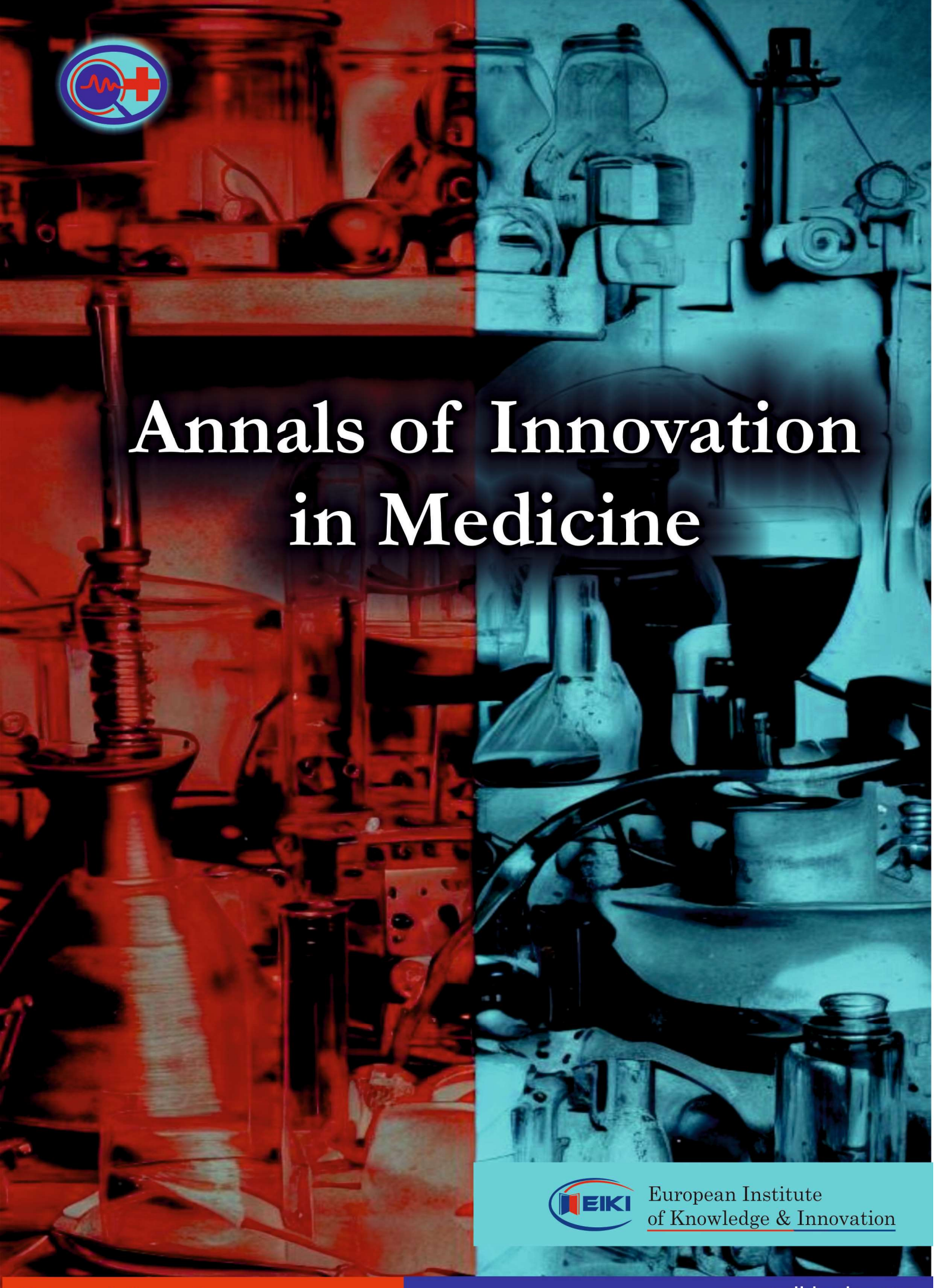

Annals of Innovation in Medicine

European Institute of Knowledge & Innovation

Volume 1, Issue 1

www.eikipub.com

Foreword

Foreword by Editor

Dr. Preet Pal Singh Bhinder [1]*

Welcome to the inaugural edition of the Annals of Innovation in Medicine! It is with great pleasure and enthusiasm that I introduce this landmark publication, which marks the beginning of a remarkable journey towards advancing healthcare through research and discovery.

The creation of this journal has been driven by a shared vision among a diverse group of esteemed professionals who recognize the paramount importance of fostering innovation and collaboration in the field of medicine. Our mission is clear: to provide a platform for groundbreaking research, to encourage interdisciplinary dialogue, and to inspire transformative change that benefits patients and healthcare systems worldwide.

In today's rapidly evolving healthcare landscape, innovation is not just a buzzword; it is an imperative. We are witnessing extraordinary advancements in technology, diagnostic techniques, therapeutic interventions, and healthcare delivery models. The potential for improving patient outcomes and transforming the way we practice medicine has never been greater. It is our duty as researchers, clinicians, and healthcare professionals to embrace this era of innovation and push the boundaries of medical knowledge.

The Annals of Innovation in Medicine is dedicated to showcasing the cutting-edge work that is shaping the future of healthcare. We welcome submissions from all corners of the medical community, be it original research articles, systematic reviews, case reports, or thought-provoking perspectives. By providing a platform for the dissemination of knowledge and ideas, we aim to catalyze collaboration, inspire creativity, and foster meaningful change.

As the Editor of this esteemed journal, I am committed to maintaining the highest standards of scientific integrity, editorial excellence, and transparency. Each article published in the Annals of Innovation in Medicine will undergo a rigorous peer-review process to ensure that only the most impactful and reliable research finds its way into our pages. We strive to provide our readers with thoughtfully curated content that informs, challenges, and inspires.

I would like to express my sincere gratitude to the dedicated reviewers, esteemed editorial board members, and the entire team who have worked tirelessly to bring this vision to life. Without their expertise, passion, and commitment, this journal would not have been possible. I also extend my appreciation to the authors who have entrusted us with their innovative research. Your contributions are invaluable, and we are honored to have the opportunity to showcase your work.

I invite all readers, authors, and reviewers to join us on this exciting journey as we explore the frontiers of medical innovation. Together, let us push the boundaries of knowledge, revolutionize patient care, and shape the future of medicine.

Warm regards,

Dr. Preet Pal Singh Bhinder

Editor, Annals of Innovation in Medicine

Literature review

Effectiveness of corticosteroids in the treatment of patients with Covid 19

Dr. Preet Pal Singh Bhinder [1,*]

[1] European Institute of Knowledge and Innovation;

* Correspondence: preetpalsb@gmail.com

https://doi.org/eiki/xxxxx

Abstract: The COVID-19 pandemic caused by the SARS-CoV-2 virus has emerged as one of the most significant health crises of the 21st century, with a devastating impact on global health. Understanding the disease pathogenesis and finding effective treatment strategies are crucial to mitigate its mortality rate. COVID-19 exhibits a biphasic illness, characterized by a viral response phase followed by a hyperinflammatory response phase, also known as the cytokine storm. This cytokine storm, rather than direct viral activity, has been identified as the major contributor to the high mortality associated with severe cases.

In this article, we explore the effectiveness of corticosteroids in managing the cytokine storm and reducing mortality in COVID-19. Corticosteroids have been extensively studied for their immunosuppressive properties and have shown potential in suppressing the hyperinflammatory response associated with the disease. The RECOVERY trial, a large-scale multicenter clinical trial conducted in the UK, demonstrated a significant reduction in mortality with the use of corticosteroids, particularly in critically ill patients requiring invasive mechanical ventilation.

However, the timing of corticosteroid therapy initiation is crucial, as early administration or use in milder cases may not yield the same benefits and could potentially increase mortality. Current evidence suggests that corticosteroids should be reserved for hospitalized patients with severe COVID-19, specifically those requiring oxygen therapy or invasive mechanical ventilation. In contrast, corticosteroid therapy has shown limited or even detrimental effects in non-severe cases.

Keywords: COVID-19, cytokine storm, corticosteroids, mortality, disease pathogenesis, RECOVERY trial.

Received: 01 June 2023

Accepted: 20 June 2023

Published: 25 June 2023

Introduction

The pandemic caused by the SARS-COV-2 virus was first identified in December 2019. Covid-19 causes illness that is unlike other respiratory infections. Covid-19 pandemic has come as a surprise. It is the most significant pandemic of the 21st century. In fact, only the Spanish flu pandemic almost a century ago can be compared with it. Moreover, it is worth understanding that this pandemic has cost more than 5 million lives till now, despite such progress in medicine during the last century or so. Numbers or mortality are only going to increase as the pandemic is showing no sign to decline.

As the disease has a considerably high mortality rate, especially in older adults, researchers are looking for ways to manage it more effectively. Studies show that adding

corticosteroids to disease treatment may help reduce mortality. However, how corticosteroids work and understanding their efficacy requires some understanding of the disease pathogenesis.

Covid-19 disease pattern

In most individuals, it would perhaps cause some mild illness resembling influenza. Thus, it would cause fever, body aches, cough, headaches, changes in taste and smell. However, in a small number of cases, it would cause pneumonia, further complicated by the hyperinflammatory response and multiorgan failure[1].

Based on the pathogenesis and cells affected, covid-19 can be divided into three phases2:

1. Stage 1 - is an asymptomatic stage, when the virus attaches to the nasal cavity lining and replicates. This stage continues for 1-2 days.

2. Stage 2 – is when the virus starts invading the upper respiratory tract. This stage continues for the next few days. In about 80% of people, the virus will be eliminated at this stage. Such people only develop a mild illness.

3. Stage 3 – Unfortunately, about 20% of people will progress to the third stage, when the disease starts infiltrating pulmonary cells, causing severe illness. It infects the alveolar cells, causing severe damage. It has an overall mortality rate of about 2%, though it is much higher in older adults[2].

Covid-19 causes a biphasic illness. An increasing viral load causes the first illness, and the second phase is caused by an increased inflammatory response to the virus. This second phase of illness occurs in some patients only. This second phase of hyperinflammatory response is also called a cytokine storm. In covid-19, it appears that greater mortality is due to immune dysregulation rather than direct damage caused by the virus. Since more severe illness occurs in the second stage, causing hospitalization, ARDS (acute respiratory distress syndrome), most fatal outcomes happen in this phase. Since, in this stage, viral load is low, targeting the virus with antivirals has limited benefit. Thus, the target of therapy in severely ill patients should be in managing hyperinflammatory response/cytokine storm and its ill effects[1].

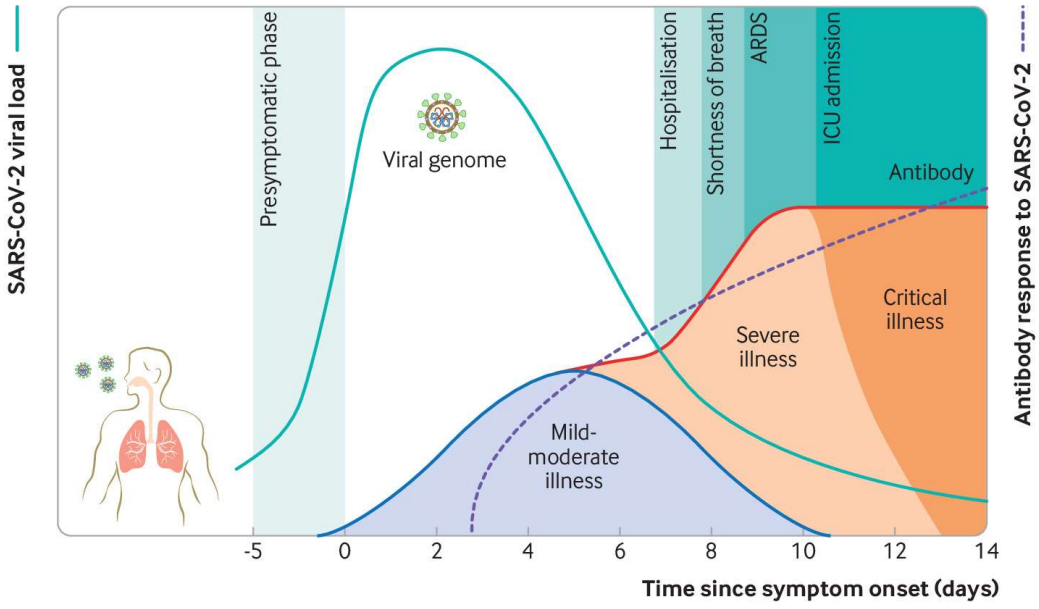

Figure 1 Biphasic response to covid-19[1]

Calming the cytokine storm

Hyperinflammatory response or dysregulated immune response or cytokine storm as now most like to call is a phenomenon known since long. This phenomenon is associated with high mortality related to sepsis, plaque, and other conditions. Researchers think that even the high mortality rate of the 1918-1919 influenza pandemic was associated with this cytokine storm. However, now researchers understand that cytokine storms in response to various infections differ. Thus, its early biomarkers vary, and hence therapeutic approach that worked for cytokine storms caused by other illnesses may not essentially work in covid-19[3].

Cytokine is an umbrella term used to describe a severe illness that causes immune dysregulation, high levels of cytokines, systemic inflammation, and multiorgan dysfunction. Its onset may differ and depend on the initial treatment given to patients. However, it has similar signs in later stages like high fever, fatigue, headaches, rashes, diarrhea, joint pains, muscular pains, and neuropsychiatric changes. The disease can progress swiftly, causing coagulopathy, hemorrhages, hypoxia, dyspnea, hypotension, severe changes in hemodynamics, vasodilatory shock, and death[3].

In cytokine storm, related to covid -19, laboratory findings show an increase in nonspecific markers of inflammation like C-reactive protein, abnormalities in blood count, leukopenia, anemia, thrombocytopenia. Among cytokines, IL-6, IL-10, interferon-gamma are elevated in the early phase. Highly elevated IL-6 is especially characteristic of the cytokine storm in covid-19. In addition, indicators of coagulopathy like elevated D-dimer value plays a vital role in disease prognosis[3,4].

Since cytokine storm and not damage due to direct viral activity is related to high mortality in the disease, thus the need to calm this cytokine storm. Studies show that using an antiviral drug like remdesivir may help reduce hospital stay, but managing cytokine storm is essential to reduce mortality. There are two approaches to calming this cytokine storm. The first is to use monoclonal antibodies targeting IL-6 or IL-1β. Another approach is of using corticosteroids. Corticosteroids have some distinct benefits, like they are widely available and are not expensive. Hence, a need to understand their role and efficacy in the condition4.

Effectiveness of corticosteroids in the treatment of covid-19

The recommendation for using corticosteroids for suppressing cytokine storms to reduce mortality comes from the large-scale multicenter clinical trial RECOVERY done in the UK. This has led various guidelines to include the use of corticosteroids in severely ill patients5,6.

WHO has two recommendations regarding the use of corticosteroids in covid-195.

Recommendation 1: WHO strongly recommends using corticosteroid (i.e., dexamethasone, prednisolone, hydrocortisone) in critically ill patients.

Recommendation 2: WHO advises against the use of corticosteroids in non-severe cases of covid-19.

This recommendation to use corticosteroids is built upon clinical experience accumulated over the decades. There has been extensive research regarding the role of corticosteroids in managing septic shock. Early studies showed that low-dose corticosteroid therapy might help reduce mortality[7].

Although corticosteroids appear to help, they only help when therapy is initiated at the right moment. Moreover, some early studies regarding the use of corticosteroids in covid-19 failed to show much benefit. Thus CAPE COVID trial in 149 patients did not show the benefit of corticosteroid therapy[7].

However, the following and much larger clinical trial, REMAP in 903 patients, demonstrated considerable benefit and reduction in mortality by as much as 26%. Another trial, CoDEX, with 299 patients deployed early use of corticosteroids. It found that although corticosteroids increased ventilator-free days, but early use of corticosteroids had no impact on 28-day mortality. These and similar other clinical trials provided some initial information and direction for more extensive clinical trials like the RECOVERY[7].

RECOVERY trial and its success is the basis of recommending corticosteroids in severe covid-19 patients. It remains the largest of its kind of clinical study. It was a multicenter, open-label adaptive trial done in the UK. It has a sample size of 6425. Out of them, 2104 got dexamethasone along with standard care, and 4321 just got standard care. The mean age of patients was 66 years. The duration of intervention or corticosteroid therapy in the trial was 10 days6.

The key findings of the RECOVERY trial regarding the effectiveness of corticosteroids in covid-19 were[6]:

- The mortality rate was 25.7% in the standard care group and 22.9% in dexamethasone and standard care. Thus, it is a statistically significant benefit.

- However, effectiveness was highest in those requiring invasive mechanical ventilation (IMV), with mortality of 29.3% in the dexamethasone group and 41.4% in the non-dexamethasone group. Thus, it clearly shows massive benefits in such a category.

- Benefits were lower in those who needed oxygen but not IMV. There was 23.3% mortality in the dexamethasone group in this category against 26.2% in the non-dexamethasone group.

- However, there was no survival benefit in less severe cases, and on the contrary, dexamethasone increased mortality. Thus, in those not requiring oxygen, the mortality rate in the dexamethasone group was 17.8% and 14% in the standard care arm.

RECOVERY trial demonstrated that only hospitalized and severely ill patients benefit from corticosteroids. Further, it shows that the timing of initiation of corticosteroid therapy is vital. Thus, therapy started early like those not on IMV had minimal benefit. However, there was a massive benefit in those on IMV. Further, there is no role for corticosteroids in less severely ill patients, and on the contrary, corticosteroid therapy may increase the mortality rate.

Further, there have been trials regarding the use of inhaled corticosteroids. Inhaled corticosteroids may reduce airway inflammation, reduce pulmonary obstruction, and also appear to impair covid-19 replication. However, the results of inhaled corticosteroids like Budesonide had contradictory results. Thus, there is neither evidence in its favor or against such a use[6].

It is worth noticing that further meta-analysis of clinical trials confirms that corticosteroids only help in severe cases in those requiring oxygen therapy. However, in less severe cases, they prolong viral clearance, hospital stay and increase mortality[8].

Future direction for identifying the role of corticosteroids in covid-19

The covid-19 pandemic is still ongoing, and lots have to be understood about its pathogenesis. Further, it also has many delayed complications. Thus, a delayed multisystem inflammatory syndrome of adults (MIS-A) and children (MIS-C) still remains poorly understood. Although, it is causing significant mortality. In this syndrome, the viral activity does not appear to play any role. It is just another immune dysregulation syndrome. Therefore,

researchers are studying the role of IL-6 inhibitors like tocilizumab and corticosteroids in such a group.

Conclusion

There is no doubt that corticosteroid therapy may significantly reduce covid-19 associated mortality. However, the timings of initiation of such therapy are critical. Therapy initiated too early or in less severe cases may do more harm than good. It appears most beneficial in those with a severe condition, like those requiring invasive mechanical ventilation (IMV). Further, studies seem to show that this approach is also effective in severely ill pediatric patients. However, there are some limitations to present understanding, like inadequate data regarding the efficacy of corticosteroids in patients older than 80 years of age. Similarly, data is limited from the pediatric population. Further, guidelines remain unclear regarding the use of corticosteroids in the delayed multisystem inflammatory syndrome of children and adults.

References

1. Cevik M, Kuppalli K, Kindrachuk J, Peiris M. Virology, transmission, and pathogenesis of SARS-CoV-2. *BMJ*. 2020;371:m3862. doi:10.1136/bmj.m3862

2. Mason RJ. Pathogenesis of COVID-19 from a cell biology perspective. *European Respiratory Journal*. 2020;55(4). doi:10.1183/13993003.00607-2020

3. Fajgenbaum DC, June CH. Cytokine Storm. *New England Journal of Medicine*. 2020;383(23):2255-2273. doi:10.1056/NEJMra2026131

4. Cron RQ, Caricchio R, Chatham WW. Calming the cytokine storm in COVID-19. *Nat Med*. 2021;27(10):1674-1675. doi:10.1038/s41591-021-01500-9

5. Coronavirus disease (COVID-19): Dexamethasone. Accessed November 1, 2021. https://www.who.int/news-room/q-a-detail/coronavirus-disease-covid-19-dexamethasone

6. Corticosteroids. COVID-19 Treatment Guidelines. Accessed November 1, 2021. https://www.covid19treatmentguidelines.nih.gov/therapies/immunomodulators/corticosteroids/

7. Carlet J, Payen D, Opal SM. Steroids for sepsis and ARDS: this eternal controversy remains with COVID-19. *Lancet*. 2020;396(10259):e61-e62. doi:10.1016/S0140-6736(20)32132-2

8. Sahu AK, Mathew R, Bhat R, et al. Steroids use in non-oxygen requiring COVID-19 patients: a systematic review and meta-analysis. *QJM: An International Journal of Medicine*. 2021;(hcab212). doi:10.1093/qjmed/hcab212

Literature review

Comparative Pharmacology and Toxicology of Tramadol & Tapentadol

Sarwar Naseer Siddiqui [1,*]

[1] KazGNMU;

* Correspondence: snsdr69@hotmail.com

https://doi.org/eiki/xxxxx

Abstract: Pain is a common symptom in various health conditions and can significantly impact a person's quality of life if not managed properly. Although non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen are widely used for mild to moderate pain, they may not suffice for moderate to severe pain requiring combination therapy. In such cases, synthetic drugs like Tramadol and Tapentadol offer effective pain relief with improved safety profiles. This article aims to compare the pharmacokinetics, pharmacodynamics, and safety profiles of Tapentadol and Tramadol.

Tapentadol, a direct-acting synthetic opioid, demonstrates a reliable mode of action as it starts working upon reaching the bloodstream. In contrast, Tramadol requires metabolic conversion into active metabolites, resulting in a delayed onset of action. Furthermore, Tramadol's effectiveness is dependent on the presence of the CYP2D6 enzyme, with approximately 6% of Caucasians being deficient in this enzyme. Dosage adjustments may be required for individuals with impaired liver or kidney function.

Both Tapentadol and Tramadol primarily affect mu-opioid receptors (MOR), providing potent pain relief. However, Tramadol also inhibits the reuptake of noradrenaline and serotonin, while Tapentadol lacks an effect on serotonin. Tapentadol exhibits a higher affinity for MOR receptors, making it a more potent central acting painkiller compared to Tramadol. Nevertheless, Tapentadol's increased opioid activity increases the likelihood of mild and transient opioid-like side effects, such as drowsiness, constipation, and respiratory depression.

In terms of toxicology, both Tapentadol and Tramadol offer a safer alternative to morphine with reduced side effects. Tapentadol's greater opioid activity translates into a higher potential for opioid-related side effects, whereas Tramadol's serotonergic activity is associated with a higher incidence of vomiting and nausea. The absence of significant effects on CYP450 enzymes distinguishes Tapentadol from Tramadol, reducing the likelihood of drug interactions.

Overall, Tapentadol demonstrates several advantages over Tramadol, including faster onset of action, greater pain relief, and fewer side effects related to serotonergic activity. However, it is essential to consider that Tapentadol, although more effective, carries a higher probability of side effects associated with its increased opioid activity. Clinicians should carefully evaluate individual patient characteristics and requirements when selecting between these two medications for pain management.

Keywords: pain management, Tapentadol, Tramadol, opioids, pharmacokinetics, pharmacodynamics, safety profile.

Received: 07 June 2023

Accepted: 20 June 2023

Published: 25 June 2023

Introduction

Pain is the primary symptom in a range of health conditions. Poorly managed acute or chronic pain may negatively influence numerous aspects of a person's life. However, managing pain adequately remains a challenge in many conditions[1].

For mild to moderate pains, NSAIDs (non-steroidal anti-inflammatory drugs) remain the mainstay of treatment. NSAIDs like ibuprofen have some distinct benefits like they are readily available. In addition, they do not cause dependence. However, they might often fail in moderate to severe pain requiring combination drug therapy[2].

In moderate to severe pain, synthetic drugs like Tramadol and Tapentadol may provide excellent relief. These are synthetic analogues of morphine with a considerably improved safety profile. It means that they can be readily prescribed for various painful conditions, infrequently cause side effects, and rarely cause any dependence.

However, it is worth knowing that sometimes these medications may work better when combined with NSAIDs. It is because, unlike NSAIDs, they do not have anti-inflammatory properties. These drugs are primarily painkillers.

Although Tapentadol and Tramadol share many traits, with quite a similar mode of action, they differ considerably in pharmacokinetics (how the body processes drugs) and pharmacodynamics (mechanism of action).

Tapentadol vs Tramadol – Pharmacokinetics

Although they may have similar effective dosages in many conditions, and both are commonly available as 50 mg tablets. Still, there are many differences between the two.

First and foremost, tramadol works mainly through active metabolites, and tapentadol is directly active. It means that tapentadol starts working as soon as it reaches the bloodstream, with a reliable mode of action. However, tramadol is first metabolized into active metabolites, with different modes of action. These metabolites of tramadol are more potent than the parent molecule. Since tramadol needs to be metabolized, it generally has a delayed onset of action and less reliable effect in some individuals[3].

The second significant difference between the two is that tramadol is dependent on the enzyme CYP2D6 for conversion into active metabolites. Its two major active metabolites are (+) and (-) enantiomers. These two enantiomers have a different modes of action4. In practice, it means that those deficient in these enzymes may not get sufficient benefit from the drug. Studies show that about 6% of Caucasians may be deficient in this enzyme[5].

Both drugs are effective from 50 mg onwards. However, unlike Tapentadol, Tramadol may need a loading dosage (starting dose) of 100 mg, followed by 50 mg every 6 hours, or as required. These differences are mainly due to differences between the two in pharmacokinetics[5,6].

Ultimately, both the drugs are metabolized in the liver, and their inactive metabolites are excreted via kidneys. Generally, mild to moderate kidney or liver disease does not affect their metabolism. However, those living with severe kidney or liver disease may need dosage correction.

Tapentadol vs Tramadol – Pharmacodynamics

Both these medications share numerous traits with morphine. However, these drugs were created as effective and yet much safer analogues of morphine. Although both the drugs work by influencing opioid receptors (especially mu-opioid receptors or MOR), there is a difference[3]. Activation of MOR receptors results in the potent painkilling effect of opioids.

Tramadol

It is a MOR activator and powerful Noradrenaline (NA) and 5HT (serotonin) reuptake inhibition. As it is metabolized to (+) and (-) enantiomers, it is worth knowing that its (+) enantiomer has more potent action on MOR receptors, causing higher pain relief. Unfortunately, it also means that tramadol has poor efficacy in those deficient in CYP2D6 enzyme, which may be close to 6% of the European population[7].

Studies show that most of its actions are due to its effects on MOR receptors and inhibition of NA uptake, with 5HT inhibition playing a minor role[7].

Tapentadol

Quite like tramadol, it affects MOR receptors and inhibits NA receptors. However, unlike tramadol, it does not influence 5HT. Moreover, tapentadol is not a prodrug. Thus, it starts acting soon after absorption by the body. It is not dependent on liver enzymes for conversion to active forms[8].

As tapentadol's affinity to MOR receptors differs from tramadol, further lack of action on 5HT means it differs in efficacy and safety.

Studies show that tapentadol has a more significant influence on MOR (that is, opioid) receptors than NA inhibition. Therefore, it appears to be a more potent central acting pain killer than tramadol. Some experts think it is 2-3 times more potent than tramadol, though it is less potent and safer than morphine[9].

Tapentadol vs Tramadol – toxicology

Both Tapentadol and Tramadol were created as a safer alternative to morphine. Morphine is more potent than both these drugs, but it causes numerous side effects characteristic of opioids like dry mouth, constipation, vomiting, nausea, sedation, respiratory depression, addiction10. Tapentadol and tramadol are much safer alternatives.

Tapentadol is much more potent than tramadol. It is because it has a greater influence on opioid receptors than tramadol. However, it also means greater chances of opioid-like side effects (but much milder and transient) like drowsiness, constipation, respiratory depression. But it also means that tapentadol has fewer chances of side effects associated with the serotonergic activity of tramadol like vomiting and nausea[9,11].

How does tapentadol compare to tramadol?

To conclude, it appears that tapentadol has the edge over tramadol. It is more effective in many ways[12].

Feature	Tapentadol	Tramadol	Advantage
Opioid activity	Higher opioid activity	Moderate action	Greater painkilling effect
Other actions	NA reuptake inhibition, no action on 5HT	NA and 5HT reuptake inhibitor	Fewer side effects related to serotonergic activity
Role of metabolites	Active drug	Mainly prodrug	Faster onset and reliable effect of tapentadol
Onset of action	32 min	Within 60 min	Faster action
Drug interactions	No effect on CYP450 enzymes	Metabolized by CYP450 enzymes	Greater chances of tramadol's interaction with other drugs

Variation of action	Not dependent on CYP pathway	Dependent of activity of CYP pathway	Less effective in individuals who are genetically deficient in these enzymes

Table 1 Adapted from; Singh DR, Nag K, Shetti AN, Krishnaveni N. Tapentadol hydrochloride: A novel analgesic. Saudi J Anaesth. 2013;7(3):322-326. doi:10.4103/1658-354X.115319)

As is evident from Table 1 that, tapentadol is better than tramadol in some ways. Nonetheless, it is worth noticing that tapentadol, though more effective than tramadol, is not essentially safer as it is more probable to cause side effects related to its higher opioid activity.

Conclusion

In conclusion, the comparative analysis between Tapentadol and Tramadol reveals distinct differences in their pharmacokinetics, pharmacodynamics, and safety profiles. Tapentadol emerges as a more effective painkiller, offering faster onset of action and greater affinity for mu-opioid receptors. Its unique properties make it a valuable option for moderate to severe pain management. However, it is important to note that Tapentadol's increased opioid activity also poses a higher risk of opioid-related side effects. Clinicians must carefully consider individual patient characteristics and balance the benefits and risks when selecting between these medications. Further research and clinical studies are warranted to gain a deeper understanding of their optimal use in specific patient populations.

References

1. Sinatra R. Causes and Consequences of Inadequate Management of Acute Pain. *Pain Medicine*. 2010;11(12):1859-1871. doi:10.1111/j.1526-4637.2010.00983.x

2. Blondell RD, Azadfard M, Wisniewski AM. Pharmacologic Therapy for Acute Pain. *AFP*. 2013;87(11):766-772.

3. Giorgi M. Tramadol Vs Tapentadol: Anew Horizon in Pain Treatment? *American Journal of Animal and Veterinary Sciences*. 2012;7:7-11.

4. Grond S, Sablotzki A. Clinical Pharmacology of Tramadol. *Clin Pharmacokinet*. 2004;43(13):879-923. doi:10.2165/00003088-200443130-00004

5. Tramadol Hydrochloride 50mg Capsules - Summary of Product Characteristics (SmPC) - (emc). Published October 8, 2021. Accessed August 23, 2021. https://www.medicines.org.uk/emc/product/5924/smpc#gref

6. Palexia 50 mg film-coated tablets - Summary of Product Characteristics (SmPC) - (emc). Published May 7, 2021. Accessed August 23, 2021. https://www.medicines.org.uk/emc/product/5159/smpc#gref

7. Scott LJ, Perry CM. Tramadol. *Drugs*. 2000;60(1):139-176. doi:10.2165/00003495-200060010-00008

8. Raffa RB, Buschmann H, Christoph T, et al. Mechanistic and functional differentiation of tapentadol and tramadol. *Expert Opinion on Pharmacotherapy*. 2012;13(10):1437-1449. doi:10.1517/14656566.2012.696097

9. Roulet L, Rollason V, Desmeules J, Piguet V. Tapentadol Versus Tramadol: A Narrative and Comparative Review of Their Pharmacological, Efficacy and Safety Profiles in Adult Patients. *Drugs*. 2021;81(11):1257-1272. doi:10.1007/s40265-021-01515-z

10. Glare P, Walsh D, Sheehan D. The adverse effects of morphine: a prospective survey of common symptoms during repeated dosing for chronic cancer pain. *Am J Hosp Palliat Care*. 2006;23(3):229-235. doi:10.1177/1049909106289068

11. Tsutaoka BT, Ho RY, Fung SM, Kearney TE. Comparative Toxicity of Tapentadol and Tramadol Utilizing Data Reported to the National Poison Data System. *Ann Pharmacother*. 2015;49(12):1311-1316. doi:10.1177/1060028015604631

12. Singh DR, Nag K, Shetti AN, Krishnaveni N. Tapentadol hydrochloride: A novel analgesic. *Saudi J Anaesth*. 2013;7(3):322-326. doi:10.4103/1658-354X.115319

Literature review

Adaptogenic plants within food supplement

Anshul Agrawal [1,*]

[1] Ultra Nutritions, Delhi;

* Correspondence: anshul_agr@hotmail.com

https://doi.org/eiki/xxxxx

Abstract: Adaptogenic plants have been recognized for their ability to enhance the body's capacity to adapt and withstand various stressors. This article explores the concept of adaptogens and their role in promoting resilience, tolerance, and adaptation to stress. Plant adaptogens are preferred over synthetic alternatives due to their safety, ability to normalize body functions, and the complex combination of compounds they contain. These natural extracts work synergistically to provide health benefits, unlike isolated compounds. Adaptogens act on multiple levels, modulating immunity, endocrine function, neurotransmitters, and signaling pathways. They help maintain homeostasis and can be used to prevent and manage health disorders resulting from imbalances in the body. The modern lifestyle's increasing prevalence of lifestyle disorders necessitates the consideration of adaptogenic food supplements. These supplements can prevent chronic diseases, improve quality of life, and counteract the declining ability of the body to combat stress. Taking adaptogens in the form of gummies offers distinct advantages, including convenience, compliance, and higher bioavailability. Gummies bypass the liver's first-pass metabolism, ensuring the efficient absorption of active ingredients. As adaptogens are often used long-term, gummies provide a suitable and enjoyable means of incorporating these beneficial plant extracts into daily routines. Choosing high-quality brands is essential for optimal results.

Keywords: adaptogenic plants, food supplement, resilience, stress management, gummies.

Received: 25 May 2023

Accepted: 20 June 2023

Published: 25 June 2023

Introduction

"*It is not the strongest of the species that survives, nor the most intelligent that survives. It is the one that is most adaptable to change.*" – Charles Darwin.

Darwin rightly noticed that living beings must be adaptable to survive for a long time. Unlike other mammals, humans are intelligent beings. Thus, they can find various ways to adapt and boost their body's capacity to adapt to various stressors.

Humans have long known that certain plants are exceptionally good at boosting the body's ability to adapt, like Rhodiola, Ginseng, and many more. By the mid of the 20th-century, the researcher started to develop the concept of adaptogens and study various herbs in clinical studies.[1]

Adaptogens are herbs that increase the body's ability to adapt, resilience, tolerance, and adaptation to stress. Adaptogens are essentially natural extracts derived from plants. However, adaptogens can also be synthetically produced. Synthetic adaptogens are called actoprotectors.[2] For example, vitamins these days can be synthetically produced, and many vitamins boost the body's ability to fight stress and adapt.

Why use plant adaptogens?

There are many reasons to prefer plant adaptogens. They are safe and help the body fight stress without increasing energy requirements. It is also vital to understand that adaptogens normalize various body functions. It means that they can fine-tune different body responses. Hence, they can increase or decrease various metabolic processes.[1] That is why adaptogen may help reduce blood pressure but even increase it if needed. In addition, these substances can boost immunity and still help suppress hypersensitivity or fight allergies.

The reason to use plant adaptogens is simple; science cannot create substances as potent as natural adaptogens. Natural adaptogens are quite complex. They contain tens or even hundreds of compounds that act in synergy with each other. Thus, they contain antioxidants, terpenes, stilbenes, lignans, and more.[3]

Natural extracts like Rhodiola or Ginseng are a cocktail of numerous organic compounds. Science still does not know how this cocktail of natural compounds works. Isolated organic compounds from these plants or herbs do not provide much health benefit. To work as an adaptogen, various organic compounds must work in synergy and be present in specific proportions. In what proportions different compounds must be present to act as an adaptogen is nature's best-kept secret.

Adaptogens act on various levels. For example, they might modulate immunity, alter endocrinal function, and may influence the working of neurotransmitters. They might also modulate signaling pathways between the cells in a way that no known synthetic compound can do.[1]

Adaptogens are suitable for regular use. They help maintain homeostasis. That is, they help maintain the body in a steady state even during periods of extreme stress and illness. So, they may be used for preventing ailments. But they are also helpful in managing health disorders, as they essentially occur due to specific imbalances in the body.

Modern lifestyle and the importance of adaptogens

There is a firm scientific reason why everyone must consider taking food supplements containing adaptogens. It is because the human lifestyle has significantly changed in the last century. It means that now people are more likely to die of lifestyle disorders than infections.

Not only that, lifestyle disorders cause significant disability. In addition, these disorders cause a significant decline in quality of life. For example, joint diseases may not kill an individual. Still, they cause much distress, years of disability, and a significant decline in quality of life (QoL).

These days people are more likely to die due to heart disease, stroke, diabetes, Alzheimer's, liver and kidney disease, cancer, and so on.[4] As per WHO, 74% of all deaths occur due to non-communicable/non-infectious diseases.[5] Many of these can be prevented through lifestyle interventions and supplements.

Adaptogens are not just for preventing untimely death or prolonging life. They also help you stay active for longer and enhance your quality of life. These days most adults are living with one or another chronic health issue. Thus, for example, one in four (about 25%) of adults are living with joint pain[6], about 30% live with depression, anxiety, and stress disorder[7], and 11%-40% of adults are living with chronic pain at any given time[8].

There is something common between all these health issues. These health conditions occur or are made worse by the body's declining ability to fight stress and adapt. They are caused by significant oxidative stress, high level of stress hormones, chronic inflammation, and changes in metabolic activity.

Adaptogens can help fine-tune various body functions and thus help prevent these disorders. They can not only help prevent these health issues but also manage these problems. Adaptogens can also exert anti-aging effects, prevent mitochondrial dysfunction, reduce fatigue, and help you feel energized.

Taking adaptogens as gummies have some distinct benefits

Food supplements come in many shapes and forms. However, among various forms, gummies are perhaps the best way to take natural supplements.

One of the most common complaints about health supplements is that many people fail to experience adequate benefits. There are multiple reasons for it, like lack of compliance and poor bioavailability. Hence, gummies try to overcome these deficiencies.

Below are some of the distinct benefits of using gummies:

Convenience and Compliance: These concepts are interrelated. If a supplement is not convenient to take, one is less likely to take it regularly. Health supplements must be taken regularly to experience their health benefits. Gummies are easy to carry; they can be taken without water; not only that, they have an amazing flavor. Hence, gummies are equally good for children and busy adults. They are even good for adults who find it difficult to swallow pills. Higher compliance always translates into better health effects.[9]

Higher bioavailability: It is perhaps an even more important reason to use gummies. Natural extracts have one significant issue – they have low bioavailability when ingested. However, low bioavailability is not only due to poor absorption of natural ingredients but also due to the so-called first-pass metabolism. It means that many natural compounds never reach the bloodstream as the liver neutralizes them after absorption.[9]

Gummies can overcome all these hurdles as they are chewed and broken in the mouth. Their active ingredients are quickly absorbed via the tongue, reaching the bloodstream by bypassing the liver. Whatever is left is ingested and absorbed via the intestine like other health supplements.

Gummies are the perfect way to take adaptogens, considering that adaptogens must be used for a long. Food supplements containing adaptogenic plants or extracts are made in such a way that they are suitable for regular use for years. Of course, not all gummies are created equal, and thus it is vital to choose high-quality brands.

Conclusion

In conclusion, adaptogenic plants within food supplements offer a natural and effective way to enhance the body's resilience and ability to adapt to stress. These plant extracts, such as Rhodiola and Ginseng, contain a complex combination of compounds that work synergistically to normalize various body functions. Unlike synthetic alternatives, natural adaptogens are safe and can fine-tune metabolic processes without increasing energy requirements. In today's modern lifestyle, where lifestyle disorders are prevalent, incorporating adaptogens into daily routines becomes crucial for preventing and managing chronic diseases. Gummies, as a convenient and compliant form of supplementation, offer higher bioavailability, ensuring the efficient absorption of active ingredients. By harnessing the power of adaptogenic plants and utilizing gummies as a delivery method, individuals can optimize their health, improve their quality of life, and better adapt to the challenges of the modern world.

References

1. Panossian AG, Efferth T, Shikov AN, et al. Evolution of the adaptogenic concept from traditional use to medical systems: Pharmacology of stress- and aging-related diseases. *Medicinal Research Reviews.* 2021;41(1):630-703. doi:10.1002/med.21743

2. Oliynyk S, Oh S. The Pharmacology of Actoprotectors: Practical Application for Improvement of Mental and Physical Performance. *Biomol Ther (Seoul)*. 2012;20(5):446-456. doi:10.4062/biomolther.2012.20.5.446

3. Todorova V, Ivanov K, Delattre C, Nalbantova V, Karcheva-Bahchevanska D, Ivanova S. Plant Adaptogens—History and Future Perspectives. *Nutrients*. 2021;13(8):2861. doi:10.3390/nu13082861

4. FastStats. Published January 18, 2023. Accessed April 13, 2023. https://www.cdc.gov/nchs/fastats/leading-causes-of-death.htm

5. Non communicable diseases. Accessed April 20, 2023. https://www.who.int/news-room/fact-sheets/detail/noncommunicable-diseases

6. Arthritis Data and Statistics | CDC. Published October 12, 2021. Accessed April 20, 2023. https://www.cdc.gov/arthritis/data_statistics/national-statistics.html

7. Mirzaei M, Yasini Ardekani SM, Mirzaei M, Dehghani A. Prevalence of Depression, Anxiety and Stress among Adult Population: Results of Yazd Health Study. *Iran J Psychiatry*. 2019;14(2):137-146.

8. Dahlhamer J. Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States, 2016. *MMWR Morb Mortal Wkly Rep*. 2018;67. doi:10.15585/mmwr.mm6736a2

9. Simon A, Pizzolo CC. Bioavailability of micronutrients in a gelatin matrix. *The FASEB Journal*. 2006;20(5):LB86-LB86. doi:10.1096/fasebj.20.5.LB86-c

Literature review

Irritable Bowel Syndrome: The Functional Medicine Approach

Sandra Lacy, [1,*] Kumar Prasad [2]

[1] School of Medicine, Santiago;

[1] Delhi University, Delhi;

* Correspondence: sandra_l@gmail.com

https://doi.org/eiki/xxxxx

Abstract: Irritable bowel syndrome (IBS) is a complex functional gastrointestinal disorder with limited success in pharmacological therapy. The functional medicine approach aims to identify the root causes and personalize diagnosis and treatment. IBS is a chronic disorder characterized by abdominal pain, altered bowel movements, and other gastrointestinal symptoms. Diagnosing the condition remains challenging due to the lack of specific biomarkers or tests, resulting in frequent misdiagnosis.

The pathogenesis of IBS involves factors such as altered gastrointestinal motility, visceral hypersensitivity, intestinal barrier disorder, stress, dietary factors, small intestinal bacterial overgrowth (SIBO), changes in intestinal flora, low-grade mucosal inflammation, and genetic predisposition. The biopsychosocial model highlights the interaction between physiological and psychological factors.

The management of IBS involves a multidimensional approach tailored to each patient. Pharmacological therapy aims to alleviate symptoms but does not cure the condition. Non-pharmacological therapies, including dietary interventions, probiotic therapy, mind therapies, exercise, and complementary therapies, play a crucial role in IBS management.

Keywords: irritable bowel syndrome, functional medicine, pathogenesis, pharmacological therapy, non-pharmacological therapy.

Received: 02 July 2023

Accepted: 10 July 2023

Published: 15 July 2023

Introduction

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder caused by multiple factors[1]. The disease has poorly understood etiology and pathology; thus, there is a limited success of pharmacological therapy. Functional medicine looks at the conditions more broadly (in social, family, psychological, and other contexts) trying to identify the root causes, have an individual approach to diagnosis and treatment. It mixes drug therapy with complementary or alternative therapies for better clinical outcomes[2,3]. This report summarizes the latest scientific evidence in epidemiology, etiology, pathogenesis, and treatment of the condition with a particular focus on the functional medicine approach.

Understanding IBS and its prevalence

IBS is a chronic functional gastrointestinal disorder. Although bowel symptoms predominate, other symptoms like anxiety, changes in the working of different organs may also be present. Diagnosing the condition remains a challenge due to difficulties in identifying the organic changes in the body and the lack of specific biomarkers or tests. It remains a commonly misdiagnosed condition[1,4].

IBS is a condition characterized by bowel discomfort, abdominal pain, altered bowel movement. It may be characterized by either frequent episodes of diarrhea or constipation. While in some individual bouts of constipation may be followed by diarrhea. Other gastrointestinal symptoms like bloating, distention, are common[5].

The first attempts to understand the condition were made in the 19th century. However, efforts to standardize or formalize diagnostic criteria were only made in the mid-20th century. Manning first created the diagnostic criteria, which formed the basis of Rome criteria. Rome criteria for the diagnosis of IBS are now most widely accepted, and they are in their fourth iteration[6].

Rome IV diagnostic criteria states that the onset of symptoms should be at least 6 months before the diagnosis. A person should have gastroenterological symptoms like abdominal pain at least one day in a week for the last three months, along with the association of symptoms with defecation, changes in the frequency of stool, change in the appearance of stool[6].

Additionally, it should be noted that some patients may present with more severe signs and symptoms, related or unrelated to IBS. There are so-called "red flags" or warning signs to look for, like severe anemia, weight loss, severe bowel inflammation, family history of colorectal cancer[6].

There have been some studies regarding the sensitivity and specificity of Rome criteria, and it seems that they are precise enough for accurate diagnosis of IBS in most cases without the need for additional investigations[7].

Functional gastrointestinal disorders (FGIDs) are common and account for almost 40% of all the referrals to gastroenterologists[6]. Of all the recognized FGIDs, IBS is the most prevalent condition. Researchers estimate that about 11% of the population is affected by IBS globally. Females are more prone to be diagnosed with the disease. Further, there is vast variance in the prevalence of the condition between different ethnic groups and nations. This could be explained by the differences in dietary habits, environmental conditions, psychological health, and so on[8,9].

Pathogenesis or pathological factors in IBS

The pathogenesis of IBS is still not fully understood, that is because multiple factors perhaps cause the disease. In most people, a combination of the number of factors leads to IBS. Factors involved in the pathogenesis of the disease will differ among individuals, and thus the therapeutic approach. Some of the well-known factors predisposing or leading to the disease are genetics, environment, post-infection inflammation, altered gastric motility, altered immune response, changes in gut permeability, psychological reasons, and so on. This report looks at some of the better-known pathological factors.

GI motility disorder

Changes in GI motility is one of the essential diagnostic criteria in IBS. Such changes are present in all the patients, in some motility is increased, in others decreased, while in others there is an alternating pattern[10].

It seems that one of the reasons for altered motility is the changes in serotonin (5-HT) signaling. There is reason to believe in the role of serotonin in modified gut motility, as most of it is produced by enterochromaffin cells in gut affecting both the efferent and afferent nerves. Moreover, experience from empirical drug therapy shows that drugs altering 5-HT signaling may help patients. Thus, antidepressants may help in some cases, a class of drugs that alter 5-HT signaling (tricyclic antidepressants or serotonin selective reuptake inhibitors, and other drugs)[11].

Visceral hypersensitivity

It is another widely accepted concept which states the gut of people living with IBS responds excessively to various stimuli. This hypersensitivity could be due to increased sensitivity of local receptors, inflammation, changes in spinal reflexes, or even alterations in the brain (due to stress or other reasons)[12,13].

Intestinal barrier disorder

It means altered gut permeability, or some may call it leaky gut syndrome. It is about changes or rather disruption in the tight junctions. These changes can be caused by various means like inflammation, food intolerance, visceral hypersensitivity, changes in gut flora, certain infections, and much more.

Stress and altered gut-brain interaction

Numerous studies have shown that stress is one of the major contributing factors to altered intestinal motility, permeability, and visceral hypersensitivity. Chronic worry and psychological stress may especially increase the risk of developing IBS[14,15]. Mental stress is frequently associated with the exacerbation of the symptoms[16]. Stress may cause IBS in multiple ways, by altering local immune responses (altered mast cell stability and modulation of corticotrophin-releasing factor, and much more), affecting gut flora[17].

In recent years role of the altered gut-brain axis, caused by chronic stress, has received a lot of attention. Stress causes changes in the hypothalamic-pituitary-adrenal (HPA) axis and autonomic nervous system responses[18].

Dietary factors

Although dietary factors are not included in the diagnostic criteria, it is no secret that the kind of diet plays a vital role in the pathogenesis of any gut-related disease, and IBS is not exclusion. It is well known that dietary changes can help relieve symptoms in many cases. Further, many people living with IBS are known to report worsening of symptoms or exacerbations after a certain kind of food items.

Food allergies, intolerance, gluten intolerance, does play a role in the disease[19]. Diet high in fermentable oligo-, di- and monosaccharides and polyols (FODMAPs) have especially been shown to cause worsening of symptoms in IBS[20,21].

Studies also show that those living with IBS have some common dietary patterns like they are more probable to consume canned food, processed meat, and so on. This underlines the importance of the individual approach and the need for understanding the dietary pattern of a person living with IBS[22].

Small intestinal bacterial overgrowth (SIBO)

Although IBS is not an infectious disease, nonetheless, some studies indicate improvement in IBS symptoms after antibiotic therapy[23]. Some studies show the correlation between SIBO and IBS based on the correlation of results of various breathing tests and worsening or improvement of symptoms of IBS[24,25].

Changes in intestinal flora

Correlation between the incidence, prevalence, exacerbation, and severity of IBS and alterations in intestinal flora is yet not fully understood. Nonetheless, what studies show that intestinal flora in those living with IBS differs a lot from healthy subjects. Moreover, there are many reports of benefits from the use of various probiotics[26–28].

Low-grade mucosal inflammation

It is well known that most patients living with IBS have low-grade mucosal inflammation of the gut. Moreover, there is evidence that the level of inflammation increases during exacerbation. Although the functioning of T and B lymphocytes is known to be altered, special attention has been given to the altered activity of mast cells. This low-grade inflammation may be behind leaky gut and visceral hypersensitivity[29].

Genetics

Although poorly understood, genetic predisposition is undoubtedly one of the major contributing factors. Some genes are now known to be associated with altered gut motility and a higher risk of developing IBS[19].

Summing it up – the Biopsychosocial Model

Above mentioned are just some of the factors and mechanisms involved in disease development. It is necessary to visualize IBS as a multidimensional disorder. In most cases, it is caused by multiple reasons or even all of the above factors playing a role to a degree. The bio-psycho-social model sums up the things and proposes that the disease is caused due to interaction between psychological and physiological factors, whereas genetics and early life are predisposing factors. Prolonged psychological distress leads to physiological changes in gut health and motility and vice-versa[30].

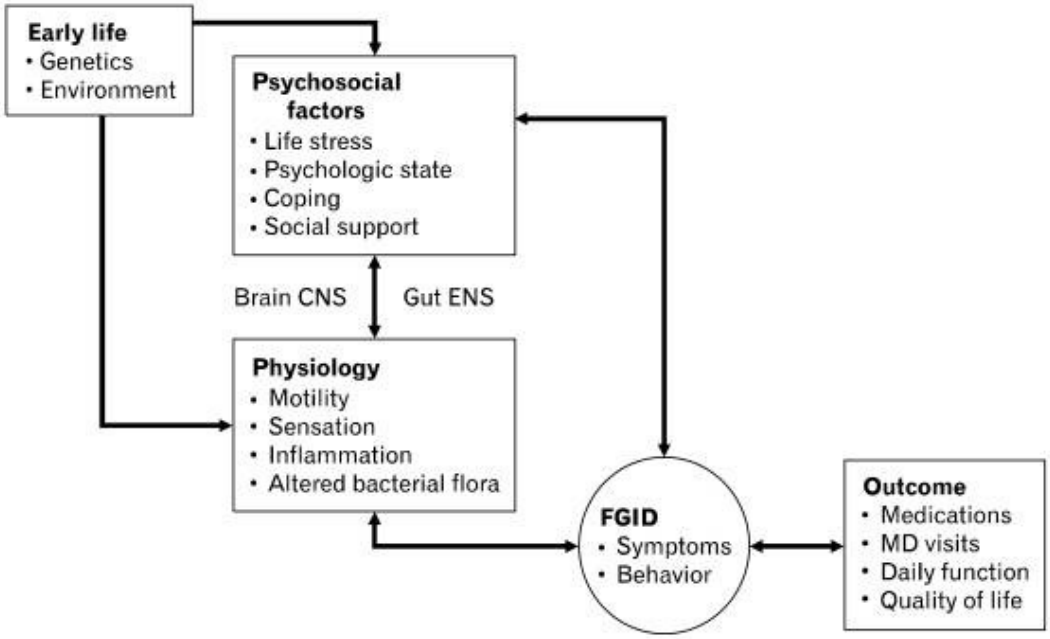

Figure 1 Biopsychosocial model of IBS (**Image source**: Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial Model of Irritable Bowel Syndrome. J Neurogastroenterol Motil. 2011;17(2):131-139. doi:10.5056/jnm.2011.17.2.131)

Instrumental Diagnosis of IBS

Using Rome IV criteria, already mentioned in the article, is the primary way to diagnose the condition. However, in practice, things are more complex, and diagnosing the condition is quite challenging. Although there are no specific biomarkers for IBS, nonetheless physicians need to do several tests to exclude other organic diseases and assess the health status of the individual.

Functional medicine specialists need to pay attention to other non-intestinal symptoms, pay particular attention to the family and social history of the individual. Those living with IBS may complain about dyspepsia, nausea, unexplained heart pains. There is a need to pay special attention to the presence of other functional disorders like fibromyalgia, chronic fatigue syndrome, migraine, PTSD, mood disorders, sleep, and sexual disorders, as one or some of them may coexist with the condition[31].

To exclude red flags or other severe disorders, physicians would frequently need to order complete blood count and chemistries, tests for inflammatory markers like erythrocyte sedimentation rate or C-reactive protein, may order specific stool tests (understanding digestive issues and excluding parasitic manifestation). Some cases may require endoscopy or colonoscopy; others may need motility studies. Serological tests may help exclude autoimmune disorders. Other tests like breathe tests may help diagnose SIBO[12].

Functional medicine specialists may frequently ask for additional tests to assess the GI effects like a test for pancreatin elastase, SCFA, F/B ratio, pathogens, tests for mycology, zonulin test, calprotectin, lactulose/mannitol. These tests help asses both the status of digestive health and the severity of leaky gut syndrome[32].

Management of IBS

The multidimensional disease would certainly require multi-component therapy. Moreover, every patient would differ from another, and what worked in one may not help others. This underlines the importance of the individual approach towards each patient.

Another important thing worth understanding is that modern medicine primarily aims at the management of symptoms and cannot cure the condition. Whereas, functional medicine has a different approach as it seeks to understand the root cause of the disease and thus find a remedy that could bring prolonged remission of the condition.

Pharmacological therapy of IBS

Medical drug therapy primarily aims at alleviating the symptoms and providing relief. Most of these drugs would require prolonged treatment, as none of them seek to cure the condition. Drug therapy is primarily aimed at alternating gastrointestinal motility and secretions, manage pain, stabilize mood disorders, alter sensation[33].

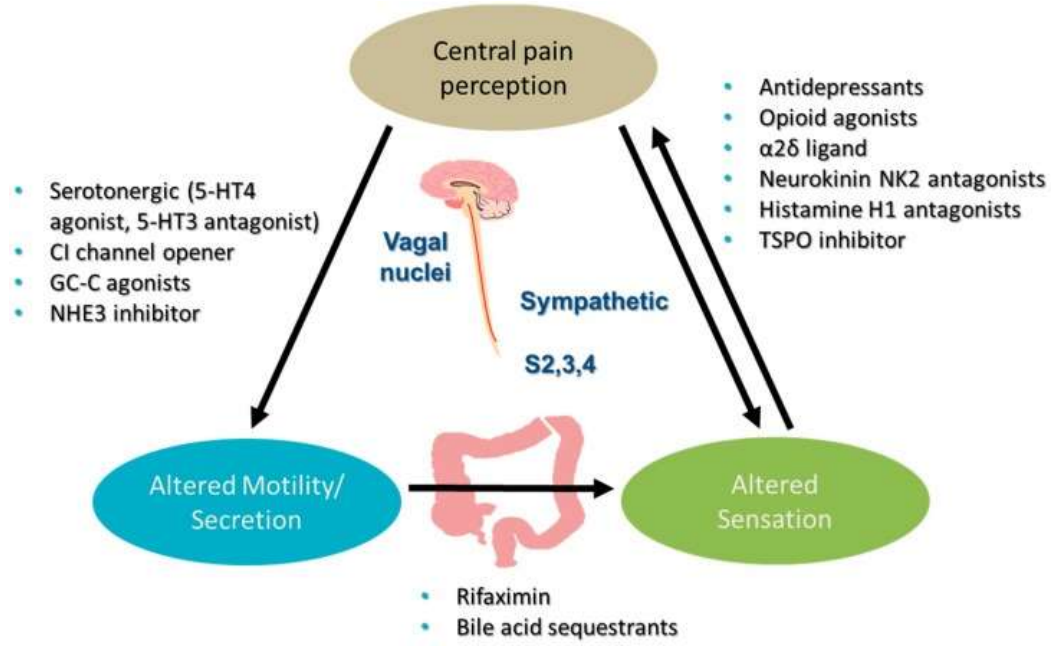

Figure 2 Pharmacological treatment of IBS (**Image source**: Camilleri M, Ford AC. Pharmacotherapy for Irritable Bowel Syndrome. J Clin Med. 2017;6(11). doi:10.3390/jcm6110101)

Some of the most commonly used pharmacological agents used to treat IBS are **antispasmodics** like otilonium bromide, dicyclomine, hyoscyamine. These medications help reduce pain, abdominal distention, and may also help normalize intestinal motility[33,34]. Cochrane systemic review shows that these classes of drugs may help relieve pain and some other symptoms[35].

Bulking agents may also help in some cases; they are widely used to treat IBS due to an excellent safety profile. However, the benefit of such a treatment is not fully understood[35].

Antidepressants like tricyclic or selective serotonin reuptake inhibitors (SSRIs) are widely used to treat IBS as psychological disorders are common among people with IBS. Further, these drugs affect intestinal motility, secretions, and may change the response to pain stimuli. They may help reduce intestinal irritation, distention[33,34]. Nonetheless, clinical evidence favoring their use to treat the condition is limited[35].

Anti-diarrheal opioids like loperamide remain widely used drugs. They are especially useful for those with diarrhea as a predominant complaint. It may not only help control stool frequency, but may also affect stool consistency, and help reduce abdominal pain[33,34].

Serotonin receptor (5-HT3) antagonists and serotonin receptor (5-HT4) agonists may help correct intestinal motility by either increasing or decreasing the transit time. Apart from it, these medications may reduce visceral sensitivity and pain. 5-HT3 antagonists like alosetron may reduce intestinal motility, bloating, and pain. Whereas, 5-HT4 agonists like tegaserod may increase motility. These classes of drugs have been specially approved to treat IBS, though their clinical efficacy is limited[34].

Other drug therapies commonly used by functional medicine practitioners are **antibiotics (like rifaximin) to treat various infections or SIBO, bile acid sequestrants, intestinal secretagogues (lubiprostone, linaclotide, or plecanatide), GABAergic agents, Histamine antagonists, mast cell stabilizers**, and others[33].

Non-pharmacological therapy of IBS

Despite the availability of a plethora of drug therapies, very few of them seem to work in most of the cases. Moreover, drug therapies are primarily aimed at symptomatic relief. Systemic reviews show that most traditional and newer drug therapies are just a little more effective than placebo. This means that **non-pharmacological treatment must be an essential part of IBS management**.

Dietary therapy may work in a number of cases since it is well-known that in many patients, symptoms of IBS worsen after prominent meals[36]. Most dietary interventions work by restricting the intake of certain food items, and at the same time, adding specific nutrient-rich food items to the diet. Among restrictive diets, the gluten-free and low FODMAP diet are the most researched diet forms, and there is enough clinical evidence to suggest that they may work in many cases[37,38]. Another approach is to increase the intake of dietary fiber, which can have a mild benefit in some cases. However, researchers warn that in some cases, dietary fiber may even worsen the symptoms[39].

Probiotic therapy is one of the well-researched fields. There is a reason to believe that manipulating gut microbiota may help in some cases as the human gut contains a tremendous amount of microbiota. Although there is no doubt that intestinal microbiota is essential for gut health, its complete role in well-being is poorly understood. Moreover, researchers are still not sure about the role of the various strains in health and disease. There are moderate evidence that different commercially available probiotic formulations may help in IBS. Probiotics may help reduce pain and severity of the disease, but the magnitude of benefit is still not evident. Nonetheless, keeping in mind the safety of the therapy, it is something worth including in the treatment-plan[40–42].

Mind or psychological therapies should be included in IBS treatment. The role of psychological factors in the disease pathogenesis is well established. Further, the efficacy of mood-altering drugs like antidepressants shows that any non-pharmacological psychotherapy may help too. There are various options available, like practicing mindfulness, yoga, tai-chi, cognitive behavior therapy, psychotherapy, bio-feedback. Functional medicine therapists must pay particular attention to family status and relations, as individuals with inter-family conflicts may have worse symptoms. Mind therapies or psychotherapies whether given in clinics or from a distance, may help reduce the severity of the condition. Moreover, these therapies are entirely free from adverse effects[43–48].

Mechanical interventions like exercise, reflexology, massage, acupuncture may help patients feel better, reduce stress, and thus improve symptoms. These therapies also promote lifestyle changes like people doing regular exercise (biking, strength training, aerobic exercise, walking, and so on) are more probable to make a healthy lifestyle choices[49]. There is a strong case in support of exercise therapy, especially considering its feasibility and numerous health benefits. Even if exercise does not help directly, it can help relieve many symptoms like constipation, mood disorders, reduce pain severity[50,51]. Evidence in support of some complementary therapies like acupuncture is mixed with some reviews showing no benefits while others demonstrating significant improvement in symptoms[52,53].

Herbal therapies remain widely used for various functional disorders, especially for gastrointestinal disorders. It is estimated that about half of all the patients living with IBS would try some or another herbal remedy[54]. There are numerous herbal treatments available[49], and this report looks at some of the better-known therapies.

Peppermint oil is a well-known natural remedy for digestive disorders, and it is also one of the most well-researched treatments too. It is available in various forms as oils, liquids, capsules, and so on. It is known to help with non-ulcer dyspepsia. It may be useful in relieving pain related to colonic spasms and may help relax smooth muscles. Its topical application may have a mood-elevating effect and may help with tension headaches. A systemic review of clinical data shows that it is a moderately effective therapy for short-term relief of the symptoms. However, its role in prolonged IBS therapy is unclear[55,56].

Turmeric extract or curcumin is the most researched herbal extract in modern times. It is known to have anti-inflammatory, antioxidant, gut microbiota modulating, anti-microbial, pain-relieving properties with extremely high safety profile. Apart from current research, it has been used in various Asian cuisines and traditional medicines to help with digestion and improve gastrointestinal health. Although, at present, there is a lack of robust clinical evidence, nonetheless, it seems to be a remedy worth using[57,58].

Plantago psyllium may be especially helpful for those living with constipation. It is an excellent source of fiber and thus may help with peristalsis, reduce intestinal irritation, increase secretions, normalize gut microbiota, normalize immune responses, and may also help lower cholesterol levels, blood pressure, and improve glycemic control. There is moderate clinical evidence that it may help with IBS[59,60].

There are numerous other well-researched herbal remedies for IBS, and discussing all of them is beyond the scope of this report. However, some of the other herbal remedies worth looking at are Aloe Vera, Artichoke, Fumaria officinalis, Hypericum perforatum, Padma Lax, and many more[49,61]. Additionally, vitamins, minerals, and other food supplements may help too.

Conclusion

To conclude, IBS is a multi-dimensional illness requiring a multi-directional treatment approach. No single approach will work in all cases. There are numerous pharmacological and non-pharmacological therapies to choose from. However, this choice and lack of strong evidence in favor of any single treatment option make treatment tasks difficult. Nonetheless, with a broader approach towards a patient, like that proposed in functional medicine, one may identify the root causes of the disease and choose the right treatment options. When diagnosing and treating the condition, both somatic and psychological disturbances should be considered.

References

1. Enck P, Aziz Q, Barbara G, et al. Irritable bowel syndrome. *Nat Rev Dis Primer*. 2016;2:16014. doi:10.1038/nrdp.2016.14

2. What is Functional Medicine? | IFM. The Institute for Functional Medicine. Accessed January 18, 2020. https://www.ifm.org/functional-medicine/what-is-functional-medicine/

3. Hung A, Kang N, Bollom A, Wolf JL, Lembo A. Complementary and Alternative Medicine Use Is Prevalent Among Patients with Gastrointestinal Diseases. *Dig Dis Sci*. 2015;60(7):1883-1888. doi:10.1007/s10620-014-3498-3

4. Frissora CL, Koch KL. Symptom overlap and comorbidity of irritable bowel syndrome with other conditions. *Curr Gastroenterol Rep*. 2005;7(4):264-271. doi:10.1007/s11894-005-0018-9

5. Definition & Facts for Irritable Bowel Syndrome | NIDDK. National Institute of Diabetes and Digestive and Kidney Diseases. Accessed January 18, 2020. https://www.niddk.nih.gov/health-information/digestive-diseases/irritable-bowel-syndrome/definition-facts

6. Lacy BE, Patel NK. Rome Criteria and a Diagnostic Approach to Irritable Bowel Syndrome. *J Clin Med*. 2017;6(11). doi:10.3390/jcm6110099

7. Ford AC, Bercik P, Morgan DG, Bolino C, Pintos–Sanchez MI, Moayyedi P. Validation of the Rome III Criteria for the Diagnosis of Irritable Bowel Syndrome in Secondary Care. *Gastroenterology*. 2013;145(6):1262-1270.e1. doi:10.1053/j.gastro.2013.08.048

8. Canavan C, West J, Card T. The epidemiology of irritable bowel syndrome. *Clin Epidemiol*. 2014;6:71-80. doi:10.2147/CLEP.S40245

9. Lovell RM, Ford AC. Global Prevalence of and Risk Factors for Irritable Bowel Syndrome: A Meta-analysis. *Clin Gastroenterol Hepatol*. 2012;10(7):712-721.e4. doi:10.1016/j.cgh.2012.02.029

10. Kellow JE, Phillips SF. Altered small bowel motility in irritable bowel syndrome is correlated with symptoms. *Gastroenterology*. 1987;92(6):1885-1893. doi:10.5555/uri:pii:0016508587906202

11. Sikander A, Rana SV, Prasad KK. Role of serotonin in gastrointestinal motility and irritable bowel syndrome. *Clin Chim Acta*. 2009;403(1):47-55. doi:10.1016/j.cca.2009.01.028

12. Soares RL. Irritable bowel syndrome: A clinical review. *World J Gastroenterol WJG*. 2014;20(34):12144-12160. doi:10.3748/wjg.v20.i34.12144

13. Zuo XL, Li YQ, Shi L, et al. Visceral hypersensitivity following cold water intake in subjects with irritable bowel syndrome. *J Gastroenterol*. 2006;41(4):311-317. doi:10.1007/s00535-005-1766-x

14. Song SW, Park SJ, Kim SH, Kang SG. Relationship between Irritable Bowel Syndrome, Worry and Stress in Adolescent Girls. *J Korean Med Sci*. 2012;27(11):1398-1404. doi:10.3346/jkms.2012.27.11.1398

15. Irwin C, Falsetti SA, Lydiard RB, Ballenger JC. Comorbidity of posttraumatic stress disorder and irritable bowel syndrome. *J Clin Psychiatry*. 1996;57(12):576-578. doi:10.4088/JCP.v57n1204

16. Blanchard EB, Lackner JM, Jaccard J, et al. The role of stress in symptom exacerbation among IBS patients. *J Psychosom Res*. 2008;64(2):119-128. doi:10.1016/j.jpsychores.2007.10.010

17. Larauche M. Novel insights in the role of peripheral corticotropin-releasing factor and mast cells in stress-induced visceral hypersensitivity. *Neurogastroenterol Motil*. 2012;24(3):201-205. doi:10.1111/j.1365-2982.2011.01867.x

18. Qin HY, Cheng CW, Tang XD, Bian ZX. Impact of psychological stress on irritable bowel syndrome. *World J Gastroenterol WJG*. 2014;20(39):14126-14131. doi:10.3748/wjg.v20.i39.14126

19. Lee YJ, Park KS. Irritable bowel syndrome: Emerging paradigm in pathophysiology. *World J Gastroenterol WJG*. 2014;20(10):2456-2469. doi:10.3748/wjg.v20.i10.2456

20. Giorgio RD, Volta U, Gibson PR. Sensitivity to wheat, gluten and FODMAPs in IBS: facts or fiction? *Gut*. 2016;65(1):169-178. doi:10.1136/gutjnl-2015-309757

21. El-Salhy M, Østgaard H, Gundersen D, Hatlebakk JG, Hausken T. The role of diet in the pathogenesis and management of irritable bowel syndrome (Review). *Int J Mol Med*. 2012;29(5):723-731. doi:10.3892/ijmm.2012.926

22. Chirila I, Petrariu FD, Ciortescu I, Mihai C, Drug VL. Diet and Irritable Bowel syndrome. :7.

23. Spiegel BMR. Questioning the bacterial overgrowth hypothesis of irritable bowel syndrome: an epidemiologic and evolutionary perspective. *Clin Gastroenterol Hepatol Off Clin Pract J Am Gastroenterol Assoc*. 2011;9(6):461-469; quiz e59. doi:10.1016/j.cgh.2011.02.030

24. Pimentel M, Chow EJ, Lin HC. Normalization of lactulose breath testing correlates with symptom improvement in irritable bowel syndrome. a double-blind, randomized, placebo-controlled study. *Am J Gastroenterol*. 2003;98(2):412-419. doi:10.1111/j.1572-0241.2003.07234.x

25. Lupascu A, Gabrielli M, Lauritano EC, et al. Hydrogen glucose breath test to detect small intestinal bacterial overgrowth: a prevalence case-control study in irritable bowel syndrome. *Aliment Pharmacol Ther*. 2005;22(11-12):1157-1160. doi:10.1111/j.1365-2036.2005.02690.x

26. Kassinen A, Krogius-Kurikka L, Mäkivuokko H, et al. The fecal microbiota of irritable bowel syndrome patients differs significantly from that of healthy subjects. *Gastroenterology*. 2007;133(1):24-33. doi:10.1053/j.gastro.2007.04.005

27. Malinen E, Rinttilä T, Kajander K, et al. Analysis of the fecal microbiota of irritable bowel syndrome patients and healthy controls with real-time PCR. *Am J Gastroenterol*. 2005;100(2):373-382. doi:10.1111/j.1572-0241.2005.40312.x

28. Ghoshal UC, Shukla R, Ghoshal U, Gwee KA, Ng SC, Quigley EMM. The Gut Microbiota and Irritable Bowel Syndrome: Friend or Foe? *Int J Inflamm*. Published online 2012. doi:https://doi.org/10.1155/2012/151085

29. Ford AC, Talley NJ. Mucosal inflammation as a potential etiological factor in irritable bowel syndrome: a systematic review. *J Gastroenterol*. 2011;46(4):421-431. doi:10.1007/s00535-011-0379-9

30. Tanaka Y, Kanazawa M, Fukudo S, Drossman DA. Biopsychosocial Model of Irritable Bowel Syndrome. *J Neurogastroenterol Motil*. 2011;17(2):131-139. doi:10.5056/jnm.2011.17.2.131

31. Sperber AD, Drossman DA. Irritable bowel syndrome: a multidimensional disorder cannot be understood or treated from a unidimensional perspective. *Ther Adv Gastroenterol*. 2012;5(6):387-393. doi:10.1177/1756283X12460420

32. Herbst A. The Functional Medicine Approach to IBS/GI complaints. In: ; 2017. Accessed January 22, 2020. http://www.acofp.org/ACOFPIMIS/Acofporg/PDFs/ACOFP17/handouts/saturday/Sat_am_1030_Herbst,%20Aunna_The%20Functional%20Medicine%20Approach%20to%20IBS%20GI%20Complaints.pdf

33. Camilleri M, Ford AC. Pharmacotherapy for Irritable Bowel Syndrome. *J Clin Med*. 2017;6(11). doi:10.3390/jcm6110101

34. Hadley SK, Gaarder SM. Treatment of Irritable Bowel Syndrome. *Am Fam Physician*. 2005;72(12):2501-2506.

35. Quartero AO, Meineche-Schmidt V, Muris J, Rubin G, de Wit N. Bulking agents, antispasmodic and antidepressant medication for the treatment of irritable bowel syndrome. *Cochrane Database Syst Rev*. 2005;(2):CD003460. doi:10.1002/14651858.CD003460.pub2

36. Alpers DH. Diet and irritable bowel syndrome. *Curr Opin Gastroenterol*. 2006;22(2):136-139. doi:10.1097/01.mog.0000208462.92136.02

37. Halmos EP, Power VA, Shepherd SJ, Gibson PR, Muir JG. A Diet Low in FODMAPs Reduces Symptoms of Irritable Bowel Syndrome. *Gastroenterology*. 2014;146(1):67-75.e5. doi:10.1053/j.gastro.2013.09.046

38. Dionne J, Ford AC, Yuan Y, et al. A Systematic Review and Meta-Analysis Evaluating the Efficacy of a Gluten-Free Diet and a Low FODMAPS Diet in Treating Symptoms of Irritable Bowel Syndrome. *Am J Gastroenterol*. 2018;113(9):1290-1300. doi:10.1038/s41395-018-0195-4

39. Bijkerk CJ, Muris JWM, Knottnerus JA, Hoes AW, Wit NJD. Systematic review: the role of different types of fibre in the treatment of irritable bowel syndrome. *Aliment Pharmacol Ther*. 2004;19(3):245-251. doi:10.1111/j.0269-2813.2004.01862.x

40. Aragon G, Graham DB, Borum M, Doman DB. Probiotic Therapy for Irritable Bowel Syndrome. *Gastroenterol Hepatol*. 2010;6(1):39-44.

41. Didari T, Mozaffari S, Nikfar S, Abdollahi M. Effectiveness of probiotics in irritable bowel syndrome: Updated systematic review with meta-analysis. *World J Gastroenterol WJG*. 2015;21(10):3072-3084. doi:10.3748/wjg.v21.i10.3072

42. Moayyedi P, Ford AC, Talley NJ, et al. The efficacy of probiotics in the treatment of irritable bowel syndrome: a systematic review. *Gut*. 2010;59(3):325-332. doi:10.1136/gut.2008.167270

43. Laird KT, Tanner-Smith EE, Russell AC, Hollon SD, Walker LS. Short-term and Long-term Efficacy of Psychological Therapies for Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol*. 2016;14(7):937-947.e4. doi:10.1016/j.cgh.2015.11.020

44. Gerson MJ, Gerson CD, Awad RA, et al. An international study of irritable bowel syndrome: Family relationships and mind-body attributions. *Soc Sci Med*. 2006;62(11):2838-2847. doi:10.1016/j.socscimed.2005.10.019

45. Naliboff BD, Fresé MP, Rapgay L. Mind/Body Psychological Treatments for Irritable Bowel Syndrome. *Evid Based Complement Alternat Med*. Published online 5. doi:https://doi.org/10.1093/ecam/nem046

46. Craske MG, Wolitzky-Taylor KB, Labus J, et al. A cognitive-behavioral treatment for irritable bowel syndrome using interoceptive exposure to visceral sensations. *Behav Res Ther*. 2011;49(6):413-421. doi:10.1016/j.brat.2011.04.001

47. Hutton J. Cognitive behaviour therapy for irritable bowel syndrome. *Eur J Gastroenterol Hepatol*. 2005;17(1):11-14.

48. Ljótsson B, Hedman E, Lindfors P, et al. Long-term follow-up of internet-delivered exposure and mindfulness based treatment for irritable bowel syndrome. *Behav Res Ther*. 2011;49(1):58-61. doi:10.1016/j.brat.2010.10.006

49. Grundmann O, Yoon SL. Complementary and alternative medicines in irritable bowel syndrome: An integrative view. *World J Gastroenterol WJG*. 2014;20(2):346-362. doi:10.3748/wjg.v20.i2.346

50. Zhou C, Zhao E, Li Y, Jia Y, Li F. Exercise therapy of patients with irritable bowel syndrome: A systematic review of randomized controlled trials. *Neurogastroenterol Motil.* 2019;31(2):e13461. doi:10.1111/nmo.13461

51. Daley AJ, Grimmett C, Roberts L, et al. The Effects of Exercise upon Symptoms and Quality of Life in Patients Diagnosed with Irritable Bowel Syndrome: A Randomised Controlled Trial. *Int J Sports Med.* 2008;29(9):778-782. doi:10.1055/s-2008-1038600

52. Chao GQ, Zhang S. Effectiveness of acupuncture to treat irritable bowel syndrome: A meta-analysis. *World J Gastroenterol WJG.* 2014;20(7):1871-1877. doi:10.3748/wjg.v20.i7.1871

53. Manheimer E, Wieland LS, Cheng K, et al. Acupuncture for irritable bowel syndrome: systematic review and meta-analysis. *Am J Gastroenterol.* 2012;107(6):835-848. doi:10.1038/ajg.2012.66

54. Comar KM, Kirby DF. Herbal Remedies in Gastroenterology. *J Clin Gastroenterol.* 2005;39(6):457-468. doi:10.1097/01.mcg.0000165650.09500.3a

55. Khanna R, MacDonald JK, Levesque BG. Peppermint Oil for the Treatment of Irritable Bowel Syndrome: A Systematic Review and Meta-analysis. *J Clin Gastroenterol.* 2014;48(6):505-512. doi:10.1097/MCG.0b013e3182a88357

56. Kligler B, Chaudary S. Peppermint Oil. *Am Fam Physician.* 2007;75(7):1027-1030.

57. Bundy R, Walker AF, Middleton RW, Booth J. Turmeric Extract May Improve Irritable Bowel Syndrome Symptomology in Otherwise Healthy Adults: A Pilot Study. *J Altern Complement Med.* 2004;10(6):1015-1018. doi:10.1089/acm.2004.10.1015

58. Ng QX, Soh AYS, Loke W, Venkatanarayanan N, Lim DY, Yeo WS. A Meta-Analysis of the Clinical Use of Curcumin for Irritable Bowel Syndrome (IBS). *J Clin Med.* 2018;7(10):298. doi:10.3390/jcm7100298

59. Chouinard LE. The Role of Psyllium Fibre Supplementation: In Treating Irritable Bowel Syndrome. *Can J Diet Pract Res.* 2011;72(1):e107-e114. doi:10.3148/72.1.2011.48

60. El-Salhy M, Ystad SO, Mazzawi T, Gundersen D. Dietary fiber in irritable bowel syndrome (Review). *Int J Mol Med.* 2017;40(3):607-613. doi:10.3892/ijmm.2017.3072

61. Bahrami HR, Hamedi S, Salari R, Noras M. Herbal Medicines for the Management of Irritable Bowel Syndrome: A Systematic Review. *Electron Physician.* 2016;8(8):2719-2725. doi:10.19082/2719

Literature review

Impact of Physical Activity on Prostate Cancer Incidence

Mark Leitzmann, [1,*] Michael Gronberg [2]

[1] UMCH, Hamburg;

[1] UMCH, Hamburg;

* Correspondence: leitzmann_1153@gmail.com

https://doi.org/eiki/xxxxx

Abstract: Prostate cancer is a leading cancer in men, with its incidence varying among different countries and ethnic groups. The introduction of serum prostate-specific antigen (PSA) testing has led to increased early detection rates, particularly in high Human Development Index (HDI) countries. Several extrinsic or modifiable factors have been implicated in the development of prostate cancer. Diet, including high meat and dairy consumption, alcohol intake, and dietary supplements, has shown inconsistent associations. Obesity has emerged as a significant risk factor for prostate cancer and can worsen prognosis and treatment outcomes. Conversely, consumption of fish and fish oil has been associated with a lower incidence and mortality rate of prostate cancer.

The relationship between physical activity and prostate cancer risk has been extensively studied, yielding mixed results. While physical activity has consistently shown protective effects against other cancers, its association with prostate cancer risk is less clear. Some studies suggest a potential benefit, particularly with vigorous physical activity, while others find no significant association. However, physical activity has demonstrated positive effects on survival rates and disease progression among men already diagnosed with prostate cancer.

Keywords: prostate cancer, risk factors, physical activity, prevention, survival rate.

Received: 02 July 2023

Accepted: 12 July 2023

Published: 15 July 2023

Introduction

The incidence of most types of cancers is much higher in countries with very high Human Development Index (HDI) when compared to countries with low HDI, and prostate cancer is no exception [1]. Globally lung cancer remains the most common cancer in men followed by prostate cancer [2], however, in developed nations like US prostate cancer is the most commonly diagnosed cancer in men [3]. Epidemiological studies show a considerable difference in the incidence of prostate cancer among various geo locations and ethnic groups, thus necessitating the study of multiple risk factors [4]. It also underlines the importance of lifestyle factors like diet and physical activity in cancer development or prevention along with genetics or ethnicity [5].

One of the reasons for the higher incidence of prostate cancer in high HDI countries could be an early diagnosis. Epidemiological studies indicate a sharp rise in prostate cancer incidence after the introduction of serum prostate-specific antigen (PSA) testing in the western world. PSA has enabled detection of latent prostate cancer resulting in a sharp rise in prostate cancer detection since the mid-1980s [6,7]. Early detection of prostate cancer in the western world may also explain lower mortality rates when compared to low HDI nations [8].

Despite the importance of PSA in the early detection of prostate cancer, it is still not a tool for mass screening [9,10]. Moreover, early aggressive treatment remains controversial, though radical proctectomy may help. Nonetheless, early detection may help in both clinical decision making and prolonging survival of the patient [11]. Early detection of prostate cancer results in high 10-year survival rate [12].

Understanding risk factors of Prostate cancer

PSA cannot be used for mass screening due to its low specificity and risk of over-treatment, thus understanding risk factors for the development of prostate cancer may help in risk assessment and early recognition of prostate cancer [13]. Despite the high incidence rate of prostate cancer, little progress has been made in understanding the risk factors. At present familial history, age, and genetics remain as the only widely accepted risk factors for prostate cancer, since all these factors are non-modifiable, they have little practical importance in disease prevention and management. This necessitates the importance of identifying the modifiable risk factors or lifestyle factors that may help prevent the disease [14].

Numerous researches into the development of various cancers suggest that intrinsic factors play a minor role in comparison to extrinsic factors. There is enough evidence to propose that intrinsic factors only contribute 10-30% to the risk of cancer development. Whereas, extrinsic factors heavily influence the risk of cancer development [15]. Numerous extrinsic or modifiable factors are known to be implicated in the development of prostate cancer, and their understanding may help estimate the lifetime risk of developing the disease, take preventive measures, and manage the condition more effectively. Although, data regarding extrinsic risk factors are not always consistent. Among the preventive factors physical activity, intake of cruciferous vegetables, tomatoes and soy seem to be significant [16].

Several factors that increase the risk of developing prostate cancer has been identified. It is possible that diet high in meat products and dairy products may increase the risk. Studies regarding the role of alcohol in prostate cancer development mostly remain inconclusive. Similarly, various dietary supplements have failed to show a protective effect. Smoking shows a weak association with higher risk of prostate cancer though it may increase mortality among those diagnosed with cancer [14].

Obesity seems not only to increase the risk of prostate cancer, but it may also worsen the prognosis of those already diagnosed with prostate cancer. It appears that individuals with higher BMI are at greater risk of developing an aggressive form of prostate cancer, higher risk of failure of radical prostatectomy, and radiotherapy. Obesity also reduces the efficacy of androgen-deprivation therapy in prostate cancer. Thus, obesity also makes treating prostate cancer more difficult. On the other hand, weight reduction may slow down the disease progress [17].

Consumption of fish and fish oil has also been subject to lots of research in recent times. One of the crucial evidence comes from the systemic review that indicated a small reduction in prostate cancer incidence among those who consumed fish in higher amounts. In the study, 5777 cases were compared to 9805 control subjects. Research not only demonstrated a lower risk of prostate cancer associated with fish consumption but significantly lower mortality rate (63%), thus providing strong evidence in favor of fish consumption [18].

Relation of physical activity with prostate cancer development

Physical activity and its relationship to risk of developing prostate cancer sometime in life require specific consideration as it is now well-established fact that lack of physical activity has lots to do with epidemics of non-communicable diseases. Increased physical activity can reduce the risk of obesity, diabetes, and had a modulating effect on the endocrine system. Therefore, it would be safe to hypothesize that it may help prevent prostate cancer. Although earlier studies have failed to produce a consistent result, nonetheless, most seem to show a certain degree of benefit in cancer prevention.

Earlier studies have been more consistent in establishing the benefit of physical activity in non-prostate cancers. A cohort study has found a much lower risk of developing cancer among the elite athletes in Finland when compared with a general male population in the country [19]. Epidemiological studies indicate that physical activity may reduce the risk of colon cancer by as much as 30-40%. It seems that 30-60 minutes of moderate or vigorous physical activity a day is enough to reduce the risk. Similarly, studies indicate that physically active individuals are 20-30% less probable to develop breast cancer when compare to physically inactive individuals. There are fewer studies regarding the benefit of physical activity in preventing lung cancer and prostate cancer. Nonetheless, most seem to favor physical activity for preventing these cancers [20].

Further, it seems that physical activity during a young life may have a long-term protective role against various types of cancers. Thus, in a cohort study of 31,158 Finnish men born in 1958 and followed up to 2014, it was found that higher BMI was associated with greater risk of cancer. Even those with a healthy weight but with poor physical conditioning were at higher risk than those with normal weight and good physical conditioning. And those with higher body weight and poor physical conditioning were at the most significant risk. It means that good physical conditioning during early adulthood may have long term protective role against various cancers [21(p158)].

In the Iowa 65+ rural health study, 1050 men aged 65 to 101 years of age were followed for ten years, and out of them 71 developed prostate cancer. The study took smoking, BMI, and physical activity into consideration and found the relative risk for cigarettes smoking 2.9 (RR=2.9) when smoking more than 20 cigarettes a day in comparison to non-smokers, RR = 1.7 for BMI greater than 27.8 kg/m2 when compared with BMI lower than 23.5. In the study, physical activity was also found to be an independent risk factor for prostate cancer with RR =1.9 for a high level of inactivity. Thus, the study concluded smoking, overweight, and physical inactivity are independent risk factors for the development of prostate cancer in later life [22].

In another study, 452 prostate cancer cases were identified and classified into five categories of physical activity. Researchers found a negative association between the proportion of life spend doing sedentary work and prostate cancer risk. Investigators found this negative association to be dose-dependent, unrelated to ethnicity and socio-economic status, nutritional risk factors, or job associated chemical exposures. Results were less consistent for young men in comparison to older men. Although the study was inconclusive, nonetheless, it did suggest that physical activity may help reduce the risk of prostate cancer [23].

One of the more extensive studies on the subject has been regarding the evaluation of the risk of prostate cancer among physically less active health professionals. In the study, 47,542 health professionals aged 40-75 were assessed for physical activity. The study also calculated the vigorousness of physical activity among the subjects by calculating weekly metabolic equivalents (METs) score. 1,362 cases of prostate cancer were identified between 1986 and Jan 1994. The study did not find any relation between the incidence of prostate cancer and physical activity. However, it found lower risk among those with the highest category of vigorous physical activity. Although, the study failed to show that physical activity may reduce the incidence of prostate cancer, but it did prove the protective effect of highly vigorous physical activity, thus warranting further studies [24]. Similar findings were confirmed in a study by Sormunen et al. when data for the perceived physical workload (PPWL) for 239,835 cases were compared with 1,199,175 control subjects. In the study physical activity only marginally and statistically insignificantly reduced the prostate cancer risk (0.90 hazard ratio from lowest to highest PPWL). Nonetheless, the study indicated that physical activity significantly decreased the risk of invasive prostate cancer [25].

Interestingly enough, studies are quite consistent when it comes to estimating the benefits of physical activity in those already diagnosed with prostate cancer. It seems that even moderate physical activity like brisk walking on a regular basis may significantly delay the

progression of prostate cancer among men already diagnosed with prostate cancer, and it may also help to keep cancer localized [26]. Physical activity may meaningfully increase survival rate with vigorous physical activity. One of the studies indicates that those who walked briskly for more than 90 minutes a week had a 46% lower risk of all-cause mortality when compared to those involved in low-level physical activity. Similarly, men doing vigorous physical activity for more than 3 hours a week had 61% lower risk of all-cause mortality when living with prostate cancer [27,28]. Additionally, supervised physical activity may also be used to reduce the toxicity of prostate cancer therapy, improve social and mental functioning, thus influencing positively on the quality of life [29].

Conclusion

Although studies regarding the beneficial effect of physical activity in preventing prostate cancer remain inconclusive, nonetheless, most seem to indicate some benefit thus necessitating further investigation. Most studies seem to show that physical activity may improve survival rate, help inhibit prostate cancer, make it less aggressive, prevent it from spreading. Further, it should be understood that physical activity has many other health benefits like helping normalize metabolism, blood pressure, body weight, sleep quality, mood, which finally reduces the risk of various oncological conditions. There is no doubt that physical activity will help prevent prostate cancer to a certain extent, what remains controversial is the degree of benefit of physical activity in disease prevention. Besides, the benefit of physical activity in those already diagnosed with prostate cancer must not be neglected.

References

1. WCRF. Comparing more and less developed countries. World Cancer Research Fund. Published August 22, 2018. Accessed January 31, 2019. https://www.wcrf.org/dietandcancer/cancer-trends/comparing-more-and-less-developed-countries

2. WCRF. Worldwide cancer data. World Cancer Research Fund. Published August 6, 2018. Accessed January 31, 2019. https://www.wcrf.org/dietandcancer/cancer-trends/worldwide-cancer-data

3. U.S. Cancer Statistics Working Group. USCS Data Visualizations. Published 2017. Accessed January 31, 2019. https://gis.cdc.gov/grasp/USCS/DataViz.html

4. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. *Int J Cancer*. 2000;85(1):60-67. doi:10.1002/(SICI)1097-0215(20000101)85:1<60::AID-IJC11>3.0.CO;2-B

5. Gronberg H. Prostate cancer epidemiology. *The Lancet*. 2003;361(9360):859-864. doi:10.1016/S0140-6736(03)12713-4

6. Jacobsen SJ, Katusic SK, Bergstralh EJ, et al. Incidence of Prostate Cancer Diagnosis in the Eras Before and After Serum Prostate-Specific Antigen Testing. *JAMA*. 1995;274(18):1445-1449. doi:10.1001/jama.1995.03530180039027

7. Potosky AL, Miller BA, Albertsen PC, Kramer BS. The Role of Increasing Detection in the Rising Incidence of Prostate Cancer. *JAMA*. 1995;273(7):548-552. doi:10.1001/jama.1995.03520310046028

8. Center MM, Jemal A, Lortet-Tieulent J, et al. International Variation in Prostate Cancer Incidence and Mortality Rates. *Eur Urol*. 2012;61(6):1079-1092. doi:10.1016/j.eururo.2012.02.054

9. Heidenreich A, Bellmunt J, Bolla M, et al. EAU Guidelines on Prostate Cancer. Part 1: Screening, Diagnosis, and Treatment of Clinically Localised Disease. *Eur Urol*. 2011;59(1):61-71. doi:10.1016/j.eururo.2010.10.039

10. Wolf AMD, Wender RC, Etzioni RB, et al. American Cancer Society Guideline for the Early Detection of Prostate Cancer: Update 2010. *CA Cancer J Clin*. 2010;60(2):70-98. doi:10.3322/caac.20066

11. Johansson JE, Holmberg L, Johansson S, Bergström R, Adami HO. Fifteen-Year Survival in Prostate Cancer: A Prospective, Population-Based Study in Sweden. *JAMA*. 1997;277(6):467-471. doi:10.1001/jama.1997.03540300035030

12. Johansson JE, Adami HO, Andersson SO, Bergström R, Holmberg L, Krusemo UB. High 10-Year Survival Rate in Patients With Early, Untreated Prostatic Cancer. *JAMA*. 1992;267(16):2191-2196. doi:10.1001/jama.1992.03480160049033

13. Stephan C, Rittenhouse H, Hu X, Cammann H, Jung K. Prostate-Specific Antigen (PSA) Screening and New Biomarkers for Prostate Cancer (PCa). *EJIFCC*. 2014;25(1):55-78.

14. Leitzmann MF, Rohrmann S. Risk factors for the onset of prostatic cancer: age, location, and behavioral correlates. *Clin Epidemiol*. 2012;4:1-11. doi:10.2147/CLEP.S16747

15. Wu S, Powers S, Zhu W, Hannun YA. Substantial contribution of extrinsic risk factors to cancer development. *Nature*. 2016;529(7584):43-47. doi:10.1038/nature16166

16. Richman EL, Carroll PR, Chan JM. Vegetable and fruit intake after diagnosis and risk of prostate cancer progression. *Int J Cancer J Int Cancer*. 2012;131(1):201-210. doi:10.1002/ijc.26348

17. Allott EH, Masko EM, Freedland SJ. Obesity and Prostate Cancer: Weighing the Evidence. *Eur Urol*. 2013;63(5):800-809. doi:10.1016/j.eururo.2012.11.013

18. Szymanski KM, Wheeler DC, Mucci LA. Fish consumption and prostate cancer risk: a review and meta-analysis. *Am J Clin Nutr*. 2010;92(5):1223-1233. doi:10.3945/ajcn.2010.29530

19. Sormunen J, Bäckmand HM, Sarna S, et al. Lifetime physical activity and cancer incidence--a cohort study of male former elite athletes in Finland. *J Sci Med Sport*. 2014;17(5):479-484. doi:10.1016/j.jsams.2013.10.239

20. Lee IM. Physical activity and cancer prevention--data from epidemiologic studies. *Med Sci Sports Exerc*. 2003;35(11):1823-1827. doi:10.1249/01.MSS.0000093620.27893.23

21. Sormunen JTJ, Arnold M, Soerjomataram I, Pukkala E. Effects of physical condition and body composition on cancer risk in a nationwide cohort of 31,158 men from Finland. *J Clin Oncol*. 2017;35(15_suppl):1565-1565. doi:10.1200/JCO.2017.35.15_suppl.1565

22. Cerhan JR, Torner JC, Lynch CF, et al. Association of smoking, body mass, and physical activity with risk of prostate cancer in the Iowa 65+ Rural Health Study (United States). *Cancer Causes Control*. 1997;8(2):229-238. doi:10.1023/A:1018428531619

23. Le Marchand L, Kolonel LN, Yoshizawa CN. Lifetime Occupational Physical Activity and Prostate Cancer Risk. *Am J Epidemiol*. 1991;133(2):103-111. doi:10.1093/oxfordjournals.aje.a115849

24. Giovannucci E, Leitzmann M, Spiegelman D, et al. A Prospective Study of Physical Activity and Prostate Cancer in Male Health Professionals. *Cancer Res*. 1998;58(22):5117-5122.

25. Sormunen J, Talibov M, Sparén P, Martinsen JI, Weiderpass E, Pukkala E. Perceived Physical Strain at Work and Incidence of Prostate Cancer – a Case-Control Study in Sweden and Finland. *Asian Pac J Cancer Prev APJCP*. 2018;19(8):2331-2335. doi:10.22034/APJCP.2018.19.8.2331

26. Richman EL, Kenfield SA, Stampfer MJ, Paciorek A, Carroll PR, Chan JM. Physical Activity after Diagnosis and Risk of Prostate Cancer Progression: Data from the Cancer of the Prostate Strategic Urologic Research Endeavor. *Cancer Res*. Published online May 24, 2011. doi:10.1158/0008-5472.CAN-10-3932

27. Kenfield SA, Stampfer MJ, Giovannucci E, Chan JM. Physical Activity and Survival After Prostate Cancer Diagnosis in the Health Professionals Follow-Up Study. *J Clin Oncol*. 2011;29(6):726-732. doi:10.1200/JCO.2010.31.5226

28. Thorsen L, Courneya KS, Stevinson C, Fosså SD. A systematic review of physical activity in prostate cancer survivors: outcomes, prevalence, and determinants. *Support Care Cancer*. 2008;16(9):987-997. doi:10.1007/s00520-008-0411-7

29. Cormie P, Galvão DA, Spry N, et al. Can supervised exercise prevent treatment toxicity in patients with prostate cancer initiating androgen-deprivation therapy: a randomised controlled trial. *BJU Int*. 2015;115(2):256-266. doi:10.1111/bju.12646