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# AL- KINDY COLLEGE MEDICAL JOURNAL

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***Manuscript Preparation:***

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The journal embraces the so-called "IMRAD" structure (Introduction, Methods, Results, And Discussion). Manuscripts should be divided into:

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**Abstract**: manuscript submission should contain an abstract of up to 250 words in a structured form, consisting of:

- **Background:** provide the motivation for the study.
- **Objective:** state the study's purpose.
- **Subjects and Methods**: basic procedures including selection of participants, settings, measurements, and analytical methods.
- **Results:** address the main findings, giving specific effect sizes and their statistical and clinical significance (if possible).
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**Keywords:** 3-5 keywords for indexing purposes.

## Introduction

- It should summarize the motivation (the nature of the problem and its significance) and offers a concise research background, but not a meticulous review.
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- Do not include any results or conclusions from the work being reported.

## Subjects and Methods

- Should provide a comprehensive protocol of the study involving; design type, setting and duration of the study, sample groups definition (eligibility, inclusion and exclusion criteria) interventions and investigations performed throughout the study (however, methodological details previously published are not needed).
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- Specifications (including the manufacturer, city, and the country) should be given for the main drugs, chemicals, and instruments.
- The statistical methods used in analyzing study results should be indicated and statistical significance should be identified. Moreover, define statistical terms, abbreviations, symbols, and specify the statistical software package and version used.
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- Should be presented in logical sequence to reveal the main or most important findings first.
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- Do not repeat in details data or other information given in other parts of the manuscript, such as in the introduction or the results sections.
- It is useful to begin the discussion by briefly summarizing the main new and important outcomes, and then explore possible mechanisms or explanations for these findings.
- Compare and contrast the results with other relevant studies, in the context of the entirely of the best available evidence (evade citing references that do not have a close relationship with the present result).
- State the limitations of the study and explore the implications of the findings for future research and for clinical practice.

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- Link the conclusions with the goals of the study but avoid unqualified statements and conclusions not adequately supported by the data (in particular, distinguish between clinical and statistical significance, and avoid making statements on economic benefits and costs unless the manuscript includes the appropriate economic data and analysis).

- Avoid claiming priority or mentioning work that has not been completed.
- Whenever warranted, state new suggestions and recommendations, but make them as simple and clear as possible.

**Acknowledgments**

- If present should be placed in a separate section after the conclusion.

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- 20-40 references should be stated for original articles.
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- References to journal articles should include, in order (1) authors (expecting a maximum of 3 author names before 'et al ' , (2) title, (3) journal name (as abbreviated in MEDLINE), (4) year of publication, (5) volume and issue number, (6) page numbers.
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***Journal article:***

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***Book chapter:***

Herring JA. Limb Deficiencies. In: Herring JA, Tachdjian's Pediatric Orthopeidatrics, 4th ed. Philadelphia (PA): Saunders Elsevier; 2008, p.1983-2023.

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3- Introduction: Provide the impetus for reporting the study.
4- Case presentation: should consist of a full description and information about the case that was available only at presentation.
5- Comprise in a logical sequence all the tests performed as part of the management.
6- Treatment: comprised in a logical sequence all the interventional performed as part of the management.
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9- Discussion, conclusion, acknowledgment (if applicable), and references, 5-10 references should be stated.
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## Editorial



## Review Articles



## Research Articles

## Commentary

**Al-Kindy College Medical Journal (KCMJ)**

*Editorial*

# The Impact of Personalized Medicine on Enhancing Quality of Life in Chronic Diseases Management

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**ABSTRACT**

Personalized Medicine represents a revolution in healthcare practice, focusing on tailoring different therapies to be precise for a specific individual; this is aided by exploring the number of genetic predispositions and lifestyle choices that fit each individual. In this article, the authors utilize and gather recent literature and opinions to discuss the impact of personalized medicine on chronic disease management and patient quality of life with additional attention paid to deal with limitations and possible ethical issues. Chronic diseases such as Hypertension, Diabetes, and chronic kidney diseases adversely affect multiple health indicators, including Quality of Life (QoL) and well-being. This will have additional impacts on physical and mental health that require further mitigations and to deal with more ongoing mental health. Personalized medicine is a revolutionary step that could be used to manage chronic disease by improving patients' QoL through tailored treatments. However, it is crucial to handle equity, ethics, and the limitations in infrastructure issues.

## Introduction

Personalized Medicine represents a transforming period in health practice, making a shift in disease management from the traditional to a precise and tailored approach that fits each individual [1-2].

Chronic diseases, such as hypertension, diabetes, and chronic renal diseases, have a negative impact on a variety of health indices, including quality of life and overall well-being. Additionally, there will be effects on both physical and mental health, which will necessitate further preventative measures and the management of more ongoing mental health issues [3-5].

**Modulating Effects on Chronic Disease Management**

In the context of chronic diseases, Personal Medicine addresses individual differences in responding to therapies; this is addressed through the customization of treatment plans to fit each patient separately.

**Designed Interventions:** By utilizing genomic information, biomarkers related to a specific condition can be used to predict disease progression and outcome. For example, the Presence of the apolipoprotein E (APOE) genotype, including three alleles (e2, e3, e4), is linked to a higher risk of developing dementia and cardiovascular events; additionally, e4 alleles are linked to higher low-density lipoprotein cholesterol levels resulting in high cardiovascular events, tailoring medicine could be beneficial to target these specific patients. Another example, Tirzepatide, a Dual-Acting Insulinotropic Polypeptide, may be adjusted for specific patients with obesity and Type 2 Diabetes Miletus by using different doses tailored

for each patient with the possibility for future trials for more promising Tirzepatide and other antidiabetic drugs combinations [6-8].

**Proactive Care:** Personalized medicine enables healthcare to transition from reactive to proactive approaches. Wearable devices combined with artificial intelligence enable early disease exacerbation detection, which leads to prompt medical interventions. Proactive methods enable patients to manage their health independently, which leads to better QoL.

**Pharmacogenomics (Medication Optimization):** Treatment acts differently through different gene expressions influencing drug metabolism; therefore, optimal drug selection and dosing could be adjusted. For example, trastuzumab could be used for patients with breast cancer showing overexpression of Human epidermal growth factor receptor-2 (HER2), a protein that promotes malignant cell growth. Additionally, recent evidence shows a relation between HER2 and poor prognosis of gastric malignancy. All these will aid in tailoring drug selection toward each specific group of patients [9].

### Improving Quality of Life: A Focus on Patient-Centered Approaches

QoL includes aspects of well-being, emotional, and social components that contribute to overall life satisfaction; the influence on these domains is complex and involves a wide range of experiences [3].

**Physical Well-Being:** Improving symptom management and eliminating side effects enhance physical functioning. Additionally, personalized insulin treatments and ongoing glucose monitoring in customized diabetic care plans to improve glycemic control and lower complications.

**Emotional Resilience:** Several negative consequences associated with chronic illnesses can cause psychological distress. Personalized medicine will help patients feel confident and reassured by offering individualized, evidence-based treatment plans.

**Social Engagement:** Improved health results empower patients to engage in essential social activities, reducing feelings of isolation often associated with long-term illnesses.

### Limits and Ethical Concerns

Although promising, the integration of personalized medicine presents major ethical issues [10-11].

**Equity in Access:** Different therapies and instruments used to implement Personalized Medicine may be expensive and make it difficult for many individuals to access them. Authorities should act to equal healthcare services to individuals and minimize variations in accessibility [12].

**Data Privacy and Ethics:** As the aspect of personalized medicine deals with genetic and health data related to each patient, ethical issues raised concerning data security which need to be addressed correctly.

**Healthcare Infrastructure**: To be implemented, personalized medicine requires investment in genomic databases, bioinformatics, and clinical training. However, limited funds may make further improvements in this field difficult [10,13].

## Future Perspectives

The integration of artificial intelligence with recent advancements in genomics and digital health has the potential to improve the outcomes of patients with chronic diseases enhancing individuals' quality of life. The Human Genome Project promises to demonstrate the potential for global information exchange to accelerate progress. Furthermore, patient education and empowerment will be crucial. Involving patients as active partners in their care promotes collaborative decision-making and enhances compliance with individualized treatment programs.

## Conclusion

Personalized medicine is set to revolutionize chronic disease management by improving patients' QoL through tailored treatments. Nonetheless, handling issues involving equity, ethics, and infrastructure is crucial for its wide application. By synchronizing technology with diversity, personalized medicine can realize its transformational promise in global healthcare.

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**Conflict of Interest**

Authors declare no conflict of interest.

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Al-Kindy College Medical Journal (KCMJ)

*Review Article*

# Regenerative Medicine with Recombinant Human Granulocyte-Colony Stimulating Factor: Insights and Applications

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**ABSTRACT**

Regenerative medicine is an interdisciplinary approach which introduces treatment modalities that mimic natural biological mechanisms. These treatment modalities include growth factors, cytokines modulation of the signaling cascade, and customized tissue engineering therapies with the least invasive methods. Granulocyte colony-stimulating factor (G-CSF) is a hematopoietic cytokine that enhances granulocyte lineage cell proliferation, differentiation, and activation. Evidence-based studies have analyzed the effect of using recombinant human rh G-CSF on stem cell and progenitor cell recruitment and tissue repair and regeneration via anabolic protein upregulation and antiapoptotic mechanism enhancement. Promising regenerative effects of rh G-CSF administration have been reported in medical fields, such as providing long-term effects of neuroprotection in Parkinson's, Huntington's, and Alzheimer's diseases, ischemic disease, wound healing, diabetic foot repair, cardiovascular disease, reproductive biology, liver disease, and osteoid tissue regeneration.

## Introduction

The regenerative field integrates numerous technological approaches and replacement modalities accomplished by multiple strategies involving surgery and prosthetic devices, including hip replacements and adjuvant biomaterial scaffolds. Organ and bone marrow transplants also play significant roles in regenerative medicine [1]. However, these treatments could lead to side effects that prevent patients from being considered in a "natural health" state post-treatment. For instance, organ transplant recipients often require immunosuppressive drugs, metal hip replacements might loosen over time, biomaterial scaffolding for tissue growth could induce inflammation, and bone marrow sources could vary in quality and might be contaminated during cell extraction procedures [2].

Regenerative medicine primarily depends on human cells, such as somatic cells, adult and embryonic stem cells, and those obtained from sources like the placenta, adipose tissue, and urine. Contemporary regenerative techniques incorporate a blend of cutting-edge technologies, advancing beyond conventional transplantation and tissue replacement [3]. These methods include molecular therapies, transplantation or activation of stem cells, tissue engineering, and preparing the human body to maximize safety and effectiveness. Such innovations aim to improve therapeutic outcomes and accelerate the transition of regenerative therapies into clinical practice, offering promising advancements [4,5].

**Host environment modulation in the regenerative medicine approach**

For any regeneration strategy to support function and tissue architecture effectively, it must achieve a harmonious integration in host innervation, vascularization, and the immune system [5]. Vasculature development during angiogenesis is facilitated by key angiogenic growth factors, such as vascular endothelial growth factor (VEGF), angiopoietin (Ang), platelet-derived growth factor (PDGF), and basic fibroblast growth factor (bFGF). Enhancing the host's regenerative potential by modulating its environment, whether through the administration of growth factor proteins or allogenic molecules, could trigger therapeutic responses indirectly [6]. This approach might involve activating a cascade of additional growth factors, followed by anabolic interactions with the host's target cells. These therapeutic protein analogs present notable advantages for pharmaceutical development. Protein products have a lower risk of toxicity and facility regarding route of administration and risk-benefit effect, and they could be more cost-effective to formulate and manufacture [7]. Thus, therapeutic strategies, such as growth factors and /or pluripotent stem cell induction, are among the blockbuster products of biotechnology [8].

**Granulocyte-colony stimulating factor**

G-CSF is a polypeptide glycoprotein produced by fibroblasts, bone marrow cells, connective tissue cells, macrophages, endometrial cells, and natural killer (NK) cells. It targets neutrophil precursors and mature neutrophils [9]. In its natural state, G-CSF has a three-dimensional structure. Its protein is made up of four helices that are linked together by amino acid loops [10]. G-CSF was initially cloned and first isolated from mice in 1983, followed by successful isolation outside the human body in 1986 [11]. rhG-CSF from a 175 amino acid sequence with two disulfide bonds has a molecular weight of 18,798.88 and molecular formula C845H1339N223O243S9 [12]. It is structurally different from the original G-CSF in terms of the total number of amino acids (presence of methionine at the "0" site) and the absence of a glycoside chain [13]. The control of neutrophil induction and proliferation is the main function of G-CSF in a healthy person. In addition, it has a role in regulating granulopoiesis via increasing granulocyte lineage cell proliferation and differentiation activation by interacting with its receptor located on the cell membrane [14]. There has been mounting interest in utilizing rhG-CSF to mobilize CD34+ hematopoietic stem cells from the stem cell-generating cells into the bloodstream.

Peripheral blood stem cells (PBSC) for use in hematopoietic transplantation in place of bone marrow [15], rh G-CSF, a genetically engineered drug, was granted endorsement from the US Food and Drug Administration (FDA) in 1991, which could be used in numerous aspects [16]:

- Treat severe congenital neutropenia [17].
- Used with patients receiving myelosuppressive anticancer medications to decrease the risk of infection (as manifested by febrile neutropenia).
- Enhancement of hematopoietic recovery after bone marrow transplantation [18].
- In healthy donors, rh G-CSF facilitates the growth, maturation, and survival of hematopoietic cells by regulating the expression of stromal-derived factor-1 (SDF-1) in bone marrow [19].

An average-sized adult generates approximately 120 billion granulocytes daily to replace the regular losses and support the regeneration of circulating neutrophils 20.

The production capacity of G-CSF may be amplified by at least 10-fold during strain environments such as injury or pathogen exposure to regulate the neutrophil response to inflammatory stimuli with effective anti-inflammatory properties [21]. As mentioned, the G-CSF is the fundamental influencer of neutrophilic granulocyte production regulation. This biological process establishes the framework for host defense systems [22]. Also, rh G-CSF has been found to enhance the availability of circulating hematopoietic stem cells to the heart, brain, and osteoid tissue as well as their capacity for mobilization and proliferation and promote the differentiation of mesenchymal stem cells derived from marrow to stimulate vascularization, innervation and to boost the anti-inflammatory properties [23].

**Biological role of G-CSF**

The G-CSF is a well-known hematopoietic cytokine, and G-CSF's biological effects are not confined to hematopoietic tissues; it has a wide variety of immunomodulatory functions, including the ability to enhance migratory activity, survival, and regeneration of many cellular elements in a dose-dependent manner [24]. G-CSF promotes the production of interleukin-10 by CD4+ and CD25+ regulatory T cells, which is utilized in higher macro-organism tolerance of the graft. Thus, the immunological tolerance is linked to the level of IL-10 production by T cells [25]. Recently, more evidence of rh G-CSF's immunoregulatory influence, particularly its effects on T cell function, has been obtained [21] (Figure 1).

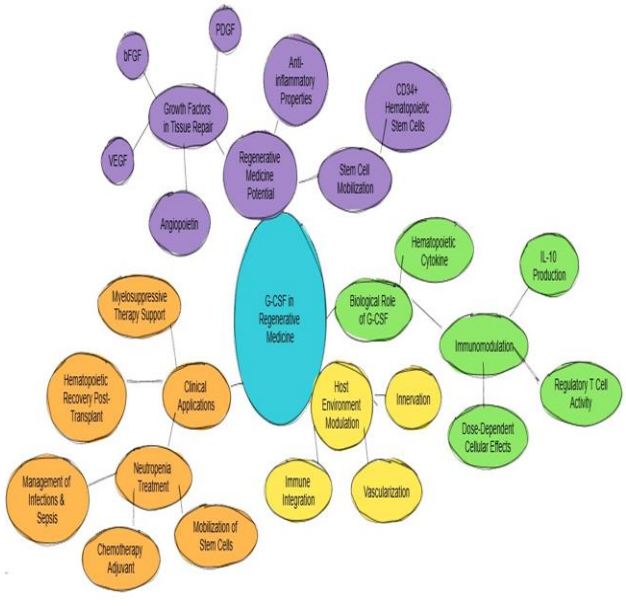


**Figure 1:** Overview of granulocyte-colony stimulating factor (G-CSF) in regenerative medicine. The diagram highlights the essential roles and applications of G-CSF, emphasizing its contributions to the host environment modulation through vascularization, immune integration, and innervation.

**Roles of rh G-CSF in clinical practice**

**1- Treatment of neutropenia**

The guidelines protocol of clinical practice recommends using rh G-CSF before hematopoietic stem cell transplants as a therapeutic approach to mobilize peripheral blood progenitor cells from healthy donors [26]. It is used in boosting the neutrophil recovery after consolidation chemotherapy in peripheral stem cell/bone marrow transplants in patients undergoing myelosuppressive chemotherapy for solid tumors and blood cancers, and myelogenous leukemia [27], and management of neutropenia caused by various diseases such as genetic disorders or immune deficiency syndrome [28]. The rh G-CSF could also be used as an adjuvant therapy, like in the case of neutropenia linked with medication-induced agranulocytosis, neonatal bacterial sepsis, pneumonia, infection, and burns [29].

**2- Treatment of cardiac diseases**

Recently, the rh G-CSF has been investigated to induce stem cells into the peripheral bloodstream to see if it could help with stroke [30], myocardial infarction, and congestive heart failure by either mobilizing the stem cells or its effect on reducing cells' apoptotic rate, improving mitochondrial function, angiogenesis enhancement, and fibrosis mechanism regulation [31].

**3- Neuroprotective role of rh G-CSF**

In neurology, the rh G-CSF has been utilized as a neuroprotective factor because of its unique properties, including anti-inflammatory effects, antioxidant and anti-apoptotic properties [32]. Long-term neuroprotective properties of the rh G-CSF have been shown in Alzheimer's, Parkinson's, and Huntington's diseases by suppressing brain shrinkage, initiating somatic growth, and strengthening neurocognitive processes such as short-term memory, motor functions, reflexes, and muscle strength [33].

**4- Immunomodulation role of rh G-CSF**

After myelosuppressive chemotherapy, when rh G-CSF is injected in combination with epithelial growth factor, it will regulate hematopoietic stem cell regeneration and proliferation [34]. In addition, to avoid febrile neutropenia (FN) events in patients with cell lung cancer, non-Hodgkin lymphoma, or breast cancer, the rh G-CSF as prophylaxis is regarded as a cost-effective modality for receiving therapy for patients who were at risk for FN [35].

Another regenerative property was reported in a meta-analysis by Qiu and colleagues in 2023, which proposes that rh G-CSF treatment has the potential for acute-on-chronic liver failure therapy, with significant improvements in liver function and survival rates [36].

**5- Role of rh G-CSF in reproductive medicine**

In the last several years, many meta-analyses and in-depth reviews have reported that rh G-CSF contributes significantly to successful pregnancy and decreases the abortion and infertile rate; this could be a viable option for women facing infertility who are undergoing in vivo fertilization (IVF) and experiencing thin endometrium or recurrent implantation failure [37-42]. Meng and colleagues studied the effect of intrauterine rhG-CSF infusion on the successful rate of pregnancy outcomes in patients with repeated implantation failure. The implantation success rate (28.44% vs. 12.44%, p = 0.012) and clinical pregnancy rate (48.95% vs. 27.35%, p = 0.011) in the rhG-CSF group were significantly higher than those in the control group [43].

**6- Role of rh G-CSF in osteoid tissue healing**

Regarding skeletal tissue repair, upon completing five consecutive doses of rh G-CSF, there was a substantial rise in CD34+ bloodstream cells [18], which could be distinguished into osteogenic, including vasculogenic, lineages [44]. Froberg et al. suggested that rh G-CSF stimulates osteoblastic activity via its ability to elevate bone formation indicators such as osteocalcin, bone-specific alkaline phosphatase enzyme, and transforming growth factor (TGFβ1), which has a positive effect on fracture healing [45]. Furthermore, rh G-CSF, when administered parenterally, neutralizes the negative consequences of non-steroidal anti-inflammatory drugs on bone repair. Moreover, the synergy between rhG-CSF and stem cell factor significantly improved osteoblast activity. It promoted local blood vessel formation, facilitating the regeneration of necrotic bone tissue and enhancing bone mechanical strength [46.47]. The mesenchymal stem cells activated by rhG-CSF led to elevated mRNA expression of bone morphogenetic protein (BMP2), a key regulator in bone formation and healing [48]. Several studies have explored the impact of administering rhG-CSF via injection on fracture healing in animal models [18], demonstrating that rhG-CSF enhanced bone healing in rats. However, the dosages in these experiments were 2.5 to 5 times higher than the standard dose recommended for human clinical use in healthy individuals [18]. Previous research has also highlighted that rhG-CSF administration significantly enhanced the healing of femur fractures, suggesting its potential application in human clinical procedures, such as planned osteotomies and fracture treatment [49,50]. In distraction osteogenesis experiments using a rat model, it has been indicated that the rh G-CSF administration speeds up the bone-healing process and regulates the release of progenitor cells [51]. Furthermore, Looi et al stated that the administration of rh G-CSF, besides inducing hematopoiesis, promotes fracture healing as well as non-union bone defects [52]. Since the rh G- CSF primarily targets neutrophil precursors and mature neutrophils [9], it also could enhance bone formation in an indirect mechanism by the role of neutrophil, as proved that the interaction between neutrophil and bone mesenchymal stem cells, leveraging innate and adaptive immune mechanisms could lead to the design of pioneering biomaterials that boost self-driven bone repair [53]. Additionally, the neutrophil cells which are stimulated by rh G-CSF injection have shown pro-angiogenic characteristics, this particular group of angiogenic neutrophils secretes matrix metalloproteinase-9 into the extracellular matrix to release pro-angiogenic growth factors, VEGF and FGF-2 into the extracellular matrix, which promote angiogenesis and in turn enhance bone regeneration [54]. All previous evidence-based studies reported the significant anabolic efficacy of rh G-CSF in enhancing osteoid tissue regeneration.

**Bidirectional effect of rh G-CSF**

The rh G-CSF has a bidirectional effect on osteoclast in a dose-dependent manner. Walsh and Choi stated that in a low dose of rh G-CSF, activated cells of the adaptive immune system, B lymphocytes, which are responsible for producing approximately more than half of the bone marrow-derived osteoprotegerin, which in turn inhibits osteoclast differentiation. In contrast, in heavy dose rh G-CSF; B lymphocytes activating osteoclast formation and enhance bone

resorption [55]. Furthermore, Oshitani and coworkers reported that injection of a heavy dose of rh G-CSF (250 µg/kg/day) intraperitoneally every 12 hours for 4 days before tooth extraction in a rat model might delay socket bone healing post-extraction by affecting bone metabolism, specifically through the inhibition of osteoblast activity and the increase of osteoclast activity [56].

**Side effects of rh G-CSF**

Typically, the rhG-CSF is widely accepted and safe in healthy people. Daily safe doses are 5-10 µg/kg [57]. Bone discomfort, fatigue, headach, nausea, high fever (potentially with sweating and chills), anorexia, diarrhea, and myalgia are the most frequently reported side effects of overdoses or prolonged intake [58].

**Bioavailability of rh G-CSF**

The rh G-CSF was combined with polyethylene glycol (peg-filgrastim, lipeg-filgrastim) to extend the decay rate after injection of the rh G-CSF to approximately 30–53 hours by reducing renal excretion. This made it possible to apply only once a time and avoid daily and traumatic injections until tissue regeneration is accomplished [35].

**Future embodiment and potential contributions**

Regenerative techniques utilizing biological therapies, including growth factors, cytokines, and glycoproteins like rh G-CSF, which mimic the biological anabolic action, could offer a key innovation in the oncologic field, craniofacial anomaly, congenital malformations, and traumatic injuries. Researchers work to deliver ideal treatment approaches, incessantly boosting treatment outcomes. Moreover, an international collaboration of laboratories and clinics focusing on bioengineering, backed by adequate funding, is a key to driving forward cutting-edge regenerative medicine strategies.

## Conclusion

Stem cell enhancement-based regenerative techniques could support the treatment of damaged tissue deterioration and/or irritated processes. Their mutual main goal should be to deliver safe, cost-effective, long-term effect restorative therapies widely applicable in translational medicine and interventional therapeutics. Furthermore, the potential regenerative properties of rh G-CSF in terms of angiogenesis, innervation, and immunity modulation could be utilized in biomedical tissue engineering applications. Hence, growth factors and cytokines additive will be expected to perform a key role, and the biomaterial will have complementary qualities that encourage cell development, tissue restoration, and infection prevention, ultimately leading to the growth of hybrid biomaterials for personalized scaffolds or tissue repair that fully restore tissue function [59].

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**Conflict of Interest**

The authors declare no competing interests.

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*Review Article*

# Obesity-Induced Mechanisms in Colorectal Cancer Development: A Narrative Review

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**ABSTRACT**

Obesity is a significant risk factor for colorectal cancer (CRC), influencing its development through multiple biological pathways. Elevated levels of insulin, insulin-like growth factor-1 (IGF-1), leptin, resistin, and inflammatory cytokines such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) contribute to colonic cell proliferation and tumor formation. Additionally, obesity-induced hormonal imbalances, including decreased adiponectin and ghrelin, further increase CRC risk. Changes in gut microbiota due to obesity also play a role in carcinogenesis, highlighting the complex interplay between metabolic, inflammatory, and microbial factors. This review explores the pathophysiological mechanisms linking obesity to CRC, emphasizing its role as a modifiable risk factor. Insulin resistance, chronic inflammation, oxidative stress, and dysregulated adipokine secretion are key contributors to CRC progression in obese individuals. By analyzing molecular and epidemiological evidence, this review underscores the importance of early CRC screening for obese individuals, along with lifestyle modifications such as weight loss, dietary improvements, and increased physical activity. Furthermore, microbiome-targeted interventions, including probiotics and prebiotics, may help counteract obesity-driven dysbiosis and reduce CRC risk. Emerging biomarkers and therapeutic targets offer potential for developing obesity-specific CRC treatments. Given the rising global burden of CRC, integrating preventive healthcare strategies, public health initiatives, and clinical interventions is essential for reducing its incidence and improving patient outcomes. Addressing obesity through targeted preventive measures can significantly lower CRC-related morbidity and mortality, making it a crucial aspect of cancer prevention and management

## Introduction

Colorectal cancer (CRC) provokes the scenario of serious global health concern in terms of cancer-related deaths worldwide. The fatality rates reported from CRC are surging, although there may be improvements in detection and treatment. It accounts for up to a percentage of 8–9% of all cancer-related death rates, making it accountable as the third most common yet unavoidable cause of cancer mortality [1]. In 2018, Around 4,880,000 new cancer diagnoses and 3,400,000 cancer-related fatalities were caused by gastrointestinal origin cancers (esophagus, stomach, colon-rectum, pancreas, liver), which accounted for around 26% of incidence and 34% of mortality. On the other hand, CRC accounted for about 1.8 million of the new cases. Most gastrointestinal malignancies are currently CRCs [2]. East Asia, South America, and Eastern Europe had a historically low rate

of incidence in cases of CRC, but between 1960 - 2018, that all changed due to dietary and lifestyle changes [2].

The rising incidence of CRC is strongly correlated with weight gain, which can be assessed by the comparative study of certain molecules released between lean and obese individuals as mentioned in Figure 1 below. Obesity affects the tumor microenvironment, according to recent epidemiological and molecular studies. Obesity factor is usually associated with a heightened risk of developing colorectal neoplasms, with research indicating a 26% and 47% greater risk for overweight and obese adults, respectively [3]. Intricate signaling cascades and deregulated cellular mechanisms under the influence of obesity factors assembled to generate cancer [4]. Obesity was described as a major factor responsible for a challenging metabolic disorder that affects cancer biology [5]. Chronic low-grade inflammation and obesity define it. Due to the complex interaction with adipose tissue, obesity promotes carcinogenesis by increasing adipokines, pro-inflammatory cytokines, and insulin resistance [6]. Patients with early-onset CRC demonstrate unique risk factors, wherein obesity plays a role in metabolic syndrome and intestinal inflammation, potentially expediting carcinogenesis. Chronic inflammation linked to obesity modifies macrophage metabolism, facilitating tumor growth [7].

There are certain biological interlinked mechanistic pathways which are induced due to obesity. Insulin resistance, hyperinsulinemia, and modified adipocytokine concentrations are the primary pathways connecting obesity to CRC [8]. The PI3K/AKT pathway, modulated by hormones regulated by obesity parameters, is integral to carcinogenesis [9]. Obesity, as a modifiable risk factor, interacts complexly with genetic predisposition and lifestyle factors, requiring a comprehensive approach to understanding the method needed for the prevention and thereby understanding the treatment modality required for patients with CRC.

A primary idea concerning the origin of this association suggests that being overweight causes a chronic sub-inflammatory state, which in turn causes macrophage polarization and a decrease in cells that inhibit the immune system, like T cells and natural killers [10].

The exact mechanisms driving this epidemiological shift are inadequately comprehended, necessitating an extensive inquiry into the elements influencing the onset and advancement of EOCRC. The linked concepts of obesity-based hormones like leptin and adiponectin, along with the macrophage-specific metabolite itaconate, which promotes cancer growth through many pathways involving changes in inflammatory gene expression, is one potential explanation [11].

Metabolic shifts induced by adipokines or cytokines related to obesity act as stressors, leading to tissue damage that might hasten the onset of neoplasia. Inflammation promotes cell proliferation, tumor development, growth, and metastasis after a genetic mutation activates an oncogene. CRC is a prominent neoplasm form profoundly associated with chronic inflammation. The epidemiological evidence linking obesity to CRC is reviewed in this comprehensive analysis. This review will specifically focus on recent studies, evaluate the molecular mechanism by which obesity may cause colorectal carcinogenesis, and discuss prevention and treatment.

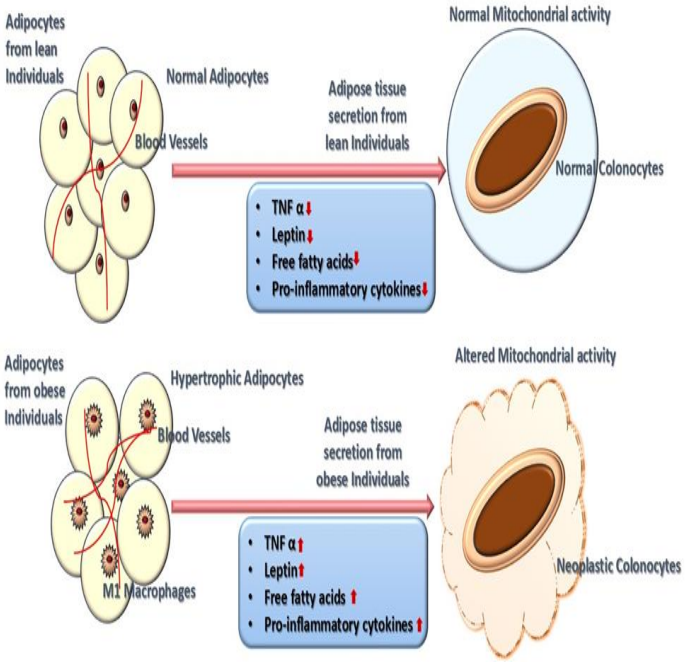


**Figure 1:** Essential molecular factors (TNF α, Leptin, Free fatty acids, Pro-inflammatory cytokines) released by adipose tissue and their comparative regulatory levels observed in lean and obese individuals

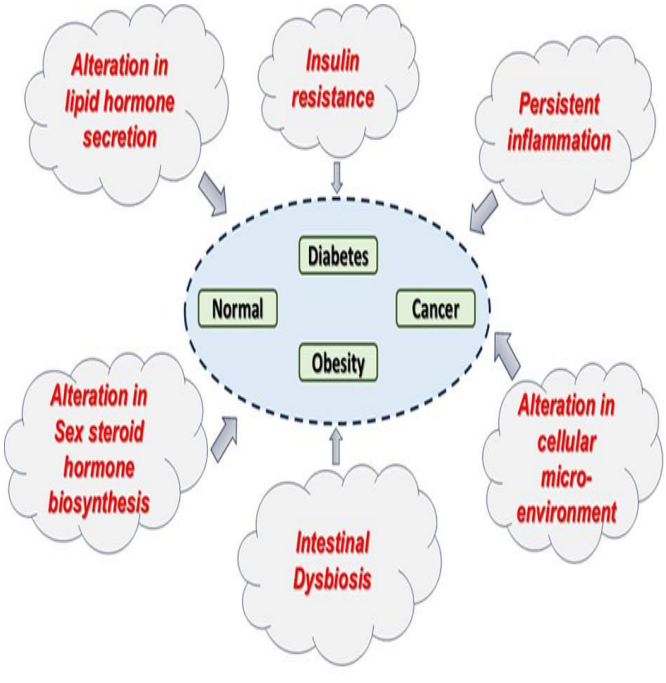


**Figure 2:** Evident obesity-based factors and their abnormal alteration accumulate so that normal cells are forced to transform into cancerous cells in CRC patients.

**Table 1:** Certain evidence from the literature review

| PAPER- (Author & Year) | Objectives | Inference |
|---|---|---|
| Arnold et al., 2020 (2) | Global Burden of 5 Major Forms of Gastrointestinal Cancer | The global burden of gastrointestinal malignancies, particularly CRC, emphasizes the need for better preventive and early detection techniques. |
| Giovannucci E., 2022 (4) | Obesity and CRC: A Review of the Epidemiological Research and its Cancer Epidemiology Biomarkers & Prevention. | CRC is way more common in obese people and has worse results. |
| Iyengar et al., 2019 (12) | Association of the body fat index and its risk factor in the development of breast cancer in postmenopausal women with a normal body mass index: A proper secondary analysis of a randomized clinical trial is carried out, and an observational study is recorded. | Obesity-CRC is linked to chronic inflammation, adipokine signalling dysregulation, insulin resistance, gut microbiome changes, and metabolic dysregulation. |
| Jiang et al., 2022 (13) | Study of 1. | Obese people have higher pro-inflammatory adipokines and lower anti-inflammatory ones, which contribute to CRC development and progression. |
| Miranda et al., 2024 (14) | Obesity and CRC | Obesity-induced dysbiosis changes gut microbiota, causing intestinal inflammation and CRC-linked genotoxic chemicals. |
| Liu et al., 2019 (15) | Association of obesity as a base factor with risk of developing early-onset CRC (EOCRC) among women | Women with obesity are more likely to develop early-onset CRC, emphasizing the need to address obesity as a modifiable risk factor. |
| Singh et al., 2023 (1) | Harnessing the gut microbiome and CRC prevention: A review specifying current knowledge and future directions | Modulating gut microbiome diversity and function may reduce obesity-related CRC risk. |
| Colombo et al., 2022 (16) | Obesity-Associated Alterations in the gut microbiota composition and metabolite profile: Implications for CRC progression and therapeutic targeting. | Obesity-associated biomarkers predict CRC incidence, prognosis, and treatment response in longitudinal investigations, highlighting their therapeutic potential in personalized therapy. |
| Otani K et al., 2017 (17) | Adiponectin in gastrointestinal diseases. | Adiponectin, an anti-inflammatory adipokine, protects against gastrointestinal illnesses, suggesting it may treat obesity-associated CRC. |
| Xu, Yang et al., 2024 (18) | Role of tumor in obesity-associated CRC Progression and therapeutic resistance | A comprehensive investigation of obesity-associated biomarkers shows various molecular subtypes of CRC with varying therapy responses, emphasizing the necessity for obesity-specific treatment. |
| Jones, et al., 2024 (9) | Metabolic reprogramming in obesity-associated CRC: Therapeutic implications and future directions. | Adding obesity-associated biomarkers to CRC screening methods enhances early detection and risk stratification, especially in obese people. |
| Himbert et al., 2017 (19) | The Impact of Obesity on the Tumor Immune Microenvironment in CRC: Implications for Immunotherapy Response and Resistance | Integrating obesity-related biomarkers into standard clinical practice and population screening initiatives is feasible and economically viable, with the potential to reduce the burden of CRC occurrence in obese populations. |

The role-play of such variable factors is involved in addressing the events of development into CRC. Obesity plays a pivotal role in being the actual baseline risk factor for the development of CRC, with several studies demonstrating its influence on both incidence and prognosis. The complexity involved in the association between the two factors that is obesity and CRC is quite a lot complex, so we can think of encompassing various epidemiological findings linked to interrelated molecular pathways. Obesity-related gut microbiota changes lead to the cause of CRC development risk, thereby highlighting the complex link between host metabolism and the intestinal microbiome in cancer etiology [20].

Pathophysiology factors induced by obesity for CRC development.

As genetic alterations accumulate, normal colonic epithelium becomes dysplastic. Numerous complicated pathophysiological parameters are indulged in mechanistic pathways which involve multiple variables in carrying forward the carcinogenic events from the normal epithelium of the colon and rectum. Connected processes include an increase in the concentration range and bioavailability of

insulin and insulin-like growth factor IGF-1; abnormal secretion of adipokines; chronic inflammation; elevated levels of locally produced sex steroids (such as estrogen); altered immune response; oxidative stress; and the composition of the colony of microflora in the intestines [21], all mentioned in Figure 2. Possible associations between obesity and metabolic dysfunctional syndrome categorization, insulin resistance mechanism with an altered form of lipid metabolic issues, endocrine abnormalities, and oxidative stress all together contribute towards the procedure leading to the actual development of CRC [22].

**Obesity & the inflammatory molecules-derived pathways**

The relationship between inflammation and CRC is well established, indicating that inflammatory mediators may significantly contribute to the onset of CRC at younger ages. Variants of CRC, including those arising from the sporadic microsatellite instability pathway and other epigenetic mutations, have been associated with inflammatory processes. These processes may occur before tumour development, result from tumours inducing an inflammatory response in the host, or arise from therapeutic interventions [23]. Chronic inflammatory processes, such as infections associated with irritable bowel diseases creating infectious conditions intertwined with several environmental factors like smoking and suboptimal dietary habits, have been an evident scenario to increase the observational developmental risk of CRC [23,24].

Inflammation that results in DNA damage occurs due to the imbalanced activation of cytokine receptor-mediated aspects of signaling pathways, which include the promotable chain auto-activation of major cellular components like nuclear factor kappa-light-chain-enhancer of activated B cells component (NF-kB), secondly that of tumor necrosis factor (TNF), and specific interleukin-1 (IL-1) [23,25]. Interleukin-1 (IL-1) functions as a major key factor in the activation of inflammatory mediators among the synthesized factors by stroma-based cells, monocytes, and mainly in the tumor epithelial cells, significantly contributing to the initiation and progression of cancer [25]. These processes are involved in the actual regulation of events which lead to tumor initiation and mode of progression. Interleukin-1 (IL-1) hereby also activates the STAT3 signaling pathway to get initiated. Inflammation is capable enough to lead direction towards the epigenetic modifications that can result in accordance deactivation of major prominent factors like tumor suppressor faction form of genes, such as IL-1β, IL-6, and TNF, which are involved in the regulation of major DNA methyltransferases within specific forms of the classical p53 and NOTCH pathways [23,26-27]. Inflammation undermines the integrity and hampers the intestinal barrier, exposing the actual intestinal stem cells to environmental pathogenic entities and increased interaction with gut microbiota, including bacteria that may facilitate tumorigenesis. It facilitates getting forward with events associated with tumor progression via the involvement of the hypoxia condition and thereby the recruitment of a certain group of myeloid plus lymphoid cells within the tumor microenvironment condition is certain. Hypoxia activates fibroblasts associated with cancer by enabling the synthesis of hypoxia-inducible factor 1-alpha (HIF1Σ). Because of this mechanism, chemokines like that of transforming growth factor-beta (TGFβ) are released into the tumor microenvironment (TME), which leads to a greater variety of cells inside it. Reducing the body's natural immune defence, increased adipose tissue causes hypoxia, which inhibits the creation and development of T cells [23,28]. CRC begins with inflammation and advances due to it. Inflammatory processes have long been linked to CRC onset; however, not all inflammatory processes have been linked to early-onset CRC development [29]. The association between the sporadic form of CRC formation and the rate of inflammation is a plausible hypothesis, yet these factors have been shown in Figure 3 below.

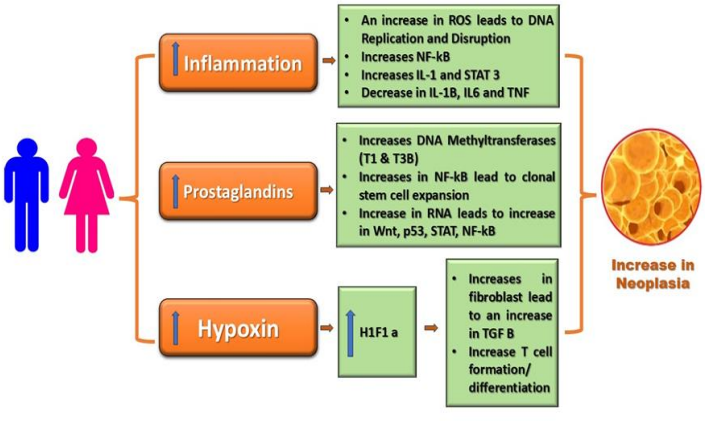


**Figure 3:** This diagram specifies the increased levels of three parallel factors involved, i.e., inflammation and prostaglandins, leading to an increase in Hypoxia condition in Obese subjects which leads to activation of a typical series of events and parameters in CRC neoplasia growth.

**Obesity-Induced Components Involved in CRC Development**

Type 2 diabetes mellitus & Insulin, insulin-like growth factors in CRC development

Obesity is associated with type 2 diabetes, which is further associated with CRC. Elevated insulin levels and insulin-like growth factor (IGF-1) correlate with enhanced proliferation of colon cells, leading to malignancy. The risk is significantly elevated in patients utilizing diabetic medications such as sulfonylureas and insulin [30]. Elevated glycated hemoglobin levels have been strongly associated with adverse clinical outcomes in CRC patients [31]. It also must be conducted and presented in a specific study with 976 individuals with a previous history of colonoscopies [32]. The findings demonstrated that individuals with DM had a greater prevalence of one or several colonic polyps and cancers than those without the condition [32]. Increased observation in insulin and glucose levels can develop the function to carry out the translocation and thereby induce the up regulatory factor of Rho-associated protein kinase 1 (ROCK-1)-tyrosine kinase-mediated pathway involvement, leading to the activation of proliferating cell nuclear antigen (PCNA) and subsequent centrosome mediated amplification, which is linked to an increased probability of carcinogenesis [33-34]. Insulin, insulin-like growth factor (IGF), insulin receptor (IR), signaling pathways, and IGF-binding protein contribute to cell-mediated proliferation and the inactivation of apoptosis, thus enabling carcinogenesis [35]. These

factors are mentioned and are affected by multiple factors, including diabetes mellitus, acromegaly, excess energy intake, hypertriglyceridemia, dietary patterns, and obesity [36]. Numerous pathways are implicated in the progression of CRC. In obese patients, there is an overexpression of insulin and IGF, which activates the mode of the PI3K/Akt signaling pathway. This activation contributes to enhanced cell survival and evident growth, thereby promoting the amplification of the carcinogenesis process. Src is an oncogenic protein, specifically a protein tyrosine kinase is activated, and that enhances cell growth, the proliferation of cells, its survival rate, and migration [36-37]. The protein possesses multiple domains like that of SH2, SH3, regulatory tails, etc, in its inactivated state within the normal cells. Upon activation, it typically induces phosphorylation and activates the PI3K/Akt pathway, thereby facilitating the progression of CRC (36-37). IGF-1 induces another cytoplasmic degradation method of P53, a tumor suppressor gene, resulting in unregulated cell proliferation effect and neoplasia [38] mentioned altogether in Figure 4.

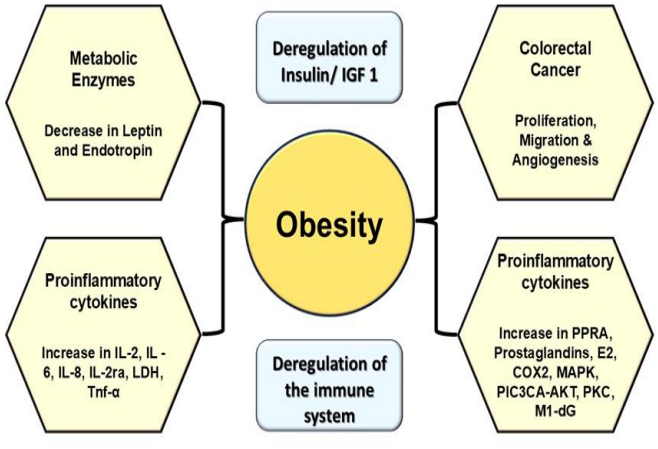


**Figure 4:** Deregulation in certain specific mechanisms: Insulin/IGF-1 factor and imbalances in the levels of immunological factors indulged in metabolic enzymes, Proinflammatory Cytokines which are majorly responsible in Proliferation, Migration and Angiogenesis phenomenon in CRC development.

**Certain Obesity-Related Hormonal Factors in CRC**

About Leptin in CRC Development

Due to its interference with signaling protein pathways along with that of the colon's adipokine receptor end, the leptin hormone contributes to the pathogenesis of CRC associated with obesity. Leptin is mostly produced by fat cells in the body and is one of many adipokines [39-40]. The signal-based protein, which acts as a transducer and source activator factor involving transcriptional, mitogen-activated protein kinase, and PI3K pathways, are among those it activates. Angiogenesis, cell proliferation/growth, and apoptosis are all aided by its activation, making it an essential player in CRC carcinogenesis. Scientific investigations have shown that different subgroups of CRC exhibit different levels of the leptin receptor, suggesting that leptin can trigger different tissue responses [41]. One potential function of the soluble leptin receptor (SOB-R) is to regulate leptin's functional properties. Interactions between SOB-R levels in the blood and the risk of colon cancer were found to be inverse in case-control research conducted by Aleksandrova et al., which included 1129 patients diagnosed with CRC and 1129 healthy controls [42]. Excessive levels of the leptin hormone, which is produced by fat cells, are commonly observed in obese people [43]. It starts a cascade of signaling pathways after regulating hunger via the Ob receptor. Resistance to the hormone leptin may develop in obese people whose blood leptin levels are already high. Activation of SOCS-3, a suppressor of cytokine signalling, decreases the actual sensitivity profile of the vagal nerve's projecting afferent dendritic branch and promotes carcinogenesis in obese individuals [43].

**Adiponectin's role in tumour initiation and CRC development**

Adiponectin is a major protein hormone secreted by adipocyte tissues, exhibiting an inverse relationship with adipocyte levels; consequently, its concentrations are reduced in individuals with obesity [44]. This promotes the AMPK pathway, which in turn curbs cell proliferation rate and retards the advancement of CRC [44]. The regulation of various cell growth homeostasis is primarily governed by the adiponectin hormone [17]. The risk of CRC is greatly exaggerated when the colonic epithelium is exposed to carcinogens and there is a drop in circulating adiponectin levels [17]. According to Yoneda et al. [45], the involvement of adiponectin receptors 1 and 2 in both normal colonic mucosa and CRC. Another study found that adiponectin has the efficiency to give protection against CRC and aids in glucose regulation by increasing insulin sensitivity, decreasing Bcl2, and starting the reactions directed towards the cell death mediated cascade through enhanced over-activation of P53 and Bax gene [46].

**Itaconate evoking immune-based factor in CRC development**

The macrophage metabolite itaconate is made up of the two main M1-like and M2-like types of macrophage structures. According to the consensus, M1-like macrophages make this chemical to control their inflammatory stress reactions [8]. Aconitate decarboxylase 1 (ACOD1) is a protein that is encoded by the gene IRG1, which is responsible for itaconate production. ACOD1 is an enzyme that converts cis-aconitate into the metabolite itaconate in the tricarboxylic acid (TCA) cycle [47]. By controlling glycolysis and inhibiting succinate dehydrogenase, it regulates cellular metabolism and causes succinate buildup. Through mediating oxidative stress reduction and promoting the components of anti-inflammatory associated transcription factors including nuclear factor erythroid-2 related factor 2 (NRF2), it a conate also serves to reduce inflammation. Several transcription factors are also affected by it, such as NF-kB, HIF1α, STAT3, and AP-1 [8,47.] Evidence suggests that peroxisome PPARγ is a need for IRG1 expression in macrophages. In peritoneal mouse macrophages, downregulation of PPARγ results in elevated IRG1 expression, indicating that PPARγ controls macrophage metabolism [8]. Furthermore, PPARγ is a very essential factor responsible for the differentiation of epithelial cells responsible for the differentiation of epithelial cells, and it has been shown that lower PPARγ expression in CRC (CRC) speeds up the pathology of CRC as mentioned in Figure 5 below.

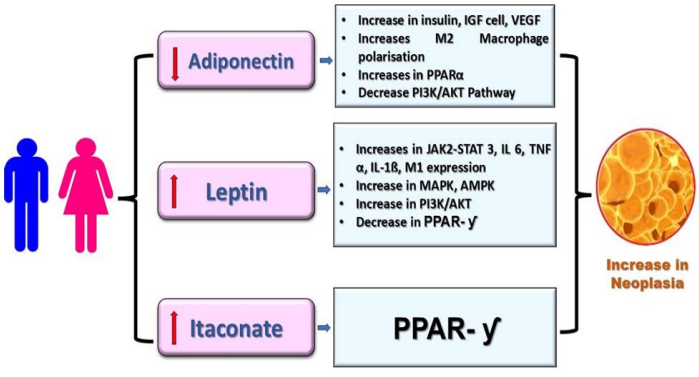


**Figure 5:** Diagram depicts the influence of hormonal components released by adipocytes showing decreased levels of Adiponectin inverse to increase in levels of Leptin and Itaconate, followed by activation of factors leading to CRC Neoplasia

**Ghrelin's Role with Accordance to CRC Development**

Ghrelin is mainly produced in the stomach, although the small intestine does release a tiny amount. Both normal and cancer cells have the potential to produce ghrelin. By binding to and activating the essential growth hormone secretagogue receptor (GHS-R), it increases the body's production of growth hormone. In the context of cancer and other critical illnesses, it helps with weight loss by maintaining energy balance. In addition, it triggers an array of signal transduction pathways (including RAS, PIK-3 form of kinases, Akt, and the mammalian target to that of rapamycin), which are essential in the development and progression of CRC [48-49].

**Resistin in CRC development**

CRC patients have levels of the adipocyte-secreted hormone resistin that are higher than normal [50]. According to Park et al. [51], the toll-like receptor-4 (TLR-4) is crucial because it can identify different parts of viruses and bacteria, trigger different immune responses, and help the host fight off illnesses caused by microbes by producing cytokines [52]. This is because resistin enhances the inflammatory response by competing with lipopolysaccharide molecules for the binding and activation of TLR-4 (53-54). Increased production of matrix metalloproteinases 1 and 2 (MMP-1 and MMP-2), as well as vascular endothelial growth factor receptors (VEGFRs), is one mechanism by which resistin increases angiogenesis and endothelial cell proliferation. According to Mu H et al. [53], resistin plays a pivotal role in the manifestation of CRC by providently activating important inflammatory pathways and promoting the angiogenesis aspect.

**Mode of estrogen-induced CRC**

Due to the periphery, the overall conversion method involved in transforming androgens to estrogen within the adipocytes, obese individuals display increased estrogen levels. Two receptor activities are quite essential, namely estrogen receptor alpha (ER-alpha) and estrogen receptor beta (ER-beta), which support this process. In CRC cells, ER-beta causes them to die off, but ER-alpha encourages them to multiply quickly. The colon's principal receptor is ER-beta, and the increased estrogen levels linked to obesity help prevent CRC by acting on this receptor [54]. In addition to improving DNA repair mechanisms, activating ER-beta reduces levels of interleukin-6 (IL-6), which has anti-inflammatory benefits. CRC (CRC) patients, including those who are overweight, have a high prevalence of estrogen receptor alpha (ER-alpha), which may have a beneficial effect on CRC progression in later life stages. A lower incidence of CRC has been linked to postmenopausal hormone replacement treatment (HRT), demonstrating the preventive function of estrogen in CRC [54].

**Role of Oxidative Stress Induced by Obesity in CRC**

Human colorectal tumours, including adenomas and carcinomas, exhibit elevated levels of various oxidative stress markers. These include increased reactive oxygen species (ROS), as measured by chemiluminescence, nitric oxide (NO), 8-oxodG in DNA, lipid peroxides, glutathione peroxidase (GPx), and catalase (CAT), alongside decreased methylation of cytosine in DNA. In addition to lipid modifications, increased leukocyte activation was observed in carcinogenic tissue [55-56], suggesting a potential role of inflammatory cells in exacerbating oxidative stress [57] Genetic abnormalities were shown to occur less frequently in the colon tissues as opposed to the rectum tissues, according to study [58]. Increased oxidative stress associated with obesity can directly and indirectly impact DNA stability, thereby influencing tumorigenesis. Specifically, under conditions of oxidative stress, DNA nucleotides are subject to oxidation. The predominant oxidative modifications in the DNA content induced by certain reactive species include factors like 7, 8-dihydro-8-oxoadenine and 8-hydroxy-2′-deoxyguanosine (8-OHdG). Guanines are regarded as the most susceptible due to their comparatively low redox potential relative to other bases [59-60]. The oxidized form of guanine bases can act as sites for replication errors leading to substitutions. There is always a probability of up to 75% that DNA polymerase will incorporate adenine in place of cytosine opposite oxidized guanine [61]. Obesity facilitates the progression and several ways for the development of CRC and much by the generation of reactive oxygen species [62-63]. Reactive oxygen species (ROS) are crucial for optimal cellular function; however, excessive levels can have harmful consequences, particularly in promoting CRC. ROS can induce DNA breaks at critical sites, including tumour suppressor genes and oncogenes [64]. Thus, it degrades the proteins involved in the regulation of cell growth and proliferation, resulting in the progression of multiple cancer types [62-63]. Obesity can lead to chronic inflammation and elevate levels of leptin, protein kinase activation, polyol pathway activation, and additional mechanisms that may elevate levels and oxidative stress within cell [64].

**Gut Microbial changes and induction mode of CRC**

Diet has an eminent role in modulating intestinal microbiota. Obesity leads to dysfunction of gut microbiota, which is linked to early-onset CRC [65]. People who suffer from Crohn's disease or ulcerative colitis may be at a higher risk of developing CRC if they have intestinal dysbiosis [66]. There are certain groups of bacterial colonization in the gut depending upon which Patients with CRC exhibit an increase in Bacteroidetes and a decrease in Firmicutes, particularly within the Clostridia class, which are responsible for fermenting dietary fiber and other carbohydrates into butyrate, a

short-chain fatty acid that mitigates colonic inflammation and carcinogenesis. Intestinal dysplasia and stem cell mutations can be accelerated by microbial dysbiosis, which in turn can cause secretion involving several inflammatory mediators such as TNF-α, ILs, and IFNs [67]. Certain microorganisms can interact with tumors through oncometabolites, which in turn promote the development of cancer [68]. In CRC patients, there has been a noticeable shift in the fecal and mucosal microbiota when quantified is observed with less ecologically varied diversity. Eleven different types of microorganisms, or once-microbes, have been found to cause cancer in humans. Notably, certain specific strains of Escherichia coli produce the component colibactin, a potent DNA-related alkylator linked to CRC [69]. Elevated levels of these 3 common microbial entities Fusobacterium, Atopobium, and Porphyromonas genera are correlated with CRC [16,70-71]. The microbiome-based pathogenesis and the increased diversity along with differentiation in normal colon epithelium, point to a likely connection between lifestyle and environmental factors involved and the elevation of microbiota colony present in response to numerous inflammatory processes that try to maintain the integrity of the gut barrier. As a suggested study by Barot et al. [72], this dysbiosis could be an indication that the microbiome helps the tumor microenvironment avoid the host's defense responses.

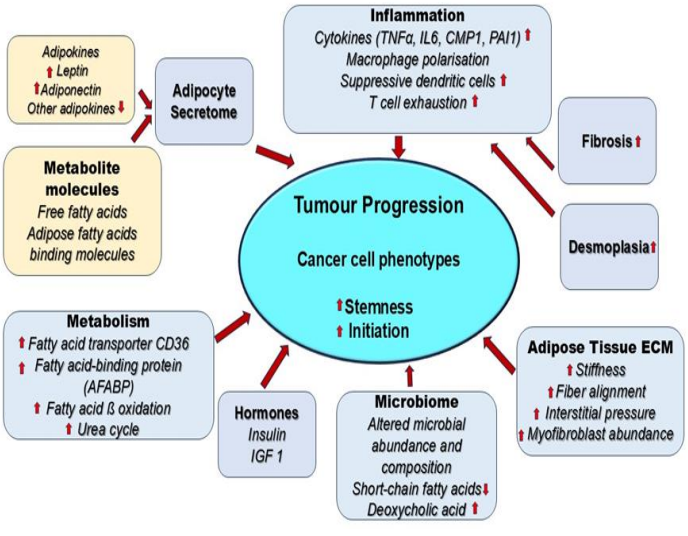


**Figure 6:** The diagram depicts the whole cumulative cross-talk networking between the metabolism of Adipocytic secretions influencing the other cell metabolic pathways and their role in tumor progression.

## Conclusion

Expanding on the risk factors and prominent processes implicated in the etiology of CRC, this article explores the instinctive relationship between the correlation of obesity and CRC in a comprehensive review manner. Factors such as insulinemia caused by obesity, increased levels of leptin and resistin in the blood and several cytokines that change the composition of the gut microbiome and lead to oxidative stress are the main drivers of the pathophysiology. Obese people should undergo regular screenings by their doctors to detect any changes in the colonic mucosa that could lead to CRC. So, the study elucidates several mechanisms contributing to CRC in individuals with obesity, as observed in Figure 6 above, some of which necessitate additional research for validation. Modifications in diet and physical activity are crucial in the development of CRC and can serve as targets for treatment and prevention strategies. The study does not address any conceptualization of the aspect of medical management.

### Recommendations

Regular screening for colorectal cancer (CRC) in obese individuals is essential, utilizing obesity-related biomarkers for better risk assessment. Lifestyle modifications, including weight loss through diet and exercise, along with a fiber-rich diet, can improve gut health and reduce inflammation. Therapeutic approaches such as adiponectin and ghrelin-based treatments, along with anti-inflammatory drugs, may help counteract obesity-driven CRC risks. Additionally, restoring gut microbial balance through probiotics and prebiotics can mitigate CRC-promoting dysbiosis. Public health initiatives should focus on raising awareness about the obesity-CRC link, implementing workplace wellness programs, and promoting obesity management to reduce CRC incidence.

Future research on obesity-associated colorectal cancer (CRC) should explore biomarkers for early detection, targeted therapies, gut microbiome interventions, and inflammation-related mechanisms. Studies on lifestyle modifications and public health strategies are essential for prevention. A multidisciplinary approach integrating molecular biology, nutrition, and clinical oncology can improve CRC management in obese individuals.

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### Conflict of Interest

The authors declare no competing interests.

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*Review Article*

# Omega-3 Supplementation is Effective in Reducing Interleukin-6 Levels After Physical Exercise: A Systematic Review

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**ABSTRACT**

Not only does physical exercise improve health, it can also trigger inflammation. Therefore, supplementation after exercise is necessary to reduce it. Omega 3 is one of the nutrients that can potentially reduce inflammation. The fundamental however, the mechanism is not well known. This study examined how omega-3 supplementation while exercise affected IL-6 levels, an inflammatory biomarker. Our systematic review analysis examined interleukin 6, inflammation, and omega 3 papers from Pubmed, Web of Science, and Science Direct during the previous five years. This systematic review assessed nine eligible papers. This research assessed standard operating procedures using PRISMA. Taking omega-3 supplements while working out has been shown to reduce IL-6 levels. IL-6 is reduced by omega-3 supplementation during exercise. So, this can be a recommendation for sportsmen in routine consumption to prevent inflammation during exercise.

## Introduction

High-intensity eccentric muscular contractions cause exercise-induced muscle damage (EMID) [1]. Due to increased inflammation, delayed onset muscle soreness (DOMS) from EIMD affects muscular strength, range of motion, and performance [2]. EIMD-induced muscle injury raises inflammatory biomarkers such as TNF-α, IL-6, IL-1, and CRP [3]. Physical activity increases nuclear transcription factor kappa beta (Nf-kB), which is impacted by ROS [4]

Myokines, signaling molecules released by skeletal muscles during exercise, benefit muscles and the body via endocrine, paracrine, and autocrine pathways [5]. High amounts of inflammatory cytokines like interleukin-6 (IL-6), which has several physiological and pathological activities, cause tissue inflammation. IL-6 is crucial to acute inflammation, especially in severe infections [6]. It also indicates viral infection [7]. persons with metabolic problems including type 2 diabetes, obesity, and chronic inflammatory illnesses like rheumatoid

arthritis have higher IL-6 levels than healthy persons [8]. During exercise, levels of IL-6, a family of myokines increase 100-fold in the blood circulation physiologically, this is as a physiological response to exercise, then IL-6 will produce a spike in the systemic, but immediately after the exercise session will return to normal levels by itself after recovery [9]. Furthermore, during physical activity, IL-6 functions as a metabolic regulator between organs by stimulating the liver to produce more glucose [10]. Liposolysis in adipose tissue is also promoted [11]. Muscle function is enhanced during single resistance exercise because the rise in IL-6 during exercise also makes it easier for muscle fibers to absorb and catabolize energy sources, such as glucose and fatty acids [12].

During physical exercise it will trigger an increase in contraction of the skeletal muscles [13]. In addition, IL-6 is produced as a "myokine" by skeletal muscle contraction; in this role, IL-6 seems to increase during exercise, studies in rats have shown to increase IL-6 when given physical exercise interventions, perhaps this increase is due to the formation of a larger energy system [14]. Which will then trigger the emergence of the training adaptation process [12]. However, in the context of exercise, IL-6 synthesis has been linked to more severe kelelahan and has been recommended to be used in a variety of exercise-related disorders [15]. However, research has demonstrated that increasing ROS causes oxidative stress (OS) to follow EIMD [16]. In this sense, exercise, which triggers acute OS and inflammatory reactions, can also control endogenous antioxidants [17]. Because OS and the inflammatory process are both directly engaged in EIMD, they must be examined and managed in tandem [18]. One strategy to lessen EIMD and avoid or reduce the consequences of OS and inflammatory processes [19].

Additional vitamins are needed to avoid exercise-related inflammation. People need omega-3 polyunsaturated fatty acids. Animal sources of DHA and EPA are more absorbable [20]. Salmon, mackerel, sardines, and tuna oil contain EPA and DHA. The body easily absorbs and utilizes long-chain omega-3 fatty acids from these marine fish [21]. Omega-3 fatty acids EPA and DHA may benefit eating disorder sufferers. Metabolic syndrome, CVD, NAFLD, diabetes, and obesity benefit from omega-3 supplementation [22]. DHA and EPA supplementation improved oxidative-antioxidative, lipid, and carbohydrate metabolism indicators, suggesting modulatory and anti-inflammatory effects [22]. For instance, EPA and DHA may reduce pro-inflammatory indicators including TNF-alpha, COX-2, IL-6, IL-8, and IL-1β [23]. Numerous studies have shown that n-3 PUFAs may also help people of different ages who regularly engage in physical activity levels maintain or improve their muscle strength [24]. Omega 3 supplementation in reducing inflammation during exercise is still not fully understood. In addition, the underlying mechanism is also not clearly understood. Therefore, this systematic review will discuss how taking an omega-3 supplement while exercising affects IL-6, one of the inflammatory indicators.

## Subjects and Methods

### Study Design

Researchers examine PubMed, Web of Science, and ScienceDirect for a comprehensive. Scientifically strong and influential publications are best collected on these venues. In the first search, duplicate articles are removed, and predetermined inclusion and exclusion criteria are used to filter.

### Eligibility criteria

The inclusion criteria the research based on five-year reviews of studies on exercise, omega-3 supplementation, inflammation, and IL-6 release. We also rejected papers that were not indexed in Web of Science, PubMed, or ScienceDirect or did not fulfill scientific validity requirements.

### Procedure

Full articles, abstracts, and titles were uploaded to Mendeley after verification and approval. The first step found 145 papers using Web of Science, PubMed, and ScienceDirect. After the second screening, 107 articles satisfied the requirements based on title relevance. After assessing titles, abstracts, and keywords, 52 articles were selected in the third round. In the last step, we carefully examined all the papers and verified that the research sample should include people, be original, focus on IL-6, contain omega-3 supplementation, and include physical activity. We sorted articles by relevancy. Nine publications that matched inclusion criteria were analyzed after a comprehensive examination. PRISMA guidelines were used for operational criteria.

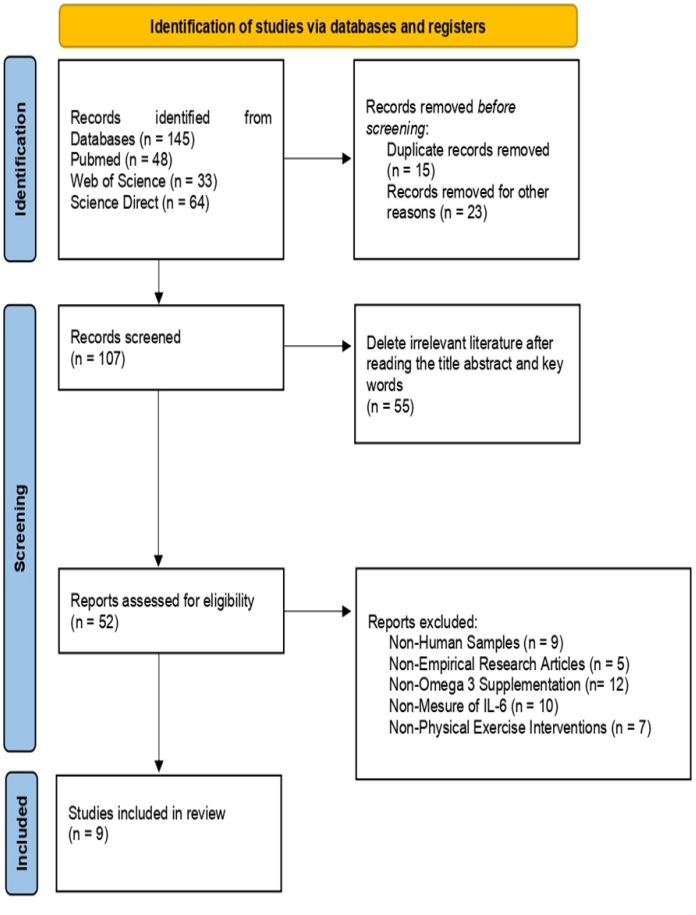


**Figure 1:** PRISMA flowchart of the article selection process

## Results

The design and intervention of the studies that were eligible for inclusion are summarized and listed in table 1

Table 1. Summary of the design and intervention of the studies

| Author | Design | Participants | Participants Age | Intervention | Outcome |
|---|---|---|---|---|---|
| (Barquilha et al., 2023) [25] | Randomized controlled trial | 21 healthy men | 20-30 years old | Pre-workout and six weeks post-workout phases of training, a single strength training session was implemented, consisting of six sets of no more than ten repetitions with a one-minute break in between sets.<br>In summary, the participants followed the following training plan: 6 sets of 10 reps with 1-minute intervals (6×10 with 1-minute intervals) for weeks 1, 3, and 6 (hypertrophy); 5×5 with 3-minute intervals for weeks 2 and 4 (strength); and 2×20 with 1-minute intervals for week 5 (resistance).<br>The participants received three fish oil capsules daily, including 606 mg of DHA and 780 mg of EPA.<br>Six weeks of supplementation were administered. | The group receiving an omega 3 + physical exercise intervention saw a significant drop in IL-6 levels. |
| (Tsuchiya et al., 2021) [26] | Randomized controlled trial | 22 healthy recreational untrained men | 19-20 years old | The fitness regimen lasted four weeks.<br><br>Participants sat on a preacher curl bench with shoulder joints at 45° flexion during eccentric contraction.<br><br>Maximal voluntary contraction torque at 90° was translated to kg for dumbbell usage.<br><br>Participants did six sets of 10 maximum elbow flexor eccentric contractions, with a 90-second rest period between sets.<br><br>After releasing the dumbbell, participants returned their arm to the starting position for the next eccentric contraction.<br><br>Participants took eight softgel capsules containing 300 mg of EPA-rich fish oil daily, totaling 2,400 mg (600 mg EPA, 260 mg DHA).<br><br>The supplementing phase lasted four weeks. | The omega 3 intervention group's IL-6 levels significantly decreased.<br>The IL-6 reduction peaked on the second day following the exercise intervention. |
| (Mullins et al., 2022) [27] | Randomized controlled trial | 38 football player | - | As usual, participants train for soccer.<br>The intervention lasted for twenty-six weeks.<br>Participants in the treatment group were told to consume 3.5 g of DHA+EPA daily. | There was a significant reduction in IL-6 levels after 26 weeks of intervention. |
| (Kyriakidou et al., 2021) [28] | Randomized controlled trial | 23 healthy, physically active males | 18-35 years | Research participants ran downhill for 60 minutes at 65% VO2max on a -10% gradient as part of the EIMD protocol.<br>During the study, RPE and HR were recorded every ten minutes.<br>Participants were seated and blood samples were taken right after the muscle-damaging bout (post-EIMD). After rating their perceived level of muscle discomfort, participants' strength and power output were evaluated using the Wingate and MVIC tests, respectively, following EIMD.<br>Omega 2 supplementation (3 g/day of n-3 PUFA) was carried out. | Twenty-four hours following the EIMD session, IL-6 levels significantly decreased. |

| | | | | | |
|---|---|---|---|---|---|
| | | | | Omega-3 supplementation included three gelatin-coated capsules daily (one taken in the morning, one at lunch, and one at night).<br>Participants took 3900 mg of fish oil daily, each capsule containing 1040 mg of n-3 PUFA, comprising 715 mg of EPA and 286 mg of DHA.<br>Each pill included 3g of n-3 PUFA for four weeks. | |
| (Ha et al., 2022) [29] | Randomized controlled trial | Sixty-one participants | 65-85 years old | Participants received weekly vibration training on a Galileo® side-change plate under organization supervision.<br>The training consisted of three minutes of 1.5-2 mm dynamic and static squats, a one-minute warm-up at 12 Hz.<br>Every participant was also given instructions for three times a week of resistance exercise at home.<br>In these approximately 45-minute sessions, participants completed three sets of bodyweight exercises including sit-up.<br>The doctor advised taking 3.5 mL of algal oil daily with high-fat meals. | The group receiving omega-3 supplementation showed a significant reduction in IL-6 levels. |
| (Lee & Directo, 2023) [30] | Randomized controlled trial | Twenty healthy older women | 65 years old | For eight weeks, every participant engaged in twice-weekly resistance exercise.<br>For the five main upper and lower body muscular groups (leg press, calf raise, biceps curl, seated row, and lat pull-down), the exercise program comprised three sets of twelve repetitions or until failure, whichever occurred first. To guarantee correct execution and reduce the chance of damage during resistance training sessions, study team members actively monitored the training sessions.<br>The beginning exercise intensity was 50% of 1 RM. The training load was raised by 5% each week if the individual performed the recommended effort, reaching 70% of 1 RM by the second week to produce adaptive hypertrophic response.<br>If participants are unable to complete 10 RM, the load is carried over to the following session. Each training session started with stretching and low-intensity activities<br>Omega-3 supplement included DHA (0.24 g) and EPA (0.7 g).<br>For a daily total of 0.72 g DHA and 2.1 g EPA, the supplement group consumed three fish oil capsules, one with each meal. | There is a significant decrease in IL-6 in those that consume omega-3 fatty acids and exercise. |
| (Domingo J et al., 2020) [31] | Randomized controlled trial | Fifteen healthy male amateur endurance athletes | 18-45 years | Using a multipowe machine, athletes completed eight sets of six half squat repetitions at 110% of 1-RM during the training session, with two minutes of rest in between sets.<br>Two assistance lifted the weight to begin the subsequent repetition, but the athlete only executed the eccentric phase. The athletes had three seconds to drop the weight.<br>The Borg scale assessed the athlete's felt effort (RPE) after completing the activity.<br>Participants completed 8 sets of 10 drop vertical leaps on a 60 cm platform, taking a 1-minute break sets and five minutes after completing the last half-squat exercise.<br>The athletes were told to jump as high as they could as soon as they were off the box.<br>Volunteers consumed either PLA (500 mg olive oil placebo) or six DHA + EPA soft gels (Brudy Plus, Brudytechology, Barcelona, Spain), all of which looked the same.<br>A DHA + EPA soft gel the study included taking | Following exercise and omega-3 therapies, IL-6 levels dramatically dropped.<br>Twenty-four hours following activity, the omega-3 fatty acid level peaked. |

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| | | | | a single dosage of 2.34 g of total omega-3 PUFA fatty acids in the morning before breakfast for 10 weeks. | |
| (Jaworska et al., 2023) [32] | Randomized controlled trial | Twenty-four male long-distance runners | 33-35 years | The eccentric workout regimen (downhill run) is finished by the participants.<br>Using a treadmill that was adjusted to run backwards on a -16% gradient, each participant ran downward for 30 minutes.<br>After three minutes, the pace was raised until an HR equal to 70% VO2max was attained. The test started at 6 km/h.<br>It has been proposed that following a downhill run, this regimen causes a considerable amount of muscle injury.<br>Participants took six capsules of 3,000 mg concentrated fish oil (three in the morning and three in the evening) or six capsules of gelatin (three in the morning and three in the evening) made by the same company for three weeks. | The intervention of omega-3 and physical activity significantly reduced IL-6 levels. |
| (Haß et al., 2023) [33] | Randomized controlled trial | Sixty-one participants | 65-85 years | Weekly vibration training on alternating vibration plates is provided to all participants.<br>This included three minutes of 1.5–2 mm amplitude dynamic and static squats frequency of 12 Hz, and a one-minute cool-down with a frequency of 12 Hz.<br>Every participant was also given instructions for three times a week of resistance exercise at home. During these roughly 45-minute sessions, participants performed three sets of body weight exercises sit-up crunches.<br>At baseline, each participant's vibration of repetitions of the workouts were assessed separately to take into consideration their physical condition and prevent under- or over-exercising throughout the intervention period.<br>Each participant's training program started at their personal maximum performance level and advanced each week by increasing the vibration (+2 Hz) and repetition count (+2). Compliance with the training protocol was documented in a training journal.<br>The protein + omega-3 group received 3.5 mL of algal oil daily, including 2,195 mg Omega,1,397 mg DHA, 749 mg EPA, and 49 mg docosapentaenoic acid). The plasma omega-3 index assessed to determine compliance at the conclusion of the research. | There was a significant decrease in IL-6 levels in the omega 3 intervention group. |

## Discussion

This research examined how omega-3 supplementation after exercise affected interleukin-6 levels, an indication of inflammation. The investigation showed that omega-3 supplementation during exercise significantly reduced IL-6 levels, an inflammatory biomarker. The previous research found that 780 mg EPA and 606 mg DHA supplementation during interval physical exercise for 6 weeks effectively reduced IL-6 levels [34]. Earlier study showed that 300 mg of fish oil per day and 4 weeks of weight training lowered IL-6 levels [26]. Other studies demonstrate that soccer players supplementing with 3.5 g DHA + EPA 5 times a week for 26 weeks reduced IL-6 levels [27]. Omega-3 supplementation after exercise significantly lowers IL-6, an indicator of inflammation.

The results of earlier research indicates that physical activity causes muscle damage in the form of downhill running which is done 60 minutes with 65% VO2max by giving omega 3 supplementation at a dose of 3 grams given for 4 weeks is significantly proven to reduce IL-6 levels [28]. Other research results omega 3 intervention provided by doing home-based resistance training and performed 45 minutes per session 3x a week which includes marching, squats, chair lifts, chair dips, and three rounds of sit-up crunches proved significant in reducing IL-6 levels [29]. The outcomes of previous research omega 3 supplementation given while doing programmed resistance training consisting of leg press, calf raise, biceps curl, seated row, and lat pull-down performed twice a week for 8 weeks significantly reduced IL-6 levels [30]. It also supports the discovery that omega 3 supplementation during IL-6 levels may be significantly reduced by exercise following the intervention [35]. The research found that omega-3 supplementation during exercise significantly lower IL-6. Further is needed how to omega-3 supplementation affects IL-6 levels after exercise.

**Physical Exercise Increases Interleukin-6**

Low-molecular-weight proteins called cytokines control hematopoiesis, inflammation, and immunity. Numerous cells, including as fibroblasts, endothelial cells, immunological cells, and

other stromal cells, generate them. Stromal cells to control hematopoiesis, inflammation, and immunity [36]. Cytokines are classified into family groups based on their secretion from secondary and tertiary structures or cells [37]. Immunomodulatory IL-6 has several physiological impacts. Pro- and anti-inflammatory cytokines may rise with exercise. Regular moderate exercise is essential for mental and physical health; nevertheless, severe exercise is associated with transient immunosuppression, which may be caused by higher cortisol levels or inhibitory cytokines after hard exercise [38]. Furthermore, it is believed that intense exercise suppresses cellular immunity [39]. According to Gill et al., 2015 blood samples taken from competitors showed that there was transient bacteremia following severe endurance sports.

Epidemiological research has identified a link between the amount of physical activity and the strength of the body's immune. Skeletal releases IL-6 into interstitial systemic circulation during exercise, which redirects energy to contracting muscles through endocrine, autocrine, and paracrine processes [41]. During exercise, plasma IL-6 concentrations rise exponentially and peak at the conclusion of the workout [42]. Circulating IL-6 increased most when exercise was done for longer periods of time, utilizing larger muscle groups and at greater intensities [43]. IL-6 from muscles has a five-minute half-life and is removed from plasma after exercise because skeletal muscle synthesis decreases and hepatic clearance increases [44]. After vigorous exercise, muscle damage increases cytokine expression, resulting in elevated muscle IL-6 levels [45]. In another research, energy substrates increase IL-6 levels, which may explain athletes' higher IL-6 levels [46].

Omega 3 Supplementation During Physical Training Lowers Interleukin-6 Levels

The Greenland Eskimos, whose fish-rich diet reduced multiple sclerosis, asthma, type 1 diabetes, and coronary heart disease, first promoted omega-3 fatty acids like EPA and DHA (Patted et al., 2024). Omega-3s are needed for cell membrane development and receptor function, according to many studies. Lipids are the principal source of clotting, inflammation, and arterial contraction and relaxation hormones. Additionally, these lipids may bind to cell receptors that influence genetic activity. Omega-3 fats may prevent cancer, cure lupus, dermatitis, and rheumatoid arthritis, and lessen heart disease and stroke risk [47]. Seals, whales, cod, halibut, salmon, mackerel, and menhaden contain omega-3 polyunsaturated fatty acids. Most fish oils contain minimal DPA, while EPA and DHA are the main marine omega-3s [48].

Omega 3 has numerous double bonds [49]. Most omega-3 fatty acids consist of DHA, EPA, and ALA (50). Omega 3's anti-inflammatory properties are well known **51**. Additionally, research has shown that omega-3 supplements help preserve muscle function and alleviate pain following muscle damage caused by eccentric exercise **52**. By reducing TNF-α release, omega-3 fatty acids affect cytokine secretion, which in turn affects the immunological response [53]. By inhibiting TNF-α signals and triggering muscle protein reactions, omega 3 can reduce inflammation [54]. Gutiérrez-Pliego et al. (2018) suggest may reduce TNF-α levels [55]. The results of the study (Coghill et al., 2018) reported that Omega-3 can reduce CRP and IL-6 because omega 3 contributes to the uncontrolled inflammatory process, so it will naturally reduce discomfort [56]. Research result from Corder et al., 2016 illustrates how taking supplements can improve muscle strength and lessen the severity of pain. Omega 3 can enhance mitochondrial activity by integrating into mitochondrial membranes [57]. Because omega 3 supplements lower the cost of oxygen, they may increase aerobic endurance, particularly at submaximal workloads [58], and can even to an increase in VO2max [59]. Increased muscle protein synthesis has been shown in studies examining how omega 3 affects muscular strength [60] and the possibility of gaining more strength in adults [60],[61]. Omega 3 supplements work well for hyperinsulinemia and hyperaminoacidemia in young, healthy persons [62].

Acute inflammatory responses reduce damage and infection risk via cellular and molecular interactions. This reduces acute inflammation and restores tissue homeostasis. Acute inflammation may become chronic and cause inflammatory illnesses if not controlled [63]. The total inflammatory response decreases. These metabolites reduce inflammatory cell invasion, suppress proinflammatory cytokines, and help remove cellular debris to stop the inflammatory process. For example, EPA-derived resolvin E1 reduces proinflammatory cytokines by inhibiting the NF-κB pathway, a critical regulator of inflammation [64]. Through prolonged inflammation, this mechanism may also cause neurodegeneration [65].

Omega-3 fatty acids may also increase myogenesis [66]. Nuclear receptors termed peroxisome PPARs regulate satellite cells, facilitate skeletal muscle adaptation after exercise, and prevent metabolic disorders [67]. PPARs regulate genes required for inflammation, lipid and glucose metabolism, and development. Research suggests omega-3 acids activate PPARs and change inflammation-regulating gene expression [68]. Omega-3 also decreases cytokine and inflammatory protein production, including TNF-α and IL-6, and NF-kB activation. When inflammation is reduced, satellite cells proliferate and differentiate more in muscle [66]. Research indicates that omega-3 supplementation and exercise may reduce inflammation by lowering CRP, IL-1, IL-6, IL-10, and TNF-α. This reduction in inflammation alleviates pain, which subsequently enhances performance during exercise programs, especially those focused on muscle building [69].

**Strength and Limitations**

The samples used were human-based, ensuring that the data is homogeneous and not mixed with animal samples like those from mice or other animals.

However, a limitation of the review is the lack of discussion on how omega-3 supplementation during exercise reduces IL-6 levels, which are a key marker of inflammation. Therefore, conducting further research on this topic is crucial to deepen our understanding of how omega-3 supplementation impacts IL-6 levels during physical activity, as well as to explore the underlying mechanisms. Such studies could provide valuable insights and recommendations for athletes to incorporate omega-3 supplements as part of their nutrition strategy.

## Conclusion

According to the evaluated publications, omega-3 supplementation during exercise reduces IL-6 levels, which indicate inflammation. However, the appropriate dose to reduce IL-6 during

exercise is unknown. Thus, further study is needed to establish the best dosage.

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**Conflict of Interest**

Authors declare no conflict of interest.

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*Research Article*

# An Epidemiological Review of the Impact of COVID-19 on Achilles Tendon Rupture Injuries, Experience from a Large London District General Hospital

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**ABSTRACT**

***Background:*** During the lockdown for COVID-19, hospitals experienced a reduction in the number of trauma admissions related to high energy, sport, and occupational injuries. As lockdown measures began to ease, hospitals experienced a high admission rate of patients presenting with Achilles Tendon Rupture [ATR]. However, in the post-pandemic phase, the number of cases reduced. The aim of this paper is to report changes in incidence and identify changes in demographics, mechanism of injury, and Achilles Tendon Rupture management pre- and post-pandemic.

***Subjects and Methods:*** We undertook a review during six different time periods of our Achilles Tendon Rupture patients, the time periods included: pre-pandemic, during the first after the first lockdown, during the second lockdown, after the second lockdown and the post-pandemic period. Patient's demographics, mechanism of injury, past medical history, the use of steroids and patient management, Achilles tendon Total Rupture Score (ATRS) were all included.

***Results:*** One hundred and sixty-three patients were included in the study. During the second lockdown, the average age of patients was significantly lower than any other group [p <0.005]. 40% of patients after the first lockdown [August 2020- December 2020] were treated surgically and this was significant [p-value <0.005], during all other time periods; the vast majority of patients were treated conservatively. For the entire cohort, 71.78% of patients were treated conservatively, whilst the other 28.22% were treated surgically. There was no statistical difference in the Achilles Tendon Rupture Score-based [p-value - 0.729] when comparing the management of Achilles Tendon Rupture, at least 8 months post-treatment.

***Conclusions:*** During each national lockdown, there was a decrease in the number of patients who presented with Achilles Tendon Rupture to hospital. Following the second lockdown, the number of patients who presented with ATR has significantly increased. However, in the post-pandemic phase, the number of cases decreased again. The study also found no significant difference in long-term outcomes as measured by the Achilles Tendon Rupture Score (ATRS), regardless of treatment approach. These findings suggest that the pandemic had a transient but marked impact on Achilles Tendon Rupture incidence, and further research is needed to explore the underlying mechanisms of this pattern, as well as the long-term outcomes and potential preventive strategies for Achilles Tendon Rupture in the post-pandemic era.

## Introduction

The Achilles tendon [AT] ranks as the strongest tendon in the human body and is the largest, multifunctional, and most crucial tendon [1]. The tendon connects gastrocnemius, plantaris and soleus muscles to the calcaneus bone. In addition, it plays a pivotal role in knee flexion, ankle plantar flexion, and inversion of the hindfoot [2].

However, despite being the strongest tendon, it is known to be the most commonly ruptured tendon in the lower extremity [1]. The incidence rates of Achilles tendon ruptures [ATR] vary in the literature [3-5]. Huttunen et al [2012], reported an increase in the incidence of ATR in Sweden between 2001 and 2012, with an increase of 17% in men and 22% in women [3]. I

In a recent study, by Costa ML et al [6] reported that Achilles rupture affects over 11,000 people each year in the UK, and the incidence is increasing as the population remains more active into older age. The injury usually occurs in adults in their third to fifth decade [7]. ATR has several common locations for the injury, studies have shown that a 2-6 cm area that is proximal to calcaneal insertion is the commonest area for injury as it corresponds to a watershed region of poor vascularization [8,9]. Given the broad array of critical functions that the AT helps to provide, injury can be devastating. The incidence of ATR tends to be higher among episodic athletes or so-called "weekend warriors" [10].The causes and mechanisms of ATR are multifactorial ranging from patient-related factors to external factors such as sporting injuries. ATR is typically produced by a single high-load impact, through violent or sudden ankle dorsiflexion and long-standing tendinopathy or intratendinous degenerative conditions [11-15].

The World Health Organization [WHO] declared a pandemic alert after the spread of COVID-19 on March 10, 2020. As a result of this of the global pandemic, countries had to implement different measures to reduce transmission [16]. In the United Kingdom, the first lockdown was announced on the 23rd of March with strict measures including stopping all outdoor activities. This resulted in the cessation of group sporting and public activities until June 2020. However, due to the increased number of cases in the Winter of 2020, there was another lockdown from January 2021 until April 2021.

Interestingly, during lockdown periods there was a decrease in the number of ATR admissions to our hospital compared to the period pre-pandemic and post-lockdown. In light of this, we undertook a retrospective epidemiological review of the ATRs, which had presented to our large London district general hospital during five different time periods pre-pandemic, during the pandemic, and post-pandemic. The aim of this paper is to report changes in incidence and identify changes in demographics, mechanism of injury, and ATR management pre and post-pandemic.

## Subjects and Methods

A retrospective case series utilising data from a large London-based district was undertaken between December 2018 and May 2022. The analysis was undertaken between six time periods: pre-pandemic [12th December 2018 - 10th March 2020] – Group 1, during the first lockdown [11th March 2020 – 31st July 2020] – Group 2, after the first lockdown [1st August 2020- 31st December 2020]- Group 3, during the second lockdown [1st January 2021- 11th April 2021] – Group 4, after the second lockdown [12th April 2021 – 31st December 2021] – Group 5and the post-pandemic period [1st January 2022 until 22nd May 2022] – Group 6 [16].

Medical records of the patients who presented with ATR during the six time periods at our hospital were collected through our trust electronic health record system, CERNER Millenium [North Kansas City, MO, USA ™]. Data collected included: Patient's demographics, mechanism of injury, past medical history, and patient management. The line of treatment; conservative versus surgical treatment was decided following a discussion between the patient and the doctor and obtaining informed consent.

The Achilles tendon Total Rupture Score (ATRS)

The ATRS is a patient-reported, injury-specific instrument developed in 2007 to specifically evaluate outcomes after treatment in patients with ATR. This questionnaire is a self-administered instrument, filled out by the patient and scored by the clinician. It consists of ten items evaluating aspects of symptoms and function following the presentation of ATR. Each item has scores ranging between 0 and 100 on a Likert scale. The instrument, therefore, has a maximum score of 100, which corresponds to no symptoms and full function.

Data were tabulated using Microsoft Excel [Microsoft, Redmond, WA™] and analysed using SPSS Version 23 [IBM, SPSS Statistics ™]. Statistical significance was determined using Fisher Exact test and Mann-Whitney U Test, with a significance level set at 0.05.

## Results

One hundred and sixty-three patients were included in this study of which 127 [77.91%] were male with an average age of 41.44 years and 36 [22.09%] were female with an average of age 43.49 years. A Mann-Whitney U test showed males were statistically younger [P<0.005] at the time of their ATR injury when compared to females. Figure 1 shows a graph with the number of cases during each time period from pre-pandemic to post-pandemic.

The average age of patients during the second lockdown was statistically significantly lower than any other group [p-value <0.005] From the entire cohort of patients who presented with ATR, 99 patients had no existing comorbidities recorded. Of the 60 patients with reported co-morbidities, of these two patients reported having osteoarthritis and rheumatoid arthritis, four patients reported having previous orthopaedic surgery unrelated to the ATR and three patients reported a contralateral ATR.

80.98% [132] of the patients suffered an ATR due to a sporting injury and 19.01% [31] suffered an ATR due to a fall. During each time, the sporting injury was statistically higher [P<0.005] compared to patients having a fall

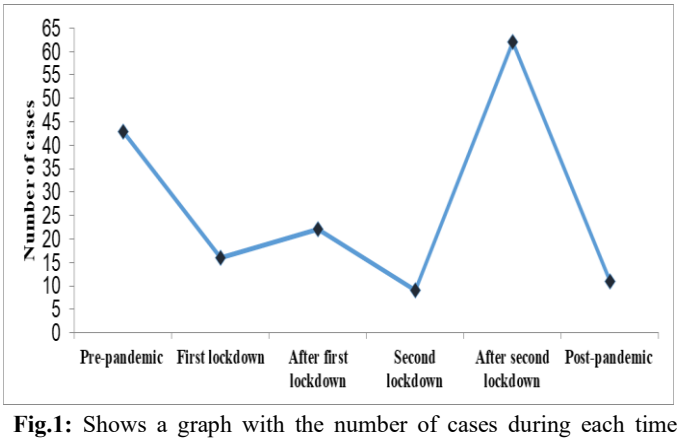


**Fig.1:** Shows a graph with the number of cases during each time period.

**Table 1:** Shows a breakdown of the number of cases, average cases per month, number per 100,000 per annum, the average age at injury, and the mechanism for injury

| Dates | Time period | Number of Cases [M:F] | Average per month | Number of per 100,000 per annum | Average Age at Injury Years | Mechanism of injury [Number of Sporting: Number of falls] |
|---|---|---|---|---|---|---|
| 12th December 2018- 10th March 2020 | Pre-pandemic – Group 1 | 43 [33:10] | 3 | 9 | 45.75 | 35:8 |
| 11th March 2020 – 31st July 2020 | First [1st] Lockdown – Group 2 | 16 [12:4] | 4 | 10 | 41.85 | 14:2 |
| 1st August 2020- 31st December 2020 | After first [1st] Lockdown – Group 3 | 22 [19:3] | 5 | 14 | 41.17 | 16:6 |
| 1st January 2021- 11th April 2021 | Second [2nd] Lockdown – Group 4 | 9 [7:2] | 2 | 7 | 36.67 | 6:3 |
| 12th April 2021-22nd May 2022 | After second [2nd] Lockdown –Group 5 | 62 [46:16] | 5 | 14 | 40.11 | 52:10 |
| 1st January 2022 – 22nd May 2022 | Post-pandemic _ Group 6 | 11 [10:1] | 2 | 7 | 43.64 | 9:2 |

**Table 2:** Shows a breakdown of the treatment management for the patients.

| Date | Operative management | Percentage [%] | Conservative Treatment | Percentage [%] |
|---|---|---|---|---|
| Pre-pandemic – Group 1 | 12 | 26.19 | 31 | 73.81 |
| 1st Lockdown –Group 2 | 3 | 18.75 | 13 | 81.25 |
| After 1st Lockdown – Group 3 | 9 | 40.90 | 13 | 59.09 |
| 2nd Lockdown – Group 4 | 2 | 22.22 | 7 | 77.78 |
| After 2nd Lockdown – Group 5 | 15 | 24.19 | 47 | 75.81 |
| Post-pandemic – Group 6 | 5 | 45.45 | 6 | 54.55 |

Table 3. Shows females had statistically lower ATRS when compared to males [p<0.003]

| **Gender [N]** | **Average ATRS [SD]** | **Range** |
|---|---|---|
| Male – 106 | 70.61[11.50] | 43-94 |
| Female - 30 | 62.61 [14.06] | 40-88 |

Table 4. Shows the average ATRS depending on the treatment type.

| **Treatment** | **Average ATRS [SD]** | **Range** |
|---|---|---|
| Surgical | 66.33 [12.32] | 45-91 |
| Conservative | 67.5 [14.15] | 40-94 |

For the entire cohort, 71.78% of patients were treated conservatively, whilst the other 28.22% were treated surgically, this was statistically significant [p-value <0.005]. Each time-point, the number of patients opting for Conservative Treatment was statistically significant when compared to surgical intervention.

The Achilles tendon Total Rupture Score [ATRS].

83.44% [136 out of 163] patients completed their ATR score following the presentation of ATR in the hospital. The average score [SD] was reported as 68.79 [12.54]. The lowest score was reported as 40 and the highest score was reported as 94. The median ATRS was 69 for the entire cohort of patients.

## Discussion

To the best of our knowledge, this is the first study to conduct a comprehensive retrospective analysis of differences in incidence, demographics, and management in ATR between six different time periods pre and post-COVID-19 pandemic.

Due to the increase in involvement in a variety of sports, the incidence has been on the rise since the 1980s; significantly in the past 50 years 8. A review of the literature to date demonstrates demographically that the classical presentation for ATR is experienced in sportsmen in their fourth decade, with a ratio of 20:1 for males to females respectively8. Our data correlate with the literature and shows that patients presented to our hospital were predominantly male [115 male: 35 female]. Our data also demonstrates that sporting injuries are the most common cause of ATR during all time periods.

Interestingly, our study indicates that the average age for patients presented to our hospital during the six different time periods was 41.44 years for males and 43.49 years for females. Males were statistically younger [P<0.005] at the time of their ATR injury when compared to females. This is higher than what was demonstrated by Lemme et al, [2018], they showed that the highest age group presenting with ATR is between 20-39 years old [17]. This can be explained by the likelihood of increased physical activity and sports involvement in the older age group [18,19]. However, the average age for patients presenting during the second lockdown [January 2021-April 2021] was significantly lower [p-value <0.005] than the other groups with an average of 36.67 years. The increase in ATR incidence in the younger age group after the second lockdown can be explained by the rapid return to physical activity after a long period of inactivity.

Puga et al, [2022] [20], looked into different injury incidents among football players during American National Football League [NFL] in 2020. Their data showed a significantly increased number of overall injuries prevalence during the 2020 season compared to the 2018 and 2019 seasons. Puga et al. further braced their findings with Myer et al. study [21] finding, which reported that there was an increase in ATR incidence among players in the 2011 pre-season, after the NFL shutdown in 2011. These two studies support our findings; after the second lockdown, there was a noticeable jump in the number of patients who presented with ATR compared to all other times period. Also, the number of ATR after the second lockdown, from April 2021-Decemeber 2021 was more than the number who presented pre-covid and post-Covid era. In contrast to our findings and the aforementioned studies, a recent retrospective case-control study that was conducted by Murphy et al [10], in which they reviewed the incidence of ATR managed surgically in their unit between 27th of March 2019 – 29th of July 2019 [control group], against 27th of March 2020 - 29th of July 2020 period which represents the period after a lockdown in the republic of Ireland. Return to play after COVID-19 pandemic restrictions and inactivity does not increase the incidence or rate of Achilles tendon rupture. In this study operatively managed Achilles tendon ruptures were included, and data were obtained from electronic theatre logbooks over the study period. This study only discussed operatively treated ATR, therefore it might not be comparable to our study, 71.78% of patients in our study were treated conservatively. Conservative management currently is the preferred method of management [22-24].

A study from another London hospital showed a higher incidence of lower limb tendon rupture [25]. They observed a significant increase in the incidence of both Achilles and patellar tendon ruptures in 2020. The reported ATR incidence was the highest in 2020 with 16 in comparison to 8 in 2019 and 14 in 2021. The increase in ATR occurred as exercise allowance increased.

Puga et al [20], stated that The astronomical increase in sport injury prevalence during the 2020 season over the previous years raises the possibility that there was a reduced physiological adaptation to stress, due to the limited amount of training as a result of the closure of practice facilities to slow the spread of COVID-19.

During all time periods, our study shows that there was no change in the management trend of ATR between pre and post-COVID-19 periods; with the number of patients treated conservatively significantly higher than the number of patients who opted for surgical intervention; 71.78% to 28.22%.

In conclusion, COVID-19 has affected the number of patients presented to our hospital with ATR. There was a decrease in the number of patients who presented with ATR during each lockdown as opposed to an incidence increase after the second lockdown was lifted. Moreover, our data show a change in the average patients' age presented with ATR compared to other studies, with no change in the management plan. There was no statistical difference in the ATRS-based [p-value - 0.729] on the management of ATR.

Further research is needed into potential preventative measures, and longer-term outcomes. Future work should include multi-centre studies to analyse the correlation between changing periods of inactivity and increased incidence of ATR.

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**Conflict of Interest**

Authors declare no conflict of interest.

**Data availability**

Data are available upon reasonable request.

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*Research Article*

# Comparative Analysis of Short-Term Outcomes in Thoracoscopic Minimally Invasive Versus Traditional Mitral Valve Replacement: Randomized Clinical Trial Study

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**ABSTRACT**

***Background:*** The standard approach for mitral valve surgery was a sternotomy, but with the new trends, mitral valve surgery can now be performed with right mini thoracotomy incision. Minimally invasive mitral valve surgery has demonstrated superior cosmetic outcomes, less surgical trauma, shortened intensive care unit and hospital stays, cost effectiveness, and faster recovery, while the efficacy is comparable to conventional sternotomy.

***Objective:*** The aim of this research is to investigate the short-term outcomes of thoracoscopic minimally invasive mitral valve replacement in comparison with the conventional technique.

***Subjects and Methods:*** This study included 100 patients with isolated mitral valve disease, who were randomly divided into two equal groups. Group A underwent a right anterolateral video-assisted mini-thoracotomy, while Group B was approached via a conventional median sternotomy.

***Results:*** The minimally invasive group had significantly longer total operative time (291.3±48.89 min vs. 227.68±49.18 min, $p = 0.001$). However, Group A demonstrated better post-operative outcomes, including shorter ICU stay (2.1±1.07 vs. 3.82±1.49 days, $p = 0.002$), shorter extubation time (4.24±1.12 vs. 8.45±4.55 hours, $p = 0.0001$), reduced post-operative blood loss (271.7±107.09 ml vs. 449.2±230.93 ml, $p < 0.0001$). Post-operative pain scores were significantly lower in Group A (VAS 3.84±1.53 vs. 7.58±1.62, $p < 0.0001$), and hospital stay was shorter (7.22±1.37 vs. 11.21±3.53 days, $p < 0.0001$).

***Conclusions:*** Minimally invasive mitral valve surgery can be a safe and effective alternative to traditional MVS in patients with mitral valve disease.

## Introduction

Mitral valve disease (MVD) is one of the most common cardiac disorders, caused by malfunction of the valve that controls blood flow from the left atrium into the left ventricle. The disease may result in mitral valve stenosis, mitral valve regurgitation, or both. Rheumatic heart disease is the most common cause of mitral valve stenosis, whereas mitral valve regurgitation can result from degenerative changes, infective endocarditis, and ischemic heart disease. MVD is a major global health burden, especially in developing countries where rheumatic heart disease is still a leading

cause. When untreated, it can lead to complications such as heart failure, pulmonary hypertension, arrhythmias and increased mortality [1].

Conventional mitral valve surgery (MVS) over the last few decades is performed through a median sternotomy, which provides great exposure of the heart and mitral valve. This method, however, carries high surgical trauma, postoperative pain along with prolonged recovery period. Minimally invasive mitral valve surgery (MIMVS) has become an alternative approach to conventional sternotomy in recent years. MIMVS has smaller incisions, in many instances via a right mini-thoracotomy, allowing for thoracoscopic assistance for access to the mitral valve. It reduces the surgical trauma, postoperative pain, and recovery time while achieving outcomes at least equal to traditional sternotomy [2].

The history of MIMVS dates back to the late 1990s when surgeons began exploring less invasive techniques to reduce the morbidity associated with traditional sternotomy. Over time, advancements in surgical instruments, imaging technology, and cardiopulmonary bypass techniques have made MIMVS a viable option for many patients. Indications for MIMVS include isolated mitral valve disease, particularly in younger patients with fewer comorbidities. Contraindications may include severe peripheral vascular disease, previous right chest surgery, right ventricular dysfunction or complex mitral valve pathology requiring extensive repair [3].

Despite its advantages, MIMVS presents unique challenges, particularly in terms of cardiopulmonary bypass management and myocardial protection. These challenges necessitate specialized surgical expertise and careful patient selection to ensure optimal outcomes. The choice between MIMVS and conventional sternotomy often depends on patient-specific factors, including age, comorbidities, and the complexity of the mitral valve pathology [4].

Study aims to evaluate the short-term outcomes and 30-days mortality in thoracoscopic minimally invasive versus traditional mitral Valve replacement.

## Subjects and Methods

### Study Design and randomization

This randomized clinical trial study was carried out at Cardiac Surgery Department, National Heart Institute, Giza, Egypt, from September 2018 to October 2020. A total of 100 patients diagnosed with isolated mitral valve disease (MVD) who underwent mitral valve replacement (MVR) were randomly assigned to two equal groups. Group A comprised 50 patients who underwent MVR through a right anterolateral video-assisted mini-thoracotomy, representing a minimally invasive approach. In contrast, Group B included 50 patients who underwent conventional median sternotomy. To ensure that patients were equally divided between the groups, randomization was carried out using a computer-generated sequence in the Rj Editor module of Jamovi software (Version 2.4.8.0). Blinding was not possible because of the surgical procedure; hence the research was carried out as an open-label trial.

### Inclusion and Exclusion Criteria

Patients were selected according to defined inclusion and exclusion criteria. The study exclusively involved patients undergoing isolated MVR, thereby excluding any involvement of the tricuspid valve. Patients were excluded if they had concomitant aortic valve disease, ischemic heart disease, contraindications to femoral cannulation, peripheral arterial disease, or a history of right lung surgery or radiotherapy to the right chest. Reoperation cases were excluded to preserve homogeneity in baseline characteristics. Also, pediatric age group and emergency cases were excluded.

### Preoperative Assessment

All patients included in this study received a full preoperative assessment, that included history, physical examination, full labs, ECG, and chest imaging. Full detailed transthoracic and transesophageal echocardiography evaluation was performed to assess mitral valve pathology. CT aortogram and carotid duplex ultrasonography were performed in selected cases, especially for patients over 60 years, to assess vascular integrity and confirm eligibility for femoral cannulation. Preoperative risk stratification was conducted using EuroSCORE, a validated prediction model for assessing mortality risk in patients undergoing cardiac surgery. EuroSCORE considers patient-related factors (e.g., age, comorbidities), cardiac-related factors (e.g., NYHA classification, left ventricular function), and procedural risk variables to provide a risk score that categorizes patients into low, middle, and high-risk groups[5]. Due to its predictive accuracy, EuroSCORE was employed in our study to provide a uniform evaluation of surgical risk profiles for both minimally invasive and conventional sternotomy groups. The New York Heart Association (NYHA) functional classification system, an established method for evaluating heart failure degree depending on symptoms and physical activity restrictions, was utilized to classify patients [6].

### Surgical Technique

All surgeries were performed under general anesthesia using double-lumen endotracheal intubation by a single surgeon assisted by the same team. During the operation cardiac functions were monitored by transesophageal echocardiography and deairing during weaning from CPB assisted with cardiac functions monitoring. In Group A, femoro-femoral cannulation was inserted, and the vacuum-assisted venous drainage was used to enhance the venous drainage and reduce the likelihood of retrograde aortic dissection. The surgical approach involved a 5–7 cm right anterolateral mini-thoracotomy, with additional 1 cm incisions for thoracoscopic camera placement, an atrial retractor, and a Chitwood aortic cross-clamp (Figure 1). The pericardium was opened with care to preserve the phrenic nerve, and the mitral valve was accessed through a left atrial incision. Cardioplegia was administered via an aortic cannula following cross-clamping of the ascending aorta, allowing for safe valve replacement. After MVR, atrial closure, deairing, weaning from CPB, decannulation, and hemostasis were performed, with rib adaptation using Vicryl sutures and chest tube placement as required.

### Postoperative Assessment

Postoperatively, patients were closely monitored for ICU and hospital stay duration, ventilatory support, arrhythmias, cerebrovascular events, the need for inotropic support or mechanical circulatory assistance and complications such as bleeding, wound infection, and thromboembolic events. Other parameters assessed included postoperative pain scores, the need for blood transfusion, cosmetic satisfaction, and time to return to normal activities.

**Follow-Up**

Follow-up was conducted for up to one year postoperatively through clinic visits and telephone consultations to assess long-term outcomes and patient satisfaction.

**Ethical Approval**

Ethical approval for the study was obtained from the Institutional Review Board (IRB), and written informed consent was obtained from all participants before enrollment.

**Statistical Analysis**

Statistical analysis was performed using Jamovi software (Version 2.4.8.0). Qualitative variables were expressed as frequencies and percentages, with comparisons made using the Chi-square test, while quantitative data were presented as means ± standard deviation (SD) and analyzed using the student's t-test. A p-value of <0.05 was considered statistically significant.

## Results

This study compared the outcomes of MVR performed using a minimally invasive right anterolateral video-assisted mini-thoracotomy (Group A) versus the conventional median sternotomy approach (Group B). A total of 100 patients were randomly assigned to either group.

**Preoperative Patient Characteristics**

The demographic data and preoperative clinical characteristics of the study population are summarized in Table 1.

**Table 1:** Preoperative Patient Characteristics.

| Variable | GroupA(n=50) | GroupB (n=50) | P-value |
|---|---|---|---|
| Demographic Data | | | |
| Age (Mean±SD) | 41.12 ± 11.54 | 44.82 ± 12.29 | 0.124 |
| Gender n (%) | | | 0.817 |
| - Males | 13 (26%) | 12 (24%) | |
| - Females | 37 (74%) | 38 (76%) | |
| BMI (Mean±SD) | 25.80 ± 4.73 | 24.75 ± 4.59 | 0.261 |
| NYHA Classification | | | 0.129 |
| Class I | 7 (14%) | 4 (8%) | |
| Class II | 19 (38%) | 25 (50%) | |
| Class III | 20 (40%) | 18 (36%) | |
| Class IV | 4 (8%) | 3 (6%) | |
| Average NYHA Class | 2.42 ± 0.83 | 2.4 ± 0.73 | |
| Pre-Operative Echocardiographic Data | (Mean±SD) | | |
| EF (%) | 58.54 ± 6.48 | 61.52±7.02 | 0.030 |
| ESD ($cm^2$) | 3.56 ± 0.57 | 3.23 ± 0.67 | 0.012 |
| EDD ($cm^2$) | 5.25 ± 0.70 | 5.07 ± 0.85 | 0.256 |
| LA ($cm^2$) | 5.27 ± 0.87 | 5.23 ± 0.86 | 0.774 |
| PASP (mm/hg) | 48.34 ± 14.50 | 47.64±12.53 | 0.797 |

BMI – Body Mass Index, NYHA – New York Heart Association classification, EF – Ejection Fraction, ESD – End Systolic Diameter, EDD – End Diastolic Diameter, LA – Left Atrium, PASP – Pulmonary Artery Systolic Pressure.

**Operative Findings**

The intraoperative parameters showed significant differences between the two surgical techniques. The mean total bypass time (TBT) was significantly longer in Group A (146.12 ± 29.79 min) compared to Group B (109.48 ± 25.00 min, p = 0.001). Similarly, the mean cross-clamp time (CCT) was longer in Group A (108 ± 18.54 min) versus Group B (79.70 ± 19.73 min, p = 0.001). The total operative time (TOT) was also significantly longer in the minimally invasive group (291.3 ± 48.89 min) compared to the sternotomy group (227.68 ± 49.18 min, p = 0.001). (Table 2)

The length of the surgical incision was considerably smaller in Group A (7.44 ± 1.16 cm) compared to Group B (19.18 ± 2.32 cm, p = 0.001), confirming the minimally invasive nature of the procedure. (Figure 2)

**Table2:** Comparison of Intraoperative Parameters Between Minimally Invasive and Conventional Sternotomy Approaches.

| Variable | Group A | Group B | P-value |
|---|---|---|---|
| Total Bypass Time (min) | 146.12±29.79 | 109.48±25.00 | 0.001 |
| Cross-Clamp Time (min) | 108 ± 18.54 | 79.70±19.73 | 0.001 |
| Total Operative Time (min) | 291.3 ± 48.89 | 227.68±49.18 | 0.001 |
| Surgical Incision Length (cm) | 7.44 ± 1.16 | 19.18 ± 2.32 | 0.001 |

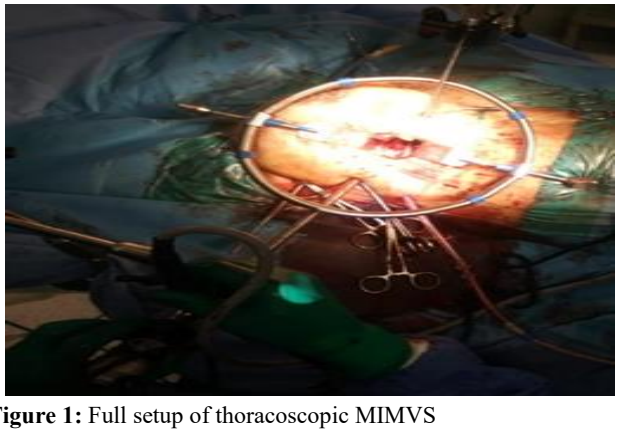

**Figure 1:** Full setup of thoracoscopic MIMVS

**Figure 2:** The length of the surgical incision

**Postoperative Outcomes**

Postoperative recovery metrics showed significant differences between the two groups. Group A had a shorter time to extubation, shorter ICU stay, lower postoperative blood drainage, and lower blood transfusion requirements compared to Group B (p-values < 0.05 for all parameters). These findings suggest that Group A had a faster recovery and less postoperative complication than Group B. (Table 3)

**Table 3:** Postoperative Recovery Metrics Comparison Between Group A and Group B

| Variable | Group A | Group B | P-value |
|---|---|---|---|
| Time to Extubation (hours) | 4.24±1.12 | 8.45±4.55 | 0.0001 |
| ICU Stay Duration (days) | 2.1 ± 1.07 | 3.82±1.49 | 0.002 |
| Postoperative Blood Drainage (mL) | 271.7±107.09 | 449.2±230.93 | <0.0001 |
| Blood Transfusion (units) | 0.12 ± 0.43 | 0.6 ± 0.95 | 0.029 |

**Postoperative Complications**

There was no statistically significant difference in the overall incidence of postoperative complications between the two groups. Arrhythmias occurred in 6 patients (12%) in Group A and 7 patients (14%) in Group B (p > 0.05). Wound infections were observed in 4 patients (8%) in Group A and 6 patients (12%) in Group B (p > 0.05) (Figure 3). One case of left ventricular systolic dysfunction (EF = 40%) was reported in Group A, whereas Group B had one case of complete heart block requiring a permanent pacemaker. One mortality rate was recorded in Group B due to right-sided heart failure, while no mortality were reported in Group A. (Table 4)

**Table 4:** Post-operative complications of both groups.

| | Group A n (n%) | Group B n (n%) | Significance p-value |
|---|---|---|---|
| Arrhythmias | 6 (12%) | 7 (14%) | >0.05 |
| Wound infection | 4 (8%) | 6 (12%) | >0.05 |
| LV systolic dysfunction | 1 (2%) | 0 | >0.05 |
| Heart block | 0 | 1 (2%) | >0.05 |

**Figure 3:** Post-operative wound infection in minimally invasive group.

**Follow-up Echocardiographic Findings**

Echocardiographic evaluation at six months postoperatively revealed no significant differences in left ventricular dimensions, left atrial size, or pulmonary artery systolic pressure (PASP) between the two groups. (Table 5)

**Table 5:** Follow up echocardiography in both groups.

| Variable | Group (A) | | Group (B) | | |
|---|---|---|---|---|---|
| | (Mean±SD) | Range | (Mean±SD) | Range | P-value |
| EF (%) | 55.72±6.30 | 40-70 | 56.31±3.88 | 50-65 | 0.578 |
| ESD($cm^2$) | 3.58±0.48 | 2.8-4.9 | 3.38±0.52 | 2.54.5 | 0.052 |
| EDD($cm^2$) | 5.29±0.66 | 4.2-6.5 | 5.04±0.71 | 3.46.9 | 0.085 |
| LA ($cm^2$) | 4.9±0.54 | 4-6.5 | 5.19±0.94 | 3.37.4 | 0.058 |
| PASP (mm/hg) | 43.36±9.57 | 25-70 | 42.38±10.67 | 2067 | 0.633 |

Ejection Fraction (EF), End Systolic Diameter (ESD), End Diastolic Diameter (EDD), Left Atrium (LA), Pulmonary Artery Systolic Pressure (PASP).

**Operative Costs and Cost-Effectiveness**

While the total operative costs were higher for Group A than for Group B, the overall cost-effectiveness of the minimally invasive technique was evident in the significantly shorter ICU stay, less hospital stay, lower transfusion requirements, and improved postoperative recovery metrics. (Table 6)

**Hospital Stay and Pain Scores**

The total hospital stay duration was significantly shorter in Group A compared to Group B. The postoperative pain score (VAS scale) on the fifth postoperative day was significantly lower in Group A than in Group B, indicating a clear advantage of the minimally invasive approach in terms of patient comfort and recovery. (Table 6)

**Table 6:** Total hospital stays, postoperative pain, and operative costs between both groups.

| Variable | Group A | Group B | P-value |
|---|---|---|---|
| Total Hospital Stay (days) | 7.22±1.37 | 11.21±3.53 | <0.0001 |
| Postoperative Pain (VAS, Day 5) | 3.84±1.53 | 7.58 ± 1.62 | <0.0001 |
| Total Operative Costs (USD) | 6578±295.6 | 5728±365.18 | <0.0001 |

## Discussion

The results of this study highlight the superiority of minimally invasive mitral valve surgery (MIMVS) over conventional sternotomy in terms of short-term recovery, including reduced postoperative pain, shorter ICU and hospital stays, and less blood loss. These findings align with previous studies that have demonstrated the

advantages of MIMVS in reducing surgical trauma and promoting faster recovery [2,4]

In our study, the mean age of patients undergoing mitral valve replacement was 41.12 ± 11.54 years in Group A and 44.82 ± 12.29 years in Group B, indicating a relatively younger patient population compared to other studies. Grossi et al. reported an average age of 58 years in patients who had undergone MIMVS. The younger population in our study is likely due to the high incidence of rheumatic heart disease (RHD) in developing nations, which still largely contributes to mitral valve disease [7].

The left ventricular ejection fraction (LVEF) was nearly equivalent in both groups after surgery and showed no statistically significant differences. This corresponds to the results given by Cao et al., who noted preserved LVEF in patients who underwent MIMVS. It is essential to protect cardiac function, and our results show that the invasive procedure does not compromise the myocardial function [8].

The smaller incision size noted in Group (A) is in accordance with the principles of minimally invasive surgery aimed at lessening surgical incision. Furthermore, less surgical trauma likely results in reduction in postoperative ventilation time coupled with blood loss and the amount of required transfusions. These results in line with a meta-analysis conducted by Al Shamry., where MIMVS was associated with less blood loss and lower transfusion requirements in comparison to conventional sternotomy [4].

The short duration of ICU and hospital stays in Group A indicates a relatively quicker recovery. This has considerable impact on patient turnover and the spending of healthcare resources. These findings are also supported by Pojar et al., who showed that patients who had MIMVS had reduced hospital stays when compared to patients who had conventional surgery [9].

Even with the benefits noted, it is important to recognize the longer times for CPB and cross-clamp in the minimally invasive group. This has been noted in previous studies which have explained the prolonged times in MIMVS set by the complexities and the learning curve of the technique. Nevertheless, these times are likely to shorten with the experience gained by surgical teams [10].

With regards to complications, we noted that Group A had a lower arrhythmia incidence of 12% in comparison to the 20% new-onset atrial fibrillation incidence noted by Modi et al., while analyzing MIMVS outcomes [11]. Moreover, our study noted strokes in none of the cases of the minimally invasive approaches, though some other studies have documented low, yet notable, rates of stroke; for example, Ko et al., noted 0.3% stroke in his cohort [12]. The absence of stroke in our study may be attributed to meticulous surgical technique and patient selection.

When comparing our results to recent literature, a meta-analysis by Eqbal et al., found that minimally invasive approaches to MVS are associated with similar mortality and morbidity rates as conventional sternotomy, with the added benefits of reduced hospital stay and faster recovery. These findings are in line with our observations, further supporting the viability of minimally invasive techniques [13].

From a clinical standpoint, the lower postoperative pain scores in Group A further suggest that minimally invasive techniques are associated with improved patient comfort. This is an important finding, as it aligns with the growing emphasis on patient-centered care, which prioritizes minimizing postoperative pain and improving the overall patient experience [4].

This study has several limitations. The sample size is relatively small, and the follow-up period is limited to early postoperative outcomes. Long-term outcomes and potential late complications were not assessed. Additionally, the study was conducted at a single center, which may limit the generalizability of the findings.

## Conclusion

In conclusion, our findings suggest that minimally invasive MVR via a right anterolateral video-assisted mini-thoracotomy is a safe and effective alternative to conventional median sternotomy.

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**Conflict of Interest**

Authors declare no conflict of interest.

**Data availability**

Data are available upon reasonable request.

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*Research Article*

# A Bibliometric Analysis of Global Research on Dementia and its Cognitive Function

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**ABSTRACT**

**Introduction:** Dementia is a neurocognitive disease manifested by progressive and global declination in cognition. However, there is a lack of visualization analysis on research in the field of dementia and cognitive function. To evaluate the impact and compare the scholarly work output and productivity among organizations, bibliometrics was used.
**Material and methods** Literature related to dementia and cognitive function were searched from Scopus database. In the area of dementia bibliometrics was used to analyze the leading authors, the journals with higher citation, higher collaboration between the countries, and keywords. Scopus analysis and Biblioshiny R-package were used in the analysis of country collaboration and global cited documents.
**Results:** Total 1753 articles were identified from Scopus database and among these 425 articles were included in the study on basis of inclusion criteria. United states, China and Japan has the highest productivity and China, USA, Australia, Canada and Indonesia and has strong collaboration. The research hotspots in this field focused on Dementia and its impact on cognitive function. According to Lotka's Law, the studies in the field of dementia is limited and need to be conducted further.
**Conclusion:** Dementia is a major public health issues in India and this study has thrown light on all articles which has manifested the current trends and important areas of research on dementia. After an intensive analysis the study concluded that there is still a gap in international collaboration among leading countries. In India dementia can be a research gray area and focus of future attention.

## Introduction

Dementia is a syndrome occurring as a result of disease of the brain, which is usually chronic or progressive in nature caused by different types of diseases in which the nerve cells of the brain are damaged over time and may lead to deterioration in cognitive functions.[1, 2]

It is also considered that Dementia is a major neurocognitive disorder and required residential care among older adults. Worldwide roughly

around 46 million people are undergoing this condition and affecting their executive, psychic and physical spheres.[3]

The neurons of the brain are damaged in dementia caused different disease condition leads to progressive deterioration in executive brain function. [4] In the course of dementia there is progressive deterioration in functional activities and require assistance to manage day-to-day activities due to cognitive and functional impairment. Physical impairment associated with reduced quality of life in people with dementia and increased health care expenditure. [5]

Worldwide dementia and cognitive impairment are rising and expected to increase more and more in developing countries. [6] Dementia is manifested by speech difficulties, memory, decision making and other executive functions which put impact on an individual's ability to carry out daily activities. [7]

India is augmenting with its population and embracing highest aging composition and expected to excel China as the world's most populous country. India is a dwelling place of 1.37 billion people, entailing 18% of the total world population in 2019. India population by 2050 is expected to increase about 20% (319 million) of total Indian population on or above 60 years of age and holding 15.4% of Indian people aged 60 years and older globally. This demographic shift exhibits that there is increased longevity, because in India life expectancy rate has remarkably rising from 42.9 years in 1960 to 70.4 years in 2020 which is enlightening that India is in potential alarming stage because aging is the most common and aggravating risk factor for dementia. [8]

The early onset of dementia occurs before the age of 65 years (working age) and those people affected with dementia after 65 years of age is called late-onset of dementia. The etiological theory of dementia is not clearly understood yet but due to dementia the anatomical and chemical changes occurs in brain, leading to damage of nerve cells and shrinkage of brain cell occurs. [1]

The course of mental and physical dysfunction of early or mild intellectual disability is nearly 20 years and lacked with knowledge to improve their disability through different modalities.[9]

The research on dementia currently has covered broad array. Nevertheless, the extensive investigation of the present research publication ground has not been considered to throw light on the content of published research. This type of bibliometric analysis would be contributively to portray the worldwide trends in the field of research pertaining to health and interventions for dementia patients to fulfil the purpose of the research and to find answers to the research questions.[10]

People living with dementia have difficulties in carrying out activities of daily living (ADLs) and Instrumental activities of daily living (IADLs) considered as global cognitive dysfunction, and they are lacked with adequate support and leads to increase dependency and vulnerability. [11]

The current study aims to reveal the global research publication trends, and its impact related to health and interventions for dementia client. However, the investigator tried to throw a comprehensive insight into the present global research status on the health of and interventions for dementia patients which consider global productivity among topmost countries and their research collaboration and keyword trends. To evaluate the impact and compare the scholarly work output and productivity among organizations, bibliometrics was used.[12 13]

One of the most common types of iMetrics is bibliometrics. Bibliometrics is supposed to give a "dynamic view of concepts and semantics".[14] Bibliometrics is the analysis of published information (e.g., books, journal articles, datasets, and blogs) and its related metadata (e.g., abstracts, keywords, and citations) by using statistics to describe or show relationships between the published works and considered as a quantitative performance indicators of published research, to recover from the disadvantage of bias in peer review and expert decisions. [15,16]

## Subjects and Methods

Bibliometric analysis method was used in present study to achieve the purpose of the research and to get the answers to the unsolved research problems. Bibliometrics is described as the analysis of published documents which includes books, published articles, datasets, and blogs and its related metadata such as abstracts, author keywords, and document citations by using different statistical methods to find out or justify the relationships between the published documents .[17]

Hence visualized analysis method of bibliometrics was used by the researcher to explore the global trends of selected articles including journal article, country, organization and key word along with Scopus analysis descriptive data. Biblioshiny R-packages were also used to find out the research trends of dementia and cognitive function globally by exploring research gray areas, topmost author as well as total link strength of countries collaboration and citations by analyzing the relevant local and international studies through bibliometric methods.

### Data collection

Scopus data base was used to collect the secondary data and didn't require any human interaction for which there was zero ethical issues attached to it and also institutional review board's permission was not needed. Articles from Scopus database were obtained between 18th and 21st October. The review of literature was done by using the keywords "dementia" AND "cognitive function". Then, from Scopus database the studies were filtered as per set categories (nursing, medicine, neuroscience, psychology and health profession), time period (1989-2024), publication type (final article) and language (English), source type (all open access journal). As a result of this inclusion criteria 1753 published articles were searched. Titles, abstracts, or full texts were cross checked to find out whether the documents are meeting the criteria or not. The selected articles were assessed and screened by two independent reviewers. The exclusion criteria of the studies were as follows: (1) publications without keywords (2) publications without abstract; (3) repeated publications Finally, 425 number of articles were retrieved from the database.

All the bibliographic information from Scopus database was extracted to an Excel datasheet. The downloaded bibliographic data included details of the author including contact information, study title, year of publication, abstract, keywords, and journal details

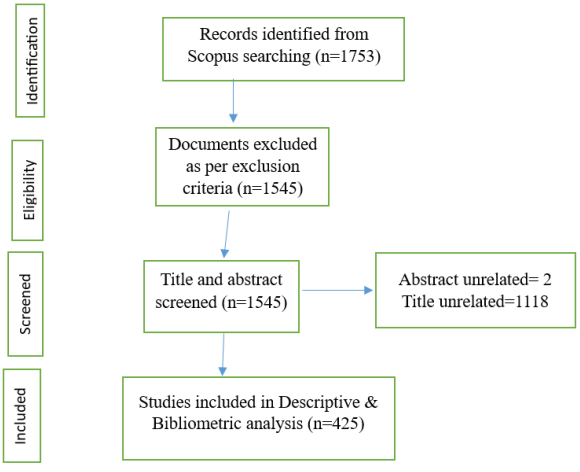


**Figure 1:** Flow chart for inclusion of publications on Dementia and cognitive function**.**

## Results

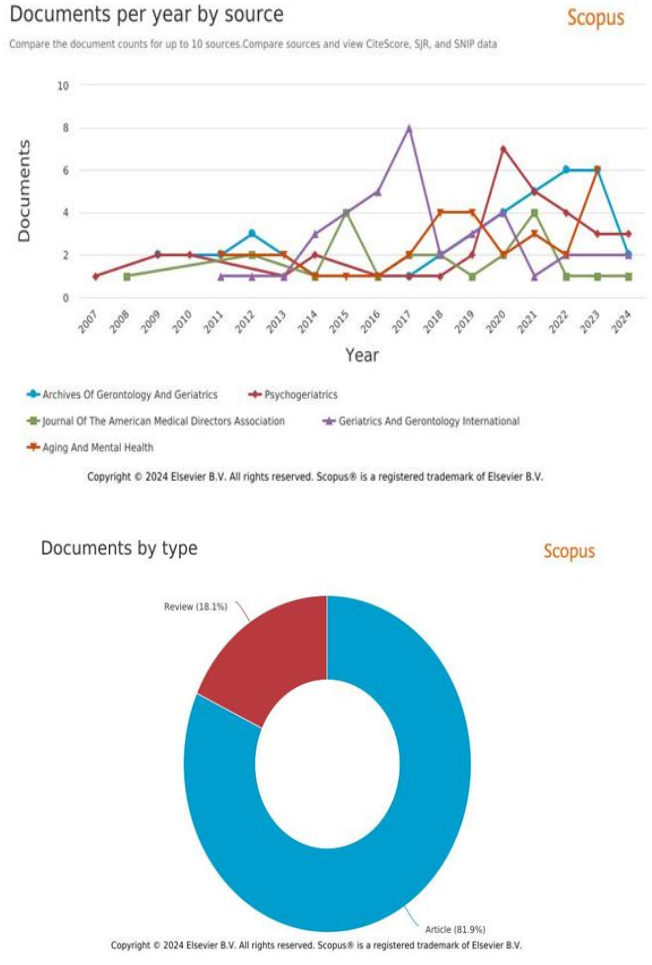


**Figure 2:** Distribution of publication by document types, subject area, and document per year by journal source.

**Table-1:** Top 10 Countries who published studies on Cognitive function and Dementia.

| Name of the country | Number of publications |
|---|---|
| United state | 80 |
| Japan | 73 |
| China | 54 |
| Taiwan | 42 |
| South Korea | 41 |
| United Kingdom | 31 |
| Hong Kong | 22 |
| Canada | 20 |
| Spain | 18 |
| Australia | 17 |

United State has the highest number of publications (80) and in top position among 50 countries across the globe that has researched the topic 'Cognitive function and Dementia' followed by other countries like Japan (72 publications), China (54 publications). Taiwan and South Korea also has done a fair number of studies 42 and 41 respectively and next to these countries United Kingdom (31), Hong Kong (22), Canada (20), Spain (18) and Australia has 17 numbers of publications. This country wise comparison showed the wide range of research has been conducted in these top 10 countries.

**Bibliometric Analysis**

Keywords and cluster analysis

Co-occurrence with author keywords

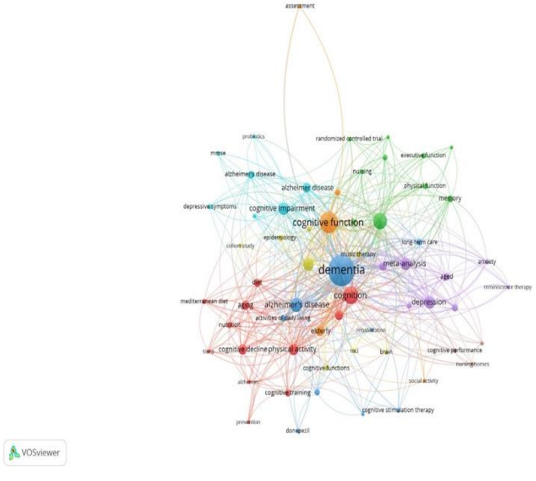


**Figure 3:** VOS viewer analysis of Co-occurrence with author keywords

The author keywords of the selected articles were analyzed using VOS viewer in which the minimum number of occurrence of keywords are 4. Among 913 keyword 62 keywords met the threshold which were selected for analysis. As shown in Fig 3 the 62 keywords were categorized into 8 clusters: cluster 1 cognition related search (bottom center in red), cluster 2 cognitive impairment related search (right top corner in green), cluster 3 dementia and cognitive

stimulation related search (center in sky blue), cluster 4 cognitive functioning related search (left center in yellow ), cluster 5 quality of life related search (top right corner in purple) and cluster 6 Alzheimer's disease related search (top left corner in light blue), cluster 7 elderly and cognitive function related search ( top in orange ) and cluster 8 cognitive disorder and rehabilitation related search (right bottom in brown color).

In cognition related cluster, the most occurring key words are "cognition'' (65 times), "physical activity" (26 times), "cognitive decline" (23 times). In the cluster cognitive impairment, the frequently used keywords are "mild cognitive impairment" (58 times), "memory" (10 times), "physical function" (7 times). In the cluster dementia and cognitive stimulation most occurring key words are "dementia" (202 times), "Alzheimer's disease" (43 times), "cognitive stimulation" (4 times). In cognitive function related search, the most frequently used keywords are "older adults" (32 times), "music therapy" (7 times) "cognitive functioning" (6 times). In quality-of-life cluster, the most occurring keywords are "depression" (33times), "quality of life" (11 times), and Cognitive dysfunction (7 times). In Alzheimer's disease related cluster "cognitive impairment" (34 times), "Alzheimer disease" (22 times). In elderly and cognitive function related cluster most occurring key words are "cognitive function" (95 times), "elderly" (25 times) and in last cluster of cognitive disorder and rehabilitation related the most frequently used key words are "cognitive performance" (5 times). Cognitive disorder (4 times).

Publication with keywords", "cognitive function", "cognitive impairment", "Alzheimer's disease" focuses on cognitive health of dementia patient and publication with keywords "cognitive stimulation", "Cognitive stimulation therapy", "occupational therapy", "rehabilitation", "non- pharmacological intervention", "psychosocial intervention" and "cognitive training" focuses on intervention for the target population.

**Co-authorship analysis with author**

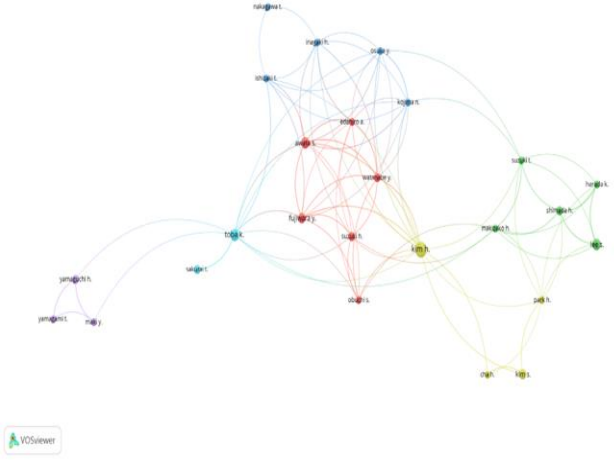

Figure 4: VOS viewer analysis of Co-authorship with author

Fig 4 depicts a collaboration map among the principal author who have published articles on dementia based on co-authorship analysis. In co-authorship analysis among 67 documents 25 documents are connected. In respect to co-authorship and author analysis the author's name mentioned in the circle, the larger the size of the circle wider the network of collaboration. The lines connecting the author to author represents the related research in the field of dementia.

Among the top authors Kim h. has highest number of documents (n=11) and total link strength is 27 and coming under cluster 4.

**C. R- Biblioshiny analysis**

**Country Collaboration Map**

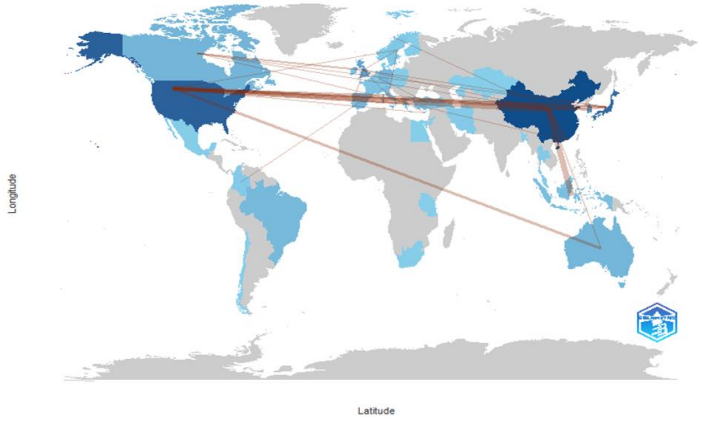


**Figure 5:** Country collaboration map

The map illustrates the country collaboration in the field of research on dementia. The blue color justifies the intensity of the shaded country proportionate to the total number of productions of the country. In the field of dementia, the deeper the color the higher the number of published documents. The deep blue indicated countries has higher number of publications such as China, USA, Australia, Canada and Indonesia and has strong collaboration with each other.

**Citation analysis of documents**

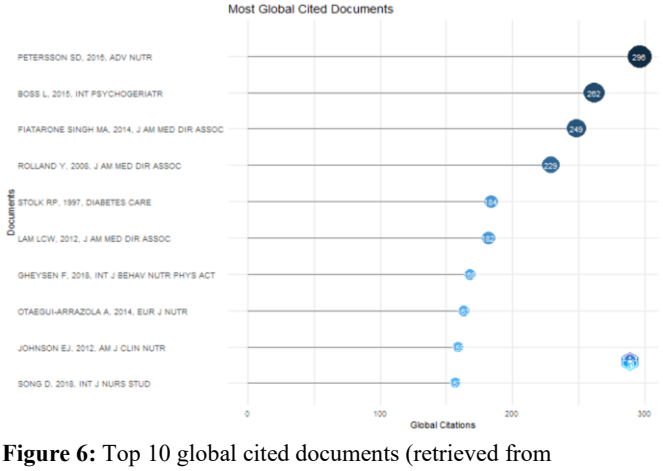


**Figure 6:** Top 10 global cited documents (retrieved from Biblioshiny)

The top ten cited global documents were examined from R studio Biblioshiny. In terms of most cited documents Petersson SD, 2016, ADV NUTR obtained the highest number (n=296) of citation. The next highest cited document is Boss L, 2015, INT psychogeriatric has gathered 262 citations. Following these documents Fiatarone Singh MA, 2014, J AM MED DIR ASSOC received 249 citations. The remaining seven more documents has accumulated a total of 1242 citations. Those documents were authored by Stolk RR etal, LAM LCW et al, Gheysen F et al, Otaegui- Arrazola A et al, Jhonson Ej et al and Song D et al.

**Research trend analysis through Word cloud**


**Figure 7:** Trend analysis through word cloud

The word cloud for current paper is used to study the most occurring words, indicating that the majority of the analysis is done in those areas. [12]

While analyzing the most recurrent research keywords in figure 7, it remarked that the font size of the keywords is positively correlated with the frequency of words. Hence the words which were used more often were seen in bigger font size in the word cloud. [18]

The most frequently used words are aged (558 times), cognition (545, female (435), dementia (419) and so on.

**Author productivity analysis through Lotka's Law**

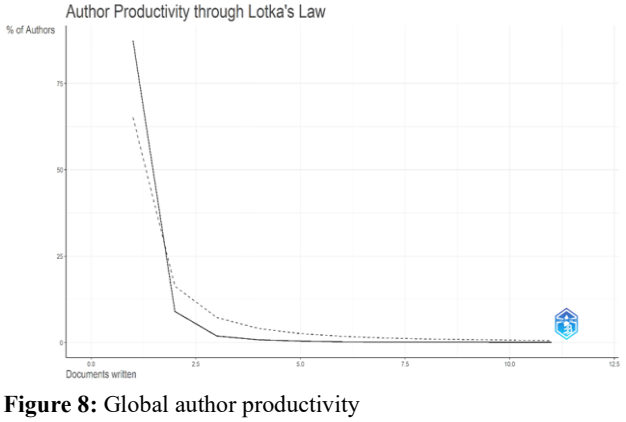


**Figure 8:** Global author productivity

Bibliometrics explains the scientific productivity and its distribution among authors globally based on Lotka's law which was started by Alfred J. Lotka. Agreeing to Lotka's law the number of papers published by the authors is inversely proportional to that number. It uses mathematical distribution of power law. It benefits the author to comprehend the depth of technical productivity and has utilization for study trend assessment, organizational or country collaboration, and study output patterns. [4]

Fig.8 depicts author productivity on dementia and cognitive function. About 87.4% of authors have published one and only paper on dementia and cognitive function, 9% authors published two articles and three papers have published by 1.9% of authors. As per Lotka's law these findings justify that there is a less number of very prolific authors, a substantial quantity of moderately productive authors.

## Discussion

Bibliometric analysis helps to comprehend and explore the history and trends of a research area. [19] The aim of this study was to explore bibliometric research productivity and to throw a light on global productivity in the field of dementia. The significance of dementia and cognitive functioning associated elderly was clearly visible in this bibliometric analysis.

The descriptive Scopus analysis revealed a mark-able growth in research output on dementia which are original article. In terms of country wise research production United States has done extensive investigation on this part and followed by other countries like Taiwan, China and Japan.

In author keyword and cluster analysis in VOS viewer "dementia" is the highest occurring keywords and next to it is "Cognition" and "cognitive impairment" focuses on cognitive health of dementia patient and in terms of collaboration map among the principal author who have published articles on dementia based on co-authorship analysis Kim h. has highest number of documents.

In social structure countries collaboration world map through Biblioshiny analysis China, USA, Australia, Canada and Indonesia and has strong collaboration with each other and possessing utmost number of publications in the area of dementia whereas India has very less publications and collaboration on this aspect may be due to elderly composition is less in comparison to these countries.

In terms of most global cited documents Petersson SD, 2016, ADV NUTR obtained the highest number (n=296) of citation. The next highest cited document is Boss L, 2015, INT psychogeriatric has gathered 262 citations. Following these documents Fiatarone Singh MA, 2014, J AM MED DIR ASSOC received 249 citations.

The world cloud showed the most common keywords were clearly "aged". It is essential to highlight that this keyword could be used as a probing that the document was about clinical research. [12]

At last, a majority of authors have published only one paper, signifying that the total number of authors focusing on the selected area remains inadequate. Lotka proposed the Law of scientific productivity, which describes the frequency of publications by authors in a given field. Lotka's law states that the number of authors who have published in that area should not surpass 60% of the total number of authors, if it is then it is considered to be developed. [20] Those who have published two works should be ¼ of those who have published

one work, and those who have published three works should be 1/9 of those who have published one work (Lotka, 1926). As per Lotka's law the author productivity in current study is less by prolific authors.

The results of the study recommended that the topic should be related to the concern of people living with dementia. [12]. Hence it is clinched that the relevant content related to dementia is limited and needs further research on this aspect.

Though there was a detailed descriptive and quantitative analysis still the study is limited to some areas as publications were limited to Scopus database only which does not index all journals, so articles from other databases (e.g., WOs and PubMed) may have failed to spot. In addition, the publications restricted to nursing field only, which may introduce publication bias. For example, the research in other field like medical science, social science, humanities and psychology may have a greater number of publications which would have given a wide range of research in the field of Dementia.

## Conclusion

Bibliometric analysis is newer adaptive method of published article analysis in medical field by using different software like Vos viewer analysis and R studio Biblioshiny analysis and this study identified significance of conducting study related to dementia as there is still a gap in international collaboration among prolific countries engaged in the field of dementia. As the elderly composition is increasing, India has to take more research initiative in the field of Dementia and their cognitive function. Dementia can be a research hotspot or grey area and may be the focus of future thoughtfulness.

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**Conflict of Interest**

Authors declare no conflict of interest.

**Data availability**

Data are available upon reasonable request.

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**Al-Kindy College Medical Journal (KCMJ)**

*Research Article*

# Effect of Vitamin D3 on Colonization Genes Expression of Haemophilus influenzae Isolated from Children with Otitis Media Associated with Temporomandibular Joint Pain

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***Keywords***: Acute Otitis Media; Gene expression; Haemophilus influenzae; Vitamin D3



**ABSTRACT**

***Background:*** Acute otitis media (AOM) is the middle ear inflammation caused by various microorganisms, including bacteria. Haemophilus influenzae is a common bacterium that causes this inflammatory condition. This study aimed to determine the role of cholecalciferol (D3) in the expression of colonization genes in H. influenzae isolated from children with otitis media, which is associated with temporomandibular joint pain.

***Subjects and Methods:*** A total of 160 ear swabs and blood samples were collected from children with recurrent acute otitis media (AOM) for culture and sensitivity tests. The number of patients with pain in the TMJ was recorded, whether by pressure on the joint area or during mouth opening. Vitamin D3 was measured using an Enzyme-Linked Immunosorbent Assay. The minimum inhibitory and bactericidal concentrations of vitamin D3 were identified. Quantitative real-time PCR was used to evaluate the impact of this vitamin on the expression of pilA, hmw1, and hmw2.

***Results:*** This study showed that H. influenzae caused 28.12 % of AOM, and this inflammation occurred in 30.6% of children aged 1-2 years. Interestingly, 14.38 % of AOM patients had TMJ pain, while 85.62 % did not. Vitamin D3 levels in AOM patients were lower than those in normal children. The current study demonstrated that the expression of colonization genes in H. influenzae, the most common bacterium causing AOM, is upregulated in the absence of vitamin D3. However, these genes' expressions are downregulated in the presence of this vitamin.

***Conclusions:*** This study demonstrated that vitamin D3 inhibited the colonization gene expression of H. influenzae and altered the expression of these genes, suggesting therapeutic roles in infection prevention.

## Introduction

There are two types of ear infections, which are acute suppurative otitis media (ASOM) and chronic otitis media (COM) [1,2]. Acute OM (AOM) usually affects children younger than 2 years old. It starts quickly and shows up as fever and pain in the ear of a child who is already sick in other ways; it is mainly caused by bacteria. If the eardrum perforates, which happens about 5% of the time but has been seen at higher rates, it might be associated with ear discharge [1-3]. In addition, in some cases, the infection from the middle ear can spread to the temporomandibular joint (TMJ), which is a small, complicated

joint in the body. The mandibular ramus joins the condylar process, an ellipsoid hard tissue (bony structure) with a thin neckline [4,5]. Several potential reasons for OA have been recognized. They are inflammatory, metabolic, and mechanical [6]. Pain is the most characteristic sign of TMJ OA [7]. Growth disruption of the craniofacial bone may develop from otitis media on the TMJ. The patient's clinical findings indicate that long-term follow-up is essential to track changes in craniofacial growth in persons with a history of recurrent otitis media [8]. Upper respiratory tract infections caused by bacteria are strongly associated with AOM, which are mainly caused by Streptococcus pneumoniae, Haemophilus influenzae, and Moraxella catarrhalis [9,10]. Respiratory tract infections and invasive diseases like meningitis and septicemia, with underlying illnesses, are caused by nontypeable Haemophilus influenzae (NTHi) among children. Several adherence factors, such as hemagglutinating, pili, and colonization proteins, encourage upper respiratory tract colonization, a necessary condition for illness [11]. Whether particular adhesions contribute to the microorganism's diffusion inside the respiratory tract or to sterile regions is debatable. Over the last ten years, it has become clearer that bacteria have developed various strategies to control gene expression to survive and multiply in hosts during the many stages of infection [12]. Vitamin D3 receptors are found in many cells, suggesting that Vitamin D3 may play a role in the development of infection [1-3]. All immune system cells, especially active T and B lymphocytes, macrophages, and dendritic cells, have vitamin D3 receptors. Researchers found that chemotactic and phagocytic qualities increase in places where vitamin D3 is present. This means that these properties make them better at killing microbes, and now people are interested in how vitamin D3 affects the immune system [2,9,11]. In addition, the development and progression of degenerative joint illnesses, such as temporomandibular joint osteoarthritis, may be significantly influenced by vitamin D3 due to its direct and indirect effects on bones and joints [13]. It was shown that vitamin D and its derivatives may serve as promising molecular therapies for treating bacterial infections, particularly multidrug-resistant (MDR) strains. Vitamin D exhibits antibacterial activity against both Gram-positive and Gram-negative microorganisms. The potential anti-infective effects of antibiotic-free vitamin D treatment and/or adjuvant therapy, in combination with antibiotic compounds, are being explored for the treatment of infectious disorders such as Mycobacterium tuberculosis and H. pylori infections [14]. This study aimed to determine the role of cholecalciferol (D3) on the expression of colonization genes (pilA, hmw1, and hmw2) of H. influenzae isolated from children's otitis media, which is associated with temporomandibular joint pain.

## Subjects and Methods

This study included the collection of 160 ear swabs and blood samples from AOM patients in the otolaryngology department at Al-Khalis Hospital in Diyala. The patient's age was between one and 12 years old. The patients were distributed to 83 males and 77 females. The number of patients with pain in the TMJ was recorded, whether due to pressure on the joint area or during mouth opening. The blood samples were used to measure the levels of vitamin D3.

Patients with acute otitis media (AOM) who were diagnosed in the otolaryngology department at Al-Khalis Hospital, and the number of patients with pain in the temporomandibular joint (TMJ) were included during the study period (individuals aged 1-12 years).

while patients with other AOM diseases in the middle ear and patients who are under antibiotic therapy, which may affect the culture results. Additionally, patients aged 13 years or older were excluded.

**Enzyme-linked Immunosorbent Assay for vitamin D3 measurement**

The levels of vitamin D3 in the AOM patients were measured by ELISA using their blood samples, and a level less than 15 ng/mL was considered vitamin D insufficiency according to the company's instructions (Sigma Aldrich, USA).

**Bacterial growth conditions**

Ear swabs were cultured on MacConkey, Blood, and Chocolate agar medium, supplemented with Vitox (Oxoid Ltd., Basingstoke, Hampshire, UK) at 37°C in the presence of 5% CO2. Positive growth was assessed based on morphological characteristics, including shape, size, margin, consistency, and colour of colonies, as well as microscopic features and biochemical tests. Furthermore, the Vitek II system was used for detecting bacterial proliferation and conducting antibiotic sensitivity tests according to the manufacturer (bioMérieux, France) [15,16].

**Minimum inhibitory (MIC) and bactericidal concentration (MBC)**

H. influenzae colonies were collected from agar plates and cultured into Brain Heart Infusion broth. The inoculated broth was then incubated 24 hours at 37°C with 5% CO2. The bacterial culture was centrifuged at 1600g for 5 minutes, after which the supernatant was discarded. Bacterial cell suspensions (0.2 OD600) were prepared in Brain Heart Infusion (BHI) medium. The microdilution process was performed in a sterile 96-well plate with a total volume of 200 µL. Each concentration of vitamin D (6 mg/ml, 3 mg/ml, 1.5 mg/ml, 1 mg/ml, 0.5 mg/ml, and 0.25 mg/ml) was examined in a doubling dilution series using triple positive controls (BHI and H. influenzae alone). A plate reader was used to measure the optical density (OD600) of the solutions at baseline and over 24 hours at 37°C with 5% CO2. The negative control for each vitamin D concentration consisted of BHI supplemented with each vitamin D concentration alone, without the addition of bacteria. To determine the MBC value for each concentration, decimal dilutions were performed from the MIC solutions. Agar plates were inoculated with 50 µl and incubated overnight at 37°C with 5% CO2. Lastly, the colonies were counted. The MIC and MBC assays were conducted three times [17,18,19].

**Antibiotic Sensitivity Test for H. influenzae**

All bacterial isolates underwent antimicrobial susceptibility testing to identify resistance patterns to commonly used antibiotics, as recommended by the Clinical and Laboratory Standards Institute (CLSI). The Kirby-Bauer disc diffusion method was used as the principal susceptibility testing technique [19]. Briefly, the turbidity of the McFarland standard was adjusted to 0.5 to create bacterial suspensions, which were injected onto Mueller-Hinton agar plates. The inoculation plates were covered with antibiotic discs, which were then incubated for 18 to 24 hours at 35 to 37 °C. The groups of antibiotics that were tested in this study, which are most common antibiotics used to treat this bacterium included aminoglycosides (gentamicin, tobramycin, and streptomycin), carbapenems

(imipenem), extended spectrum cephalosporin (cefotaxime and ceftazidime), penicillins (penicillin and amoxicillin), macrolide (azithromycin and erythromycin), phenicols (chloramphenicol), tetracyclines (tetracycline), lincosamides (clindamycin), glycopeptide (vancomycin), and rifamycins ( rifampicin) [20,21]. Based on the CLSI breakpoints, the results were interpreted as susceptible, intermediate, or resistant. The diameter of the inhibition zones surrounding the antibiotic discs was assessed.

**RNA Extraction of H. influenzae**

The RNA of H. influenzae isolates was extracted by culturing this bacterium in Brain Heart Infusion (BHI) broth supplemented with Haemophilus Test Medium Supplement under conditions of 5% CO2. RNA extraction was performed in the mid-log phase of bacterial culture using the RNeasy Mini Kit (Qiagen, Germany). And then 20 U of RNase-free DNase (QIAGEN S.p.A.) was added to the RNA for 20 minutes at 25°C on the RNeasy columns, according to the manufacturer's guidelines, to remove the contaminated DNA. The extracted RNA was visualised using 1.0% agarose gel electrophoresis [22].

**Determination of Colonization Genes Expression in H. influenzae**

The primers for gene expression were designed using the core-binding domain sections of hmw1A, hmw2A, pilA, and 16SrRNA using DNAMAN sequence analysis software (version 5.2; Lynnon Corp., Quebec, Canada) [23] (Table 1). The primers were used in a LightCycler 2.0 system (Roche, Mannheim, Germany) for quantitative real-time PCR (qRT-PCR) using the SuperScript III Platinum SYBR Green One-Step qRT-PCR kit (Invitrogen Life Technologies Corp). The housekeeping gene (16SrRNA) was used, 1.0 µl One-step enzyme mix, 10.0 µl Syber green 2× (MgSO4 3 mM), 1.0 µl BSA 20×, and 0.25 µM of each primer were included in the qRT-PCR mixture (total volume 20 µl). The RNA was extracted using the RNeasy kit (Qiagen, Germany). The Quantiscript RT kit was used for cDNA production. 10 µL of SYBR Green I (Roche) and 0.5 µL of forward and reverse primers were used. Then, 5 µl of cDNA was mixed with them, and the volume was completed to 20 µl by the addition of nuclease-free water and put in a thermocycler (Roche, Switzerland).The reverse transcriptase steps were firstly, at 50°C for 2 minutes and then a denaturation step at 95°C for 2 minutes, there were 35 amplification cycles, each lasting five seconds at 95°C, ten seconds at 55°C, and ten seconds at 72°C. By amplifying an internal fragment of the 16SrRNA gene using ten-fold serial dilutions of known concentrations (100 ng/µl, 10 ng/µl, 1 ng/µl, 0.1 ng/µl, and 0.01 ng/µl) as templates of genomic DNA to produce quantitative standard curves [22]. For every gene from every H. influenzae isolate, three separate assays were done, each in triplicate.

Expression of H. influenzae Colonization Genes in the Presence of Vitamin D3 as established by the MIC assay, the MIC is 0.5 mg/ml. Therefore, the concentration 0.25 mg/ml of vitamin D3 was used to examine the impact of this vitamin on the expression of genes of H. influenzae, which was treated with this concentration of vitamin D3, and the no-treatment (control) group. Brain heart infusion broth (BHI) containing cholecalciferol at the above concentration was inoculated with H. influenzae. Following the manufacturer's recommendations, the cultures were cultured for 24 hours at 37°C and 5% CO2 before being pelleted at a weight of more than 10,000g. The RNA from the collected cells was extracted using the RNeasy kit (Qiagen, Germany). A spectrophotometer (DeNovix, USA) was then used to determine the amount of RNA, and the Quantiscript RT kit (Qiagen) was used to generate equimolar amounts of cDNA. SYBR Green I (Roche) was used in qPCR experiments, with 10 µL and 0.5 µL of each forward and reverse primer per well. Then, 5 µl of cDNA was added to them. Then the volume was completed to 20 µl by addition of nuclease-free water after being placed in a thermocycler (Roche, Switzerland), and the samples were subjected to denaturation (95°C) and activation (50°C). 40 amplification cycles at 60°C for 1 minute and 95°C for 3 seconds were achieved, and then, the cooling phase and melting curve were programmed. Because it is stable in various environmental settings, the housekeeping gene (16SrRNA) was used to normalize the gene expression data [24].

**Table 1:** The RT-PCR primers used to determine the gene expression.

| Primers | Sequence (5′–3′) | Size (bp) |
|---|---|---|
| *16SrRNA-F* | TCCTAAGAAGAGCTCAGAGAT | 120 |
| *16SrRNA-R* | TGATCCAACCGCAGGTTCC | |
| *PilA-F* | CTATATACACATAATTCCACATCAGCCTTA | 125 |
| *PilA-R* | CCACCATCGCAATTCCTTCTT | |
| *hmw1-F* | CCGGTGGTTTTGTGGAGACGTCG | 133 |
| *hmw1-R* | TGAAGTATTGCTGCGTCCTG | |
| *hmw2-F* | CCGGTGGTTTTGTGGAGACATCG | 121 |
| *hmw2-R* | GCGAAGGGGGTCTTCGGCTTCA | |

The Statistical analysis was done by using Packages for the Social Sciences program (SPSS, 2019) to identify the differences among the groups and factors in this study [25]. The Chi-square test was used to determine the significant differences between percentages at 0.05 and 0.01 probability levels. Results were categorized as Significant (P≤0.05), Highly Significant (P≤0.01), and NS = non-significant.

## Results

This study revealed a distribution of 83 males (51.87%) and 77 females (48.13%), with no significant differences found between the two groups. This study showed that 30.63 % of AOM patients were less than two years of age. However, the cases of AOM decreased in children older than six years old. It was found in this study that the AOM patients who had TMJ pain were 5.63% male compared to 8.75% female, and the AOM patients without TMJ pain were distributed as 46.25% male and 39.38% female. The number of patients who had pain in the TMJ, whether from pressure on the joint area or while opening the mouth, was recorded (Table 2), and the results of current study showed that 14.38 % of AOM patients had TMJ pain and 85.62 % of patients without TMJ pain, with a significant difference between them (P≤0.0001).

**Table 2:** Distribution of patients according to results of TMJ pain.

| TMJ pain | No | Percentage (%) |
|---|---|---|
| Yes (+ve) | 23 | 14.38 |
| No (-ve) | 137 | 85.62 |
| Total | 160 | 100% |
| Chi-Square: $\chi^2$ | --- | 81.225 *** |
| (P-value) | | (0.0001) |
| **** (P≤0.0001) | | |

This study showed that the mean ± SEM of Vitamin D3 in AOM patients was 13.13 ± 0.457 ng/mL, which is considered vitamin D insufficiency in these patients (Figure 1).

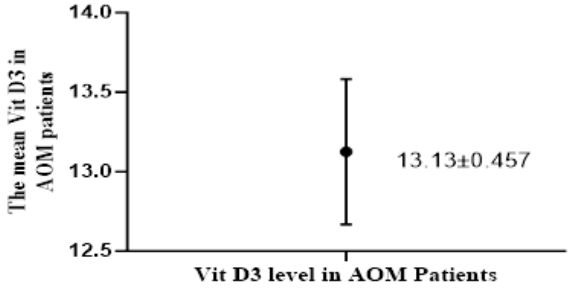


**Figure 1:** The mean of vitamin D3 in AOM patients

**Table 3:** Fold difference in expression of genes of H. influenza in the presence of vitamin D3 relative to their expression in the absence of vitamin D3 using qRT-PCR. '- 'indicates down-regulation of genes, ± represents the standard deviation for three measurements Gene taq.

| Gene name | Gene Function | Fold difference in the absence of vitamin D3 | Fold difference in the presence of vitamin D3 |
|---|---|---|---|
| *pilA* | Colonization, biofilm formation | 61.12 ± 0.03 | -2.8 ± 0.05 |
| *hmw1* | Adhesion, colonization | 4.07 ± 0.08 | -3.3 ± 0.02 |
| *hmw2* | Adhesion, colonization | 2.8 ± 0.45 | -4.01 ± 0.12 |

This study identified the bacterial species that caused AOM in patients. It showed that 28.12% of AOM cases were caused by H. influenzae, followed by S. pneumoniae (15%), Pseudomonas aeruginosa (14.73%), and K. pneumoniae (12.5%). However, Serratia appeared to be one of the few bacteria that cause AOM, as its percentage is 3.13%.

The results showed that azithromycin, vancomycin, and cefotaxime were the most effective antibiotics for H. influenzae growth because this bacterium appeared sensitive against them at 84.4%, 84.4%, and 80%, respectively. However, this bacterium appeared to be 100% resistant to tobramycin, 84.4% resistant to gentamicin, and 73% and 62.2% resistant to tetracycline and erythromycin, respectively.

The results showed that the expressions of pilA, hmw1, and hmw2 appeared to be downregulated in the presence of vitamin D3. On the other hand, the expression of these genes appeared up-regulated in the absence of this vitamin (Table 3).

## Discussion

Acute otitis media is more likely to happen during winter when upper respiratory tract infections are most common. This is because viral and bacterial respiratory tract illnesses raise the risk of AOM. The existing study exhibited that the percentage of TMJ pain in patients was 14.38%. This may be clarified by the fact that the side effects of otitis media that lead to septic arthritis involve the transmission of infection from the middle ear to the temporomandibular joint (TMJ) [26,27]. Direct or hematogenous spread through the synovial blood vessels can cause involvement of the TMJ. One of three routes (congenital cartilaginous canal dehiscence, dehiscent squamotympanic fissures, or unable to close Huschke's foramen) can spread from the ear to the TMJ [27,28]. Additionally, reports suggest that distinguishing between septic and reactive arthritis can be challenging, particularly in atypical cases, such as those involving H. influenzae infections. Currently, there are no guidelines addressing the potential for concurrent arthropathies, which complicates treatment strategies. While corticosteroids are typically prescribed for reactive arthritis, they may adversely affect septic arthritis. Early initiation of antibiotic therapy aimed to prevent sepsis and complications from septic arthritis. Continued suspicion of septic arthritis, even when symptoms suggest reactive arthritis, led to effective treatment outcomes. There is a pressing need for evidence-based guidelines to assist physicians in managing multiple arthropathies [29].

Microflora bacteria that live in the nose and throat often cause AOM illnesses. This study showed that H. influenzae and S. pneumoniae were the most common bacteria that cause AOM. Similarly, it was reported that S. pneumoniae, and H. influenzae are the most critical bacteria and cause 10 to 40 percent of AOM cases. If the right care isn't given, problems can happen that can be life-threatening [30]. Individual sensitivity is shown by the different infection rates in children from the same social background. The current study showed that all the AOM patients had vitamin D3 insufficiently as determined in the serum of patients using ELISA, which is the best serological method [31,32]. A vitamin D3 insufficiency was reported among the OM patients, which shows a link between OM and vitamin D3. Vitamin D targets have been present in the skin, stomach, liver, thymus, breast, parathyroid glands, and lymphocytes. These studies have shown that vitamin D does more than help the body utilize calcium [2, 9]. There is a strong link between vitamin D and both innate and acquired immunity. Microorganisms are killed by antimicrobial peptides (defensin, cathelicidin) and reactive oxygen products released by natural defence [33,34]. Calprotectin and S100 proteins, which are natural immune system factors that play a significant role, also increase when Vitamin D is active [33]. Cathelicidin is made when there is an infection

in the skin because it activates the Toll-like receptor (TLR) in keratinocytes. Vitamin D and the body's natural immune system are thought to work together to protect against germs in the surroundings. This affects the location of the infection [35]. It has been shown that when Vitamin D3 is present, the monocytes and macrophages' chemotactic and phagocytic abilities improve, as well as their ability to kill microbes. [36,37]. The results of this study showed that vitamin D3 plays a significant role in the expression of colonization genes in H. influenzae, and these results agreed with other studies that found that not getting enough vitamin D3 has been linked to a higher chance of sinusitis, upper and lower respiratory tract infections [24]. It was suggested that Vitamin D3 could raise these levels. Vitamin D3 has also been shown in some tests to be effective as an extra treatment for many illnesses [38,39,40]. Furthermore, it was reported that vitamin D3 decreases P. gingivalis growth and diminishes the expression of its virulent factor genes. This dual effect on P. gingivalis with the inflammatory response in host cells promises to develop an innovative and cost-effective therapeutic approach. Specifically, 1,25(OH)2D3 lowers the virulence of P. gingivalis by reducing the expression of genes responsible for virulence factors, including adhesins (fimA, hagA, and hagB) and proteinases (rgpA, rgpB, and kgp) [41]. In addition, this study is the first to determine the role of vitamin D in the colonization genes expression in a fastidious bacterium that causes the majority of AOM.

**Conclusion**

We investigated the role of cholecalciferol (D3) in the expression of colonization genes of H. influenza. The microbe isolated from children's otitis media. Vitamin D3 may improve the outlook for individuals with severe otitis media. There is a strong link between vitamin D3 deficiency and the long-term effects of otitis media. H. influenzae is the most common cause of AOM. This current study showed that the expression of colonization genes in H. influenzae is up regulated without vitamin D3. On the other hand, these genes' expressions are downregulated in the presence of this vitamin. In summary, Vitamin D3 plays a significant role in the expression of genes in this bacterium.

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**Conflict of Interest**

Authors declare no conflict of interest.

**Data availability**

Data are available upon reasonable request.

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*Research Article*

# Applying the Principles of Sustainability to Diabetes Care in Low Resources Settings: Reduce, Reuse, Recycle

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**ABSTRACT**

***Background:*** Sustainability in healthcare is a relatively new concept that aims to integrate environmental, financial, and social factors. Diabetes care in low socioeconomic communities relies on disposable medical supplies, leading to increased waste. This study aims to propose the application of the (reduce, reuse and recycle) framework in diabetes care to enhance sustainability

***Subjects and Methods:*** This study used a mixed-methods approach, including both a literature review and a pilot survey. The literature review included fifty studies focusing on sustainable healthcare practices. A survey was conducted among fifty healthcare professionals and fifty patients to assess their baseline knowledge about practices related to sustainability in healthcare. Results were analyzed to assess similarities or differences between high and low socioeconomic communities

***Results:*** The survey revealed that 63% of patients thought treatment costs was the primary barrier to sustainability, while 50% of healthcare providers pointed to limited resources. Both groups emphasized the need for government support and education to enhance sustainability efforts. Reusable insulin pens and eco-friendly packaging were the most viable solutions.

***Conclusions:*** Applying sustainability to diabetes care can reduce both environmental and economic burdens. This is particularly challenging in low-resource settings, where cost and infrastructure limitations persist. Policy reforms, education, and innovation to reduce waste is essential to achieve a sustainable healthcare system.

## Introduction

Sustainability in healthcare is an evolving concept that aims to integrate the environment's health, equal distribution of resources, and economic stability to build enduring communities for future generations. It is a multidimensional concept that requires a systematic approach to managing current resources in a responsible way for the future [1]. While sustainability is often seen as a modern concept, it is a deeply rooted tradition of Indigenous communities, who have long honored the natural cycles and limits of the environment [2].

In healthcare, sustainability extends beyond financial consideration. It also encompasses the social and environmental responsibilities. The treatment of diabetes involves the frequent use of disposable medical supplies, such as insulin pens, blood glucose monitors, and test strips, which generate substantial waste. This issue is even more pronounced in low-resource communities, where the

environmental burden can further exacerbate the financially strained healthcare system.

The Centre for Sustainable Healthcare has proposed four key principles to reduce healthcare's environmental footprint while maintaining or improving health outcomes: prevention, patient empowerment and self-care, lean pathways, and the use of low-impact technologies [3]. Despite these guidelines, healthcare remains a significant contributor to global carbon emissions, with the sector responsible for 3-10% of national carbon footprints in countries such as Mexico, the UK, and the USA [4].

The financial implications of diabetes care are concerning. The total estimated cost of diagnosed diabetes in 2017 was $327 billion in the USA, including $237 billion in direct medical costs of treatment and investigations and $90 billion in reduced productivity of affected patients [5]. Besides financial costs, the environmental impact of diabetes management, including the disposal of plastic waste from medical supplies, has become an emerging topic of concern [6]. Studies have shown that in diabetes care, the product often represents only a small portion of the total waste generated, with packaging materials accounting for up to 90% of the volume [7]. Diabetes mellitus affects approximately one out of every eleven people worldwide, and the International Diabetes Federation (IDF) predicts that 1.1 million children and adolescents between the ages of 14 and 19 have T1DM [8].

Efforts to address this issue have led to the concept of "green diabetology," which aims to reduce medical waste by encouraging practices such as using reusable insulin pens, optimizing packaging, and recycling medical products [9].

This study aims to explore how the principles of sustainability (reduce, reuse, and recycle) can be applied to diabetes care in low-resource settings such as Iraq, whose healthcare system suffered from multiple crises 10. The role of healthcare facilitators is also highlighted as models for sustainable practices who can promote the adoption of eco-friendly initiatives [11]

## Subjects and Methods

This study uses a mixed-methods approach using a literature review and a survey. The systematic review gathered findings from existing literature, while the pilot survey collected data from healthcare professionals to assess practical challenges and opportunities in implementing sustainable diabetes practices.

Regarding the literature review section, Databases including Scopus, PubMed, and Google Scholar were searched for studies on sustainability in diabetes management and its environmental impact. The review included studies from 2013 to 2024. According to PRISMA guidelines, the main points extracted from each study included sustainability initiatives (e.g., reusable insulin pens, eco-friendly packaging), outcomes related to waste reduction, patient empowerment, and cost savings and challenges faced in implementing these initiatives in low-resource settings. At the same time, a pilot survey was distributed to 100 healthcare professionals, including endocrinologists, diabetes educators, and nurses, and 100 diabetic patients who visited outpatient clinics over two months (July–September 2023). The survey questions were grouped into the following categories:

1. Awareness of sustainable healthcare practices and their importance.
2. Challenges in implementing sustainable interventions.
3. Willingness to adopt new technologies like telemedicine and eco-friendly medical devices.

The research team self-developed the survey questionnaire based on a review of the existing literature on sustainable healthcare practices. Two physicians independently reviewed it and pre-tested it on a small group of participants for clarity and relevance.

Data from the literature review and the pilot survey were synthesized through a thematic analysis approach. The literature review provided insight into the theoretical frameworks, which were compared against the survey results, which reflect real-world practices, challenges, and proposed solutions.

Ethical Considerations: The ethics committee of Al-Kindy College of Medicine gave ethical approval. All participants gave informed consent.

## Results

PRISMA flow chart

Records were identified through database searching (PubMed, Scopus), and 200 additional records were identified through other sources (e.g., reference lists): 30. After removing duplicates, 180 were screened based on title and abstract. One hundred records were excluded due to irrelevance or studying the wrong population.

Eligibility: Full-text articles assessed for eligibility:80Full-text articles excluded (e.g., irrelevant focus, incomplete data): 30 Studies included in qualitative synthesis: 50

The final PRISMA flow chart summary is summarized in Figure 1.

Ten studies were randomized controlled trials, 15 were cohort studies, and 25 were systematic reviews or meta-analyses.

Most studies (n = 30) involved patients with Type 2 diabetes across various countries, with sample sizes ranging from 500 to 10,000 participants. Ten studies focused specifically on healthcare providers and their role in delivering sustainable care.

Twenty studies evaluated the implementation of sustainable practices in healthcare (e.g., reducing waste and designing energy-efficient hospitals). In contrast, other studies examined the impact of community interventions, such as promoting sustainable diets for diabetes prevention.

Fifteen studies focused on diabetes outcomes (HbA1c control, complication reduction), while 25 studies examined sustainable healthcare interventions' environmental and economic impact.

Thirty studies were conducted in high-income countries (e.g., the U.S., the U.K., and Australia), while 10 studies were conducted in low-resource settings (e.g., sub-Saharan Africa and Southeast Asia).

Studies consistently found that sustainable practices, such as plant-based diets and energy-efficient healthcare practices, positively impacted environmental and patient health outcomes. Table (1) includes a summary of study characteristics.

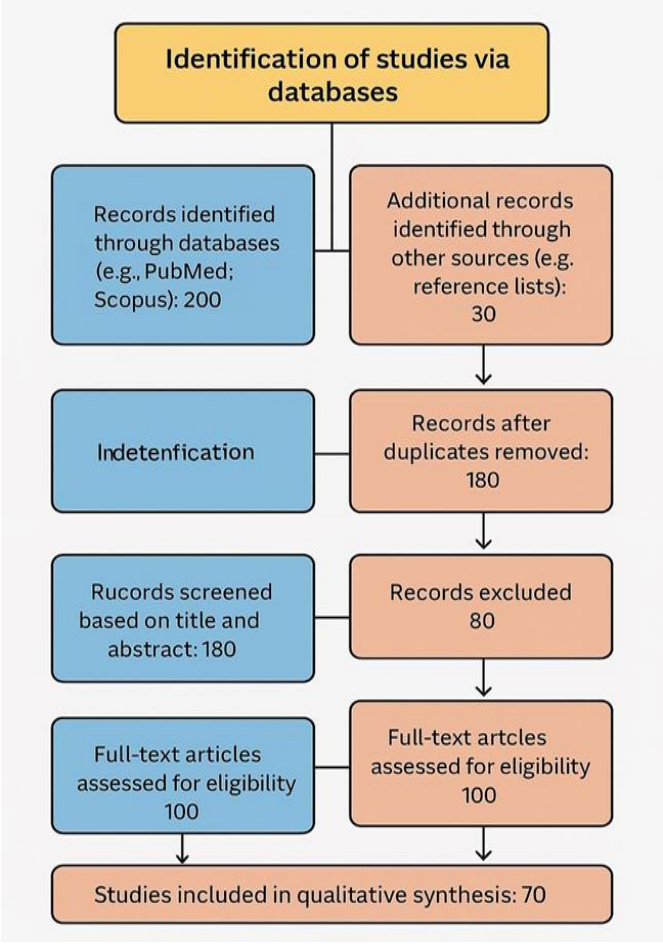


Figure 1: Summary of PRISM flow chart 1

**Table 1:** Study Characteristics

| Characteristic | Details |
|---|---|
| Study Design | RCT (n=10) |
| | Cohort (n=15) |
| | Meta-analyses (n=25) |
| Population | DM2 patients(n=30) |
| | Healthcare providers (n=20) |
| Interventions focus | Sustainable healthcare practices (n=30) |
| | Community practices (N=20) |
| Outcomes | Health outcome (n=15) |
| | Environmental impact (n=25) |
| Geographical Location | Low resources settings n=30. |
| Time frame | (2010-2024) |
| Key Findings | Positive impact on both health outcomes and environmental sustainability. |

The review includes 50 studies. They were categorized into three groups based on study design, type of intervention, health outcomes, and population studied. Most of the studies were meta-analyses (n = 25), followed by 15 cohort studies (15) and 10 randomized controlled trials.

Twenty studies focused on healthcare-sustainable practices, such as waste reduction, while 15 studies examined the effect of sustainable nutrition on diabetes control. Most studies took place in high-income countries (n = 30), while twenty in low- and middle-income countries. Summary of categorical grouping of studies is illustrated in table (2) and table (3).

**Table 2:** categorical grouping of studies

| Category | Number of studies |
|---|---|
| Study design | |
| RCT | 10 |
| Cohort | 15 |
| Meta-analyses | 25 |
| Type of intervention | |
| Healthcare | 20 |
| Community | 15 |
| Environmental | 10 |
| Outcome | |
| DM control | 20 |
| Environmental impact | 25 |
| Economy | 15 |

The largest age group is 55-65 (45%), followed by 25-35 (32%). The sample was predominantly male (62%). The majority (52%) use oral medication, while 30% use oral medications and insulin, and only 18% are insulin dependent. Most patients get treatment from private pharmacies (57%), while 43% get treatment from governmental centers. Approximately 70% of participants lived in urban areas, while 30% were from rural or semi-urban settings. Regarding the educational background, 28% had completed only primary education, 42% had secondary education, and 30% held a college degree.

A significant proportion (68%) were unaware of the concept of sustainability and its benefits to healthcare. Similarly, 25% were unaware of the environmental benefits. Only 12% have attended formal diabetes care programs, while 85% received basic education from healthcare providers.

The most mentioned challenge was the high monthly cost of treatment (63%), followed by availability issues (22%) and distance (11%).

The most common suggestion (45%) was for the government to provide more treatment options and Continuous Glucose Monitors (CGMs). Educational activities (18%) and more nearby centers (12%) were also important.

The majority of healthcare professionals surveyed were doctors, including 25 specialists and 18 residents. Most professionals (42%) had 10-15 years of experience.

Challenges were limited Resources (50%) and lack of supportive infrastructure (34%) were the most frequently mentioned challenges, followed by lack of Faculty Training (29%).

Regarding awareness, while 59% had read or heard about sustainability, many still lack a deep understanding of how to apply these principles practically in healthcare.

**Table 3:** Categorization of Studies on Sustainability in Diabetes Care

| Category | Study | Focus/Topic | Study Type | Key Findings/Outcome |
|---|---|---|---|---|
| Sustainability in Healthcare Practices | Aziz et al. (2018) | Integrating sustainability into diabetes care | Systematic Review | Sustainability in diabetes care reduces cost and improves patient outcomes. |
| | Boulet et al. (2020) | Climate change and respiratory health impact | Observational Study | Climate change indirectly worsens diabetes management. |
| | Peters et al. (2019) | Addressing diabetes epidemic | Case Study | sustainable practices in healthcare systems are crucial to fight diabetes epidemic. |
| Sustainable Diets | Augustin et al. (2020) | Use of vegetarian diets for diabetes prevention | Meta-analysis | Plant-based diets lower the risk of type 2 diabetes. |
| | McCombie et al. (2020) | lifestyle interventions to induce DM remission | Randomized Controlled Trial | Lifestyle sustainable interventions can lead to diabetes remission |
| Social Determinants and Equity | García-Pérez et al. (2019) | Impact of social determinants on diabetes | Observational Study | Socioeconomic factors influence diabetes outcomes. |
| | Khunti et al. (2020) | Socioeconomic disparities in diabetes care | Systematic Review | Addressing disparities in diabetes care requires targeted and sustainable health policies. |
| Economic Impact and Cost-Effectiveness | Bommer et al. (2017) | Global economic burden of diabetes | Economic Analysis | Diabetes-related costs are rising globally; sustainability initiatives can reduce these costs. |
| | Luo et al. (2020) | Cost-effectiveness of diabetes interventions | Cost-Effectiveness Study | Sustainable diabetes interventions are cost-effective in both short and long-term outcomes. |
| Technological Interventions | Frier et al. (2020) | Technology in diabetes management | Systematic Review | Technology-driven care improves diabetes management and sustainability. |
| | Kang et al. (2020) | Impact of technology on glycemic control | Observational Study | Digital tools enhance glycemic control, offering sustainable diabetes solutions. |
| Environmental Factors and Diabetes | Kolb et al. (2020) | Environmental determinants of type 2 diabetes | Observational Study | Environmental pollution and urbanization contribute to diabetes prevalence. |
| | Mohammadi et al. (2020) | Built environment's effect on diabetes | Meta-analysis | Walkable, green environments reduce type 2 diabetes risks. |
| Global and Regional Trends | GBD 2017 Diabetes Collaborators (2019) | Global diabetes burden | Global Health Report | Rising global burden of diabetes necessitates sustainable care models across different regions. |
| | Gregg et al. (2018) | Global trends in diabetes complications | Systematic Review | Complications of diabetes are increasing globally, demanding sustainable interventions. |
| Category | Study | Focus/Topic | Study Type | Key Findings/Outcomes |
| Sustainability in Healthcare Practices | Aziz et al. (2018) | Integrating sustainability into diabetes care | Systematic Review | Sustainability in diabetes care reduces cost and improves patient outcomes. |
| | Boulet et al. (2020) | Climate change and respiratory health impact | Observational Study | Climate change worsens respiratory conditions, indirectly affecting diabetes management. |
| | Peters et al. (2019) | Addressing diabetes epidemic | Case Study | Using sustainable practices in healthcare systems is vital for managing the diabetes epidemic. |
| Social Determinants and Equity | García-Pérez et al. (2019) | Impact of social determinants on diabetes | Observational Study | Socioeconomic factors significantly influence diabetes outcomes. |
| | Khunti et al. (2020) | Socioeconomic disparities in diabetes care | Systematic Review | disparities in diabetes care requires targeted and sustainable health policies. |
| Economic Impact and Cost-Effectiveness | Bommer et al. (2017) | Global economic burden of diabetes | Economic Analysis | sustainability initiatives can reduce Diabetes-related costs |
| | Luo et al. (2020) | Cost-effectiveness of diabetes interventions | Cost-Effectiveness Study | Sustainable diabetes interventions are cost-effective on short and long term. |
| Technological Interventions | Frier et al. (2020) | Technology in diabetes management | Systematic Review | Technology-driven care improves diabetes management |
| | Kang et al. (2020) | Impact of technology on glycaemic control | Observational Study | Digital tools enhance glycaemic control in sustainable way. |
| Environmental Factors and Diabetes | Kolb et al. (2020) | Environmental determinants of type 2 diabetes | Observational Study | Environmental pollution and urbanization contribute to diabetes prevalence. |
| | Mohammadi et al. (2020) | Built environment's effect on diabetes | Meta-analysis | Walkable, green environments reduce type 2 diabetes risks. |
| Global and Regional Trends | GBD 2017 Diabetes Collaborators (2019) | Global diabetes burden | Global Health Report | burden of diabetes necessitates sustainable care models |
| | Gregg et al. (2018) | Global trends in diabetes complications | Systematic Review | Complications of diabetes demand sustainable interventions. |

**Solutions**

Training for Faculty: 20 professionals (29%) believe that faculty training is essential to spread sustainability knowledge.

Government Resources: The most popular solution (50%) involved the government providing sustainable tools, such as Continuous Glucose Monitors (CGMs) and e-records.

Infrastructure Improvements: 34% suggested upgrading waste disposal systems and healthcare infrastructure to facilitate the adoption of sustainable practices.

Integration of systematic review findings with pilot study results

Challenges

Literature: The systematic review identified several barriers to implementing sustainable practices in healthcare, including the high cost of sustainable technologies, lack of governmental support, and limited healthcare infrastructure.

Patients: 63% of patients reported the biggest challenge as the cost of diabetes treatment. Other challenges include the unavailability of some medications (22%), long travel distances to healthcare facilities (11%), and storage problems (4%).

Healthcare Professionals: The primary challenges for professionals are limited resources (50%) and a lack of supportive infrastructure (34%). Of these, 29% mentioned inadequate faculty training.

Integration: Both patients and healthcare professionals pointed to similar problems limiting optimal sustainable care, mainly cost and resource limitations, similar to the challenges outlined in the literature. The financial burden of diabetes care is a major barrier for patients, while professionals see unsupportive infrastructure and limited training as key obstacles. This highlights the need for infrastructural reforms and economic facilities to support sustainable healthcare. These comparisons are summarized in Table 4.

Awareness and Education

Literature: The review advocates for increased education on sustainability in healthcare for healthcare providers and patients.

Patients: Only 12% of patients attended formal diabetes education programs, and 85% reported receiving only basic education from healthcare providers. 68% were unaware of sustainability principles and benefits in healthcare.

Healthcare Professionals: Although 59% were aware of sustainability concepts, only 29% believed that faculty training was sufficient to spread awareness of these principles.

Integration: Both patients and healthcare professionals demonstrated an awareness gap consistent with the literature. This further supports the literature's call for education and awareness campaigns targeting patients and professionals.

Practical Solutions

Literature: The systematic review highlights practical solutions, such as using reusable insulin pens, reducing packaging waste, and improving recycling in healthcare facilities to reduce the environmental footprint and achieve cost savings over time.

Patients: Regarding solutions, 45% of patients suggested that the government should provide more treatment options, including Continuous Glucose Monitors (CGMs); 18% believed that educational activities focused on diet and insulin use would improve care.

**Table 4:** challenges in implementing sustainability

| Source | Challenges for the patient | Challenges for HCP | Challenges in literature |
|---|---|---|---|
| Cost | 63% cited the high cost of treatment | 50% faced struggles of limited resources due to high expenses | High cost of sustainable technologies |
| Availability | 22% complain from lack of availability of necessary treatments | Limited resources | Lack of infrastructure in low resources countries |
| Distance | 11% suffer from distance to nearby health centre | 34% complained from lack of infrastructure | Logistical challenges |
| Storage | 4% suffered from degraded treatment due to lack of necessary storage Environment | Lack of faculty training (29%) | Limited education and institutional support |

**Table 5:** awareness and education of sustainability

| Source | Patients | Healthcare Professionals | Literature |
|---|---|---|---|
| General Awareness | 68% are unaware of sustainability principles | 59% are familiar with sustainability principles | Need for greater sustainability education |
| Formal Education | Only 12% attended formal diabetes education program or course | 29% believe there is lack of faculty training | Education of patients and healthcare providers is essential |
| Basic Knowledge | 85% received basic education from their HCP | | Training is essential to widespread adoption |

Healthcare Professionals: 50% of professionals thought that the government should supply resources like CGMs and insulin pens, while 29% emphasized the need for training to spread awareness

about sustainability. Infrastructure improvements that focus particularly on waste disposal were mentioned by 34% of respondents.

Integration: Both patients and healthcare professionals align with the literature in calling for governmental support in providing sustainable technologies like CGMs and insulin pens. This mirrors the literature's emphasis on long-term cost savings and reduced waste through reusable medical devices. The need for patient education, identified by both groups, is consistent with the literature's emphasis on sustainability-driven healthcare reforms. Figures 2 and 3 illustrate a summary of the review outcomes and policy suggestions.

**Table 6:** suggested solutions for sustainable diabetes care

| Source | Patients | HCP | Literature |
|---|---|---|---|
| Treatment options | 45% want more treatment options such as CGM. | 50% suggested more support from government regarding CGM and insulin pens. | Use of reusable insulin pens and ecofriendly packaging. |
| Educational programs | 18% want more education about diet and insulin use. | 29% suggested faculty training to improve awareness. | Importance of education to promote sustainability. |
| Government support | 45% want the government to supply more resources. | 50% want the government to be more involved. | Government policy and funding. |
| Infrastructure | | 34% recommended infrastructure improvement. | Infrastructure development in the form of waste reduction. |

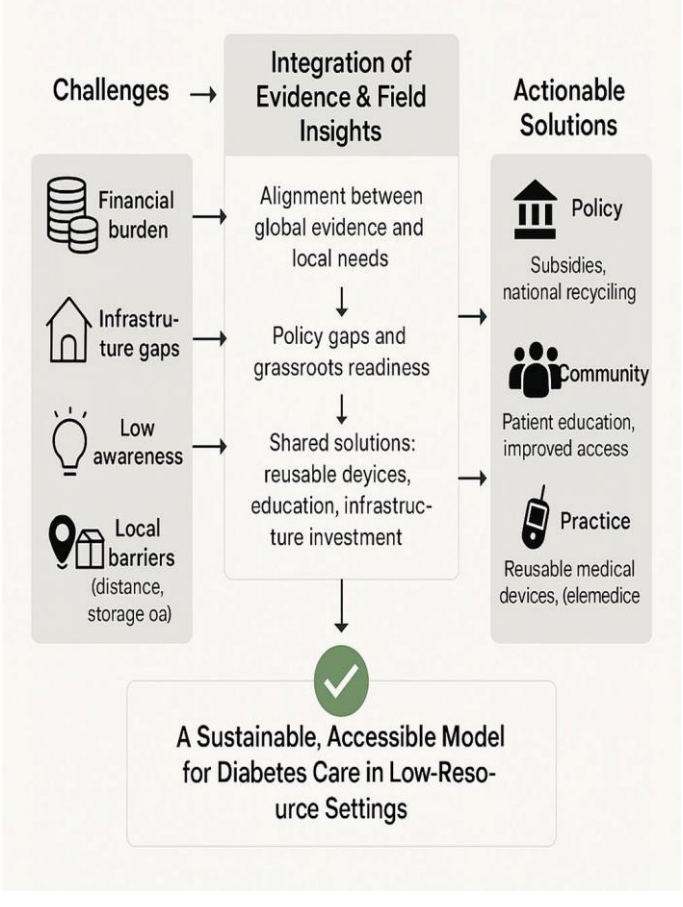


Figure 2: A Conceptual Framework for Implementing Sustainable Diabetes Care in Low-Resource Settings: From Challenges to Actionable Solutions.

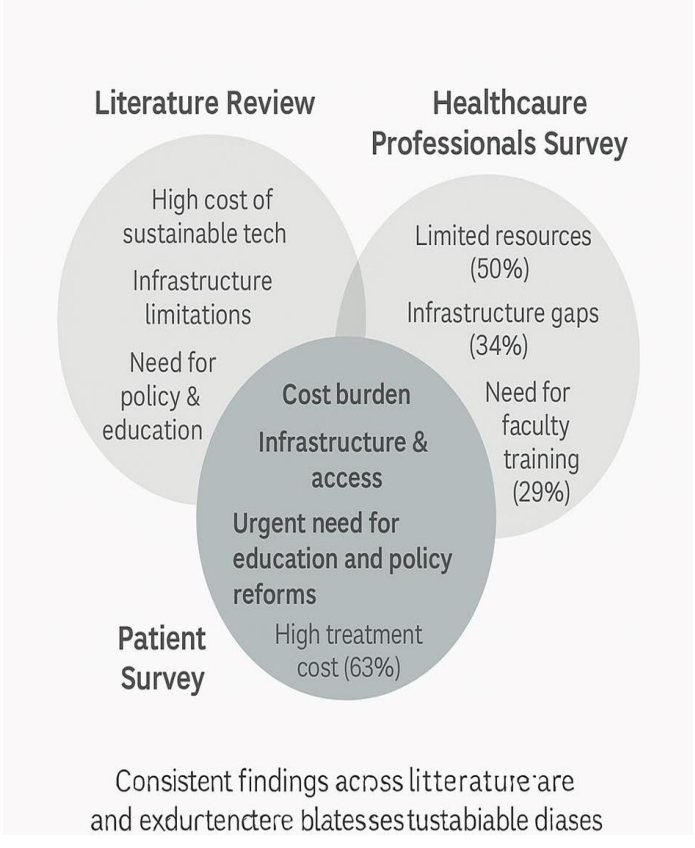


Figure 3: Triangulated Findings from Literature, Patient, and Healthcare Professional Surveys Highlighting Key Barriers and Policy Needs in Sustainable Diabetes Care

## Discussion

Applying the 3R framework in Diabetes Care: Reducing Waste, Reusing Resources, and Recycling for a Sustainable Future.

The "Reduce, Reuse, Recycle" framework provides an actionable approach to integrating sustainability into the diabetes healthcare system. Given the significant waste generated by diabetes care, real-world case studies discuss and support each component of the 3R model.

**Reduce: Minimizing Waste in Diabetes Care**

Reducing waste is fundamental to minimizing the environmental impact of diabetes care, such as plastic and packaging waste generated by essential supplies like blood glucose test strips, CGM systems, and insulin pens [28].

In Germany, diabetes clinics replaced paper information booklets with QR codes on packaging, reducing paper waste by 25%. Patients could access instructions digitally without the need for excessive printed materials. [29].

In the UK, another project switched to biodegradable packaging for insulin pens and test strips and reduced plastic waste by 30% over two years [30]. According to Defruyt, only 2% of plastic packaging is recycled into new materials, with much of it dumped in landfills 29.

**Reuse: Promoting Reusable Insulin Pens and Medical Devices**

Using reusable devices presents an opportunity for substantial environmental and cost savings.

In Denmark, Novo Nordisk's switch to reusable insulin pens reduced plastic waste by 50%, saving over 80 tons of plastic annually, the equivalent of more than 1.5 million disposable pens. The program also reduced healthcare costs for patients and providers, demonstrating how reusability can benefit both the environment and the healthcare system [31].

The NHS documented that reusable insulin pens significantly save plastic waste and costs. The program reduced the overall carbon footprint by 4.5 kgCO2e per patient, with annual cost savings of up to £22.30 per patient [31].

**Recycle: Enhancing Recycling Programs for Medical Waste**

Recycling medical waste is essential, but it remains a challenge due to the complexity of medical products. For example, recycling CGM sensors and insulin pumps involves disassembling plastic components and properly disposing of biohazardous materials [32].

A successful initiative in Sweden where patients mailed back used needles, lancets, and CGM components significantly reduced the amount of inappropriately disposed medical waste [30]. Roche also introduced a program to recycle used glucose monitors and infusion sets for future manufacturing 30. Some glucose test strips are now made from biodegradable materials, which can significantly reduce the amount of non-recyclable waste generated by daily testing [30].

**Equitable access and distribution**

One significant ethical concern is the fair distribution of sustainable healthcare technologies, such as reusable insulin pens or biodegradable medical products. While these innovations can reduce environmental harm and lower costs in the long run, they may not be affordable or readily available to all patients, particularly in low—and middle-income countries. To address this, governments and health organizations should ensure equitable access to environmentally friendly medical products for low-income patients.

Rural communities and individuals with lower socioeconomic status often face barriers to healthcare facilities. For example, reducing packaging waste or switching to reusable devices may be environmentally beneficial but unavailable in low-resource communities [33].

A significant difference is noted between high- and low-resource settings in terms of sustainable diabetes care. While studies from high-income countries mention reusable insulin pens, biodegradable packaging, and governmental policies to reduce waste, these solutions are largely inaccessible in low-income regions.

**Comparison Between Low-Resource and High-Resource Settings**

There is a notable difference between high- and low-resource settings regarding the implementation of sustainable healthcare. Switching to reusable insulin pens resulted in 80 tons of waste reduction annually, [34]. Similarly, a study from the Netherlands documented the successful use of recycling systems to segregate waste [35]. This success is contrasted by the results of a survey from sub-Saharan Africa, which reported that lack of infrastructure and insufficient training were the main barriers to sustainable healthcare [36,37,38]. These disparities underscore the urgent need to adopt practical, sustainable solutions in resource-limited areas and highlight the fact that effective solutions in high-income communities cannot be simply imported without practical modifications.

**Limitations**

Financial obstacles faced by healthcare systems in these regions. The adoption of reusable medical devices or the development of waste management systems requires initial investment. This financial barrier often leads to a focus on short-term, cost-effective solutions rather than long-term sustainability strategies.

Lack of infrastructure to support sustainable practices. Many healthcare facilities in low-resource settings lack proper waste disposal systems, limited access to sustainable medical products, such as reusable insulin pens and face logistical challenges, such as

unreliable electricity or water supply that is used in sustainable efficient power supply.

Educational barriers also play a role in limiting the application of these principles. Many healthcare workers and patients lack awareness of the environmental impact of certain medical practices or may not be trained in using sustainable alternatives.

Lack of Inferential Statistical Analysis: This study is a pilot study with exploration nature and small sample size; therefore, descriptive statistics were used to interpret the results. Future studies with larger sample and statistical comparisons between subgroups are recommended.

## Conclusion

Applying the (Reduce, Reuse, Recycle) framework, along with eco-friendly technologies (illustrated in Figure 4), can significantly lower healthcare's environmental impact. The key ethical challenge is ensuring these benefits are accessible to all communities, including low-income and rural areas.

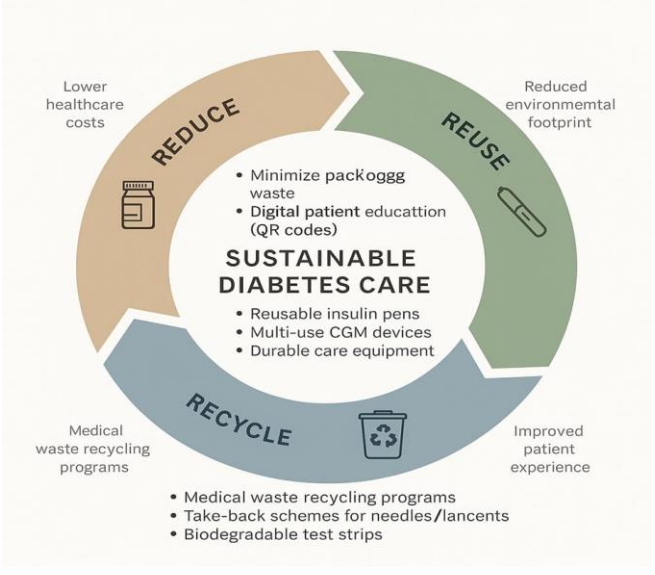


Figure 4: A Circular Framework for Integrating the 3Rs (Reduce, Reuse, Recycle) into Sustainable Diabetes Care

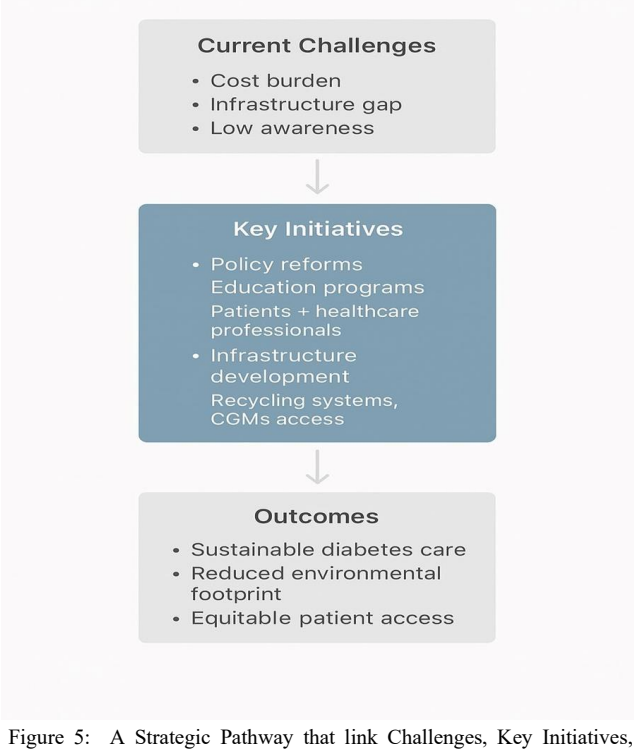


Figure 5: A Strategic Pathway that link Challenges, Key Initiatives, and Outcomes for Achieving Sustainable Diabetes Care

**Recommendations**

There are practical solutions that can be applied in low-resource settings such as the use of national recycling programs for medical waste.

Localized manufacturing of biodegradable medical products could reduce both environmental impact and cost.

Mobile health technologies that reduce the need for physical infrastructure, enabling healthcare delivery that minimizes resource use while reaching underserved populations.

Governments and international organizations need to prioritize sustainability in healthcare in terms of funding and infrastructure development. As illustrated in Figure (5), addressing current healthcare challenges through key initiatives, such as policy reforms, improvement of infrastructure, and education, can eventually achieve more sustainable diabetes care.

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**Conflict of Interest**

Authors declare no conflict of interest.

**Data availability**

Data are available upon reasonable request.

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*Research Article*

# A Global Misuse of Semaglutide for Cosmetic Weight Loss in Non-diabetic Young Population, an FDA Public Database and Google Trends Data Analysis

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***Keywords***: Aesthetic weight loss; FAERS; Google Trends; Medication misuse; Off-label use; Ozempic; Semaglutide; Wegovy



**ABSTRACT**

***Background:*** in a world full of aesthetic trends and a pervasive focus on physical appearance, often driven by celebrities and social media influencers. The misuse of medications and increased demand on aesthetic surgeries have been documented and become increasingly concerning. Recently, the use of GLP-1 analog medications for aesthetic weight management, particularly Semaglutide (brand name Ozempic and Wegovy) has gained increasing popularity among the public on these platforms.

***Subjects and Methods***: Our study aimed to investigate the potential for Semaglutide misuse, particularly Ozempic based on FAERS database and Google Trends tool. We also explored the potential adverse events associated with Semaglutide medication's misuse.

***Results:*** Our findings showed a surge in Semaglutide medication (Ozempic) for weight loss as opposed to T2DM treatment worldwide. Moreover, Ozempic popularity for weight loss outweighs the popularity of Wegovy, which was approved for weight management indications in obese patients with at least one weight-related comorbidity. Furthermore, our results demonstrated an annual increase in the number of Semaglutide-related AERs on FAERS from January 2018 to September 2024, including a rise in death related AERs. A wide verity of Semaglutide related AERs have been documented, including both serious and non-serious outcomes, with death being the most serious outcome reported. Current results have also documented a worldwide shortage in Semaglutide medications, particularly Ozempic and Wegovy, due to increased demand and off-label use of these medications.

***Conclusion:*** collectively, our findings provide clear evidence of Ozempic and Wegovy misuse outside their approved indications to achieve aesthetic weight goals among young non-diabetic individuals. This misuse is often driven by media platforms without stressing on the potential adverse events and ethical concerns associated with the misuse of these medications.

## Introduction

Semaglutide is a class of medication known as Glucagon-like peptide-1 (GLP-1) analog [1,2], which acts as an agonist to GLP-1 receptors to mimic the effect of incretin hormone (GLP-1) and hence lowers blood glucose levels and enhancing both insulin production and release from beta cells of the pancreas in type 2 diabetes mellitus (T2DM) patients [3].

Diabetes mellitus (DM) is a chronic and progressive metabolic disorder with a growing burden on public health globally, affecting more than 400 million people in the world today, with an ongoing

increase that is expected to reach 629 million DM patients by 2045 [4-6]. T2DM is the most common type of DM, accounting for 90% of total DM cases [7].

T2DM is characterized by chronic hyperglycemia due to insulin resistance and progressive pancreatic beta cell damage over time [8]. Generally, management of T2DM focuses on glycemic control [9]. This is typically done through a combination of medications and lifestyle management [10]. Medication-wise, metformin is considered the first line of treatment for T2DM alongside medical nutrition treatment, increasing physical activity, and improving the overall quality of life [11]. Despite advancements in medical approaches to T2DM management, clinical glycemic control in diabetic patients remains challenging, thus supporting the need for more innovative hypoglycemic agents [12]. Recently, advancements in pharmaceutical research have focused on developing hypoglycemic agents that agonists native GLP-1 [13]. Such hypoglycemic agents have been clinically used and achieved a successful approach in minimizing dosage frequency and better glycemic control of diabetic patients. [14]

One such hypoglycemic agent developed by Novo Nordisk, is Semaglutide with extended release and 94% homology to native GLP-1 the medication was launched clinically under brand name Ozempic® [15]. During clinical trials, Semaglutide contribution to a substantial amount of weight loss was documented; thereafter, Semaglutide was approved for chronic weight management indications in obese individuals with one or more weight-related comorbidities [16], and by 2021, Novo Nordisk clinically launched Semaglutide under brand name Wegovy which was approved for weight management indications in obese patients with weight-related comorbidities and under medical supervision [17]. The growing concern regarding weight loss in both obese and non-obese individuals has increased the demand for aesthetic and plastic surgery approaches as a means of weight loss [18]. With the growing obsession with following celebrities and social media trends, the unauthorized use of some medications for cosmetic purposes was normalized on these platforms [19]. Recently, an increased surge in the use of Semaglutide medications as a means of aesthetic weight loss has been popularized among the public [20]. This trend has raised concerns about Semaglutide misuse among young, non-diabetic individuals [21]. The current study aims to analyze the potential of Semaglutide misuse among the young population for cosmetic weight management purposes, based on data analysis from the FDA public database and Google Trends tool to raise awareness on the emerging issue of medication misuse for esthetic purposes and the potential health risks associated with off-label use of Semaglutide medications and to provide a novel insight into an emerging public health concern that has received limited regulatory and academic attention.

## Subjects and Methods

Data was collected from the FDA Adverse Event Reporting System (FAERS) Public Dashboard to conduct a retrospective observational study by analyzing the adverse events of Semaglutide from January 2018 to November 2024. CASEID and FDA_DT filters were applied to deduplicate the collected data and ensure the usage of the most recent data. The cases that involved age groups less than 18 years were excluded due to irrelevance to the aim of the study, as well as the duplicate cases to avoid redundancy. The selected data were analyzed to assess trends in total adverse reports (AERs) over time, the distribution of AERs by gender, age group, severity, and the outcome during the selected timeframe. Moreover, the collected data were categorized into “serious” and “nonserious” outcomes based on FDA regulations (21 CFR) and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. All collected data were subsequently submitted for statistical analysis.

Regression analysis was done to assess the relationship between Year and total reported cases. Using the regression equation, yielding the regression equation Total Cases = −3,895,000 + 1930.04 × Year, the intercept (−3,895−3,895) was used as a theoretical starting value, which holds little practical relevance within the given timeframe. Similar regression analysis for total death cases over time was performed, and the resulting regression equation Total Death = -18.179 + 30.107 × Year.

Statistical significance analysis

Statistical significance analysis was performed using analysis of variance (ANOVA) to evaluate the significance of changes in Total AERs and total death cases over time. The Chi-squared test was used to analyze the distribution of adverse event severities and the AERs severity level frequency between Ozempic and Wegovy. The Shapiro-Wilk and linearity diagnostic tests were conducted to validate the reliability of the regression model results.

Google Trends tool analysis

Google Trends (http://google.com/trends) Search tool was used as a marker to assess the relative public interest in search terms (Ozempic), (Wegovy), and (Ozempic for weight loss vs Ozempic for diabetes) during a given time frame (January 2018– November 2024) and (Jun 2021– November 2024) respectively and (worldwide) was selected as the location for the given search term. Google Trends tool uses a relative search volume (RSV), which is calculated by the normalized volume of a particular search interest during a particular time and location compared to all searches at the same time and location. The RSV is scaled from 0 to 100 as an interest index, with 100 representing the peak popularity of the search for the selected period and location. This tool has been widely used to evaluate the public interest of search terms of interest in many research studies [22,23].

## Results

From January 2018 to September 2024, a total of 37,693 AERs were submitted on FAERS. An increase in the total number of Semaglutide-related AERs over the years can be observed (Figure1a.). From 2021 to September 2024, when the medication gained popularity for cosmetic weight loss, a significant increase of about 3-fold in AERs was observed (Figure1a.) [24]. As can be seen in (Figure 2.), the majority of Semaglutide-related AERs were from female users, which could be linked to body anxiety in women who are under relentless societal pressure to achieve the "ideal body" that is mainly driven by internet and social media efforts for advertising what is known now as body industry [25]. As for the age group, most AERs concerned younger adults age group (18–64 years) (Table 1b.). As can be seen in (Figure 1c.) An annual increase of approximately 1,930 cases was observed with an F-statistic of 52.45

and a p-value of 0.0008, and the slope's p-value (<0.001) confirming the significant linear relationship with an upward trend in total cases over the years. The Shapiro-Wilk test results showed a p-value of 0.594, which is greater than 0.05, indicating that the residuals follow a normal distribution, further supported by the Q-Q plot (Figure 1b.). The correlation coefficient was 0.955 (p= 0.00078), indicating a strong and statistically significant linear relationship.

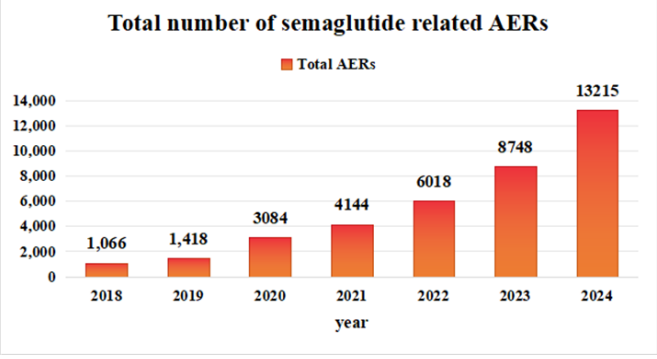


**Figure 1a:** Total number of semaglutide-related AERs over the years

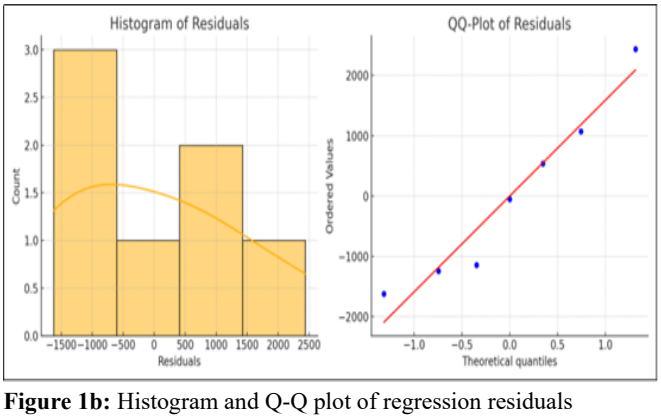


**Figure 1b:** Histogram and Q-Q plot of regression residuals

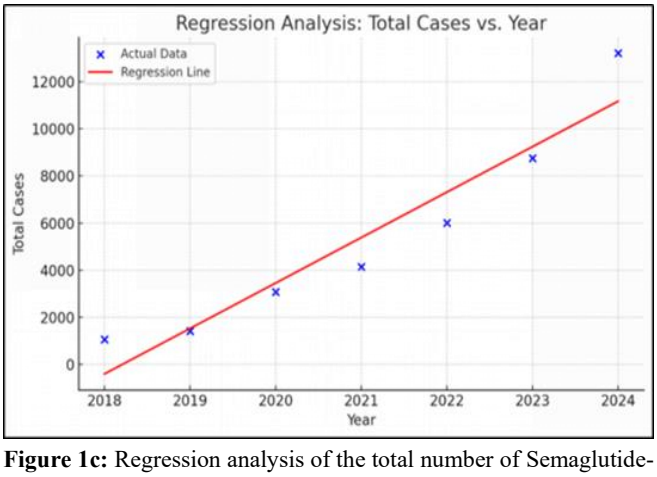


**Figure 1c:** Regression analysis of the total number of Semaglutide-related AERs over the years

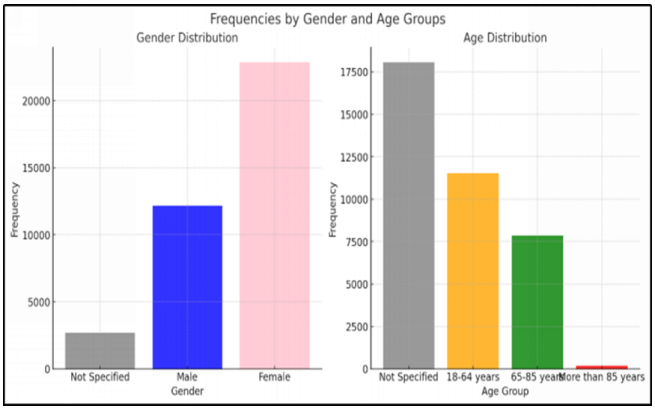


**Figure 2:** semaglutide-related AERs distribution by age and gender groups

**Table 1:** Semaglutide-related AERs distribution by age and gender groups

| Groups | | Total AERs (n) | n (%) | | p-value | |
|---|---|---|---|---|---|---|
| **Gender** | Not specified | 2694 | 7.15% | | 0.035 | |
| | | | | Male | 12165 | 32.27% |
| | | | | Female | 22844 | 60.59% |
| **Age** | Not specified | 18052 | 47.95% | | 0.048 | |
| | | | | 18–64 years | 11529 | 30.63% |
| | | | | 65–85 years | 7868 | 20.90% |
| | | | | more than 85 years | 195 | 0.52% |

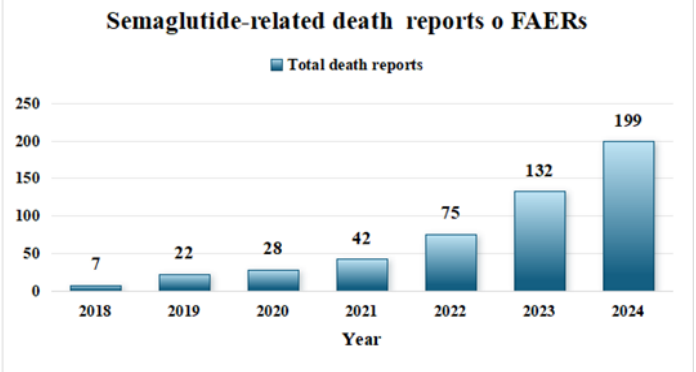


**Figure 3a:** Semaglutide-related death reports over the years

From January 2018 to September 2024, a total of 505 death reports were submitted to FAERS. A significant increase in death reports can be seen over the years, peaking at (199) death reports in 2024 as the medication gained trending popularity for cosmetic weight loss among young, non-diabetic populations (Figure 3a). This can be seen in (Figure 3b) which indicates a linear relationship where the number of total deaths increases by approximately 30.107 units

for each additional unit of the year variable. Semaglutide-related AERs distribution by age and gender groups shows no significant difference between males and females; however, most of these reports were from a younger population of 18–64 years of age (Table 2.).

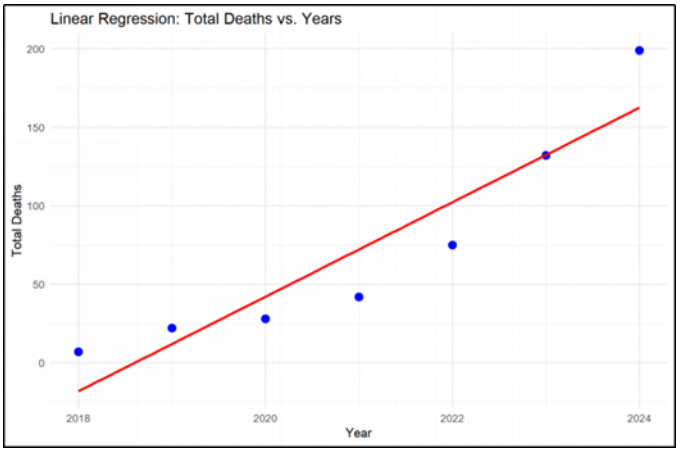


**Figure 3b:** Regression analysis of semaglutide-related death reports over the years

**Table 2:** Semaglutide-related death reports distribution by gender and age groups

| Groups | | Total AERs (n) | n (%) |
|---|---|---|---|
| **Gender** | Not specified | 25 | 4.95% |
| | Male | 267 | 52.87% |
| | Female | 213 | 42.18% |
| **Age** | Not specified | 146 | 28.91% |
| | 18–64 years | 180 | 35.64% |
| | 65–85 years | 136 | 26.93% |
| | more than 85 years | 14 | 2.77% |

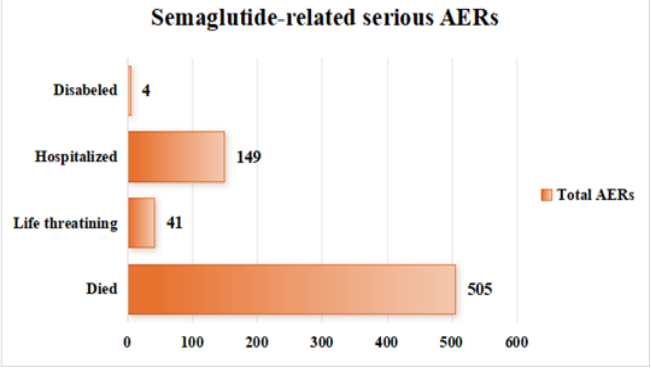


**Figure 4: Semaglutide**-related serious adverse event reports on FAERS

Both serious and non-serious Semaglutide-related adverse event reports were submitted on FAERS from 2018-2024, during that time frame Semaglutide-related adverse event reports ranged from non-serious conditions like injection site reaction and general fatigue among others to more serious outcomes like death, life-threatening conditions and disabilities (Figure 4), (Table 3). Among serious outcomes, most cases (72.25%) resulted in death. Hospitalizations account for 21.32% of the cases, while life-threatening events represent 5.87%, only a small fraction (0.57%) of cases resulted in disability (Table 4).

**Table 3:** Semaglutide-related AERs distribution by system

| Semaglutide related AERs by system | Total AERs (n) | n (%) |
|---|---|---|
| - Gastrointestinal disorders | 15694 | 41% |
| - General disorders (fatigue, malaise and administration site condition) | 10136 | 27% |
| - Injury, poisoning complication | 9824 | 26% |
| - Nervous system disorders | 6456 | 17% |
| - Metabolism disorders | 6415 | 17% |
| - Skin and subcutaneous tissue disorders | 3128 | 8% |
| - Psychiatric disorders | 2942 | 8% |
| - Mucuskeletal and connective tissue disorders | 2529 | 7% |
| - Eye disorders | 2240 | 6% |
| - Renal disorders | 1549 | 4% |
| - Cardiac disorders | 1320 | 4% |
| - Hepatobiliary | 1105 | 3% |
| - Neoplasm (Benign and Malignant) | 1011 | 3% |

**Table 4:** semaglutide-related AERs distribution by serious outcomes

| Semaglutide-related serious outcomes | Total AERs (n) | n (%) | P-value |
|---|---|---|---|
| Died | 505 | 72.25% | < 0.001 |
| Life-threatening | 41 | 5.87% | |
| Hospitalized | 149 | 21.32% | |
| Disabled | 4 | 0.57% | |
| Total | 699 | 100.00% | |

*Significant ($p < 0.05$)

Both Ozempic and Wegovy are Semaglutide brand names manufactured by Novo Nordisk. While Ozempic is FDA-approved for T2DM, Wegovy is FDA-approved for weight management in obese patients. Both brand names were linked to the majority of AERs on FAERS; However, Ozempic was linked to more AERs compared to Wegovy (Figure 5.). As can be seen in (Table 5) for Semaglutide brand name Ozempic, 56.51% of cases are "Not Specified," 42.31%

are "Serious Cases," and 1.18% are "Death Cases." Similarly, for Wegovy, the majority (66.43%) fall under "Not Specified," followed by 32.99% as "Serious Cases," and 0.58% as "Death Cases." While both drugs show a high proportion of unspecified cases, Ozempic reports a significantly larger proportion of serious cases (42.31% vs. 32.99%) and death cases (1.18% vs. 0.58%) compared to Wegovy. Which could be due to the longer timeframe for Ozempic availability in comparison to Wegovy which was approved four years later as well as the increased public interest in Ozempic for weight loss on internet and media platforms [26] (Figure 6 and 7).

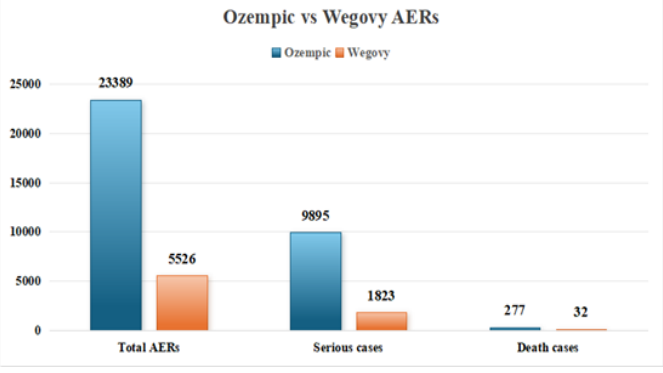


**Figure 5:** Ozempic vs Wegovy AERs on FAERS

**Table 5:** Ozempic vs Wegovy AERs on FAERS

| Outcome groups | Ozempic | | Wegovy | |
|---|---|---|---|---|
| | Total AERs (n) | (n) % | Total AERs (n) | (n) % |
| Not specified | 13217 | 56.51% | 3671 | 66.43% |
| Serious cases | 9895 | 42.31% | 1823 | 32.99% |
| Death cases | 277 | 1.18% | 32 | 0.58% |
| Total AERs | 23389 | 100.00 % | 5526 | 100.00 % |
| Chi Squared Test | | 186.4 | | |
| P-value | | < 0.001 | | |

*Significant (p< 0.05)

Google Trends tool data analysis has shown clear evidence of increasing popularity in Semaglutide medication (Ozempic) for weight loss indications as opposed to type 2 diabetes mellitus treatment worldwide over the years (Figure 6.). Moreover, Google Trend data analysis showed increasing public interest in off-label use of Ozempic for weight loss compared to Wegovy, which was approved for weight management indications (Figure7).

Off-label use of Semaglutide for cosmetic weight loss as can be seen in (figure 5 & 6) has led to a persisting global shortage in Semaglutide medication (Ozempic) from at least October 2022 and is expected to continue throughout 2024 (Table 6.), (as per FDA Drug Database and Single Point Of Contact (SPOC) working party data). This shortage raises moral concerns regarding the availability of the drug for T2DM patients who rely on prescribed Ozempic for their condition's treatment

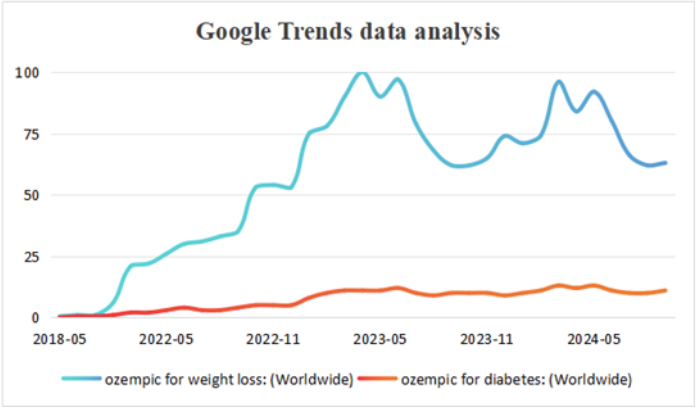


**Figure 6:** Google Trends data analysis for public interest in semaglutide medication Ozempic

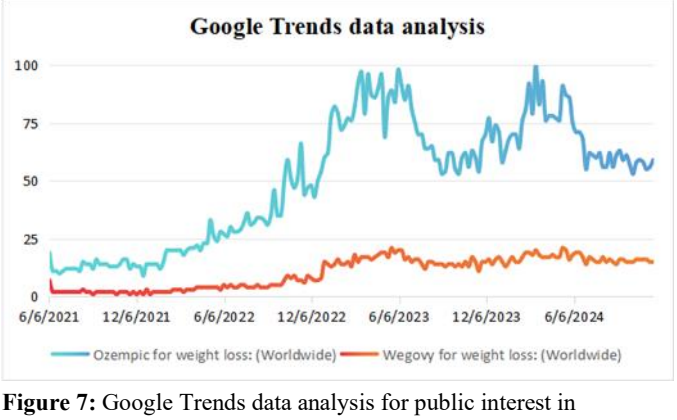


**Figure 7:** Google Trends data analysis for public interest in Semaglutide medications Ozempic vs Wegovy for weight loss indications

**Table 6:** Ozempic and Wegovy worldwide shortage due to off-label use for cosmetic weight management

| | *FDA Drug shortage list | *SPOC shortage register | Listed reasons per SPOC |
|---|---|---|---|
| Drug name | Semaglutide injections (Ozempic and Wegovy) | Ozempic | Increased demand for Ozempic above the capacity constraints at some of the manufacturing sites |
| Month | Status | Status | |
| Oct-Dec-2022 | in shortage | in shortage | Off-label use for weight management |
| Jan-Dec-2023 | in shortage | in shortage | Off-label use for weight management |
| Jan-Jul-2024 | in shortage | in shortage | Off-label use for weight management |

## Discussion

In the present study we aimed to explore the potential of Semaglutide medications misuse, particularly Ozempic, among the public for cosmetic weight loss purposes. Our study used public data from FAERS and Google Trends to evaluate the potential of Semaglutide misuse/abuse out of their approved indications. Our results showed that off-label use of Semaglutide brand name Ozempic, which was initially approved for T2DM management indications, was trending among the public for weight loss indications as opposed to diabetes management worldwide. Moreover, Ozempic popularity for weight loss indications outweighs the popularity of Wegovy, which was originally approved for weight management indications globally. In parallel with Semaglutide medications growing popularity for cosmetic weight loss, FAERS database showed an annual increase of approximately 1,930 AERs, this increase highlights a substantial and consistent rise in total AERs from 2018 to 2024 which could be associated with the growing popularity of Semaglutide medications for off-label use as a means of cosmetic weight loss achievement in non-diabetic young individuals [24]. Knowing that Semaglutide brand name Ozempic and Wegovy were the most reported brand names on FAERS would probably further support the association between the annual increase in AERS and off-label use of these medications for aesthetic purposes, as those brand names are trending among public for weight loss indications driven by celebrities and influencers on social media platforms [20]. The influence of celebrities and media platforms on cosmetic trends including medical choices of surgeries, dentistry and pharmaceuticals were previously documented [27-29]. Recently, GLP-1 analog Semaglutide gained great popularity as a breakthrough treatment not only for diabetes but other disorders like chronic obesity with at least one weight-related comorbidity, reduces the risk of cardiovascular diseases and showed a promising potential for alcohol use disorder management [30-32]. However, Semaglutide medication's potential in substantial weight loss has gained great popularity among non-diabetic young individuals who are seeking the use of Semaglutide to achieve weight loss for aesthetic purposes [33]. Misuse of pharmaceutical agents such as beta 2-agonists, dinitrophenol/DNP and others for weight loss has been previously documented, moreover, the potential misuse of Semaglutide among other GLP-1analog molecules have been recently suggested [34-36]. However, the former pharmaceutical agents like DNP and Clenbuterol are associated with toxicity and were linked to mortality [37,38]. Popularizing Semaglutide medications for weight loss on different media platforms without stressing on the potential health risks associated with abusing such medications has potentially led to increase AERs on FAERS each year [39]. A wide spectrum of Semaglutide-related adverse events has been reported on FAERS over the past years ranging from injection site reaction to life-threatening threatening events and death, most of these AERs concerned young adult females; Thus, emphasizing the need of limiting the use of these medications in prescription form and under medical supervision. However, Semaglutide medications possess an overall favorable risk/benefit profile for patients with T2DM and obese patients with cardiovascular risks [40]. Research has shown Ozempic effectiveness in lowering mortality rates among diabetes patients [30]. However, the mortality reports linked to Ozempic exceed any other serious outcome on FAERS database as well as mortality reports linked to Wegovy on FAERS, which could possibly indicate misuse of these medications outside their approved indications by the young population. Moreover, our study documents a persisting worldwide shortage in semaglutide medication (Ozempic) from at least October 2022 and is expected to continue throughout 2024 as per FDA Drug Database and SPOC data. Increased public demand and off-label use of Semaglutide medications for esthetic use were documented as the cause of this global shortage, which intern raises ethical concerns regarding prioritizing patient's needs potentially through restricting off-label prescription and dispensing of Semaglutide medications as well as establishing regulatory enforcement against off-label medications promotion and beauty trends involving pharmaceuticals on internet and social media platforms [41,42]. However, although FAERS and Google Trends data are widely used research tools certain limitations associated with these tools must be highlighted, our study relies on FAERS data which is subjected to reporting biases and unproven causality. Moreover, these data either self-reported or reported by medical health professionals hence “not specified” categories and the lack of raw data from Google Trends tool which interns lead to a lack of context of these trends that may reflect overall interest rather than an actual action thus collectively these limitations may potentially alter the context of the reported data which suggest the need for further empirical studies to further support these data.

## Conclusion

Collectively, our study highlights a potential misuse pattern of Semaglutide medications for cosmetic weight loss proposed by celebrities and social media platforms without stressing on the potential adverse events associated with Semaglutide medications use outside their approved indications which led to an ongoing shortage of these medications. Thus, raising ethical concerns regarding the availability of these medications for T2DM and obese patients with cardiovascular risks and prioritizing patients need. Collectively, our study highlights the need for stricter regulatory policies for Semaglutide medication's prescription and dispensing guidelines, as well as the need for raising public awareness on the potential adverse events associated with the misuse of these medications and calls for establishing regulatory enforcement against beauty trends that involves the off-label use of pharmaceuticals on the internet and social media platforms.

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**Data availability**

Data are available upon reasonable request.

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*Commentary*

# A Cautionary Perspective on Artificial Intelligence and Novel Imaging Technologies in Patient Selection for Retrograde Intrarenal Surgery

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**ABSTRACT**

The advancement of retrograde intrarenal surgery (RIRS) has been accompanied by the evolution of many promising tools that aim at improving patient selection and predicting surgery outcomes in terms of stone fragmentation and expected complications. The incorporation of artificial intelligence (AI) into the advanced imaging technologies such as dual-energy CT scan (DECT), three-dimensional (3D) reconstruction, and radiomics resulted in a number of clinical tools and algorithms forwarded to surgeons to use in their daily practice.
This commentary critically examines these clinical algorithms, highlighting the absence of prospective validation, the potential for overreliance, and the possible limitations of their clinical applicability. AI-driven predictive models often rely on retrospective, uniform datasets taken from a single center, with evident interpretability concerns. Similarly, DECT and 3D reconstructions might provide detailed information about the anatomy of the renal collecting system and stone composition, but they do not account for real-time surgical dynamics. Radiomics, in the other hand, provides excellent insights into stone behavior, but their reproducibility and clinical relevance are still to be tested.
The take-home message of this commentary is that conventional CT metrics—such as stone size and density—continue to outperform novel techniques in reliability and accessibility, and the adoption of emerging technologies in RIRS must be cautious, ethically sound, and evidence-based, reinforcing the primacy of clinical judgment in urologic care.

Retrograde intrarenal surgery (RIRS) has quickly become the first-line therapy for renal stones, especially stones smaller than 20 mm in size. As the ureteroscopy and laser technologies have improved, patient outcomes have also improved dramatically. However, the new frontier in RIRS looks like it is preoperative precision – who are the patients most likely to gain, with the least risk and best stone clearance?

AI algorithms and sophisticated imaging techniques, including dual-energy CT (DECT) and three-dimensional (3D) reconstructions, are driving this ambition [1,2]. Although these new technologies present exciting opportunities, surgeons contend that their clinical implementation at present is premature. Without robust, prospective validation, over-credence in these technologies poses the danger of injecting a misleading sense of objectivity into nuanced, personalized surgical decision making.

**AI and Predictive Algorithms: Promise Meets Prematurity**

Artificial intelligence (AI) has been utilized to improve diagnosis and management in medicine in general [3]. In urology and stone

disease in specific, AI models (especially machine learning classifiers) have been built to forecast stone-free rates, complication risks, and procedural complexity in RIRS [4]. These models frequently include information from electronic patient records, imaging characteristics, and operative details to produce predictive probabilities. Investigations similar to those of Aminsharifi et al. and Pérez-Fentes et al. have reported predictive accuracy greater than 85% using support vector machines and logistic regression model trained on retrospective data [5,6].

In spite of this, these tools still carry substantial limitations when it comes to their clinical applicability as most of them use single-center datasets with minimal demographic and anatomical diversity [7]. In addition, many models are complex, making it difficult for clinicians to understand the way a certain prediction was made [8]. RIRS requires intraoperative judgment that considers stone migration, renal anatomy, infundibular angles, and laser dynamics, so a "black-box" risk prediction model cannot be relied upon to make the final treatment decision. Until these algorithms are prospectively validated across multiple centers, they should be considered experimental tools only, not clinical decision aids.

**Dual-Energy CT: Sophisticated Imaging with Limited Clinical Leverage**

Among the advantages of dual energy CT are its ability to distinguish stone composition based on attenuation differences at varying energy levels, particularly between calcium oxalate and calcium phosphate stones [9,10]. DECT can provide an accurate estimate of effective atomic number and iodine content that can be effectively related to stone response to shockwave lithotripsy and laser fragmentation, this in turn will help the treating clinician choosing the appropriate, high yield modality of treatment.

In real life, this is not the situation because mixed-composition stones make the majority of stones. These mixed-composition stones do not show a predictable attenuation pattern that can be related to a specific type of stone or fragmentation response [11,12]. Furthermore, the scene is more complicated when taking into consideration the technical variabilities in terms of the manufacturer, software used, and the tube current modulation [13]. To summarize, DECT at present can provide valuable information to take into consideration when making decisions on stone treatment but cannot be relied on in dictating patient selection for RIRS.

**3D Reconstruction: Intuitive Planning or Unnecessary Complexity?**

When exploring how 3D reconstruction might improve RIRS planning, researchers are building on successes seen in PCNL procedures. Just as detailed 3D kidney maps-showing calyces, stone locations, and infundibular dimensions-are created from CT scans using specialized software [14], some teams are testing "virtual RIRS" simulations to help surgeons rehearse maneuvers and predict challenges before stepping into the operating theaters [15]. But here's the catch: while these models look impressive, there's little proof they actually boost surgery success rates or save time [16]. Unlike PCNL, where choosing the skin access point is half the procedure, RIRS relies largely on the surgeon's real-time adaptability and the scope's flexibility. Moreover, static 3D images cannot simulate breathing patterns, patient positioning, or fluid dynamics during live surgery, all of which can detriment the best made plan [17]. Until well-designed studies confirm their practical value, 3D reconstruction images remain more of a "nice-to-have" than essential tools for RIRS.

**Radiomics and AI-Augmented CT Interpretation: A Double-Edged Sword**

Imagine if CT scans could tell surgeons not just where kidney stones are, but how easily they will fragment with laser. That's the promise of radiomics, a smart imaging analysis that looks beyond basic shapes to decode texture patterns of renal stones. Early studies suggest these "digital fingerprints" (characteristics like stone roughness, density variations, and internal complexity) might predict which stones will fragment quickly and which will need more laser time or energy [18]. Studies by Xiang et al. and Lyu et al. have even linked radiomic features to stone composition, and potentially stone fragmentation efficiency [19,20].

Radiomics however, share most of the limitations of other AI tools. The accuracy of feature extraction is highly dependent on the precise definition of the region of interest and the quality of the imaging data, raising concerns regarding reproducibility across different CT scanners and imaging protocols [21]. Furthermore, the lack of interpretability of radiomic signatures and the absence of prospective clinical trials limit the current applicability of these findings in routine clinical practice. Consequently, similar to dual-energy CT (DECT) and 3-D reconstruction techniques, radiomics remains primarily a research tool rather than a validated clinical instrument.

**Revisiting Basic Imaging Metrics: A Cautionary Contrast**

A comparison between advanced imaging modalities and established, conventional parameters underscore the enduring clinical value of the latter. In many studies, renal stone density measured in Hounsfield units (HU) on non-contrast CT was identified as a robust predictor of shock wave lithotripsy (SWL) outcomes, with stones exhibiting HU values below 800 demonstrating a significantly higher likelihood of successful fragmentation under shockwave therapy [22,23]. This observation is corroborated by multiple independent investigations, which consistently report that lower HU values are associated with improved SWL efficacy, whereas stones exceeding 1000 HU are linked to higher rates of treatment failure and the need for alternative interventions [23,24].

Although these researches focused on SWL, these findings highlight a broader principle: fundamental CT-derived metrics, when interpreted within the appropriate clinical context, can serve as powerful predictors of treatment outcomes. In the context of retrograde intrarenal surgery (RIRS), stone volume and density-whether assessed manually or through automated volumetric analysis-remain among the most reliable predictors of operative duration and surgical success [25]. Prior to the widespread adoption of advanced imaging technologies or artificial intelligence-driven platforms, it is imperative that the urologists ensure these foundational parameters are fully standardized, readily accessible, and rigorously validated in clinical practice.

**The Ethical and Economic Imperative for Validation**

Integrating advanced technologies such as dual-energy CT (DECT), three-dimensional (3D) reconstruction, and AI-based predictive tools into everyday clinical practice brings with it important

ethical and financial considerations. Without thorough validation, these innovations risk widening disparities in healthcare access, particularly for patients in resource-limited settings, as the costs and infrastructure required may not be universally available [26]. Additionally, reliance on proprietary software and hardware introduces further challenges, including concerns about transparency, data ownership, and the accountability of algorithms-issues that are not yet sufficiently addressed in the current urologic literature [27,28].

The medical field has previously witnessed enthusiasm for new technologies that, despite their initial promise, ultimately failed to deliver on their expectations. For example, the introduction of robot-assisted surgical systems and fusion biopsy platforms generated significant excitement, yet subsequent experience revealed that, in the absence of robust validation, such innovations can lead to inappropriate use, inefficient allocation of resources, or even diagnostic errors[29]. As the adoption of AI and advanced imaging in RIRS accelerates, it is crucial that the lessons of the past guide current practice. Ensuring that new technologies are rigorously evaluated before widespread implementation will help prevent repeating cycles of overpromising and underdelivering and will safeguard both patient outcomes and healthcare equity.

**Conclusion: Precision Demands Prudence**

The ongoing evolution of retrograde intrarenal surgery (RIRS) increasingly depends on precise patient selection, which remains central to optimizing outcomes. While technological advances such as dual-energy computed tomography (DECT), three-dimensional (3D) reconstruction, and artificial intelligence (AI)-driven analytics are impressive, it is essential to distinguish between what is technologically feasible and what is clinically necessary. Current guidelines and expert consensus emphasize that, in the absence of robust evidence from prospective, multicenter trials demonstrating clear benefits-such as improved stone-free rates, reduced complications, or enhanced procedural efficiency-these advanced tools should be regarded primarily as investigational rather than standard of care.

The potential pitfalls of premature adoption are not theoretical. Over-reliance on unvalidated technologies risks shifting clinical decision-making away from individualized, bedside assessment toward algorithm-driven abstraction. This may undermine the nuanced judgment required in patient care, as precision unsupported by strong evidence can be misleading. Until these innovations are validated through rigorous, outcome-focused studies, they should be viewed as adjuncts to, rather than replacements for, clinical expertise and judgment.

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