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ACKNOWLEDGEMENT

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Mesenchymal Stem Cell-Derived Exosomes in Clinical Trials

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Mesenchymal stem cells, also known as MSCs, are pluripotent stem cells originating from embryonic mesoderm that can develop into a range of cell types and self-renew. Because of this property, MSCs are an effective treatment for various types of diseases. MSCs are widely distributed in the body and can be obtained from bone marrow, umbilical cord, umbilical cord blood, embryo, adipose tissue, dental pulp, skeletal muscle, amniotic fluid, skin, and other tissues. Among these, human umbilical cord-based MSCs are easy to collect and isolate, have a more effective immunomodulatory function and proliferation potential than other MSCs, are natural, non-invasive, and do not raise ethical questions. They also exhibit minimal immunity and proliferate readily in vitro. These cells have attracted the attention of many researchers due to their powerful tools for treating various diseases.

Extensive research studies on the clinical applications of MSC-based therapies including cancer diseases, heart, neurological, and orthopedic disorders have been carried out in recent years. However, compared to intact MSCs, MSC-derived exosomes offer many potential advantages when used as therapeutic agents. First of all, their application prevents the transfer of cells that can have DNA damage or mutations. Second, the exosomes are small (30-100 nm in diameter) and move easily, while MSCs are too big to move through capillaries, and most of them don't make it past the first pass capillary bed. Third, unlike whole cells, exosomes can be transported and stored at low temperatures for lengthy periods of time without losing bioactivity. Furthermore, their lipid bilayer walls can protect content molecules' bioactivity in a complicated physiological environment. Fourth, exosomes can be quantitatively applied to patients in a clinic to improve clinical outcomes and can be engineered through exogenous exosome modification or endogenous cell bioengineering to acquire specific properties((Hu et al, 2022; Dilsiz, 2024).

Therapeutic deliverable exosomes are emerging as viable cargo delivery vehicles because to their natural intercellular communication, great biocompatibility, low immunogenicity, low toxicity, lengthy blood circulation ability, and aptitude to traverse a range of biological barriers. Since exosomes are membrane-bound nanoparticles, they usually create a lower immune system reaction than stem cells. This makes exosomes more biocompatible and enhances the possibility that a therapy will be successful. Exosomes are easily made from cultured stem cells and can be stored for a longer period of time in optimal conditions. This makes MSCs possible to produce exosomes in high quantities and use them to treat various types of diseases. Based on preclinical research, 39 clinical trials are now investigating the use of MSC-derived exosomes for a range of disorders(available online: http://www.clinicaltrials.gov/)some of which have published their results.

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Review Article

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Deliberating Effects of Sedentary Lifestyle on Young Adults: A Review of Literature

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ABSTRACT

The term sedentary behavior means "any activity that occurs during the day that involves sitting, laying, or reclining that requires less energy than or equal to 1.5 metabolic equivalents (METs)." Six or more hours a day of sitting or lying down combined with little or no physical exercise during daily activities define a sedentary lifestyle. According to international guidelines, adults should perform at least 150 minutes of moderately vigorous physical activity each week, which equates to 30 minutes/day for five days/week. Adults also require 2 days of muscle strengthening activity every week. About one-third of adults over the age of 15 worldwide suffer from poor health due to inadequate physical activity. Negative effects of sedentary behaviors include a risk of stroke, cancer, high cholesterol, high blood pressure, cardiovascular disease, obesity, diabetes mellitus, osteoporosis and depression. Short bursts of inactivity paired with irregular physical activity contribute to improved wellbeing.

INTRODUCTION

The term sedentary behavior means "any activity that occurs during the day that involves sitting, laying, or reclining that requires less energy than or equal to 1.5 metabolic equivalents (METs)." Six or more hours a day of sitting or lying down combined with little or no physical exercise during daily activities define a sedentary lifestyle [1]. According to international guidelines, adults should perform at least 150 minutes of moderately vigorous physical activity each week, which equates to 30 minutes/day for five days/week. Adults require muscle-strengthening activities twice a week [2]. About one-third of adults over the age of 15 worldwide suffer from poor health due to inadequate physical activity. Sedentary habits have various adverse consequences for the human body. These include a high risk of cancer, cardiovascular disease, depression all-cause mortality and metabolic disorders i.e. dyslipidemia, hypertension and diabetes mellitus, musculoskeletal disorders i.e. osteoporosis and arthralgia. It is crucial to reduce sedentary behavior and encourage physical activity to improve public health [3]. According to recent data, 25% of adults and 81% of teenagers do not get enough exercise. When economies develop, the rate of inactivity rises to a staggering ratio of 70% which may partially be linked to changes in transportation, the development of technology for cultural values, business and an increase in sedentary activities [4]. The relationship between sedentary behavior and different health consequences in adults has been the result of multiple longitudinal research studies, but the findings have been conflicting. There is an association between sedentary behaviour and health impacts. It was found that adults (mean age 28.5 years) with high levels of sedentary behavior had higher BMI, waist circumference, and body fat [5]. Long-term television viewing has been linked to

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decreased cognitive function in people between the ages of 18 and 30 [6]. However, several research have found no correlation as there was no association between obesity and sedentary time in adults aged 20 to 35 [7]. The amount of time adults (mean age 33.6 years) spent sitting in work environments did not correlate with their cognitive ability [8].

Sedentary lifestyle has emerged as a major global public health concern, particularly among young adults, leading to increased risks of cardiovascular diseases, diabetes, obesity, depression, and other chronic conditions. Although extensive literature describes individual health outcomes of physical inactivity, findings remain inconsistent across studies, and evidence specifically focusing on young adults (18–35 years) is still fragmented. Moreover, most existing research is observational and lacks clarity on dose–response relationships and contextual behavioral patterns of sedentary time. Therefore, this review aims to critically examine and synthesize current evidence on the health effects of sedentary behavior in young adults to provide a comprehensive understanding and guide future preventive strategies and research directions.

The study is a narrative review focusing on the effects of a sedentary lifestyle on young adults. PubMed and Google Scholar were used to search the data. Search terms and keywords used were "sedentary lifestyle", "sedentary behaviors", "physical inactivity", "young adults", "health effects", "health risks", "risk factors", psychological impact", Boolean operators (e.g., AND, OR) were used in refining the search. In Inclusion Criteria, Peer-reviewed, open access literature was considered. Both primary and secondary studies on young adults aged 18–35, published in English language, within the last 10 years, addressing health outcomes linked to sedentary behavior. Policy documents and guidelines were also included in discussing and correlating the findings. Studies focusing on older adults, animal studies, and articles not directly addressing the effects of sedentary behavior were excluded. Ten effects of physical inactivity were found most frequently in the literature including cardiovascular diseases, stroke, high blood pressure, muscle degradation & weakness, diabetes, high cholesterol, obesity, osteoporosis, depression, and cancer (Figure 1).

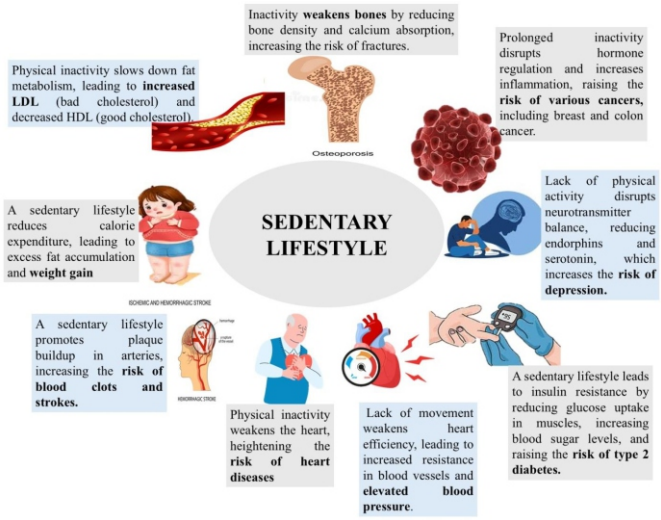

Figure 1: The effects of a sedentary lifestyle on young adults

Cardiovascular Diseases

Cardiovascular disease (CVD) is an aggregate term for various circumstances that influence blood arteries or heart. The most prevalent cardiovascular condition linked to a sedentary lifestyle is coronary artery disease. When the main blood vessels (coronary arteries) that provide your heart with oxygen, nutrients and blood are harmed or diseased, coronary artery disease occurs [4]. Physical inactivity and sedentary behavior are the major modifiable factors for cardiovascular illness and all cause demise worldwide [9]. Being sedentary can cause fat to accumulate in your arteries, which can obstruct them and cause a heart attack [10]. According to study of Wu Jingjie *et al.*, which demonstrated that those in the category with highest sedentary time (median duration: 10.2 hours/day) were more likely to die from CVD-related causes than those in the category with lowest sedentary time (median duration: 2.98 hours/day) [11]. Whitaker *et al.*, found that continuous lack of activity may raise the risk of cardiovascular disease [12]. A meta-analysis of 34 prospective study designs with 1,331,468 individuals found a non-linear relationship between total sedentary time and cardiovascular disease mortality that was independent of level of physical activity [13].

Stroke

A stroke, also referred to as a brain attack or cerebral vascular accident (CVA), occurs when a brain blood vessel ruptures or anything keeps blood away from reaching a specific part of the brain. One of the significant modifiable risk factors of stroke is inactive lifestyle [14]. Sedentary lifestyles are a global issue, particularly in Europe and North America.Unfortunately, the danger of many diseases/disorders, including cerebrovascular diseases, has increased significantly over the past few decades due to an increase in physical inactivity [15]. According to study of 2022, sedentary behavior has been associated positively to an elevated risk of stroke and the risk of stroke increased

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by 21% for every hour of extra sedentary time when it exceeded 11 hours per day [16].A study of 2024 concluded that a sedentary lifestyle is a significant predictor of pathophysiological changes linked to inactivity, which results in decreased muscle mass and strength, increased insulin resistance, and worse cardiac function, all of which raise the risk of cardiovascular diseases [17].

Hypertension

The changes in the cardiac output and total peripheral vascular resistance both, as well as other factors, might affect blood pressure because of sedentary lifestyle. Sedentary behaviour impacts insulin sensitivity and vascular function, promotes the low-grade inflammatory cascade, raises oxidative stress, and activates the sympathetic nervous system. [18]. The fact that 1.56 billion individuals worldwide predicted high blood pressure by 2025, based on conservative estimates, is thrilling [19]. According to a study, they found a correlation between sedentary activity and a higher incidence of high blood pressure (HR, 1.48; 95% CI, 1.01–2.18; P value < 0.03) [20]. The risk of hypertension to be higher for non-interactive habits of inactivity such as watching the television for longer periods of time and taking a nap rather than for the interactive sedentary activities such as driving a car and working on a computer. Various strategies, such as enthusiastically modifying the cardiac output and total peripheral vascular resistance, can be employed to modify blood pressure resulting from a sedentary lifestyle [21].

Muscle Weakness

Muscle deterioration and weakening can result from leading a sedentary lifestyle. Increased levels of inactivity are linked to several musculoskeletal disorders, including osteoarthritis, back pain, and neck/shoulder discomfort, according to epidemiological research [22, 23].The recovery of the skeletal muscle function and regeneration of the muscle cells are aided by appropriate exercise, which also promotes compensatory muscle hypertrophy, increases muscle strength and elasticity, and trains muscle coordination [24]. According to a study conducted in 2021 it is now known with strong evidence that mitochondrial dysfunction plays a significant role in aging, cancer chemotherapy, muscle degeneration and atrophy brought on by extended periods of inactivity, and muscle wasting in various diseases (including sepsis and cancer) [25]. According to a study conducted in 2016 long-term inactivity of the skeletal muscle linked to the release of calcium from sarcoplasmic reticulum, which raises the levels of free calcium in the cytosol [26].

Diabetes

Long periods of inactivity, high fat and high sugar diets, obesity, high visceral fat, and excessive eating all contribute to sedentary behavior, which negatively influences a person's health by creating diabetes mellitus [27]. Individuals who tend to watch television or work on a computer for more than 40 hours a week are three times more at risk of developing type 2 diabetes mellitus as compared to those watching less TV or using a computer. Insufficient physical activity levels constitute major public health concerns, increasing the risk of multiple diseases such as type II diabetes [28]. People with type 2 diabetes should engage in physical activity regularly and be encouraged to reduce sedentary time and break up sitting time with frequent activity breaks. Any activities undertaken with acute and chronic health complications related to diabetes may require accommodation to ensure safe and effective participation [29]. Weight management, lack of motivation and pain are key PA motives and barriers in people with obesity and should be addressed in future interventions to facilitate PA initiation and maintenance [30]. The latest Physical Activity Guidelines for Americans are applicable to most individuals with diabetes, including youth, with a few exceptions and modifications. Physical activity undertaken with health complications can be made safe and efficacious, and exercise training undertaken before and after bariatric surgery is warranted and may enhance its health benefits [29].

High Cholesterol

Visceral and abdominal fat grow due to a sedentary lifestyle. The risk of being overweight and gaining belly fat tends to increase with every hour of inactivity. The release of the pro inflammatory cytokines and reduction of anti-inflammatory signals from the adipose tissue can be facilitated by an increase in the visceral and intermuscular fat, which would catabolize muscle tissue [31]. Inactivity triggers this process, which is considered a stressor mechanism. It causes the muscles to use less glucose, become more insulin resistant, and use less energy when the muscles are not working. These fat-packed adipocytes activate their metabolism and generate anti-inflammatory chemicals while inhibiting release of adiponectin, which is an anti-inflammatory substance [32]. Sedentary behavior hindered the activity of lipoprotein lipase enzyme, and this was associated with less levels of HDL as well as lower levels of plasma triglyceride uptake. Still, prolonged treatments are necessary to modify the levels of lipids. Consequently, it proves that an inactive lifestyle and a lack of exercise are bad for the metabolism of lipids in the body. Over time, these factors may cause visceral and central abdominal fat to accumulate, which increases the risk of developing several cardiovascular illnesses [33].

Obesity

An abnormal or excessive build-up of fat that puts at risk one's health is referred to as obesity. It is a body mass index also known as BMI more than the value of 30 [34]. An excessive or abnormal amount of fat negatively affects an individual's health. Obesity and other co-morbidities are on the rise due to rapid urbanization and industrialization, which has revealed hidden predisposing genetic features through physical inactivity. Changing calorie intake as well as energy expenditure is necessary to reduce obesity.

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Physical activity will help to better match energy expenditure and intake at lower body weights [35]. The risk of being overweight and belly fat increases with every hour of physical inactivity [36]. According to a study of 2024 by Musijowska and Edyta, they concluded that students who were enrolled in physical education showed highest levels of physical activity and the lowest percentage of obesity. Furthermore, this study also highlights the necessity of putting preventive measures and programs in areas with high rates of sedentary behavior to help prevent obesity [37]. Research performed at Silesian Medical University revealed that the percentage of 19.2 students do not participate in the necessary amount of physical activity [38].

Osteoporosis

Osteoporosis develops when bone mass and bone mineral density decrease. This can weaken the bones, leading to an increased risk of fractures. Because it is often undetected until a symptomatic fracture occurs, osteoporosis is referred to as a "silent disease" [39]. The amount of 20% to 40% of an adult's peak bone mass is thought to be influenced by lifestyle factors, and adverse lifestyle choices can result in inadequate bone deposition, which raises the risk of osteoporosis and related fractures [40]. Maintaining bone mass can be achieved with regular exercise, hence maintaining physical activity is favorable to establishing a sedentary lifestyle [41].

Depression

One common mental health condition is depression. It is estimated that around 5% of adults worldwide suffer from this condition. Its prominent features are long-term sorrow and a loss of excitement or delight in once satisfying or enjoyable activities. It can also disrupt your sleep and appetite.Fatigue and difficulty concentrating are also common [42]. Sedentary behavior may increase the risk of depression by reducing social gatherings and reducing engagement in physical activities. These are some possible mechanisms for the relation between sedentary behavior and depression [43]. Kim J *et al.*, stated that a positive association found between the prevalence of depression and sedentary habits [44].

Cancer

Cancer occurs when certain cells in the body grow and attack other areas of the body. As the human body consists of trillions of cells, cancer can occur almost anywhere. Sedentary behavior is an independent risk factor, being active lowers your risk of cancer. You are still more likely to develop cancer even if you exercise for at least half an hour each day if you spend many of your days sitting down [45]. One-third of the global population aged fifteen years and above executes insufficient physical activities, which affects health on general. Sedentary behaviors lead towards a variety of adverse effects on the human body including but not limited to increased all-cause mortality and cancer risk [46]. In 2020, World Health Organization provided guidelines for Physical Activity based on the latest evidence on sedentary behavior and health, along with interactions between sedentary behavior and Moderate to Vigorous Physical Activity [47].

This review is limited by its reliance on secondary literature and narrative synthesis, which may introduce selection bias and lack quantitative comparison between studies. Additionally, variability in study designs, measurement tools for sedentary behavior, and population characteristics may affect the consistency of findings. Most included studies are cross-sectional, limiting causal interpretations. Future research should focus on longitudinal and interventional studies to establish causality and quantify safe thresholds of sedentary time. It is also recommended to standardize measurement tools for sedentary behavior and explore culturally specific lifestyle patterns in young adults to develop targeted prevention strategies.

CONCLUSIONS

Sedentary lifestyles have several detrimental implications on health, such as increased risk of cancer, cardiovascular disease, obesity, diabetes mellitus, high cholesterol, high blood pressure and musculoskeletal conditions like osteoporosis. Longer daily inactive periods have a more detrimental influence on health. This is why it is critical to minimize the amount of time spent inactively. The results of research identifying the worst kind of sedentary behavior differed from study to study. According to studies, short bursts of inactivity paired with irregular physical activity, basic muscle training or minimal exercise, periodic breaks from inactivity during rest, and work when combined with physical activity all contribute to improved wellbeing.

Authors' Contribution

Conceptualization: HI, MM, VA, MQ
Methodology: HI, MM, VA
Formal analysis: HI, MM
Writing and Drafting: HI, MM, WP
Review and Editing: HI, MM, WP

All authors approved the final manuscript and take responsibility for the integrity of the work.

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Review Article

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Therapeutic Effect of Fennel Seeds in the Management of Obesity

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ABSTRACT

Obesity is characterized by complex disorder associated with the accumulation of abnormal and huge amount of fat inside the body. Diabetes, metabolic problems and cardiovascular illnesses are only a few of the serious health hazards associated with obesity, a complex and multifaceted condition. Traditional treatments, especially those derived from herbal therapy, have drawn attention as supplemental approaches to obesity management. As popular herb in cooking and medicine, fennel seeds *(Foeniculum vulgare)* have been shown to have probable health advantages, including helping people to lose weight. It is thought that fennel seeds' active ingredients, which include flavonoids, fiber, and essential oils, work in a variety of ways to prevent obesity. These include lipid metabolism changes, improved digestion, and appetite control. Fennel seeds may assist people lose weight by increasing feelings of fullness, enhancing fat burning, and controlling blood sugar and cholesterol levels. Furthermore, fennel's antioxidant and anti-inflammatory qualities might provide metabolic health even more. Regardless of encouraging initial data, additional clinical studies are required to completely clarify the mechanisms and prove the effectiveness of fennel seeds in the treatment of obesity. This review examined the use of fennel seeds in the treatment of obesity, emphasizing both its traditional medical use and scientific foundation.

INTRODUCTION

Being overweight is the fifth leading cause of mortality globally, and obesity and its related diseases have grown to be important health issues. A WHO report states that obesity is defined as "harmful or huge extent of fat deposition that may hinder with health," and that a calorie imbalance between caloric intake and expenditure is the main cause of overweight and obesity [1]. In addition to being a chronic medical problem, obesity can cause new conditions and exacerbate pre-existing ones. Çakmur H. claim that obesity can harm nearly all organ systems, including the cardiovascular, endocrine, central neurological, and gastrointestinal systems. Additionally, obesity is associated with an increased risk of heart attacks and other cardiovascular conditions such atrial fibrillation, coronary heart disease, and high blood pressure. Significant obesity clusters have been seen in particular geographic locations due to certain lifestyle and genetic characteristics that raise an individual's risk of adult obesity. The following scenarios also highlight the influence of socioeconomic and environmental factors in "obesogenic" settings [2]. There are also a number of variables to obesity. According to earlier studies, lists a few of the significant variables that affect adult overweight or obesity. As an example Zhang X *et al.*, carried out a study demonstrating that: (a) people with poor health are more likely to be lean; (b) irregular eaters, and those with low living standards are more likely to be overweight; and (c) middle age people, People who are depressed and anxious, or who don't feel satisfied with their lives, a Individuals with low annual household incomes frequently exhibit obesity

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[3]. Additionally, a number of studies have shown that exercise is either infrequent or nonexistent and personal educational attainment as determinants of obesity. Additional research has also revealed that a variety of chronic conditions may resemble obesity, particularly which many variables combine to create an imbalance in energy that causes the body to gain weight. Consequently, environmental, biological, and genetical. Obesity is determined by behavioral variables. As a result, differences in the frequency of obesity among different socioeconomic groups could be impacted by a variety of environmental and behavioural factors. In several research, obesity has also been linked to a person's level of education and their frequency of exercise [4]. Seeds (Fennel) and essential oils show promise for safe use as superfood additives and unrefined ingredients in pharmaceutical and culinary endeavors. Body weight increased as a result of the anise oil. Anise oil has been said to have a positive impacts food absorption, even while anise oil caused a decrease in the degree of LDL-c, fatty oil, and cholesterol levels. Despite being believed to be a native Mediterranean plant, fennel (Foeniculum vulgare) is now grown on arid soils by streams or by the sea in many regions of the world. Iran, Syria, Turkey, Egypt, and India are important fennel-producing countries. Flavonoids, glycosides, and other phytoconstituents are among its ingredients that are used to treat illnesses. Fennel phenolic intensifiers can rise to the human well-being. In addition to a few partners with particularly designed human body instruments, this plant has produced trans-anethole, estragole, fenchone, and bioactive mixtures of kaempferol, quercetin, and rosmarinic acid.The reason for fennel association with weight management is that its trypsin inhibitors reduce food intake, activate cholecystokinin release, and increase satiety.Weight decrease Fennel helps the pancreas and liver better digest carbohydrates and lipids. It also allows fat to be used as an energy source by breaking down fat deposits in the circulatory system. These opinions, together with its consistent diuretic effect and reputation is an excellent weight-loss tool because it suppresses hunger [5]. Obesity is now the world's fifth leading cause of death, and obesity and related illnesses have become important health concerns. Obesity is defined by the World Health Organization (WHO) as "an abnormal or excessive fat accumulation that may damage physical well-being," and the main cause of overweight and obesity is an energy imbalance between caloric intake and expenditure [6]. A WHO prediction states that by 2022, one in eight individuals globally would suffer from obesity. There were 2.5 billion persons over 18 who were deemed overweight in 2022.There were 890 million people who were obese. 43% of those over 18 were overweight in 2022, and 16% were obese. 37 million children under five were overweight in 2022.160 million of the 390 million overweight children and adolescents between the ages of 5 and 19 in 2022 were obese [7].

Obesity is a rapidly increasing global health concern strongly associated with metabolic, cardiovascular, and endocrine disorders, while current pharmacological interventions often carry side effects or limited long-term efficacy. Although fennel seeds have been traditionally used for weight management, scientific evidence regarding their precise anti-obesity mechanisms and clinical effectiveness remains fragmented and inconsistent. Existing literature largely consists of animal studies and small-scale human trials, with limited standardized dosing and outcome measures. Therefore, this review aims to critically evaluate the therapeutic potential of fennel seeds in obesity management by synthesizing available evidence on their effects on lipid metabolism, appetite regulation, and body weight reduction.

Family History: Your body's ability to regulate calories and energy is influenced by your genes. Children of overweight parents are likewise more prone to be overweight themselves. You cannot change your genetic makeup by willpower, any more than you can make yourself taller or shorter by want. You can still lose weight and keep it off, though, even if you have a family history of being overweight.

Culture: Our parents' usually follow cooking and eating habits, and the foods we choose are often ones we were introduced to as children. At social events like weddings, holiday parties, and family get-togethers, food is usually the main attraction.

Physical Inactivity: Lack of exercise may lead to being overweight. Most people spend a lot of time watching TV, playing video games, and doing other low-energy pastimes.

Emotional or Psychological Aspects: For many people, food can be a source of joy or comfort. Some people eat when they're anxious or unhappy. For weight management, you must learn better coping strategies for your emotions.

Gender: Because men have more lean muscle mass than women, women are more prone to be overweight. Males burn 10–20% more calories than women, and muscle utilizes more energy than fat when at rest.

High-Fat/High-Calorie Diets: Meals at restaurants tend to be heavy in calories and fat. When a lot of salad dressing is added, even items that seem healthy, like salads, can become heavy in fat. Compared to protein or carbohydrates, fat has over twice as many calories per ounce [8].

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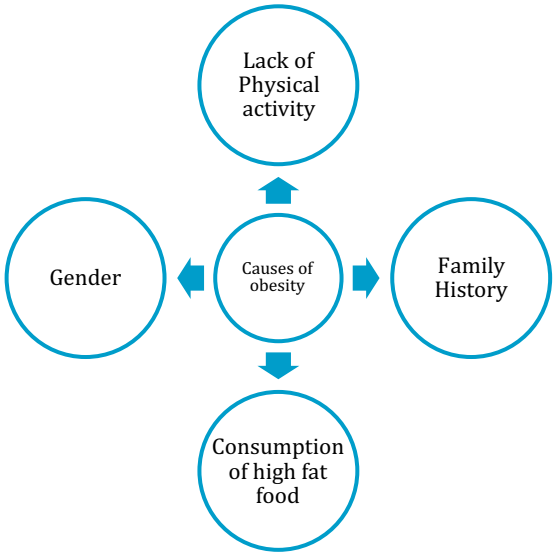

Figure 1: Causes of Obesity

Challenges

The two leading causes of death, heart disease and stroke, are among the cardiovascular diseases for which being overweight or obese is a major risk factor. Being overweight can also result in diabetes and its associated problems, including blindness, neuropathy, and the need for dialysis. Additionally linked to obesity include malignancies of the endometrium, breast, ovaries, liver, gallbladder, kidney, and colon. A person's chance of developing certain non-communicable diseases rises with their Body Mass Index (BMI), even if they are only slightly overweight. Numerous serious health problems and an increased risk of acquiring related diseases earlier than anticipated are associated with childhood obesity [9].

Pathophysiology of Obesity

Overweight and obesity are significant risk factors for cardiovascular diseases, which include the two main causes of death, heart disease and stroke. Furthermore, being overweight can cause diabetes and its associated problems, including blindness, neuropathy, and the need for dialysis. Obesity is also associated with endometrial, breast, ovarian, liver, gallbladder, kidney, and colon cancers. A person's chance of developing certain non-communicable diseases rises with their Body Mass Index (BMI), even if they are only slightly overweight. Numerous serious health problems and an increased risk of acquiring related diseases earlier than anticipated are associated with childhood obesity. These signals, whether anorexigenic or orexigenic, are transmitted to various brain regions, including the periventricular nucleus, which help regulate eating and physical activity. The interplay of these hormones, enteric neuronal communication, and efferent autonomic signaling via the vagus nerve influences nutritional signaling and distention, affecting processes like stomach emptying, gastric accommodation, and other digestive functions [10].

Fennel Seeds Phytology

The leading causes of death, cardiovascular diseases, which include heart disease and stroke, are significantly increased by obesity and overweight. In addition, diabetes and its complications, such as blindness, neuropathy, and dialysis requirements, can be brought on by obesity. Additionally, linked to obesity include malignancies of the endometrium, breast, ovaries, liver, gallbladder, kidney, and colon. A person's chance of developing certain non-communicable diseases rises with their Body Mass Index (BMI), even if they are only slightly overweight. Numerous serious health problems and an increased risk of acquiring related diseases earlier than anticipated are associated with childhood obesity [12]. Fennel seeds composition every component of fennel is utilized, including the fruit, roots, seeds and leaves [13]. Fennel seeds are composed of 42.3% carbohydrates, 9.5% protein, 10% fat, 13.4% mineral, 18.5% fibre, and 6.3% water. The leaf contains sodium, calcium, potassium, phosphorus, iron, thiamine, riboflavin, niacin, and vitamin C [14]. The 10–12% oil in seeds is preserved by the cotyledons of the fruit. Fennel fruit oil is composed of roughly 6% petrocyclic acid, 22% oleic acid, 14% linoleic acid, and 4% palmitic acid. The fruit's essence content ranges from 4 to 6%, and the component combination is influenced by the plant's growing environment [15]. Fennel's fragrant qualities are derived from its essence. Between 50 and 80 percent trans-anethole and 5 percent limonene are the two most important terpene compounds found in fennel essential oil. Phenolic chemicals are also present in this plant [16].

Bioactive Components Present in Fennel Seeds

Chemicals called phytochemicals are made by plants. The methanolic extract of fennel seed contains a wide range of phytochemicals, including alkaloids, terpenoids, phenols, saponins, tannins, and glycosides. Gallic acid equivalent (GAE) was found to be the entire phenolic content of F. vulgare seed extracts in ethanol and water. Phenolic acids include 3-O-caffeoylquinic acid, 4-O-caffeoylquinic acid, 5-O-caffeoylquinic acid, 1-3-O-di-caffeoylquinic acid, 1-4-O-dicaffeoylquinic acid, and 1-5-O-di-caffeoylquinic acid respectively [17].

Table 1: Bioactive Components Present in Fennel Seeds

Bioactive Components	Categories	Health Benefits	References
Essential oils (estragole, anethole, and fenchone)	Volatile Oils	weight control, appetite control, anti-inflammatory, antibacterial, and anti-cancer properties. Anethole has been connected to fat metabolism and appetite reduction	[18]

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The flavonoids luteolin, quercetin, and rutin	Flavanoids	antioxidant that lowers oxidative stress, enhances lipid metabolism, and has anti-inflammatory and anti-cancer properties. Quercetin may help with metabolic control and weight loss	[19]
Saponins	Triterpenoid Saponins	antioxidant, anti-inflammatory, promotes thermogenesis, aids in fat metabolism, and may lessen the buildup of fat	[19]
Both soluble and insoluble fiber	Dietary Fiber	enhances digestion, encourages fullness, and aids in weight loss through blood sugar regulation and meal restriction	[20]
Caffeic acid and ferulic acid are examples of phenolic acids	Polyphenols	Antioxidant, anti-inflammatory, improves metabolic health, and aids in controlling fat buildup	[20]
Fatty Acids: Palmitic Acid, Linoleic Acid	Fatty acids	helps control weight, maintains appropriate cholesterol levels, controls adipogenesis, and modifies lipid metabolism	[21]

Obesity and overweight are major risk factors for cardiovascular illnesses, which include heart disease and stroke, the leading causes of mortality. Furthermore, being overweight can cause diabetes and its associated problems, including blindness, neuropathy, and the need for dialysis. Cancers of the endometrium, breast, ovary, liver, gallbladder, kidney, and colon are also linked to obesity. A person's chance of developing certain non-communicable diseases rises with their Body Mass Index (BMI), even if they are only slightly overweight. Numerous serious health problems and an increased risk of acquiring related diseases earlier than anticipated are associated with childhood obesity [20]. Furthermore, it works very well to treat diabetes, bronchitis, kidney stones, and chronic cough [21]. Fennel seeds are used in cream-based dishes. The plant's diuretic qualities make it useful for treating bladder and kidney issues. Additionally, it is utilized to reduce nausea and stop vomiting. The herbs can be used to treat both persistent fever and blockages in the urinary, respiratory, gastrointestinal, and hepatic systems. The respiratory, reproductive, endocrine, and digestive systems, as well as conditions affecting the eyes and stomach, are also treated with them. Moreover, it is used to treat nursing moms as a galactagogue drug [22].

Table 2: Pharmacological and Nutraceutical Properties of Fennel Seeds

Properties	Efficacy	References
Activity of Antioxidants	Antioxidant substances found in aqueous and ethanolic extracts of fennel seeds, including flavonoids and phenols	[23]
Anti-I Antiinflammatory Properties	Methanol extract offers protection against acute and subacute illnesses by inhibiting cyclooxygenase and lipoxygenase allergic reactions of type 4	[24]
Hepatoprotective Properties	Decreased levels of bilirubin, AST, ALP, and cytokines responsible for the formation of fibrosis	[25]
Anti-Cancer Properties	Examples of active ingredients include the presence of anethole, an inhibitory effect the activation of TNF factor hence served as anti-cancer	[26]
Activity that Protects the Stomach	Treatment for chronic colitis and gastrointestinal spasms, GI ulcers and acidity	[27]
Hormonal Action	Anatole and other compounds are known to improve milk supply, lessen infertility, ease menstrual discomfort, facilitate childbirth, and treat primary dysmenorrhea	[28]
Anti-Lipid Properties	Anti-lipid characteristics Hypolipidemic effects include decreased plasma TG, decreased total cholesterol, lowers LDL, decreased apolipoprotein B, increased HDL, and elevated apolipoprotein A-1 with anethole	[29]
Cardiovascular Activity	Reduced water excretion, sodium, potassium, fennel extract, and systolic blood pressure	[30]
Activity that Prevents Diabetes	The hypoglycemic effect raises muscle and liver glycogen storage,lowers blood sugar levels, and increases glutamine peroxide activity	[31]

Role of Fennel Seeds Against Obesity

Diabetic patients' blood glucose levels significantly decreased after two hours of fennel treatment, suggesting that it had effective short-term anti-diabetic effects. For patients receiving 100 mg per kg body weight, Prior to fennel treatment, the mean values were 313.5 ± 108.69, and after getting 50 mg per kg body weight, they were 279.33 ± 96.24. The mean blood glucose levels after two hours were 262 ± 88.69 for those taking 100 mg/kg body weight and 246.5 ± 91.93 for those taking 50 mg/kg body weight. Additionally, the control group's mean values were 272.16 ± 89.84 before and 330.5 ± 91.87 after two hours [32]. A new study assessed how well heated fennel therapy works to speed up the recovery of gastrointestinal function. Because the trypsin inhibitors in fennel seeds reduce food intake, increase cholecystokinin production, and enhance satiety, this prospective investigation masked 381 patients with pancreatic, stomach, fennel, and weight control issues. Fennel aids in weight loss by assisting the liver and pancreas in properly breaking down fats and carbs. By accelerating the breakdown of adipose tissue into blood, it facilitates the mobilization of fat for use as fuel for energy. Because of their high fiber content, fennel seeds assist

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manage obesity by increasing satiety and reducing the hormone ghrelin, which increases appetite. It has been demonstrated that fennel seeds are an effective appetite suppressor[33].

The current evidence on fennel seeds is limited by a lack of large-scale, well-designed randomized controlled trials in human populations, along with variability in study designs, dosages, and extract preparations. Most findings are derived from experimental or short-term studies, which restricts generalizability and long-term safety conclusions. Future research should focus on standardized clinical trials with defined dosages, treatment durations, and uniform outcome measures to validate efficacy. Additionally, mechanistic studies are needed to better understand bioactive compounds and their role in metabolic regulation and sustained weight management.

CONCLUSIONS

In conclusion, fennel seeds show encouraging therapeutic promise in the management of obesity. Flavonoids, essential oils, and dietary fiber are just a few of the bioactive substances found in fennel that can help control hunger, promote fat metabolism, and enhance general metabolic health. Because of research showing that fennel seeds may help reduce body weight, fat accumulation, and associated risk factors including insulin resistance, they are a valuable supplement in the treatment of obesity. More thorough human clinical trials are necessary to confirm these effects, identify the ideal dosages, and guarantee long-term safety, even in cases where the results are encouraging.

Authors' Contribution

Conceptualization: BG
Methodology: SQA
Formal analysis: AL, AY
Writing and Drafting: UZ, AF, UAA, RM, SR, HMNS
Review and Editing: UZ, AF, UAA, RM, SR, HMNS

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Knowledge, Attitudes, and Practices Regarding Obesity and Type 2 Diabetes Mellitus among Middle-Aged and Elderly People in District Narowal, Pakistan

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ABSTRACT

Type 2 diabetes affected 95% of people in Pakistan and rest of the globe. Diabetics increase is approximately to 69.9 million from 40.9 million by 2025 unless preventive measures are taken. **Objective:** To evaluate the knowledge, attitudes, and practices regarding obesity and type 2 Diabetes Mellitus among middle-aged and elderly people in District Narowal, Pakistan. **Methods:** A cross sectional study was conducted from December 2022 to May 2023. Simple random sampling was used for the selection of diabetic patients. Socio-demographic information, diabetes-related knowledge, attitudes, and practices were gathered using semi-structured, pre-tested questionnaire after taking verbal informed consent. Following analysis, appropriate tests were performed on the data using SPSS version 25.0. **Results:** Out of 300 patients, 241(80.33%) were overweight or obese. The mean knowledge score was 21.51 ± 6.13 for men and 20.57 ± 6.29 for women. Attitude scores averaged 35.96 ± 14.33 for men and 33.55 ± 14.03 for women. Practice scores were 17.06 for men and 4.53 ± 4.72 for women. No significant differences were found between weight groups in knowledge (2,297) = 1.72, p-value > 0.18, attitude, or practices. **Conclusion:** The low evaluations for the same suggested that the survey participants' attitudes, knowledge, and practices toward diabetes were deemed inadequate.

INTRODUCTION

Diabetes progress when the body or pancreases cannot utilize the insulin. In type 2 diabetes, the pancreas generated less insulin than normal and the body becomes more insulin-resistant. Over 96% of the diabetes cases are Type 2 Diabetes Mellitus(T2DM), which is the most common form of the disease [1]. Adipose tissue stores energy, secretes hormones, and impacts the endocrine, nervous, and cardiovascular systems. Abnormal fat hormone secretion can lead to insulin resistance, contributing to the development of Type 2 Diabetes Mellitus (T2DM) [2, 3]. Obesity is a chronic, relatable neurobehavioral disease marked by excess body fat, leading to adipose dysfunction and abnormal physical forces. This results in harmful metabolic, biomechanical, and psychosocial health impacts [4]. Obesity, driven by poor diet and sedentary lifestyles, is a rising global epidemic with significant health impacts, including Type 2 diabetes. The World Health Organization classifies both obesity and diabetes as major public health concerns due to their increasing prevalence [5]. Obesity, defined by a BMI of 30 kg/m^2 or higher, increases the risk, with elevated insulin and glucagon levels indicating early risk [6]. Obesity and diabetes rates in China are rising due to changing lifestyles, with projections indicating 140.5 million adults will have diabetes by 2030. This leads to serious health risks and increased economic burdens from related comorbidities [7]. Most of the knowledge on epigenetic dysregulation in human obesity and T2D has developed in the past 10 years [8]. A study revealed that in non-Hispanic Black (NHB) and Hispanic individuals, the risk for the development of Type 2 Diabetes

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(T2D) is higher as compared to non-Hispanic Whites (NHW); the reason for this prevalence is unknown. Body fat distribution, insulin sensitivity, and β-cell function are the phenotypic risk factors that vary across the racial/ethnic groups [9]. The global prevalence of diabetes is rising according to International Diabetes Federation with 536.6 million people affected in 2021, projected to increase to 783.2 million by 2045. About 239.7 million people were unaware of their diabetes, representing 44.7% of cases. Many individuals experience 5–6 years of undiagnosed pre-diabetes or type 2 diabetes. The rate of undiagnosed diabetes varies significantly between high-income and low-to-middle-income regions [10]. Metabolically unhealthy obesity refers to individuals who are classified as obese based on their BMI and also display characteristics of metabolic syndrome, including hypertension, elevated blood glucose, and dyslipidemia [11]. Between 50% and 75% of individuals with Type 2 Diabetes Mellitus (T2DM) have Non-Alcoholic Fatty Liver Disease (NAFLD) . In the US, the prevalence of overweight and obesity in adults with Type 1 Diabetes Mellitus (T1DM) is similar to the general population, but it is increasing more rapidly, reaching up to 62%. As a result, many individuals with T1DM also exhibit characteristics of Type 2 Diabetes Mellitus (T2DM), including both insulin deficiency and resistance [13].

The goal of this study was to evaluate the knowledge, attitudes, and practices regarding obesity and type 2 Diabetes Mellitus among middle-aged and elderly people in District Narowal, Pakistan, and to explore the factors influencing these health outcomes. Through this research, we seek to provide important insights into the regional health challenges faced by these populations and to propose recommendations for improving health outcomes in this under-studied area.

METHODS

From December 2022 to May 2023, the descriptive cross-sectional study of diabetic and obese middle aged and elderly people (29-65) (above 80 years were excluded from study) who also had other conditions was carried out at several hospitals in the area of Narowal. The study was approved by the ethical committee (Reg. No. Fa2021-M.Phil.-Zoo-008), of Lahore Garrison University, DHA phase VI Lahore. An investigation on Knowledge, Attitudes, and Practices (KAP) related type 2 diabetes, obesity, and other illnesses such as renal, pancreatic, liver, high blood pressure, and heart disease was undertaken in December utilizing a structured questionnaire. To reach the study's objective, we had to finish 300 surveys in total. The commonly used formula for sample size calculation in cross-sectional studies was used: The sample size was estimated using prevalence of Type II Diabetes Mellitus 16.98% at 4.2% margin of error and 95% confidence level using following formula,

$$n = \frac{Z^2 - \frac{\alpha}{2} p(1-p)}{d^2}$$

Where;

p= Prevalence of Type II Diabetes Mellitus = 0.1698 [14]

d= Marginal error set at 8%

α= 0.05

Z= Standard normal deviation for 95% confidence interval

To represent the various subgroups within the population fairly stratified random sampling technique was employed. Population was divided into groups (for example, by age, gender, or socioeconomic status) and then randomly selecting respondents from each stratum. Participants were informed that their information will remain confidential and will solely be used for the purpose of research, and they had the right to withdraw any time without any consequences. They were also told the procedures that were involved, the study purpose, and the potential risks and benefits. Before the survey, a questionnaire was developed to gauge each participant's knowledge, attitude, and behaviors about type 2 diabetes, obesity, and other variables such kidney damage, pancreatic illness, liver problems, high blood pressure, and heart problems. The questionnaire has three sections: Knowledge, Attitude, and Practices, as well as sociodemographic data. Socio-demographic information, such as sex, education, age, place of residence, smoking, drinking, and other factors, made up the first portion of the questionnaire. The second section of the questionnaire asks about information such as the causes of type 2 diabetes, its symptoms, its signs and causes of obesity, as well as diagnosis in order for kidney damage, pancreatic disease, liver problems, hypertension, and heart problems. It also asks about general weight, whether or not you have heard of type 2 diabetes, obesity, and other diseases, as well as the duration of these conditions in middle-aged and elderly people and whether they are curable. The third section of the questionnaire focused on respondents' attitudes and practices. It asked about respondents' practices for preventing middle-aged and elderly people from developing kidney disorder, pancreatic disease, liver problem, high blood pressure, and heart problem, as well as their attitudes and perceptions about the severity of diabetes type 2 and obesity and other problems like kidney damage, pancreatic disease, liver issue, and hypertension. SPSS Version 25.0 of the Statistical Software for Social Sciences was utilized to analyze the data. While quantitative data were displayed using the mean and Standard Deviation (SD), qualitative data were presented using frequency and percentage. To compare the two groups' means, an unpaired t-test was used. One-way ANOVAs were used to compare three or more categories. P-value<0.05 was considered as significant.

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RESULTS

A total of 300 diabetic individuals were interviewed. Sixty-three percent of the 189 participants were female while 111 thirty-seven present were male. Most subjects (29%) had completed secondary school, whereas 27% were illiterate, 25% had just completed elementary school, and 19% had completed high school or beyond. Sixty-five percent of the people were from rural areas. Eighty-two percent of them were married. The participants of the medium socioeconomic group were 41%, and 64% of them had private employment on average. The majority of people (98%), did not smoke or drink alcohol. Sixty-six percent had Type 2 diabetes for at least five years, and nearly all of them (100%) had it. While 64% of the individuals had a negative family history of DM, 36% of the subjects had a favorable family history. The most common co-morbid condition was hypertension (44%), which was followed by liver problems (3%), pancreatic disease (1%), renal disease (5%), and cardiac problems (6%). While the other patients had an obesity rate of 36% (n=109) and 20% (n=59) of BMI 23 to 24 kg/m2, the participants with a BMI of 18 to 23 kg/m2 were considered normal weight. We found that adding fruits to their diet was a positive habit for most people (55.04%) and green leafy vegetables (93.02%). Natural therapies were not used by 94.58% of them. The majority of subjects (79.07%), however, lacked a glucometer. Table 1 displayed the sociodemographic data of the research participants.

Table 1: Sociodemographic Data of the Sample

Variables	Frequency (%)
Gender	
Men	111 (37%)
Women	189 (63%)
Qualification	
Illiterate	80 (27%)
Primary	75 (25%)
Secondary	88 (29%)
Graduate or Above	57 (19%)
Residence	
Urban	104 (35%)
Rural	196 (65%)
Marital Status	
Married	246 (82%)
Unmarried	54 (18%)
Sector of Employment	
Public	108 (35.5%)
Private	194 (63.8%)
Socio Economic Class	
High	84 (28%)
Middle	122 (41%)
Low	94 (31%)
Diabetic Duration	
Upto 5 Years	197 (66%)
More than 5 Years	103 (34%)
Body Mass Index	
Normal (18-23)	59 (20%)
Overweight (23-24)	109 (36%)
Obese (>25)	132 (44%)
Family History of Diabetes	
Yes	107 (36%)
No	193 (64%)
Yes	103 (34%)
No	197 (66%)
Types of Addiction	
Tobacco	96 (32%)
Tobacco and Alcohol	7 (2%)
None	197 (66%)
Complications with Diabetes	
Kidney Disease	14 (5%)
Pancreatic Disease	3 (1%)
Liver Problem	10 (3%)
Hypertension	132 (44%)
Heart Problem	18 (6%)
None	123 (41%)

*Socio economic class was observed using the information of employment, salary and daily wages

For knowledge, attitude, and practice for males and females the mean score was shown in table 2. An excellent knowledge, attitude and practices towards the disease was investigated. An average knowledge score for men was found to be 21.51, with a standard deviation of 6.13, whereas the average knowledge score for women was found to be 20.57, with a standard deviation of 6.29. The findings of the t-test were non-significant since the obtained value was 1.26 and the p-value was more than 0.05. Men's mean scores were 35.96 with a standard deviation of 14.33 in terms of attitude, while women's average scores were 33.55 with a standard deviation of 14.03. Non-significant findings were observed since the results achieved was 1.27 and the p-value was more than 0.05. The mean score for male practices were found to be 17.06 and a standard deviation of 4.53, while female practices had a mean score of 16.66 and a standard deviation of 4.72. These findings were not statistically significant since the t-test's resulting value was 0.71 and the p-value was higher than 0.05.

Table 2: Mean Comparison of Diabetic Patients on the Basis of Gender Among Knowledge, Attitude, and Practice (n=300)

Variables	Gender		t (300)	p-Value
	Female (Mean ± SD)	Male (Mean ± SD)		
Knowledge	20.57 ± 6.29	21.51 ± 6.13	1.26	0.20
Attitude	33.55 ± 14.03	35.96 ± 14.33	1.27	0.15
Practice	16.66 ± 4.72	17.06 ± 4.53	0.71	0.47

*p-value < 0.05, **p-value < 0.01, ***p-value < 0.001

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The knowledge, attitude, and practices scores for people who are normal weight, overweight, and obese are displayed in Table 3 together with their means, SDs, and F-values. Results indicated non-significant mean differences across weight groups on Knowledge F (2,297) = 1.72, p >0.18. Findings revealed that there were no mean differences or minor differences. Results indicated non-significant mean differences across weight groups on Attitude as F (2,297) = 1.95, p>0.14. Findings revealed that people with normal weight were higher as compared to Overweight and Obese. Results indicated non-significant mean differences across weight groups on practices F (2,297) = 1.62, p > 0.20. Findings revealed that there were no major mean differences or minor differences.

Table 3: Mean Differences Regarding Body Mass Index BMI (Kg/m^2) Using One-Way ANOVA (n=300)

Variables	Normal 18-23 Mean ± SD	Overweight 23-24 Mean ± SD	Obese > 25 Mean ± SD	F (2,297)	p-Value
Knowledge	21.86 ± 6.05	21.27 ± 6.12	20.20 ± 6.38	1.72	0.18
Attitude	36.62 ± 13.05	35.38 ± 13.60	32.69 ± 14.97	1.95	0.14
Practice	17.49 ± 4.33	17.07 ± 4.56	16.29 ± 4.84	1.62	0.20

*p-value < 0.05, **p-value < 0.01, ***p-value < 0.001

An average, standard deviation, and F-values for knowledge, attitude, and practices among age groups were calculated. Significant mean differences across age groups on Knowledge F (3,296) = 6.35, p- value=0.00 were observed. According to these findings, people with age group 25-35 and 36-45 Years, their score was higher on Knowledge as compared to others. Results indicated significant mean differences across age groups on Attitude as F (3,296) = 3.69, p-value=0.01. Findings revealed that people with age group of 25-35 were higher at attitude as compared to other. Results indicated non-significant mean differences across age group on practices F (3,296) = 2.31, p-value=0.07. These findings revealed that there were no major mean differences or minor differences on practices (table 4).

Table 4: Mean Differences Between Age of Diabetic Patients Regarding Knowledge, Attitude and Practice Using One-Way ANOVA

S.No.	Variables	Respondents	Mean ± SD	F (3,296)	p-Value
1	Knowledge	25-35 Years	22.86 ± 5.51	6.35	0.00
		36-45 Years	22.57 ± 5.73		
		46-55 Years	19.11 ± 6.35		
		55 Above	20.64 ± 6.30		
2	Attitude	25-35 Years	38.30 ± 12.59	3.69	0.01
		36-45 Years	37.08 ± 13.50		
		46-55 Years	31.27 ± 14.50		
		55 Above	34.05 ± 14.34		
3	Practices	25-35 Years	18.05 ± 4.01	2.31	0.07
		36-45 Years	17.48 ± 4.35		
		46-55 Years	16.24 ± 4.83		
		55 Above	16.28 ± 4.86		

*p-value < 0.05, **p-value < 0.01, ***p-value < 0.001

The average, standard deviation, and F-values for knowledge, attitude, and behaviours about tobacco, alcohol, and other drug addictions are shown in Table 6. Results indicated non-significant mean differences across addiction on Knowledge F (2,297) = 0.97, p>0.38. Findings revealed that people with addiction of tobacco and alcohol were higher at Knowledge as compared to others. Results indicated non-significant mean differences across addiction on Attitude as F (2,297) = 0.37, p>0.69. Findings revealed that people with addiction of tobacco and 26 alcohols were higher at attitude as compared to others. Results indicated non-significant mean differences across addiction groups on practices F (2,297) =0.51, p>0.60. Findings revealed that people with addiction of tobacco and alcohol were higher at practices as compared to others*(table 5).

Table 5: Mean Differences Regarding Addiction Using One-Way ANOVA (n=270)

Variables	Tobacco Mean ± SD	Tobacco & alcohol Mean ± SD	None Mean ± SD	F (2,297)	p-Value
Knowledge	20.93 ± 6.29	24.14 ± 4.91	20.79 ± 6.25	0.97	0.38
Attitude	34.25 ± 15.33	39.00 ± 13.00	34.38 ± 13.64	0.37	0.69
Practice	16.79 ± 4.67	18.57 ± 3.77	16.76 ± 468	0.51	0.60

*p-value < 0.05, **p-value < 0.01, ***p-value < 0.001

The mean, SD, and F-values for knowledge, attitude, and behaviors across fasting blood sugar level. Results indicated significant mean differences across Fasting blood sugar level on Knowledge F (2,297) = 68.73, p>0.00. Findings revealed that

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people with fasting blood sugar level of >140 were higher at Knowledge as compared to others (table 6).

Table 6: Mean Differences Regarding Fasting Blood Sugar Level (mg/dl) Using One-Way ANOVA (n =300)

Variables	<110 Mean ± SD	110-140 Mean ± SD	>140 Mean ± SD	F (2,297)	p-Value
Knowledge	14.10 ± 3.22	20.71 ± 6.27	25.34 ± 2.86	68.73	<0.001
Attitude	22.07 ± 10.56	33.87 ± 14.63	42.94 ± 7.88	40.54	<0.001
Practice	12.67 ± 4.40	16.63 ± 4.73	19.62 ± 1.92	41.55	<0.001

p-value < 0.05, **p-value < 0.01, ***p-value < 0.001

The mean, standard deviation, and F-values for Knowledge, attitude, and behaviours throughout Postprandial blood sugar levels are shown in Table 8. There were significant mean differences across postprandial blood sugar level on Knowledge F (2,297)= 40.73, p- value > 0.00 (Table 7).

Table 7: Mean Differences Regarding Post Prandial Blood Sugar Level (mg/dl) using One-Way ANOVA (n = 300)

Variables	<140 Mean ± SD	140-180 Mean ± SD	>180 Mean ± SD	F (2,297)	p-Value
Knowledge	16.35 ± 5.51	20.91 ± 6.23	25.21 ± 3.12	40.73	<0.001
Attitude	26.01 ± 13.29	34.00 ± 14.33	43.53 ± 8.05	29.29	<0.001
Practice	14.08 ± 4.91	16.69 ± 4.71	19.69 ± 1.72	27.57	<0.001

p-value < 0.05, **p-value < 0.01, ***p-value < 0.001

DISCUSSION

Hospitals in the Narowal served as the sites for the current descriptive epidemiological investigation. From December 2022 to May 2023, the experiment had 300 participants with type II diabetes. Sixty-three percent of them (n=189) were female. Most of the subjects completed secondary school (29%) and were illiterate, while 25% had just completed elementary school and 19% had earned a bachelor's degree or more.Sixty-five percent of the participants reside in rural areas. They were married in 82% of cases. About 41 percent of the subjects were middle-class, and 64 percent of the participants worked in the private sector. Most of the participants did not use alcohol (98%) or smoke (66%). The findings of this study, which examined diabetes patients' mean knowledge, attitudes, and practices by gender, were not statistically significant. The study's preponderance of female patients may have resulted from the survey's afternoon timing, when the majority of the community's male residents were at work. Women comprised 63% of the total subjects (n=189) in the current research. Most of the patients were between the ages of 40 and 60.41% of the participants in this study came from the medium socioeconomic group, and around 64% of the participants worked for private enterprises. The mean comparison of diabetes patients' knowledge, attitudes, and practices by gender in this study did not yield statistically significant findings. Moreover, these results align with research conducted in Kuala Muda District, Kedah, Malaysia assessed the Knowledge, Attitude, and Practice (KAP) of type 2 diabetes patients in Malaysia, revealing high KAP levels but emphasizing the need for educational interventions, especially for those with lower education or poor management practices.Key factors such as academic qualification, income, and health status were strongly correlated with KAP levels. Trend in diabetes prevalence increasing with increasing age has been reported [15]. Another study on 149 patients, had a positive attitude toward physical exercise but a less favorable attitude toward dietary changes. While 63.4% (n = 83) reported exercising regularly, two-thirds did not consistently monitor their weight, and the adoption of controlled diets was poor.The mean age of 137 respondents was 56 years, with 69.8% being women. The majority had secondary education (43.2%), and 42.6% were pensioners. A quarter of respondents were current smokers (22.2%) or drinkers (26.3%). Despite good knowledge, with 94.6% learning from healthcare professionals, the majority (87.3%) understood that lifestyle modification involves diet and exercise. However, many still struggled to implement these practices. However, the study highlights the gap between knowledge and practice, with respondents showing poor attitudes toward dietary changes and inconsistent exercise routines [16]. A study done in Palestine on T2DM patients showed KAP as the key predictors that contribute to higher levels of knowledge, positive attitudes, and effective disease management practices among patients [17]. The use of Complementary Medicine (CAM) products is prevalent among the Pakistani diabetic population. Common CAM practices include the use of herbs and specific diets. The adoption of CAM is notably associated with factors such as female gender, older age, lower education levels, unemployment, prolonged diabetes duration, diabetes-related complications, and poor glycemic control [18]. Another finding explains that Knowledge is the most important factor in managing diabetes, serving as the foundation for control. In developing countries, awareness is influenced

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by age, socio-economic status, and education. Previous studies highlight the importance of education in dispelling myths and misinformation about the disease [19]. In contrast to these findings, a cross-sectional household survey was conducted from 31st January to 3rd February 2019 to assess diabetes-related knowledge, attitudes, and practices among Singaporeans aged 30-64 years without diabetes. Results from 806 participants showed that 72.2% did not meet physical activity recommendations. Physical activity was linked to better diabetes knowledge, stronger beliefs in prevention, and lower worry about diabetes. However, knowledge and attitudes were not associated with dietary habits. The findings suggested the need to emphasize physical activity and healthy diets in diabetes prevention, with behavior change interventions likely required for improving dietary choices [20]. In inverse relation to these research studies a survey revealed a lack of knowledge, poor attitudes, and inadequate practices within the community, highlighting the need for structured educational programs for diabetic patients. Education should particularly target males, newly diagnosed individuals, and those with low education levels [21]. It was found that most patients had no idea what DM was. This is consistent with a study done on 163 patients and revealed a lack of diabetes-related knowledge regarding exercise ($p < 0.001$). Most participants with T2DM 163, (81.9%) were unaware that physical activity and exercise are distinct. About 158 participants (70.4%) believed their daily work was sufficient as a substitute for exercise. Over 50% exhibited positive attitudes and practices toward reap the advantages for T2DM ($p < 0.001$). Despite poor knowledge and negative attitudes toward diabetes, participants demonstrated satisfactory diabetes-related practices [22]. It was also found that several of the participants knew that kidney impairment might occur from untreated diabetes mellitus. In a research conducted at six educational academy in Beharampur, Orissa, Malini DS *et al.*, found that 18.75% of patients with diabetes also had high blood pressure [23]. Blood sugar levels and diabetes-related practice scores were shown to be substantially correlated among those with low practice scores who also had insufficient glycemic. Over half of the patients with low ratings did not take their prescription drugs on time, did not follow a diabetic diet, or did not practice other healthy lifestyle practices including regular exercise and checkups. According to current knowledge skipping doses of diabetic medications would negatively affect the ability to regulate patient's condition.

Future research should incorporate larger, multi-center samples and longitudinal designs to establish causal relationships and improve generalizability. Structured educational interventions and community-based awareness programs are recommended to bridge the gap between knowledge and practice. The study is limited by its cross-sectional design, relatively small sample size, and reliance on self-reported data, which may introduce recall and response bias. Additionally, the findings may not be generalizable beyond similar rural or semi-urban populations.

CONCLUSIONS

The survey participants' knowledge, attitudes, and behaviors about diabetes were deemed inadequate, as seen by the low evaluations for the sample. Sample size was small with approximately one-third of people having a background of diabetes. An interrelation between practice score and patient glycemic control was observed along with a strong correlation between diabetes and obesity.

Authors' Contribution

Conceptualization: SS
Methodology: SF, HSB, AB, SA, AT
Formal analysis: SA, AK
Writing and Drafting: SF, HSB, AT
Review and Editing: SF, HSB, AT, AB, SA

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

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Comparison of Outcomes of Kidney Transplantation in Diabetic and Non-Diabetic Patients

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ABSTRACT

When opposed to long-lasting dialysis, kidney transplantation offers patients with end-stage renal illness a higher chance of mortality and a better standard of life. It is still up for debate whether kidney transplantation is more beneficial for diabetic individuals in contrast to those lacking the disease. **Objective:** To compare outcomes of kidney transplantation in diabetic and non-diabetic patients. **Methods:** Data from 100 patients was collected from Sheikh Zayed Hospital Lahore, Pakistan.The following variables were assessed to compare the consequences of transplants in patients with and without diabetes: per graft fluid collection, superficial infection of the wounded area, cut-off hernia, shallow injury dehiscence, cellulitis, seroma, fascial breaking down, deep wound contamination, hypertension, and mortality and recuperation. Fisher's exact test was applied to test statistically significant variances in outcomes and p-value≤0.05 was considered significant. **Results:** A statistically significant variance was observed in per graft fluid collection among diabetic and non-diabetic kidney transplant patients i.e., 68% vs 32% respectively with p-value≤0.05. A significant difference was observed in the occurrence of incisional hernias between the two groups, with a high rate in non-diabetic patients. Facial dehiscence also showed a statistically significant difference, with a higher incidence in non-diabetic patients (p=0.010). **Conclusions:** It was concluded that diabetes significantly impacts certain post-transplant outcomes, such as fluid collection. In contrast, other outcomes like incisional hernia and facial dehiscence are more prevalent in non-diabetic patients who had kidney transplants.

INTRODUCTION

When contrasted with long-lasting dialysis, kidney transplantation offers those suffering from end-stage renal disease (ESRD) a better standard of life and a higher chance of survival, perhaps saving their lives [1, 2]. However, there are several inconsistencies in earlier research, such as the fact that adherence to glycemic objectives was not taken into account and that diabetes therapy administered over time changed [3]. Because of the tiny sample size, our estimations are not as precise as possible. The regression models did not account for the incidence of medicated acute rejection or the Kidney Donor Profile Index. However, the success of a kidney transplant can be influenced by various factors, including the recipient's underlying health conditions [4]. Diabetes mellitus (DM), a leading cause of ESRD, is particularly significant due to its pervasive effects on multiple organ systems, including the cardiovascular system, immune function, and wound healing [5, 6]. All but one study had a larger proportion of male respondents than female ones [7]. From Saudi Arabia to Australia, studies were carried out all over the world, although most came from China (n=6) and Poland (n=3). Diabetes was the condition most often evaluated result (n=14) [8]. According to estimates, the prevalence of diabetes in all age categories was 2.8% worldwide in 2000 and is expected to increase to 4.4% by 2030 [9]. According to a 2006 research by the WHO

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Collaborating Center for Diabetes and the Diabetic Association of Pakistan, the incidence of Type II diabetes was 2.5% in rural women and 6.9% in men, whereas it was 3.5% in women and 6.0% in men living in cities [10]. According to these standards, the incidence of diabetes worldwide was 8.8% (95% CI 7.2–11.3%) in 2017 (standardized for the 20–79 age range), and by 2045, it is predicted to rise to 9.9% (95% CI 7.5–12.7%). The incidence of diabetes has steadily increased worldwide [11]. The effectiveness of kidney transplantation in patients with diabetes as opposed to patients without diabetes is still debatable [12-14]. While some studies found that diabetic patients had poor graft survival and mortality, others found no appreciable differences between patients with and without diabetes [13, 14].

This study aims to compare the outcomes of kidney transplantation in diabetic (DM) and non-diabetic patients (NDM).

METHODS

It was a retrospective study and data were collected from Sheikh Zayed Hospital Lahore after approval from the ethical review committee. The study duration was from Sep 2024 to Dec 2024. Ethical Approval was given by the ethical review board of The University of Lahore. (REC-UOL-/401/08/24). A sample size of 100 with a 95% confidence level and 5% margin of error was calculated using Rao software. The sample selection technique involved was non-probability purposive sampling from patients who had kidney transplants between 20-50 years of age. Both male and female patients were included. ABO conflicting or human leukocyte antigen-sensitized kidney transplantation and immunocompromised patients were excluded. After getting informed consent from patients a total of 100 patients were enrolled in this study. To compare outcomes of transplant in diabetic and non-diabetic patients' variables that were measured include: 1) per graft fluid collection, 2) superficial wound infection, 3) incision hernia, 4) superficial wound dehiscence, 5) cellulitis, seroma, 6) fascial dehiscence, 7) deep wound infection, 8) hypertension, 9) death and recovery. SPSS version 23.0 was used to analyze the data. The distinction between the final results of kidney transplant recipients with DM and those with NDM was described using frequency and percentage. To look for statistically significant variances in results, Fisher's exact test was applied and a p-value<0.05 seemed significant.

RESULTS

Out of 100 patients that had kidney transplantation 48% were in the age group of 41-50 years of age. Seventy-nine percent of patients were female. A statistically significant variance was investigated in per graft fluid collection among diabetic and non-diabetic kidney transplant patients i.e., 68% vs 32% respectively with p-value≤0.05 (Table 1).

Table 1: Demographic Analysis of Diabetic Kidney Transplant Patients

Variables	%	p-value
Gender		
Female	79%	--
Male	21%	
Age		
41-50 Years	48%	--
Graft Fluid Collection		
Diabetic Kidney Transplant Patients	68%	≤0.05
Non-Diabetic Kidney Transplant Patients	32%	

A significant variance was noticed in the occurrence of incisional hernias between groups, with an elevated occurrence incidence in non-diabetic patients. Facial dehiscence also gives a statistically significant difference, with an elevated occurrence in non-diabetic patients (p=0.010). Six diabetic kidney transplant patients died compared to 3 non-diabetic patients (Table 2).

Table 2: Outcome of Kidney Transplant in DM and NDM Patients

Outcomes	DM	NDM	p-value
Superficial Dehiscence	52	43	0.530
Per Graft Fluid Collection	68	32	0.003
Superficial Wound Infection	61	39	0.086
Incisional Hernia	28	72	0.003
Cellulitis	43	57	0.271
Seroma	39	61	0.086
Facial Dehiscence	34	66	0.010
Deep Wound Infection	59	41	0.177
Hypertension	51	49	0.903
Death	6	3	0.683
Recovery	44	47	0.898

DISCUSSION

The outcomes of kidney transplant patients often vary based on underlying health conditions, with diabetes being a critical factor that can influence post-operative recovery and complications [15]. This research sought to understand the post-transplant outcomes between NDM and DM patients. Our findings showed considerable differences in some outcomes, emphasizing the unique challenges of diabetic patients after kidney transplantation. The frequency of per graft fluid collection was considerably higher in the DM group than in the NDM group (p=0.003). This implies that diabetic patients might be at increased risk of having fluid-related complications after transplant, based on diabetes's impact on wound healing and vascular integrity [16]. The incidence of incisional hernias was notably distinguished between the two groups, with the NDM group showing a higher rate. This result is surprising, considering a greater risk might be expected in diabetic patients based on more compromised tissue quality. It may represent variation in surgical

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methods, post-operative care, or overall health of the patients [17]. For superficial dehiscence, superficial wound infection, cellulitis, seroma, deep wound infection, HTN, death, and recovery for other outcomes, there were no differences between DM and NDM groups. This implies that although diabetes mellitus affects some aspects of post-transplantation recovery, its effects may not be felt across all aspects [18, 19]. The comparable hypertension and overall recovery rates between the two groups show that both DM and NDM patients can have similar long-duration outcomes under proper management [20]. The results of this study highlight the need for individualized post-operative care in diabetic patients who undergo kidney transplantation. The substantially increased rates of fluid accumulation in the DM group imply that these patients may require more stringent observation and possibly more intensive fluid and wound management.

The study is limited by its small sample size, single-center design, and use of non-probability sampling, which may restrict generalizability. Additionally, important clinical variables such as long-term outcomes, glycemic control, and immunological factors were not fully considered. Future research should include larger, multicenter cohorts with longitudinal follow-up and incorporate detailed clinical and biochemical parameters. Such studies would provide more comprehensive insights to optimize individualized care strategies for both diabetic and non-diabetic transplant recipients.

CONCLUSIONS

It was concluded that diabetes significantly impacts certain post-transplant outcomes, such as fluid collection, in kidney transplant patients. In contrast, other outcomes like incisional hernia and facial dehiscence are more prevalent in non-diabetic patients. These findings highlight the need for nuanced post-operative care strategies that address the specific risks associated with both diabetic and non-diabetic patients.

Authors' Contribution

Conceptualization: MAN
Methodology: AN, SN, MAB
Formal analysis: AN, UN
Writing and Drafting: SN, AR, IR
Review and Editing: SN, AR, IR

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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Lived Experiences of Direct Care Givers of Stroke Patients in Khyber Pakhtunkhwa, Pakistan: A Qualitative Study

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ABSTRACT

Each year, approximately 15 million new people are diagnosed with strokes across the globe. Stroke is a profoundly debilitating condition that extends its impact beyond the individual affected, placing a significant burden on the caregivers.**Objectives:** To explore the lived experiences of direct givers of stroke patients in Khyber Pakhtunkhwa, Pakistan. **Methods:** In a qualitative study, purposive sampling technique was used in which the caregivers fulfilling the inclusion criteria of the current study were recruited. After ensuring the ethical considerations, total eight in-depth interviews were conducted, and the data saturation was achieved. Interviews were audiotape recorded, transcribed and then thematic analysis approach was followed. **Results:** The data of eight participants were included in the analysis. Five themes emerged from the data: early disappointment, economic burden, impact on personal life, impact on social life, and coping mechanism. **Conclusions:** Caregivers often face a multitude of challenges when taking on unexpected responsibilities of care of the loved ones. These difficulties encompass physical demands, psychological strain, social isolation, and financial burdens. Healthcare professionals should consistently educate caregivers on patient care and regularly evaluate their need for counseling and psychological support. Providing caregivers with essential knowledge and addressing their emotional and mental health needs are crucial for ensuring effective and compassionate care for patients.

INTRODUCTION

Stroke is a devastating disease that leads to a considerable proportion of deaths worldwide. It is the second major cause of mortality after ischemic heart disease (IHD) globally [1]. Each year, approximately 15 million new people are diagnosed with stroke across the globe [2]. Keeping the risk factors and growing prevalence in view, it is expected that the most common disease after IHD would be stroke worldwide [3]. Pakistan, being a developing country, also has a high burden of stroke. According to a study conducted in 2015, it was estimated that per one lac population, there are about 250 Pakistani patients having stroke [4]. A survey conducted in Khyber Pakhtunkhwa (KP) in 2017 randomly selected 22500 participants and identified the prevalence of stroke as 1.2%, translated to 1200 per one lac population [5]. The incidence of stroke in the urban population as compared to rural areas is much higher in Pakistan due to a sedentary lifestyle and other habits [6]. Stroke is such a debilitating disease that it does not affect the sufferer only, but it also places a significant burden on the family and especially the caregiver. A stroke patient is entirely dependent on others because he cannot move, clean or feed himself, and he is at a very high risk for falls and injuries. Since the onset of this disease is acute and everything happens suddenly, none of the family

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members is ready and aware to bear the load of new responsibilities. Direct caregiver plays a key role in rehabilitating such patients and their adaptation to the disability [7]. The caregiver in the family is usually a spouse, son or daughter. Caregiving is a formal process, but when the family caregivers shoulder this responsibility, they are unaware of how to begin because they are not educated or trained for it. This sometimes stresses out the caregiver and makes them burn out [8]. In addition, the caregivers often provide care without any planning or defined goals, probably due to unawareness; this drags all their attention towards their patient's care, and thus, they ignore their own health [9]. The socio-economic, physical and psychological consequences of stroke extend beyond the patient to the whole family and direct caregivers, especially [10]. It is essential to explore the experiences of direct caregivers of stroke patients. There are many quantitative studies conducted on various aspects of stroke in Pakistan that have identified the prevalence, determinants, associated factors, post-stroke depression, etc. However, the researcher did not find any qualitative study that talked about the caregivers' lived experiences in KP, Pakistan. This study aimed to explore the lived experiences of caregivers directly involved in the care of stroke patients. Although stroke is becoming common, especially in developing countries like Pakistan, little attention has been paid to caregivers' challenges, either emotionally, physically or financially. Quantitative studies have produced information about stroke prevalence, but there is a lack of research on stroke caregiving from the perspective of those directly involved. This study is based on caregivers' views to explore how caregiving affects the health, social life, and economic well-being of the caregiver in depth. Moreover, it stresses the necessity for targeted interventions and support systems to benefit the caregivers' quality of life and, therefore, their ability to provide good care to stroke patients.

Stroke places a substantial physical, emotional, social, and financial burden not only on patients but also on their caregivers, particularly in low-resource settings like Pakistan. Despite increasing stroke prevalence, existing research has largely focused on clinical and epidemiological aspects, with limited attention to caregivers' lived experiences, especially in Khyber Pakhtunkhwa. There is a clear gap in qualitative evidence exploring how caregiving affects caregivers' personal, social, and economic well-being. Therefore, this study aimed to explore the lived experiences of direct caregivers of stroke patients to better understand their challenges and coping mechanisms.

METHODS

A qualitative study was conducted from October 2022-March 2023 to explore the lived experiences of direct care givers of stroke patients. An ethical consent (No: 255/BKMC) was provided by the Ethical Committee of Bacha Khan Medical College prior to the study. Nonprobability, purposive sampling technique was used to recruit study sample because this is a method widely used in qualitative research to get deep insights from people with different experiences. Total of eight in-depth interviews were conducted because data saturation achieved at the sixth one and two more were held to verify that there were no more emerging sentiments. Data saturation is one of the basic principles in qualitative research and therefore deciding to include only eight interviews was based on the concept of data saturation. In terms of participants, this was sufficient to give meaningful insights while staying within the bounds of practical limits of time and resources for in-depth qualitative analysis. Participants in the current study were recruited as having the characteristics of being aged above 18 years, provided care to stroke patient for more than one month, and could speak Pashto, Urdu, or English. Participants were approached in a tertiary care hospital as they brought their patients for follow-up visits. Study purpose was explained and written informed consent was signed by all the participants. They were ensured for data confidentiality and anonymity throughout. Questions were asked through interview guide and probing questions developed by the researcher. A review of the existing literature was done to develop the interview guide; the consultation with the healthcare professionals was also part of such a process. With the problem in mind of exploring the emotional, social and economic challenges for caregivers, the guide was developed. It consisted of open-ended questions that allowed participants to talk about themselves in their own words with regards to their experiences, feelings and coping mechanisms. The interviews were in Pashto and Urdu, the two primary languages spoken in Khyber Pakhtunkhwa, on an individual basis in Urdu for all, other major ethnic groups where Pashto was spoken also being permitted. All the interviews were transcribed and then translated into English by the researcher, who is well versed in the Pashto and Urdu languages. The translation was done very carefully so that meaning of participants' response was not affected. The interview guide included important areas of study such as psychological difficulties, economic difficulties, social life problems, mental and physical wellness and stress management techniques. Firstly, the audio recordings were listened to several times and then translated and transcribed. Each transcript was read and reread while listening to audio recordings. Following the thematic analysis, and open codes were identified by underlying the meaning segments within the transcripts. Axial coding was done by segregating open codes into relevant axis. Themes were developed which had common meaning for all the participants and the pertinent codes were then brought

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under the relevant themes. Certain irrelevant codes were omitted since those were misfit under any theme. Themes were supported by the participants' quotes.

RESULTS

Table(1)shows the characteristics of direct caregivers of stroke patients who participated in the current study.

Table 1: Characteristics Of Direct Caregivers of Stroke Survivors

Participant	1	2	3	4	5	6	7	8
Age in Years	30	24	31	28	32	34	30	26
Gender	Male	Male	Male	Male	Male	Male	Male	Male
Marital Status	Married	Single	Married	Married	Married	Married	Married	Single
Level of Education	Matric	Middle	Middle	Matric	Inter	Master	Matric	Middle
Profession	Shop-keeper	Labor	Driver	Electrician	Shopkeeper	Teacher	Labor	Shopkeeper
Working Status	Part time	Unemployed	Unemployed	Unemployed	Part time	Full time	Part time	Part time
Ethnicity	Pashtun	Pashtun	Pashtun	Pashtun	Pashtun	Pashtun	Pashtun	Pashtun
Relationship with Patient	Son	Son	Son	Son	Son	Son	Son	Son
Duration of Care in Months	04	06	08	06	06	08	10	12
Diagnosis of Stroke Survivor	Don't know	Ischemic	Ischemic	Ischemic	Ischemic	Ischemic	Don't Know	Ischemic

Thematic analysis was done and total five themes were identified which are: Early-stage disappointment, Economic burden, Impact on personal life, Impact on social life, and Coping mechanism. The theme **"Early-Stage Disappointment"** captured the participants' experiences regarding disappointment due to people's bizarre labeling, prolong nature of disease, and no initial improvement despite provision of care. Some of participants stated that stroke is a dangerous name, and this bizarre labeling would discourage us as one of the participants said: People in the surroundings used to say that Mr. so and so has got stroke. They should pray for his (patient's) peaceful death as he would not come to normal state of health again. The family should not waste their money on his treatment (Participant 6). Similarly, the participants also shared that they were disappointed due to the chronic nature of the disease and said: We have seen stroking patients and heard that stroking patients either die soon or live in a diseased condition for years and never return to normal condition. We were really frightened when we found out that our father had got stroke (Participant 8). Despite the consistent efforts, caregivers did not see any improvement in the condition of their patients as the patients remained dependent as they were on the first day. One participant said: Initially we were hopeless despite the efforts because he was not able to talk, he was not able to take food, he was unable to change his position in the bed, and he was not able to attend the washroom. For long time we cared for him, and we did not see any improvement in his condition which made us unhappy (Participant 1). The second theme of **Economic Burden** talks about three main categories which are taken out from the codes namely reduced income, augmented expenditures, and difficulty managing finances. Leaving the job or making it part time to take care of loved ones decreased their income as one said: I am basically a shopkeeper. I have a small general store, and I used to sit in the store from morning till evening before the disease. When my father got this disease I divided my time and most of the day time I had to be in the home with my father. Due to this lack of duty, my earnings have been affected badly. (Participant 7). Another participant shared: This disease has affected my financial condition a lot. Before this disease, I used to drive a loading vehicle but as my father got this disease, I had to leave that duty and take care of my father (participant 3). In this category, the participants share their views about the expenses: About the expenses, you know the current situation. Along with my household expenses I must take my father to the big hospital, pay for the doctor, labs and medicines. We live in far-flung areas so we spent a lot on transportation to the hospital because such paralyzed patients cannot be moved in public transport (participant 5). The participants shared grievous concern about financial and resources management. One respondent shared: In the initial days of the disease, I had some of my savings which I have spent on my father. Now there is nothing left and as I told you that income from my shop has been decreased because I cannot give enough time to it. I thought that my wife had some gold for our wedding in her possession, so I will sell it to manage the expenses in intense need (participant 1). All the participants shared that they have taken loans from their relatives or friends to manage the financial crisis. The theme of **"Impact on Social Life"** captured the participants' experiences regarding their social life, focused on two main categories i.e. abandoned social gatherings and restricted to home. The participants shared they had friends' circles with whom they had to spend some time in the day to refresh themselves. After the disease of their patient, they had quit all those activities to spend more time at home as one participant said: This disease of my father has affected

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my social life a lot. I cannot go for outings with my friends because I must be with my father all the time. We often went to riverside previously but now I cannot. I am unable to attend the friends' functions due to this disease. Mr. ABC is my close friend here in the village; I could not attend his marriage ceremony unfortunately (Participant 3). In taking care of their loved ones, the participants said that they were compelled to be homebound and that they are unable to attend marriages and other happy events of relatives because such events need spare time. Before the disease, I used to carry my family to the relatives' homes for happy events but now I cannot afford this. In addition, this is the demand of our culture that if someone visits you at the time of different events, you must visit him at the same events as well, due to this disease many of my relatives are not happy with me because I have skipped many of their events (Participant 1). Similarly, the participants also shared a serious concern about their inability to appear at the funerals of people as one person shared: One of my best teachers Mr. ABC died, I heartedly wished to attend his funeral and set for the prayers at home, but I could not manage to spare time and go there since my father needed me at home. There are many such examples of happy and sorrowful events which I wished to attend but due to my father's disease I could not attend any (Participant 3). The fourth theme **"Impact on Personal Life"** emerged by two major categories which included effects on personal health and effects on immediate family. The participants shared: One thing I must say is that due to this disease, I have forgotten myself and my total focus is on my father. I cannot visit a doctor for my own illness which sometimes worsens; thus, my personal health is affected (Participant 4). Similarly, another participant said: Before the disease I would play games regularly, I would go friends for swimming in the river; now after the disease I cannot spare time for such activities. Even if I go out for some tasks my mind is towards my father because of his dependence, so I avoid going out (Participant 5). The caregivers also shared that they have much disturbed sleep. One of the respondents said: I give most of my time to the care of my father. My sleep has been disturbed. I never sleep during the daytime and at night when I fall asleep, I must get up after some time and sit with my father (Participant 1). About personal life, the participants said that being a husband and a father, there are certain responsibilities which one should carry out and due to problems of finances and time, such activities cannot be accomplished which affects the relationship of immediate family even if they don't verbalize. One of the participants said: I am a married man, and I have kids, I cannot give proper time to them. I used to take my wife shopping and kids for short trips once a month or so. After this disease, I cannot afford all these things; however, they still demand such activities because they were used in it (Participant 6). According to the last theme of **"Coping Mechanism",** caregivers adopted various strategies to deal with liability of care to the loved ones having this devastating disease i.e. stroke. These include awareness, support system, belief system, and time management. They shared that they were instructed about every aspect of care in each visit which made them confident in care provision as one shared: By visiting the hospital, the doctor and nurses would teach us to take care of him and give him massage, exercise and medicine regularly. They would advise us that he will get better with the passage of time. Such statements from a medical associated person would give us courage and hope (Participant 4). The caregivers shared that they live in joint family system. Living together provides moral support and strength to cope up with shouldered responsibilities. It is difficult to handle everything single handedly, so many of such tasks which someone else can do for me, my family members perform it for me and spare me for the care of my father. Sometimes I discuss care related matters with my close family members, and they provide me with good advice and courage (Participant 1). Religious beliefs and practices were highly highlighted by the caregivers as significant coping strategy. They shared that, being Muslims, it should be the belief that Allah tests individuals through various troubles and He removes the troubles away. They also shared that they increased the regularity of performing prayers and recitation of the Holy Quran which would give them satisfaction and hope. Before the disease, I was not very regular in performing religious activities. Now, I have started offering regular prayers and recitation of the holy Quran. This diversion into religious activities provided more satisfaction and gave me hope that our father will get better (Participant 6). The caregivers also highlighted time management as an effective coping strategy. One participant shared: When this disease came, we changed our life in such a way that we left certain activities of roaming out because now we give most of our time at home to be available to our patient (Participant 5). Some of the caregivers said that their patient is given food, medicine and other required care in the afternoon, after which the patient sleeps peacefully for some time. So, one of the participants shared: Usually in the afternoon my father used to sleep after he is given medicine and care; this is the only best time in which I can go out of my home towards my friends for some time or bringing something from the market (Participant 8).

DISCUSSION

The current study found out that the participants face disappointment in the early phase of their loved ones' disease. They related this stress and hopelessness to prolong nature of disease and no obvious improvement in

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the first month. These findings are in line with a study which identified that the caregivers are often unaware and untrained when they start care for their patient; this leads to stress and burnout [8]. Another Pakistani study also reported that informal caregivers of chronic patients face negative psychological impact. It also added that family caregivers are at more risk for developing depression as compared to non-caregiver members of the family [11]. A quantitative study conducted in China in 2020 revealed that frequency of hospitalization of stroke survivors, financial pressures and dependent nature of patients are the primary factors of disappointment and stress among the caregivers [12]. A significant finding in the current study was economic burden on caregivers related to decreased income and increased expenditures. In Pakistani communities and especially in KP province, commonly the bread earners are the men. When such earning members quit their jobs or make it part time, this leads to decreased earnings. The study participants related their heightened expenditures to their patients' disease costs along with household expenses. These findings are similar with other Pakistani studies which identified that more than two third of the participants had to quit their jobs in order to make themselves available for care and transportation of their patient for follow ups [13, 14]. Regarding expenses, another Pakistani study revealed that transportation of patient and paying his hospital and medicine charges increase the expenses of caregivers [11]. Impact on social life due to the disease of the loved one was another finding of the current study. The participants said that they have abandoned social gatherings, friend circle activities, going for outings, and being restricted to homes. These findings are in line with a quantitative study which revealed that majority of participants expressed that their social lives are badly affected due to caregiving process [15]. Similar findings are identified by a South African study which reported that stroke restricts the caregivers' social life and disrupts the whole family system [10]. Likewise, a Chinese study has similar findings of affected the physical, psychological, and social lives of caregivers [16]. The fourth theme in this study was impact on personal life. The participants shared significant concerns about the effects of dedicated caring on their personal health and immediate family relationship. They stated that, after their loved ones' dependence, they are unable to go to doctor for their own checkup in case of any minor illness, unable to play games, cannot go for any mind refreshing activity or even sleep properly. Similar findings are reported by a study conducted in Karachi, Pakistan which stated that the care drags all of the caregiver's attention towards the care of their patient and thus they ignore their own health. The caregivers often feel tired, exhausted, and do not have enough sleep due to constant care provision [9, 17]. Similarly, the findings of disrupted immediate family routines in the current study are supported by a Spanish study which reported that the caregivers face loss of independence, inability to plan normal patterns of life, and loss of autonomy due to burden of care. These lead to negative psychological experiences of spouses [18]. The findings of the current study showed that caregivers coping mechanism was related to awareness of care and prognosis by healthcare professionals, the support system, belief system, and time management. A study conducted in Ireland stated that it is helpful for the caregivers to seek counseling from the professional healthcare workers. This decreases their anxiety and provides them motivation towards better caring [19]. The findings of increased religious activities as a matter of satisfaction in the current study are also in line with another Pakistani research which revealed that caregivers usually increase religious rituals and prayers in hard times [15].

Due to cultural limitations, female caregivers were not added as a study participant. In current study, the female were approached, and the purpose and process of interview were explained, however, they were reluctant regarding tape recording of their interviews. The future research should focus on data from both genders. Moreover, as the family caregivers of stroke survivors experience altruism and burdens [20], there is a dire need for collaborative efforts and support from communities and occupational therapy.

CONCLUSIONS

Stroke is a debilitating disease, and the caregivers experience various hardships because of the sudden responsibilities of the care of stroke survivors. These include physical, psychological, social, and financial implications. The current study identified specific coping strategies to help them ease the trouble. The healthcare professionals should always teach the caregivers about the care process and assess their counselling and psychological support needs. The hospital administration shall keep instructional pamphlets regarding the care of stroke patients in outpatient departments and stroke units.

Authors' Contribution

Conceptualization: DM, SK[1]
Methodology: HK, ZA
Formal analysis: HK, SK[2]
Writing and Drafting: HK, DM, SK[1]
Review and Editing: HK, DM, Sk[1]

All authors approved the final manuscript and take responsibility for the integrity of the work.

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Conflicts of Interest

All the authors declare no conflict of interest.

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Frequency of Functional Depression and Coping Strategies in Medical Students and Doctors

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ABSTRACT

Functional depression, marked by intermittent depressive episodes while maintaining normal functionality, is common among medical professionals and students. Understanding the prevalence of functional depression in these populations and identifying effective coping mechanisms is crucial for supporting their mental health. **Objectives:** To determine the Frequency of functional depression and coping strategies in medical students and Doctors. **Methods:** This cross-sectional study was conducted at FRP-Medical College from June 2022 to May 2023, involving 260 participants (160 medical students and 100 recent medical graduates). Participants completed an online questionnaire distributed via WhatsApp and email, with informed consent obtained electronically.The study utilized the 21-item Beck Depression Inventory (BDI) to assess depression severity and the 28-item Brief-COPE questionnaire to evaluate coping mechanisms. Data were analyzed using SPSS version 23.0. **Results:** The questionnaire was distributed to a total of 260 individuals (160 were medical students and 100 were medical professionals). The mean age of undergraduates and doctors was 20.53 ± 1.12 years and 28.77 ± 3.63 respectively. A high frequency of functional depression was noted in which (57%) of undergraduates and (53%) of doctors had functional depression (p=0.017). Female students were more inclined to be affected by depression than their male competitors (p=0.041). The family structure and marital status, on the other hand, were not linked to depression. **Conclusions:** The findings demonstrated that medical scholars are a susceptible population with high rates of mental morbidity, including anxiety and sadness. Moreover, problem-focused coping methods were the most adopted by them.

INTRODUCTION

Mental well-being is about life going well. It combines a satisfying experience with effective performance. Being happy all the time is not necessary for sustained well-being; it is necessary to be able to control painful feelings such as grief, disappointment, and other negative emotions because they are a natural part of life. The phrase "functional depression" is frequently used to refer to a person who occasionally experiences depression but generally appears to be functioning normally. According to Rebecca Brendel, the American Psychiatric Association's incoming president, the phrase emphasizes "the important point that people can have mental illness and still appear to be capable of living their lives or not seem mentally ill to an external observer" [1]. Medical professionals might perform in ways that appear routine and habitual to everyone while secretly battling and going through difficult times. According to "The Diagnostic and Statistical Manual of Mental Disorders", in order to diagnose depression, the

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following parameters must be necessarily fulfilled: feeling down for the majority of the day, significantly decreased interest or enjoyment in practically all activities, significant weight reduction while not on a diet, weight gain, or practically daily changes in appetite, a decrease in physical activity and a slowing of mind (visible by others, not only internal emotions of agitation or being pushed down), daily exhaustion or energy loss, nearly daily feelings of worthlessness or excessive or unjustified guilt, decreased mental clarity, difficulty focusing, or indecision often daily and consistent notions of suicide, repeated suicidal ideas without a clear scheme, a self-harm attempt, or a clear suicide plot [2]. A minimum of five symptoms must be present for at least two weeks, and at least one of those symptoms must be either a sad mood or a lack of enthusiasm or delight [3]. Because they study and train in high-pressure settings, medical students are known to experience significant levels of stress, anxiety, and depression [4]. Large populations generally and healthcare personnel specifically are experiencing stress, and this anxiety has been augmented after the coronavirus epidemic [5]. They employ various coping mechanisms as a natural reaction to manage their stress and endure the demanding atmosphere present in medical institutions. Coping is defined as the cognitive and behavioral attempts to control circumstances that are seen to be taxing or surpassing a person's resources [6]. Problem-focused coping (PFC) and emotion-focused coping (EFC) are two general categories of coping strategies. There is a distinction between dispositional and situational coping, according to the literature. The group of coping mechanisms known as dispositional coping are those that have a comparatively long lifespan [7]. Comparatively, situational coping refers to coping strategies that adapt to various circumstances as a stressful transaction progress through its many stages. Using a vast array of cognitive, emotional, and behavioral factors, the framework was created to conceptualize generic coping strategies. Coping might be primarily an attitude-based process that includes several mental strategies. "Positive thinking" techniques, such as reframing, humor, or optimism, "social support" techniques, such as asking for emotional and practical help from others, and "turning to religion" techniques, such as placing one's faith in higher forces, are all common coping mechanisms. There are very fewer data in Pakistan on psychological issues and especially on functional depression. Moreover, prior research did not conclusively prove a connection between coping mechanisms and varying degrees of depressive symptoms. This study aimed to identify the prevalence of functional depression in medical students and medical practitioners. Another objective is to investigate the coping mechanisms that are commonly used to deal with it.

Functional depression is increasingly observed among medical students and doctors, who often maintain daily functioning despite experiencing significant psychological distress. However, in Pakistan, there is limited empirical evidence on the true frequency of functional depression and its association with different coping mechanisms in medical professionals. Existing studies have not clearly established how coping strategies relate to varying levels of depressive symptoms in this population.. This study aimed to identify the prevalence of functional depression in medical students and medical practitioners. Another objective is to investigate the coping mechanisms that are commonly used to deal with it.

METHODS

A cross-sectional study was conducted at the FRP-Medical College. The Ethics and Research Committee of Fazaia Ruth Pfau Medical College provided the approval (Ref No: IRB/58) for conducting this research. The same size was calculated using the single population proportion formula as follows,

$$n = \frac{z^2.p.(1-p)}{E^2}$$

n = Required sample size

Z = Z-score corresponding to the desired confidence level (1.96 for 95%)

p = Estimated proportion of the population with the characteristic of interest (80%, based on prior studies [8]).

E = Margin of error (5%)

A total of 260 participants were selected among which 160 were medical students and 100 were medical professionals. The medical students and doctors who were exposed to medical studies for at least six months were included in this study but those who already suffer from mental health issues and those exposed to medical education studies for less than 6 months were excluded. Written and verbal consent was taken from participants prior data collection. The data were collected over the course of three months using a questionnaire created on Google Forms and distributed online link via WhatsApp groups or email. The Beck Depression inventory (BDI) was used to determine the intensity of the symptoms over the course of the preceding week, respondents were given the task to score each item using one of four possible responses that included lack of a symptom (1-10), Mild Mood Disturbance (11-20), Borderline Depression (21-30), Severe Depression (31-40), Extreme depression (>40). On the other hand, to determine the efficacy of coping mechanisms, the Brief-COPE, a 28-item feedback Likert scale response type questionnaire was used to and the score for each item ranged 0-3, with higher scores indicating more frequent use of a particular coping

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mechanism. For labeling depression using the Brief COPE, there isn't a direct cut-off value for depression as it primarily assesses coping strategies rather than diagnosing depression. However, certain coping strategies may be associated with depressive symptoms. Researchers or clinicians may use additional scales or diagnostic criteria to assess depression. The collected data were analyzed using IBM SPSS version 23.0. Descriptive statistics, such as mean and standard deviation, were computed for continuous variables. Categorical variables were summarized using frequencies and percentages. For the analysis of functional depression, the prevalence rates were calculated, and chi-square tests were used to compare the proportions of depressed individuals among medical students and practitioners. Regarding coping methods, average scores of different coping styles were calculated. Overall, the significance level was set at p≤0.05 for all statistical tests.

RESULTS

There were 160 (61%) medical students and 100 (39%) practicing physicians among the total of 260 participants. The average age of medical students was 20.53 + 1.12 years, whereas the average age of doctors was reported to be 28.77 + 3.63 years. There were 106 men (40% of the participants) in this research. Participants with nuclear families made up 103 (40%), while those with combined families made up 157(60%) of the participants in Table 1.

Table 1: Descriptive Statistics of Study Variables

Variables	Maximum		p-value
	Students (n= 160)	Medical Practitioners (n = 100)	
Gender			
Male	67 (41.88%)	39 (39.00%)	0.646
Female	93 (58.13%)	61 (61.00%)	
Mean Age			
Male Mean Age	20.60 ± 1.30	30.62 ± 4.00	<0.001
Female Mean Age	20.48 ± 0.96	27.59 ± 2.82	<0.001
Combined Mean Age	20.53 ± 1.12	28.77 ± 3.63	<0.001
Birth Order*			
1st Child	59 (36.88%)	39 (39.00%)	>0.050
2nd Child	6 (3.75%)	0 (0.00%)	
Middle Child	61 (38.13%)	36 (36.00%)	
Youngest	32 (20.00%)	19 (19.00%)	
Only Child	2 (1.25%)	6 (6.00%)	
Family Structure			
Nuclear Family	115 (71.88%)	42 (42.00%)	<0.001
Joint Family	45 (28.13%)	58 (58.00%)	
Family Monthly Income*			
<= Rs.25,000/-	7 (4.38%)	0 (0.00%)	<0.001
>Rs.25,000/- to <=Rs. 50,000/-	34 (21.25%)	0 (0.00%)	
> Rs.50,000/- to <=Rs.100,000/-	38 (23.75%)	34 (34.00%)	
> Rs.100,000/-	81 (50.63%)	66 (66.00%)	
Marital Status*			
Single	160 (100.00%)	44 (44.00%)	<0.001
Married	0 (0.00%)	46 (46.00%)	
Divorced	0 (0.00%)	6 (6.00%)	
Separated	0 (0.00%)	4 (4.00%)	

Out of 260 medical professionals, 145 (or 55%) had functional depression, according to the screening results. Then it was discovered that 92 (57%) of medical students and 53 (53%) of practitioners had depression (p=0.017). The percentage of students and physicians who were mildly depressed peaked at 40 (25%) and 25 (25%) respectively as mentioned in Figure 1. Functional depression was detected in substantially more female (63%) than male (p=0.041). Frequency of family structure and marital status, on the other hand, were not significantly different among those with and without depression.

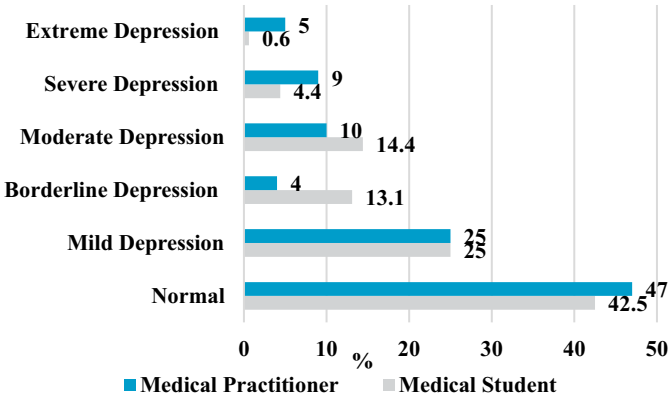

Figure 1: Functional Depression among study participants

The majority of individuals were found to utilize problem-focused coping methods (p=0.022) and (average 2.49 of 4). Emotion-focused coping was the second most used coping style by our medical professional's participant. Religion was the most common coping strategy (average 2.69 out of 4) along with active coping, planning, and acceptance. Participant adoption of avoidant was found to be the lowest. Substance use was the least adopted coping style (average 1.37 of 4) as reported in Table 2.

Table 2: Coping Methods among Study Participants

Coping Methods	Designation	N	Mean ± SD	p-value*
Problem Focused Coping	Medical Student	160	2.56 ± 0.80	<0.001
	Medical Practitioner	100	2.01 ± 0.81	
Emotion Focused Coping	Medical Student	160	2.30 ± 0.69	<0.001
	Medical Practitioner	100	1.95 ± 0.71	

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Avoidant Coping	Medical Student	160	1.86 ± 0.65	0.317
	Medical Practitioner	100	1.77 ± 0.70	

*Independent t-test

DISCUSSION

Functional depression among medical students commonly goes unrecognized and untreated. Additionally, because mental health is stigmatized and shamed, medical students are less likely than other students to seek professional help [9]. In this study, the prevalence of functional depression among medical professionals was evaluated and compared between medical students and doctors was (61%) and (39%) respectively. A high prevalence of depression was found in both groups, with medical students exhibiting a slightly higher rate than doctors. This aligns with previous research showing a significant burden of depression among medical students worldwide and study also shows that women were bound to encounter more depression than men. Moreover, majority of individuals tended to use religious, active planning, and accepting coping strategies. This study discovered that medical students had a high rate of depression (57.5%). An identical poll was carried out in Pakistan, where 70% of medical students acknowledged suffering from depression [10] 60% of students at Ziauddin Medical University in Karachi were depressed, according to different research. In the current research, depression prevalence was considerably greater compared to the worldwide incidence (28.0%) computed from 62,728 medical students and 1845 non-medical students who were gathered across 77 papers for the meta-analysis [11], as well as 10,147 medical learners in Asia were included in a meta-analysis that put the overall frequency at 11.0% [12]. On the other hand, previous research revealed a smaller prevalence of depression, ranging from 15 to 24% in the United States, 30.6% in Cameroon , 29.5% in Turkey , and 37.2% in Malaysia [13]. The cause of such high functional depression among medical professionals was because various stressors that they have to face in their normal daily life. Because in addition to the usual stressors of daily life, medical undergraduates need to oversee stressors well defined for clinical schools, such as knowledge and input overwork, financial debt, a lack of free time, and demands from jobs, work relationships, and career decisions. Accessing functional depression in doctors of current survey revealed that 53% of doctors have functional depression in real life. Interns and residents may suffer from functional depression in part as a result of their night shifts, extended workdays, hectic schedules, excessively demanding patients, few resources, and challenging or hard decisions [14]. They may be unable to take time out for exercise, sleep for fewer hours, and partake in fewer activities outside of the hospital due to their lengthy hospital hours and intense continual medical training, which has a detrimental effect on their health [15]. It has been documented that extremely long working hours, sleep deprivation and depression in doctors are all intertwined [16]. Another explanation is that young doctors who work in hospitals may experience functional depression more frequently because they are studying for their post-graduate exams at a younger age, which requires more time, money, and effort. Functional depression may also result from failing these exams. Additionally, it has been observed that doctors who are just starting in their careers are more self-conscious and concerned about the future, which might make them depressed [17]. Significant levels of depression in women were also discovered in this study. It was found that 59.2% of women had functional depression, compared to 40.7% of male. This is in agreement with a previous study that severe depression was more common among female doctors (14%) than in male doctors (3.1%). One of the contributing causes to the rise in depression among women is probably the frequent handling of several responsibilities as moms, wives, professionals, and homemakers. Furthermore, this investigation revealed that the majority of the study population utilized problem-focused coping (average score of 2.49 out of 4) the most frequently overall. In contrast, it was found that the majority of pupils employed active coping and planning when learning about problems. [18]. Religious coping (average score of 2.69 out of 4) was the most favored strategy utilized by medical professionals in this study. The average score for using substances as a coping method was (1.37 out of 4). The fact that all participants were Muslims and Islam forbids alcohol usage may account for the lowest scores on questions on substance misuse. Participants were inclined to choose active coping, acceptance, or positive reframing as their coping methods. All of this is explained by the possibility that undergraduates majoring in general well-being and prophylactic healthcare have a better grasp of and experience addressing medical problems. The most often mentioned activities were hanging out with friends, then sleeping, music, sports, and solitude. Hostilities utilized smoking as a coping method twice as often as day students, which was a startling contrast. Peer pressure and being away from one's family were blamed for the formation of such a bad habit. Additional research discloses other coping strategies for functional depression and numerous psychiatric conditions besides the ones addressed within our study. Daily exercise has a variety of health benefits, including improving the state of mind. Strong evidence exists to support physical inactivity increases the risk of depression and that exercise lessens the severity of depression [19]. The greatest method to

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treat functional depression is to stop it in its origins; therefore, stress management should be seen more as a preventative measure than a therapeutic one. The greatest method to solve issues is to identify them and approach them in a proactive, constructive manner. In this regard, a comprehensive strategy should be used for the efficient management of functional depression, including individual counseling, psycho-social assistance, medical and occupational counseling, support from society, activities to relax, and managing the effects of overwork. The greatest method to solve issues is to identify them and approach them in a proactive and constructive manner [20].

The study's limitations include a relatively small sample size despite meeting minimum requirements, potential sampling bias from a single institution, reliance on subjective self-reporting measures susceptible to social desirability bias, and a cross-sectional design limiting the ability to establish causality or track changes over time. These factors may impact the generalizability and reliability of the findings, suggesting the need for larger, more diverse samples, use of objective measures, and longitudinal study designs for future research. Exploring interventions and intervening variables is crucial, alongside considering cultural and contextual factors. By addressing these recommendations, future research can better inform strategies to improve mental health outcomes in the medical community.

CONCLUSIONS

Conclusively, the current study has the reported high prevalence rate of functional depression among medical students and doctors, hence underlining the high mental health risk of the medical professionals. The study also outlines the participants' most frequently used problem-focused coping strategies: religious coping, planning, and acceptance. These outcomes extend prior studies by indicating that healthcare workers use culturally and contextually applicable techniques in stress regulation. Subsequent cross-sectional investigations must investigate the long-term outcome of these coping strategies and introduce culturally relevant psychiatric care for medical learners and professionals in low-resource countries.

Authors' Contribution

Conceptualization: AM, NB
Methodology: AM, FF, BN, S, SEF, MF, MIA, NM, AA
Formal analysis: BN, NB, MIA, MA
Writing and Drafting: AM, FF, BN, NB, SEF, MF, NM, AA, MA
Review and Editing: AM, FF, BN, NB, SEF, MF, NM, AA, MA

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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Original Article

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Analysis of Genetic Variants of *ANGPTL4* Gene Responsible for Atherosclerosis Severity in Cardiac Patients

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ABSTRACT

ANGPTL4 gene is a major factor in the onset of atherosclerosis and exacerbation of its severity. *ANGPTL4* regulates lipoprotein lipase (LPL), but its inhibitory effect causes decreased triglyceride clearance. The E40K mutation reduces *ANGPTL4* oligomer formation, reducing LPL activity suppression. **Objectives:** To correlate *ANGPTL4* N-terminal chain variations with atherosclerotic cardiovascular disease severity in Pakistani individuals, enabling diagnosis, treatment, and prevention. **Methods:** A case control study was conducted at Surgimed Hospital, Lahore on 100 Pakistani cardiovascular patients and 50 healthy control subjects. The N-terminal chain of the *ANGPTL4* gene was sequenced revealing 14 individuals (9.33%) were heterozygous carriers of the *ANGPTL4* gene variant (rs116843064; G>A, E40K) in our population (n=150). **Results:** Among the participants, four (2.67%) individuals had severe atherosclerosis with heterozygous genotype (GA), eight (5.33%) had mild atherosclerosis with heterozygous genotype (GA), and two were healthy controls (1.33%) with heterozygous genotype (GA). This study showed the significant association of E40K variant of N-terminal chain of *ANGPTL4* with less likely chance of severe atherosclerosis in our cardiovascular patients. The E40K alters the regulation of lipoprotein lipase, affecting lipid levels and impacting cardiovascular health. **Conclusions:** E40K mutation carriers exhibit a lower risk of severe atherosclerosis in cardiovascular patients due to better lipid profiles as HDL levels were lower in non-carriers and higher in carriers.

INTRODUCTION

Cardiovascular Diseases CVD stand as the primary global cause of mortality and a significant factor in healthcare spending. CVDs are identified to be the main cause of death worldwide, taking toll of mortality up to 17.7 million per year [1-3]. Atherosclerosis is a condition caused by the buildup of cholesterol and low-density lipoproteins (LDL) in the inner walls of blood arteries that thickens and reduces the flexibility of the walls which can make it more difficult for blood to reach organs. In utmost conditions, blood vessels may get completely blocked [4, 5]. Risk factors for the emergence and progression of cardiovascular diseases may include factors like age, hypertension, obesity, smoking, dyslipidemia and diabetes mellitus Effects and associations of these risk factors in individuals may vary depending on the age and particular genetic structure. That is the very reason due to which specific individuals have greater chances of becoming victim of cardiac diseases [6]. As per findings of different studies, it is concluded that not only traditional but genetic factors also play a vital role in the development of atherosclerosis. A wide range of genes including *ANGPTL4*, APOB, CETP, LDLR, LIPC, and LPL are directly involved in progression

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and extremity of atherosclerosis [7]. Another research reveals that in humans, rare loss-of-function mutations found in the *ANGPTL3* and *ANGPTL4* genes are directly linked with low levels of triglyceride levels. Furthermore, LPL gene mutations are associated with high levels of triglycerides [8]. *ANGPTL4* gene is found on chromosome 19p 13.3, in humans. It has six introns and seven exons in it and encodes for 406-amino-acid glycoprotein. *ANGPTL4* is known to encode glycosylated protein with a coiled-coil N-terminal domain and a fibrinogen-like C-terminal domain. At specific times and in specific tissues,*ANGPTL4*, *ANGPTL3,* and *ANGPTL8* act as significant regulators for LPL to control LPL activity and partitioning of lipid [9]. Catalyzing the breakdown of triglycerides (TG) into glycerol and fatty acids (FAs) is one of the major roles that is played by LPL [10].It is considered that atherosclerosis gets prevented by this enzymatic nature of LPL.Contrarily, LPL's function is inhibited by *ANGPTL4* that ultimately reduces the number of circulating triglycerides.This inhibition from *ANGPTL4's* end results in formation of a chronic inflammatory response that is directly linked to atherosclerosis [11]. As per revelations of a population-based study, low levels of triglycerides and high levels of HDL cholesterol are linked directly with E40K, one of the *ANGPTL4's* mutation [12]. By interrupting the stability of oligomers, this mutation acts directly on *ANGPTL4's* ability to inhibit LPL.Due to this phenomenon, carriers (either homozygotes or heterozygotes) have better metabolic conditions, such as lower plasma triglyceride levels and greater HDL-C levels than non-carriers. Moreover, another conclusion has also been made that individuals that carry E40K mutation in their *ANGPTL4* gene have lower chances of getting heart related disease [13]. So, N-terminal chain of *ANGPTL4* has this mutation called E40K that may directly have impact on development of atherosclerosis [14].

Atherosclerosis remains a leading cause of cardiovascular morbidity and mortality, with both environmental and genetic determinants influencing disease severity. Although the *ANGPTL4* E40K (rs116843064) variant has been associated with favorable lipid profiles in global populations, there is limited evidence regarding its distribution and clinical significance in the Pakistani population. Moreover, existing studies have not sufficiently explored its direct relationship with severity levels of atherosclerosis (mild vs severe). The main purpose of this study is to analyze the genetic mutations in N-terminal chain of *ANGPTL4* in Pakistani patients with atherosclerotic cardiovascular disease.

METHODS

A case-control study was conducted from March 2023 to May 2023 to analyze the genetic variants of N-terminal chain of *ANGPTL4* in cardiovascular patients.RaoSoft Sample size calculator was used for calculating the sample size keeping the margin of error as 5% and confidence interval as 95%. A collective of 100 patients from a total of 150 with atherosclerotic cardiovascular conditions as well as age-matched healthy control subjects were thus collected in K3 EDTA vials from Surgimed Hospital Lahore, Punjab. Control samples were also picked from individuals who went to same hospital (Surgimed Hospital, Lahore) and had no history of cardiovascular disease, diabetes or any other major illness and had been for routine checkups. Controls were matched to the patients in terms of age and sex of the patients. Blood samples and data of CVD patients were collected by using a proforma (Annexure 1). A written and verbal consent from the participants and an approval (Reg No: IMBB/BBBC/23.050) from the Institutional Review Board was taken prior to the study. Blood samples were also evaluated for biochemical parameters such as lipid profile including Cholesterol, Triglyceride, HDL, LDL, VLDL and Cholesterol/ HDL Cholesterol ratio biochemistry analyzer as per manufacturer's instructions (CHOLESTECH LDX™ ANALYZER, Abbott, IL, USA). The DNA was extracted from the fresh blood samples by using the DNA extraction kit (QIAamp DNA Blood Mini Kit) as per the manufacturer's instructions.For silico analysis The *ANGPTL4* gene sequence was retrieved from GenBank database of NCBI. Primer3 software was used to design primers for the N terminal chain of the *ANGPTL4* gene (http://frodo.wi.mit.edu).The sequences of primers along with their melting temperature (TM) and GC content are given in Table 1.

Table 1: PCR Primers Used for Amplification of N-Terminal Chain of *ANGPTL4* Gene.

Gene name	Primer Name	Maximum	Tm (°C)	GC content
ANGPTL4	F1	ATTCTTTCCAGCGCCTTCTG	61.8	50
	R1	TGCGCCAGGACATTCATCTC	60.5	55
	R2	TGCGCCAGGACATTCATCTT	58.4	50

F1 = Forward Primer for N-terminal Chain of *ANGPTL4* gene R1 = Reverse Primer 1 (having C at 3' end) for binding with Allele G R2 = Reverse Primer 2 (having T at 3' end) for binding with Allele A

The N-terminal chain of ANGPTL 4 gene was amplified from genomic DNA by using primer F1 and R1 and PowerPol 2X PCR mix with dye (RK20719) as per manufacturer's instruction (ABclonal, Inc. MA, USA). For amplification of the N-terminal chain, a reaction mixture comprising 10 ng of genomic DNA, 0.8ρM of each oligonucleotide primer, and a 1X PCR mix was used, resulting in a total volume of 25µl. The PCR cycling parameters were as follows: an initial denaturation step at 95°C for 2 minutes, followed by 35 cycles consisting of denaturation at 95°C for 30 seconds,

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annealing at 52°C for 30 seconds, and extension at 72°C for 30 seconds. This was followed by a final extension step at 72°C for 2 minutes before holding at 72°C. The purified DNA samples isolated from the blood samples of CVD patients were electrophoresed on 0.8% of agarose gel for quality check of DNA. Moreover, the amplified PCR products of N-terminal chain of ANGPTL 4 were analyzed on 2 % agarose gel to confirm the fragment length in base-pair (bp) and specificity of N-terminal chain product. The 100bp DNA marker (ZOKEYO) was used as a size standard to validate the fragment length of PCR product (264bp). The prominent bands of PCR product of N-terminal chain of ANGPTL 4 were observed at their respective size on agarose gel, when visualized in UV gel documentation system. The purified products were subjected to sequencing using forward primers, following the manufacturer's instructions from Applied Biosystems' Big Dye Sequencing Kit. DNA sequencing was conducted through the Sanger sequencing method using an ABI PRISM 3100 Automated sequencer (Applied Biosystems), with sequencing services provided by Macrogen, Inc. Subsequently, the sequencing results were compiled using ABI PRISM sequencing analysis software version 3.7 (Applied Biosystems), and chromatograms were examined using Chromas software, accessible at www.technelysium.com.au/chromas.html. Following the sequencing process, chromatograms were scrutinized using Chromas version 2.5.1 and Chromas pro, available at (http://technelysium.com.au/wp/chromas/). Multiple alignments were carried out on the sequences extracted from atherosclerosis patients (CVD) and individuals with normal gene sequences obtained from Ensemble. Variants were detected by analyzing the multiple aligned sequences and confirmed by manual inspection of the sequencing chromatograms.

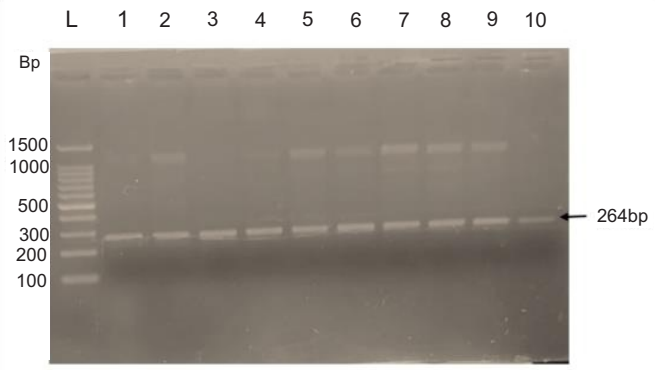

Figure 1: Agarose Gel (2%) Showing the Amplified PCR Products (264bp) from DNA Samples of Cardiovascular Patients; Lane L: 100bp DNA Ladder (SOLIS BIODYNE), 1-10: Amplified PCR Product of Samples (1-10)

RESULTS

The study comprised 100 male and female cardiovascular patients with atherosclerosis, who were visiting Surgimed Hospital, Lahore from various regions of Pakistan. Additionally, 50 healthy control subjects of the same age group were randomly selected and included. DNA was extracted from the blood samples to sequence variants in N-terminal chain of *ANGPTL4* gene responsible for severity in atherosclerosis in Pakistani patients. The extracted DNA was electrophoresed on 1% agarose gel to check the quality of DNA as shown in gel image as an example for 5 samples. The N-terminal chain of *ANGPTL4* gene of patients and the control subjects' samples were subjected to amplification using specific primers.The PCR samples were examined through agarose gel electrophoresis (2%) to confirm the specific amplification.The gel image in figure 1 shows the amplified PCR product size (264bp) of N-terminal chain of *ANGPTL4* gene. The amplified PCR products of N-terminal chain of *ANGPTL4* gene from all cardiovascular patients and control subjects were sequenced by utilizing Sanger sequencing method. The sequencing chromatograms for selected patients (having G or A allele) and control subjects are shown as an example in Figure 2.The following sequencing chromatogram is showing two variants (variant G & A of rs116843064) found in N-terminal chain of *ANGPTL4* gene of Pakistani cardiovascular patients.

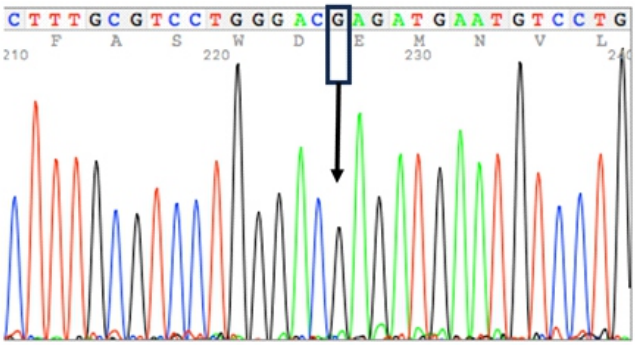

Figure 2(A): Selected Chromatogram of PCR Product From N-Terminal Chain of *ANGPTL4* Gene Amplified of Sample CAD-06 (Variant G of Rs116843064)

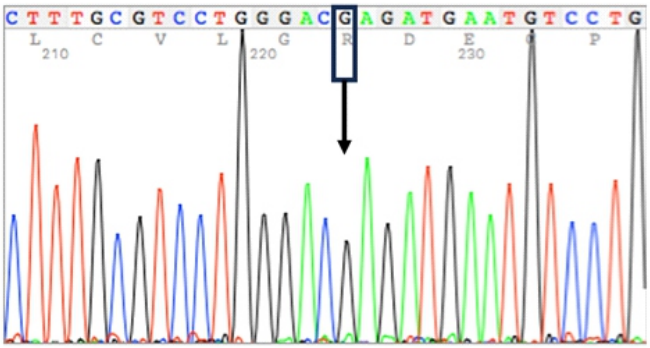

Figure 2(B): Selected Chromatogram of PCR Product From N-Terminal Chain of *ANGPTL4* Gene Amplified of Sample CAD-17 (Variant G Of Rs116843064)

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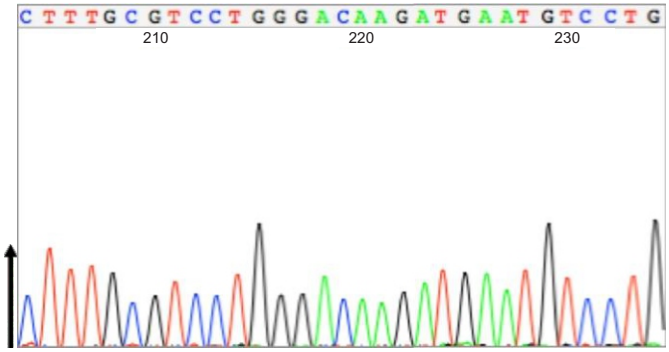

Figure 2(D): Selected Chromatogram of PCR Product From N-Terminal Chain of *ANGPTL4* Gene Amplified of Sample CAD-10 (Variant A Of Rs116843064)

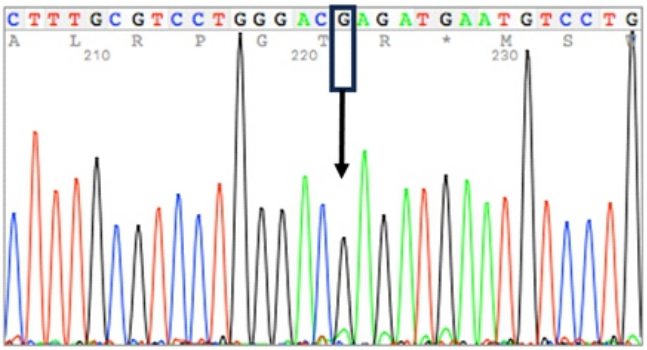

Figure 2(C): Selected Chromatogram of PCR Product From N-Terminal Chain of *ANGPTL4* Gene Amplified of Sample CAD-29 (Variant G Of Rs116843064)

The genotypes of N-terminal chain of *ANGPTL4* gene in 100 atherosclerotic cardiovascular patients and 50 normal healthy control subjects in Pakistani population were observed. Fourteen individuals (14) were heterozygous carriers of variant (rs116843064; G>A) in N-terminal chain of *ANGPTL4* gene out of total 150 individuals, including four individuals having severe atherosclerosis (2.67%), eight individuals having mild atherosclerosis (5.33%), and two healthy control subjects (1.33%). A list of genotypes of all cases and control samples for variant (rs116843064) found in N-terminal chain of *ANGPTL4* gene are shown (Table 2).

Table 2: List Of Genotypes for Variant Rs116843064 of N-Terminal Chain of *ANGPTL4* Gene Found in Atherosclerotic Cardiovascular Patients and Control Subjects from Pakistan.

Sample Ids	Controls		Sample Ids	Mild Atherosclerosis		Sample Ids	Severe Atherosclerosis	
	Genotypes			Genotypes			Genotypes	
CAD-04	G	A	CAD-01	G	G	CAD-03	G	G
CAD-06	G	G	CAD-02	G	G	CAD-10	G	A
CAD-13	G	G	CAD-05	G	G	CAD-15	G	G
CAD-16	G	G	CAD-07	G	A	CAD-18	G	G
CAD-19	G	G	CAD-08	G	G	CAD-23	G	G
CAD-22	G	G	CAD-09	G	G	CAD-28	G	G
CAD-24	G	G	CAD-12	G	G	CAD-29	G	G
CAD-25	G	G	CAD-14	G	G	CAD-33	G	G
CAD-27	G	G	CAD-17	G	G	CAD-34	G	G
CAD-37	G	G	CAD-32	G	A	CAD-39	G	A
CAD-38	G	G	CAD-35	G	G	CAD-40	G	G
CAD-45	G	G	CAD-36	G	G	CAD-41	G	G
CAD-47	G	G	CAD-43	G	G	CAD-42	G	G
CAD-48	G	G	CAD-46	G	G	CAD-44	G	G
CAD-50	G	G	CAD-51	G	G	CAD-49	G	G
CAD-59	G	G	CAD-52	G	G	CAD-54	G	G
CAD-60	G	G	CAD-53	G	G	CAD-55	G	G
CAD-61	G	G	CAD-58	G	A	CAD-56	G	G
CAD-62	G	G	CAD-66	G	G	CAD-57	G	G
CAD-63	G	G	CAD-67	G	G	CAD-68	G	G
CAD-64	G	G	CAD-71	G	G	CAD-69	G	G
CAD-65	G	G	CAD-72	G	G	CAD-70	G	G
CAD-79	G	G	CAD-74	G	A	CAD-73	G	G
CAD-80	G	G	CAD-77	G	G	CAD-75	G	G
CAD-81	G	G	CAD-78	G	G	CAD-76	G	G
CAD-86	G	G	CAD-82	G	G	CAD-83	G	G
CAD-87	G	G	CAD-85	G	G	CAD-84	G	G
CAD-88	G	G	CAD-96	G	A	CAD-100	G	G
CAD-89	G	G	CAD-97	G	G	CAD-101	G	G

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CAD-90	G	G	CAD-98	G	G	CAD-103	G	A
CAD-91	G	G	CAD-99	G	G	CAD-104	G	G
CAD-92	G	G	CAD-102	G	G	CAD-105	G	G
CAD-93	G	G	CAD-107	G	G	CAD-106	G	G
CAD-94	G	G	CAD-108	G	A	CAD-109	G	G
CAD-95	G	G	CAD-110	G	G	CAD-111	G	G
CAD-112	G	G	CAD-113	G	G	CAD-114	G	G
CAD-117	G	G	CAD-116	G	G	CAD-115	G	G
CAD-118	G	G	CAD-124	G	G	CAD-125	G	G
CAD-119	G	G	CAD-126	G	G	CAD-129	G	G
CAD-120	G	G	CAD-127	G	G	CAD-130	G	G
CAD-121	G	G	CAD-128	G	G	CAD-131	G	G
CAD-122	G	G	CAD-132	G	G	CAD-133	G	G
CAD-123	G	A	CAD-135	G	G	CAD-134	G	A
CAD-136	G	G	CAD-11	G	A	CAD-143	G	G
CAD-137	G	G	CAD-150	G	G	CAD-144	G	G
CAD-138	G	G	CAD-151	G	G	CAD-145	G	A
CAD-139	G	G	CAD-152	G	G	CAD-146	G	G
CAD-140	G	G	CAD-153	G	G	CAD-147	G	G
CAD-141	G	G	CAD-154	G	A	CAD-148	G	G
CAD-142	G	G	CAD-155	G	G	CAD-149	G	G

The angiographic images determined severe, mild and low atherosclerosis based on stenosis levels with ≥70% stenosis classifying as severe while 30-69% stenosis was mild and <30% stenosis or no plaque buildup indicated low severity. Chi-square analysis was conducted for SNP rs116843064 genotypes in both atherosclerosis patients and control groups using the online software SHEsis. The genotypes of a total of 50 samples of cardiac patients with severe atherosclerosis along with 50 healthy control subjects were utilized for calculation of p-values. Similarly, the genotypes of a total of 50 samples of cardiac patients with mild atherosclerosis along with 50 healthy control subjects were also utilized for calculation of P-values separately. p-values for the variant rs116843064 and its association with Atherosclerosis severity is shown in Table 2. Carriers of the E40K variant (A of rs116843064 of *ANGPTL4*) significantly showed a less likely chance of atherosclerosis severity than non-carriers (Pearson's p-value=0.045518).

Table 3: Association of variant (rs116843064) of N-terminal chain of *ANGPTL4* with Extent of Atherosclerosis in Cardiovascular Patients

Gene	rs116843064 Genotypes	Frequency (Cases)	Frequency (Controls)	95% CI	Fisher's p-value	Pearson's p-value
ANGPTL4 Mild Atherosclerosis	A	0.080	0.020	[0.919362~22.730947]	0.04555	0.04551
	G	0.920	0.980			
*ANGPTL*Severe Atherosclerosis	A	0.040	0.020	[0.364506~11.948753]	0.39974	0.39970
	G	0.960	0.980			

The lipid parameters of randomly selected male and female atherosclerotic cardiovascular patients and healthy controls are shown in Table 4 (Severe Atherosclerosis), 5 (Mild Atherosclerosis) and 6 (Healthy Controls Subjects). Mean of circulating triglyceride levels were 200.3 mg/dl in severe atherosclerotic patients, 160.7 mg/dl in patients with mild atherosclerosis. However, the mean of triglycerides in healthy control subjects was 148.9 mg/dl. The patients with severe atherosclerosis showed increased levels of VLDL in both severe and mild cases, mean of which was 41mg/dl and 36.7 mg/dl respectively, in comparison to healthy control subjects with mean value of 22.5 mg/dl. The decreased HDL level was also observed in both severe and mild patients (mean values; 40.2 mg/dl and 42.3 mg/dl respectively). While healthy control subjects showed HDL levels in normal range with mean value of 83.7 mg/dl.

Table 4: The Lipid Profiles of Randomly Selected Male and Female Cardiovascular Patients Having Severe Atherosclerosis

Sample Ids	Total Cholesterol (mg/dl)	Total Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (Cholesterol) (mg/dl)	Cholesterol/ HDL Cholesterol ratio	Age (years)
Normal	< 200*	< 150*	> 60*	< 100*	< 30*	3.5 to 5.0*	25 to 80*
CAD-03	194	236	31	121	42	6.26	35
CAD-10	212	182	33	104	44	6.45	47

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CAD-15	230	190	37	114	33	6.23	43
CAD-18	214	174	39	102	48	5.50	28
CAD-23	244	222	40	98	39	6.12	39
CAD-28	239	187	43	110	47	5.57	70
CAD-34	213	192	48	102	42	5.09	65
CAD-39	237	214	44	110	41	5.39	51
CAD-44	219	196	36	111	40	6.11	54
CAD-49	240	210	51	93	34	4.70	72
Mean	224.2	200.3	40.2	106.5	41	5.74	50.4

HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, VLDL: Very Low-Density Lipoprotein

Table 5: The Lipid Profiles of Randomly Selected Male and Female Cardiovascular Patients Having Mild Atherosclerosis

Sample Ids	Total Cholesterol (mg/dl)	Total Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (Cholesterol) (mg/dl)	Cholesterol/ HDL Cholesterol ratio	Age (years)
Normal	< 200*	< 150*	> 60*	< 100*	< 30*	3.5 to 5.0*	25 to 80*
CAD-01	209	158	41	107	40	5.11	60
CAD-02	129	169	51	45	31	2.53	53
CAD-05	218	159	38	112	35	5.75	42
CAD-07	215	155	40	109	39	5.39	39
CAD-08	195	170	39	117	48	5.01	35
CAD-09	239	164	49	102	19	4.88	51
CAD-14	220	157	41	114	44	5.37	69
CAD-17	237	168	42	103	32	5.65	47
CAD-30	219	152	40	114	38	5.47	54
CAD-46	210	155	42	108	41	5.00	62
Mean	209.1	160.7	42.3	103.1	36.7	5.016	51.2

HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, VLDL: Very Low-Density Lipoprotein

Table 6: The Lipid Profiles of Randomly Selected Male and Female Healthy Control Subjects

Sample Ids	Total Cholesterol (mg/dl)	Total Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (Cholesterol) (mg/dl)	Cholesterol/ HDL Cholesterol ratio	Age (years)
Normal	< 200*	< 150*	< 60*	< 100*	< 30*	3.5 to 5.0*	25 to 80*
CAD-04	116	125	44	51	21	2.64	44
CAD-13	88	106	49	20	19	1.8	53
CAD-19	170	105	55	87	18	3.09	66
CAD-22	183	174	47	102	22	3.89	29
CAD-25	162	124	52	86	22	3.12	48
CAD-27	169	91	42	110	16	4.02	59
CAD-38	129	169	51	45	31	2.53	71
CAD-47	181	154	401	110	31	4.5	41
CAD-45	131	141	44	77	19	2.98	55
CAD-50	160	98	52	61	26	3.07	47
Mean	148.9	128.7	83.7	74.9	22.5	3.164	51.2

HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, VLDL: Very Low-Density Lipoprotein

The circulating triglycerides and VLDL levels were significantly lower in mutated carriers (SNP rs116843064; G>A, E40K) as compared with noncarriers as shown in table 6. Meanwhile, significantly higher levels of HDL, the good cholesterol were observed in mutated carriers (SNP rs116843064; G>A, E40K) showing deviated values from the normal ones (Table 7).

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Table 7: Comparative Mean values of lipid profiles of atherosclerotic cardiovascular patients (Severe Atherosclerosis (n=10), Mild Atherosclerosis(n=8)and Healthy Control Subjects(n=10)

Atherosclerosis	Total Cholesterol (mg/dl)	Total Triglycerides (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (Cholesterol) (mg/dl)	Cholesterol/ HDL Cholesterol ratio
Severe Atherosclerosis (Mean Lipid Profiles)	224.2	200.3*	40.2	106.5	41	5.74
Mild Atherosclerosis (Mean Lipid Profiles)	209.1	160.7	42.3	103.1	36.7	5.01
Healthy Control Subjects (Mean Lipid Profiles)	148.9	128.7	83.7	74.9	22.5	3.16
Normal Values (Ranges)	< 200	< 150	> 60	< 100	< 30	3.5 to 5.0

HDL: High Density Lipoprotein, LDL: Low Density Lipoprotein, VLDL: Very Low-Density Lipoprotein

DISCUSSION

The primary outcomes of this research involve computing allele frequencies and validating a link between the E40K variation in the N-terminal segment of *ANGPTL4* and a reduced likelihood of severe atherosclerosis in individuals with cardiovascular conditions. This study found 9.33% of heterozygous genotype (GA) of variant (rs116843064; G>A) in cardiovascular patients and control subjects of this population (n=150) i.e., 2.67% heterozygous genotype (GA) in severe atherosclerosis patients, 5.33% in mild atherosclerosis patients and 1.33% in healthy control subjects.Furthermore, this research unveiled that individual who carried the E40K variant (SNP rs116843064; G>A) in the N-terminal segment of *ANGPTL4* exhibited a 30.3% reduction in triglyceride levels and a 19.1% decrease in very-low-density lipoprotein (VLDL) levels compared to those who did not carry the variant (E40K,SNP rs116843064; G). Additionally, carriers of the E40K variant demonstrated a 2.1% increase in high-density lipoprotein (HDL) cholesterol levels.In addition to serving as components for energy preservation, fatty acids (FA) and glucose are the primary fuel sources for satisfying the body's requirements for energy.Fatty acids are carried by triglycerides, which are produced by the liver or diet and are utilized to create triglyceride rich lipoproteins (TRL) [15]. The lipoprotein lipase (LPL) enzyme aids in the hydrolysis of the circulating TG. Cardiomyocytes and adipocytes produce LPL, and the endothelium-derived protein GPIGBPI helps it adhere to the capillary surface [16]. It has been already proven that increased LPL levels are due to truncating mutations that are very much linked with and a lower risk of cardiovascular disease and the lower triglyceride levels.On the contrary, mutations with decreased LPL levels become cause of increased triglycerides levels. In humans, at start *ANGPTL4* gene was known as fasting induced adipose factor (FIAF) and is situated on chromosome 19p13.3. *ANGPTL4* is helpful in controlling LPL production.The angiopoietin-like 4 proteins, which is produced by the gene *ANGPTL4*, inhibits endothelial-bound LPL activity that resultantly impact levels of serum triglycerides [17]. *ANGPTL4* is direct controller of LPL that further controls triglyceride levels. With the help of LPL, these triglycerides (TG) and very low-density lipoproteins (VLDL) are broken down into glycerol and fatty acids (FFAs) [18]. As per related data, *ANGPTL4* prevents the elimination of circulating triglycerides by limiting LPL function, being the inhibitor of LPL. This is how this gene exerts influence on the occurrence and progression of atherosclerosis [19]. In cardiovascular patients with cardiac diseases, E40K (SNP) alters *ANGPTL4's* capacity to inhibit lipoprotein lipase (LPL), which impacts triglyceride clearance.The single nucleotide polymorphism, E40K, alters *ANGPTL4's* ability to inhibit lipoprotein lipase (LPL). In cardiovascular patients, LPL then further influences the clearance process of triglyceride. *ANGPTL4's* N terminal segment has the mutation E40K that is possibly involves in occurrence of Atherosclerosis [20]. E40K mutations are associated with fluctuated levels of triglycerides and high-density lipoprotein (HDL) cholesterol, resulting in a decreased risk or severity of CAD [21]. As per the statistical data of research conducted, atherosclerotic patients have higher chances of carrying the E40K mutation as compared to the controls.Occurrence of A/G and G/G in sever atherosclerotic patients is 0.080 and 0.920, respectively. On the other hand, the ratio of prevalence in the normal subjects are 0.020 and 0.980 for alleles A/G and G/G. Allelic frequencies for mild atherosclerotic groups in A/G and G/G are 0.160 and 0.840, respectively. For control group it is 0.040 and 0.960 for A/G and G/G, respectively. It is like the findings of the study conducted for European population. E40K variation of the *ANGPTL4* gene is correspondent with suppressed levels of triglycerides, HDL cholesterol levels and VLDL as per preliminary studies [22]. According to data, people who carried the E40K variation were less likely

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than non-carriers to develop coronary artery disease (CAD).Thus, it is proved that chances of occurrence of severe atherosclerosis are limited in carriers of E40K mutation of N-terminal chain of *ANGPTL4*.

This study is limited by a relatively small sample size and single-center design, which may affect the generalizability of findings. The absence of homozygous mutant (AA) genotype and lack of longitudinal follow-up further restrict causal inference. Additionally, potential confounders such as diet, lifestyle, and other genetic factors were not extensively controlled. Future studies should include larger, multi-center cohorts with diverse populations, incorporate longitudinal designs, and explore gene–gene and gene–environment interactions to better understand the role of *ANGPTL4* variants in cardiovascular disease progression.

CONCLUSIONS

This study concluded that individuals with SNP rs116843064 of E40K variant of *ANGPTL4* gene owned favorable lipid profiles that lower the risks of atherosclerosis. Fourteen individuals were heterozygous carriers of the variant E40K in the N-terminal chain of the *ANGPTL4* gene, out of 100 cardiac patients.Therefore, these observations point to the role that carriers of the E40K variant (A of rs116843064 of *ANGPTL4*) showed a less likely chance of atherosclerosis severity significantly than non-carriers.Therefore, assessing genetic connections with atherosclerosis in *ANGPTL4* gene will be a useful tool for diagnosis, treatments and prevention CVDs.It also concluded the findings that non-carriers have higher triglyceride (TG) and VLDL levels but lower HDL levels compared to carriers.So, the heterozygous genotype of the *ANGPTL4* variant (SNP rs116843064;E40K) was observed in the Pakistani population, while the homozygous genotype (A/A) was absent.

Authors' Contribution

Conceptualization: AT
Methodology: KZ, AS, SA
Formal analysis: KZ, AS, SA, ZH, MSS, MKA
Writing and Drafting: KZ, ZH, MSS, MKA, IT
Review and Editing: KZ, ZH, MSS, MKA, IT

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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Systematic Review

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Effectiveness of Mindfulness-Based Cognitive Therapy on Quality of Life among Oral Cancer Patients Undergoing Chemotherapy and Radiotherapy

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ABSTRACT

Cancer is the second leading cause of death globally, with oral cancer representing a significant portion of head and neck cancers. It disproportionately affects developing nations, including Pakistan, where it is the second most common cancer. Oral cancer patients often endure treatment-related side effects, leading to reduced quality of life. Evidence suggests that mindfulness interventions, particularly mindfulness-based cognitive therapy, can improve quality of life by addressing psychological distress and promoting emotional resilience. **Objectives:** To assess the effectiveness of mindfulness-based cognitive therapy in improving the quality of life of oral cancer patients undergoing chemotherapy and radiotherapy. **Methods:** The literature review used various electronic databases: PubMed, Academia, Science Direct, Cumulative Index to Nursing and Allied Health Literature, and Google Scholar. The PRISMA flowchart approach documented the literature review process. We included 26 out of 294 studies that fulfilled inclusion criteria in the final review, which included the last five years, and researched the effects of mindfulness-based cognitive treatment on quality of life among oral cancer patients. Data were synthesized using quantitative methodologies to identify similar findings across studies. **Results:** Research indicates that mindfulness-based cognitive treatment significantly improves the quality of life for oral cancer patients receiving chemotherapy and radiotherapy. **Conclusions:** It was concluded that these findings provide baseline data for this study highlighting the significant impact of mindfulness-based cognitive therapy on improving the quality of life for patients with oral cancer receiving chemotherapy and radiotherapy.

INTRODUCTION

Cancer is the second foremost cause of death worldwide, responsible for almost one in every six deaths [1]. Every year, the world diagnoses approximately 18.1 million new cancer cases, leading to approximately 9.6 million deaths [2]. Research by Tufail and Wu highlights that cancer is the primary cause of mortality in a significant portion of the world, impacting 91 out of 172 nations [3]. Furthermore, projections by Wong estimate that by 2040, there will be 29.5 million new cancer cases and 16.3 million cancer-related deaths globally [4]. The sixth most frequent disease worldwide, oral cancer is rising rapidly in southern Asia. Annually, there are around 450,000 newly diagnosed cases of oral carcinoma globally. Furthermore, there has been a significant rise in the prevalence of oral cancer recently. Oral cancer is a major concern in public health worldwide [5]. Oral cancer is the most prevalent type of head and neck cancer, which accounts for 10% of all cancers. Smoking cigarettes, drinking alcohol, using tobacco products, and being infected with the human papillomavirus are all causes of oral cancer [6]. Approximately, 14,000 new instances of oral squamous cell carcinoma (OSCC) are reported each year in Pakistan with Karachi having one of the highest rates worldwide. The disease is in an advanced stage (III or IV) in almost fifty percent of these patients [7]. Pakistan ranks among the top ten tobacco consumers, with 46 percent of its

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population using gutka and paan (chewable betel nut products) daily. Nearly 56–80% of mouth cancer survivors suffer oral dysfunction with significant financial, social, and psychological effects on their quality of life [8]. The clinical course and management of oral cancer cause distress to patients. This condition and its management may result in the loss of bodily parts, scarring, alopecia, deformities, and weight variations, all of which can affect self-perception. Functional disability also affects swallowing, speaking, and social interactions. These side effects can significantly diminish patients' quality of life [9]. Mindfulness involves intentionally being present and nonjudgmentally addressing thoughts, feelings, and experiences. A decade of RCTs has tracked the effects of mindfulness-based therapies on anxiety, depression, psychological distress, and health-related quality of life among oral cancer patients [10].

Oral cancer patients undergoing chemotherapy and radiotherapy experience severe physical, psychological, and social burden, which significantly reduces their quality of life. Although mindfulness-based cognitive therapy (MBCT) has shown promising effects in reducing anxiety, depression, and stress in cancer populations, its evidence in oral cancer patients remains scattered across different studies with limited consolidated findings. Most available literature focuses on general cancer groups rather than specifically addressing oral cancer patients receiving active oncological treatment. Therefore, there is a need to systematically evaluate and synthesize existing evidence regarding the effectiveness of MBCT in improving quality of life in this population. The aim of this study is to assess the impact of MBCT on quality of life among oral cancer patients undergoing chemotherapy and radiotherapy through a systematic review of recent literature.

METHODS

Various search strategies were utilized for the literature review, drawing from multiple databases, including Academia, PubMed, Research Gate, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Google Scholar. Boolean operators (AND, OR, NOT) were applied on PubMed, along with a custom date range filter (2019-2024), yielding 26 articles. The most recent and relevant publications were selected from this pool, while those unrelated to the research topic were excluded. Similarly, peer-reviewed academic publications were searched and filtered for the same date range, and the results were 294 relevant articles. A comparable approach was employed for Research Gate and Google Scholar. Keywords such as mindfulness-based intervention, quality of life, oral cavity, head-and-neck, oral tumor, lip-and-mouth cancer, oropharyngeal cancers, chemotherapy, and radiotherapy were used to refine the search and identify pertinent studies. The initial search yielded 23,902 results. After applying the filter for duplicates, 15,804 were removed; further application removed 2,809 in five years. After studies screened eligibility in full-text 4,995, Filtering the citation and abstract reduced the results to 294. After reviewing the titles and abstracts, we excluded 268 and selected 26 for the final review, which is most relevant to our study. PRISMA chart was shown for this study (Figure 1).

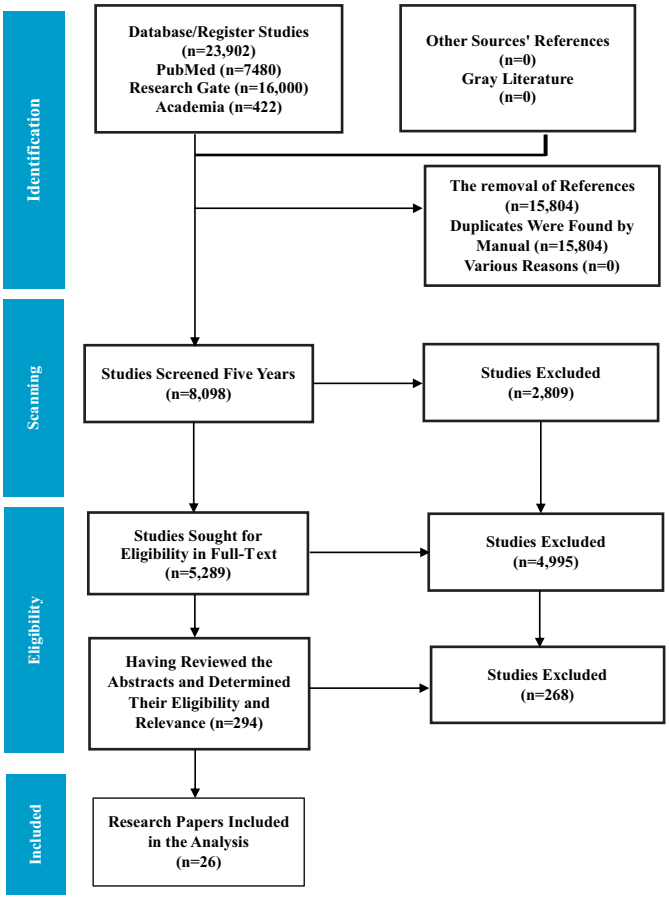

Figure 1: PRISMA flow chart for the study

RESULTS

From an initial search of 23,902 articles, 26 were selected for this study. Findings suggest that the effectiveness of Mindfulness-Based Cognitive Therapy (MBCT) on Quality of Life (QoL) among oral cancer patients undergoing chemotherapy and radiotherapy significantly impacts the QoL among oral cancer Patients. comprehensive information regarding the phases of the article search was presented (Table 1).

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Table 1: Maintain Information Articles

S.No	References	Country	Method	Sample Size	Objective	Result
1	[11]	Korea	Quasi-Experimental	61	The study looks at how a full mouth care program affects the oral health of people with head and neck cancer (HNC) who have been treated with radiation.	Dental specialists' complete oral care interventions enhanced HNC patients' oral health and QoL.
2	[12]	France	Cross-Sectional	72	The study assesses patient concerns about head and neck squamous cell carcinoma (HNSCC) treatment and long-term QOL.	HNSCC patients' quality of life improved when multidisciplinary teams identified patient requirements and managed persistent symptoms and psychosocial difficulties.
3	[13]	Singapore	Quasi-experimental	61	The study examined the initial impact of a program that teaches cancer survivors to practice mindfulness-based psychoeducation.	Cancer survivors considerably improved their abilities to relax, practice mindfulness, and feel psychologically well.
4	[14]	Germany	Retrospective Analysis	1,657	The study aimed to investigate oral mucositis impairments and how they affect post-treatment quality of life.	Standardizing early supportive management for oral mucositis promotes better post-therapy results and QoL for oral cancer patients.
5	[15]	United States	Randomized Controlled Trial	97	The main goal is to identify whether online or smartphone mindfulness therapies might reduce cancer patients' discomfort and improve QOL.	Well-powered efficacy studies could enlighten clinicians about implementing this scalable intervention to improve cancer patients' and carers' QOL.
6	[16]	Malaysia	Longitudinal Observational	76	This research aimed to determine the effect of oral cancer treatment on HRQOL in patients.	Oral cancer patients' HRQOL changes with surgery and various treatments.
7	[17]	United Kingdom	Prospective Clinical Cohort	5,511	The goal is to find out how people's HRQOL changes when they are told they have head and neck cancer.	Higher physical and social functioning had better survival.
8	[18]	Canada	Systematic Review	3053	To assess the correlation between mindfulness-based interventions (MBI) and the alleviation of anxiety severity in cancer patients.	Up to 6 months after the intervention, MBIs were linked to lower levels of anxiety and depression in people with cancer.
9	[19]	Iran	Quasi-Experimental	40	To examine how MBCT affected patients' cognitive function, illness adaptability, quality of life, and perceived stress levels throughout chemotherapy.	MBCT markedly enhanced perceived stress, sickness resilience, and QoL.
10	[20]	Saudi Arabia	Descriptive Cross-Sectional	148	The goal is to evaluate the mental and physical suffering, symptoms of depression, and social problems of patients with cancer undergoing radiotherapy.	There was a significant association ($P<0.05$) between the type of cancer patients had and their levels of physical suffering, distressing emotions, and depressive symptoms.

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11	[21]	Taiwan	Prospective Study	127	This study aimed to evaluate individuals' QoL and utility assessments following survival from HNC.	Survivors of cancer scored lower than average. Married patients had more utility than single patients.
12	[22]	Iran	Descriptive Analytical Cross-Sectional	205	The purpose of the research was to find out if stress, quality of life, and mindfulness were all related for cancer patients.	Cancer patients' QOL was affected by mindfulness and stress. Mindfulness may help cancer patients both directly and indirectly.
13	[23]	India	Prospective Longitudinal	130	This study aimed to identify the characteristics that influence the QoL of people with HNC.	HNC treatment and intervention should focus on survival and QoL during managed intervention and recovery.
14	[24]	Sri Lanka	Prospective Longitudinal	90	This study looked at the oral health-related quality of life (OHRQOL).	There were statistically remarkable changes in OHRQOL between the periods ($p<0.05$).
15	[25]	Pakistan	Analytical Cross-Sectional	250	To determine how various factors affect HNC patients' QoL.	Poor QoL is linked to psychological problems.
16	[26]	Pakistan	Cross-Sectional	79	This research aimed to assess OHRQoL.	Poor oral health after HNC treatment lowers QoL.
17	[27]	Netherlands	Randomized controlled Trial (RCT)	125	The purpose of this research was to forecast cancer patients' engagement with and success with the eMBCT program.	The study revealed that patient outcomes improved by adherence.
18	[28]	India	Prospective Study	150	The study assesses QoL to determine oral cancer patients' satisfaction with current treatment.	The results of this study show that oral cancer patients are happy with their existing treatment options.
19	[29]	Pakistan	cross-sectional	96	The study's goal is to examine the OHRQoL and the factors that are linked to it one year after cancer treatment.	The study found high mean OHRQoL scores in HNC.
20	[30]	Pakistan	cross-sectional	120	The study aimed to recognize the post-treatment problems met by OSCC clients.	Patients with tongue cancers highlighted significantly reduced scores for anxiety, mood,swallowing, and pain.

DISCUSSION

The study sought to evaluate the efficacy of MBCT in improving the QoL of oral cancer patients receiving chemotherapy and radiotherapy. The findings are consistent with prior studies and provide compelling evidence supporting the utility of MBCT as a non-pharmacological intervention for managing psychological issues and improving quality of life. The current study corroborates previous research highlighting the positive impact of MBCT on QoL. A systematic review demonstrating that mindfulness-based intervention significantly reduced depression anxiety in cancer patients. This result aligns with a study in Singapore and Canada that revealed the psychological benefits of MBCT and found that mindfulness-based psychoeducation improved relaxation and psychological well-being in cancer survivors [31, 32]. A notable similarity between this study and the research is the identification of improvements in cognitive function, illness adaptability, and stress reduction in cancer treatment [33]. Both studies also found a link between early supportive interventions and better quality of life after treatment, which is in line with this study's focus on using MBCT during active treatment phases [34]. Despite these similarities, studies that solely focused on physical health interventions showed some differences in outcomes. However, this study enhanced oral health-related quality of life due to dental care interventions for HNC patients. In contrast, the present study emphasizes the enhancement of psychological and emotional well-being through MBCT. Moreover, it underlines the importance of psychosocial therapies to

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counteract poor psychological outcomes in HNC patients. This study emphasizes the importance of MBCT [35]. This study highlights the need to incorporate MBCT into the care plans of oral cancer patients to address QoL challenges effectively. It also suggests the scalability of mindfulness-based interventions, as indicated by [36], can make them accessible to a broader population of cancer patients. Future research should explore the long-term effects of MBCT and its potential integration with other psychosocial and physical health interventions to provide a holistic care model.

The major limitation of the existing evidence is the predominance of quasi-experimental and cross-sectional designs, with relatively fewer large-scale randomized controlled trials specifically targeting oral cancer patients. Variations in MBCT protocols, intervention duration, and outcome measurement tools also limit comparability across studies. Additionally, most studies are short-term, with limited follow-up data to assess sustained effects on quality of life. Future research should focus on well-designed multicenter randomized controlled trials with standardized MBCT protocols and long-term follow-up. It is also recommended to explore integration of MBCT with other supportive care interventions to develop a more holistic, patient-centered approach for improving outcomes in oral cancer care.

CONCLUSIONS

It was concluded that the study underscores the significant role of mindfulness-based cognitive therapy (MBCT) in enhancing the quality of life for oral cancer patients undergoing chemotherapy and radiotherapy. This research validates prior evidence on the potential integration of care plans with a holistic approach to patient well-being. Future studies should investigate its long-term impacts and synergy with other interventions to optimize cancer care outcomes.

Authors' Contribution

Conceptualization: RK
Methodology: YA, B
Formal analysis: RK
Writing and Drafting: YA, B, AAJ
Review and Editing: YA, B, AAJ, RK

All authors approved the final manuscript and take responsibility for the integrity of the work.

Conflicts of Interest

All the authors declare no conflict of interest.

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