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Review Article

Multimodal Treatment Approaches to Chronic Diseases

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Abstract

The prevalence of chronic diseases, which is a worldwide public health problem, is increasing with prolonged life expectancy worldwide. Cardiovascular diseases (CVD), diabetes, respiratory system diseases, and cancers are among the most important chronic diseases. Chronic diseases, which affect individuals physically, psychologically, and sociologically, negatively affect daily self-care activities, treatment costs, length of hospital stay, and quality of life. Therefore, a multimodal approach is required to protect or regain the health of individuals with bio-psycho-socio-cultural and spiritual dimensions. A multimodal approach to chronic diseases deals with risk assessment, classification, diagnosis, pharmacological treatment, lifestyle changes, management of psychosocial factors, and surgical intervention with a multidisciplinary approach. It is known that this approach, which expresses patient-centered and holistic care, increases patient satisfaction, reduces health costs and inequalities, and improves the quality of care and health outcomes by addressing the biological, physiological, social, cultural, and spiritual needs of patients. In this review, the multimodal approach to CVD, diabetes, and chronic obstructive pulmonary disease is included in line with current guidelines.

Introduction

The World Health Organization (WHO) explains chronic diseases as a combination of long-term and slowly progressive genetic, physiological, environmental, and behavioral factors. Chronic diseases usually last longer than 1 year, require continuous follow-up, and negatively affect the activities of daily living. Cardiovascular diseases (CVD), diabetes, respiratory system diseases, and cancers are among the most important chronic diseases. Chronic diseases are responsible for 70% of all deaths worldwide. Most of the deaths are caused by chronic diseases.[1]

The prevalence of chronic diseases, which is a universal problem, is increasing with the prolonged life expectancy worldwide. According to the Centers for Disease Control and Prevention (CDC) 2020 report, 34.2 million people of all ages, 34.1 million of those aged ≥18 years, and approximately one-third of 88 million adult individuals have prediabetes.[2] Approximately 18.2 million (6.7%) of adults aged ≥20 years have coronary artery diseases.[3]

In 2017, 544.9 million people worldwide were reported to have a chronic respiratory disease. Chronic obstructive pulmonary disease (COPD) continues to be important among chronic respiratory diseases and affects more than half of men and almost half of women for chronic respiratory disease worldwide.[4]

Chronic diseases are increasing in the world and Turkey, and this causes a serious increase in health expenditures. According to the CDC, chronic diseases are responsible for approximately three-quarters of the total health expenditure in the US, which results in an estimated USD 5,300 per capita annual expenditure. It is estimated that the total cost of chronic diseases in the US will exceed USD 42 trillion by 2030, costing USD 8,600 per person.[5]

Although there are effective drug applications for the treatment of chronic diseases with developing technology, the management of chronic diseases should be organized within an integrated disease care system. This integrated system should include training on preventive interventions, exercise, lifestyle changes, communication with the patient and family, and adopting and maintaining healthy behavioral changes.[6] The multimodal approach to chronic diseases consists of a combination of two or more treatment modes from these applications. A multimodal and individual

Keywords: Chronic diseases; Disease management; Multimodal treatment; Holistic care; Holistic medicine.

Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; ESC, European Society of Cardiology; GOLD, The Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; RYGB, roux-en-y gastric bypass.

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approach should be preferred to increase treatment efficacy and achieve an optimal survival rate.[7] In this review, the multimodal approach of current guidelines for CVD, diabetes, and COPD is included.

Cardiovascular diseases

Risk assessment

Risk factors for atherosclerotic cardiovascular disease (ASCVD) include low-density lipoprotein (LDL-C), high blood pressure, smoking, diabetes, and adiposity. According to the European Society of Cardiology (ESC) 2016 prevention guidelines, it is recommended the systematic coronary risk evaluation algorithm should be used. In the guideline, it is that LDL-C levels are reduced as much as possible to prevent CVD, especially for patients in high and very high-risk groups.[8]

Pharmacological treatment

The prevalence of CVD, especially diseases, such as coronary heart disease, hypertension, stroke, and heart failure, is 65–70% in people aged 60–79 years, and 79–86% in people aged ≥80 years. Since CVD is common in older adults, cardiovascular drugs are frequently used. In the treatment of CVD, the estimated prevalence was 50.1% for 3-hydroxy-3-methyl-glutaryl coenzyme A reductase inhibitors (statins), 43.0% for antiplatelet agents, 30.4% for angiotensin-converting enzyme inhibitors, 29.5% for diuretics, 13.2% for angiotensin II receptor blockers, 12.4% for antihypertensive agents, 10.5% for calcium channel blockers, and 6.4% for vitamin K antagonists.[9]

The use of statins, fibrates, bile acid sequestrants, selective cholesterol absorption inhibitors (*e.g.*, ezetimibe), and proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are recommended in the treatment of dyslipidemia. Recently, low-dose colchicine [0.5 mg once a day (OD)] is recommended due to the inflammatory components in the atherosclerosis process. A combination of two drugs is more effective than monotherapy in the initial treatment of hypertension.[10]

The use of aspirin (CVD secondary prevention 75–100 mg daily) is recommended for the antithrombotic treatment of myocardial infarction, stroke, or lower extremity artery disease The use of proton pump inhibitors (*e.g.*, omeprazole or esomeprazole) is recommended to decrease the risk of gastrointestinal bleeding and increase safety in individuals that use antiplatelet medication.[10]

Surgical intervention

Coronary artery bypass surgery

Coronary artery bypass surgery is the most used surgical method in the treatment of coronary artery diseases. It is an effective method in patients with left main, triple, or double vessel coronary artery disease that involves the proximal left anterior descending artery.[11]

Carotid endarterectomy

Carotid endarterectomy is performed in patients with recent symptomatic cerebrovascular disease and patients with carotid stenosis rates of 70–99%. It is recommended in many guidelines.[11]

Valve replacement

Aortic valve replacement for aortic stenosis is the most common surgical procedure in patients with severe symptoms. In addition, mitral valve surgery or balloon valvuloplasty is performed for symptomatic, chronic mitral stenosis.[11]

Lifestyle changes

Elimination of modifiable risk factors, including unhealthy lifestyle, can prevent 80% of CVD cases. Targeted lifestyle changes include not smoking, physical exercise, healthy eating, and having a body mass index (BMI) <25. Barriers to lifestyle changes should be identified, and targeted and individually tailored approaches that increase self-efficacy and coping abilities should be used.[12]

It is recommended that all adults get ≥30 m of exercise 5 days a week. Alcohol intake, psychological stress, sleep, and social problems have been associated with cardiovascular risks. Work-related stress and acute stress associated with social isolation, being diagnosed with cancer, or receiving bad news, such as the loss of a loved one, can increase CVD risk.[13] Dietary lifestyle changes include a pattern of more plant and less animal food intake. The use of trans fats and unsaturated fatty acids should be limited, and processed foods should be avoided. The total daily salt intake should be reduced to <5 gms, and ≥30–45 g of fiber foods, 200 g of fruit (≥2–3 portions), and 200 g of vegetables (≥2–3 portions) should be consumed per day. Consumption of red meat should be limited, and especially, processed meat should be avoided. Alcohol consumption should be limited to a maximum of 100 g per week. With energy restriction, it is necessary to avoided weight gain.[10] Medication compliance should be ensured in elderly individuals, the underlying causes of non-compliance should be determined, and methods should be developed to predict non-compliance. Identifying effective methods and technologies to develop treatment adherence should be a priority.[9]

Management of psychosocial factors

Maintaining a life that is compatible with CVD varies according to individual characteristics. However, this can be affected by socioeconomic factors (*e.g.*, health literacy), stress response, and the patient's psychological state. Depression and anxiety accompanying the disease are seen in 20% of individuals with temporary or chronic CVD. Depression is a condition that reduces adaptation to illness, hinders behavioral changes, and the adoption of a healthy lifestyle. It interferes with the cardiac rehabilitation of patients and affects the quality of life, hospitalization, and risk of death. Therefore, it is necessary to determine this high-risk patient group in clinical practice. Conditions that affect individuals, such as depression, anxiety, anger, lack of social support, and chronic stress might increase the risk of CVD.[14] Individual and effective practices should be designed for psychosocial risk factors. For effective risk factor management, a treatment approach that includes physical, social, and psychological steps should be adopted. Therefore, efforts should be made for integrated care in cardiac rehabilitation. During cardiac rehabilitation, increasing the movement of individuals, eliminating risk factors, psychoeducation, and psychosocial

support should be handled by accounting for the individual characteristics of the patient.[14]

Diabetes

Risk assessment

Evaluation of risk factors for diabetes or screening with an assessment tool is recommended to prevent or delay diabetes. Testing high-risk patients for prediabetes would be beneficial because laboratory evaluation is cost-effective and provides a significant time to intervene before type 2 diabetes develops and its complications occur. Currently, there are no clinically validated screening programs accepted outside the clinical setting. However, islet autoantibody testing is recommended for relatives of people with type 1 diabetes for risk assessment in a clinical trial setting.[15]

Classification and diagnosis

Classification for diabetes (*e.g.*, type 1 and type 2 diabetes, specific types of diabetes (monogenic diabetes syndromes), and gestational diabetes) is important for determining treatment. Although difficulties might be seen in distinguishing the type of diabetes in all age groups initially, the diagnosis becomes more pronounced in people with β-cell deficiency. Diabetes diagnosis, according to plasma glucose criteria; fasting plasma glucose (ABG) value is determined according to the 2-hour plasma glucose (2-hour PG) value or A1C criteria during the 75 g oral glucose tolerance test. The same tests are used to screen for diabetes and identify individuals with prediabetes. In patients with classical symptoms, plasma glucose measurement is sufficient for the diagnosis of diabetes.[16]

Pharmacological treatment

Insulin therapy is essential for patients, who have no β-cell function and type 1 diabetes. Rapid and long-acting insulin analogs with different pharmacokinetics have been produced. In these patients, the use of short-acting insulin before meals is recommended, and the combined use of a longer-acting drug at night is recommended.[17] It is important to explain and teach the insulin injection technique to patients and caregivers for the regulation of blood glucose and to optimize the safety of insulin use. Therefore, it is important to deliver insulin to the appropriate tissue correctly.[18]

Injectable and oral glucose-lowering drugs are used in addition to insulin treatment of type 1 diabetes in noninsulin treatments. Pramlintide is a β-cell peptide that is approved for use in adults with type 1 diabetes. In adults with type 1 diabetes, the addition of metformin, sodium-glucose cotransporter 2 (SGLT2) inhibitor, glucagon-like peptide 1 (GLP-1) receptor agonist (RA) liraglutide, or exenatide is recommended.[17]

The American Diabetes Association and European Association for Diabetes Research consensus report, and 2019 update recommend a patient-centered approach to select the appropriate pharmacological treatment of blood glucose.[19] If there is no contraindication at the time of diagnosis of type 2 diabetes, metformin should be started. For many patients, monotherapy with lifestyle changes is sufficient. Metformin is an effective, safe, inexpensive drug that can decrease the risk of CVD. Type 2 diabetes creates a progressive condition in most patients. Therefore, maintenance of glycemic targets with monotherapy is possible for several years, and then combination therapy is required. When the A1C glycemic index is above ≥1.5% (12.5 mmoL/moL), a dual combination will be required. Insulin should be considered as part of any combination therapy if hyperglycemia is severe and weight loss, high triglyceride level, and ketosis are present. Insulin therapy should be initiated in patients with polyuria, polydipsia, weight loss, blood glucose level ≥300 mg/dL (16.7 mmol/L) or A1C >10% (86 mmoL/moL).[17]

Surgical intervention

Type 1 diabetes surgical treatment

Pancreas and islet transplantation

Pancreatic and islet transplantation involved in the surgical treatment of type 1 diabetes can normalize glucose levels and reduce microvascular complications. Patients undergoing this type of surgery are treated with lifelong immunosuppression to prevent graft rejection, autoimmune islet destruction, or both. Because of non-compliance with immunosuppressive treatment, serious consequences, such as treatment failure, rejection, graft loss, and even death might occur.[20]

Surgical treatment of type 2 diabetes

Roux-en-Y gastric bypass and sleeve gastrectomy

Patients with type 2 diabetes account for >95% of bariatric procedures in the US. Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy support an effective and permanent cure for type 2 diabetes. RYGB significantly improves glycemic control and provides remission of type 2 diabetes.[21,22]

Lifestyle changes

Diabetes prevention efforts are effective in promoting lifestyle and behavioral change programs and in reducing the incidence of type 2 diabetes in many countries. Therefore, the UK launched the Diabetes Prevention Program (NHS-DPP) in 2016 as a behavioral intervention in prediabetic adults with high blood sugar levels, to slow or stop the development of type 2 diabetes.[23]

Moderate-intensity physical activity is highly recommended for children and young adults, because it improves insulin sensitivity and reduces belly fat in patients with prediabetes. Patients should be referred to a lifestyle and behavioral change program to increase moderate-intensity physical activity *(i.e.*, brisk walking) to ≥150 m/week and to achieve and maintain 7% weight loss. Dietary counseling for weight loss should be given to patients who are overweight or obese and at a high risk of developing type 2 diabetes. It is necessary to reduce the total amount of dietary fat and calories to prevent diabetes. Mediterranean-style and low-carbohydrate diet plans should be recommended.[15] Therefore, all individuals identified that are at risk of type 2 diabetes should be encouraged to participate in a DPP-style program that focuses on physical activity.[15]

Management of psychosocial factors

Individuals with type 1 and type 2 diabetes are faced with environmental, social, behavioral, and emotional psychosocial prob-

lems. Patient-centered care is essential to achieve optimal medical and psychological well-being in these patients. Personalized patient-centered psychosocial care involves the patient and their family in the treatment, monitoring the patient's self-management behaviors, and evaluating living conditions that might affect the physical and psychological health outcomes. People with diabetes should be followed-up and evaluated annually until their diabetes self-care skills develop and they become competent in the use of technological devices. The impact of diabetes complications and associated chronic pain on the quality of life should be routinely monitored. Early diagnosis and treatment of clinical conditions, such as depression, anxiety disorder, and eating disorders that might occur in young and adult patients should be applied, and the negative effects of these problems in diabetes management should be minimized.[24]

Chronic respiratory diseases

Risk assessment

A multidimensional risk assessment is recommended in diseases, such as disease COPD. COPD should be considered, and the diagnosis should be confirmed by spirometry in those with shortness of breath, chronic cough, or secretion, and a history of exposure to COPD risk factors (*e.g.*, occupational organic-inorganic dust, smoke, tobacco smoke, chemicals, and biomass fuel fumes).[25,26]

Classification and diagnosis

Spirometric evaluation is measured by grading of airflow limitation according to FEV1 after a bronchodilator. Other tools frequently used in classification are the modified Medical Research Council (mMRC), and COPD assessment test. Other diagnostic methods are alpha-1 antitrypsin deficiency, chest X-ray, exercise testing, and assessment of physical activity, oximetry and arterial blood gas measurement, lung volumes and diffusing capacity, and biomarkers (*e.g.*, C-reactive protein, and procalcitonin).[26]

Pharmacological treatment

The management strategy for stable COPD relies on the assessment of symptoms and risk of future exacerbations. Short-acting bronchodilators should be started in all patients for immediate relief of symptoms.[26]

A short-or long-acting bronchodilator therapy is recommended for all Group A patients, depending on its effect on dyspnea. If the patient benefits, it should be continued. A long-acting bronchodilator should be included in the initial treatment of Group B patients. Initial therapy with two bronchodilators should be used in patients with severe dyspnea. A single long-acting bronchodilator should be included in the initial treatment of Group C patients. In patients in this group for COPD, it is recommended to start treatment with a long-acting muscarinic antagonist (LAMA) since it is superior to long-acting beta-agonists (LABA) for the prevention of exacerbations. In Group D patients, treatment should be initiated with a LAMA, because it has effects on dyspnea and exacerbations. LAMA/LABA should be chosen as initial therapy, particularly for patients with severe symptoms due to greater dyspnea, exercise limitations, or both. In pharmacological treatment, beta-2-agonists, methylxanthines, combination bronchodilator therapy, anti-inflammatory agents, inhaled corticosteroids (ICS), ICS in combination with long-acting bronchodilator therapy, blood eosinophil count, triple therapy (LABA/LAMA/ICS), oral glucocorticoids, phosphodiesterase-4 (PDE4) inhibitors, antioxidant agents, mucolytic agents, and antibiotics are used. Other pharmacological treatments are antitussives, vasodilators, and Alpha-1 antitrypsin augmentation therapy. In addition, the influenza vaccine is recommended for all patients with COPD, and PCV13 and PPSV23 pneumococcal vaccines are recommended for all patients >65 years of age.[26]

Lifestyle changes

According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) 202 guidelines, it is recommended that individuals diagnosed with COPD be first given counseling and pulmonary rehabilitation.[26] The pulmonary rehabilitation program is effective in improving patients' symptoms, reducing hospital readmissions, anxiety, and depression levels, and increasing activity levels. Evaluation of smoking history and initiation of a cessation program should be part of the treatment plan for all COPD patients. Strengthening adherence to medication, appropriate inhaler technique, encouraging physical activity, and referral to pulmonary rehabilitation should be the most important parts of this counseling program. Recommended treatments for smoking cessation include nicotine replacement therapy with agents, such as an inhaler, nasal spray, sublingual tablets, lozenges, nicotine gum, and transdermal patches. Teaching COPD patients breathing cough exercises and pursed lip breathing to increase respiratory muscle strength and reduce air trapping in the lungs reduces the feeling of dyspnea. Pursed lip breathing, which reduces increased air trapping, is a practical and simple technique that can be taught quickly and can make a significant difference for patients.[27] In addition, in the GOLD guidelines 2021 update, it is recommended that patients with COPD have all specified vaccines (*e.g.*, pneumococcal pneumonia, influenza, Tdap (Tetanus, Diphtheria, Pertussis), and Zoster), because this will help to reduce exacerbations and other adverse outcomes.[26]

Management of psychosocial factors

Coping with a progressive disease, such as COPD, can lead to high levels of anxiety, depression, or both. It has been reported that disease severity in patients with COPD is associated with psychosocial states, such as low quality of life, living alone, female gender, smoking, low socioeconomic status, and high levels of anxiety and depression. Psychological problems can have negative consequences on treatment outcomes because psychological problems negatively affect the functional status, dyspnea, risk of exacerbation, quality of life, treatment adherence, and even survival. Therefore, it is necessary to improve the emotional state of the patient and intervene in their self-management. Cognitive-behavioral therapy or psychological interventions are recommended when psychological difficulties might hinder disease self-management, compliance with pulmonary rehabilitation, and outcomes.[28,29]

The multimodal treatment approach integration

Historically, health education and practice have tried to reduce problems with organs and biochemical levels. Traditional treatment approaches are based on diagnosis and treatment methods that depend on the patient's current complaint, on the underlying etiology, or pathology, or both. Such an approach has failed to yield optimal results, because it ignores the interaction between individuals' intrinsic factors, such as neural, endocrine, and im-

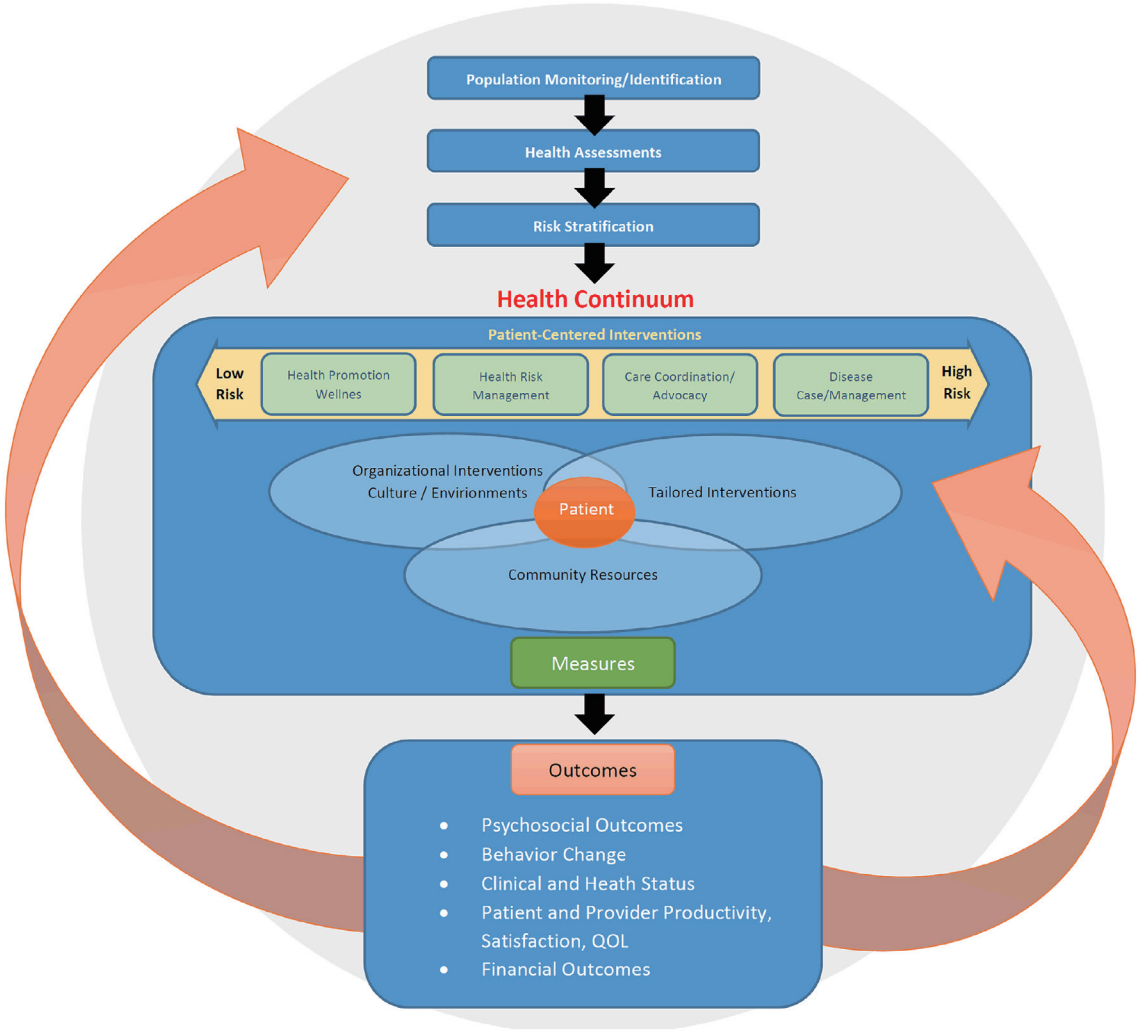

Fig. 1. Population health conceptual framework refers to the general components and stakeholders of population health-related to chronic diseases. This aims to keep the population healthy by responding to the individual needs of patients for the prevention and treatment of chronic diseases. The core of the model includes patient-centered interventions and continuity of care.

munity, and external factors, such as environmental, chemical, nutrition, and infection. The traditional approach, which does not rely on the interaction between disease components, has failed to reveal important etiological principles, disease stages, and disease mechanisms by focusing on a single component. The evidence-based multimodal approach reveals a potential difference with the aims of healthy living, health promotion, and disease prevention. Multimodal health approaches focus on identifying individuals at risk, lifestyle changes, behavioral change, and stress reduction that use a range of holistic and systematic medical approaches.[30] As a result of the increasing elderly population, chronic diseases and technological innovations, the demands for health services are increasing for multimodal care. Providing high quality, evidence-based, and low-cost care is becoming an important imperative for many healthcare systems. Therefore, the health requirements of the chronically ill and the elderly should be managed with a holistic paradigm beyond medical care.[31] The integration of the multimodal approach based on the holistic paradigm includes known biological, psychological, social, and environmental factors. The holistic paradigm is possible with the creation and integration of a new health system that is comprehensive, systematic, and multidimensional. Integration covers three processes for health protection, diagnosis, treatment, and prevention of diseases.[32]

The WHO recommends integrated health system practices for the management of chronic diseases. Integrated care programs aim to design an integrated care model that treats patients with minimal complexity, safely, promptly, efficiently and as close to home as possible The Integrated Care Program for the Prevention and Management of Chronic Diseases (ICPCD) focuses on a range of chronic diseases that affect a large number of healthcare users.[33] In the use of the integration model in practice approaches, such as Population Health Management for Chronic Diseases, which aim to identify risk groups, integrate services between disease prevention, social care and welfare, have been developed. This aims to keep the population healthy by responding to the individual needs of patients for the prevention and treatment of their chronic diseases. It is based on six goals to improve the quality of care and the health of the population and to reduce the cost per person. These are: patient population identification, health assessment, risk stratification, engagement, patient-centered interventions, and impact evaluation (Fig. 1).[31]

The main factor needed to reflect the integration into clinical practices is multidisciplinary teams. A team is a diverse group of healthcare professionals, each with their field of competence, with common goals in providing healthcare. All professionals aim to address the patient with a holistic approach using up-to-date scientific approaches. Team members should take a comprehensive view of the individual, focus on symptoms, physical, and mental health rather than illness, and organize care by working in an organized patient-centered care perspective that follows the work of doctors and nurses.[34]

Future directions

There are three main reasons for the necessity of using multimodal care systems for future applications. First, the number of individuals with ≥1 risk factors and a diagnosis of chronic disease in society is gradually increasing. It makes sense to provide health care services to these patients within the framework of an integrated system. Second, the care demands and management of many chronic diseases from healthcare systems and healthcare professionals are similar, regardless of etiology. Third, most chronic diseases have common primary and secondary risk factors. Therefore, it is essential to consider the individual for social, physical, and spiritual aspects with a multimodal health care system in the management of chronic diseases. The most important question for future applications is how the multimodal health care system can be implemented and how change occurs in health system applications. The most basic practice for the inclusion of integrated programs in the health system and the change in national or international policies should be the use of evidence-based practices. Placing the patient at the center of this new paradigm will require a challenging and complex process of change, and the system-wide implications could be enormous.[35]

Although the demands for multimodal care and the management of chronic diseases are well defined, the main obstacle is how to provide care cost-effectively. The results of studies on the cost-effectiveness of chronic diseases within integrated systems are beginning to emerge; however, there are still deficiencies in the cost assessment of comorbid conditions. Future research should include cost-effectiveness and health outcomes data. Health outcomes of integration practices should be collected pragmatically, and these outcomes should be measured in a meaningful way for integrated care programs.[36] Research that examines the future economic and health outcomes of integrated care programs could provide long-term information about the target population with chronic diseases in primary and secondary care settings.[36] For future applications, full longitudinal economic evaluations should be planned and conducted simultaneously, with the implementation of multimodal care programs. However, it is imperative to attach importance to the infrastructure of the existing health system for the adoption of cost-effective integrated care programs and the delivery of appropriate services with the available information technologies.[36]

Conclusions

Chronic diseases that affect individuals physically, psychologically, and sociologically negatively affect daily self-care activities, treatment costs, length of hospital stay, and quality of life. With the multimodal approach, a deep understanding of the human being as a bio-psycho-social being and their care needs is provided. The multimodal approach increases patients' satisfaction with health services and enables them to accept and take on their responsibilities. This approach, which expresses individual and holistic care, re-establishes the balance by addressing the physical, emotional, social, and spiritual needs of the patients and increases their quality of life by enabling them to cope with their diseases. A comprehensive understanding of the multimodal approach could facilitate professional autonomy, and enable patients to address their needs more systematically and scientifically. This holistic paradigm, which is found in the health systems of many cultures, should be at the core of medicine and nursing care.[37]

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Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Study concept and design (GM, YS), acquisition of data (GM), analysis and interpretation of data (GM, YS), drafting of the manuscript (GM), critical revision of the manuscript for important intellectual content (GM, YS), administrative, technical, or material support (GM, YS), and study supervision (GM, YS). All authors have made a significant contribution to this study and have approved the final manuscript.

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