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EDITORIAL

ENCOURAGING WOMEN IN MEDICAL SCIENCES AS A MEDICAL STUDENT JOURNAL

As the position of women in society has evolved over the years, it is inevitable that their roles within professional groups will also change. However, stigma, anxiety, and both verbal and physical abuse against women have not yet disappeared (1). The challenges of studying medicine are already significant in terms of mental health, and the additional burdens placed on women put those striving to advance their careers in medical sciences at a disadvantage (2).

This is why we still need women to be present in scholarly publications, conferences, and leadership positions as role models. Increased representation can inspire other women and girls, and by sharing diverse experiences, we gain valuable perspectives that contribute to a more comprehensive understanding of the issues we face in our field.

To that end, it is essential to increase the publication of female medical students, support them in their publishing endeavors, and provide guidance throughout their careers. As medical student journals, it is both our vision and honor to represent the views and opinions of women in their research fields, along with their experiences and challenges. We must strive to create a future where women feel safe and healthy in their careers by ensuring our publication processes use neutral and unbiased language and maintain gender balance on the editorial board (1).

With our February issue, we celebrate International Day of Women and Girls in Science and International Women's Day in support of a more equal and healthier future.

Sıla Ece Tiryaki

Editor-in-Chief, Turkish Medical Student Journal

REFERENCES

1. Geagea A, Mehta S. Advancing women in academic medicine: ten strategies to use every day. Can J Anaesth. 2020;67(1):9-12. [Crossref]
2. Koçyiğit B. Mental health in academia. Turk Med Stud J. 2022;9(3):0-0. [Crossref]

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REVIEW

EPIGENETIC REGULATION OF ADIPOSE TISSUE: INSIGHTS INTO METABOLIC FUNCTIONS AND DYSFUNCTION

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ABSTRACT

Adipose tissue, the body's primary energy-storing tissue, has additional roles in hormone regulation and thermogenesis. While it has been traditionally examined through the lens of hormonal and nervous system interactions, recent advancements have highlighted the importance of epigenetic modifications in adipose tissue function and dysfunction. This review examines how epigenetic modifications impact the functions of white adipose tissue, brown adipose tissue, and beige adipose tissue, how these alterations contribute to the development of obesogenic memory, and how they indirectly affect the central nervous system to sustain obesity. Additionally, it explores the impact of epigenetic alterations on obesity susceptibility and the outcomes of metabolic diseases such as obesity and type 2 diabetes, following a brief overview of epigenetic modifications, the types of adipose tissue, and their functions. Epigenetic mechanisms such as deoxyribonucleic acid methylation, histone modifications and non-coding ribonucleic acid modulations have a considerable role in adipocyte differentiation, lipid metabolism, and thermogenesis in brown and beige adipose tissue. In white adipose tissue, these modifications are linked to dysregulated lipid storage and metabolic impairments associated with obesity. Brown and beige adipose tissue, adipose tissues responsible for non-shivering thermogenesis, are also regulated by a network of transcription factors and epigenetic regulators that modulate their differentiation and function. Studies have indicated that transgenerational epigenetic inheritance may be a contributing factor to the rising prevalence of metabolic diseases, including non-alcoholic liver disease, obesity, and type 2 diabetes. Furthermore, differential deoxyribonucleic acid methylation patterns in genes associated with obesity and type 2 diabetes have been revealed, offering insights into the mechanisms of these diseases and potential therapeutic targets. Interestingly, bariatric surgery appears to have an effect that resets the obesogenic memory, making it a more effective long-term treatment than conventional weight loss methods. This provides a link between epigenetics and weight loss interventions. Furthermore, the potential role of epigenetics in central nervous system regulation of appetite and energy homeostasis underscores its systemic impact on metabolic pathways using the reward circuitry involved in hedonic regulation. This review emphasizes the significance of epigenetic regulation in adipose tissue functions and its implications for metabolic diseases. The comprehension of these mechanisms serves as a foundation for the development of innovative therapeutic approaches to address the growing prevalence of metabolic diseases, including obesity and diabetes.

Keywords: Adipose tissue, diabetes mellitus, epigenomics, lipogenesis, obesity

INTRODUCTION

Adipose Tissue

Adipose tissue (AT) has traditionally been divided into two types, white AT (WAT) and brown AT (BAT), which are visually distinguished by the color of the tissue (1). These two tissue types exhibit distinct characteristics, resulting in unique physiological roles within the body (Figure 1) (1). WAT represents the most prominent energy reserve in humans, yet it is also responsible for several endocrine functions (2). White adipocytes typically have a spherical shape, and each contains a single large lipid droplet that pushes the other organelles to the side and can grow up to 100 µm (1, 3).

Brown AT is predominantly found during the postnatal period in infants and plays a crucial role in non-shivering thermogenesis (1). This process is driven by the protein uncoupling protein-1

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(UCP-1), which facilitates adenosine triphosphate utilization for heat production (1, 3, 4). Unlike white adipocytes, brown adipocytes are distinguished by their multiple lipid droplets dispersed throughout a larger ellipsoidal-shaped cell rich in mitochondria, which contains iron (1). This gives the cell and the BAT overall a brownish color (1, 3). The adipose cells forming this tissue are typically smaller in size (3). Although it was once believed to exist exclusively during the postnatal period, imaging studies have revealed its presence in adults, particularly in the supraclavicular and thoracic regions (1).

Recently, two additional types of ATs have been identified: beige and pink adipose cells (1). Beige AT (BeAT) displays characteristics of both brown and white fat tissues (Figure 1), which will be elaborated on later (1). Pink AT, on the other hand, has been observed in pregnant rodents and is believed to arise from the reversible transformation of subcutaneous AT into mammary glandular tissue (3). However, studies focusing on this specific tissue type remain limited (3).

Lipid Metabolism and Thermogenesis

Lipid metabolism is a complex network of pathways influenced by internal and external factors. Dysregulation in processes such as adipogenesis, lipolysis, and lipid oxidation is often associated with obesity, diabetes, non-alcoholic fatty liver disease, and cardiovascular disorders (5). AT regulates lipid metabolism by balancing triglyceride storage and breakdown in response to nutritional and hormonal signals, though fat is also stored in visceral organs such as the liver (1, 6).

Adipocytes store triglycerides via two mechanisms: absorbing dietary lipids from the bloodstream as free fatty acids released from circulating triglycerides by lipoprotein lipase (LPL), and de novo lipogenesis, synthesizing fatty acids from acetyl coenzyme A, especially following carbohydrate-rich meals (1, 4). These fatty acids undergo esterification with glycerol to form triglycerides (1, 4). During periods of elevated energy demand, such as fasting or exercise, lipolysis releases fatty acids and glycerol from adipocytes (4). Hormones such as noradrenaline activate lipolysis via β-adrenergic receptors and protein kinase A, which in turn activates hormone-sensitive lipase and adipose triglyceride lipase (4). Insulin exerts an inhibitory effect on lipolysis by reducing cyclic adenosine monophosphate levels (1, 4).

As previously mentioned, BAT differs from WAT by producing heat through non-shivering thermogenesis via UCP-1 (1, 7-9). The activity of BAT is known to increase during periods of cold exposure, which is linked to adaptive thermogenesis (8-10). This may play a role in regulating body weight (9, 10). Additionally, research has shown that leaner individuals tend to have higher BAT activity than those with a higher body mass index (BMI) (9, 10). This further supports the idea that BAT activity may be associated with weight control.

Epigenetic Mechanisms in Gene Regulation

Epigenetics is the study of heritable modifications to gene expression that do not involve changes to the underlying deoxyribonucleic acid (DNA) sequence (11). Nutrition, metabolic abnormalities, physical activity, oxidative stress, inflammation, and medications are among the environmental factors identified as contributors to these alterations (11). Such alterations may be reversed, but they may also be transmitted to subsequent generations (11). Epigenetic data is stored in chromatin, which is composed of multiple nucleosome units (DNA-wrapped histone

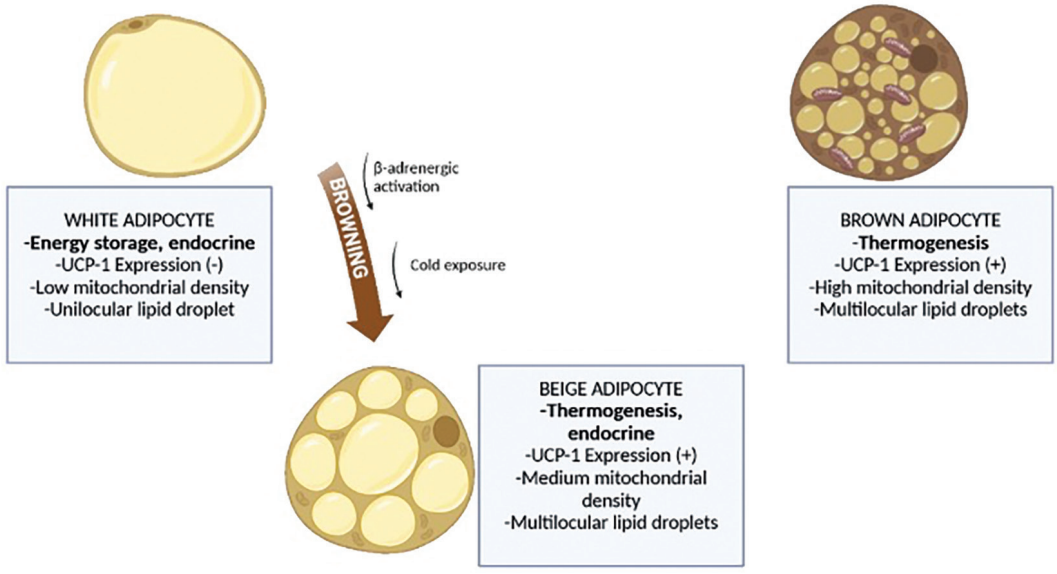

Figure 1: White, brown and beige adipocytes. White adipocytes primarily serve as the body's main energy storage while also playing key endocrine roles (2). In contrast, brown adipocytes are responsible for non-shivering thermogenesis (1-4). Beige adipocytes exhibit characteristics of both white and brown adipocytes (1). These cells originate from white adipocytes and are activated by factors such as β-adrenergic stimulation and cold exposure (7). This figure was created using the program: BioRender.

UCP-1: Uncoupling protein 1

octamers) (11). The chromatin structure is of great importance in identifying the transcriptional state of DNA (11). Unlike the euchromatin region, which is more open and transcriptionally active, the heterochromatin region of DNA is densely packed and transcriptionally inactive (11). These chromatin states are regulated by epigenetic modifications (11). The most prominent epigenetic modifications include DNA methylation, histone modifications, and non-coding ribonucleic acid (ncRNA) modulations (Figure 2), which are briefly described below (11-13).

DNA methylation is the process in which a methyl group from S-adenosyl methionine is added to a cytosine residue in DNA, a reaction catalyzed by DNA methyltransferases (DNMTs) (11). This modification inhibits transcription by preventing DNA-binding proteins, from accessing the methylated site (11). DNA methylation occurs predominantly at cytosine followed by guanine, commonly referred to as "CpG methylation" (11, 12). Among the other epigenetic alterations, DNA methylation is considered to be the key epigenetic mechanism (13). In histone acetylation, histone acetyltransferases (HATs) add an acetyl group to the lysine residues on the N-terminal tails of histones, enhancing transcriptional activity (14). Histone methylation is the process by which histone methyltransferases (HMTs) transfer the methyl group to the N-terminal of the lysine and arginine residues of histone tails (11, 15). Unlike histone acetylation, histone methylation can either stimulate or inhibit transcription (15). Histone crotonylation can either activate or suppress gene transcription by adding a crotonyl group to the lysine residues of histones (11). Histone ubiquitination is the process in which the E1, E2, and E3 ligases attach ubiquitin molecules to the lysine residues of histones, marking them for proteasomal degradation (11). Histone phosphorylation occurs when serine, threonine, or tyrosine residues on histone proteins are modified by histone kinases (11). This modification can alter the structure and function of histone tails, influencing chromatin dynamics and gene expression. In addition to influencing adaptors, transcription factors, chromatin-modifying enzymes, repressors, and transcription regulation, these modifications to the amino-terminal tails of histones also affect how histones interact with DNA (11, 16). Furthermore, these modifications are believed to create a "histone code" on the N-terminal histone tails that signals proteins or complexes to "read" and use to initiate signaling pathways (14). The hypothesis "histone code" states that post-translational changes to these histone proteins have a significant impact on DNA transcription (17). As a result, histones are crucial for the epigenetic control of gene transcription and may also be involved in nuclear signaling complexes (14).

Non-coding RNAs, which are not translated into proteins, also play a role in gene regulation (11). These include microRNA (miRNA), long non-coding RNA (lncRNA), and small interfering RNA (siRNA) (11). Non-coding RNAs (ncRNAs) were previously believed to regulate gene expression solely at the post-transcriptional level; however, recent studies indicate their growing significance in epigenetic regulation (18).

MicroRNAs typically interact with the 3' untranslated region of target messenger RNAs (mRNA), leading to mRNA degradation and translational repression (19, 20). However, miRNAs have also been observed to bind other regions, such as the 5' untranslated region, coding sequences, and gene promoters (20). Additionally, miRNAs contribute to epigenetic modifications (21). For instance, at least two miRNAs, which are downregulated by oncogenes or other tumorigenic factors, appear to target the histone methyltransferase enhancer of zeste homolog 2 (EZH2), ultimately leading to its overexpression (21). Similarly, miR-214 has been shown to suppress EZH2 expression, thereby promoting skeletal muscle differentiation (21). Furthermore, miRNAs influence DNA methylation by modulating DNA methyltransferases (18). Notably, the miR-29 family (including miR-29a, miR-29b, and miR-29c) exhibits reduced expression in non-small cell carcinoma, while DNMT3a and DNMT3b are significantly upregulated (18).

Long non-coding RNAs represent a class of regulatory RNA molecules typically exceeding 200 nucleotides in length (18). These molecules have critical roles in the cytoplasm and beyond, including roles in translation regulation, metabolism, and signaling (22). lncRNAs often possess modular structures enriched in repetitive elements, which have been increasingly recognized as functionally significant (22). Early research on genomic imprinting and X chromosome inactivation identified the lncRNAs H19 and X-inactive specific transcript as key players in epigenetic regulation (18). Several studies have reported elevated H19 expression in cancer cell lines and patient-derived samples, suggesting its potential role in tumorigenesis (23). In gastric cancer cells, H19 upregulation has been linked to increased miR-675 expression, with both genes promoting cell proliferation and inhibiting apoptosis, whereas their suppression has the opposite effect (23).

Small interfering RNAs silence gene expression through RNA interference (RNAi) pathways, operating at both the transcriptional and post-transcriptional levels (24). RNAi is a biological process in which double-stranded RNA triggers gene silencing by directing the degradation of complementary mRNA (25). Within this mechanism, Argonaute (Ago) proteins, in association with siRNAs, form the core components of RNA-induced silencing complexes (RISC) and RNA-induced transcriptional silencing complexes (RITS), both of which are essential effectors of RNAi (24). The guide strand of siRNA base-pairs with its target RNA, enabling precise cleavage of the target transcript (24).

In addition to miRNAs and siRNAs, another class of small ncRNAs, known as piwi-interacting RNAs (piRNAs), has been implicated in epigenetic regulation (26). The Piwi protein functions as an epigenetic regulator by binding to genomic polycomb group (PcG) response elements in conjunction with PcG proteins, leading to the silencing of homeobox genes (18). This association suggests that piRNAs play a crucial role in epigenetic regulation (18).

Epigenetics and White Adipose Tissue

As with many other organs and tissues, it is inevitable that epigenetics will have a considerable impact on the development and functions of AT. In the context of WAT, recent interest has focused on alterations in the epigenome, particularly in relation to obesity and its associated comorbidities (Figure 3).

Epigenetics and Adipose Tissue Memory

People with obesity often have challenges with weight regain after losing weight (27). This phenomenon, known as weight recidivism, is frequently attributed to difficulties in maintaining dietary and physical activity routines (28). However, it is well-established that a wide range of physiological

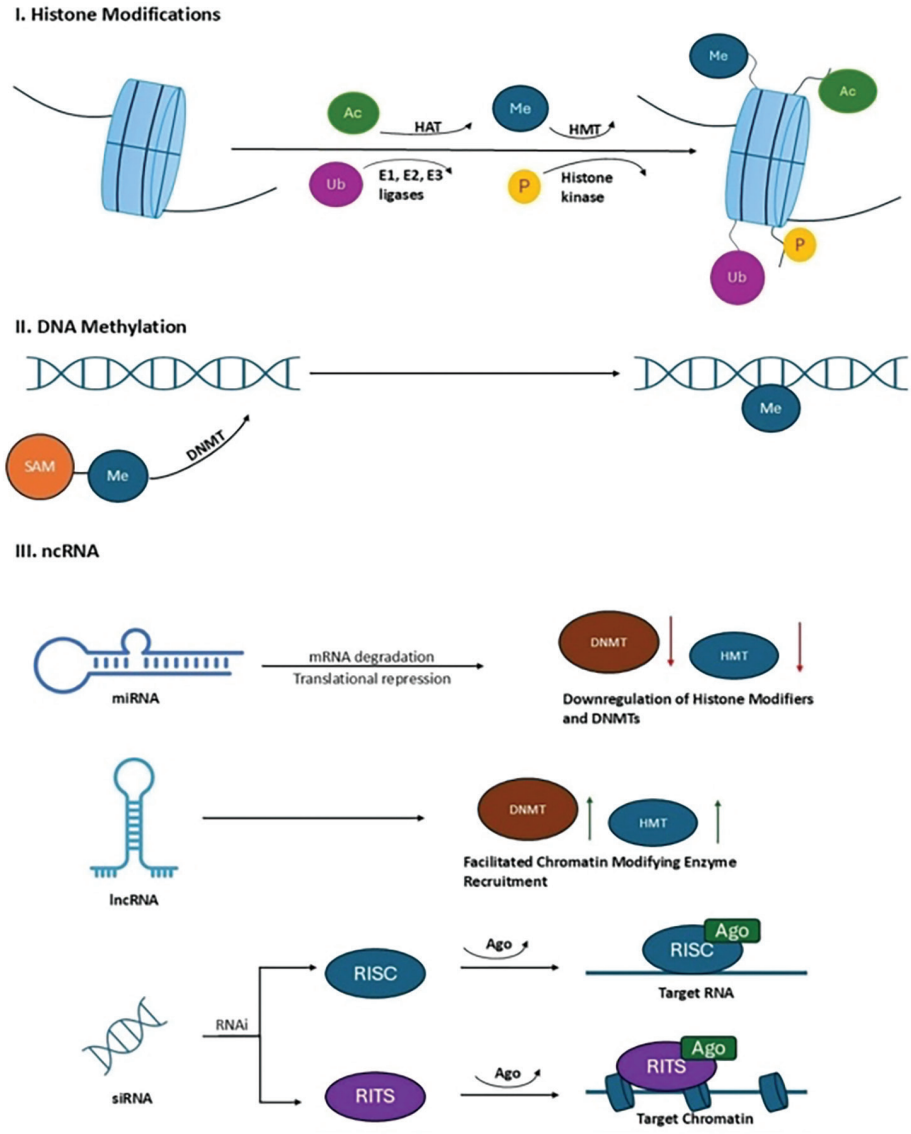

Figure 2: Epigenetic regulation of gene expression. Gene expression is controlled by three key epigenetic mechanisms: Histone modifications-modifications such as histone methylation, acetylation, and phosphorylation alter gene expression by modifying the amino acid residues on histone tails (11, 12-15). DNA methylation-this process involves the transfer of a methyl group from S-adenosyl methionine to the cytosine residue in DNA, leading to transcriptional repression (11, 12). ncRNAs, such as miRNAs, siRNA and lncRNA interact with various factors to regulate transcription (18-25). miRNA downregulates the histone modifying enzyme recruitment by either mRNA degradation, or translational repression (19). This results in altered gene expression. Though the roles and functions of most lncRNAs are yet to be discovered, the prevalent insights regarding lncRNAs indicate that they promote the recruitment of chromatin-modifying enzymes to particular genomic loci, thereby altering the chromatin or DNA state (26). siRNAs function via RNAi mechanisms to inhibit gene expression at either the transcriptional or post-transcriptional stage (24). Ago proteins, in conjunction with siRNA, constitute the central components of RISC and RITS, which are key effectors in the RNAi pathway (24). The interaction between the guide strand and the target RNA through complementary base-pairing facilitates the cleavage of the target RNA (24). This figure was created using the program: Microsoft Powerpoint.

Ac: Acetylation, DNMT: DNA methyltransferase, Me: Methylation, miRNA: microRNA, SAM: S-adenosyl methionine, P: Phosphorylation, Ub: Ubiquitination, HAT: Histone acetyltransferase, HMT: Histone methyltransferase, ncRNA: Non-coding RNA, mRNA: Messenger RNA, siRNA: Small interfering RNA, RNAi: RNA interference, RISC: RNA-induced silencing complex, RITS: RNA-induced transcriptional silencing complex, Ago: Argonaute proteins, lncRNA: Long non-coding RNA, RNAi: RNA interference, DNA: Deoxyribonucleic acid, RNA: Ribonucleic acid

processes, beyond diet and exercise alone, play a significant role in regulating body weight and fat mass (28). One of the physiological processes contributing to the frequency of weight regain is epigenomic alteration, which creates an "obesogenic memory" that diminishes the long-term benefits of calorie restriction (29-31). This obesogenic memory not only promotes a persistent tendency to regain weight but may also underlie the metabolic impairments observed in individuals with obesity (30). Hinte et al. (30) recently demonstrated, through single-nucleus RNA sequencing, that both human and mouse ATs retain cellular transcriptional changes even after significant weight loss. Furthermore, they found that the epigenomes of mouse adipocytes remain persistently altered by obesity, impairing their functionality and responsiveness to metabolic stimuli (30).

While metabolic adaptations in response to weight loss are known to persist long-term, the duration of this persistence varies based on the method by which the weight loss was achieved (29, 30). Bariatric surgery is a common treatment for obesity, particularly in severely obese patients who have not succeeded with non-invasive weight loss methods (32). One of the most recent findings is that, compared with patients who lost weight by calorie restriction, those who underwent bariatric surgery had only a transient decrease in basal metabolic rate (BMR), as opposed to persistently low BMR rates (29, 33). This suggests that bariatric surgery may be more effective than conventional methods in countering treatment against epigenetic obesogenic memory. However, the exact molecular mechanisms underlying this phenomenon remain unknown, making it difficult to overcome this barrier to achieving long-term treatment success (30).

Influence of Epigenetic Alterations in Obesity and Its Comorbidities

Obesity is an increasingly problematic health issue, as the worldwide incidence of obesity has markedly escalated over the last four decades, rising from 3% to 11% among men and from 6% to 15% among women during the same timeframe (34). Type 2 diabetes, cardiovascular disease, and several types of cancer are the primary adverse effects of obesity, which have already contributed to a reduction in average life expectancy (35). The development of obesity-related comorbidities, such as type 2 diabetes, cardiovascular diseases, and non-alcoholic fatty liver disease, is influenced by a combination of pathophysiological and environmental factors (36). Given that epigenomic alterations influence various biological systems, it is reasonable to assume that epigenetics also plays a reciprocal role in the development of obesity and its related comorbidities. A study conducted in a young cohort identified multiple CpG sites associated with obesity and found that the variance in DNA methylation was greater in obese individuals compared to lean controls (37, 38). The study also demonstrated that obesity could be predicted with 70% accuracy using both differential methylation and differential variability (37, 38). Another study newly identified 33 CpG sites associated with waist circumference and 70 CpG sites linked to BMI (39). These CpG sites accounted for 25.9% of the variation in waist circumference and 29.2% of the variation in BMI, respectively (39). Another study identified 3529 differentially methylated regions (DMRs) located within or near genes in adipocytes, using a combination of DNA methylation capture sequencing and reduced representation bisulfite sequencing in 11 lean and 12 obese pigs (40). This study also identified 276 differentially expressed transcripts with at least one DMR by sequencing the transcriptome from the same fraction of isolated adipocytes (40). These transcripts were found to be overrepresented in insulin signaling, metabolic, and mitogen-activated protein kinase gene pathways (40).

One of the most common comorbidities of obesity, type 2 diabetes, has also been shown to involve epigenomic changes that contribute to its pathophysiology (38). It was discovered that the islets from type 2 diabetes donors exhibited lower expression of key genes and increased DNA methylation, which were associated with impaired insulin secretion (38). Additionally, elevated hemoglobin A1c and glucose levels appeared to directly increase DNA methylation of these genes (38). Nilsson et al. (41) demonstrated that in the livers of type 2 diabetes patients, individuals with the condition showed reduced DNA methylation at 94% of the significant CpG sites. The observed hypomethylation in the livers of diabetic subjects could be attributed to reduced folate levels (41). Indeed, those with type 2 diabetes had significantly lower erythrocyte folate levels compared to individuals without diabetes (41). Even more interestingly, another study found that women with higher folate intake had a lower risk of developing diabetes (38, 42). This suggests that epigenetic changes influenced by folate intake might play a role in the development of diabetes. However, genetic studies indicate that the effect size of each CpG site is relatively small (38). This is not surprising, as type 2 diabetes is a complex, multifactorial, and polygenic disease, making it unlikely that methylation of a small number of CpG sites would have a significant impact on the disease (38).

Epigenetics and Susceptibility to Obesity

Studies indicate that individuals with a genetic predisposition for AT accumulation are also more susceptible to adverse environmental factors, which renders them more prone to weight gain (43). This phenomenon is known as gene-by-environment interaction, and it is mediated through epigenetic mechanisms (43). Viable yellow (Avy) mutation in the agouti mouse model illustrates how epigenetics influence obesity (43, 44). For context, it is worth mentioning that Avy mutation is one of two dominant mutations of the *Agouti* gene on mouse chromosome 2 (45). This mutation manifests a phenotype characterized by yellow fur, significant obesity, insulin resistance, and vulnerability to tumorigenesis (45). When these mice are fed a diet high in methyl donors, the mutation that disrupts melanocortin-4 receptor and causes obesity can be reversed (43, 44). This demonstrates a connection between

environmental-driven epigenetic changes and obesity (43, 44). Another study discovered that in obese subjects, weight was inversely correlated with the rate of DNA methylation at the leptin gene's promoter region (46). Additionally, the study's results indicated a negative correlation between DNA methylation levels and total cholesterol, insulin resistance (measured by the homeostatic model assessment), glucose, and fasting insulin (46). Compared to non-obese subjects, obese individuals also exhibited higher expression of DNMT1 and DNMT3b (46). This finding suggests that the epigenomic profile of leptin is likely associated with obesity and its risk factors, thereby increasing the likelihood of comorbidities (46).

There is limited research supporting transgenerational epigenetic inheritance in humans, and the dynamic, transient nature of epigenetic modifications presents additional challenges in this area of study (38). Outside of human research, actual transgenerational epigenetic effects are still poorly understood, with most observations being made in Caenorhabditis elegans (38). However, several studies have attempted to investigate the transmission of epigenetic mechanisms across generations and their relationship to type 2 diabetes and obesity (38). The rapid rise in the prevalence of metabolic and chronic diseases may partly explained by the fact that obese mothers can pass on their metabolic phenotypes to their children, increasing the risk of chronic metabolic diseases (8). One proposed mechanism for this is epigenetic inheritance.

Epigenetics in Central Nervous System (CNS) Regulation of Appetite and Metabolic Pathways

It is well-established that the CNS has a major influence on other organs and systems (47-49). Given this, it is reasonable to suggest that the CNS also plays a critical role in the gastrointestinal and endocrine systems (48, 50, 51). One of the mechanisms through which the CNS may exert its influence is

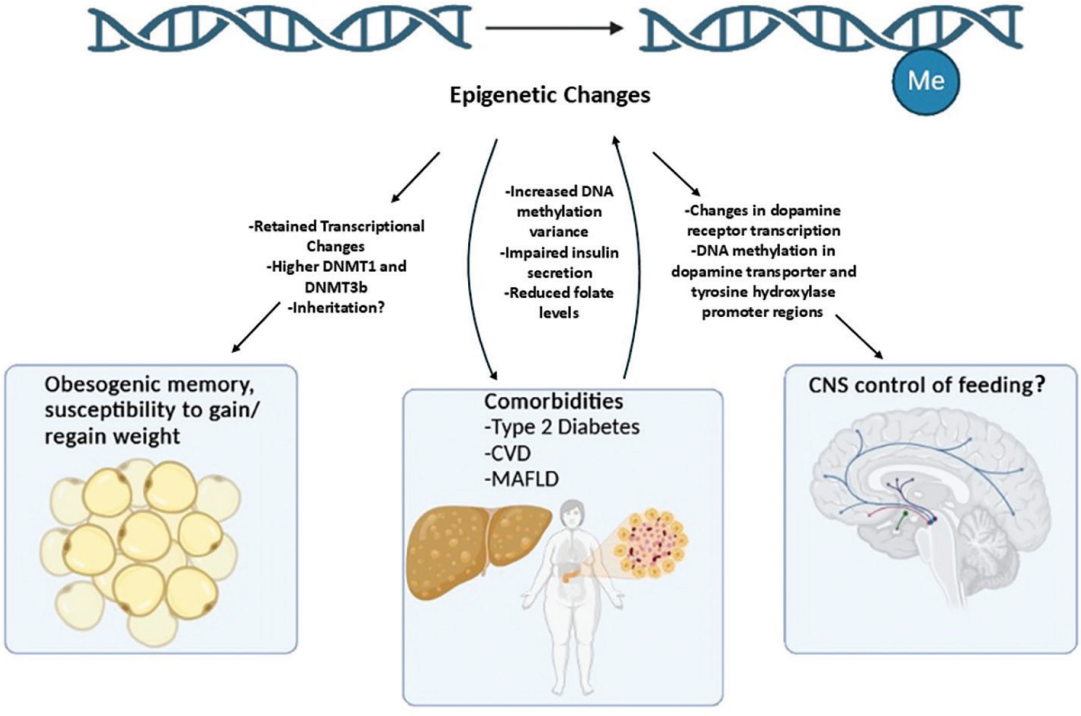

Figure 3: Epigenetics and White Adipose Tissue. Epigenetic changes play a significant role in both weight gain and weight maintenance, influencing the development and persistence of obesity (8, 29-31, 43, 50). It was recently demonstrated that both human and mouse ATs retain cellular transcriptional changes even after significant weight loss (30). Furthermore, the epigenomes of mouse adipocytes remain persistently altered by obesity, impairing their functionality and responsiveness to metabolic stimuli (30). Studies indicate that individuals with a genetic predisposition for AT accumulation are also more susceptible to adverse environmental factors, which renders them more prone to weight gain (43). This phenomenon is known as gene-by-environment interaction, and it is mediated through epigenetic mechanisms (43). Epigenetic changes also exhibit a reciprocal relationship with obesity-related comorbidities. Multiple CpG sites associated with obesity were identified and found that the variance in DNA methylation was greater in obese individuals compared to lean controls (37, 38). It was also observed that the islets from type 2 diabetes donors exhibited lower expression of key genes and increased DNA methylation, which were associated with impaired insulin secretion (38). People with type 2 diabetes had significantly lower erythrocyte folate levels compared to individuals without diabetes (41). Additionally, in a study, women with higher folate intake had a lower risk of developing diabetes (38, 42). This suggests that epigenetic changes influenced by folate intake might play a role in the development of diabetes. Epigenetic modifications may have the potential to regulate appetite through transcriptional changes in the CNS. It has been observed that rodents chronically fed a high-fat diet show significant changes in dopamine receptor transcription (50). More notably, differential DNA methylation was found in the dopamine transporter and tyrosine hydroxylase promoter regions, and the pattern of this methylation response corresponded with changes in gene expression (50). This figure was created using the programs: BioRender and Microsoft Powerpoint.

CNS: Central nervous system, CVD: Cardiovascular diseases, MAFLD: Metabolic-associated fatty liver disease, Me: Methylation, AT: Adipose tissue, DNA: Deoxyribonucleic acid, WAT: White adipose tissue, DNMT: Deoxyribonucleic acid methyltransferase

through epigenetic changes. This idea is further supported by Gupta-Agarwal et al. (52), who identified 507 epigenetically related genes in the hippocampal cornu ammonis (CA1 region of the hippocampus). Given the CNSs important role in the hedonic control of appetite, it is reasonable to question whether epigenetics also plays a role in appetite regulation. Studies suggest that this may indeed be the case. It has been observed that rodents chronically fed a high-fat diet show significant changes in dopamine receptor transcription (50). More notably, differential DNA methylation was found in the dopamine transporter and tyrosine hydroxylase promoter regions, and the pattern of this methylation response corresponded with changes in gene expression (50). This suggests that the reward circuitry involved in the hedonic regulation of feeding may be influenced by epigenetic changes. However, much remains unknown about the functional role of these epigenetic modifications in the CNSs control over energy and glucose metabolism (29).

Epigenetics and Brown Adipose Tissue

As mentioned previously, recent studies suggest the existence of at least two types of thermogenic AT: pre-existing BAT and inducible BeAT (1, 7, 8). Classical BAT originates prenatally from a specific group of dermomyotome cells and is mainly found in specialized BAT locations, which typically diminish in adult humans (7). In contrast, BeAT, also referred to as "inducible BAT", is believed to originate from WAT and is induced under conditions such as cold exposure and exercise (7). Although it is known that BeAT is derived from WAT, the precise origin of this tissue remains unclear. However, it seems likely that epigenetic modifications play a significant role in the development of these cells.

Recent studies have identified approximately 50 transcriptional and epigenetic regulators that either promote or inhibit the development of BAT and BeAT (53). Notably, nearly all of these regulators function through four key transcriptional factors: *peroxisome proliferator-activated receptor γ*, *CCAAT-enhancer-binding protein*, *PPARγ co-activator-1α*, and *PR domain containing 16* genes (Figure 4) (53). Some of these epigenetic factors include several miRNAs, dimethyltransferases such as euchromatic histone lysine methyltransferase 1 and euchromatic histone lysine methyltransferase 2, and a lncRNA called Brown fat lncRNA 1 (53).

CONCLUSION

Adipose tissue plays several critical roles beyond fat storage and lipid regulation in the body's physiological and pathological functions, including thermogenesis and hormone regulation. These functions are governed by various mechanisms, one of which, epigenomic modifications, has gained recent attention. Studies on BeAT/BAT and WAT highlight the significant role of epigenetics. While epigenetics may also influence pink AT, there

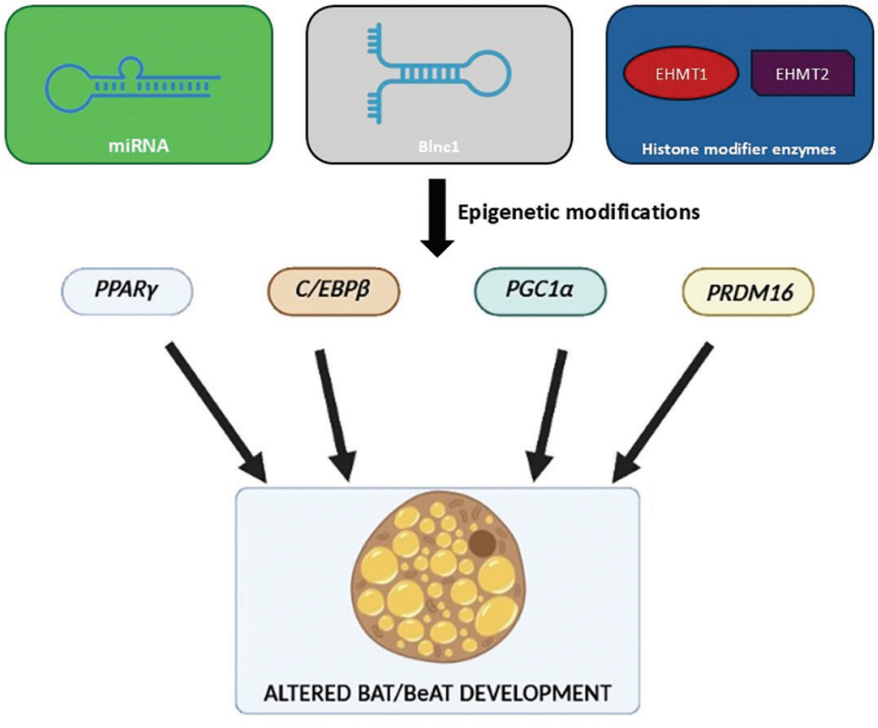

Figure 4: Epigenetic regulation of BAT/BeAT development. Nearly all epigenetic modifications involved in the development of BAT and BeAT function through the *PPARγ*, *C/EBPβ*, *PGC1α*, and *PRDM16* genes (53). Some of these epigenetic factors include several miRNAs, dimethyltransferases such as EHMT1 and EHMT2, and a long non-coding RNA called Blnc1 (53). This figure was created using the programs: BioRender and Microsoft PowerPoint.

BAT: Brown adipose tissue, BeAT: Beige adipose tissue, C/EBPβ: CCAAT-enhancer-binding protein, PGC1α: PPARγ co-activator-1α, miRNA: micro ribonucleic acid, Blnc1: Brown fat lncRNA-1, EHMT: Euchromatic histone-lysine N-methyltransferase

is still limited research in this area, making it unclear. However, when it comes to pathological conditions like obesity and its comorbidities, there is a wealth of evidence to explore. Several studies suggest that epigenetic mechanisms may contribute to the development and maintenance of obesity through various pathways, such as creating an obesogenic memory, increasing susceptibility to environmental factors that promote weight gain, affecting the central CNS and indirectly controlling appetite, and possibly through epigenetic inheritance. Since epigenetic changes are reversible, there is hope for therapeutic interventions that target these changes, offering potential treatments for major diseases such as obesity and type 2 diabetes.

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REFERENCES

1. Richard AJ, White U, Elks CM, et al. Adipose tissue: physiology to metabolic dysfunction. In: Feingold KR, Anawalt B, Blackman MR, et al., editors. Endotext. South Dartmouth (MA): MDText.com; 2000-. [Crossref]
2. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab. 2004;89(6):2548-56. [Crossref]
3. Fève B, Cinti S, Beaupère C, et al. Pink adipose tissue: a paradigm of adipose tissue plasticity. Ann Endocrinol. 2024;85(3):248-51. [Crossref]
4. Braun K, Oeckl J, Westermeier J, et al. Non-adrenergic control of lipolysis and thermogenesis in adipose tissues. J Exp Biol. 2018;221(Suppl 1). [Crossref]
5. Saponaro C, Gaggini M, Carli F, et al. The subtle balance between lipolysis and lipogenesis: a critical point in metabolic homeostasis. Nutrients. 2015;7(11):9453-74. [Crossref]
6. Shuster A, Patlas M, Pinthus JH, et al. The clinical importance of visceral adiposity: a critical review of methods for visceral adipose tissue analysis. Br J Radiol. 2012;85(1009):1-10. [Crossref]
7. Lidell ME, Betz MJ, Dahlqvist Leinhard O, et al. Evidence for two types of brown adipose tissue in humans. Nat Med. 2013;19(5):631-4. [Crossref]
8. Katzmarzyk PT, Barlow S, Bouchard C, et al. An evolving scientific basis for the prevention and treatment of pediatric obesity. Int J Obes (Lond). 2014;38(7):887-905. [Crossref]
9. Marlatt KL, Ravussin E. Brown adipose tissue: an update on recent findings. Curr Obes Rep. 2017;6(4):389-96. [Crossref]
10. Liu X, Zhang Z, Song Y, et al. An update on brown adipose tissue and obesity intervention: function, regulation and therapeutic implications. Front Endocrinol. 2023;13:1065263. [Crossref]
11. Ragini, Sakshi, Mani I, et al. Applications of bioinformatics in epigenetics. Prog Mol Biol Transl Sci. 2023;198:1-13. [Crossref]
12. He Y, Ecker JR. Non-CG methylation in the human genome. Annu Rev Genomics Hum Genet. 2015;16:55-77. [Crossref]
13. Panera N, Mandato C, Crudele A, et al. Genetics, epigenetics and transgenerational transmission of obesity in children. Front Endocrinol. 2022;13:1006008. [Crossref]
14. Wapenaar H, Dekker FJ. Histone acetyltransferases: challenges in targeting bi-substrate enzymes. Clin Epigenetics. 2016;8(8):59. [Crossref]
15. Jambhekar A, Dhall A, Shi Y. Roles and regulation of histone methylation in animal development. Nat Rev Mol Cell Biol. 2019;20(10):625-41. [Crossref]
16. Rossetto D, Avvakumov N, Côté J. Histone phosphorylation: a chromatin modification involved in diverse nuclear events. Epigenetics. 2012;7(10):1098-108. [Crossref]
17. Shahid Z, Simpson B, Miao KH, et al. Genetics, histone code. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2025. [Crossref]
18. Wei JW, Huang K, Yang C, et al. Non-coding RNAs as regulators in epigenetics. Oncol Rep. 2017;37(1):3-9. [Crossref]
19. Melone MAB, Valentino A, Margarucci S, et al. The carnitine system and cancer metabolic plasticity. Cell Death Dis. 2018;9(2):228. [Crossref]
20. O'Brien J, Hayder H, Zayed Y, et al. Overview of microRNA biogenesis, mechanisms of actions, and circulation. Front Endocrinol (Lausanne). 2018;9:402. [Crossref]
21. Peschansky VJ, Wahlestedt C. Non-coding RNAs as direct and indirect modulators of epigenetic regulation. Epigenetics. 2014;9(1):3-12. [Crossref]
22. Mattick JS, Amaral PP, Carninci P, et al. Long non-coding RNAs: definitions, functions, challenges and recommendations. Nat Rev Mol Cell Biol. 2023;24(6):430-47. [Crossref]
23. Ghafouri-Fard S, Esmaeili M, Taheri M. H19 lncRNA: roles in tumorigenesis. Biomed Pharmacother. 2020;123:109774. [Crossref]
24. Verdel A, Vavasseur A, Le Gorrec M, et al. Common themes in siRNA-mediated epigenetic silencing pathways. Int J Dev Biol. 2009;53(2-3):245-57. [Crossref]
25. Dana H, Chalbatani GM, Mahmoodzadeh H, et al. Molecular mechanisms and biological functions of siRNA. Int J Biomed Sci. 2017;13(2):48-57. [Crossref]
26. Chen J, Xue Y. Emerging roles of non-coding RNAs in epigenetic regulation. Sci China Life Sci. 2016;59(3):227-35. [Crossref]
27. Franz MJ, VanWormer JJ, Crain AL, et al. Weight-loss outcomes: a systematic review and meta-analysis of weight-loss clinical trials with a minimum 1-year follow-up. J Am Diet Assoc. 2007;107(10):1755-67. [Crossref]
28. Busetto L, Bettini S, Makaronidis J, et al. Mechanisms of weight regain. Eur J Intern Med. 2021;93:3-7. [Crossref]
29. Contreras RE, Schriever SC, Pfluger PT. Physiological and epigenetic features of yoyo dieting and weight control. Front Genet. 2019;10:1015. [Crossref]
30. Hinte LC, Castellano-Castillo D, Ghosh A, et al. Adipose tissue retains an epigenetic memory of obesity after weight loss. Nature. 2024;636(8042):457-65. [Crossref]
31. Hahn O, Drews LF, Nguyen A, et al. A nutritional memory effect counteracts benefits of dietary restriction in old mice. Nat Metab. 2019;1(11):1059-73. [Crossref]
32. Wolfe BM, Kvach E, Eckel RH. Treatment of obesity: weight loss and bariatric surgery. Circ Res. 2016;118(11):1844-55. [Crossref]
33. Fothergill E, Guo J, Howard L, et al. Persistent metabolic adaptation 6 years after "The Biggest Loser" competition. Obesity. 2016;24(8):1612-9. [Crossref]
34. Jaacks LM, Vandevijvere S, Pan A, et al. The obesity transition: stages of the global epidemic. Lancet Diabetes Endocrinol. 2019;7(3):231-40. [Crossref]
35. Haslam DW, James WP. Obesity. Lancet. 2005;366(9492):1197-209. [Crossref]
36. Kloock S, Ziegler CG, Dischinger U. Obesity and its comorbidities, current treatment options and future perspectives: challenging bariatric surgery? Pharmacol Ther. 2023;251:108549. [Crossref]
37. Xu X, Su S, Barnes VA, De Miguel C, et al. A genome-wide methylation study on obesity: differential variability and differential methylation. Epigenetics. 2013;8(5):522-33. [Crossref]
38. Ling C, Rönn T. Epigenetics in human obesity and type 2 diabetes. Cell Metab. 2019;29(5):1028-44. [Crossref]
39. Sayols-Baixeras S, Subirana I, Fernández-Sanlés A, et al. DNA methylation and obesity traits: an epigenome-wide association study. The REGICOR study. Epigenetics. 2017;12(10):909-16. [Crossref]
40. Jacobsen MJ, Havgaard JH, Anthon C, et al. Epigenetic and transcriptomic characterization of pure adipocyte fractions from obese pigs identifies candidate pathways controlling metabolism. Front Genet. 2019;10:1268. [Crossref]
41. Nilsson E, Matte A, Perfilyev A, et al. Epigenetic alterations in human liver from subjects with type 2 diabetes in parallel with reduced folate levels. J Clin Endocrinol Metab. 2015;100(11):E1491-501. [Crossref]
42. Hong SM, Woo HW, Kim MK, et al. A prospective association between dietary folate intake and type 2 diabetes risk among Korean adults aged 40 years or older: The Korean Multi-Rural Communities Cohort (MRCohort) Study. Br J Nutr. 2017;118(12):1078-88. [Crossref]

43. Trang K, Grant SFA. Genetics and epigenetics in the obesity phenotyping scenario. Rev Endocr Metab Disord. 2023;24(5):775-93. [Crossref]
44. Dolinoy DC. The agouti mouse model: an epigenetic biosensor for nutritional and environmental alterations on the fetal epigenome. Nutr Rev. 2008;66(8):7-11. [Crossref]
45. Klebig ML, Wilkinson JE, Geisler JG, et al. Ectopic expression of the agouti gene in transgenic mice causes obesity, features of type II diabetes, and yellow fur. Proc Natl Acad Sci USA. 1995;92(11):4728-32.[Crossref]
46. Sadashiv, Modi A, Khokhar M, et al. Leptin DNA methylation and its association with metabolic risk factors in a northwest Indian obese population. J Obes Metab Syndr. 2021;30(3):304-11. [Crossref]
47. Urfy MZ, Suarez JI. Breathing and the nervous system. Handb Clin Neurol. 2014;119:241-50. [Crossref]
48. Faber CL, Deem JD, Campos CA, et al. CNS control of the endocrine pancreas. Diabetologia. 2020;63(10):2086-94. [Crossref]
49. Dampney RA. Central neural control of the cardiovascular system: current perspectives. Adv Physiol Educ. 2016;40(3):283-96. [Crossref]
50. Vucetic Z, Carlin JL, Totoki K, et al. Epigenetic dysregulation of the dopamine system in diet-induced obesity. J Neurochem. 2012;120(6):891-8. [Crossref]
51. Browning KN, Travagli RA. Central nervous system control of gastrointestinal motility and secretion and modulation of gastrointestinal functions. Compr Physiol. 2014;4(4):1339-68. [Crossref]
52. Gupta-Agarwal S, Franklin AV, Deramus T, et al. G9a/GLP histone lysine dimethyltransferase complex activity in the hippocampus and the entorhinal cortex is required for gene activation and silencing during memory consolidation. J Neurosci. 2012;32(16):5440-53. [Crossref]
53. Inagaki T, Sakai J, Kajimura S. Transcriptional and epigenetic control of brown and beige adipose cell fate and function. Nat Rev Mol Cell Biol. 2016;17(8):480-95. [Crossref]

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REVIEW

BACTERIAL THERAPIES IN CANCER TREATMENT: ADVANCES, MECHANISMS, AND FUTURE PROSPECTS

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ABSTRACT

Cancer is one of the leading causes of death, and despite remarkable advances in treatment, chemotherapy remains the primary therapeutic approach. However, the emergence of drug resistance presents a major challenge, often limiting the efficacy of conventional treatments. As a result, developing novel therapeutic strategies has gained increasing importance in recent years. One such emerging approach is the use of bacteria in cancer therapy. Bacterial therapies offer unique mechanisms to target cancer cells and stimulate the immune response, providing a promising alternative to traditional treatments. This review aims to explore the potential of bacterial-based therapies in overcoming drug resistance and improving cancer treatment outcomes.

Keywords: Bacteria, cancer, immunostimulation, treatment

INTRODUCTION

Cancer is the second leading cause of death globally, after cardiovascular diseases (1). In 2020, an estimated 19.3 million cancer patients were newly diagnosed, and ten million deaths due to cancer occurred worldwide (2). The most frequent diagnoses included lung, prostate, colorectal, and breast cancers (3). Lung cancer, for instance, is the most prevalent form of cancer among men (1). These statistics underscore the urgent need to develop novel therapeutic approaches, and one such promising strategy is the use of bacterial therapies in cancer treatments (4). These strategies can be categorized into the following four sub-methods (5):

1. Bacterial vectors utilized for the targeted delivery of genetically engineered therapeutic agents.

2. Bacterial toxins for the inhibition of tumor growth.

3. Bacteria-mediated immunostimulation in cancer treatment.

4. Combination therapies integrating bacterial treatments with immunotherapy and chemotherapy.

Bacterial Vectors Utilized for the Targeted Delivery of Genetically Engineered Therapeutic Agents

Bacterial vectors have emerged as promising tools for the targeted delivery of genetically engineered therapeutic agents in cancer therapy. These vectors leverage the natural properties of bacteria to selectively home in on tumor sites, offering unique methods for localized treatment and minimizing damage to healthy tissues (6). A landmark study by Minton et al. (7) demonstrated that bacterial spores could inhibit cell growth, highlighting their potential in anticancer therapies. This early research laid the foundation for subsequent explorations into the use of bacterial vectors in cancer treatment.

Further advancements were made in a 1997 study by Pawelek et al. (8), in which the anticancer effects of a genetically modified *Salmonella* strain were observed. This study revealed that *Salmonella* could selectively colonize the tumor microenvironment (8). Once in the tumor, the bacteria activated the immune system and produced therapeutic genes and toxins that specifically targeted tumor cells, offering a novel approach to cancer treatment (8).

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Subsequent studies have demonstrated that bacteria selectively colonize tumor tissues, proliferate in hypoxic environments, and induce cancer cell destruction by producing enzymes and toxins (9). Genetic engineering techniques have enabled a more precise control of the bacteria's tumor-targeting abilities as well as the incorporation of novel functions to enhance their therapeutic potential (10).

Several different studies have been conducted in bacterial vector-based cancer immunotheraphy (Table 1).

Bacterial Toxins for the Inhibition of Tumor Growth

Bacterial toxins exhibit high cytotoxic effects and specific targeting capabilities, which make them promising agents in cancer treatment that selectively target specific surface receptors on cancer cells or exploit the characteristics of the tumor microenvironment (17). Treatment strategies employing these toxins include immunotoxins, targeted therapies, and gene therapy (18). Immunotoxins, which are generated through the conjugation of bacterial toxins with monoclonal antibodies, enable more precise targeting of cancer cells (19). In contrast, targeted therapies aim to modify tumor cells to enhance their binding to specific surface antigens, thereby reducing the likelihood of damaging normal cells (20). Additionally, incorporating bacterial toxin genes into gene therapy strategies facilitates the targeted production of toxins within tumor cells, a mechanism that can be categorized into three key subheadings (21).

a. Direct Cytotoxicity

Certain bacterial toxins, such as diphtheria toxin and Pseudomonas exotoxin, can infiltrate cancer cells and disrupt essential cellular processes, particularly protein synthesis (22). This disruption ultimately leads to cell death. These toxins can be engineered to specifically target overexpressed receptors in cancer cells, thereby minimizing damage to healthy tissues.

b. Immune Modulation

Toxins such as superantigens are known for their ability to activate the immune system by triggering a significant release of cytokines (23). This cascade recruits immune cells, particularly T cells, to the tumor microenvironment, enhancing the immune-mediated destruction of tumor cells and inhibiting further tumor growth (24).

Table 1: Comparative objectives and outcomes of bacterial vector-based cancer immunotherapy studies.

Title	Objective	Results
Pleiotropic Immunomodulatory Functions of Radioactive Inactivated Bacterial Vectors for Enhanced Cancer Radio-immunotherapy	This study aimed to develop a safer IRT using inactivated bacterial vectors labeled with $^{125}I/^{131}I$, which were designed to retain radioactivity at tumor sites, target tumor cells and TAMs, and enhance the antitumor immune response (11).	*In vivo* studies showed that $^{125}I/^{131}I$-labeled bacterial vectors effectively targeted tumor cells and TAMs. They inhibited tumor growth and prolonged survival in a murine breast cancer model while enhancing TIL infiltration and anti-tumor immunity (11).
A Safe Bacterial Microsyringe for *in vivo* Antigen Delivery and Immunotherapy	This study aimed to engineer a novel antigen delivery system that utilizes the *Pseudomonas aeruginosa* T3SS as a microinjector, employing the "KBMA" strategy to enhance safety for potential human applications (12).	The study demonstrated the potential of an attenuated *P. aeruginosa* strain as a safe antigen delivery vehicle since it effectively targeted antigen-presenting cells and induced a strong anti-tumor immune response in a murine model (12).
Intracellular Bacterial Vectors That Induce CD8 (+) T Cells with Similar Cytolytic Abilities but Disparate Memory Phenotypes Provide Contrasting Tumor Protection	This study compared the efficacy of *Listeria monocytogenes* and *Salmonella typhimurium* in inducing functional CD8(+) T cell responses and tumor protection (13).	The study revealed that while both *L. monocytogenes* and *S. typhimurium* induced functional CD8 (+) T cells, only *Listeria* generated long-lasting memory T cells crucial for effective tumor protection (13).
Optimization of Antitumor Immunotherapy Mediated by Type III Secretion System-based Live Attenuated Bacterial Vectors	The primary objective of this study was to optimize the efficacy of live attenuated *P. aeruginosa* vectors, which utilize the type III secretion system for antigen delivery, inducing robust and durable anti-tumor immune responses (14).	This study demonstrated that optimized *P. aeruginosa* vectors can enhance CD8 (+) T cell responses and improve tumor rejection in murine models, highlighting their potential for clinical use in cancer immunotherapy (14).
Cancer Immunotherapy Using *L. monocytogenes* and Listerial Virulence Factors	This study explored the potential of *S. typhimurium* as a cancer immunotherapy agent by assessing its ability to selectively infect tumor cells and enhance immune responses (15).	The findings demonstrated that *S. typhimurium* efficiently targeted tumors, induced the release of tumor-associated antigens, activated CD8 (+) T cells, and promoted significant tumor regression, suggesting its potential for bacterial-mediated cancer immunotherapy (15).
Cancer immunotherapy using *L. monocytogenes* and listerial virulence factors	This study investigates the use of *Listeria monocytogenes* as a vector for cancer immunotherapy, focusing on its ability to deliver tumor-associated antigens directly into the cytoplasm of host cells to elicit robust CTL responses (16).	The study shows that *L. monocytogenes* targets tumor cells, promotes tumor antigen presentation via the MHC Class I pathway, and activates CTLs, leading to strong anti-tumor responses (16).

IRT: Internal radioisotope therapy, TAMs: Tumor-associated macrophages, TIL: Tumor-infiltrating lymphocyte, T3SS: Type III secretion system, KBMA: Killed but metabolically active, CTL: Cytotoxic T lymphocyte, MHC: Major histocompatibility complex, P. aeruginosa: *Pseudomonas aeruginosa*, L. monocytotogenes: *Listeria monocytogenes*, S. typhimurium: *Salmonella typhimurium*

c. Apoptosis Induction

Certain bacterial toxins can induce programmed cell death (apoptosis) in tumor cells (25). For instance, toxins produced by Clostridium perfringens can disrupt cellular membranes, promoting apoptosis, particularly in the hypoxic conditions often present in tumor cores (Table 2) (26).

Bacteria-Mediated Immunostimulation in Cancer Treatment

The entry of bacteria into the host initiates a rapid and robust immune system stimulation that leads to an immediate immune response critical for combating malignancies (Figure 1) (31). This response predominantly activates innate immune cells, such as macrophages, dendritic cells, and natural killer (NK) cells, which collectively enhance the body's defenses against cancer cells. Key molecular components found in bacterial cell walls, such as lipopolysaccharides (LPS) and peptidoglycans, function as pathogen-associated molecular patterns recognized by pattern recognition receptors on immune cells (32). This recognition triggers a cascade of signaling events that culminate in significant immune activation.

The immunostimulatory effects of bacteria are mediated through several mechanisms. First, bacteria can be directly introduced into the tumor microenvironment, where they induce local inflammation and attract immune effector cells to the tumor site (33). Second, certain bacteria can produce toxins capable of selectively inducing apoptosis in cancer cells, thereby reducing tumor burden and further stimulating the immune response (34). Third, bacteria can induce long-lasting immunological memory, enhancing the host's ability to mount a rapid response against recurrent tumors (35). Finally, innovative therapeutic strategies involving engineered bacteria exploit these mechanisms to enhance the efficacy of existing cancer treatments, including checkpoint inhibitors and other immunotherapeutic approaches (36).

In summary, bacteria-mediated strategies highlight the potential of leveraging microbial interactions to enhance immune function in cancer therapy. By targeting tumor cells directly and modulating the immune system, these approaches may establish a durable antitumor response, representing a promising avenue in the fight against cancer.

Combination Therapies Integrating Bacterial Treatments with Immunotherapy and Chemotherapy

Bacterial therapies are gaining attention in cancer treatment due to their ability to both directly target tumors and stimulate the immune system. These therapies, when combined with immunotherapy and chemotherapy, offer a synergistic approach, potentially enhancing therapeutic outcomes and addressing drug resistance (37).

Bacteria can activate the immune system through molecules like LPS and peptidoglycans that are present in their cell walls. These components are recognized by immune cells such as macrophages, dendritic cells, and NK cells, leading to a strong immune response (38). When used alongside checkpoint inhibitors, like Programmed cell death protein 1/Programmed death-ligand 1 (PD-1/PD-L1) blockers, bacterial therapies can further boost the immune system's ability to attack cancer cells, which helps to overcome immune evasion mechanisms (39).

Table 2: Several studies that have been conducted in the field of using bacterial toxins for inhibition of tumor growth.

Title	Bacterial toxin	Objective	Result
CRM197 (NT diphtheria toxin): Effects on Advanced Cancer Patients	NT diphtheria toxin	The primary objective of this study was to investigate the therapeutic potential of CRM197, a non-toxic mutant of diphtheria toxin, as a novel immunotherapeutic agent for various advanced cancers (27).	This clinical trial showed that subcutaneous CRM197 administration induced a strong immune response, was well-tolerated, and demonstrated promising anti-tumor activity in patients with advanced cancers, suggesting its potential as a novel immunotherapy (27).
Safety, Tolerability, and Tumor Response of IL4-*Pseudomonas Exotoxin* (NBI-3001) in Patients with Recurrent Malignant Glioma	P. exotoxin	The primary objective of this open-label, dose-escalation study was to evaluate the safety and efficacy of intratumorally administered IL-4 *P. exotoxin* (NBI-3001) in patients with recurrent malignant glioma (28).	Intratumoral administration of NBI-3001 was well-tolerated in patients with recurrent malignant glioma and showed promising anti-tumor activity, indicated by an increased tumor necrosis on MRI (28).
Intratumoral Injection of *Clostridium novyi*-NT Spores in Patients with Treatment-refractory Advanced Solid Tumors	*C. novyi*-NT	The primary goal of this clinical trial was to evaluate the safety and efficacy of intratumoral injection of *C. novyi*-NT, an attenuated bacterial strain, in patients with advanced solid tumors (29).	Intratumoral injection of *C. novyi*-NT showed promising anti-tumor activity with tumor regression and systemic immune response, but it caused significant toxicities, including sepsis and gas gangrene at higher doses (29).
Major Cancer Regressions in Mesothelioma After Treatment with an Anti-mesothelin Immunotoxin and Immune Suppression	*P. exotoxin* A (with anti-mesothelin)	The study aimed to assess the efficacy of an anti-mesothelin immunotoxin combined with immune suppression for treating mesothelioma (30).	In preclinical models, the combination treatment resulted in major tumor regressions. Clinical trial results indicated that the anti-mesothelin immunotoxin was well-tolerated and showed significant therapeutic potential, with some patients experiencing tumor shrinkage. Immune suppression was found to enhance the response by mitigating immune-mediated resistance (30).

MRI: Magnetic resonance imaging, NT: Non-toxic, IL: Interleukin

Additionally, bacterial therapies complement chemotherapy by localizing within the tumor microenvironment, allowing for more targeted drug delivery. This improves drug efficacy while minimizing side effects on healthy tissue. Bacteria also help disrupt the tumor's physical barriers, enhancing drug penetration and overall treatment effectiveness (40).

Genetically engineered bacteria add further precision to this approach. Modified bacteria can deliver chemotherapeutic agents directly to tumors, ensuring higher concentrations at the target site while reducing systemic toxicity (41). This targeted delivery is particularly beneficial for combating resistant tumors and improving the safety profile of chemotherapy (42). A comprehensive treatment strategy is achieved by combining bacterial therapies with immunotherapy and chemotherapy (Figure 2). While immunotherapy amplifies the immune response against cancer, chemotherapy directly attacks proliferating tumor cells, and bacteria enhance these effects by improving immune activation and drug targeting. This multi-pronged approach can reduce the likelihood of resistance, a major challenge in cancer treatment.

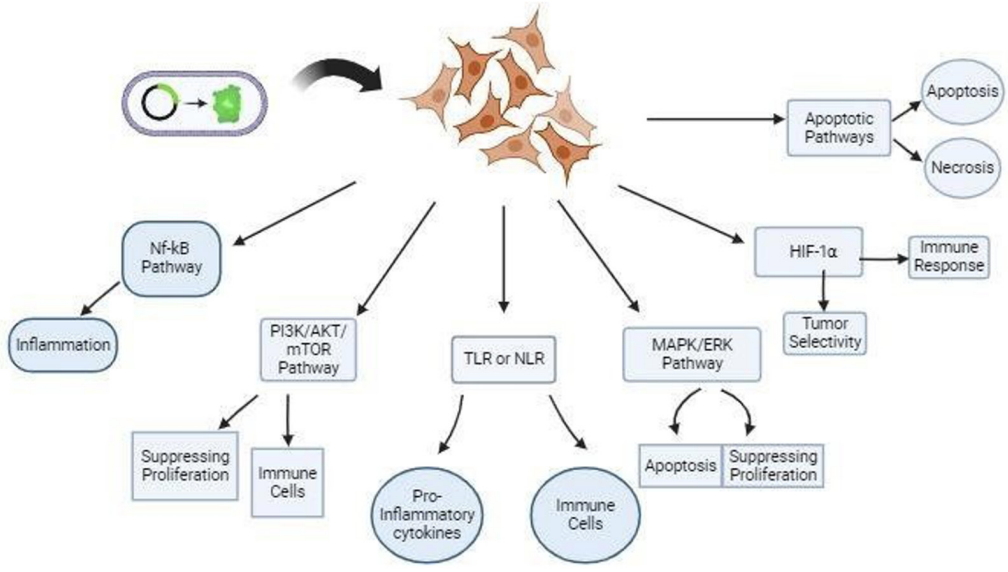

Figure 1: Mechanisms of host signaling pathway modulation by bacterial vectors in cancer therapy.
Nf-kB: Nuclear factor kappa-light-chain-enhancer of activated B cells, Pl3k: Phosphoinositide 3-kinase, Akt: Protein kinase B, Mtor: Mammalian target of rapamycin, TLR: Toll-like receptor, NLR: Nod-like receptor, MAPK: Mitogen-activated protein kinase, ERK: Extracellular signal-regulated kinase, HIF-1a: Hypoxia-inducible factor 1-alpha

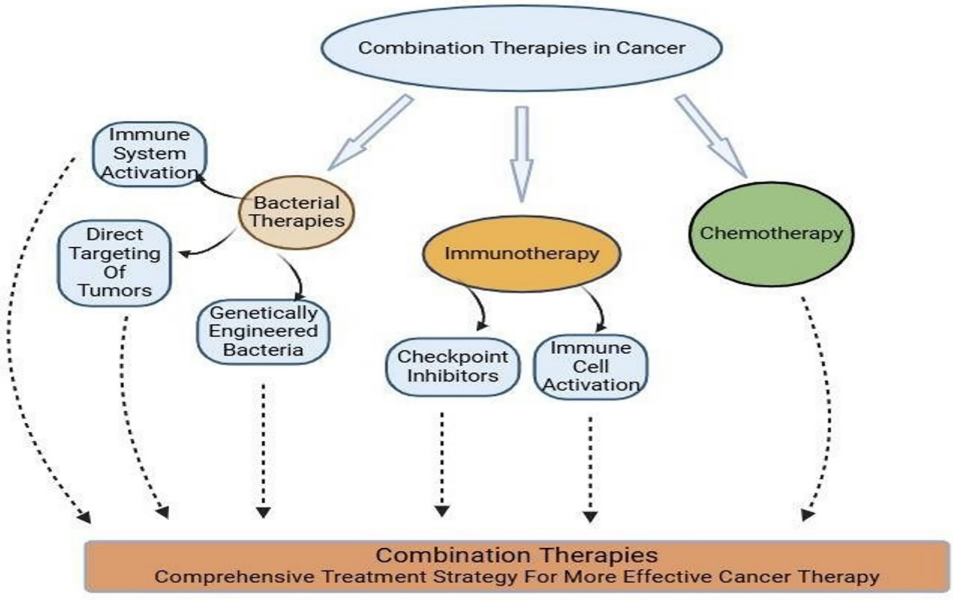

Figure 2: Combination therapies in cancer: integration of bacterial therapies, immunotherapy, and chemotherapy.

CONCLUSION

Bacterial treatment methods are emerging as promising alternatives in cancer therapy. Through various strategies such as tumor targeting, immunotherapy, gene therapy, and oncolytic bacteria, bacterial vectors can be effective in eliminating cancer cells. In particular, bacterial treatment methods offer significant advantages alongside traditional therapies by enhancing the immune system, modulating the tumor microenvironment, and providing targeted therapeutic approaches.

However, several challenges and limitations exist in the clinical applications of bacterial treatment methods. Issues such as the control of bacterial infections, minimizing side effects during treatment, and determining appropriate dosages should be the focal points of research. Furthermore, it is essential to integrate bacterial treatment methods with immunotherapies to enhance their effectiveness.

Future research should focus more on both preclinical and clinical studies to improve the efficacy and safety of bacterial treatment methods and deepen the knowledge in this field. In conclusion, bacterial treatment strategies open a new horizon in cancer therapy and play a significant role in the fight against cancer through a multidisciplinary approach.

Ethics

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Footnotes

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REFERENCES

1. World Health Organization. (2020). Cancer. Avaliable from: [Crossref]
2. Sung H, Ferlay J, Siegel RL et al. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209-49. [Crossref]
3. American Cancer Society. (2021). Cancer Facts & Figures 2021. Available from: [Crossref]
4. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. Cell. 2011;144(5):646-74. [Crossref]
5. Luo M, Chen X, Gao H et al. Bacteria-mediated cancer therapy: a versatile bio-sapper with translational potential. Front Oncol. 2022;12:980111. [Crossref]
6. Duong MTQ, Qin Y, You SH et al. Bacteria-cancer interactions: bacteria-based cancer therapy. Exp Mol Med. 2019;51(1):1-15. [Crossref]
7. Minton NP, Mauchline ML, Lemmon MJ et al. Chemotherapeutic tumour targeting using clostridial spores. FEMS Microbiol Rev. 1995;17(3):357-64. [Crossref]
8. Pawelek JM, Low KB, Bermudes D. Bacteria as tumour-targeting vectors. Lancet Oncol. 2003;4(9):548-56. [Crossref]
9. St. Jean AT, Zhang M, Forbes NS. Bacterial therapies: completing the cancer treatment toolbox. Curr Opin Biotechnol. 2008;19(5):511-7. [Crossref]
10. Chen Y, Liu X, Guo Y et al. Genetically engineered oncolytic bacteria as drug delivery systems for targeted cancer theranostics. Acta Biomater. 2021;124:72-87. [Crossref]
11. Pei P, Zhang Y, Jiang Y et al. Pleiotropic immunomodulatory functions of radioactive inactivated bacterial vectors for enhanced cancer radio-immunotherapy. ACS Nano. 2022;16(7):11325-37. [Crossref]
12. Le Gouëllec A, Chauchet X, Laurin D et al. A safe bacterial microsyringe for *in vivo* antigen delivery and immunotherapy. Mol Ther. 2013;21(5):1076-86. [Crossref]
13. Stark FC, Sad S, Krishnan L. Intracellular bacterial vectors that induce CD8 (+) T cells with similar cytolytic abilities but disparate memory phenotypes provide contrasting tumor protection. Cancer Res. 2009;69(10):4327-34. [Crossref]
14. Wang Y, Le Gouëllec A, Chaker H et al. Optimization of antitumor immunotherapy mediated by type III secretion system-based live attenuated bacterial vectors. J Immunother. 2012;35(3):223-34. [Crossref]
15. Avogadri F, Martinoli C, Petrovska L et al. Cancer immunotherapy based on killing of *Salmonella*-infected tumor cells. Cancer Res. 2005;65(9):3920-7. [Crossref]
16. Wood LM, Guirnalda PD, Seavey MM et al. Cancer immunotherapy using *Listeria monocytogenes* and listerial virulence factors. Immunol Res. 2008;42(1-3):233-45. [Crossref]
17. Zahaf NI, Schmidt G. Bacterial toxins for cancer therapy. Toxins (Basel). 2017;9(8):236. [Crossref]
18. Pahle J, Walther W. Bacterial toxins for oncoleaking suicidal cancer gene therapy. Recent Results Cancer Res. 2016;209:95-110. [Crossref]
19. Akbari B, Farajnia S, Ahdi Khosroshahi S et al. Immunotoxins in cancer therapy: review and update. Int Rev Immunol. 2017;36(4):207-19. [Crossref]
20. Pastan I, Hassan R, Fitzgerald DJ et al. Immunotoxin therapy of cancer. Nat Rev Cancer. 2006;6(7):559-65. [Crossref]
21. Keyvani K, Baur I, Paulus W. Tetracycline-controlled expression but not toxicity of an attenuated diphtheria toxin mutant. Life Sci. 1999;64(19):1719-24. [Crossref]
22. Dieffenbach M, Pastan I. Mechanisms of resistance to immunotoxins containing Pseudomonas Exotoxin A in cancer therapy. Biomolecules. 2020;10(7):979. [Crossref]
23. Antunez MI, Cardoni RL. Superantígenos: una particular interacción entre microorganismos y el sistema inmune [Superantigens: a particular interaction between microorganisms and the immune system]. Medicina (B Aires). 1997;57(5):608-16. [Crossref]
24. Vallera DA, Jin N, Shu Y et al. Retroviral immunotoxin gene therapy of leukemia in mice using leukemia-specific T cells transduced with an interleukin-3/Bax fusion protein gene. Hum Gene Ther. 2003;14(18):1787-98. [Crossref]
25. Zhang X, Hu X, Rao X. Apoptosis induced by *Staphylococcus aureus* toxins. Microbiol Res. 2017;205:19-24. [Crossref]
26. Navarro MA, McClane BA, Uzal FA. Mechanisms of action and cell death associated with *Clostridium perfringens* toxins. Toxins (Basel). 2018;10(5):212. [Crossref]
27. Buzzi S, Rubboli D, Buzzi G et al. CRM197 (non-toxic diphtheria toxin): effects on advanced cancer patients. Cancer Immunol Immunother. 2004;53(11):1041-8. [Crossref]
28. Weber F, Asher A, Bucholz R et al. Safety, tolerability, and tumor response of IL4-Pseudomonas exotoxin (NBI-3001) in patients with recurrent malignant glioma. J Neurooncol. 2003;64(1-2):125-37. [Crossref]
29. Janku F, Zhang HH, Pezeshki A et al. Intratumoral injection of *Clostridium novyi*-NT spores in patients with treatment-refractory advanced solid tumors. Clin Cancer Res. 2021;27(1):96-106. [Crossref]
30. Hassan R, Miller AC, Sharon E et al. Major cancer regressions in mesothelioma after treatment with an anti-mesothelin immunotoxin and immune suppression. Sci Transl Med. 2013;5(208):208ra147. [Crossref]
31. Roe JM, Seely K, Bussard CJ et al. Hacking the immune response to solid tumors: harnessing the anti-cancer capacities of oncolytic bacteria. Pharmaceutics. 2023;15(7):2004. [Crossref]
32. Medzhitov R. Toll-like receptors and innate immunity. Nat Rev Immunol. 2001;1(2):135-45. [Crossref]
33. Iida N, Dzutsev A, Stewart CA et al. Commensal bacteria control cancer response to therapy by modulating the tumor microenvironment. Science. 2013;342(6161):967-70. [Crossref]
34. Keppler-Hafkemeyer A, Brinkmann U, Pastan I. Role of caspases in immunotoxin-induced apoptosis of cancer cells. Biochemistry. 1998;37(48):16934-42. [Crossref]

35. Goto Y, Iwata S, Miyahara M et al. Discovery of intratumoral oncolytic bacteria toward targeted anticancer theranostics. Adv Sci (Weinh). 2023;10(20):e2301679. [Crossref]
36. Huang X, Pan J, Xu F et al. Bacteria-based cancer immunotherapy. Adv Sci (Weinh). 2021;8(7):2003572. [Crossref]
37. Deb D, Wu Y, Coker C et al. Design of combination therapy for engineered bacterial therapeutics in non-small cell lung cancer. Sci Rep. 2022;12(1):21551. [Crossref]
38. Mokrozub VV, Lazarenko LM, Sichel LM et al. The role of beneficial bacteria wall elasticity in regulating innate immune response. EPMA J. 2015;6(1):13. [Crossref]
39. Li F, Yang Z, Savage TM et al. Programmable bacteria synergize with PD-1 blockade to overcome cancer cell-intrinsic immune resistance mechanisms. Sci Immunol. 2024;9(100):eadn9879. [Crossref]
40. Shuwen H, Yifei S, Xinyue W et al. Advances in bacteria-based drug delivery systems for anti-tumor therapy. Clin Transl Immunology. 2024;13(7):e1518. [Crossref]
41. Harimoto T, Danino T. Engineering bacteria for cancer therapy. Emerg Top Life Sci. 2019;3(5):623-9. [Crossref]
42. Zhao X, Xie N, Zhang H et al. Bacterial drug delivery systems for cancer therapy: "why" and "how". Pharmaceutics. 2023;15(9):2214. [Crossref]

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ORIGINAL ARTICLE

THE RELATIONSHIP BETWEEN IMMUNE THROMBOCYTOPENIA WITH THE SEASONS AND COVID-19

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ABSTRACT

Aims: The aim of this study is to observe the correlation between viral infections and seasonal changes and the disease.

Methods: This study was conducted retrospectively with 98 patients diagnosed with immune thrombocytopenia between 2018 and 2022. Data regarding patients' demographic information, laboratory results, presence of coronavirus disease 2019 infection, seasonal and monthly distribution of infection, coronavirus disease 2019 vaccination history, and presence of active treatment were collected. The relationship between immune thrombocytopenia and viral infections according to seasons, the change in the number of patients diagnosed with immune thrombocytopenia before and after March 2020 due to the restrictions during the pandemic period, and the difference in platelet counts in patients who were vaccinated against coronavirus disease 2019 were investigated.

Results: In immune thrombocytopenia cases, which are possibly triggered by viral infections, when we investigated whether there was a seasonal difference, it was seen that the number of patients diagnosed with immune thrombocytopenia was higher in spring and summer. However, when statistical analysis was performed, no significant difference was found in terms of new diagnoses between seasons. On the other hand, a statistically significant difference was found between months. When examined on a monthly basis, it is seen that patients were diagnosed more frequently in June and October.

Conclusion: It was determined that the months of diagnosis were close to each other in our study, and the literature showed us that we need to consider the characteristics of these months in etiology.

Keywords: Coronavirus disease 2019, hematology, immune thrombocytopenia

INTRODUCTION

The hematological condition known as immune thrombocytopenia is typified by autoantibodies targeting platelets in the reticuloendothelial system and destroying them (1). Immune thrombocytopenia in children is typically acute, self-limiting, and tends to appear in winter and fall, possibly triggered by viral infections or vaccinations. Many affected children report flu-like symptoms in the weeks before developing immune thrombocytopenia. On the other hand, immune thrombocytopenia in adults is generally chronic, and the seasonal variability of this disease is unknown (2).

Autoantibodies against platelet surface glycoproteins contribute significantly to both the impaired production and destruction of platelets in immune thrombocytopenia. Cytotoxic T lymphocytes also play a role in the pathophysiology of immune thrombocytopenia, involving interactions between B and T lymphocytes and inflammatory cytokines. In primary immune thrombocytopenia, autoantibodies against antigens

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like Glycoprotein IIb/IIIa (GP IIb/IIIa) and GPIb/IX lead to reduced platelet production and increased destruction. Studies have identified autoreactive T cell clones against GPIIb/IIIa in immune thrombocytopenia patients, alongside cytotoxic T cells targeting autologous platelets. Additional evidence includes an imbalanced T helper cell type 1(Th1)/Th2 ratio, increased Th17 cells, elevated interleukin-17 levels, and reduced regulatory T cells (2).

Immune thrombocytopenia can be a primary condition or occur secondary to other disorders. Secondary causes include viral infections such as Epstein-Barr virus, cytomegalovirus, and hepatitis C; certain medications; and autoimmune diseases such as antiphospholipid antibody syndrome (2, 3).

Primary immune thrombocytopenia is an acquired immune disorder characterized by isolated thrombocytopenia, defined as a peripheral blood platelet count of less than $100x10^9$/L. This condition is caused by the presence of pathogenic anti-platelet autoantibodies, T cell-mediated destruction of platelets, and impaired function of megakaryocytes. In adults, primary immune thrombocytopenia typically progresses to a chronic state, making it necessary to seek treatment aimed at restoring a durable platelet count to ensure adequate hemostasis (4).

In adults, primary immune thrombocytopenia affects about 80% of patients, with secondary immune thrombocytopenia affecting the remaining 20%. Primary immune thrombocytopenia can affect up to 9.5 out of every 100,000 individuals, and as people age, its incidence rises to about 3.3 out of every 100,000 adults annually. Immune thrombocytopenia is more common in women, but in children and the elderly, it is observed more frequently in men (5).

Petechiae, purpura, and mucosal bleeding in the mouth, gastrointestinal tract, and urinary tract, including nosebleeds, are possible symptoms. Additionally, a lower quality of life may be experienced. In approximately 0.2% of cases, cerebral hemorrhages can be fatal in the worst circumstances (4).

Depending on the disease duration, immune thrombocytopenia is classified into newly diagnosed, persistent, and chronic. Immune thrombocytopenia that is newly diagnosed is classified as occurring within three months of diagnosis, persistent immune thrombocytopenia occurs between three and twelve months after diagnosis, and chronic immune thrombocytopenia lasts more than twelve months (2).

Treatment strategies for immune thrombocytopenia aim to restore platelet counts to levels that support adequate hemostasis rather than striving for normal physiological platelet counts. First-line treatments primarily focus on inhibiting the production of autoantibodies and reducing platelet degradation. Second-line treatments include immunosuppressive medications, such as rituximab, and may involve splenectomy. Finally, third-line treatments seek to stimulate platelet production by megakaryocytes (4).

The mechanism of immune thrombocytopenia remains incompletely known, but it is believed to be linked to viral infections. Data about its association with the coronavirus disease 2019 (COVID-19) is scarce (6). Furthermore, numerous studies indicate that it is associated with seasonal variations and fluctuates by month (2). Due to the paucity of available research on the effects of these two conditions on the disease, we conducted a retrospective study including patients diagnosed with immune thrombocytopenia at the Hematology Department of Trakya University School of Medicine between 2018 and 2022.

MATERIAL AND METHODS

This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (approval number: 08/31, dated: 08.05.2023).

Data for this study were collected through the Trakya University School of Medicine Database between January 2018 and December 2022. This study was conducted retrospectively with 98 patients, 64 women and 34 men, who were diagnosed with immune thrombocytopenia at Trakya University Hematology Clinic between 2018 and 2022.

Patients

In our study, the diagnosis of immune thrombocytopenia was made based on the criteria: "Thrombocytopenia (<100,000/μL), absence of anemia (excluding anemia due to bleeding and/or iron deficiency), normal leukocyte count (though mild abnormalities in leukocyte count may be observed), and no morphological evidence of dysplasia in any blood cell type in the blood smear". A total of 98 patients who met these criteria were included. No specific gender distinction was made, and individuals of all genders and ages who were diagnosed with immune thrombocytopenia at our clinic during the specified years were included in the study. Patients with additional diseases other than immune thrombocytopenia were not included in the study. These patients presented to our clinic between 2018 and 2022, either with complaints of bleeding or other symptoms, and received this diagnosis. Additionally, patients who were referred to our clinic from other departments of our hospital due to low platelet counts and were diagnosed with immune thrombocytopenia were also included. Hemoglobin, platelet count, activated partial thromboplastin time, and prothrombin time values were recorded for the patients.

Collected Data

The diagnosis of COVID-19 was based on positive polymerase chain reaction test results. Patients who had already been diagnosed with immune thrombocytopenia were categorized as "positive", "negative", or "unknown" based on their COVID-19 infection status during the study.

The vaccination status of 55 patients in the study was obtained. The vaccines administered were Sinovac and BioNTech. However, since the study did not focus on the distribution of these vaccines by manufacturer, the only parameter examined was whether the patients were vaccinated with one of these two vaccines.

Platelet values before vaccination were available for 45 patients, and platelet values after vaccination were available for 37 patients. The study aimed to determine whether there was a significant difference in platelet counts following vaccination.

The study also focused on the seasons and months in which the patients were diagnosed. The data were analyzed to investigate whether there was a correlation between the diagnosis of immune thrombocytopenia and the seasons or the months of the year.

The presence or absence of active treatment was recorded for 94 patients. Data on the patients' demographic information, laboratory results, presence of COVID-19 infection, the infection's seasonal and monthly distribution, COVID-19 vaccination history, and presence of active treatment were collected.

The relationship between immune thrombocytopenia and viral infections by the seasons, the change in the number of immune thrombocytopenia diagnoses before and after March 2020 due to the restrictions during the pandemic, and the difference in platelet counts in patients who were vaccinated for COVID-19 were investigated.

Statistical Analysis

The data were analyzed with IBM SPSS version 23.0. The comparison of categorical data groups was performed using Fisher's exact test to detect new diagnoses according to seasons and the chi-squared test as appropriate. The Kruskal-Wallis test was used to evaluate the significance of differences between patient groups that were aware of the diagnostic platelet value of patients diagnosed in different seasons. The Wilcoxon test was used to compare the values of patient groups whose platelet values were measured before and after vaccination. The chi-squared test was used to evaluate the difference between gender groups diagnosed in different seasons. For all analyses, a p-value threshold of <0.05 was accepted as statistically significant.

RESULTS

The number of newly diagnosed patients each year was as follows: 2018: 21 (21.4%), 2019: 25 (25.5%), 2020: 25 (25.5%), 2021: 20 (20.4%), and 2022: 7 (7%). Of the newly diagnosed cases, 63 were female and 35 were male (Table 1).

When the platelet values of the patients before the COVID-19 vaccination were examined, it was seen that this data was available in 45 patients, the mean value was 126,177 [standard deviation (SD) 104,147], and the median was 86,000. When the post-vaccination data of the 37 patients were examined, it was determined that the mean platelet count was 91,837 (SD 87,174) and the median was 61,000. No significant difference was found in platelet count before and after the COVID-19 vaccine (p=0.053) (Table 2).

When we investigated whether there was a seasonal difference, no difference was found in terms of new diagnoses according to the seasons (p=0.059). However, significant differences were found on a monthly basis (p<0.001).

In our study, 98 patients with immune thrombocytopenia were diagnosed more frequently in summer (30.3%) (30 patients) and spring (27.3%) (27 patients). However, there was no statistically significant difference in the number of newly diagnosed cases between seasons (Figure 1).

When we examined the times of new diagnoses on a monthly basis, it was found that diagnoses were made more frequently in June (14.28%) (14 patients) and October (13.26%) (13 patients). On the other hand, we found September (4.08%) (4 patients) and November (4.08%) (4 patients) to be the months with the least number of diagnoses. A statistically significant difference was found in diagnosis according to months (Figure 2).

During the same period, 19.4% of patients (19 patients) were diagnosed with COVID-19, 39.8% (39 patients) were undiagnosed, and the COVID-19 status of 40.8% (40 patients) was unknown (Figure 3).

Out of 98 patients, 25.8% (25 patients) were actively receiving treatment, while 74.2% (73 patients) were not (Figure 4).

Table 1: Number of patients diagnosed with immune thrombocytopenia.

	Female	Male
Number of patients (min.-max.)	63 (18-80)	35 (18-93)
Average age + SD	45.05+16.068	48.65+22.49

SD: Standard deviation, min.-max.: Minimum-maximum

Table 2: Pre and post vaccination values of platelet.

	Pre-vaccination	Post-vaccination
Median (min.-max.)	86000 (4000-438000)	61000 (4000-299000)
Avarage age + SD	126177+104147	91837+87174

SD: Standard deviation, min.-max.: Minimum-maximum

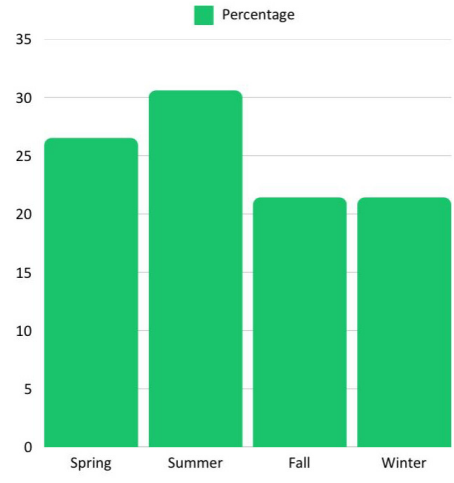

Figure 1: Seasonal distribution of patients diagnosed with immune thrombocytopenia.

COVID-19 vaccination information is available for only 55 patients. 96.4% (53 patients) of whom were vaccinated and 3.6% (2 patients) were not vaccinated (Figure 5).

DISCUSSION

The exact mechanism of immune thrombocytopenia is not fully understood. Numerous studies have proposed that the disease is initiated by a viral infection, with pre-formed antibodies cross-reacting with platelet surface integrins such as glycoprotein Ib-IX-V or glycoprotein IIb/IIIa6,7. While immune thrombocytopenia has been linked to numerous viral infections, there is limited information about its connection to COVID-19 (6).

In the study of Bhattacharjee and Banerjee (7), examining 45 cases of new-onset immune thrombocytopenia due to COVID-19, it is stated that immune thrombocytopenia may occur secondary to COVID-19 infections. In another case report, evidence from the treatments' effectiveness and the absence of other underlying factors indicated that COVID-19 was the cause of immune thrombocytopenia in this instance (8). In our study, we found the number of newly diagnosed patients higher in 2019 and 2020. However, it should be discussed whether this supports our conclusion.

The relationship between immune thrombocytopenia and viral infections is known, so we wanted to investigate whether there was a seasonal difference (6). In a multicenter study conducted by Tombak et al. (2) in Türkiye, the rate of patients diagnosed with immune thrombocytopenia, especially in the spring, was much higher than in other months. Some studies in the literature also support the fact that immune thrombocytopenia diagnosis differs significantly according to months (2). We did not find a significant seasonal difference in our study, but when we looked at the rate of patients diagnosed according to months, we found a significant difference between months in our hospital. We found that the rate of patients diagnosed in June and October was higher than in other months.

Immune thrombocytopenia is a diagnosis of exclusion in the evaluation of thrombocytopenia. Although its pathogenesis is not completely clear, the leading theory suggests that viral antigens cross-react with normal platelet antigens in a molecular mimicry manner, triggering the destruction of platelets (8). It is conceivable that a comparable mechanism exists with COVID-19 or that COVID-19 could lead to a worsening of a

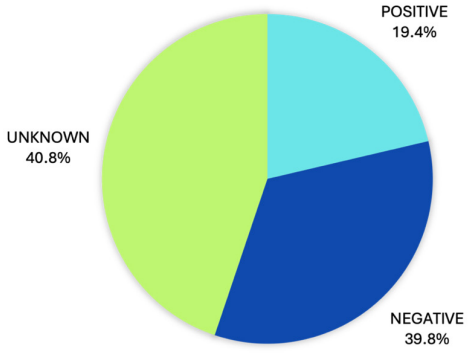

Figure 2: Percentage distribution of patients on a monthly basis.

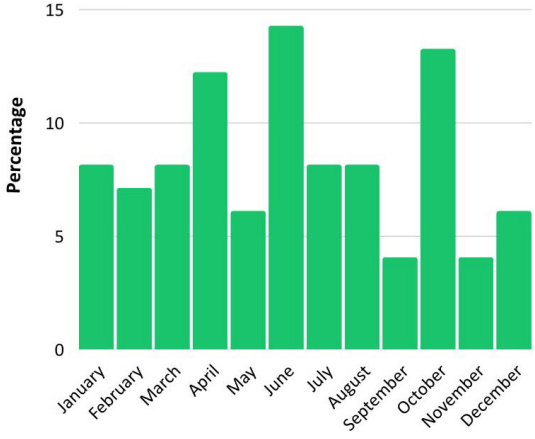

Figure 3: COVID-19 diagnosis rates of patients.
COVID-19: Coronavirus disease 2019

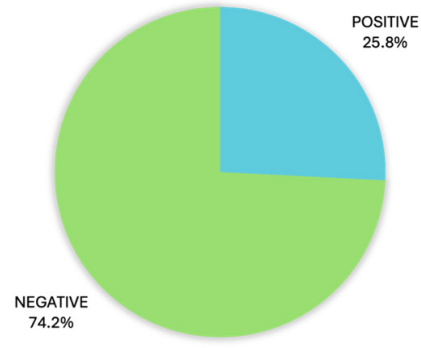

Figure 4: Treatment situations of patients diagnosed with immune thrombocytopenia.

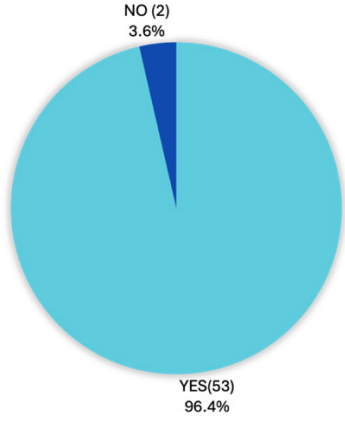

Figure 5: COVID-19 vaccination status of patients.
COVID-19: Coronavirus disease 2019

pre-existing low-grade immune thrombocytopenia disorder (8). Since we could not fully access the data on patients' COVID-19 infection in our study, our results on this subject are open to improvement.

In one study, thrombocytopenia flare-ups occurred in 12% of chronic immune thrombocytopenia patients after COVID-19 vaccination. Thrombocytopenia flare-ups usually occurred 2-5 days after vaccination, but despite this, recommendations for the first dose of the COVID-19 vaccine continued (9). In our study, no significant relationship was found between the COVID-19 vaccine and pre- and post-vaccination platelet values. The mean platelet values of patients before vaccination were found to be higher than the platelet values after vaccination.

In our study, we did not find gender differences in the occurrence of immune thrombocytopenia according to the seasons. The fact that Tombak et al. (2) reached the same conclusion in their study supports our result.

Study Limitations

Our study was limited in evaluating some dates due to limitations in accessing patient data. However, the fact that the months of diagnosis in our study were consistent with the literature was a supportive study for the limited studies conducted on this subject. However, more comprehensive studies using larger patient groups are needed on this subject.

CONCLUSION

In our study, the number of patients diagnosed with immune thrombocytopenia was significantly higher in June and October. This result, which is consistent with the literature, shows that changes in etiology depending on the months should be taken into consideration.

Various studies demonstrate the relationship between COVID-19 and immune thrombocytopenia and suggest that it may have a negative effect on the prognosis of the disease. In our retrospective study, 19 of the patients with immune thrombocytopenia had COVID-19 infection. Fifty-three patients whose data we could access had COVID-19 vaccines. There was no significant difference in the platelet values of patients who received the COVID-19 vaccine before and after vaccination. However, more detailed studies are needed on the long-term effects of COVID-19 and its vaccine on a larger number of patients diagnosed with immune thrombocytopenia.

As revealed in our study, immune thrombocytopenia has been observed to be more prominent, especially in the months of seasonal transition and during epidemic periods when viral infections are frequently seen, and it should be kept in mind in patients presenting with isolated thrombocytopenia.

Ethics

Ethics Committee Approval: *This study was approved by the Scientific Research Ethics Committee of Trakya University School of Medicine (approval number: 08/31, dated: 08.05.2023).*

Informed Consent: *Retrospective study.*

Footnotes

Conflict of Interest: *The authors declared no conflict of interest.*

Author Contributions: *Surgical and Medical Practices: B.D., Concept: B.D., B.A., B.S., F.A.O., F.G., H.M.U., M.Y.K., N.T.A., H.O.K., Design: B.D., B.A., B.S., F.A.O., F.G., H.M.U., M.Y.K., N.T.A., H.O.K., Analysis and/or Interpretation: B.D., B.A., B.S., F.A.O., F.G., H.M.U., M.Y.K., N.T.A., H.O.K., Literature Search: B.D., B.A., B.S., F.A.O., F.G., H.M.U., M.Y.K., N.T.A., H.O.K., Writing: B.D., B.A., B.S., F.A.O., F.G., H.M.U., M.Y.K., N.T.A., H.O.K.*

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REFERENCES

1. Güneş AM. İmmun trombositopenik purpura tanı ve tedavisine güncel yaklaşım. Güncel Pediatri. 2003;1(1):73-8. [Crossref]
2. Tombak A, Boztepe B, Tiftik N et al. Seasonal association of immune thrombocytopenia in adults. Balkan Med J. 2015;32(4):347-51. [Crossref]
3. Wu Z, Zhou J, Wei X et al. The role of Epstein-Barr virus (EBV) and cytomegalovirus (CMV) in immune thrombocytopenia. Hematology. 2013;18(5):295-9. [Crossref]
4. Zufferey A, Kapur R, Semple JW. Pathogenesis and therapeutic mechanisms in immune thrombocytopenia (ITP). J Clin Med. 2017;6(2):16. [Crossref]
5. Schoonen WM, Kucera G, Coalson J et al. Epidemiology of immune thrombocytopenic purpura in the General Practice Research Database. Br J Haematol. 2009;145(2):235-44. [Crossref]
6. Aydın FY, Demircan V. Diagnosis and management of coronavirus disease-associated immune thrombocytopenia: a case series. Rev Soc Bras Med Trop. 2021;54:e0029. [Crossref]
7. Bhattacharjee S, Banerjee M. Immune thrombocytopenia secondary to COVID-19: a systematic review. SN Compr Clin Med. 2020;2(11):2048-58. [Crossref]
8. Bennett J, Brown C, Rouse M et al. Immune thrombocytopenia purpura secondary to COVID-19. Cureus 2020;12(7):e9083. [Crossref]
9. Kuter DJ. Exacerbation of immune thrombocytopenia following COVID-19 vaccination. Br J Hematol. 2021;195(3):365-70. [Crossref]

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CASE REPORT

ULTRASOUND-ASSISTED THROMBOLYSIS THERAPY FOR THE TREATMENT OF ACUTE PULMONARY EMBOLISM IN AN INTERMEDIATE-HIGH-RISK PATIENT WITH MULTIPLE COMORBIDITIES: A CASE REPORT

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ABSTRACT

Venous thromboembolism is an event that occurs within two components: deep venous thrombosis and pulmonary embolism. With many risk factors including old age, hospitalization and recent surgeries, malignancies, and the use of oral contraceptives, it occurs to be a relatively common condition. The European Society of Cardiology divides patients with acute pulmonary embolism into high-risk pulmonary embolism, low-risk pulmonary embolism, intermediate-high-risk pulmonary embolism, and intermediate-low-risk pulmonary embolism. This division is made based on three main criteria: hemodynamic stability, right ventricular dysfunction, and elevated troponin levels. Patient management based on risk stratification plays a vital part during the treatment. A 57-year-old woman arrived at the emergency department with syncope, abrupt shortness of breath, and unusual pleuritic chest pain. The patient had hypertension, insulin-dependent diabetes mellitus, and coronary artery disease dating back to 2012, which began with an anterior myocardial infarction treated with a left anterior descending stent. The patient later required additional stents in the left coronary artery and circumflex artery due to restenosis. At the date of approach, a three-vessel coronary artery bypass graft procedure was performed on her a month ago. With this medical history and being assessed as an intermediate-high-risk group, she was considered a candidate for catheter-directed therapy. Ultrasound-assisted thrombolysis therapy was performed with EkoSonic® Endovascular System and the patient was discharged with a total cure. This case serves as an example regarding the issue of a proper approach to patient management.

Keywords: Breast cancer, cardiovascular disease, echocardiography, pulmonary embolism

INTRODUCTION

Venous thromboembolism (VTE) is a thromboembolic event that further divides into deep venous thrombosis (DVT) and pulmonary embolism (PE) (1). VTE occurs when a blood clot is circulating in the bloodstream after breaking off its original site, most commonly a lower extremity (2). VTE is a relatively common condition, having an annual incidence of 1-2 per 1,000 persons in Europe and the United States of America (USA) (3). Although VTE has various risk factors, including old age, hospitalization and recent surgeries, malignancies, and the use of oral contraceptives, it can also occur unprovoked (4). PE is one of the most common complications in cancer patients and the occurrence of VTE in cancer patients has a substantial prognostic significance (5). Cancer increases the risk of PE/VTE because it impacts all the components of Virchow's triad, which consists of blood vessel alterations, circulation stasis, and hypercoagulability state. Apart from the disease itself, some anti-cancer treatments can also increase the risk of PE. Studies have shown that chemotherapy increases the risk of developing PE by six times, and surgery also serves as another significant factor contributing to the increased risk of PE (6).

A study was conducted to compare PE patients with and without malignancy. The study showed that the group that had both PE and malignancy showed compromised vital signs, and they

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were more frequently in the high-risk category compared to the group that only had PE without malignancies. The cancer group also demonstrated higher mortality rates and increased complications to thrombolytic therapy (7).

Pulmonary embolism is the leading and most severe complication of DVT, so PE requires risk stratification according to the severity of the condition to guide treatment (8). The European Society of Cardiology (ESC) guidelines recommend using a combination of imaging, clinical scoring systems, and biomarkers for risk stratification. The ESC divides patients into acute PE into high-risk PE, low-risk PE, intermediate-high-risk PE, and intermediate-low-risk PE (9). The first step is identifying if the patients are high-risk because they have higher mortality rates compared to the others, if the patient is hemodynamically unstable, has right ventricular dysfunction (RVD) and elevated troponin levels, then they are classified as high-risk PE patients (10). Hemodynamic instability is defined as having a systolic blood pressure lower than 90 mmHg without hypovolemia, arrhythmias, or sepsis, and/or the need for vasopressors with end-organ hypoperfusion, so high-risk PE patients are directed immediately to reperfusion therapies and organ support. Low-risk and intermediate-risk (both low and high) PE patients are all hemodynamically stable; however, intermediate-high-risk PE patients have both RVD and elevated troponin levels. On the other hand, intermediate-low-risk PE patients have either RVD or elevated troponin levels, and at last, low-risk PE patients do not present with hemodynamic instability, RVD, and elevated troponin levels (11).

There are several treatment options for PE and they all depend on the risk group of the patient. Patients with high-risk status require urgent reperfusion therapy or catheter-directed treatments (CDTs) (12). CDTs are also considered in patients developing hemodynamic instability regardless of the risk group. However, proceeding with anticoagulant treatment alone is usually enough for most patients with low-risk or intermediate-low-risk PE. According to the ESC Guidelines, advanced therapies (systemic lysis, catheter lysis, or surgical/catheter thrombectomy) should be considered in those with intermediate-high-risk PE and deteriorating clinical signs (9, 13).

This case report aims to present a patient with acute PE accompanied by multiple comorbidities, serving as an example of CDT.

CASE REPORT

A 57-year-old woman arrived at the emergency department with syncope, unusual pleuritic chest pain, and abrupt shortness of breath. The patient's medical history includes hypertension, insulin-dependent diabetes mellitus, and coronary artery disease dating back to 2012, which began with an anterior myocardial infarction treated with a left anterior descending stent. The patient later required additional stents in the left coronary artery and circumflex artery due to restenosis. Subsequently, a three-vessel coronary artery bypass graft procedure was performed on February 9, 2024, to address the restenosis. The patient also had a decreased left ventricle ejection fraction (LVEF) of 40-45%. Additionally, the patient had a history of breast cancer for which she was treated with bilateral mastectomy, followed by chemotherapy with cyclophosphamide and tamoxifen. However, chemotherapy was completed before the onset of PE. The patient was taking multiple medications including aspirin, clopidogrel, fenofibrate, perindopril, amlodipine, indapamide, metoprolol, sitagliptin and insulin glargine.

Upon arrival at the emergency department, the patient exhibited acute distress, tachycardia with a heart rate of 108 beats per minute (bpm), a blood pressure of 120/75 mmHg, and moderate hypoxemia with oxygen saturation of 91%. An electrocardiogram showed sinus tachycardia and a pattern consistent with S1Q3T3 pattern, which suggested acute PE. Physical examination revealed decreased breath sounds on the right side, as well as murmurs of mitral and tricuspid regurgitation, both graded as 3/6. The bilateral lower extremity venous system was examined using color Doppler ultrasonography. Because DVT was the initial diagnosis, the Valsalva maneuver was not performed. Widespread acute-to-subacute thrombotic alterations were detected by the imaging, which included filling deficiencies in the lumens of both common femoral veins, the bilateral superficial femoral veins along their whole course, both popliteal veins, and the visible proximal portions of the crural veins.

The right great saphenous vein terminated as a stump in its proximal portion, according to further observations; surgery was started at this level. Bilateral saphenopopliteal junctions and the left great saphenous vein were found to be patent.

Echocardiography revealed LVEF of 45%, moderate mitral and tricuspid regurgitation, a reduced tricuspid annular plane systolic excursion of 1.3 cm reflecting mild RVD, and elevated systolic pulmonary artery pressure (sPAP) of 45 mmHg, indicating pulmonary hypertension. Laboratory findings showed an elevated D-dimer at 11.1 µg/L consistent with thromboembolism, and positive troponin suggesting myocardial strain. Pulmonary computed tomographic angiography showed the right main pulmonary artery and the lobar and segmental branches of the upper, middle, and lower lobes of the right lung showed an embolism-like filling defect on multidetector computer tomography (Figure 1). In the right pleural space, a 10 mm pleural effusion was observed. A triangle-shaped region of consolidation with elevated density and ground-glass opacity was seen in the lateral portion of the right lung's middle lobe (Figure 2). This region was compatible with a pulmonary infarction secondary to embolism since it had a base connected to the pleura and showed air bronchograms. Areas of increased density next to the effusion were found in the posterobasal portion of the right lung's lower lobe. These regions were diagnosed as atelectasis because they lacked distinct borders and showed air bronchograms.

Both lungs showed a mosaic attenuation pattern, which could indicate a small airway or small vessel illness. Bilaterally, only minor emphysematous alterations were observed. The thoracic aortic and coronary vascular walls displayed calcified atheroma

plaques, while the major mediastinal vascular structures displayed normal calibration. There was no pathological wall thickening in the thoracic esophagus, and the trachea and both major bronchi were patent. There was no evidence of a left pleural or pericardial effusion. No anomalies were found in the study's upper abdominal portions. The bone structures that could be seen showed no signs of lytic or destructive lesions.

It was decided to use the EkoSonic® Endovascular System [(EKOS) EKOS Corporation; Bothell, WA, USA] for ultrasound-assisted, catheter-directed thrombolysis because of the intermediate-high-risk of PE and the elevated risk of bleeding from recent coronary artery bypass surgery. Before the EKOS procedure, a pulmonary angiography was conducted (Figure 3). During the EKOS procedure, to execute selective pulmonary angiography, a 6F JR4 catheter was inserted into the right major pulmonary artery. Massive thrombi in the right pulmonary artery's middle, lower, and upper lobe branches were visible on the angiography. A hydrophilic wire was then used to insert an EKOS catheter into the right major pulmonary artery (Figure 4). After giving a 5 mg bolus of tissue plasminogen activator (tPA), 30 mg of tPA was continuously infused over the course of 24 hours. The catheter system was successfully removed following the completion of the thrombolytic therapy. Activated partial thromboplastin time monitoring was used to maintain therapeutic anticoagulation after the patient had an intravenous heparin bolus (5,000 units) and an infusion. The patient was followed up as uneventful.

The patient's clinical condition significantly improved after receiving treatment with EKOS. Following treatment, the patient's vital signs were stable, with a heart rate of 75 bpm, blood pressure of 120/80 mmHg, and an oxygen saturation level of 95%. The resolution of pulmonary hypertension was suggested by follow-up echocardiography, which showed a stable LVEF at 45%, a decrease in tricuspid regurgitation, and a drop in sPAP to 30 mmHg. A 24-hour follow-up pulmonary angiography verified that the right-sided pulmonary thrombus had resolved (Figure 5). After being declared clinically stable,

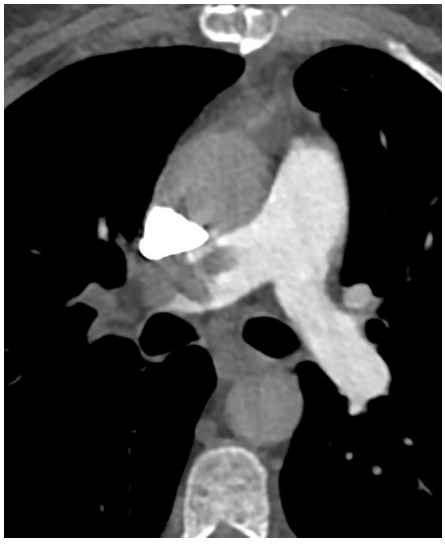

Figure 1: Computed tomography scan (superior).

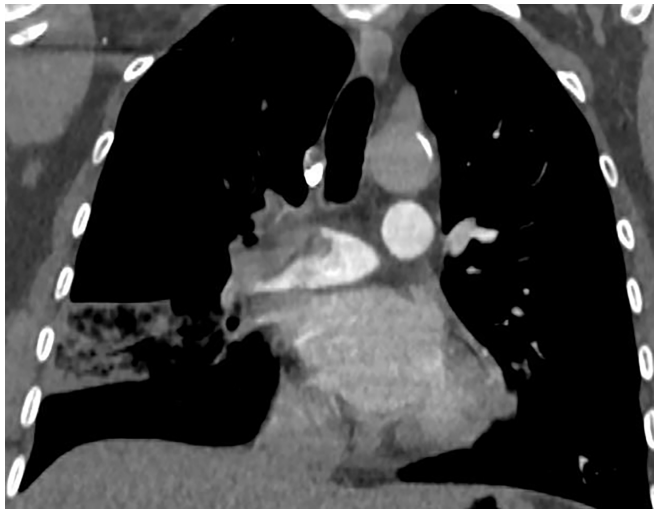

Figure 2: Computed tomography scan (frontal).

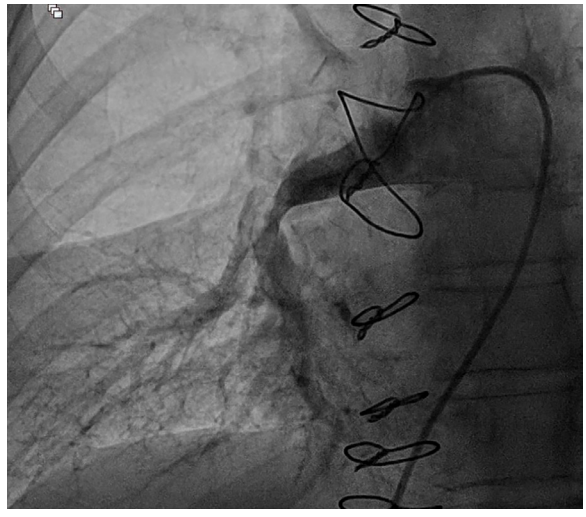

Figure 3: Pulmonary angiography before the EkoSonic® Endovascular System procedure (EKOS Corporation; Bothell, WA, USA).

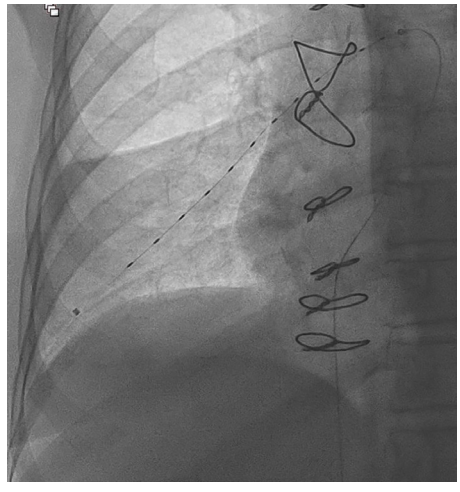

Figure 4: Insertion of EkoSonic® Endovascular System catheter in pulmonary angiography (EKOS Corporation; Bothell, WA, USA).

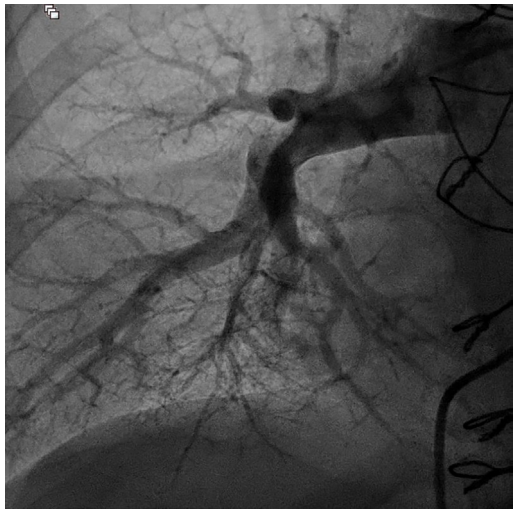

Figure 5: Pulmonary angiography after the procedure.

the patient was discharged on 6,000 units of enoxaparin (low molecular weight heparin), prescribed twice a day.

The patient was transitioned to oral rivaroxaban 20 mg once a day for continued anticoagulation at the 15-day follow-up.

DISCUSSION

Regarding the management of acute PE, a risk evaluation based on early mortality rates is a must. Hemodynamic instability, troponin levels, RVD, and clinical PE severity must be evaluated. Based on this evaluation, patients are categorized under four groups: high-risk PE, intermediate-high-risk PE, intermediate-low-risk PE, and low-risk PE (9). Besides providing ventilation and oxygen therapy, treatment options have changed drastically over time (14). For low-risk patients, anticoagulant therapy is observed to be satisfactory, and for high-risk patients, systemic thrombolytic therapy is advised, if there are no contraindications. In case of contraindications with high-risk groups, surgical treatment and CDTs must be evaluated. For intermediate-risk groups, therapy options need to be decided after patients' personal risk assessment that is done by clinicians' expertise (9). For intermediate-high-risk groups, it is vital to bear in mind that the situation may convert into high-risk; anticoagulant therapy, thrombolysis, and thrombectomy (surgical or catheter-directed) must be evaluated based on the individual (9, 15).

Based on the risk evaluation, our patient was categorized between the intermediate-high to high-risk group. With a recent history of bypass surgery, our patient was a match for CDT and was discharged with a total cure. This case serves as an example regarding the issue of a proper approach to patient management.

Ethics

Ethics Committee Approval: *N/A*

Informed Consent: *Informed consent was obtained from the patient.*

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Footnotes

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REFERENCES

1. Khan F, Tritschler T, Kahn SR et al. Venous thromboembolism. Lancet. 2021;398(10294):64-77. [Crossref]
2. Yamashita Y, Morimoto T, Kimura T. Venous thromboembolism: recent advancement and future perspective. J Cardiol. 2022;79(1):79-89. [Crossref]
3. Lutsey PL, Zakai NA. Epidemiology and prevention of venous thromboembolism. Nat Rev Cardiol. 2023;20(4):248-62. [Crossref]
4. Heit JA. Epidemiology of venous thromboembolism. Nat Rev Cardiol. 2015;12(8): 464-74. [Crossref]
5. Lubetsky A. Pulmonary embolism in cancer patients: a review. Isr Med Assoc J. 2022;24(3):179-82. [Crossref]
6. Tirandi A, Preda A, Carbone F et al. Pulmonary embolism in patients with cancer: an updated and operative guide for diagnosis and management. Int J Cardiol. 2022;358:95-102. [Crossref]
7. Hakgor A, Kultursay B, Keskin B et al. Baseline characteristics, management patterns and outcome in patients with pulmonary embolism and malignancy: insights from a single-centre study. Int J Cardiol. 2025;419:132719. [Crossref]
8. Machanahalli Balakrishna A, Reddi V, Belford PM et al. Intermediate-risk pulmonary embolism: a review of contemporary diagnosis, risk stratification and management. Medicina (Kaunas). 2022;58(9):1186. [Crossref]
9. Konstantinides SV, Meyer G. The 2019 ESC Guidelines on the diagnosis and management of acute pulmonary embolism. Eur Heart J. 2019;40(42):3453-5. [Crossref]
10. Becattini C, Agnelli G. Risk stratification and management of acute pulmonary embolism. Hematology Am Soc Hematol Educ Program. 2016;2016(1):404-12. [Crossref]
11. Leidi A, Bex S, Righini M et al. Risk stratification in patients with acute pulmonary embolism: current evidence and perspectives. J Clin Med. 2022;11(9):2533. [Crossref]
12. Kaymaz C, Tokgöz HC, Kültürsay B et al. Current insights for catheter-directed therapies in acute pulmonary embolism: systematic review and our single-center experience. Anatol J Cardiol. 2023;27(10):557-66. [Crossref]
13. Götzinger F, Lauder L, Sharp ASP et al. Interventional therapies for pulmonary embolism. Nat Rev Cardiol. 2023;20(10):670-84. [Crossref]
14. Konstantinides SV, Sanchez O, Goldhaber SZ et al. Advancing the management of acute intermediate-high-risk pulmonary embolism: the enduring legacy of Professor Guy Meyer. Presse Med. 2024;53(3):104248. [Crossref]
15. Mojaddedi S, Jamil J, Bishev D et al. Risk stratification and management of intermediate- and high-risk pulmonary embolism. J Clin Med. 2024;13(18):5583. [Crossref]

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EDITORIAL COMMENTARY

THE ALARMING SURGE OF EARLY ONSET COLORECTAL CANCER: A CALL FOR EARLY DETECTION AND PREVENTATIVE MEASURES

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Keywords: Colorectal neoplasms, life style, mass screening, young adult

The past decade has witnessed a concerning rise in colorectal cancer (CRC) among individuals under 50 years of age, a group now categorized as having early-onset colorectal cancer (EO-CRC) (1). Projections suggest that by 2030, EO-CRC will account for 11% of all colon cancer cases and 23% of rectal cancer cases (1). While approximately 20% of EO-CRC cases can be attributed to hereditary cancer syndromes, the majority occur in individuals without a known genetic predisposition (2). Factors such as increased antibiotic use, decreased physical activity, rising obesity rates, and lifestyle changes that have accelerated since the 1950s are believed to influence the gut microbiome and may be contributing to this alarming trend (3, 4). Unfortunately, due to the absence of routine screening for younger populations, many EO-CRC cases are diagnosed at advanced stages, showing the urgent need for comprehensive, long-term studies that start in childhood to elucidate the environmental and biological factors driving this disease.

Globally, CRC is named the third most common cancer, along with being one of the leading causes of cancer-related mortality (5). In high-income countries, effective screening programs have led to a reduction in CRC incidence among the population 50-75 years of age. However, these successes are overshadowed by the disturbing rise in CRC among those under 50 years (6-10). The most pronounced increase in EO-CRC cases is seen in the 20-39 year age group (7, 11), prompting reconsideration of the current age thresholds for CRC screening. Although the exact causes of this surge are not fully understood, they appear to be linked to birth cohort effects and lifestyle changes after the year 1950, including shifts in diet, physical activity, and antibiotic use (7, 12, 13).

While a small proportion of EO-CRC cases are linked to hereditary colon cancer syndromes, the majority occur in individuals without a familial history of the disease (2). The first significant report of rising CRC rates among young adults in the United States (US) was declared in 2003 with the through Surveillance, Epidemiology, and End Results (SEER) program data, covering 1973-1999 (14). During this period, CRC rates stabilized among older adults but increased by 17% for colon cancer and a staggering 75% for rectal cancer among younger adults, who often present tumors in more advanced stages, further highlighting the severity of the trend (14).

Subsequent analysis by the American Cancer Society in 2009, utilizing SEER data from 1992-2005, reinforced this troubling pattern (15). Research has shown a decline in CRC risk for individuals born before 1950 but a significant increase for those born between 1950 and 1990 (16). Notably, individuals born around 1990 have an increased risk of colon cancer by two folds, and the rectal cancer by four folds in comparison to the ones born around 1950 (16).

This phenomenon is not limited to the United States; similar increases in EO-CRC incidence have been observed in other high-income countries (17). By 2030, CRC cases among 20-34-year-olds in the US are expected to surge by 90% for colon cancer and 124.2% for rectal cancers (1). While CRC incidence is

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declining among those over 65 years, the annual increase in colon and rectal tumors among younger individuals in the US is approximately 2% (18, 19).

Numerous risk factors are thought to take part in EO-CRC formation, including type 2 diabetes mellitus, obesity, Western dietary patterns, sedentary lifestyles, antibiotic use, alcohol consumption, and smoking (20-25). Collectively, these factors play a role in the growing incidence of EO-CRC. Additionally, EO-CRC often presents distinct histopathological and molecular characteristics compared to sporadic CRC, including higher rates of perineural or venous invasion, poor differentiation, mucinous or signet-ring cell histology, with generally poorer prognoses (26). At the molecular level, EO-CRCs are more likely to be microsatellite-stable, with frequent long interspersed nuclear element-1 (LINE-1) hypomethylation and TP53 mutations, and less frequent alterations in Kirsten rat sarcoma viral oncogene homologue (KRAS), v-raf murine sarcoma viral oncogene homolog B1 (BRAF), and adenomatous polyposis coli (APC) genes (27).

In conclusion, the aggressive nature of EO-CRC and its frequent diagnosis at advanced stages significantly worsen patient outcomes. Given the increasing incidence and unique characteristics of EO-CRC, it is imperative that we enhance our understanding of its underlying causes and reconsider screening practices to improve early detection and outcomes in this vulnerable population (28).

Ethics

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Informed Consent: *N/A.*

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Author Contributions: *Concept: A.K.T., A.A.Ü., B.Ç., Design: A.K.T., A.A.Ü., B.Ç., Literature Search: A.K.T., A.A.Ü., B.Ç., Writing: A.K.T., A.A.Ü., B.Ç.*

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REFERENCES

1. Bailey CE, Hu CY, You YN et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975-2010. JAMA Surg. 2015;150(1):17-22. [Crossref]
2. Strum WB, Boland CR. Clinical and genetic characteristics of colorectal cancer in persons under 50 years of age: a review. Dig Dis Sci. 2019;64(11):3059-65. [Crossref]
3. Flemer B, Lynch DB, Brown JMR et al. Tumour-associated and non-tumour-associated microbiota in colorectal cancer. Gut. 2017;66(4):633-43. [Crossref]
4. Garrett WS. The gut microbiota and colon cancer. Science. 2019;364(6446):1133-5. [Crossref]
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;70(1):7-30. [Crossref]
6. Doubeni CA, Corley DA, Quinn VP et al. Effectiveness of screening colonoscopy in reducing the risk of death from right and left colon cancer: a large community-based study. Gut. 2018;67(2):291-8. [Crossref]
7. Akimoto N, Ugai T, Zhong R et al. Rising incidence of early-onset colorectal cancer -a call to action. Nat Rev Clin Oncol. 2021;18(4):230-43. [Crossref]
8. Vuik FER, Nieuwenburg SAV, Bardou M et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. Gut. 2019;68(10):1820-6. [Crossref]
9. Siegel RL, Torre LA, Soerjomataram I et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut. 2019;68(12):2179-85. [Crossref]
10. Lui RN, Tsoi KKF, Ho JMW et al. Global increasing incidence of young-onset colorectal cancer across 5 continents: a joinpoint regression analysis of 1,922,167 cases. Cancer Epidemiol Biomarkers Prev. 2019;28(8):1275-82. [Crossref]
11. Vuik FER, Nieuwenburg SAV, Nagtegaal ID et al. Clinicopathological characteristics of early onset colorectal cancer. Aliment Pharmacol Ther. 2021;54(11-12):1463. [Crossref]
12. Brenner DR, Ruan Y, Shaw E et al. Increasing colorectal cancer incidence trends among younger adults in Canada. Prev Med (Baltim). 2017;105:345-9. [Crossref]
13. Chung RYN, Tsoi KKF, Kyaw MH et al. A population-based age-period-cohort study of colorectal cancer incidence comparing Asia against the West. Cancer Epidemiol. 2019;59:29-36. [Crossref]
14. O'Connell JB, Maggard MA, Liu JH et al. Rates of colon and rectal cancers are increasing in young adults. Am Surg. 2003;69(10): 866-72. [Crossref]
15. Siegel RL, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. Cancer Epidemiol Biomarkers Prev. 2009;18(6):1695-8. [Crossref]
16. Siegel RL, Fedewa SA, Anderson WF et al. Colorectal cancer incidence patterns in the United States, 1974-2013. J Natl Cancer Inst. 2017;109(8). [Crossref]
17. Potter JD. Rising rates of colorectal cancer in younger adults. BMJ. 2019;365. [Crossref]
18. Siegel RL, Miller KD, Goding Sauer A et al. Colorectal cancer statistics, 2020. CA Cancer J Clin. 2020;70(3):145-64. [Crossref]
19. Araghi M, Soerjomataram I, Jenkins M et al. Global trends in colorectal cancer mortality: projections to the year 2035. Int J Cancer. 2019;144(12):2992-3000. [Crossref]
20. Chen H, Zheng X, Zong X et al. Metabolic syndrome, metabolic comorbid conditions and risk of early-onset colorectal cancer. Gut. 2021;70(6):1147-54. [Crossref]
21. Puzzono M, Mannucci A, Grannò S et al. The role of diet and lifestyle in early-onset colorectal cancer: a systematic review. Cancers (Basel). 2021;13(23):5933. [Crossref]
22. Nguyen LH, Liu PH, Zheng X et al. Sedentary behaviors, TV viewing time, and risk of young-onset colorectal cancer. JNCI Cancer Spectr. 2018;2(4):pky073. [Crossref]
23. McDowell R, Perrott S, Murchie P et al. Oral antibiotic use and early-onset colorectal cancer: findings from a case-control study using a national clinical database. Br J Cancer. 2022;126(6):957-67. [Crossref]
24. Fedirko V, Tramacere I, Bagnardi V et al. Alcohol drinking and colorectal cancer risk: an overall and dose–response meta-analysis of published studies. Ann Oncol. 2011;22(9):1958-72. [Crossref]
25. O'Sullivan DE, Sutherland RL, Town S et al. Risk factors for early-onset colorectal cancer: a systematic review and meta-analysis. Clin Gastroenterol Hepatol. 2022;20(6):1229-1240.e5. [Crossref]
26. Zaborowski AM, Abdile A, Adamina M et al. Characteristics of early-onset vs. late-onset colorectal cancer: a review. JAMA Surg. 2021;156(9):865-74. [Crossref]
27. Willauer AN, Liu Y, Pereira AAL et al. Clinical and molecular characterization of early-onset colorectal cancer. Cancer. 2019;125(12):2002-10. [Crossref]
28. Saraiva MR, Rosa I, Claro I. Early-onset colorectal cancer: a review of current knowledge. World J Gastroenterol. 2023;29(8):1289. [Crossref]

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