated by genetics. It's caused by a deficiency or dysfunction of von Willebrand factor (VWF), a protein involved in blood clotting. Factors influencing its severity include the specific gene mutations involved, inheritance pattern, and environmental factors like medications or injuries that affect clotting. Treatment often involves managing symptoms and preventing excessive bleeding episodes [11, 12]. There are many evidences found showing paradox for assessment of elevating and lowering the circulatory VWF, which is evident in increasing the level of vascular growth and fenestration. Though many of the factors are present inside the endothelial cells which increase the vessel formation leads to endothelial homeostasis but no such restrictions for bleeding to be observed [13]. Factors with poor coordination in formatting platelets are also considered to be potential regulators of the VWF factors so as the disease. Aside the adult markers neonatal markers are predominant in this regard [14]. The genetic factors are more evident in controlling type1 VWF which increase the risk associated with thromboembolism and likely arterial thromboembolism [15]. Secretion of excess tissue thromboplastin leads to release excess thrombocytes which lower the thrombin time followed by increase in the tendencies of blood coagulation leads to alter the VWF factor and the disease associated with it [16]. There are many evidences found that the platelets adhesion with the mobilized VWF is very rare to be observed, whereas the platelet adhesion with the immobilized VWF is more dominant [17]. The figure 1 discuss about the adhesion of immobilized VWF along with the platelets.

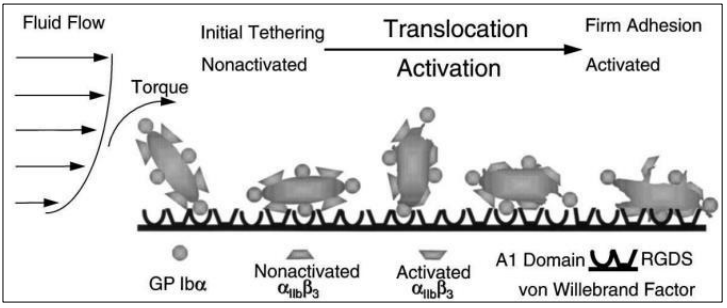

Figure 1: Dual step platelet adhesion to von Will Brand Factor [30]

From the above discussion it can be said that, there are multiple parameters found showing positive regulations of vWF and also found negative regulatory factors in altering the pathophysiological considerations. The bleeding disorders relating von will-brand factors are domain specific.

Even the stagnant once are more prone to the disorder than that of the factors flowing through the blood stream. Many biochemical markers are dominant in finding collaborations with the VW factor as well as disease. Deficiencies or abnormalities in VWF can lead to von Willebrand disease (VWD), a bleeding disorder characterized by prolonged bleeding time due to impaired platelet function and decreased clotting factor VIII actiVITAMINy [18]. Symptoms of VWD can range from mild bruising and nosebleeds to more severe bleeding episodes, particularly after surgeries or injuries. Treatment typically involves replacing deficient or defective VWF with purified VWF concentrates or desmopressin (DDAVP), a medication that stimulates the release of VWF and factor VIII from storage sites [19].

Vitamin B12 in regulating the activity of this factor

Vitamin B12 deficiency can affect the production of von Willebrand factor (vWF), which plays a crucial role in blood clotting. Without enough vitamin B12, the body may not produce enough healthy red blood cells, leading to a condition called megaloblastic anemia. This condition can affect the function of VWF, potentially causing bleeding disorders or impairing the clotting process.

Deficiency of vitamin B12 effecting Von Willebrand factor

Vitamin B12 deficiency can lead to elevated levels of homocysteine, which in turn can impair the function of von Willebrand factor (VWF). VWF plays a crucial role in blood clotting by helping platelets, which adhere to damaged blood vessel walls. When VWF function is impaired, it can result in abnormal bleeding tendencies, as seen in conditions like von Willebrand disease [20]. Thus, a deficiency in vitamin B12 can indirectly affect VWF function through its impact on homocysteine levels. Deficiency in vitamin B12 synthesis leads to cause hypo-secretion of VWF whose consequences are follows [21].

- Increased bleeding tendency: VWF plays a crucial role in blood clotting by mediating platelet adhesion to damaged blood vessels. Reduced levels of VWF can lead to impaired clot formation, resulting in prolonged bleeding time and increased risk of bleeding episodes.
- Easy bruising: Individuals with hypo-secretion of VWF may experience frequent bruising due to the inability of blood vessels to properly seal off after minor injuries.
- Nosebleeds (Epistaxis): Since VWF helps stabilize blood clots, low

levels of this factor can predispose individuals to recurrent nosebleeds, as the delicate blood vessels in the nose may rupture more easily.

- Heavy menstrual bleeding: Women with hypo-secretion of VWF may experience heavier and prolonged menstrual bleeding, known as menorrhagia, due to impaired clot formation in the uterine lining.
- Increased risk of surgical complications: Reduced levels of VWF can increase the risk of excessive bleeding during surgical procedures, making it essential for healthcare providers to take precautions and potentially administer additional clotting factors or blood products to manage bleeding effectively.

Mal effects of VITAMIN B12 deficiency

VITAMINamin B12 deficiency can have several detrimental effects on the body. Here are some potential consequences:

- Anemia: vitamin B12 is essential for the production of red blood cells. Deficiency can lead to megaloblastic anemia, where red blood cells are larger than normal and unable to function properly, resulting in fatigue, weakness, and pale skin.
- Neurological issues: B12 deficiency can cause damage to the nerves, leading to symptoms such as tingling or numbness in the hands and feet, difficulty walking, memory loss, confusion, and mood changes.
- Gastrointestinal problems: B12 is absorbed in the small intestine, so conditions that affect the gastrointestinal tract, such as Crohn's disease or celiac disease, can impair its absorption, leading to deficiency. Symptoms may include diarrhea, constipation, or loss of appetite.
- Risk of cardiovascular disease: Elevated levels of homocysteine, a compound linked to cardiovascular disease, can result from B12 deficiency. High homocysteine levels are associated with an increased risk of heart disease and stroke.
- Developmental issues in infants: Pregnant women with B12 deficiency can pass on the deficiency to their babies, potentially leading to developmental delays, poor growth, and neurological problems in infants.

Addressing Vitamin B12 deficiency typically involves supplementation and dietary changes to ensure adequate intake. Early detection and treatment are crucial to prevent long-term complications.

Other dietary factors controlling VWF

Many dietary factors like iron, vitamin C, a kind 3 fatty acids, green leafy vegetables and sufficient water may control potentially the factor Von Will brand [22, 23, 24].

- Iron: Adequate iron intake is essential for the synthesis and proper function of VWF. Iron deficiency can impair VWF production, leading to decreased levels of this clotting factor and potentially increasing the risk of bleeding disorders.
- VITAMINamin C: VITAMINamin C is necessary for the proper function of VWF. It helps stabilize VWF in the bloodstream and enhances its binding to collagen, which is crucial for platelet adhesion and clot formation. Ensuring sufficient VITAMINamin C intake can support optimal VWF actiVITAMINy.
- Omega-3 fatty acids: Omega-3 fatty acids, found in fatty fish like salmon and mackerel, have anti-inflammatory properties that can help maintain vascular health. They may also support the stability and function of VWF, potentially reducing the risk of excessive bleeding and clotting disorders (25).
- Leafy green vegetables: Foods rich in VITAMINamin K, such as kale, spinach, and broccoli, support proper blood clotting by facilitating the activation of clotting factors, including VWF. Adequate VITAMINamin K intake is essential for ensuring the efficient functioning of VWF in the clotting cascade (26).
- Hydration: Staying well-hydrated is important for maintaining proper blood viscosity and circulation, which can indirectly influence VWF actiVITAMINy. Dehydration can lead to increased blood viscosity, potentially affecting VWF function and increasing the risk of clotting or bleeding abnormalities (27).

By incorporating these dietary factors into a balanced and varied diet, individuals can support the production and function of VWF, promoting optimal blood clotting and vascular health.

Discussion & conclusion

Von Will Brand Disease is lifelong bleeding disorders which can be occur due to various genetic reasons, some are inborn or some happen due to successive mutational changes occurred to the premature bone marrow dysfunction. The disease initiates with the major concern for non-coagulation of blood. Due to lack of blood coagulation the ratio between

bleeding time and clotting time also gets hampered (28). Lifestyle management and proper dietary check-ups can make the proper growth of the VWF so as the bleeding issues can be resisted accordingly. It has been observed that VITAMINamin B12 can also alter the level of VWF and lack of VITAMINamin B12 lower the possibility of blood coagulation (29). Dietary intake of VITAMINamin B12 may enrich the level of VWF in long run. Biochemical factors regulating the pathway for synthesising blood coagulating markers are also predominantly controlled by the daily nutritional intake. No significant pathways are identified or marked to understand for earning homeostasis within the human, rather researches are still going on upon many signalling pathways to find positive regulations (31). On the contrary it can be said as bleeding disorders are obvious not only for genetic mismanagements but also dietary disorientation.

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Chapter - 2

A Review on Prevalence of Hepatitis C Among Pregnant Women

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Chapter - 2

A Review on Prevalence of Hepatitis C Among Pregnant Women

Anwesha Samanta and Manojit Bysack

Abstract

Hepatitis C is a serious public health issue that affects 3% of people worldwide. The prevalence of hepatitis C in pregnant women varies throughout the world, though. The frequency of hepatitis C in pregnant women varies from 0.7% to 36% in Pakistan alone. Unfortunately, pregnant women are becoming more susceptible to difficulties due to the increased frequency of the Hapatitis C Virus (HCV). Thus, by combining the prevalence of hepatitis C in pregnant women reported in 17 studies from Pakistan, the goal of this research is to estimate a prevalence rate that represents the true burden of the disease in this population. Studies that have been published in English since 2001 have been taken into consideration. Since there aren't many studies on this subject, no published works that meet the inclusion criteria have been disregarded. Each study's quality was evaluated using the Newcastle-Ottawa Scale; three studies were carried out in Islamabad and Khyber Pakhtunkhwa, respectively; five studies were done in Punjab; and six research were undertaken in the province of Sindh. 8342 pregnant women who had undergone hepatitis C screening out of 1,24,635 total were found to have positive anti-HCV test results. Hepatitis prevalence in Pakistani pregnant women ranged from 0.7% to 36%, with an overall frequency of 6.7% (95% CI: 6.5-6.8). Hepatitis C was present in 6.7% of pregnant women in Pakistan overall. However, these results cannot be ignored and policymakers should take them into consideration when deciding whether to screen pregnant women for hepatitis C before becoming pregnant. The research will undoubtedly assist society at large in implementing preventative measures to lower the incidence of that fatal illness, particularly in expectant mothers.

Keywords: Anti-HCV, HCV, Newcastle-Ottawa scaling, screening, world.

Introduction

When blood from an infected individual comes into touch with yours, you could contract hepatitis C, a liver infection brought on by the hepatitis C virus (HCV) [1]. HCV infection can have detrimental effects on a mother's and her child's health [2, 5]. Cholestasis, a liver condition that slows or stops the normal flow of digestive fluid, can occur during pregnancy and raise the mother's risk of developing gestational hypertension, needing a cesarean delivery, and being admitted to the intensive care unit [2, 4, 5]. Increased risk of preterm birth, low birth weight, fetal growth restriction, admission to a neonatal critical care unit, and congenital defects are among the possible negative outcomes for the infant [2, 4, 5]. Amidst the surge in HCV infection among the general population aged 20-39, the Centers for Disease Control and Prevention advised in April 2020 that prenatal care providers screen all expectant mothers for HCV infection at every pregnancy, with the exception of areas where the prevalence of HCV infection is less than 0.1% [6, 7]. The item "Infections present and/or treated during this pregnancy" was added to the 2003 iteration of the U.S. Standard Certificate of Live Birth, and it includes a checkbox for hepatitis C. In 2016, information on HCV infection from birth certificates became available for all states. This report presents trends in HCV infection among women giving birth in the United States from 2016 through 2021, along with rates of infection by maternal race and Hispanic origin, age, education level, smoking during pregnancy, timing of prenatal care, and source of payment for delivery for 2016, 2020, and 2021.

Based on all births registered in the United States between 2016 and 2021, 100% of the data used in this study comes from the birth certificate. It is advised to obtain information about hepatitis C from the mother's medical records in order to obtain a birth certificate [8]. If a mother's medical records show that she tested positive for HCV throughout her pregnancy, then the mother should be listed as having hepatitis C [8]. The overall rate of HCV infection for the years 2016–2020 and the decline for 2020–2021 were compared, as were the rates of infection by maternal race and Hispanic origin, age, education level, smoking during pregnancy, when prenatal care was received, and the method of payment for delivery. A comprehensive examination was carried out on the data from 2021 concerning the overall rates of HCV infection as well as the rates of infection by every other feature. There was missing data on HCV infection for 14,846 (0.4%) of the 3,664,292 births that were registered in the US in 2021. 5.0% (36,381) of births had missing data regarding maternal Hispanic origin, 2.1% (77.416) regarding the timing of the start of prenatal care, 1.5% (56,607) of births

regarding maternal education level (excluding births to mothers under the age of 25), and 0.4% (15,541) regarding maternal cigarette smoking during pregnancy. We imputed the age (318, or 0.01%) and race (255,181, or 7.0%) of births with missing data.

Data gaps in the records prevented them from being analyzed. The mother self-reports her race and her Hispanic heritage, which are listed separately on the birth certificate. Every racial category and Hispanic-origin group follows the 1997 Office of Management and Budget guidelines and is based on single-race reporting [9]. In order to allow for the completion of schooling, analyses of maternal education levels were limited to women who were 25 years of age or older. Data pertaining to non-Hispanic Native Hawaiian or Other Pacific Islander mothers were not included since there were not enough of them to produce accurate rates. The investigation encompassed the five most populous racial and Hispanic origin groups: non-Hispanic Asian, non-Hispanic Black, non-Hispanic White, American Indian or Alaska Native, and Hispanic.

The number of live births to moms who have HCV infection per 100,000 live births is how rates of HCV infection are expressed. Every claim on rate differences in the text has been examined for statistical significance, and any claim that a particular rate is greater or lower than another suggests that the rates are statistically different. References to declining or increasing trends in rates (e.g., trends in rates for 2016 through 2020) were evaluated using the Cochran-Armitage test for trends, a modified chi-squared test, and were found to be statistically significant at the 0.05 level using a two-tailed z test at the alpha level of 0.05 [10]. The National Center for Health Statistics' criteria were used to assess the dependability of percentages. For detailed information on the standards, see "National Center for Health Statistics Data Presentation Standards for Proportions" [20, 21, 22].

Prevalance outcome

From 2016 (16,588) to 2020 (18,246), the number of cases with HCV infection during pregnancy increased by an average of 2.5% yearly, for a total rise of 10%. Then, from 2020 to 2021, there were 7% fewer cases (16,923). From 2016 (421.4 per 100,000 births) to 2020 (506.5), the rate of HCV infection increased by 5% on average every year, for a total rise of 20%. After that, the rate fell by 8% between 2020 and 2021 (463.7).

Maternal age

Between 2016 and 2020, moms under 25 had a lower rate of HCV infection, whereas mothers over 25 saw an increase. From 141.8 per 100,000

births to 106.1 for mothers under 20 and from 428.1 to 359.3 for moms between 20 and 24 years old, the rate decreased by 25% and 16%, respectively. For moms aged 25–29 (554.8–627.4), 30–34 (394.1–566.5), 35–39 (329.9–485.1), and 40 years and older (266.8–398.1) saw the largest increases in rates, which rose by 13%, 44%, and 49%, respectively. Between 2020 and 2021, there was a drop in HCV infection rates of 19% for mothers aged 20–24 (289.3 in 2021), 14% for mothers aged 25–29, and 6% for mothers aged 30-34. There was no substantial change in rates for moms under 20 or those over 35. Moms between the ages of 25 and 29 (542.0) and 30-34 (531.9) had the highest rates of HCV infection in 2021, while mothers under the age of 20 (118.8) had the lowest rates. 2016 and 2020 showed comparable trends by age.

Maternal race and hispanic origin

Between 2016 and 2020, four out of the five racial and Hispanic origin groups saw a significant increase in the rate of HCV infection. Raising rates by 20% for White mothers (from fram 649.2 per 100,000 births to 781.7), 22% for Hispanic mothers (from 139.8 to 170.2), 28% for Black mothers (from 137.2 to 176.1), and 34% for American Indian or Alaska Native mothers (1.386.4 to 1,860.7) was not statistically significant. The 18% increase for Asian mothers (73.6 to 86.9) was less significant. For White moms, the rate of HCV infection decreased by 10% to 704.8 and for Hispanic mothers by 8% to 156.1 between 2020 and 2021. Rate adjustments starting in 2020. Mothers who were Black, Asian, or Alaska Native in 2021 did not significantly differ from one another. American Indian or Alaska Native moms had the highest rate of HCV infection in 2021 (1,652.1), followed by White mothers (704.8), Black mothers (179.3), Hispanic mothers (156.1), and Asian mothers (102.7). In the years 2016 and 2020, the same overall pattern was noted [20, 19, 18, 17].

Maternal education level

Between 2016 and 2020, the rate of HCV infection among women 25 years of age and older rose for all maternal education levels. Among mothers who did not complete high school, the rate of HCV infection rose by 40% (from 985.0 per 100,000 births to 1,378.7); among those who did, it increased by 29% (from 880.8 to 1,139.6); 22% (from 496.8 to 606.4) for mothers with some college education; and 31% (from 58.4 to 76.4) for mothers with a bachelor's degree or higher. The rate of HCV infection decreased by 5%–6% between 2020 and 2021 among moms with less than a high school education, a high school diploma or GED, some college

education, or an associate's degree; the 3% increase among mothers with a bachelor's degree or beyond was not statistically significant. Mothers who did not complete high school had the greatest rate of infection (1,308.7), while those who completed a bachelor's degree or above had the lowest rate (78.4). In 2021, the rate of HCV infection decreased as maternal education level increased. In 2016 and 2020, the same tendency was noted.

Maternal smoking during pregnancy

Between 2016 and 2020, there was a rise in the prevalence of HCV infection in both pregnant women who smoked cigarettes and those who did not. moms who smoked saw a 46% increase in the rate (from 3.579.4 per 100.000 births to 5,223.6), while moms who did not smoke saw a 30% increase (171.0 to 222.3). The incidence of HCV infection for moms who smoked during pregnancy remained relatively constant between 2020 and 2021. Mothers who smoked throughout their pregnancies had a greater rate of HCV infection in 2021 (5,302.0) than mothers who did not smoke (222.9). In addition, between 2016 and 2020, mothers who smoked during their pregnancies continuously had greater rates of HCV infection than mothers who did not smoke.

Timing of prenatal care

Between 2016 and 2020, the number of moms who contracted HCV—whether or not they received prenatal care—rose. In the first trimester, the rate increased by 22% (from 283.2 per 100,000 births to 345.3); in the second trimester, it increased by 16% (718.3 to 833.5); in the third trimester, it increased by 21% (1,033.2 to 1,245.7); and in the fourth trimester, it increased by 44% (1,686.8 to 2.422.4) for mothers who did not receive prenatal care. Among moms who started treatment in the first, second, or third trimester of their pregnancy, the rate of HCV infection decreased by 8%–10% between 2020 and 2021; the fall was not statistically significant for mothers who did not get prenatal therapy. The later prenatal care started in 2021, the higher the rate of HCV infection. In other words, moms who started prenatal care in the first trimester (318.0%) had the lowest rate, followed by those who started care in the second and third trimesters (750.0 and 1.151.1), and those who did not start prenatal care (2.267.4). Between 2016 and 2020, the rates followed the same pattern [15, 16, 14].

HCV and conception

A multitude of pathogenic mechanisms can cause both men and women to become infertile as a result of any serious chronic liver illness. However, during their reproductive era, the majority of female patients with chronic

HCV will not acquire end stage chronic liver disease. 36 thesus negative women who contracted HCV type 1b after postnatal exposure to tainted anti-D immunoglobulin were the subjects of a recent Irish investigation. Over a 20-year period, there were 100 pregnancies overall, with no difference in the incidence of spontaneous miscarriages, premature births, or obstetric interventions when compared to controls, despite the presence of biochemical abnormalities in 55% and liver fibrosis in 42%. In a major Italian study, 53 HCV RNA positive women had biopsy samples collected either before or after becoming pregnant, and none of them had cirrhosis. The majority of the patients had mild fibrosis, and HCV genotype 3a infection was more frequently the cause of bridging fibrosis. Reproductive medicine has been advised to implement stricter anti-infectious control measures in response to allegations that the virus can be contracted during artificial insemination and that HCV can be detected in semen. To reduce the possibility of transmission from sperm/egg donors who are infected with HCV, this may involve requiring mandatory HCV testing of genetic material donors [15, 16].

HCV and pregnancy

The anti-HCV prevalence in pregnancy varies from 0.6% in Japan to 4.5% in the United States, according to the findings of multiple small investigations." In the most extensive research conducted to date, spanning four years and involving over 15,000 pregnant women from northern Italy, a frequency of 2.4% was discovered. Exposure to blood products and a history of intravenous drug misuse (32%) were the main risk factors. (24%). Nonetheless, almost 40% of the women did not meet any risk indicators for HCV infection. The same study revealed that 2.1% and 4% of the patients had positive HBsAg and anti-HIV antibodies, respectively. In a recent UK study, 75% of the multi-ethnic pregnant HIV-negative women from inner cities who volunteered for testing also tested positive for HCV RNA. The study's findings revealed an anti-HCV prevalence of 0.8%. Remarkably, 73% of the pregnant women had no discernible risk indicators for hepatitis C, and 69% of them had only recently received a diagnosis. Amniotic fluid has been found to contain HCV virions, yet this may not be related to vertical transmission. Within a group of 22 pregnant women who tested positive for HCV and had amniocentesis for obstetric purposes at four months of pregnancy, found only one case of viral infection, with amniotic fluid testing positive for HCV RNA (230 copies/ml). The amniotic fluid of the remaining 21 women, 15 of whom had HCV RNA seropositive status, did not contain any virions. Soon after birth, the child of the mother whose

amniotic fluid had HCV tested negative for the virus and seemed to be free of the infection. Nine out of the 21 remaining newborns were tested for HCV RNA and determined to be negative throughout the four-day follow-up period.

Numerous investigations have demonstrated improvements in the biochemical indicators of liver injury in pregnant HCV positive women. Since the transaminase levels seem to revert to pre-pregnancy levels immediately after birth, this could be partially explained by haemodilution, which is secondary to a relative increase in circulating blood volume in the final trimester of pregnancy. However, it is probable that the host-HCV relationship is influenced by the immune response modifications that occur during pregnancy. A linear increase in HCV viraemia throughout pregnancy has been reported in a number of articles, which could be consistent with reduced immunological responsiveness. Uncertain mechanisms cause the mother's immune system to become down-regulated when she is pregnant in response to external antigens, including fetal ones. Antigen-specific helper (Th) and CD8+ cytotoxic T cells are activated in the HCV-specific immune response. It has been proposed that changes in blood oestrogen content during pregnancy may affect the process of T cell development. Activated T cells after HCV infection have a Th1 cytokine profile, with a predominance of interferon y." However, interferon synthesis occurs in the placenta, which may help the pregnant host regulate HCV. The mystery surrounding the immunological systems governing HCV management during pregnancy has been further exacerbated by a recent case report." Repeated intrauterine red blood cell transfusions between 19 and 31 weeks of gestation, including blood from a donor who HCV seroconverted four months after the last donation, were used to treat severe hemolytic disease of the fetus." The expectant mother contracted the infection, but not her child. The scientists speculate that the different results could have been caused by the mother's and the fetus's differing immune responses to the virus. Pregnancy does not appear to have a negative impact on the progression of HCV infection overall. On the other hand, no data points to a shorter duration, a rise in congenital malformations and obstetric difficulties, or a decrease in birth weight in infants born to HCV-positive mothers. The rate of obstetric indications for cesarean sections increased twofold in anti-HCV positive women (42%) according to a retrospective single-center study. This increase was likely caused by limited intrapartum fetal surveillance, which avoided fetal scalp blood sampling in an effort to reduce the risk of vertical transmission [16, 14].

Vertical transmission of HCV

For the first time, research from Japan demonstrated that three generations of the same family shared an HCV genotype with greater than 95% similarity. After anti-HCV screening for blood products became mandatory, 44% of Italian youngsters have been diagnosed with HCV infection. Yet, due to manufacturing errors or a seroconversion window among blood donors, blood products could still be a possible source of infection. One does not yet know when vertical HCV infection occurs. 49 anti-HCV positive women provided cord blood samples, and Silverman *et al*. discovered that 19% of those samples had HCV RNA. Nevertheless, Conte *et al*. demonstrated that cord blood HCV RNA testing had a poor predictive value for vertical transmission. In their investigation, six babies who had been HCV RNA negative at birth turned positive by the time they were four months old, while 16 of the 18 babies who had been HCV RNA positive at birth turned negative. The authors recommend using polymerase chain reaction on HCV RNA at 4 months of age to detect newborns who are vertically infected, based on these data. A few smaller studies that found positive testing during the neonatal period have demonstrated "Negativization" of HCV RNA later in infancy. These findings point to the possibility of either a real, transitory postnatal viraemia or potential issues with the standardization of HCV RNA PCR assays. The measurement of anti-HCV is not very useful for diagnosing infection since newborns can have passively acquired maternal antibodies that last for 15–18 months. At our facility, we test for vertical transmission using HCV RNA PCR at birth, six, eighteen, and twenty-four months of age. The estimated probability of vertical HCV transmission, which is roughly 5%, 1725–49, is not affected by geography. The risk of vertical transmission increases several times with co-infection with HIV and high viral loads of both HIV and HCV. It was discovered that intravenous drug users and receivers of blood products who were HIV negative had a 12% rate of HCV vertical transmission, compared to 2% for women without risk factors. In a UK retrospective analysis, the incidence of HCV transmission was 5.9% for emergency caesarean sections and 7.7% for vaginal deliveries, but none of the newborns delivered by elective caesarean section had infection. One study indicated that the risks of vertical HCV transmission were increased by vaginal birth and female sex of the progeny. Larger investigations did not corroborate these results. Recombinant immunoblot assay testing of a recent prospective study from northern Italy revealed that the moms who would subsequently spread the virus lacked neutralizing anti-C100 antibodies. It appears that vertical

transmission is not significantly influenced by the viral genotype. When HCV-positive women conceive again after infecting their child during a previous pregnancy, the risk of transmission does not seem to rise [13].

About 20% of viracmic mothers have colostrum and breast milk with HCV virions and evidence of vertical HCV transmission." A number of large epidemiological studies of vertical transmission failed to document a role for breast feeding. Nonetheless, Kumar and Shahul demonstrated HCV infection in newborns exclusively breastfed by viraemic women despite their HCV RNA being negative at delivery. Infants breastfed by HCV positive/HIV negative mothers had a markedly higher rate of vertical transmission, according to a recent small study from Spain." The presence of HCV in breast milk and maternal serum HCV RNA levels correlated positively in this investigation. While several retrospective investigations failed to find evidence of a higher risk of vertical transmission in breastfed infants, it is important to remember that HCV can be found in breast milk and colostrum and may have a role in late transmission. A customized approach, based on known risk factors such viral load during pregnancy and HIV/HBV co-infection, may be wise when counseling HCV positive women regarding the best delivery and breastfeeding mode. Because the overall advantages of breastfeeding outweigh the marginally elevated risk of HCV vertical transmission in developing nations, an individualized strategy should also incorporate an assessment of socioeconomic situations [13].

Literature of vertically acquired HCV infection

It is unclear what the natural course of a persistent HCV infection is, even if it was acquired vertically. The majority of kids have modest histology and biochemical anomalies and don't experience serious liver problems while they're young. Prior to the identification of HCV, a research by Tong *et al*. found that six babies born to mothers who contracted non-A-non-B hepatitis during the last trimester of pregnancy had abnormal blood alanine aminotransferase levels at 4–8 weeks of age. On the other hand, there were no biochemical abnormalities in the babies born to women who developed symptoms during the second trimester. A limited number of individuals in a short period of time had abnormal liver function tests and histology, according to a few small studies examining the course of vertically acquired HCV infection. 3 During the first year of life, Bortolotti *et al*. discovered aberrant transaminases in all 14 HIV-negative children who had vertical HCV infection. The same researchers discovered in a different report that none of the children who were vertically infected over a six-year period had eradicated HCV, and that HCV RNA levels varied very little. In

agreement with adult study findings, they found no correlation between HCV RNA levels, biochemical markers, and the disease's histological activity. In another Italian investigation, anomalous transaminase results were observed over a mean follow-up period of 5.5 years in five of the seven children who had liver biopsy and the seven children with vertically inherited HCV, all of whom were diagnosed with chronic persistent hepatitis. Nonetheless, a recent large-scale German study assessing children who acquired HCV from blood transfusions after open heart surgery found a spontaneous viral clearance rate of 45% over a 20-year span. Biopsy specimens from 16 of the 17 individuals who remained viraemic and had biochemical signs of liver injury showed very mild histological alterations. It is currently unknown if various methods of HCV acquisition have different natural histories [11, 12].

Possible mode of prevention of vertical transmission

There isn't currently a standardized pan-European policy in place to stop HCV from spreading vertically. Regarding concerns related to breastfeeding, elective caesarean sections, and selective testing during pregnancy, recommendations differ greatly." To reduce the risk of vertical HCV transmission, current international guidelines do not advise against breastfeeding and vaginal birth. Screening 5000–10,00000 pregnant women would be required to find a single incidence of infantile hepatitis C, based on an estimated 1-2% HCV prevalence and a 5% vertical transmission rate. In locations where the prevalence of HCV is relatively low, universal screening for pregnancy has been deemed unnecessary due to the absence of effective strategies to prevent transmission and treat the virus." Nonetheless, I firmly feel that pregnant women should have access to anti-HCV testing, at the very least for those in a few high-risk groups. Prenatal selective HCV screening should identify asymptomatic adults who might benefit from treatment and education, as well as children who are at risk of contracting the virus. These adults are likely highly motivated by their desire to become parents. Their drinking habits, sexual habits, and opinions on tissue and organ donation may change as a result, which could be advantageous for both the global epidemiology of HCV and each person's unique natural history. In a UK pilot research, the majority of expectant mothers accepted the offer of HCV testing without hesitation. Theoretically, earlier treatment of a moderate HCV-related illness should lead to greater HCV clearance rates if data from the major studies in adults could be transferred to children. Remember that children under the age of two should not receive interferon treatment, and children under the age of three should not receive treatment with the

currently being studied combination of interferon and ribavirin. PCR testing for HCV RNA should be performed twice on infants suspected of having HCV infection. It is important to check for the existence of HCV antibodies in children older than 18 months. Children who have been diagnosed with HCV should be monitored at tertiary centers as soon as feasible after the diagnosis is made therapies addressed with the family. Immunization against hepatitis A and B is recommended for mothers and children with chronic hepatitis C since super infection may progress more severely in those who are HCV positive." I think there needs to be a change in the way that people now view the diagnosis of HCV infection in pregnancy and infancy. There is no question that HCV testing is warranted for the specific groups of pregnant women who have risk factors. We must be conscious, nevertheless, that over half of pregnant women who test positive for HCV may be overlooked by this method. It is envisaged that better management would come from the on-going, dynamic research on HCV treatment strategies for both adults and children. This would bolster the argument for the future implementation of the currently unrecommended nationwide HCV screening program during pregnancy.

Conclusion

This comprehensive investigation and meta-analysis verified that Ethiopian expectant mothers had moderate levels of HCV infection. The results of the study suggest that in order to lower the risk of vertical transmission to fetuses, all pregnant women should be enrolled in a routine, universal HCV screening program and have access to HCV antiviral therapy. National and local health programs should also enforce screening procedures and regularly monitor them in order to reduce the chance of catching the hepatitis C virus. Raising awareness of HCV prevention and transmission pathways is also a crucial consideration.

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Chapter - 3

Dengue - Pathogenesis and Diagnostic Approaches: A Review

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Chapter - 3

Dengue - Pathogenesis and Diagnostic Approaches: A Review

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Abstract

The most prevalent arthropod-borne illness in the world today is dengue virus infection, which is becoming more widespread in tropical areas of Asia, Africa, Central America, and South America. It manifests as a range of illnesses, from a mild flu-like sickness to a serious hemorrhagic fever with a high rate of morbidity and death. Aedes aegypti and Aedes albopictus mosquitoes are the ones that spread this illness. Subclinical infections, dengue fever, dengue hemorrhagic fever (DHF), and finally dengue shock syndrome (DSS) are among the possible outcomes. The intricate interaction between the virus, host genes, and host immune response is thought to be responsible for the pathophysiology of dengue virus infection. Major predictors of vulnerability to dengue fever include host variables such autoimmune, memory cross-reactive T cells, antibody-dependent enhancement (ADE), and genetics. Caused by viruses spread by mosquitoes, dengue syndrome is an acute febrile viral exanthem that is followed by headache, myalgia, anorexia, gastrointestinal problems, and prostration. Abnormal hemostasis and increased vascular permeability are hallmarks of DHF, a severe febrile illness. A hypovolemic shock seen in certain cases of Dengue haemorrhagic illness (DHF) is the cause of DSS, or dengue shock syndrome. Dengue fever in its severe form is referred to as DHF/DSS. The pathophysiology of severe dengue was thought to be attributed to protein and anti-DENV NS1 antibodies. The connections between the etiology and diagnostic techniques explored in this work will undoubtedly aid in the development of more advanced treatments in the future that will lower mortality rates and increase the proportion of patients who recover.

Keywords: ADE, Dengue, DHF, DSS, Morbidity, Mortality, NS1

Introduction

Aedes aegypti, Aedes albopictus, and other Aede mosquito species are the main vectors of dengue, a Flavivirus infection spread via mosquitoes.

Dengue virus has four main serotypes that are antigenically different: DENV-1, DENV-2, DENV-3, and DENV-4 [1]. Dengue virus infections take four to seven days to incubate. Dengue fever is an asymptomatic infection, and its spectrum extends to more severe forms like dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS) [2]. In October 2013, the fifth serotype (DENV-5) was identified in the Malaysian state of Sarawak through isolation and genetic sequence analysis [3]. Prior to 2008, the World Health Organization (WHO) divided dengue fever into three categories: dengue fever, dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS) [21]. Dengue without warning symptoms, Dengue with warning signs, and Severe Dengue are the three categories into which symptomatic cases are placed under the current revised WHO 2009 case classification system [4]. Dengue virus infection causes over 20,000 deaths annually, particularly in secondary dengue cases linked to DHF/DSS [5]. The fact that DENV infection shows its most severe form when the virus is being cleared by the host immune system, rather than at the peak viral load, supports the theory that the human immune response plays a crucial part in the pathogenesis of the disease [6]. A comprehensive understanding of the pathogenesis of dengue fever requires consideration of the clinical, immunological, pathological, and epidemiological aspects of DENV infection. The primary objectives of this review are to comprehend the pathophysiology of Dengue, investigate the factors that contribute to an individual's risk of developing DHF and DSS, and pinpoint the genetic and environmental factors that influence variations in the risk of developing severe disease. It also seeks to summarize current theories about the pathophysiology of DHF/DSS and identify knowledge gaps that will provide serious problems down the road.

Pathogenesis of DENV infections

The outcome of DENV infections may be significantly influenced by the virus's cell and tissue tropism. The immune system, endothelial cell (EC) linings of blood vessels, and *in vitro* evidence point to three organ systems as being key players in the pathophysiology of DHF/DSS. These findings are supported by autopsy studies. The pathogenic consequences of DENV infection of these systems, the tropism of DENV for cells of the relevant systems, and the significance of these events for the general pathogenesis of DENV infection will all be discussed.

- **Cells of the immune system**

DENV is most likely injected into the circulation when mosquitoes feed on humans. This injection then likely spreads to the epidermis and dermis,

infecting keratinocytes and immature Langerhans cells, also known as epidermal dendritic cells (DC). From the infection site, infected cells then migrate to lymph nodes, where they draw monocytes and macrophages, which then become targets for infection. This initial viremia causes infection in a large number of mononuclear lineage cells, including blood-derived monocytes, myeloid DC, and splenic and liver macrophages. The fact that freshly produced virus clings to and is taken up by mononuclear cells during secondary infections with heterologous DENV should be emphasized. High concentrations of DENV-specific immunoglobulin G (IgG) will complicate the virus. It has also been demonstrated that bone marrow stromal cells are vulnerable to DENV infection [7].

- **Endothelial cells**

When there is substantial systemic inflammation, EC are crucial to the coagulation reaction. Conversely, data suggests that the pulmonary vascular endothelium contains DENV antigen. According to *in vitro* research, infection causes functional rather than morphological damage in EC, and all DENV serotypes are capable of active replication [8]. Numerous viral and host variables, including autoimmunity, memory cross-reactive T cells, DENV genome variation, non-structural protein 1 (NS1) viral antigen, and anti-DENV NS1 antibodies, have been linked to the pathogenesis of dengue. The combination of the aforementioned elements is mostly responsible for the severe dengue symptoms in people.

- **Role of Non-structural Protein 1 (NS1) viral antigen**

NS1 is the most significant non-structural protein linked to the etiology of dengue virus infections [9]. In the meantime, endothelial hyperpermeability and vascular leak are also caused by immune cells' NS1-mediated production of inflammatory cytokines. This ultimately results in fluid buildup in third space and plasma leakage, which causes dengue shock syndrome [10]. From the fifth day of sickness, there was a noticeable reduction in the NS1 concentration in the secondary infection compared to the primary infection, and a significantly greater NS1 concentration in DENV-1 infections than in DENV-2 infections. Perhaps in secondary DENV infections, an early IgG response results in the establishment of an immunological complex and severe clinical symptoms [11].

Role of anti-DENV NS1 antibodies

In addition to NS1 protein, anti-DENV NS1 antibodies were thought to play a role in the pathophysiology of severe dengue. The unorganized release

of cytokines is thought to be a crucial component in the pathophysiology of severe dengue fever. Human endothelial cells release a number of cytokines and chemokines in modest response to anti-DENV NS1 antibodies. It is impossible to overstate the significance of the immunological response mediated by anti-NS1 antibodies in the emergence of severe dengue symptoms [12]. It has been proposed that GPI-anchored NS1 proteins on cell membranes are bound by anti-NS1 antibodies, activating cellular signal transduction pathways and causing tyrosine phosphorylation of cellular proteins. One essential sign of severe dengue sickness is liver damage, and anti-DENV NS1 antibodies may also be involved. The demonstration of a hepatitis-like pathogenic effect can be achieved with either passive administration of anti-DENV NS1 antibodies or active immunization of mice with DENV NS1 [13]. Endothelial cell damage generated by anti-DV NS1 is primarily caused by two responses: inflammatory activation and cell death. By means of a Nitric Oxide (NO)-regulated mechanism, anti-DENV NS1 antibodies caused endothelial cell death. Mouse vascular endothelium and human endothelial cells interacted with mouse antibodies against DENV NS1. Following binding, caspase-dependent endothelial cell death was induced by mouse anti-NS1 Abs [14].

- **Role of T cells:**

Numerous investigations have suggested that DHF pathogenesis is mediated by cross-reactive T cells, which are activated during subsequent heterotypic infections. Humans with heterologous DENV experience preferential activation of highly cross-reactive CD8+ T cells with high avidity for the infecting virus during the acute phase of a subsequent infection [15]. Activated DENV-specific cross-reactive T cells produce higher amounts of cytokines and chemokines in DHF patients, suggesting a positive correlation between the severity of dengue-associated sickness and cross-reactive T cell activation. Low-avidity cross-reactive CD8+ T cells are preferentially increased; they respond to heterologous epitopes in a different way than to homologous ones, generating large amounts of pro-inflammatory cytokines while losing their ability to perform cytolysis. Delays in viral clearance lead to extended activation of these cross-reactive CD8+ T cells, which in turn increases TNF-α and IL-6 production. This occurrence is known as "Original antigenic sin (OAS)" [16]. All things considered, the CD4+ T cell responses to DENV infection have not been as thoroughly studied. DENV-specific CD4+ T cell epitopes are primarily found in structural proteins such the envelope and capsid, in addition to NS1 protein, in contrast to CD8+ T cell responses. There is proof that successive

infections with distinct DENV serotypes may modify the cytokine response of cross-reactive CD4+ T cells, resulting in elevated levels of pro-inflammatory cytokines that worsen dengue by triggering an adverse immunological response [17].

- **Role of Host genetic factors**

The Human Leucocyte Antigen is one of the host genetic variables that contributes to DENV pathogenesis (HLA). There is evidence linking a number of HLA class-I alleles to severe dengue in secondary infections, indicating the significance of the primed memory HLA class-I restricted cross-reactive T cells already in place. On the other hand, it has been demonstrated that HLA class-II, and particularly DRB1 alleles, provide protection against DENV infection and illness severity [18]. Additionally, it has been demonstrated that HLA-DR4 protects against DHF. Genetic polymorphisms in a number of non-HLA genes, such as Fcγ receptor II (FcγRII, CD32), vitamin D receptor (VDR), human platelet antigen (HPA), transporter associated with antigen processing (TAP), and a few cytokine polymorphisms, are also involved in the genetic susceptibility of hosts to DF and DHF, in addition to HLA genes. A few host variables, like a lack of glucose-6-phosphate dehydrogenase (G6PD), may also be involved in the enhanced DENV replication in monocytes. It is unclear if there are single gene abnormalities, as there have been for some common diseases like pneumococci and mycobacteria, that confer a significant vulnerability to DENV infection. An individual population of DHF or DSS patients who are otherwise healthy may be used to identify polymorphisms and single-gene defects that predispose to the development of the most severe forms of DENV infection [19].

Possible diagnosis

The identification of a number of presenting symptoms and indications leads to a clinical suspicion, which is the first step towards the diagnosis of dengue. Patients who have dengue frequently have a rapid fever during the early acute febrile phase of the illness. Even though these symptoms typically manifest in the latter stages of the illness, the advent of a maculopapular rash, retro-orbital discomfort, bleeding nose, or gums are more pathognomonic of dengue and would more likely prompt a differential diagnosis of dengue [20]. The DENV can be found using a variety of test types. The isolation of the DENV in cell culture, serological testing, PCR, and, more recently, biosensors and quick procedures are the conventional ways for diagnosing the virus.

Viral products (capture and detection of the secreted NS1 protein), the virus itself (virus isolation in culture or mosquitoes or the direct detection of viral genomic RNA), or the host immune response to virus infection (measurement of virus-specific immunoglobulin M [IgM] and immunoglobulin G [IgG]) are among the biomarkers that have been targeted for diagnosis. The length of time these indicators arise and remain present throughout primary and subsequent dengue infections.

Conclusion

Research into the full pathophysiology of dengue virus infection is a constantly developing field. A single theory is insufficient to explain the variety of manifestations that DENV infection can have in distinct hosts. Contrary to popular belief, EC and liver involvement in several organ systems appears to have a significant role in the pathophysiology of dengue. A high viral load or a connection to type 2 cytokine responses are the outcomes of antibody-mediated intensification of infection. It is important to look at the part that preexisting immunity to other flaviviruses plays in the development of severe dengue. Research into the full pathophysiology of dengue virus infection is a field that is constantly changing. Investigating the relationship between NS1 levels and disease severity as well as the direct impact of the dengue virus NS1 antigen on capillary permeability. This will enable us to comprehend the function of the NS1 antigen and how the severity of the disease is related to it. Surveillance is another element of dengue prevention, as it offers the data required for risk assessment and program direction.

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Chapter - 4

Aloe Vera: Bridging Tradition with Modern Science in Phytochemistry and Pharmacology

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Chapter - 4

Aloe Vera: Bridging Tradition with Modern Science in Phytochemistry and Pharmacology

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Abstract

Aloe vera, a succulent plant with a rich history of traditional medicinal use spanning millennia, has garnered significant scientific interest for its diverse pharmacological properties. This article provides a comprehensive overview of the traditional uses, phytochemistry, and pharmacological properties of Aloe vera. Through an extensive review of historical texts and contemporary scientific literature, we explore the traditional applications of Aloe vera in various cultures worldwide, ranging from wound healing and skin disorders to gastrointestinal ailments and immune modulation. Furthermore, we delve into the phytochemical composition of Aloe vera, elucidating the bioactive compounds responsible for its therapeutic effects, including polysaccharides, anthraquinones, glycoproteins, and antioxidants. Additionally, we examine the pharmacological activities of Aloe vera extracts and isolated compounds, including anti-inflammatory, antimicrobial, antioxidant, immunomodulatory, and wound healing properties, as demonstrated in preclinical and clinical studies. Moreover, we discuss the mechanisms underlying the diverse pharmacological actions of Aloe vera, highlighting its potential therapeutic applications in various disease conditions. Understanding the traditional knowledge and scientific evidence surrounding Aloe vera offers insights into its therapeutic potential and informs the development of evidence-based botanical medicines. This review underscores the importance of further research to elucidate the mechanisms of action and optimize the therapeutic use of Aloe vera in modern medicine.

1. Introduction

Efforts in discovering novel compounds against pathogens persist through the exploration of plant extracts. Approximately one-fifth of the plant species worldwide have undergone pharmacological or biological

testing, leading to the introduction of a significant number of new antibiotics derived from natural or semi-synthetic sources. The Aloe genus, a succulent herb of 80 - 100 cm in height, belonging to the Alliaceae family, typically matures within 4 - 6 years and can endure for nearly 50 years under favorable conditions. *Aloe vera* (L.) Burm. f., synonymous with Aloe barbadensis Miller, exhibits notable biological activity among its 400 species. Recognized by the World Health Organization, medicinal plants stand as a promising reservoir for diverse drug discovery [1]. Originating from southern and eastern Africa, particularly along the upper Nile in Sudan, Aloe vera has been introduced to northern Africa and naturalized in regions such as the Mediterranean. Commercial cultivation of the plant occurs in various countries including Aruba, Bonaire, Haiti, India, South Africa, the United States, and Venezuela [2], with the highest quality Aloe grown in the Southern California desert. Remarkably resilient, the plant can thrive in temperatures reaching 104 °F and endure below-freezing conditions as long as the roots remain intact.

1.1 Synonym

According to the International Rules of Botanical Nomenclature (IRBN), *Aloe vera* (L.) Burm. f. is recognized as the valid species name for this plant, although most formularies and reference books identify *Aloe barbadensis* Mill. as the correct species name, with *Aloe vera* (L.) Burm. f. considered a synonym. Various species within the Aloe genus include *Aloe barbadensis* Miller, *Aloe chinensis* Bak., *Aloe elongata* Murray, Aloe indica Royle, *Aloe officinalis* Forsk., *Aloe perfoliata* L., *Aloe rubescens* DC, *Aloe vera* L. var. littoralis König ex Bak., *Aloe vera* L. var. chinensis Berger, and Aloe vulgaris Lam [2].

1.2 Taxonomic treatment

This perennial succulent herb is characterized by a triangular, sessile stem and a shallow root system. Its fleshy serrated leaves are arranged in rosettes, reaching lengths of 30 - 50 cm and widths of 10 cm at the base, with a pea-green coloration. The plant bears bright yellow tubular flowers on axillary spikes, measuring 25 - 35 cm in length, with stamens often protruding beyond the perianth tube. Its fruits contain numerous seeds [3].

2. Active ingredients

The leaves of Aloe vera exhibit a three-layer structure. The outermost layer comprises a protective layer, approximately 15 - 20 cells thick, which synthesizes carbohydrates and proteins [4]. The active constituents of Aloe vera encompass anthraquinones, chromones, polysaccharides, and enzymes.

Anthraquinones and chromones are attributed to its anti-cancer, anti-inflammatory, and laxative properties [9]. Additionally, Aloe vera gel has been reported to contain various elements such as Al, B, Ba, Ca, Fe, Mg, Na, P, Si, among others [5].

3. Therapeutic use

3.1 Wound healing

Wound healing is a dynamic process that unfolds in three distinct phases. The initial phase involves inflammation, hyperemia, and leukocyte infiltration. Subsequently, the second phase ensues, marked by the removal of necrotic tissue. Finally, the third phase encompasses proliferation, characterized by epithelial regeneration and the formation of fibrous tissue [6].

Recent reviews corroborate the efficacy of Aloe vera in promoting healing, particularly for first to second-degree burns [7]. The wound healing potential of Aloe vera gel has been attributed to Mannose-6-phosphate [8]. Glucomannan and gibberellins, present in Aloe, interact with fibroblast growth factor receptors, enhancing their activity and proliferation, thereby augmenting collagen synthesis through both topical and oral administration [9]. Aloe administration influences collagen composition, favoring the synthesis of type III collagen and increasing collagen cross-linking, which contributes to wound contraction and improved breaking strength [10]. Moreover, it enhances the synthesis of hyaluronic acid and dermatan sulfate in the granulation tissue of healing wounds [11].

Aloe gel has been employed in the treatment of radiation burns and ulcers, demonstrating complete healing in some cases [12]. Notably, fresh gel exhibits superior efficacy compared to cream formulations, with Aloe-treated lesions healing faster [12]. Clinical studies, including placebo-controlled trials, have further supported the effectiveness of Aloe gel in treating partial-thickness burns [12].

3.2 Anti-inflammatory action

Numerous *in vitro* and *in vivo* studies have unveiled the anti-inflammatory potential of Aloe vera gel, primarily attributed to its bradykinase activity [13]. Bradykinase, a peptidase isolated from Aloe, has been demonstrated to degrade bradykinin, an inflammatory mediator implicated in pain sensation [13]. Furthermore, gel extracts have yielded a novel anti-inflammatory compound, C-glucosyl chromone [13]. Aloe vera suppresses the cyclooxygenase pathway, consequently reducing

prostaglandin E2 production from arachidonic acid. Experimental evidence suggests that fresh Aloe vera gel exhibits significant efficacy in mitigating acute inflammation in rats, particularly in carrageenin-induced paw edema models, although its effect on chronic inflammation appears limited [13]. In mice models of croton oil-induced edema, three sterols derived from Aloe vera gel demonstrated anti-inflammatory properties, with lupeol exhibiting the most pronounced activity in a dose-dependent manner. These findings indicate that specific plant sterols, including campesterol, β-sitosterol, lupeol, and cholesterol, inherent to Aloe vera, contribute to its anti-inflammatory action, alleviating inflammation-induced pain and serving as natural analgesics. Additionally, other aspirin-like compounds present in Aloe vera further augment its anti-inflammatory and antimicrobial properties. In rat models of adjuvant-induced arthritic inflammation, Aloe vera extract containing 5.0% leaf homogenate reduced inflammation by 48% [45, 46].

3.3 Effects on the immune system

Alprogen exhibits the ability to inhibit calcium influx into mast cells, thereby impeding the antigen-antibody-mediated release of histamine and leukotriene from these cells [14]. In studies conducted on mice previously implanted with murine sarcoma cells, acemannan has been shown to stimulate the synthesis and release of interleukin-1 (IL-1) and tumor necrosis factor from macrophages. This stimulation initiates an immune response that leads to necrosis and regression of cancerous cells. Additionally, several low-molecular-weight compounds demonstrate the capacity to inhibit the release of reactive oxygen free radicals from activated human neutrophils.

3.4 Moisturizing and anti-aging agent

Muco-polysaccharides play a crucial role in retaining moisture within the skin, while amino acids aid in softening hardened skin cells. Zinc functions as an astringent, tightening pores. The moisturizing properties of Aloe vera gel have been investigated, particularly in the treatment of dry skin associated with occupational exposure. Studies have shown that wearing Aloe vera gel gloves improves skin integrity, reduces the appearance of acne and wrinkles, and diminishes erythema [15]. Aloe gel provides a cooling effect and serves as a moisturizing agent, making it beneficial for skincare. Furthermore, Aloe vera has been explored for its potential in gerontology and rejuvenating aging skin, attributed to its biogenic properties. In the cosmetic industry, Aloe vera is commonly utilized as a skin tonic.

3.5 Antitumor activity

Several glycoproteins found in Aloe vera gel have been documented to possess antitumor and antiulcer properties, along with the ability to enhance the proliferation of normal human dermal cells [16]. However, the availability of statistically significant clinical studies validating the efficacy of Aloe vera gel on human health remains limited and often yields inconclusive results [17]. Recent investigations have revealed that a polysaccharide fraction exhibits the capacity to inhibit the binding of benzopyrene to primary rat hepatocytes, thereby impeding the formation of potentially carcinogenic benzopyrene-DNA adducts. Additionally, this fraction induces glutathione S-transferase activity and inhibits the tumor-promoting effects of phorbol myristic acetate, suggesting a potential role for Aloe vera gel in cancer chemoprevention [17].

3.6 Laxative effects

Anthraquinones found in Aloe latex exhibit potent laxative properties by stimulating mucus secretion, increasing intestinal water content, and promoting intestinal peristalsis. These effects are primarily attributed to 1,8-dihydroxyanthracene glycosides, namely aloin A and B (previously known as barbaloin) [18]. Upon oral ingestion, aloin A and B, which remain unabsorbed in the upper intestine, undergo hydrolysis by intestinal bacteria in the colon. Subsequently, they are metabolized into active compounds, with aloe-emodin-9-anthrone being the primary active metabolite [18]. Similar to senna, these active metabolites act as stimulants and irritants to the gastrointestinal tract [18], resulting in the laxative effect associated with Aloe latex. It is noteworthy that the laxative effect of Aloe may not manifest until at least 6 hours after oral administration, and in some cases, not until 24 hours or longer.

4. Medicinal uses

Aloe vera boasts a diverse array of medicinal properties, making it valuable in traditional and contemporary healthcare practices. Its versatile nature encompasses anthelmintic, aperient, carminative, deobstruent, depurative, diuretic, stomachic, and emmenagogue properties. The juice of Aloe vera finds application in skin care medicine, addressing conditions such as dyspepsia, amenorrhea, burns, colic, hyperadenosis, hepatopathy, splenopathy, constipation, span menorrhea, abdominal tumors, dropsy, carbuncles, sciatica, lumbago, and flatulence. Additionally, a product derived from Aloe vera juice, known as elio, serves as a remedy for helminthiasis in children and functions as a purgative, anthelmintic, and

emmenagogue. Furthermore, glycoproteins present in Aloe vera gel exhibit reported antitumor and antiulcer effects, along with the ability to stimulate the proliferation of normal human dermal cells. Aloe vera gel is beneficial in ulcerative colitis and pressure ulcers. Traditionally, it is utilized both topically, for wound and burn treatment, and internally to address various ailments including constipation, coughs, ulcers, diabetes, headaches, arthritis, and immune system deficiencies [19]. The historical use of Aloe vera spans millennia across diverse cultures including Greece, Egypt, India, Mexico, Japan, and China. In ancient Egypt, Aloe vera was employed not only for medicinal purposes but also for crafting papyrus-like scrolls and treating tuberculosis. Various preparations of Aloe barbadensis have been recognized as useful remedies for curing various ailments. Aloe vera contains a mixture of glucosides collectively known as aloin, which constitutes the active constituent of various drugs. Traditional uses of Aloe vera extend to treating urinary problems, pimples, ulcers, and promoting gerontology and rejuvenation of aging skin [19]. The juice of Aloe vera leaves serves as a stomachic tonic and purgative. While scientific evidence supporting the cosmetic and therapeutic effectiveness of Aloe vera is limited and sometimes contradictory, claims regarding its soothing, moisturizing, and healing properties are prevalent in the cosmetic and alternative medicine industries, particularly through internet advertising. Aloe vera's bioactive compounds are utilized for their astringent, hemostatic, antidiabetic, antiulcer, antiseptic, antibacterial, anti-inflammatory, antioxidant, and anticancer properties. It finds applications in treating stomach ailments, gastrointestinal problems, skin diseases, constipation, radiation injury, wound healing, burns, dysentery, diarrhea, and various skin diseases [19]. Ayurvedic formulations utilize Aloe vera as an appetite stimulant, purgative, emmenagogue, and antihelminthic agent, addressing conditions such as cough, colds, piles, debility, dyspnea, asthma, and jaundice [19].

4.1 Cosmetic & skin protection application

Aloin and Aloe vera gel are employed as skin tonics to combat pimples, while Aloe vera is utilized for its soothing properties, helping maintain skin moisture to prevent flaky scalp and dry skin in harsh weather conditions. Sugars extracted from Aloe vera are incorporated into moisturizing preparations [20]. When combined with selected essential oils, Aloe vera serves as an excellent skin-smoothing moisturizer, sunblock lotion, and forms the basis for a variety of beauty products. Maharishi Ayurveda recommends Aloe vera for addressing various skin problems due to its soothing and cooling qualities. Aloe vera extracts exhibit antibacterial and

antifungal activities, which can aid in treating minor skin infections like boils and benign skin cysts, and have shown efficacy in inhibiting the growth of fungi responsible for conditions such as tinea [21].

Presently, Aloe vera is extensively utilized in skincare, cosmetics, and nutraceuticals. Aloe vera gel is reported to offer protective effects against radiation-induced skin damage. Although the exact mechanisms are not fully understood, administration of Aloe vera gel stimulates the production of an antioxidant protein called metallothionein in the skin. Metallothionein scavenges hydroxyl radicals, preventing the suppression of enzymes such as superoxide dismutase and glutathione peroxidase. Furthermore, Aloe vera gel reduces the production and release of immunosuppressive cytokines such as interleukin-10 (IL-10) from skin keratinocytes, thereby preventing UV-induced suppression of delayed type hypersensitivity. Reported effects of Aloe vera gel include relief from skin burns and radiation dermatitis. However, some researchers have reported instances of contact dermatitis and burning sensations on dermabraded skin following topical application of Aloe vera gel. These reactions are believed to be associated with anthraquinone contaminants present in certain preparations [22].

4.2 Antiseptic

Aloe vera exhibits antiseptic properties attributed to the presence of six antiseptic agents: lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols, and sulfur. These compounds possess inhibitory actions against fungi, bacteria, and viruses. While these potential uses are intriguing, controlled trials are necessary to ascertain the effectiveness of Aloe vera in treating various diseases [23].

4.3 Anti diabetic

The five phytosterols found in Aloe vera, namely lophenol, 24-methyllophenol, 24-ethyl-lophenol, cycloartanol, and 24-methylenecycloartanol, have demonstrated anti-diabetic effects in type-2 diabetic mice [24]. Aloe vera contains polysaccharides that increase insulin levels and exhibit hypoglycemic properties [24]. Noor *et al*. [25] reviewed the beneficial effects of various medicinal plants, including Aloe vera, on diabetes management, highlighting the role of active biomolecules with anti-diabetic activity. The treatment of diabetes mellitus has been explored using various indigenous plants and polyherbal formulations [26]. While promising results have been obtained from plant extracts regarding their antidiabetic activity, only a small fraction of the plant kingdom has been investigated thus far. Medicinal plants such as Trigonella foenum graecum, Allium

sativum, Gymnema slyvestre, Syzigium cumini, and Aloe vera have been studied for their potential in diabetes management. Extracts of Aloe gum have been found to improve glucose tolerance in both normal and diabetic rats, and Aloe vera sap, when consumed for 4 - 14 weeks, has shown significant hypoglycemic effects both clinically and experimentally [27]. Aloe vera gel is utilized to reduce blood sugar levels in diabetes [3]. Traditional anti-diabetic plants hold promise in providing novel oral anti-diabetic compounds, which could address the high cost and limited availability of current medications, particularly in rural populations in developing countries [24].

4.4 Anticancer properties

The role of Aloe vera in carcinogenicity remains poorly evaluated. While chronic abuse of anthranoid-containing laxatives has been suggested to potentially contribute to colorectal cancer, no causal relationship has been established between anthranoid laxative abuse and colorectal cancer [22]. Reports on cancer prevention have been conducted. Some proponents claim that Aloe vera juice aids the body in healing itself from cancer and mitigates the damage caused by radiotherapy and chemotherapy, which can harm healthy immune cells crucial for recovery. Aloe vera emodin, an anthraquinone compound, has been purported to possess the ability to suppress or inhibit the growth of malignant cancer cells, suggesting potential antineoplastic properties.

4.5 Stress

Aloe juice contributes to the smooth functioning of the body's machinery [28]. It aids in reducing cell damage during stressful conditions and minimizes biochemical and physiological changes within the body. Oxidative stress refers to chemical reactions altering the oxidative state of compounds. While some antioxidants are intrinsic to the body's natural regulatory mechanisms, others are derived from dietary sources. Aloe vera exemplifies a functional food with a significant role in protecting against oxidative stress [19].

5. Antimicrobial activities

5.1 Antibacterial activity

Aloe vera gel has demonstrated bactericidal activity against Pseudomonas aeruginosa, and acemannan has shown efficacy in preventing its adherence to human lung epithelial cells in monolayer culture [29]. Additionally, a processed Aloe vera gel preparation inhibited the growth of

the fungus Candida albicans [29]. Comprising 99.3% water, Aloe vera gel's remaining 0.7% consists of solids, with carbohydrates being a significant component. Concentrated extracts of Aloe leaves serve as laxatives and hemorrhoid treatments, while Aloe gel can stimulate the body's immune system. Glucomannan and acemannan have been demonstrated to accelerate wound healing by activating macrophages, stimulating the immune system, and exerting antibacterial and antiviral effects. Streptococcus pyogenes and Streptococcus faecalis are among the microorganisms inhibited by Aloe vera gel [30]. In a rat model, the antibacterial effect of Aloe vera gel *in vivo* was suggested to enhance wound healing by eliminating bacteria contributing to inflammation. Aloe extract has exhibited potency against various strains of Mycobacterium, including *M. fortuitum*, *M. smegmatis*, and *M. kansasii*, as well as demonstrated strong antimycobacterial activity against *M. tuberculosis*. It also shows antibacterial activity against *P. aeruginosa*, *E. coli*, *S. aureus*, and *S. typhi*. Preliminary phytochemistry studies have revealed the presence of terpenoids, flavonoids, and tannins in *Aloe secundiflora*, suggesting its potential as a rich source of antimicrobial agents. This research can provide scientific support for its traditional use by the local people of the Lake Victoria region in Kenya.

5.2 Antifungal activity

Aloe vera was assessed for its impact on the mycelium development of *Rhizoctonia solani*, *Fusarium oxysporum*, and *Colletotrichum coccodes*, revealing an inhibitory effect of Aloe vera pulp on *F. oxysporum* at a concentration of 104 µl L-1. Additionally, the liquid fraction of Aloe vera reduced the rate of colony growth at a concentration of 105 µl L-1 for *R. solani*, *F. oxysporum*, and *C. coccodes* [31]. Aloe juice has been reported to possess anti-inflammatory, anti-arthritic, antibacterial, and hypoglycemic effects. *In vitro* studies have demonstrated that inner-leaf gel from Aloe vera inhibits the growth of Streptococcus and Shigella species [32]. Agarry *et al*. [33] found that Aloe gel inhibits the growth of Trichophyton mentagrophytes (20.0 mm), while the leaf exhibits inhibitory effects on both Pseudomonas aeruginosa and Candida albicans. However, Aloe vera extracts do not exhibit antibiotic properties against Xanthomonas species.

6. Conclusion

Other applications of Aloe vera extracts include dilution of semen for artificial fertilization of sheep, use as a fresh food preservative, and utilization in water conservation on small farms. Aloe vera also contains saponins, soapy substances from the gel with cleansing and antiseptic

properties. Saponins demonstrate antimicrobial activity against bacteria, viruses, fungi, and yeasts. The active ingredients concealed within its succulent leaves possess the remarkable ability to enhance human life and health in countless ways. Aloe vera holds significance in everyday life, offering relief for various skin ailments such as minor cuts, insect stings, bruises, poison ivy, and eczema. Its properties extend to skin moisturizing and anti-aging effects, as well as promoting digestive tract health and improving blood and lymphatic circulation. Furthermore, it supports the functioning of vital organs like the kidney, liver, and gall bladder, making it a valuable asset to humanity. Recognized as the "wonder plant," Aloe vera serves multiple roles as an antiseptic, anti-inflammatory agent, and aids in alleviating conditions like cancer and diabetes. Its versatility also extends to the cosmetic field, where it is widely utilized. However, there remains a pressing need for greater research emphasis to fully unlock the potential of this plant for the benefit of humankind. Undoubtedly, Aloe vera stands as nature's gift to humanity, offering invaluable applications in cosmetics, burn treatment, and medicinal use. It is incumbent upon us to explore its myriad benefits and express gratitude to nature for this enduring gift.

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Chapter - 5

Unraveling the Impact: Endocrine Disruption and Metabolic Health

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Chapter - 5

Unraveling the Impact: Endocrine Disruption and Metabolic Health

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Endocrine-disrupting chemicals (EDCs) have emerged as significant environmental contaminants with profound implications for metabolic health. This article comprehensively reviews the current literature on the mechanisms by which EDCs disrupt endocrine signaling pathways and adversely affect metabolic homeostasis. Through an exploration of epidemiological, experimental, and mechanistic studies, we elucidate the diverse ways in which EDCs interfere with hormone action, including disruption of thyroid, estrogen, androgen, and insulin signalling. Moreover, we examine the developmental origins of metabolic dysfunction resulting from prenatal and early-life exposure to EDCs, as well as the potential transgenerational effects. Additionally, we discuss the role of EDCs in promoting adipogenesis, impairing lipid metabolism, inducing insulin resistance, and contributing to the pathogenesis of obesity, type 2 diabetes mellitus, and metabolic syndrome. Furthermore, we explore the impact of EDCs on adipose tissue inflammation, mitochondrial dysfunction, and epigenetic modifications, underscoring their role in metabolic dysregulation. Understanding the multifaceted effects of EDCs on metabolic health offers insights into preventive strategies and regulatory measures aimed at reducing exposure and mitigating the burden of metabolic diseases. This review highlights the urgent need for interdisciplinary research and public health interventions to address the pervasive threat posed by endocrine disruption to global metabolic health.

Introduction

Over the past five decades, there has been a notable surge in global rates of obesity, diabetes, and metabolic diseases. According to data from the International Diabetes Federation, approximately 415 million people worldwide had diabetes in 2015, a figure projected to increase to 642 million by 2040 [1]. Similarly, the World Health Organization estimated in 2016 that 650 million individuals were obese and around 2 billion were overweight

globally. When considering the individual morbidity and mortality associated with these conditions, the societal and financial burden is substantial. Consequently, addressing this escalating metabolic disease epidemic requires identifying its underlying pathogenetic factors and mitigating their adverse effects. While genetic predisposition, increased caloric intake, physical inactivity, sleep deprivation, and aging are acknowledged as major pathogenetic factors in metabolic disease, existing literature indicates that the observed rise in metabolic diseases cannot be solely attributed to these risk factors. In fact, individuals today tend to weigh more than their counterparts did two to three decades ago, even when activity levels and caloric intake remain unchanged. Among the environmental factors implicated in the global decline of metabolic health, endocrine-disrupting chemicals (EDCs) have garnered significant attention from the scientific community, and for good reason. The documented increase in obesity and metabolic diseases coincides with a rise in the production and widespread use of EDCs [2]. While emerging epidemiological data underscore the close association between EDCs and the metabolic disease epidemic, experimental studies and animal models have elucidated numerous pathways through which EDCs disrupt hormonal balance and promote metabolic disease. This underscores the urgency for immediate action and policy-making.

In this review, we will present evidence demonstrating how environmental contaminants can perturb human metabolism by interfering with energy metabolism regulation and targeting multiple metabolically significant organs. Ultimately, these disruptions lead to an imbalance favoring obesity and dysmetabolism, contributing to the global metabolic crisis.

Overview of endocrine-disrupting chemicals–historical data

Endocrine-disrupting chemicals (EDCs) encompass exogenous compounds or mixtures that interfere with various aspects of endogenous hormonal signalling. This interference extends to the production, release, transport, cellular metabolism, binding action, and elimination of hormones [3]. This group comprises a diverse and expanding range of natural and synthetic chemical compounds, including industrial solvents, plastics, plasticizers, fungicides, pesticides, heavy metals, and pharmaceutical agents. The term "endocrine disruptor" was first introduced in 1991, marking a pivotal moment in the scientific community's understanding of environmental contaminants. In 2006, researchers at the University of California, Irvine, identified the role of EDCs in the global obesity epidemic

and coined the term "obesogen." Obesogens are environmental agents capable of promoting obesity by increasing fat cell numbers, enhancing fat storage in adipocytes, and shifting metabolism toward caloric storage. The obesogen concept has expanded to include chemicals associated with diabetes and other metabolic diseases [4]. Subsequently, in 2015, the Parma consensus statement introduced the term "metabolism-disrupting chemicals (MDCs)" to describe EDCs that contribute to diabetes, obesity, and fatty liver by perturbing metabolism at multiple cellular levels. EDCs have emerged as a significant global health concern, prompting official statements from organizations such as the Endocrine Society and WHO/UNEP [5]. These statements underscore the diverse array of diseases linked to EDC exposure, encompassing reproductive disorders, neurodevelopmental issues, thyroid dysfunction, metabolic disorders, and hormone-related cancers. Despite significant progress in understanding EDCs, much remains to be uncovered, suggesting that current knowledge represents merely the "tip of the iceberg." Continued research efforts are needed to fully comprehend the extent of EDC-related health risks and devise effective mitigation strategies.

EDCs characteristics and unique properties

More than 1,000 synthetic chemical compounds are recognized as endocrine-disrupting chemicals (EDCs), including plastics such as bisphenol A (BPA), plasticizers like phthalates, industrial solvents/lubricants, and their byproducts such as polychlorinated biphenyls (PCBs), polybrominated biphenyls (PBBs), and dioxins. Additionally, pesticides such as methoxychlor, chlorpyrifos, and dichlorodiphenyltrichloroethane (DDT), fungicides like vinclozolin, and pharmaceutical agents such as diethylstilbestrol are considered EDCs [6]. These compounds can be encountered through various routes of exposure, including air, water, food, and consumer products. Some have low accumulation in the human body, while others, such as persistent organic pollutants (POPs), are highly lipophilic and accumulate readily in the food chain and adipose tissue. EDCs can also be detected in various biological fluids, including sera, urine, amniotic fluid, and breast milk [7]. Despite the heterogeneity within the group, certain key characteristics delineate EDCs and aid in understanding their mechanisms of action and consequences. EDCs, akin to hormones, can elicit disruptive effects even at low levels of exposure, especially during critical developmental periods. They often exhibit a non-monotonic (U-shaped or biphasic) response, wherein low doses may exert a more pronounced impact than higher doses. Although EDCs generally have lower affinity for hormone receptors compared to natural ligands, they can still exert detrimental effects on various human tissues [8].

The timing of exposure to EDCs is crucial, particularly during sensitive developmental stages such as fetal life, infancy, puberty, pregnancy, and menopause, predisposing individuals to a spectrum of diseases [9]. Moreover, there is often a temporal lag between EDC exposure and the clinical manifestation of disease, suggesting that the effects may not be immediately apparent but can manifest years later. Given that environmental pollution involves a mixture of compounds, humans are continuously exposed to a cocktail of EDCs. In such mixtures, different classes of EDCs may interact additively or synergistically, complicating the prediction of their net effects and the establishment of cause-and-effect relationships between specific EDCs and associated diseases.

Human metabolism: A precise hormonal interplay between tissues

Energy homeostasis involves the coordinated regulation of food intake (energy inflow) and energy expenditure (energy outflow). This intricate balance is maintained by metabolically active organs including the liver, pancreas, adipose tissue, brain, gut, and thyroid. The hypothalamus plays a pivotal role in governing energy intake and appetite by integrating neural signals from various brain regions and hormonal cues [10]. Within the hypothalamic arcuate nucleus (ARC), two distinct neural populations coexist, each exerting opposing effects on appetite regulation. Neuropeptide Y (NPY) and agouti-related protein (AgRP)-expressing neurons promote orexigenic actions, while proopiomelanocortin (POMC), cocaine- and amphetamine-regulated transcript protein (CART)-expressing neurons elicit anorexigenic effects. Moreover, the gastrointestinal (GI) tract, particularly GI regulatory peptides, serves as another key player in energy homeostasis regulation [11]. Nutrient intake triggers the secretion of gut peptides such as cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide YY (PYY). These peptides, either through activation of local neuronal circuits or direct endocrine signalling to the central nervous system (CNS), establish a bidirectional gut-brain axis. Additionally, emerging evidence suggests that alterations in gut microbiota composition can disrupt the production of metabolites and substances crucial for physiological functions, potentially contributing to metabolic disorders like obesity and diabetes. Adipose tissue plays a critical role in regulating energy homeostasis and serves as an endocrine gland pivotal in nutrient metabolism [12]. Dysfunction of adipose tissue lies at the core of metabolic diseases. Adipocytes, the principal cells of adipose tissue, originate from mesenchymal stem cells (MSCs). Differentiation of MSCs into adipocytes involves commitment to the adipose lineage and subsequent terminal differentiation into mature adipocytes, with

the peroxisome proliferator-activated receptor gamma (PPAR-γ) pathway serving as the master regulator of adipogenesis [13]. Beyond mature adipocytes, the balance and receptor profile of other cell types in adipose tissue, including stem cells, preadipocytes, macrophages, neutrophils, lymphocytes, and endothelial cells, are crucial for maintaining energy homeostasis control. The pancreas, through its multiple hormones, primarily glucagon and insulin, plays a central role in regulating glucose homeostasis [14]. Elevated levels of exogenous glucose postprandially stimulate insulin secretion from β-cells. Glucose uptake by beta cells triggers intermediary metabolism, leading to increased ATP/ADP ratio and closure of plasma membrane ATP-sensitive K+(KATP) channels. This depolarizes the cells, promoting insulin release into circulation, which then interacts with receptors in target organs to facilitate insulin-mediated glucose disposal. Dysregulation at any stage of this process can result in inadequate glucose-mediated insulin release and subsequent diabetes [15]. Additionally, insulin, along with leptin, is implicated in influencing hypothalamic control of energy homeostasis, although the precise nature of this interaction requires further elucidation. Contrary to insulin's actions, glucagon is secreted in response to low blood glucose levels to increase glucose production by stimulating glycogenolysis and gluconeogenesis in the liver [16]. Glucagon also appears to play a role in food intake and satiety. Initial findings suggest that glucagon administration reduces hunger and food intake in humans and rodents, indicating that glucagon enhances satiety and decreases meal size by increasing satiation. Skeletal muscle serves as a central hub in the metabolic circulation, regulating approximately 80% of postprandial insulin-stimulated glucose disposal and serving as the primary site of energy production. Abundant in mitochondria, skeletal muscle plays a pivotal role in energy homeostasis. Insulin facilitates glucose transport in skeletal muscle by recruiting the glucose transporter GLUT4 to the plasma membrane and activating key enzymes like hexokinase and glycogen synthase to promote glycogen synthesis [17]. However, when calorie intake surpasses energy expenditure, intracellular accumulation of energy substrates occurs in skeletal muscle, leading to heightened glycolytic flux, glucose oxidation, and ultimately, increased oxidative stress and metabolic dysregulation. The liver is the primary glucose reservoir in the human body and plays a crucial role in both anabolism and catabolism. It serves as a nexus in the metabolic interplay among key organs, including skeletal muscle and adipose tissue. During fasting, the liver generates glucose as a fuel source for the body. Stimulation by the pancreatic hormone glucagon triggers a cascade of kinase activity, initiating glycogenolysis to release glucose from stored glycogen.

Once glycogen reserves are depleted, the liver engages in de novo glucose synthesis from substrates such as lactate or glycerol to provide fuel for other tissues [18].

Novel players in the metabolism disruption by EDCs (Microbiota-immune system)

The relationship between the microbiota and endocrine-disrupting chemicals (EDCs) is bidirectional, and given their implication in metabolic disease pathophysiology, this interrelationship is likely significant. On one hand, gastrointestinal (GI) bacteria possess catalytic enzymatic properties that enable them to metabolize numerous EDCs, potentially either enhancing or diminishing their toxic effects on the mammalian host. Conversely, EDCs may disrupt the composition and physiological functions of the GI microbiota, leading to adverse metabolic effects. While the exact underlying mechanisms remain unclear, it is evident that the GI microbiome serves as a novel regulator of the overall toxicity of EDCs in metabolism [20]. The role of the immune system in metabolic health has recently garnered attention, with experimental evidence demonstrating that both innate and adaptive immune reactions can profoundly affect metabolic disease progression. Immune cells and cytokine production are physiologically observed in key metabolic organs, suggesting sustained co-interaction between the immune system and metabolic tissues. Consequently, immune dysfunction can adversely influence metabolic regulation. Moreover, experimental data indicate that EDCs possess immunomodulatory properties. For instance, perinatal exposure to bisphenol A (BPA) in rodents resulted in an imbalance in proinflammatory and anti-inflammatory immune responses, potentially impacting disease susceptibility in adulthood [21]. Additionally, EDCs like BPA and phthalates can alter cytokine levels via their estrogen-like properties. Studies have shown that rats exposed to BPA exhibited reduced expression of estrogen receptor-alpha in islets, accompanied by increased proinflammatory cytokine levels in pancreatic lysates. While the evidence is still indicative, immune dysfunction emerges as another unifying mechanism underlying EDC-associated metabolic disease [22].

Extrapolating cellular mechanisms and effects to metabolic disease pathophysiology

Endocrine-disrupting chemicals (EDCs) exert detrimental effects on various critical components of human metabolism, leading to the development of metabolic diseases clinically expressed as obesity, metabolic syndrome, diabetes mellitus, and non-alcoholic fatty liver disease

(NAFLD).Obesity: A subset of EDCs known as "obesogens" promote adiposity by altering the programming of fat cell development, increasing energy storage in fat tissue, and disrupting neuroendocrine control of appetite and satiety. Around 20 environmental chemicals have been identified as obesogens, contributing to the understanding of obesity pathophysiology. Strategies to address obesity include reducing caloric intake and encouraging physical activity. However, limiting EDC exposure, particularly during sensitive developmental stages, can also be beneficial in mitigating this health issue [23]. Insulin Resistance, Metabolic Syndrome, and Diabetes Mellitus: The Parma Consensus introduced the "metabolic disruptor" hypothesis, suggesting that environmental chemicals can influence adipose tissue development and alter food intake and metabolism, thereby contributing to metabolic diseases. Susceptibility to these diseases may stem solely from EDC exposure or may require additional factors such as high-fat diet or stress for clinical manifestation. Regardless, scientific evidence indicates that EDCs play a role in the pathogenesis of metabolic diseases, emphasizing the need for further research and preventive strategies [24]. Non-alcoholic Fatty Liver Disease (NAFLD): NAFLD, a rapidly rising and prevalent liver disease worldwide, is closely associated with metabolic syndrome and diabetes mellitus. EDCs can promote NAFLD by directly or indirectly interfering with liver lipogenesis. Additionally, developmental exposure to EDCs may induce epigenetic alterations, leading to metabolic reprogramming of genes involved in hepatic lipid homeostasis and promoting NAFLD. Understanding the mechanisms by which EDCs contribute to NAFLD pathogenesis is crucial for developing effective preventive and therapeutic strategies.

Conclusions

EDCs pose an emerging global threat to human metabolic health. Over the past decade, scientific advancements have significantly enhanced our understanding of how environmental chemicals disrupt metabolism by affecting every metabolically active organ in the body. With more than 1,000 synthetic chemical compounds recognized as EDCs, it is evident that human metabolism is continuously and comprehensively under attack. While there are limitations to EDCs research, there is a clear imperative for action. Improving research strategies, raising public awareness, and implementing preventive measures in the industrial use and application of EDCs are essential steps in addressing the global deterioration of metabolic health. The health of future generations is at stake, highlighting the importance of further exploration in this scientific field to safeguard the well-being of our children in the decades to come.

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Chapter - 6

Consequences the Vital Connection: Exploring the Role of Sleep in Metabolic Health

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Chapter - 6

Consequences the Vital Connection: Exploring the Role of Sleep in Metabolic Health

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Sleep is a fundamental physiological process crucial for overall health and well-being, with emerging evidence highlighting its significant impact on metabolic health. This article reviews current research elucidating the intricate relationship between sleep patterns, duration, and quality with metabolic parameters, including obesity, insulin sensitivity, glucose metabolism, and lipid profiles. We delve into the mechanistic insights linking sleep disturbances, such as short sleep duration, poor sleep quality, and sleep disorders, with dysregulated appetite regulation, hormonal imbalances, inflammation, and altered energy metabolism. Moreover, we explore the bidirectional relationship between sleep and metabolic disorders, emphasizing how metabolic disturbances can further disrupt sleep architecture, creating a vicious cycle. Additionally, we discuss the influence of circadian rhythms, sleep hygiene practices, and lifestyle factors on sleep quality and metabolic health. Understanding the role of sleep-in metabolic regulation offers promising avenues for preventive and therapeutic interventions targeting sleep optimization to mitigate the risk of metabolic diseases. This review underscores the importance of integrating sleep management strategies into holistic approaches for promoting metabolic health and reducing the global burden of metabolic disorders.

Keywords: Obesity, circadian rhythms, metabolic disturbance, insulin sensitivity, sleeping quality.

Introduction

In contemporary times, there has been a notable surge in instances of sleep deprivation and disruption. This trend suggests a societal shift towards sleep deficiency, with empirical data indicating that the average duration of sleep has dwindled to 6.8 hours or less, in contrast to the 9-hour norm observed a century ago. It is reported that approximately 30-40% of adults experience nightly sleep durations of less than 6 hours [1]. The intricacies of

sleep patterns wield considerable influence over the maintenance of metabolic and hormonal equilibrium. The prevalence of conditions such as diabetes and obesity has escalated to reach pandemic proportions. While factors like dietary habits and reduced physical activity have undoubtedly contributed to the obesity epidemic, the role of sleep dysregulation in precipitating metabolic disturbances is gaining recognition. The nexus between sleep and weight management has unveiled promising avenues for potential intervention, particularly given the challenge of sustaining a healthy diet over prolonged periods for a limited percentage of individuals. Comprehending the interplay between sleep and metabolism is paramount, considering the burgeoning prevalence of metabolic dysregulation. Numerous unresolved questions persist, including the elucidation of causal relationships, the underlying pathogenesis, and the potential therapeutic implications.

Sleep and metabolism

Human sleep consists of two main stages: non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep. NREM sleep is further subdivided into three stages: N1, N2, and N3. N3, also known as slow-wave sleep, is regarded as deep sleep due to the body's minimal metabolic activity during this phase. REM sleep is characterized by vivid dreams, muscle atonia (loss of muscle tone), and rapid eye movements. These two stages alternate in cycles lasting approximately 90 minutes throughout the night [2]. The initial portion of the night is predominantly occupied by NREM sleep, while REM sleep predominates in the latter portion. However, the architecture of sleep is significantly influenced by various genetic and environmental factors, including sex, race, socioeconomic status, and cultural practices. Additionally, the duration of sleep-in mammals is generally correlated with the size of the animal [3].

The observation that smaller animals tend to require more sleep than larger animals suggest a potential correlation with metabolic differences. Smaller species such as bats and rats typically sleep for 13-15 hours or more, whereas larger animals like elephants and giraffes sleep for about 5-6 hours or less. This variance may be attributable to variations in metabolism, as smaller animals generally exhibit higher metabolic rates and body temperatures compared to larger animals. Metabolism, defined as the biochemical processes within an organism, encompasses anabolism (synthesis) and catabolism (breakdown), representing the energy (calories) expended by the body to sustain itself. Metabolism is associated with cellular damage due to the release of free radicals [4]. During non-REM sleep, a lower

metabolic rate and brain temperature prevail, offering an opportunity to address the damage incurred during wakefulness and periods of heightened metabolic activity, as suggested by experiments conducted by Siegel on rats. Normal sleep is characterized by a reduction in metabolic rate of approximately 15%, reaching its nadir in the morning in accordance with the circadian rhythm [5, 6]. Despite the prolonged state of physical inactivity during sleep, the basal metabolic rate accounts for 80% of the energy required to maintain cellular processes in the body. Glucose utilization is highest during wakefulness, lowest during NREM sleep, and intermediate during REM sleep [7]. Growth hormone and cortisol are two hormones known to influence glucose regulation. Growth hormone typically exhibits elevated levels at the onset of sleep, reaching its peak during slow-wave sleep, whereas cortisol levels significantly increase during the latter half of sleep, particularly in REM sleep [8]. Studies employing continuous glucose infusion during sleep, aimed at suppressing endogenous glucose production, have demonstrated a notable decrease in brain glucose metabolism, contributing to a substantial reduction (two-thirds) in systemic glucose utilization during sleep, despite concurrent increases in glucose and insulin levels. The diminished muscle tone and the anti-insulin effects associated with the surge in growth hormone levels during the initial phase of sleep further contribute to the decline in glucose utilization, thus establishing a relative state of insulin resistance during the early stages of sleep [9]. Conversely, the latter part of sleep is marked by declining glucose and insulin levels despite continuous glucose infusion. Additional research has corroborated these findings, indicating heightened glucose utilization during the REM phase of sleep, along with elevated glucose levels in the evening accompanied by reduced insulin sensitivity [10]. Furthermore, studies have illustrated that even a single night of sleep deprivation can lead to an increase in cortisol levels in the evening, exacerbating glucose dysregulation [11].

Consequences of sleep deprivation

While the influence of sleep on glucose regulation has been a subject of research for some time, our understanding of metabolic dysregulation resulting from sleep loss has only recently advanced. Previous research models primarily focused on acute sleep deprivation. However, due to the body's robust capacity for rebound, any metabolic disturbances resulting from acute Sleep loss-induced metabolic disturbances were often rectified due to the body's robust capacity for rebound. A more practical approach involves investigating recurrent, prolonged partial sleep deprivation, which

mirrors real-life situations more accurately. Numerous studies have shown that while both slow-wave sleep (SWS) and growth hormone (GH) demonstrate a rebound effect following acute sleep loss, this phenomenon is not observed during recurrent partial sleep restriction [12]. Therefore, chronic sleep deprivation models hold greater clinical relevance and are the main focus of our investigation.

While a previous study demonstrated reduced insulin sensitivity following oral glucose administration, it was limited to a single night of sleep deprivation [13]. The pioneering investigation into the effects of partial sleep deprivation on glucose tolerance was conducted by Cauter *et al*. at the University of Chicago. Their study revealed a 40% reduction in glucose tolerance (the rate of glucose clearance) following sleep deprivation. Additionally, there was a 30% decrease in glucose effectiveness, a measure of noninsulin-dependent glucose disposal, alongside a decline in the insulin response to glucose [14]. Subsequently, a randomized crossover study by the same research group corroborated these findings [15]. Collectively, these laboratory-based studies suggest that just one week of sleep deprivation can lead to significant alterations in metabolic and endocrine function.

Sleep duration and risk of diabetes

By 2010, it was anticipated that approximately 221 million individuals worldwide would be impacted by diabetes [16]. It is imperative to comprehend the influence of sleep on glucose metabolism and explore potential avenues for novel research and therapeutic approaches. Epidemiological evidence is progressively indicating that insufficient sleep duration or persistent partial sleep deprivation could elevate the susceptibility to type II diabetes. To summarize, various research investigations suggest that abbreviated sleep duration may significantly influence glucose metabolism. Nonetheless, these findings seem to be more pertinent to males than females, with reasons for this gender discrepancy remaining incompletely elucidated. Additionally, the association between extended sleep duration and the risk of diabetes remains incompletely understood.

Sleep loss and appetite

- **Leptin and ghrelin**

The appetite centre is thought to be situated within the arcuate nucleus of the hypothalamus, a region regulated by peripheral hormones like leptin and ghrelin. Leptin, an appetite-suppressing hormone, is secreted by adipose tissue, while ghrelin is predominantly released from the stomach in response

to fasting, stimulating hunger [17]. Leptin levels have been demonstrated to rapidly fluctuate in response to caloric deficits. Human studies reveal a significant increase in both leptin and ghrelin levels during sleep, although ghrelin levels tend to decline later in the night despite sustained fasting conditions [18, 19]. It is proposed that melatonin-mediated insulin-induced leptin production may sustain elevated leptin levels, potentially counteracting the effects of rising ghrelin levels during the early part of the night [20]. Leptin levels have been observed to be elevated in obese individuals and those suffering from obstructive sleep apnea. It is hypothesized that the increased levels of C-reactive protein (CRP) associated with obesity and obstructive sleep apnea bind to leptin, consequently elevating serum leptin levels [21]. This is believed to coincide with leptin resistance due to the down-regulation of leptin receptors, resulting in impaired weight regulation and potentially contributing to weight gain. The bidirectional relationship between sleep and leptin is supported by animal studies conducted by Laposky *et al*. They found that leptin-deficient mice exhibit disrupted sleep architecture, spending more time in non-rapid eye movement (NREM) sleep and overall increased sleep duration [22]. In summary, leptin may serve as a crucial link between sleep, circadian rhythm, and metabolism.

- **Orexins**

The discovery of orexins A and B, excitatory neuropeptide hormones originating from neurons in the perifornical region of the hypothalamus, has significantly enhanced our comprehension [23]. The hypothalamus regulates energy homeostasis by balancing calorie intake and energy expenditure. Orexin neurons, situated in the hypothalamus, extend their projections across various brain regions including the paraventricular nucleus of the thalamus, the locus coeruleus, and the dorsal and tuberomammillary nucleus, which are associated with wakefulness, but not the cerebellum [24, 25]. Orexins are responsive to peripheral metabolic cues such as leptin, ghrelin, and glucose, suggesting their pivotal role as a bridge between sleep and metabolism, underscoring their importance in metabolic control. Administration of orexins stimulates food intake and enhances wakefulness and energy expenditure [26, 27]. Narcolepsy, a sleep disorder resulting from orexin deficiency, is linked to reduced energy intake, increased BMI, and a higher incidence of type 2 diabetes [28]. Recent studies on glucose metabolism in orexin knockout mice have demonstrated the critical function of orexin in maintaining normal insulin sensitivity as age progresses [29]. To sum up, these findings propose that sleep deprivation might disrupt the intricate

hormonal signalling response to the body's energy needs, leading not only to heightened appetite but also a propensity for emotional eating.

Sleep deprivation and weight

More than twenty epidemiological investigations conducted globally examining the relationship between sleep deprivation and BMI in humans have consistently demonstrated an association between decreased obesity and increased sleep duration. However, these studies do not establish a causal link. Some studies have illustrated a U-shaped correlation, with the lowest mean BMI observed at 7.7 hours per night [30]. In the NHANES study, utilizing a standard benchmark of 7 hours per night, the odds ratio for obesity was found to be 2.35 for 2–4 hours per night, 1.60 for 5 hours per night, and 1.27 for 6 hours per night of sleep. The impact of inadequate sleep seemed to be more pronounced in children and young adults compared to older adults [31].

In summary, epidemiological evidence suggests a connection between weight gain and sleep deprivation, although a few studies have also indicated weight gain with prolonged sleep. Given the data on sleep duration and weight, counselling on sleep hygiene could serve as a significant tool in the management of obesity.

Obstructive sleep apnea and type ii diabetes

Obstructive sleep apnea (OSA) is a prevalent disorder, affecting approximately 2%–4% of the population. It is characterized by intermittent but repetitive interruptions in breathing, often accompanied by hypoxemia or reduced oxygen levels in the blood. OSA significantly impacts sleep architecture, leading to sleep fragmentation and a reduction in both rapid eye movement (REM) and slow-wave sleep (SWS) stages [32]. Recent data from a national survey suggests that as many as one in four adults may be at risk of OSA. Furthermore, over 50% of individuals diagnosed with type II diabetes also have obstructive sleep apnea [33]. A longitudinal study conducted in Sweden, involving over 2600 subjects, identified habitual snoring as an independent risk factor for diabetes during a 10-year follow-up period [34]. Subsequent studies have further supported these findings, demonstrating a correlation between habitual snoring and an increased prevalence of type II diabetes, with habitual snorers being at twice the risk of developing diabetes [35].

It is hypothesized that obstructive sleep apnea (OSA) can induce metabolic dysregulation through multiple pathways. One such pathway involves a surge in sympathetic activity that accompanies each apnea event.

Sympathetic activation has been demonstrated to elevate levels of circulating free fatty acids by stimulating lipolysis, thereby promoting insulin resistance [36]. Studies have also observed elevated catecholamine levels in individuals experiencing prolonged wakefulness after sleep onset [37].

Energy expenditure in sleep and sleep disorder

Numerous studies have investigated the correlation between body energy expenditure during sleep and sleep disorders, particularly obstructive sleep apnea (OSA). It has been observed that the energy expenditure of the human body decreases during sleep, reaching its lowest point [38]. This decline in energy expenditure may be influenced by factors such as circadian rhythm [39], fluctuations in body temperature [40], and reduced muscle activity [41], in addition to the depth and duration of sleep and levels of physical activity [8, 42, 43]. Furthermore, energy expenditure has been noted to vary depending on the sleep stage [8, 44]. Moreover, resting metabolic rate (SMR) decreases during sleep in correlation with body mass index (BMI), and the rate of decrease in SMR tends to be greater with higher BMI values [45].

Acute sleep loss has been associated with a slight increase in resting metabolic rate (SMR) [46, 47, 48], a trend that is similarly observed in cases of chronic sleep deprivation [49]. In summary, energy expenditure typically decreases during sleep, while sleep deprivation tends to elevate it. However, the impact of sleep apnea on energy expenditure remains inconclusive. Studies involving patients with obstructive sleep apnea (OSA) are further constrained by their small sample sizes and the absence of comprehensive body composition data, which significantly influences energy expenditure measurements [50].

Conclusions

Sleep disorders and diabetes represent rapidly growing health challenges with significant public health implications. There is a burgeoning interest and mounting evidence indicating that sleep loss and sleep disorders profoundly affect metabolism. Laboratory investigations from various research endeavors have unequivocally demonstrated that sleep deprivation can disrupt glucose metabolism and alter the levels of hormones involved in metabolic regulation, including decreased leptin levels and increased ghrelin levels. The findings from numerous large-scale epidemiological studies consistently suggest that chronic partial sleep deprivation is linked to an elevated risk of obesity and diabetes. However, the role of gender in this relationship remains somewhat ambiguous. Furthermore, the association between sleep duration and metabolic dysregulation often exhibits a U-

shaped pattern in many studies, such as the Nurse Health Study, Sleep Heart Health Study, and Massachusetts Male Health Study, indicating that not only insufficient sleep but also excessive sleep may disrupt the body's metabolic balance. Paradoxically, a similar U-shaped relationship has been observed in several studies examining the correlation between sleep duration and weight, where both insufficient and excessive sleep are associated with weight gain. The majority of epidemiological investigations have relied on subjective self-reported measures of sleep duration. Further research is warranted to thoroughly understand the roles of gender, sleep duration, and metabolism, utilizing more objective sleep measurements. Additionally, there is a need to distinguish between sleep deprivation resulting from voluntary sleep restriction versus insomnia. Developing a model focusing on nonobese patients with obstructive sleep apnea (OSA) could help disentangle the influence of adiposity on diabetes. Moreover, disparities exist between human and animal responses to sleep deprivation concerning weight regulation. Mechanisms elucidating the intricate interplay between sleep and metabolism require further exploration if we aspire to derive greater clinical benefits, especially with sleep emerging as a significant tool in combating the obesity epidemic.

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Chapter - 7

Unraveling the Gastro-Intestinal Ecology on Obesity, and Diabetes Mellitus: A Comprehensive Review

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Chapter - 7

Unraveling the Gastro-Intestinal Ecology on Obesity, and Diabetes Mellitus: A Comprehensive Review

Rupak Bera

The human gut microbiome has emerged as a crucial player in the pathogenesis of obesity and type 2 diabetes mellitus (T2DM), presenting a standard ideas in our understanding of these prevalent metabolic disorders. This review synthesizes current literature to elucidate the detailed relationship between gut microbiota composition, host metabolism, and the development of obesity and T2DM. We reach inside into the mechanisms by which alterations in gut microbial diversity, composition, and function contribute to adiposity, insulin resistance, and dysregulated glucose homeostasis. Additionally, we explore the role of microbial metabolites, such as short-chain fatty acids and bile acids, in modulating host metabolic pathways and inflammation. Furthermore, we discuss the impact of external factors, including diet, antibiotics, and environmental factors, on gut microbiota composition and metabolic health. Understanding the gut microbiome's influence on obesity and T2DM offers novel therapeutic avenues, including targeted microbiota-based interventions and personalized dietary strategies, for reducing these metabolic diseases. This comprehensive review underscores the importance of integrating microbiome research into clinical practice to combat the growing burden of obesity and diabetes mellitus.

Keywords: Microbiome, obesity, metabolic disorder, diabetes mellitus, glucose homeostasis.

Introduction

Diabetes mellitus (DM) encompasses a group of chronic metabolic disorders characterized by elevated blood glucose levels, posing a significant global health challenge and ranking among the leading causes of mortality among adults [1]. The prevalence of diabetes has surged worldwide in recent years, with type 2 diabetes mellitus (T2DM) comprising approximately 90% of all cases and arising from a combination of insulin resistance and

impaired insulin secretion. This condition can lead to a range of acute and chronic complications, including but not limited to blindness, amputations, cardiovascular disease, renal failure, and premature mortality. The etiology and progression of diabetes are influenced by a complex interplay of genetic and environmental factors. According to the latest data from the International Diabetes Federation (IDF), approximately 463 million adults globally are afflicted with diabetes, with an average annual growth rate of 5.1%. Genetic predisposition, infections, immune dysregulation, obesity, and dietary patterns have all been implicated in the pathogenesis of diabetes. While dietary control, regular exercise, oral antidiabetic medications, and insulin therapy are standard approaches for managing diabetes, none of these interventions address its underlying causes. Over the past decade, the role of the gut microbiome in diabetes has garnered significant attention worldwide. Understanding the intricate relationship between the gut microbiome and diabetes holds promise for the development of novel therapeutic strategies.

With the advent of high-throughput sequencing technology, research on gut microbiota has transcended the limitations of traditional bacterial cultivation methods. This has led to a gradual unveiling of the role and biology of gut microbiota and the intestinal microbial community. Comprising over 1000 bacterial species, the gut microbiota primarily consists of members from the Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria phyla [2]. The physiological functions of gut microbiota are diverse and encompass food digestion and absorption, enhancement of host immunity, biological antagonism, reinforcement of antitumor responses, and synthesis of beneficial compounds [3, 4]. However, when the balance of gut microbiota is disrupted, it can lead to a spectrum of diseases, including metabolic disorders, cardiovascular and cerebrovascular diseases, autoimmune disorders, inflammatory bowel disease, psychiatric disorders, and cancer [5].

Several research studies have highlighted the significant role of gut microbiota in type 2 diabetes mellitus (T2DM). Gut microbiota actively participates in the regulation of glucose metabolism and insulin sensitivity. Modifying gut microbiota has been shown to ameliorate symptoms in diabetic patients, aiding in the reversal of impaired glucose tolerance and fasting glucose levels in individuals with prediabetes. This review aims to delve into the correlation between gut microbiota and T2DM, elucidate the pathogenesis of T2DM mediated by gut microbiota, and explore therapeutic interventions centered around gut microbiota.

The metabolic action of gut microbiota

Recent data indicate that the number of bacteria inhabiting the human body is approximately 3.8 × 10^13, a figure comparable to the number of human cells. The majority of these bacteria belong to the phyla Firmicutes (gram-positive) and Bacteroidetes (gram-negative), which collectively constitute 60-80% and 20-30% of the entire gut microbiota (GM), respectively, alongside Proteobacteria and Actinobacteria [6]. A higher abundance of bacterial species within the microbiota has been associated with a reduced risk of metabolic disorders such as obesity, metabolic syndrome, and type 2 diabetes (T2D). Conversely, individuals with lower microbial diversity, particularly obese individuals, are at increased risk of weight gain, adiposity, insulin resistance, and inflammation compared to those with a higher microbial gene count [7]. Additionally, gut microbes play a significant role in the synthesis of secondary bile acids (BAs) and the catabolism of proteins, as well as the production of water-soluble vitamins [8]. Beyond these functions, gut microbiota is increasingly recognized for its essential role in fostering the development and maintenance of proper innate and adaptive immunity, as well as gut-associated lymphoid tissue (GALT). Moreover, it plays a crucial role in the process of extracting energy from indigestible foods.

Indeed, GM makes possible intestinal plant fibers fermentation, leading to the production of short-chain fatty acids, such as butyrate, propionate, and acetate. SCFAS are peculiar metabolites involved in the physiological activity of colonic cells and in the regulation of appetite, insulin response, and inflammatory processes. Impaired SCFAs levels have been shown to be involved in the pathogenesis of metabolic, cardiovascular, and oncological diseases [9]. Propionate and butyrate exert an anti-obesogenic action stimulating leptin and anorexigenic hormones synthesis [10]. while acetate predominantly presents obesogenic properties inducing ghrelin secretion and promoting fat storage [11]. Different studies revealed that microbes like Faecalibacterium prausnitzii and Roseburia intestinalis, are the most important microbiota-related features responsible for the onset and development of T2D [12].

Gut microbiota in obesity and diabetes

The gut microbiota often exhibits an overabundance of pathogenic and opportunistic gram-negative species, which can outcompete commensal bacteria. In diabetic patients, there is typically an increase in pathogenic bacteria such as Enterobacteriaceae, Escherichia coli, Bacteroides, and

Lactobacilli within the microbiota. Bacteroidetes, which are gram-negative bacteria, are associated with elevated levels of lipopolysaccharide (LPS), a marker of inflammation. Conversely, a decrease in Bacteroidetes is linked to reduced metabolic endotoxemia and a less inflammatory state. Proteobacteria, another gram-negative phylum, are known to be highly pro-inflammatory [13].

It is widely recognized that the subclinical pro-inflammatory state resulting from lipopolysaccharide (LPS)-dependent production of inflammatory cytokines, such as Interleukin-1 (IL-1), IL-6, and Tumour Necrosis Factor-α (TNF-α), plays a pivotal role in driving the development of insulin resistance and type 2 diabetes (T2D). However, conflicting evidence regarding the association between diabetes and alterations in the relative abundance or reduction of certain bacterial genera suggests that these changes may be more species-specific rather than genus-specific. The first study on the gut microbiota of T2DM was reported in 2010 [14]. For instance, while the genus Clostridium is typically considered pathogenic, certain Clostridium species are crucial for hepatic bile acid metabolism and for the synthesis of bile acids from cholesterol. Among the various functions of bile acids, their involvement in glucose metabolism and energy homeostasis is particularly complex. Bile acids encompass a diverse range of molecules essential for the absorption of lipophilic nutrients and can be metabolized by specific intestinal microorganisms. Bile acids themselves possess antimicrobial properties and serve as ligands for FXR (Farnesoid X Receptor), a nuclear receptor involved in bile acid homeostasis, carbohydrate metabolism, insulin response, and intestinal innate immune response [15].

The genus Lactobacillus has been found to exhibit a positive association with type 2 diabetes (T2D), although certain species within this genus possess anti-inflammatory properties. For example, Lactobacillus species can stimulate the production of the anti-inflammatory cytokine IL-10, which enhances insulin sensitivity in muscle cells [16]. Additionally, they can inhibit the synthesis of proinflammatory cytokines such as IL-1β, Monocyte Chemoattractant Protein-1 (MCP-1), IL-8, Interferon-γ (IFN-γ), and C-reactive Protein. Furthermore, Lactobacillus has been positively correlated with markers of glycaemic control such as fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c). In contrast, Clostridium is negatively associated with HbA1c, FBG, C peptide, insulin, and plasma triglyceride levels, while positively correlated with high-density lipoprotein (HDL) and adiponectin levels. In summary, the composition of the gut microbiota has been recognized as a potential marker of metabolic diseases, including type 2 diabetes mellitus [17].

Role of bile acids

Bile acids, primarily synthesized from cholesterol in the liver, are secreted into the intestine where they are often converted into secondary bile acids by gut microbiota. These secondary bile acids play a pivotal role in modulating glucose metabolism and insulin sensitivity via various signalling pathways [18]. One such pathway involves the activation of the thiol guanosine receptor-5 (TGR-5) receptor by secondary bile acids, which enhances muscle energy consumption and stimulates the secretion of glucagon-like peptide 1 (GLP-1) by intestinal L cells. This activation contributes to mitigating insulin resistance and abnormalities in glucose metabolism [19, 20]. The conversion of primary bile acids into secondary bile acids by gut microbiota is vital for bile acid synthesis, modification, and signal transduction. Disruptions in bile acid metabolism mediated by gut microbiota can disturb the regulation of glucose metabolism by bile acids [21-23]. Recent research suggests that patients with gut microbial dysbiosis exhibit abnormal bile acid metabolism, leading to increased secretion of secondary bile acids such as lithocholic acid and deoxycholic acid. These bile acids promote the release of 5-hydroxytryptamine by enterochromaffin cells, resulting in decreased insulin release and enhanced glucagon secretion [24]. Furthermore, bile acids can directly influence the structure, function, and stability of the intestinal flora [25].

- **LPS**

Several studies have demonstrated that patients with type 2 diabetes mellitus (T2DM) exhibit a low-grade inflammatory state characterized by increased levels of lipopolysaccharide (LPS) in the peripheral circulation [26-28]. Elevated serum LPS levels are primarily attributed to gram-negative bacteria, which contribute to increased intestinal permeability and subsequent release of LPS into the bloodstream. LPS binds to Toll-like receptor 4 (TLR4) with the assistance of CD14, resulting in macrophage activation and activation of the NF-κB inflammatory signalling pathway. This activation leads to heightened production of inflammatory cytokines such as TNF-γ, IL-1β, IL-6, and TNF-α. Subsequently, abnormal phosphorylation of insulin receptor substrate occurs, leading to insulin resistance [29]. Additionally, β cells in the pancreas are damaged, resulting in inhibited insulin secretion and downregulation of the Homeobox1 (PDX1) gene expression in both the pancreas and duodenum [30, 31].

- **BCAAs**

Branched-chain amino acids (BCAAs), namely leucine, isoleucine, and valine, are essential amino acids required by the human body. As the host

cannot synthesize these amino acids, they must be acquired through the diet and are primarily produced through gut microbiota metabolism [32]. Elevated plasma levels of BCAAs have been identified as a risk factor for type 2 diabetes mellitus (T2DM). Studies have shown that increased intake of BCAAs in the diet can promote the development of T2DM and insulin resistance [33, 34].

In Aspects of treatment gut microbiome & diabetes

Modification of dietary structure represents one of the fundamental adjunctive strategies for managing diabetes, with particular emphasis on dietary fiber due to its potent effects in improving type 2 diabetes mellitus (T2DM) [35, 36]. Extensive long-term studies spanning multiple cohorts have revealed that higher intake of total whole grains and commonly consumed whole-grain foods is associated with a reduced risk of developing type 2 diabetes. These findings provide robust evidence supporting dietary recommendations advocating for adequate consumption of whole grains as part of a health-promoting diet to prevent the onset of type 2 diabetes [37].

Probiotics, typically consisting of gram-positive bacteria, are living microorganisms recognized for conferring health benefits to human health when consumed at appropriate levels. Current research identifies three main categories of probiotics for managing diabetes:

1. Common probiotics: These bacteria, predominantly from the genera Lactobacillus and Bifidobacterium, are extensively utilized in food fermentation and are generally considered safe for consumption [38, 39]. Clinical trials investigating the use of common probiotics in patients with type 2 diabetes mellitus (T2DM) have been conducted; however, the results have been inconsistent.
2. Novel probiotics: Emerging studies have demonstrated the potential of certain probiotics to significantly improve insulin resistance and lipid metabolism, suggesting their utility as novel therapeutic agents for T2DM.

Further research is needed to elucidate the mechanisms underlying the effects of probiotics on diabetes management and to establish their efficacy and safety profiles in clinical practice.

Conclusion

Diabetes has emerged as a pressing public health concern, with the upward trajectory of diabetes cases expected to persist over the next two decades and beyond. In this narrative review, we explore the pivotal role of

gut microbiota in type 2 diabetes mellitus (T2DM), impacting both composition and function. Several factors linked to gut microbiota have been identified in T2DM, including short-chain fatty acids (SCFAs), bile acids, lipopolysaccharides (LPS), branched-chain amino acids (BCAAs), and imidazole propionate. Gut microbiota not only serves as a potential diagnostic biomarker but also represents a promising therapeutic target for T2DM. However, the precise causal relationship between specific intestinal bacteria and phenotypic outcomes remains incompletely understood. Therefore, comprehensive studies are needed to further explore this relationship. Understanding the exact role and mechanism of gut microbiota in T2DM will offer novel insights into the development of personalized therapies for T2DM patients. Further investigations utilizing fecal or bacterial transplantation and clinical studies are necessary to deepen our understanding of the roles of individual bacteria in metabolic diseases. Nonetheless, the gut microbiota is emerging as a promising therapeutic target for diabetes management.

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Chapter - 8

Brain Aging: A Gradual Change in the Physical and Cognitive Health

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Chapter - 8

Brain Aging: A Gradual Change in the Physical and Cognitive Health

Ayan Sengupta and Rajen Dey

Abstract

Ageing modifies the size, vascular structure, and cognitive function of the brain. As one ages, the brain shrinks and undergoes changes in every aspect, including shape and chemistry. Age-related increases in the risk of stroke, dementia, white matter lesions, and memory impairment are accompanied with alterations in hormone and neurotransmitter levels. The ageing brain appears to benefit from protective variables that lower cardiovascular risk, such as a good diet, regular exercise, and a low-to-moderate alcohol intake, as well as from increased cognitive exertion from education or career achievement. Living a physically and psychologically fit life may be the best defense against the alterations brought on by aging in the brain and may lead to treatable reasons.

Keywords: Brain aging, cognition, stroke, dementia, neurotransmitter.

Introduction

Brain aging is a multifaceted process that starts early in life and quickens with age, affecting everything from the subcellular to the organ level. Brain volume reduction, cortical thinning, white matter deterioration, loss of gyrification, and ventricular expansion are the main morphological characteristics of aging brains. Neuron cell shrinkage, dendritic degeneration, demyelination, small vessel disease, metabolic slowdown, microglial activation, and the development of white matter lesions are pathophysiologically linked to brain aging [1]. The field of mechanics has shown a growing interest in simulating the (bio) mechanical behavior of the brain in recent years. Constitutive modelling is used to forecast shape changes of anatomically correct specific element brain models in both health and disease. Therefore, we essentially have two goals in mind. Initially, we examine the current imaging-based information on the rates of gray and white matter shrinkage as well as the aging patterns at the organ level. In

order to validate and calibrate constitutive brain models, this data is needed. Second, we go over the most important aging mechanisms at the tissue and cell levels that cause alterations in both white and gray matter. Based on the hypothesis that the combination of imaging and mechanical modelling may assist identify the tipping point when normal aging ends and pathological neurodegeneration begins, we concentrate on aging mechanisms that ultimately materialize as changes in the form of organs. Cognitive decline is linked to major alterations in the complex microstructure of the brain caused by aging and pathology [2]. The structure and anatomy of the brain, or brain morphology, change as we age and most often experience severe atrophy, or loss of cerebral tissue volume. Memory loss [3], decreased motor function, and altered behavior are among the cognitive deficiencies that are accompanied by these changes, if not the direct cause of them. The structural characteristics of both normal and gradual brain aging have been established as a result of significant efforts in large population medical imaging studies, such as the Alzheimer's Disease Neuroimaging Initiative or the Rotterdam Study [4]. Neurodegenerative disorders have been demonstrated to hasten the aging process and cause more noticeable structural alterations in the brain in cross-sectional studies involving elderly individuals who are cognitively normal or in good health as well as those with progressive cognitive impairment or Alzheimer's disease (AD). Because it is difficult to distinguish between abnormal and healthy changes, early detection of structural abnormalities may be a suitable biomarker for rapid aging due to the initiation of neurodegeneration [5]. This makes the trajectories of cerebral atrophy in both healthy aging and dementia the subject of extensive investigation. The fact that every brain is unique makes it difficult to spot minute alterations or aberrant developments from a single or even a series of longitudinal magnetic resonance imaging, which is a significant barrier to early identification. There are several different etiologies for the broad impacts of aging on the brain and cognitive function. Aging affects the vasculature, chemicals, cells, physical morphology, and cognitive function. The volume of our brains decreases with age, especially in the frontal cortex [6]. Our white matter becomes lesions as we age and our blood pressure rises, increasing the risk of stroke and ischaemia. Age-related memory loss is often accompanied with increased bilateral brain activation during memory tests. This might be an attempt to make up for lost time and attract new networks, or it could be the result of difficult access to some locations. Ageing of the brain is influenced by hormones, experience, neurotransmitters, and genetics [7]. Higher levels of education or professional achievement, however, may operate as a protective factor, so it's not all bad. A balanced diet, moderate

alcohol use, and regular exercise are also protective. It may be able to slow biological aging and potentially lower the risk of developing age-related disorders like dementia. Biological aging is not inextricably linked to chronological aging.

As we've already discussed, there are several forms of brain aging, and each sort can have unique characteristics along with complexions. It can involve both physical and cognitive changes. Cognitive changes are those that affect memory in a mental and diagnostic way. Memory can change over time and become less reliable, and we will also learn about the mechanisms underlying these changes in the brain.

Physical changes with its attributes

Your body's central nervous system and brain serve as its command center. Their power over your body is:

Motions

Senses

Recollections and ideas

They also assist in maintaining control over your heart and intestines.

The channels that transmit and receive messages between your brain and the rest of your body are called nerves. The nerve bundle that extends from your brain down the middle of your back is called the spinal cord. Every component of your body is connected to nerves that originate in the spinal cord [8].

Age-related alterations in the brain and how they affect the nervous system

Nerve system and brain naturally alter as people get older. Atrophy is the loss of weight and nerve cells in the brain and spinal cord. It's possible that nerve cells will start transmitting messages slower than before. As nerve cells degrade, waste products or other substances, including beta amyloid, can accumulate in the brain tissue. This may lead to the formation of aberrant alterations in the brain known as plaques and tangles. In nerve tissue, lipofuscin, a fatty brown pigment, can also accumulate [9]. Nerve damage can impair your senses. You may experience diminished or absent reflexes or feeling. This increases the risk of falls and causes issues with mobility and safety. Aging-related cognitive decline is a common occurrence. Everybody experiences these changes differently. Some people's brain tissue and nerves have several alterations. Others haven't changed all

that much. These alterations don't necessarily correspond with how they affect your capacity for thought [10].

Nervous system disorders in the elderly and their limitations

Severe memory loss and dementia are not typical aspects of aging. They may be brought on by neurological conditions like Alzheimer's, which is thought to be brought on by the buildup of plaques and tangles in the brain [11]. Sudden confusion that causes behavioral and mental disturbances is called delirium. It frequently results from diseases unrelated to brain disorders. An elderly person suffering from an infection may become very disoriented. Additionally, several medications may exacerbate or cause this. Diabetes that is not well managed can also lead to issues with thinking and conduct. Blood sugar fluctuations can cause cognitive impairment [12].

Additionally, it has been generally and extensively discovered that the weight and/or volume of the brain decreases with age at a rate of around 5% each decade beyond the age of 40, with the real rate of decline probably rising with age, especially beyond the age of 70. What's less understood is how this happens. It's common knowledge that neuronal cell death causes the grey matter to decrease, however it's unclear if this is the main cause or even the main observation. According to certain theories, the aging brain is influenced by a decrease in neuronal volume rather than quantity, and it may be correlated with a person's sex, with distinct regions of the brain being impacted in men and women [13]. Furthermore, alterations in dentritic arbour, spines, and synapses may occur. It is possible for dendritic sprouting to take place, which would maintain a constant number of synapses and offset any cell death. On the other hand, there have also been reports of a decline in dendritic synapses or a loss of synaptic plasticity. It is possible for functional organizational change to transpire and compensate in a manner akin to what is observed in patients following recovery from mild traumatic brain damage [14]. Nevertheless, a lot of other important research in the latter field has a limited number of instances. It's also important to take into account how white matter functions in the aging brain. The myelin sheath begins to deteriorate at the age of 40, even in cases of normal aging. White matter lesions (WML) have been shown to mostly impact the late myelinating regions of the frontal lobes, though this theory has not been supported by all research. White matter may degrade with age. Age-related increases in leukoariosis/WML may be a sign of subclinical ischaemia [15].

Physical causes

Not every part of the brain experiences the same degree of brain alterations. A review of cross-sectional research [16] and a longitudinal study

that used two MRI scans spaced about one or two years apart support the idea that these brain alterations are not consistent. In contrast to most previous research in this field, the latter only included studies that examined groups of people who were younger (less than 30) and older (greater than 60) in order to compare a larger range of ages. The prefrontal cortex was the area most impacted by volume, according to the analysis. With the study encompassing more than seven research, the striatum came in second. There was a loss in volume observed in the prefrontal white matter (five studies), the temporal lobe, cerebellar vermis, cerebellar hemispheres, and hippocampal regions, with between eight and eighteen studies supporting this finding. According to five investigations, the occipital cortex was least damaged [17]. The results indicate that ageing mostly affects the prefrontal cortex and less so the occipital, which is consistent with the cognitive changes associated with aging. However, other research indicates that ageing primarily affects the hippocampus. There may be differences between men and women as well; in men, the frontal and temporal lobes are more affected than in women's hippocampal and parietal lobes [18]. Lastly, despite the modest number of studies, the rate of decline in brain capacity may increase with age, especially over 70. Mapping structure to function and change due to aging is a hard job because of individual differences in brain development and aging; however, several studies have shown connections between volume and neuropsychological function [19]. An association was found between increasing age, a decrease in prefrontal cortical volume, an increase in subcortical white matter lesions, and a rise in perseverative behavior (a decrease in executive function) in a study that examined the volume of cerebral cortex and proportions of white matter hyperintensity volume in 140 subjects aged 50-81 years who were pre-screened for the assessment of depression and dementia [20].

Cognitive causes

Memory impairment is the most common cognitive alteration linked to aging. The four main categories of memory function are working memory, procedural memory, episodic memory, and semantic memory [21]. When it comes to aging, the first two of these are the most significant. A form of memory in which information is stored with mental tags, about where, when, and how the information was picked up is the definition of episodic memory. A memory of your first day of school, the significant meeting you attended last week, or the lesson you took to discover that Paris is the capital of France are a few examples of episodic memories. It is believed that intermittent memory function starts to deteriorate about middle age. This is

less true for recognition and truer for recollection with normal aging [22]. It is also a feature of Alzheimer's disease (AD)-related memory loss.

Semantic memory is described as "memory for meanings," such as the knowledge that the Magic Flute was produced by Mozart that Paris is the capital of France, or that ten millimeters make one centimeter [23]. From middle age to the extremely elderly, semantic memory progressively rises but eventually falls [24]. Although the exact cause of these changes is unknown, it has been hypothesized that very old people may have fewer resources available to them, which could lead to slower reaction times, lower attentional levels, slower processing speeds, impairments in sensory and/or perceptual functions, or even a decreased capacity for strategy use [25].

A variety of memory categories have been studied in aging populations through the use of neuropsychological testing and neuroimaging. It should be noted, nevertheless, that several of these functions such as episodic memory encoding and semantic memory retrieval can be challenging to distinguish methodologically at times [26]. In spite of this, research is starting to look at how age affects memory function and how neuroimaging works. The alterations in regional brain activation are the primary focus of this area [27]. Due to either greater activation in a hemisphere that is less activated than in younger adults or decreased activation in the areas most stimulated in younger individuals, older brains have a tendency to show more symmetrical activity. This has been demonstrated for tasks involving memory and visual perception [28]. As episodic memory is believed to be rooted in this region, changes in memory performance, in particular, are consistent with changes in activation in the left and right prefrontal cortex. Additionally, it has been proposed that there may be a stronger direct correlation between memory ability and the actual level of brain activation as demonstrated by neuroimaging [29]. There is also some evidence in favor of greater symmetry in brain activation with aging from a review of research that used electroencephalograms to look at event associated potentials in response to stimuli [30].

The brain's ageing mechanism and other important factors

The bulk of studies on large samples of post-mortem human brains suggest that, if the so-called "secular" change in brain weights over time is taken into account, adults between the ages of roughly 20 and 60 yearss experience a small loss of brain weight of about 0.1%/year; however, after that, there is a more rapid loss [29], suggesting that weights remain stable until about the age of 50 years and then gradually decrease, as other work suggests.

Since the advent of non-invasive brain imaging in the 1970s, it has been discovered that brain volume also decreases with age. In cerebral white matter, this decrease is comparatively diffuse and uniform, but in grey matter, there are some regional differences. The striatum and frontal and parietal cortex are more affected than temporal and occipital cortex. Consistent with brain weight studies, brain volume losses increase from approximately 0.1–0.2%/year at age 30–50 years to 0.3–0.5%/year at age 70. When the brain volume decreases, the ventricular system enlarges to take up the empty space. As one ages, the subarachnoid space expands and the leptomeninges typically thicken significantly [31].

Conclusion

Damage and deterioration processes at the cell, tissue, and organ levels that result in morphological changes in the form of the brain are the hallmarks of brain aging. The hallmarks of brain aging have been established by large-scale cross-sectional medical imaging investigations, which depict a picture of gradual ventricular enlargement, cortical thinning, progressive brain volume loss, and degeneration of the white matter. These age-related alterations have a profound effect on the complex structure-function relationship of the brain and are frequently accompanied by memory loss, cognitive decline, and behavioral abnormalities. Specifically designed to model and replicate the ways in which damage mechanisms at the cell and tissue levels translate into morphological alterations at the organ level is the theory of continuum mechanics. Differentiating between healthy and accelerated aging would be made easier with the help of such tailored and predictive brain aging models. In particular, early detection of a specific neurodegenerative illness and prompt, tailored treatments offer the best opportunity to mitigate the long-term loss in quality of life that is common to AD and similar dementias. It is well known that the brain ages chronologically; what is less known is how quickly this change occurs, how old the brain is biologically, and the mechanisms at play. Molecular aging, intercellular and intracellular aging, tissue aging, and organ change are the stages of brain aging that may have an impact on cognition and behavior. Numerous fields are being studied in an effort to better understand the mechanics of aging and treat age-related illnesses, especially dementias, which affect the largest proportion of the population. According to research, leading a healthy lifestyle that lowers cardiovascular risk can also help prevent personal brain aging. There may even be some protection against cognitive decline from medical care in this area, but research on antihypertensive, antiplatelet, and anti-cholesterol medications is still

needed. It's also critical to recognize the limitations of research on the aging brain. Many studies are cross-sectional in nature, with small numbers of participants ranging widely in age, and no control over risk or protective factors. Additionally, education is not taken into account, which may improve performance on cognitive tests, nor is depression assessed, which may also have an impact on performance. It is important to keep in mind that the brains of the elderly may exhibit cohort effects linked to broader environmental impacts, such as a diet deficient in high-energy foods during childhood. Furthermore, it is very challenging to test and isolate individual cognitive processes in order to completely comprehend any alterations. Future research must fully account for these variables, and "cross sequential" studies a cross sectional and longitudinal study combined have been suggested. Given the amount of elderly persons in society and their potential for cognitive impairment, it is evident that our understanding of the aging brain is still developing and that considerable research is still needed. In the future, randomized controlled trials of therapeutic interventions may pave the way for deeper comprehension when applicable.

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Chapter - 9

Pathogenesis and Consequences of *C. neoformans* Infection: A Review

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Chapter - 9

Pathogenesis and Consequences of *C. neoformans* Infection: A Review

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Abstract

The opportunistic pathogenic fungus *Cryptococcus neoformans* is responsible for severe infections, primarily affecting the central nervous system (CNS). The most common way to get *C. neoformans* is by inhalation, and it is found in the environment. It is the etiological agent of cryptococcal meningitis and cryptococcosis, two severe pathologies that infect up to 10% of AIDS patients. Each year, cryptococcal meningitis causes hundreds of thousands of deaths. The three main areas of focus for research on this pathogen's pathogenesis and virulence mechanisms are: production of virulence factors; mechanism of immune evasion (which includes phenotypic variations and the ability to behave as a facultative intracellular pathogen); and adaptation to the host environment (nutrients, pH, and free radicals). Two phenotypic traits of *Cryptococcus neoformans* the capsule and melanin synthesis have a significant impact on the yeast's pathogenicity since they both have protective properties and cause host damage. Finally, understanding the mechanisms resulting in brain invasion and dissemination is crucial to understanding cryptococcal illness. I'll give a quick rundown of the key pathways in this review that determine whether *C. neoformans* is a pathogen in people who are vulnerable. With the inclusion of new research, the pathogenicity mechanisms of *Candida neoformans* and the host defences against it are examined.

Keywords: CNS, *Cryptococcus neoformans*, fungal pathogenesis, meningitis, treatment.

Introduction

Numerous microorganisms with a wide range of traits make up microscopic fungus. A few numbers of them, particularly in immunocompromised patients, can infect humans and cause disease [1]. Due of their low cost and high associated mortality, opportunistic invasive fungal

infections have drawn the attention of national health systems across the globe [2, 3]. Fungal infections can impact the skin, nails, respiratory system, and internal organs. They are caused by a variety of fungi, including *Aspergillus*, *Candida*, and *dermatophytes*. These infections are a serious health concern since they can range from superficial, moderate illnesses to severe systemic disorders. In order to effectively manage these infections, prompt identification and proper antifungal treatment are essential, particularly for those with weakened immune systems.

The pathogenic fungus *Cryptococcus neoformans* is responsible for producing cryptococcosis, which is typically seen in people with impaired immune systems. This yeast-like fungus, which is ubiquitous in the environment and is particularly prevalent in bird droppings, is extremely dangerous for those with compromised immune systems because it frequently causes infections of the central nervous system or respiratory tract. Inhaling the microscopic fungus can cause an infection with *C. neoformans*, albeit the majority of those exposed to it never become ill. Infections with *C. neoformans* are uncommon in otherwise healthy individuals; instead, they usually affect persons with compromised immune systems, especially those with severe HIV/AIDS. Prior to the HIV/AIDS pandemic and advancements in medical therapies (such as organ donation, long-term corticosteroid usage, cancer chemotherapy, chronic leukemia and lymphomas, and sarcoidosis), *Cryptococcus* was only sometimes responsible for diseases. It was first identified in the 1890s. Nowadays, a significant risk to public health, *Cryptococcus* kills hundreds of thousands of people annually and accounts for around 15% of HIV/AIDS-related fatalities. There is no human-to-human transmission of *Cryptococcus*. In the normal population, environmental exposure is frequent and asymptomatic because the fungus either goes away or goes dormant [4]. *Cryptococcus* was classified as a basidiomycete upon the discovery of its a-α bisexual reproduction in the 1970s. The discovery of unisexual reproduction between α mating type cells later on may have had a role in the >99% predominance of α isolates in natural populations. Meiotic recombination, morphological differentiation, and ploidy modifications are all involved in both sexual reproduction models [5]. Normally, *C. neoformans* develops into enclosed, spherical, budding yeast cells. The genetics of the strain and the development environment both affect capsular size [6]. For the creation of capsules, culture media with thiamine at neutral pH or thiamine plus other nutrients like glutamate and high CO_2 are usually sufficient. Glycerol can be utilized in place of glucose as the carbon source [7]. Lower temperatures, an acidic pH, and high osmolarity (16% glucose or 2.9% NaCl) all contribute to the *in vitro*

reduction in capsule size. However, some strains typically generate large, medium, or minimal capsules under the same development conditions. Unlike the majority of human pathogenic fungus, which are ascomycetes, *Cryptococcus spp.* are basidiomycetes yeasts. Because it primarily uses oxygen for metabolism, oxygen is essential to its growth. From a structural perspective, the presence of a capsule enclosing the cell body distinguishes *Cryptococcus spp.* from other species. Although *Cryptococcus* species are commonly found in the environment, two of them *Crypococcus neoformans* and *Cryptococcus gattii* have been linked to illnesses in humans [8]. Despite their close relationship, these two yeasts differ in terms of human disease and epidemiology. The most common is *Candida neoformans*, which acts as an opportunistic pathogen on people with weakened immune systems. In contrast, *Cryptococcus gattii* is less common but can still cause illness in persons who are immunocompetent. Because *Cryptococcus neoformans* has been the subject of the majority of virulence investigations, this yeast will be the primary focus of this review.

Since the 19th century, *Cryptococcus neoformans* has been identified as a disease-causing agent. It was believed that it may impact about 10% of AIDS patients, but its frequency increased dramatically at the close of the 20th century in tandem with the spread of HIV infection. Although the prevalence of cryptococcosis has decreased in wealthy nations since the introduction of antiretroviral medication, it remains a serious concern in underdeveloped nations. Although it also has a significant frequency in Asia and South America, it is thought to be the cause of about 180,000 deaths worldwide in Sub-Saharan Africa [9, 10]. Different mechanisms including both fungal and host components are implicated in invasive fungal illness. All fungal pathogens share certain pathogenic processes, like the capacity to develop at physiological temperature and resistance to immune stimuli like free radicals. However, for a number of reasons, the *Cryptococcus* example provides a great model to study fungal pathology. It is first and foremost a pathogen of concern due to its high frequency in specific geographic areas. However, this yeast has also gained certain virulence features and established certain pathogenic pathways that distinguish it as a distinct fungal pathogen. We shall outline the primary focus of the *Cryptococcus* pathogen in this review.

Characteristics of *Cryptococcus neoformans*

Taxonomy

Domain *Eukaryota*, kingdom *Fungi*; phylum *Basidiomycota*; class *Tremellomycetes*; order *Tremellales*; family *Cryptococcaceae*; genus

Cryptococcus; species *Cryptococcus neoformans* and *Cryptococcus gattii*. At least seven unique biological and phylogenetic species are included in the "*Cryptococcus neoformans*" and "*Cryptococcus gattii*" species complexes (together known as pathogenic *Cryptococcus* species), and there may be more cryptic species that have yet to be identified.

Properties

Phylogenetically, the aerobic mesophilic fungus species known as *Cryptococcus* are more closely related to mushrooms than to baker's yeast. Certain kinds of *Cryptococcus* are found in soil contaminated by bird droppings or on trees. They develop into budding yeast cells with a diameter of around 5 µm in nutrient-rich environments. The polysaccharide capsule, a distinctive trait of *Cryptococcus*, is produced in response to physiological conditions resembling those of humans, such as elevated CO_2, low iron, neutral or alkaline pH, and serum. Its capacity to synthesize melanin from a variety of phenolic substrates, such as the neurotransmitter dopamine, increases its viability in the host and sets it apart from other pathogenic yeasts [11].

Genome

Although naturally occurring diploid strains originating from inter-lineage mating or endoreplication have been obtained from certain geographical zones, the pathogenic Cryptococcus species are haploid. The haploid genome, which is divided into 14 chromosomes and has a size of around 20 Mb, is enriched in transposable elements and their byproducts at the regional centromeres. The genome's total GC content is around 48%. The genome of the *Cryptococcal* bacteria encodes around 1000 genes that may code for long non-coding RNAs in addition to about 7000 genes that code for proteins. The transcription landscapes of *Cryptococcus* are remarkably complicated and mirror those of higher eukaryotes. For example, intron(s) are present in >98% of its genes, with an average of five introns per gene. Alternative splicing, alternative transcription start and stop sites, and untranslated regions (UTRs) are common and probably biologically significant. With a length of more than 100 kb and more than 20 genes, the *Cryptococcus* mating-type locus (MAT) is particularly one of the largest of those that have been characterized. A *Cryptococcal* cell is defined by MAT as either an an or α mating type. The existence of introns and the size of intergenic regions account for the majority of the 20–40 kb variation in the mitochondrial genomes. During bisexual reproduction, mitochondrial DNA is normally acquired from the MAT parent [12].

Phylogeny

Within the pathogenic *Cryptococcus* species complex, sequence analysis identified two sizable clusters that corresponded to the *C. neoformans* and *C. gattii* species complexes, which split off from a common ancestor around 40 million years ago. Two and five different pathogenic species are also present in these subcomplexes, respectively. Between these seven species, there has been a great deal of difference in terms of chromosomal rearrangements, nucleotide polymorphisms, and chromosomal translocations that are facilitated by transposons found in the centromeres. While species in the *C. gattii* complex are frequently found in tropical and subtropical locations and affect immunocompetent persons, species in the *C. neoformans* complex are dispersed globally and cause systemic cryptococcosis in most immunocompromised patients. However, the pathogenic *Cryptococcus* species constitute a monophyletic clade, indicating a single origin of pathogenicity potential, in contrast to the closely related non-pathogenic sibling clades. Despite minor variations in disease symptoms among the *Cryptococcus* species, diagnosis and treatment protocols are generally the same [13].

Mechanism of action/pathogenesis of *C. neoformans* infection

Virulence Factors of Cryptococcus neformans

Capsule: The only known pathogenic yeast with a polysaccharide capsule is *Cryptococcus neoformans*. The following is how a capsule works:

Anti-phagocytic: Phagocytes cannot detect the chemicals found in polysaccharide capsules.

Protection under drying conditions: The yeast is shielded when the capsule bursts.

Ideal size range for alveolar deposition: The yeast is in the optimal size range for alveolar deposition due to the reduction in cell size caused by capsular collapse.

Phenoloxidase: This enzyme is in charge of producing melanin. Melanin may function as a virulence factor by strengthening the organism's defense against leukocyte assault. It has been discovered that elevated melanin synthesis can reduce the production of tumor necrosis factor and lymphocyte proliferation. Additionally, phenoloxidase shields the body against oxidants that are generated by phagocytic cells.

The stage of cryptococcosis: *C. neoformans* penetrates the alveolar space

Inhaling desiccated, ill-encapsulated haploid yeast cells or basidiospores can initiate a *C. neoformans* infection. It has long been believed that the infectious propagules of *Candida neoformans* are minimally encapsulated, dehydrated yeast cells; yet, to penetrate the lung parenchyma, particles smaller than 2μm in diameter are necessary [14]. Yeast, on the other hand, has a diameter of 4–8μm, and desiccation significantly lowers these forms' viability. With a diameter of 1.8–2μm, basidiospores can easily enter alveoli, be aerosolized with ease, and, similar to many other spores, exhibit high desiccation resistance. These characteristics seem to prefer the basidiospore as the infectious propagate of *Cryptococcus* over the yeast cell. Wickes *et al*. [15] provide more support for this claim; their findings are covered in the section that follows. The ability of some fungi to grow as either yeast or mycelium is known as dimorphism. While *C. neoformans* has the ability to develop real hyphae, it has not been classified as dimorphic since the mycelial phase is typically short-lived and results from the fusion of the two mating types of *C. neoformans*, α and a, producing the sexual stage known as *Filobasidiella neoformans* [16]. However, it has been demonstrated by Wickes *et al*. that *C. neoformans* can create hyphae and basidiospores without mating, and that this process is linked to the α-mating type. Unlike a-mating cells, the haploid α-mating type of *C. neoformans* can generate monokaryotic hyphae under the right conditions. This can result in the generation of viable basidiospores and basidia, all of which are α in mating type. Clinical and environmental isolates are primarily of the α-mating type, with varied ratios of 40:1 (α:a) for environmental isolates to 30:1 for clinical isolates, despite genetic studies showing 1:1 segregation of mating types in laboratory crosses. The idea that the basidiospore is the infectious propagule of cryptococcosis is further supported by the α-mating type's predominance, its ability to produce an asexual basidiospore through haploid fruiting, and certain characteristics of the basidiospore, such as resistance to desiccation and cell size.

***C. neoformans* inside the host**

A significant temperature change is required for the aereal displacement of *C. neoformans* propagules from the surrounding environment into the host. Therefore, cryptococcal cells need to be able to adjust so they can develop at 36–37 °C. The following data suggests that certain growth elements are necessary for fungal development in the new environment. Strong anti-cryptococcal activity was seen by Odom *et al*. [17] for the immunosuppressive medications rapamycin, FK506, and cyclosporin A

(CsA), which block signal transductions necessary for T-cell activation. At 24 °C, neither CsA nor FK506 drug was toxic to *C. neoformans*; however, at 37 °C, they both showed inhibitory effects, possibly due to their targeting of a growth factor required for fungal development at this temperature. These results, along with genetic evidence, demonstrated that *C. neoformans* survival in the mammalian host depends on the Ca^{2+} /calmodulin-dependent phosphatase calcineurin, a common target of CsA and FK506 in other organisms.

The cloning, sequencing, and disruption of the gene encoding the catalytic component of calcineurin A from *C. neoformans* verified this notion. In an animal model of *cryptococcal meningitis*, calcineurin mutants were not pathogenic; in addition, the fungal growth was temperature, CO_2, and pH-sensitive. Following transfection with the wild-type calcineurin A gene, pathogenesis was once again acquired. To sum up, this investigation showed that calcineurin is necessary for *C. neoformans* growth at 37 °C and that it is the target of CsA and FK506 antifungal activities. Alveolar macrophages that are located in the alveolar space initially face inhaled fungal cells. Neutrophils are initially detected in the pulmonary infiltrate during the subsequent infection, but they are later replaced by monocytes. One important factor that determines how an infection develops is the initial interaction between the fungus and the host defense cells. When mannose and β-glucans on the yeast cell wall are recognized, noncapsulated fungal cells can be phagocytosed in the absence of opsonins. However, the effectiveness of this process varies depending on the level of macrophage activation and potentially the quantity of antiphagocytic substances coexpressed at the yeast surface. The antifungal activity of nonactivated macrophages, such as alveolar, monocyte-derived macrophages, and macrophage-derived cell lines, is comparatively ineffective against the majority of *C. neoformans* strains [18]. The production of the capsule is widely recognized as a primary defense mechanism against phagocytosis. However, the yeast forms are not always killed by macrophages when they consume opsonized capsulated yeast cells. It is possible for certain internalized yeast to multiply within cells, which could result in cell death [19]. The progression of the *Cryptococcal* infection is determined by the virulence of the yeast strain and the activation and killing efficacy of macrophages (and other effector cells).

Studies on macrophage effector activities against *Cryptococci* in various systems have been conducted. It has been proposed that nitrite functions as an effector mechanism in murine peritoneal macrophages. Murine peritoneal

macrophages were stimulated by anticapsular antibody immunoglobulin G (IgG) and interferon-γ (IFN-γ) to produce nitrite and destroy cryptococci. While both nonopsonized and opsonized encapsulated organisms could trigger the respiratory burst, only nitrite synthesis not phagocytosis, respiratory burst stimulation, or lysosomal enzyme release could be linked to the death of fungi in this system. However, myeloperoxidase and H_2O_2 mediated the killing of *Cryptococci* by human peripheral blood PMNs [20]. Improved complement component deposition on the capsule by antibodies was linked to improved neutrophil phagocytosis and growth suppression of *Cryptococci* by human anticapsular IgM. A direct component of the host defense against *C. neoformans* is cell-mediated immunity. In a mouse model, yeast cells are confined and kept from proliferating and entering the bloodstream by the accumulation of macrophages and CD4+ T lymphocytes in the alveoli. CD4+ T lymphocytes are required for the process by which alveolar macrophages merge around the yeast to create multinucleated giant cells that release hydrolytic enzymes. Granuloma formation is linked to resistance to the cryptococcal infection, while the disseminated form is characterized by the lack of inflammation. The shortage of CD4+ T-lymphocytes in AIDS patients may account for the infection's dissemination from the main location to the brain.

The lung infection is typically under control and noninvasive in the immunocompetent host. Additional research has shown that CD8+ T cells have a role in keeping the lung as the exclusive site of the cryptococcal infection. Huffnagle *et al*. [21] shown that CD4+ and CD8+ T cells mediate recruitment of a pulmonary infiltrate of lymphocytes, macrophages, neutrophils, and eosinophils by depleting T-cell subsets in mice using monoclonal antibodies. CD4+ T-cell deficit had a more noticeable impact on the amount of inflammatory cells at the infection site than did the depletion of CD8+ T cells. In susceptible C57BL/6 mice infected with *C. neoformans*, neutralization of interleukin 5 (IL-5) markedly decreased the recruitment of macrophages, CD8+ and CD4+ T and B cells, but not neutrophils [22]. Moreover, eosinophils were drawn to and activated by IL-5; yet, they offered no defense in this system. Furthermore, it was demonstrated that B cells lacked the ability to attach to and directly suppress the proliferation of *C. neoformans*, although NK and IL-2-activated T cells could. The fact that human fetal astrocytes triggered *in vitro* by IL-1β and IFN-γ reduced the growth of *C. neoformans*, with the formation of reactive nitrogen intermediates, further exemplifies the role of nonphagocytic effector cells [23]. Recruitment of inflammatory cells into the lung harboring cryptococci requires Th1-associated cytokines, as also shown in other infections where

granuloma development confines the invasive organism. Although IFN-γ facilitates the granuloma's structure and yeast containment, IL-12 seems to inhibit its spread. TNF-α, also known as alpha tumor necrosis factor, appears to play a part in the development of delayed-type hypersensitivity (DTH), the recruitment of inflammatory cells, and the destruction of yeast during cryptococcal infection. Human alveolar macrophages produced high amounts of IFN-γ and IL-2, but not IL-4, when they were incubated with T lymphocytes and cryptococcal cells. On the other hand, encapsulated *Cryptococci* stimulate peripheral blood monocytes to generate IL-10, which in turn produces a dose-dependent suppression of TNF-α and IL-1β. Mice exposed to the cryptococcal capsular polysaccharide have shown signs of specific anemia or immunosuppression; this may be related to the lack of immune reactivity in cryptococcosis patients.

Cellular immunoprotection in experimental models

Mice immunized with a *C. neoformans* culture filtrate antigen, which likely contained the same exocellular components secreted by the fungus in the infected host, developed two functionally distinct populations of CD4+ T-lymphocytes: one population of CD4+ T-cells was able to transfer anticryptococcal DTH reactivity to naïve recipient mice, and another, called Tamp, when transferred to mice at the time of their immunization with a *C. neoformans* culture filtrate antigen in complete Freund's adjuvant, amplified the anticryptococcal DTH response [24]. However, T CD8+ cells were stimulated by the anticryptococcal DTH response to heat-killed fungal cells, and cytotoxic T cells that could kill *C. neoformans* directly were restricted by the unconventional non-major histocompatibility complex. Subsequently, Murphy *et al*. [25] noted that immunization with a *C. neoformans* culture filtrate antigen offered a notable degree of protection, while immunization with heat-killed *C. neoformans* proved futile as it did not produce Tamp cells.

Tamp cells generate a lot of Th1-associated lymphokines at the infection site but do not enhance the number of leukocytes invading. Type-1 lymphokines contribute to immunoprotection by activating macrophages and potentially other anticryptococcal effector cells. The finding that animals treated with anti-IFN-γ antibody had worsened cryptococcal infection further supported the significance of IFN-γ in protection. Furthermore, compared to either cytokine alone, the combination of IFN-γ and granulocyte-macrophage colony-stimulating factor produced a greater anticryptococcal action. By raising CR3's affinity for the yeast, TNFα and granulocyte-macrophage colony-stimulating factor improved phagocytosis [26].

Consequences

Diseases caused by *Cryptococcus neoformans*

Skin lesions, infections of the neurological system (brain), or infections of the eyes can all result from cryptococcosis. Animals may exhibit symptoms such as sneezing, snorting, nasal discharge, eye issues, behavioral changes, depression, disorientation, convulsions, and trouble moving.

A common and endemic fungal infection worldwide, cryptococcosis is brought on by the yeast complex *Cryptococcus neoformans*/*Cryptococcus gattii*. Invading fungus *Cryptococcus* causes cryptococcosis, an ailment frequently linked to immunocompromised people, when inhaled spores are inhaled. As *Cryptococcal meningitis* progresses, patients may exhibit fever, headache, malaise, photophobia, and stiff neck. The assessment and treatment of cryptococcosis are covered in this exercise, along with the importance of the interprofessional team in enhancing patient care.

Conclusion

The fungus *Cryptococcus neoformans* is responsible for about 500,000 fatalities annually. The majority of people are thought to be infected with *C. neoformans*, potentially in a form that endures in lung latency and can reactivate to cause illness if the host develops immunosuppression. The bacterium is extremely pathogenic due to its capacity to build a big capsule and excrete enormous volumes of capsular material into bodily fluids. The synthesis of mannitol, protease, phospholipase, superoxide dismutase, melanin, and other substances may increase the pathogenicity of *Candida neoformans*. Refusing to breathe in the fungus is the strongest defense against cryptococcosis. Living in a region where the fungus is present can make this challenging, but some experts suggest that wearing masks that filter particles as fine as 3 micrometers can help prevent inhalation.

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Chapter - 10

The Wonders of Fermented Foods and Their Effects on Well-Being

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Chapter - 10

The Wonders of Fermented Foods and Their Effects on Well-Being

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Abstract

Fermented foods have been used in human diets for generations, mostly for preservation and flavour enhancement. Recent scientific emphasis has switched to the health advantages of fermentation, which are linked to microorganisms such as lactic acid bacteria (LAB). These bacteria are known to produce useful chemicals like vitamins, minerals, and physiologically active peptides, which add to the health benefits of fermented meals. Notably, these foods have antioxidant, antibacterial, anti-inflammatory, and anti-diabetic properties, among others. But the scientific literature paints a complicated picture, with some research failing to find a direct link between the consumption of fermented foods and improved health. This discrepancy emphasises the necessity of doing more thorough clinical studies to support the health benefits of fermented foods. The potential advantages of fermented foods on gastrointestinal health and disease have been acknowledged despite the paucity of clinical evidence; in fact, certain fermented items have shown encouraging results in controlled trials. This chapter covers the science of fermentation as well as its importance in contemporary diets and range of health benefits.

Keywords: Fermented foods, gut health, human health, traditional foods, nutrition.

Introduction

Nutrient-dense fermented foods are superfoods that have anti-cancer properties, anti-inflammatory and anti-mutagenic properties (Jagdale *et al*., 2021). From the sour taste of yoghurt to the rich umami flavour of miso, fermented foods have substantially influenced many nations' culinary traditions, illustrating the coexistence of contemporary nutritional science and traditional culinary techniques (Akhtar *et al*., 2021). People have been consuming fermented food for thousands of years, which is good source of

good nutrients for improvement of human gut health. In addition to reduce the risk of irritable bowel syndrome and inflammatory bowel illness, it has been shown that fermentation increases the generation of neurotransmitters (Ray and Joshi, 2014; Gros *et al*., 2021). The science of fermentation is covered in this chapter along with its various health advantages and significance in modern diets.

The science of fermentation

Microorganisms such as bacteria, yeast, or fungus convert organic substances (mostly carbohydrates) into alcohol or acids through the metabolic process of fermentation (Shiferaw Terefe and Augustin, 2020). This procedure improves the food's digestion and nutritional composition in addition to preserving it. Fermentation science encompasses the study of microbial kinetics, community dynamics, and process control, with applications ranging from traditional food and beverage production to advanced industrial biotechnology. Research continues to evolve, integrating molecular and metabolic interactions to optimize fermentation processes and product quality (de Vos *et al*., 2010). There are various varieties of fermentation, such as:

- **Lactic acid fermentation:** Since its possible uses in a variety of industries, particularly in food and the production of biodegradable plastics, lactic acid fermentation has drawn a lot of attention (Reddy *et al*., 2008). This type, which is carried out by lactic acid bacteria (LAB), creates foods like kimchi, sauerkraut, and yoghurt (Park and Kim, 2019). Lactic acid, which serves as a natural preservative and adds to the sour flavour, is produced by LAB from carbohydrates (Ruiz-Rodríguez *et al*., 2017).
- **Ethanol fermentation:** The biological process known as "ethanol fermentation" uses yeast or other microorganisms to transform carbohydrates like glucose, fructose, and sucrose into ethanol and carbon dioxide (Ruane *et al*., 2010). This fermentation is carried out by yeasts, specifically Saccharomyces cerevisiae, which produces carbon dioxide and ethanol from carbohydrates. Making bread and alcoholic drinks like wine and beer requires this procedure (Heitmann *et al*., 2018).
- **Acetic acid fermentation:** Acetic acid is formed during the fermentation process, which converts starch or sugar to vinegar. Put simply, fermentation is the process that results in the creation of organic materials. However, microbial organisms are responsible

for producing these organic compounds (De Roos and De Vuyst, 2018). Vinegar is produced when acetobacter bacteria convert ethanol to acetic acid (Bhat *et al*., 2014).

- **Mold fermentation:** Aspergillus oryzae, a type of mould found in miso and soy sauce, breaks down complex proteins and carbs into simpler components, enhancing the flavour and texture of food (Nowak and Kuligowski, 2017).

Table 1: *Lactic acid bacteria (LAB) species in traditional fermented food* (So'Aib *et al*., 2018)

Food product	Main raw material	Fermentation process	LAB species
Tempe	Soybean	Mold fermentation	*E. faecium, L. mesenteroides ssp. Mesenteroides, Lb. delbrueckii ssp. delbrueckii.*
Soy sauce	Soybean	Mold fermentation (koji) followed by high salt (brine) concentration	*Weissella confuse, E. faecium*
Tapai or tape	Cassava or glutinous rice	Alcoholic fermentation	*P. pentosaceus, Weisella sp.*
Tempo yak	Durian (*Durio zabethinus*) pulp	Lactic fermentation	*Lb. plantarum, Lactobacillus sp, Weisella paramesenteroides, P. acidilactici, Lb. fructivorans, L. dextranicum, Lb. collinoides, Lb. paracasei, Lb. Plantarum, F. durionis*

Nutritional benefits of fermented foods

Fermented foods are nutritional powerhouses that offer a variety of benefits, including:

- **Increased nutrient bioavailability:** Anti-nutrients, such as phytic acid, that obstruct the absorption of minerals, can be broken down by fermentation. The bioavailability of minerals like iron, zinc, and magnesium is increased by this procedure (Samtiya *et al*., 2021).
- **High in probiotics:** A lot of fermented foods are a great source of probiotics, which are live bacteria that, when taken in sufficient quantities, have positive effects on health. By maintaining the balance of the intestinal microbiota, probiotics can enhance gut health (Franz *et al*., 2014).

- **Enhanced digestibility:** The process of fermentation reduces complicated macronutrients to more straightforward forms. For instance, lactose in milk is broken down into simpler sugars, which helps those who are lactose intolerant digest fermented dairy products more easily (Gänzle, 2020).
- **Creation of beneficial compounds:** Fermentation yields a range of bioactive substances, including organic acids that promote general health, peptides with antibacterial qualities, and vitamins such as B vitamins and vitamin K2 (Şanlier *et al*., 2019).

Health benefits of fermented foods

The benefits of eating fermented foods are varied and can be essentially grouped into four areas: immune system function, mental health, avoidance of chronic diseases, and digestive health (Şanlier *et al*., 2019).

1. **Intestinal health**
   - **Gut microbiota:** A balanced gut microbiota is essential for digestive health, and fermented foods contain probiotics that assist maintain this balance. Irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD) can be avoided and treated with a balanced microbiome (Gomaa, 2020).
   - **Digestive enzymes:** Fermented meals can help the body absorb and break down nutrients by introducing more digestive enzymes into the stomach (Boland, 2016).
2. **The immune system**
   - **Enhanced immunity:** A strong immune system depends on a healthy gut microbiome (Yoo *et al*., 2020). Probiotics have the ability to stimulate immune cells like T lymphocytes and macrophages, as well as increase the synthesis of antibodies (Perdigon *et al*., 1995).
   - **Anti-inflammatory effects:** Systemic inflammation, which is connected to a number of chronic illnesses, can be decreased by eating fermented foods (Shahbazi *et al*., 2021). Part of the reason for the anti-inflammatory qualities is the short-chain fatty acids (SCFAs) that are generated during fermentation (Fernández *et al*., 2016).
3. **Mental health**
   - **Gut-brain axis:** The gut-brain axis, which links gut health to

mental health, is being highlighted by new studies. Probiotics and other bioactive ingredients found in fermented meals can affect the synthesis of neurotransmitters and lessen depressive and anxious feelings (Shekarabi *et al*., 2024).

4. **Chronic disease prevention**

- **Heart health:** Fermented foods, such as natto and kimchi, contain bioactive ingredients that can cut cholesterol, lower blood pressure, and enhance heart health (Mukherjee *et al*., 2024).
- **Cancer prevention:** Studies have indicated that the presence of antioxidants and other bioactive compounds that impede the formation of cancer cells may provide anti-carcinogenic qualities to fermented foods (Kumar *et al*., 2010).
- **Metabolic health:** By increasing insulin sensitivity and lowering the risk of obesity and type 2 diabetes, regular consumption of fermented foods can promote metabolic health (Hirahatake *et al*., 2014).

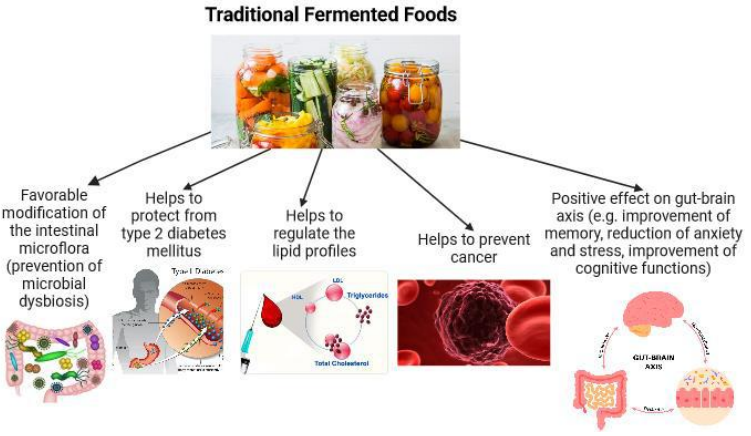

Figure 1: Traditional fermented foods against different diseases

Popular fermented foods and their specific benefits

1. **Yogurt**

- **High in probiotics:** Eating yoghurt on a regular basis helps strengthen immunity, lessen the signs and symptoms of lactose intolerance, and improve gut health.
- **Bone health:** Calcium and vitamin D, which are necessary for strong bones, are abundant in yoghurt.

2. **Kefir**
    - **Diverse microbiota:** Kefir contains a wide range of probiotics, more diverse than yogurt, which can offer broader health benefits.
    - **Anti-microbial properties:** Compounds in kefir can inhibit the growth of harmful bacteria and fungi.
3. **Kimchi**
    - **Anti-inflammatory and antioxidant properties:** The fermentation of vegetables like cabbage produces compounds that reduce inflammation and oxidative stress.
    - **Weight management:** Kimchi consumption is linked to weight loss and improved metabolic health.
4. **Sauerkraut**
    - **Digestive health:** Sauerkraut is rich in fiber and probiotics, promoting healthy digestion and preventing constipation.
    - **Immune support:** The high vitamin C content in sauerkraut boosts immune function.
5. **Miso**
    - **Rich in nutrients:** Miso provides a good source of essential amino acids, vitamins, and minerals.
    - **Cardiovascular health:** Regular consumption of miso soup is associated with lower blood pressure and reduced risk of heart disease.
6. **Tempeh**
    - **High protein content:** Tempeh is a high-protein, plant-based food that supports muscle health and repair.
    - **Bone health:** It contains significant amounts of calcium, magnesium, and phosphorus.

Fermented foods, such as yogurt, kefir, sauerkut, kimchi miso, tempeh, kombucha, and sourdough bread, are recognized for their unique flavors and potential health benefits (Gondaliya *et al*., 2024). foods are produced through controlled microbial growth andatic conversion of food components, which can lead to the production of bioactive peptides, biogenic amines, and short-chain fatty acids (Dimidi *et al*., 2019). The specific benefits of these foods are attributed to their probiotic content, which can improve

gastrointestinal health, enhance immune responses, and contribute to the reduction of risks for various chronic diseases (Farooqui, 2021; Kok & Hutkins, 2018). Interestingly, despite the broad range of fermented foods and their diverse bacterial communities, few bacteria are abundant across multiple food types, suggesting unique microbial profiles for each fermented food (Palmnäs-Bédard *et al*., 2023). Kefir, for example, has been investigated in clinical trials and shown beneficial effects for lactose malabsorption and Helicobacter pylori eradication (Dimidi *et al*., 2019). Yogurt consumption may improve intestinal health, aid in lactose malabsorption, and enhance immune responses (Kok & Hutkins, 2018). However, it is important to note that while *in vitro* studies are promising, there is limited clinical evidence for the effectiveness of most fermented foods in gastrointestinal health, and high-quality clinical trials are warranted (Dimidi *et al*., 2019). In summary, popular fermented foods offer a variety of health benefits, primarily due to their probiotic content and the metabolic byproducts of fermentation. These benefits include improved gastrointestinal health, immune system support, and potential reductions in the risk of chronic diseases (Farooqui, 2021; Kok & Hutkins, 2018). However, the evidence from clinical trials is still emerging, and further research is needed to substantiate these health claims (Dimidi *et al*., 2019).

Conclusion

The coexistence of contemporary nutritional science and traditional culinary techniques is exemplified by fermented foods. They are an essential component of our diet because of their extraordinary capacity to improve the flavour, nutritional content, and preservation of food. Adding fermented foods to your daily meals can be a tasty and practical way to improve your general health and well-being as research on their many health benefits continues. Accepting the fermentation tradition strengthens our bodies to withstand the rigours of contemporary life while also enhancing our palates.

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