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Editorial Board Member of *World Journal of Diabetes*, Athanasia Papazafiropoulou, MD, MSc, PhD, Attending Doctor, Research Scientist, 1st Department of Internal Medicine and Diabetes Center, Tzaneio General Hospital of Piraeus, Piraeus 18536, Greece

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EDITORIAL

Cystic fibrosis-related diabetes: The unmet need

Leonardo Pozo, Fatimah Bello, Yamely Mendez, Salim Surani

ORCID number: Leonardo Pozo (0000-0002-6352-1423); Fatimah Bello (0000-0002-5841-6987); Yamely Mendez (0000-0002-0863-6236); Salim Surani (0000-0001-7105-4266).

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Leonardo Pozo, Fatimah Bello, Internal Medicine, University of Texas Rio Grande Valley, Edinburg, TX 78539, United States

Yamely Mendez, Research Department, Baylor College of Medicine, Houston, Texas. 77030, United States

Salim Surani, Medical Critical Care Services, Corpus Christi Medical Center, Corpus Christi, TX 78404, United States

Corresponding author: Salim Surani, BSc, FACC, FACP, FCCP, MD, Professor, Medical Critical Care Services, Corpus Christi Medical Center, 701 Ayers street, Corpus Christi, TX 78413, United States. srsurani@hotmail.com

Abstract

Cystic fibrosis (CF) is a common autosomal recessive disease. Life expectancy of patients with CF continues to improve mainly driven by the evolving therapies for CF-related organ dysfunction. The prevalence of CF-related diabetes (CFRD) increases exponentially as patients' age. Clinical care guidelines for CFRD from 2010, recommend insulin as the mainstay of treatment. Many patients with CFRD may not require exogenous insulin due to the heterogeneity of this clinical entity. Maintenance of euglycemia by enhancing endogenous insulin production, secretion and degradation with novel pharmacological therapies like glucagon-like peptide-1 agonist is an option that remains to be fully explored. As such, the scope of this article will focus on our perspective of glucagon-like peptide-1 receptor agonist in the context of CFRD. Other potential options such as sodium-glucose cotransporter-2 and dipeptidyl peptidase 4 inhibitors and their impact on this patient population is limited and further studies are required.

Key words: Cystic fibrosis; Cystic fibrosis-related diabetes; Cystic fibrosis transmembrane conductance regulator; Gastric inhibitory polypeptide; Glucagon-like peptide 1; Glucagon-like peptide-1 receptor agonist; Dipeptidyl peptidase 4 inhibitors

Core tip: Cystic fibrosis-related diabetes is a heterogeneous entity. Currently, insulin is the agent of choice to maintain euglycemia on this patient population. Novel therapies like glucagon-like peptide-1 agonist offer an opportunity to reevaluate the way we approach this disease.

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INTRODUCTION

Cystic fibrosis (CF) is a common autosomal recessive disease that has been described to affect Caucasians and, to a lesser extent, other populations, affecting up to 1 person per every 3000 live births[1] in the United States. Its pathogenesis is secondary to a defect in the CF transmembrane conductance regulator (*CFTR*) gene that encodes for a homonymous membrane protein that conducts chloride ions across epithelial cell membranes, resulting in dysregulation of the normal pH and ionic balance of physiologic secretions and subsequent multiorgan dysfunction[2].

Despite discrepancies in the median age at death between different patient populations[3], the life expectancy of patients with CF continues to improve mainly driven by the evolving therapies for CF-related organ dysfunction. However, new challenges in the form of chronic-degenerative diseases arise from this increased life expectancy. The prevalence of CF-related diabetes (CFRD) increases exponentially when patients reach adulthood[4,5].

PATHOPHYSIOLOGY OF CYSTIC FIBROSIS-RELATED DIABETES

CFRD is a unique disease that combines features of patients with type 1 and type 2 diabetes mellitus (T1DM and T2DM) such as impaired insulin secretion and peripheral insulin resistance[6]. Due to the heterogeneity of CF, it is difficult to predict which patients will go on to develop CFRD. Some mutations, however, have a higher prevalence and predisposition to develop the disease and are associated with pancreatic exocrine dysfunction[7].

CFTR plays a dual role in insulin/glucagon hemostasis. Abnormal intracellular accumulation of chloride in β cells impairs their ability to depolarize in response to glucose, diminishing insulin release. In α cells, normal glucagon suppression is impaired by the inability of the cells to hyperpolarize in presence of high intracellular chloride, resulting in uncontrolled secretion of glucagon by potentiating adenosine triphosphate-sensitive K+ channels[8-10] (Figure 1).

Exocrine pancreatic insufficiency is an independent factor that must be accounted for. The low bicarbonate to chloride transport ratio, which reduces secretory volume, creates a protein gradient at the lumen, resulting in obstruction and interstitial edema[11]. Evidence suggests that, overtime, the resulting histopathological changes correlate with progression of the disease, damaging islet cells. Furthermore, CFRD patients have low levels of gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), which contributes to postprandial glycemic excursions and lower secretion of insulin[12,13].

Insulin resistance is associated with the fluctuant systemic inflammatory process associated with the counterregulatory response of growth hormone, cortisol and catecholamines that are released as a response to frequent pulmonary exacerbations and their treatment with steroids that these patients are typically exposed to.

THE ROLE OF INCRETINS AND GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONIST

The most recent version of the clinical care guidelines for CFRD from 2010 recommend insulin as the mainstay of treatment[14]. With the advent of GLP-1 receptor agonists (GLP-1 RA) this could change in the future for certain subtypes of the disease in which β cell structure remains preserved, but function is impaired, similar to patients with T2DM[15].

GLP-1 RA ameliorate the pathophysiology that has been previously explained (see above) by improving insulin release and slowing gastric emptying, improving glycemia[16]. Interestingly, these effects have been reproduced in the past, when GLP-1 RA were not available in the market by using pancreatic enzymes as a replacement of

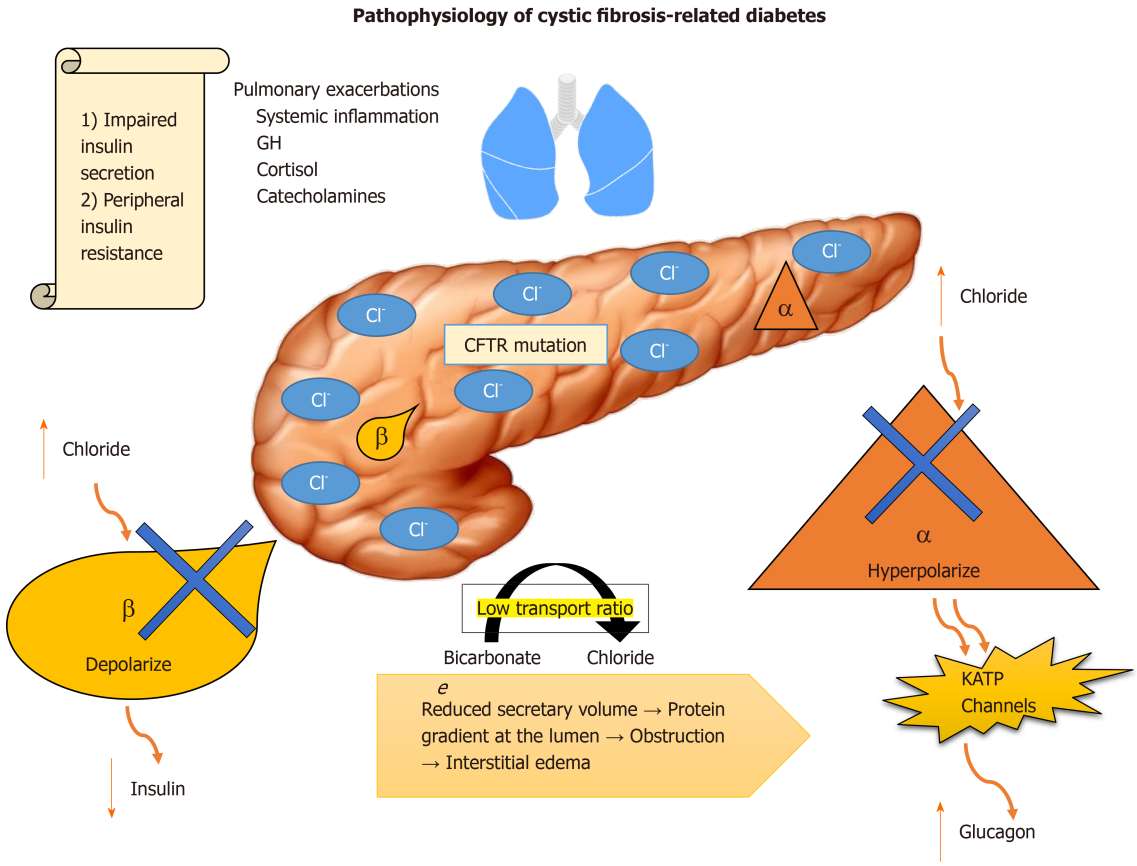

Figure 1 Pathophysiology of cystic fibrosis-related diabetes.

the exocrine function of the pancreas[17]. However, approximately 20% of the patients had refractory disease due to the diminishing bicarbonate levels secreted by the pancreas to the intestine, delaying and impairing the effectiveness of fat absorption while worsening prandial glycemic excursions as a result[18].

Currently, very few studies have been published and even less are underway to address the use of GLP-1 RA, dipeptidyl peptidase 4 inhibitors or sodium-glucose cotransporter-2 inhibitors based therapies in the treatment of CFRD. One of the limitations when designing these studies is the target population. As demonstrated by Geyer *et al*[19], exenatide demonstrated to be an effective treatment option for patients with early-onset CFRD. However, it is important to note this study was done in the pediatric population, which is arguably less affected by CFRD. Another point to consider is how heterogeneous the patient population can be due to differences in mutations and residual function of the CFTR protein in individuals that would be treated with this novel therapy.

One of the issues with GLP-1 RA in this patient population is weight loss, which is not desirable in this context. Classically, diabetic patients must limit their carbohydrate and caloric intake to limit glycemic excursions[5]. This conflicts with the current recommendations that seek to maintain a good nutritional status with high fat diets, frequent snacking and weight gain, which is associated with good prognosis[20], although this is a more important marker for early stages of the disease, which might not be applicable to CFRD since these patients usually present when they are older than 18 years of age.

With the advent of newer, novel CFTR modulating therapies such as Lumacaftor/Ivacaftor, attempts have been made to determine if these novel treatments have an impact in CFRD and related conditions[21-23] despite lack of a direct mechanism of action since β cells do not express CFTR[24]. It has been proposed that increased levels of GLP-1 and GIP with preservation of exocrine and endocrine pancreatic functions are the main drivers of these positive effects. Large randomized controlled trials are needed to verify and validate these findings[25], which also go in favor towards a broader utilization of novel therapies for CFRD.

CONCLUSION

Many patients with CFRD may not require exogenous insulin despite this being the approved therapy for all forms of CFRD despite the heterogeneity of CF as a clinical entity. Maintenance of euglycemia by enhancing endogenous insulin production, secretion and degradation *via* improved incretin (GLP-1 and GIP) stabilization and/or exogenous administration might play a central role that is currently not fully exploited.

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MINIREVIEWS

Telerehabilitation intervention for type 2 diabetes

Neslihan Duruturk

ORCID number: Neslihan Duruturk (0000-0003-4374-3130).

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Neslihan Duruturk, Department of Physiotherapy and Rehabilitation, Baskent University, Faculty of Health Sciences, Ankara 06790, Turkey

Corresponding author: Neslihan Duruturk, PhD, Associate Professor, Physiotherapist, Department of Physiotherapy and Rehabilitation, Baskent University, Faculty of Health Sciences, Ankara 06810, Turkey. nalkan@baskent.edu.tr

Abstract

Diabetes has become an increasingly important health problem worldwide due to its prevalence. Although effective treatments for diabetes management have been developed, many patients have difficulty in achieving their therapeutic goals. Regular exercise training is suggested to prevent or delay the symptoms and complications of type 2 diabetes along with other medical treatments. It has become necessary to develop new rehabilitation models and practices in order to cope with the changing needs of the population. Treatment models using technology can be effective in disease management. Telerehabilitation may be effective as part of the rehabilitation program in the home environment, especially for patients who are unable to participate in conventional center-based rehabilitation due to transport difficulties or work resumption. Telerehabilitation is defined as the delivery of rehabilitation services *via* telecommunication technology, including phone, internet, and videoconference communications between the patient and health care provider. It is possible that telerehabilitation may benefit people with type 2 diabetes in similar ways with telemonitoring and interactive health communication systems. Although the applicability of telehealth methods has been proven in previous studies, telerehabi-litation studies in type 2 diabetes are inadequate in the literature. With larger, multi-centered randomized controlled studies, established clinical guidelines can be developed that will ultimately improve patient outcomes.

Key words: Type 2 diabetes; Telerehabilitation; Exercise; Telehealth; Healthcare; Telecommunication

Core tip: Diabetes is a global burden that can have fatal consequences for human health and has a significant impact on healthcare system costs. Although effective treatments for type 2 diabetes have been developed, many patients have difficulty in achieving their therapeutic goals. Most of these problems are due to difficulties in patients reaching the relevant centers or the lack of care models. Telerehabilitation may be effective as part of the rehabilitation program in the home environment, especially for patients who are unable to participate in conventional center-based rehabilitation due to transport

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INTRODUCTION

Diabetes is a global burden, and can have fatal consequences on human health and a significant impact on healthcare system economics. Due to its high prevalence, diabetes has become a significant health problem worldwide. Diabetes is a metabolic disease that can cause severe complications and mortality if not treated effectively and quickly[1].

Diabetes is a complex disease in which self-management, training, regular monitoring, and multiple drug use are required to obtain an appropriate treatment outcome. Although an effective treatment for type 2 diabetes has been developed, many patients have difficulty in achieving their therapeutic goals. Most of these problems are due to challenges in patients reaching the relevant centers or the lack of care models[1].

Therefore, it has become necessary to develop new rehabilitation models and practices to cope with the changing needs of the population due to aging and lack of resources for public health. In addition to hospital rehabilitation practices in the acute phase of the disease, another challenge that has emerged in the modern healthcare system is the maintenance of health care outside the hospital, especially in type 2 diabetes[2]. Health care for diabetic patients includes innovative management strategies to improve disease control. Treatment models using technology can be effective in disease management[3].

Diabetes-related symptoms, co-morbidities, and complications may impair quality of life, affect mortality and lead to psychosocial problems. Consequently, these factors influence the exercise and physical capacity of patients. Patients show lower physical activity and reduced cardiorespiratory fitness than healthy individuals. Exercise therapy is thus essential for the management of type 2 diabetes[4]. Regular exercise training along with dietary approaches and pharmacological treatment is recommended to prevent or delay the symptoms and complications of diabetes[5]. Rehabilitation programs are safe and effective, with benefits including enhanced quality of life, increased functional exercise capacity, reduced hospital readmissions, and reduced mortality rate. Exercise programs performed generally consist of supervised and center-based programs[6].

Systematic reviews that have included exercise training in type 2 diabetes defined statistically and clinically significant improvements in blood glucose, HbA1c (8%-9%), lipid profile, and peak oxygen uptake (12%)[7,8]. Furthermore, exercise capacity has been observed to be a strong predictor of all-cause mortality in type 2 diabetes[9]. Exercise-based rehabilitation in a hospital or rehabilitation center results in the best outcome as evidenced by scientific studies. Based on these obvious evidence-based benefits, rehabilitation is recommended by several associations[10].

Despite the various benefits of rehabilitation, attendance at such programs is low. The regularity of rehabilitation programs is the leading problem with high drop-out levels. There are several factors for suboptimal participation which include lack of time, availability, accessibility of a program, psychological barriers, and obligations at home or work. Therefore, new models are needed to increase participation rates, and long-term adherence to recommendations, as well as support new lifestyle change[11].

Telerehabilitation may be effective as a part of the rehabilitation program in the home environment, especially for patients unable to participate in conventional center-based rehabilitation due to transport difficulties or work resumption. The factors associated with suboptimal participation in rehabilitation at home are less prevalent. In telerehabilitation, patients are not limited to the hospital or rehabilitation center environment, hence they are able to perform the exercise program during their daily routine at home[12].

CO-MORBIDITIES AND COMPLICATIONS OF TYPE 2 DIABETES

Type 2 diabetes is a leading cause of severe morbidities and disabilities. Due to the presence of comorbidities and chronic conditions in addition to type 2 diabetes; diabetes-related healthcare, treatment options, care needs, and associated costs are complicated. In order to provide effective diabetes care, the increased burden of complex comorbidity, can affect treatment quality. Previous studies examining chronic conditions in patients with type 2 diabetes have found an association between an increasing number of comorbidities, increased rates of healthcare use and impaired physical function. It is also stated that patients with type 2 diabetes have more chronic diseases than the non-diabetic population[13]. The development of specific treatments for patients with complex comorbid disease has also gained importance in disease care. Clinical guidelines have recently significantly changed diabetes care with more evidence to provide effective treatment and reduce treatment variation. However, it remains unclear how to successfully define the main goals of interventions in complex comorbid patients.

People with type 2 diabetes have a higher risk of cardiovascular complications, end-stage kidney disease and hypertension due to risk factors such as obesity, endothelial dysfunction, vascular inflammation and dyslipidemia. However, individuals with type 2 diabetes have also been shown to have a higher risk of depression, thyroid gland diseases, and chronic obstructive pulmonary disease.

Important risk factors for type 2 diabetes are overweight or obesity, an unhealthy diet and physical inactivity, which accounts for approximately 80% of the increase in the prevalence of diabetes. In addition, these risk factors are modifiable risk factors. Physical inactivity alone is estimated to cause 7% of type 2 diabetes burden According to World Health Organization (WHO) reports, as physical activity decreases, non-communicable diseases increase. Diabetes is one of the four main non-communicable diseases along with cardiovascular diseases, cancer and respiratory diseases, and diabetes accounts for most of the burden of disease and early deaths[14]. A decrease in the level of physical activity is considered an urgent public health problem worldwide. In today's conditions, the most important causes of physical inactivity are environmental and systemic factors. As our living conditions begin to become sedentary, it becomes increasingly difficult to maintain adequate levels of physical activity[15]. Therefore, more effective disease control and behavioral approaches should be integrated into patients' lives in order to reduce these comorbidities and complications.

REHABILITATION METHODS FOR TYPE 2 DIABETES

Although drug treatments have been revealed to be effective in treating type 2 diabetes, these treatment approaches are often costly and can have side effects. On the other hand, adopting a healthy lifestyle has become one of the main approaches to relieve the burden of glucose and lipid metabolic disorders in combination with appropriate drug therapy[15]. Consequently, exercise can become a parallel therapy to traditional treatment programs and diet control or medications in patients with type 2 diabetes.

Physical therapy and rehabilitation is the cornerstone of diabetes prevention and treatment. Individually developed exercise programs are clinically effective in patients with type 2 diabetes. Table 1 summarizes the major benefits of exercise in individuals with diabetes. Different modes of exercise in patients with type 2 diabetes are important due to their effects such as increased glucose uptake by muscles, improved usage, altered lipid levels, increased high-density lipoprotein and reduced triglyceride and total cholesterol. In individuals with type 2 diabetes, any type of physical activity which requires more muscle work than daily living activities can help lower blood glucose, as the vast majority involve the use of muscles during exercise[16].

Active and passive joint movement exercises, stretching techniques, strengthening exercises, and aerobic exercise training are some of the most effective physical therapy and rehabilitation techniques that can be used in patients with type 2 diabetes, such as inpatients, outpatients, and prediabetes[16]. Clinical studies in recent years have shown that the combination of both aerobic and resistance exercise training has a significant effect on glycemic control compared to aerobic exercise or resistance exercise alone[17].

Despite the benefits that can be achieved through rehabilitation, the majority of patients cannot participate in the exercise programs offered to them. Some refuse rehabilitation due to socio-demographic factors, others due to long-distance travel or

Table 1 Major benefits of exercise in individuals with diabetes

	Major benefits
1	Increases quality of life
2	Improves blood cholesterol profiles
3	Increases heart function
4	Decreases blood pressure
5	Improves insulin sensitivity and blood glucose control
6	Improves muscular strength
7	Improves gait and balance
8	Helps to lose weight

working conditions. As a result, a large number of patients do not benefit from the advantages of rehabilitation programs. For ongoing effective diabetes management, long-term adherence to exercise is required; thus, to improve this adherence rate and solve this issue, new rehabilitation models are needed. Telerehabilitation therapy may be considered part of rehabilitation, as this globally increasing method of delivering healthcare services uses information and communication technologies. Thus, telerehabilitation may be more suitable to a patient's lifestyle and thereby increase the patient's self-management[18].

TELEREHABILITATION

The progression in communication facilities and computer-based technologies has led to innovative changes in health. In recent years, with the development of new computer science technologies and advanced telehealth devices, applications in the field of telehealth have been increasing. A review stated that telehealth promises to be a novel 21st century tool in diabetes healthcare to improve quality and reduce the costs by enabling communication with patients[19].

The most encouraging applications in telehealth interventions include telerehabilitation, prevention and lifestyle interventions, chronic disease management (hypertension, diabetes, and heart failure), arrhythmia detection (early detection of atrial fibrillation), and telemonitoring of devices such as pacemakers[20].

In recent years, new telecommunications-based applications in rehabilitation are being developed in the field of medicine all over the world. These approaches are defined as telerehabilitation, which consists of a system controlling remote rehabilitation and should be considered a sub-field of telehealth[21]. "Telerehabilitation" is defined as the delivery of rehabilitation services *via* communication and information technology, including phone, internet, and video conference communications between the patient and the healthcare provider. Clinically, the term telerehabilitation covers a range of rehabilitation services, such as assessment, monitoring, intervention, supervision, education, and counseling[22].

Telerehabilitation is closely associated with and is mostly confused with telehealth or telemonitoring. "Telemonitoring" which is an automated process of data transmission regarding a patient's health status from home to the respective healthcare setting, has proven to be beneficial in patients with chronic diseases, including coronary heart disease, cystic fibrosis, and chronic obstructive pulmonary disease[23-26]. Telerehabilitation with telemonitoring and interactive health communication systems may benefit people with diabetes in a similar way.

"Telehealth" is the use of medical information through electronic communication to improve patients' health status. Telehealth, which covers a broader definition of remote healthcare, does not always include clinical services. Telehealth enables remote communication technology and computer applications to transmit the physiological signals of patients at home, in the community, and institutions to the medical units for analysis and evaluation. Telehealth services include education, patient visit-control service, emergency treatment, and disease prevention. Additionally, it also allows the transmission of physiological signals such as blood pressure or sugar ratio to real-time healthcare providers. Therefore, telehealth aims to make patients independent of the management of their condition[27,28].

According to the WHO, telehealth is the use of telecommunication and virtual technology to deliver healthcare outside traditional healthcare facilities. Well-designed telehealth programs can improve outcomes by facilitating access to

healthcare, especially for chronic disease treatment and vulnerable groups. WHO also stated that it is effective in reducing the demand for crowded facilities and is cost saving[29].

The fundamental research on telerehabilitation has been based on a telephonic conversation for follow up and to administer self-assessment measures. Furthermore, telerehabilitation continued to progress in the 1980s with pre-recorded video materials[30]. In the 1990s, live interactive video conferencing was introduced. After the 1990s, due to the emerging needs of people and the rapid development of new communication and computer technologies, the number of articles and new technological support have increased[31]. In the following years, a virtual environment was introduced to healthcare as another technological method. This method allows users to interact with the computer-generated environment in real-time. It is also possible for health professionals to use it in places such as surgery, rehabilitation, education and training (Table 2). In recent years, smartphones and the applications that can be used with them have revolutionized communication in the medical field. Today, there is a wide range of mobile applications for healthcare professionals, students, patients, and the general public[32]. Telerehabilitation also encourages patients to adopt a healthier lifestyle (smoking cessation, activity tracking) and in adhering to medication use by health information technology applications[20].

Telerehabilitation, which involves health services by using electronic communication systems, is an essential treatment option for improving sustainability in patient care and ensuring practicability. Telerehabilitation procedures can provide glycemic control, blood pressure, lipidemia, weight, diet, and complications monitoring as well as exercise awareness particularly in patients with type 2 diabetes, an essential step in disease management. Diabetes education provides interactive seminars, video conferences, and phone calls. During these conversations, patients are encouraged to exercise. Patients can also easily discuss exercises and rehabilitation programs with their physiotherapist. Telerehabilitation allows patients to take part in their treatment and thus adopt exercise by taking responsibility[6]. Using this technology in rehabilitation services is not only beneficial for the clinician but also for the patient. It promotes a sense of personal autonomy and empowerment by enabling active participation in disease management[33] (Table 3).

Another advantage of telerehabilitation is providing care to inpatients and transferring them home after the acute phase of a disease, therefore, reducing hospital stay and costs for both patients and healthcare providers. These new approaches allow treatment of the acute phase of the disease by overcoming the requirement of a traditional face-to-face inpatient rehabilitation interaction approach. This includes, in particular, patients' challenges to access traditional rehabilitation infrastructures distant from their homes.

Telerehabilitation can never replace face-to-face consultations, but aims to reduce travel and accommodation costs, waiting times and stress on the patient, the patient's family members and caregivers by combining appropriate treatment methods tailored for the patient. Based on all these effects the goal of the telerehabilitation program is to encourage patients with chronic diseases to adopt active behavior and continuously receive medical supervision, thereby enhancing the healthcare behavior of patients.

On the other hand, patients can encounter some participation problems and difficulties while using such telecommunication applications. A study investigating the predictive effect of depression and anxiety on patients' willingness to participate in a trial comparing telerehabilitation *vs* center-based cardiac rehabilitation concluded that despite the proven effectiveness of telerehabilitation, several factors influence the willingness to participate in telerehabilitation. It was demonstrated that patients with symptoms of depression are less willing to participate in telerehabilitation[34].

According to a study that evaluated the use of telehealth in diabetic patients[26], the greatest difficulties in using the monitoring systems were operational problems and equipment quality. The same study also evaluated the satisfaction of participants in telehealth using a questionnaire, which indicated that most participants were satisfied with the equipment but expected additional assistance with its operation. After the 3-mo study period, it was concluded that the program was beneficial in increasing HbA1c control.

TELEREHABILITATION IN TYPE 2 DIABETES

In the last decade, the feasibility and effectiveness of telehealth strategies in the treatment of diabetes patients have been discussed in several studies[3]. The applicability of telehealth methods has been proven; however, due to the incidence of inconsistency between the results in different studies, the actual effect of these

Table 2 Most promising applications of telerehabilitation

Chronic disease management	Physical activity telemonitoring
Prevention and lifestyle interventions	Exercise training planning
Smoking cessation	Exercise training counseling
Activity tracking	Simultaneous exercise training
Adhering to medication	Exercise training follow up

applications in specific and general clinical situations is not yet known[35,36]. With its proven clinical benefits, its use in clinical practice can become widespread and help reduce the burden of the disease[3]. In addition, there have been many telerehabilitation studies on the musculoskeletal system, neurologic, cardiopulmonary, and orthopedic diseases[37-40], but there have been few telerehabilitation studies in type 2 diabetes.

In diabetes-related telehealth applications, many systems such as computers, analog telephones, network systems, cell phones, video-conference systems, satellite technologies, and electrocardiography transmission devices are used. Previous telehealth studies in type 2 diabetes observed glycemic control, complications, and quality of life in diabetic patients. These studies indicated that telehealth applications can increase glycemic control and quality of life as well as reduce HbA1c values[41-46].

In a literature review of studies, only our study conducted in 2019 was found to use telerehabilitation methods in type 2 diabetes[6]. Earlier studies were conducted with exercise training or physical activity alone, and several studies have referred to telehealth practices, including exercise, counseling or other management strategies[47-49].

The only telerehabilitation study[6] conducted in type 2 diabetes mellitus patients was a double-blind, randomized, controlled trial. The participants in the telerehabilitation group performed breathing and callisthenic exercises, three times a week for six weeks, at home by internet-based video conferences under the supervision of a physiotherapist. To precept the exercises, only the first session of the training was performed at the clinic. The patients measured their heart rate, SpO2 with a pulse oximeter as well as blood pressure themselves during all exercises for safety after the initial intervention by the physiotherapist. At the end of the study period, the telerehabilitation intervention was found to be effective in improving exercise capacity, physical fitness, muscle strength, psychosocial status, and controlling HbA1c levels. Compliance with the intervention was excellent and the telerehabilitation interventions were found to be safe and practicable, which could be an alternative treatment model for type 2 diabetes management.

Another study that included exercise, counseling, or management strategies[47] consisted of a program designed to be delivered *via* the internet to improve the participants' diabetes self-management behaviors using behavioral and motivational strategies. Additional strategies included instructions on disease management, diet, and exercise, and the introduction to interventions to deal with the physical and emotional demands of the disease. The interaction between the caregivers and participants included both synchronous (instant messaging and chat) and asynchronous communication (e-mail and bulletin board) methods. The participants also accessed a website to enter their blood sugar readings, exercise programs, weight changes, blood pressure, and medication data. The study caregiver followed participants' logs to monitor changes in their self-management patterns. The study concluded that the participants who received a 6-month diabetes web-based intervention improved their HbA1c, systolic blood pressure, weight, high density lipoprotein, and total cholesterol levels compared to the control group.

Glasgow *et al*[48] included exercise, counseling, or management strategies and evaluated minimal and moderate support versions of internet-based diabetes combined (internet and automated telephone) self-management programs in adults with type 2 diabetes. The internet-based intervention resulted in a greater improvement, compared with the usual care condition, on three of four behavioral outcomes (healthy eating, fat intake, and physical activity). They concluded that more frequent, longer-term, or more personal support might be needed to improve the results of an effective internet-based behavioral change intervention.

Marios *et al*[49] conducted a study that included exercise, counseling, or management strategies. They used telemonitoring to improve exercise adherence, which assessed the number of hours of exercise completed, as well as peak VO_2, HbA1c and quality of life in a six-month unsupervised, home-based exercise program in people with type 2

Table 3 Advantages of telerehabilitation

	Advantages of telerehabilitation
1	Improves health service efficiency and processes
2	Improves healthcare quality or effectiveness
3	Saves paperwork and saves time for caregivers
4	Reduces healthcare costs
5	Facilitates and extends access to economic care
6	Improves sustainability
7	Facilitates long-term home care for patients
8	Promotes a sense of personal autonomy in participants

diabetes. Cost analysis was also conducted. The exercise group was instructed to record their heart rates during exercise using a monitor and received weekly telephone calls from a physiologist. Although telemonitored patients completed more hours of exercise and demonstrated improved peak VO_2 compared to controls, they neither improved HbA1c nor quality of life. The exercise volume was also insufficient to improve glycemic control. They concluded that telemonitoring has the potential to enable people with diabetes to meet exercise training guidelines.

A systematic review[2] that assessed the quality and the evidence of telerehabilitation and included 10 studies, which was conducted in patients with chronic or long-term conditions and neurologic disorders, suggested that the number of telerehabilitation experiences worldwide is growing. However, evidence of its clinical and economic effectiveness is still insufficient, particularly in routine care. Moreover, these systematic reviews have been interpreted based on a lack of methodological rigor and diversity of approaches used in the studies. There is some evidence concerning users' acceptance and satisfaction, and overall feasibility related to the discipline. However, there is insufficient evidence to state that telerehabilitation is a cost-saving or cost-effective approach, although its potential has been highlighted scientifically.

CONCLUSION

Technology-based rehabilitation applications are developing rapidly and becoming an essential component of medical care. Therefore, using these new techniques, it is necessary to continue to focus on the individual needs of the patient. Although the telerehabilitation interventions in type 2 diabetes are less well-defined, initial results of small studies are highly favorable. With more extensive, multi-centered randomized controlled studies, clinical guidelines could ultimately improve patient outcomes. However, additional research is needed to interpret long-term outcomes, as well as to enhance effectiveness and cost-effectiveness.

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MINIREVIEWS

Diabetes and cancer: Epidemiological and biological links

Mina Wang, Yingying Yang, Zehuan Liao

ORCID number: Mina Wang (0000-0002-4029-5806); Yingying Yang (0000-0001-5115-8375); Zehuan Liao (0000-0002-7500-1521).

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Mina Wang, Zehuan Liao, School of Biological Sciences, Nanyang Technological University, Singapore 637551, Singapore

Mina Wang, The Department of Acupuncture and Moxibustion, Beijing Hospital of Traditional Chinese Medicine, Capital Medical University, Beijing Key Laboratory of Acupuncture Neuromodulation, Beijing 100010, China

Mina Wang, Graduate School, Beijing University of Chinese Medicine, Beijing 100029, China

Yingying Yang, Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna 17177, Sweden

Yingying Yang, Shanghai First Maternity and Infant Hospital, Tongji University School of Medicine, Shanghai 200065, China

Zehuan Liao, Department of Microbiology, Tumor and Cell Biology (MTC), Karolinska Institutet, Solna 17177, Sweden

Corresponding author: Zehuan Liao, BSc, Teaching Assistant, Doctorand, School of Biological Sciences, Nanyang Technological University, 60 Nanyang Drive, Singapore 637551, Singapore. liao0058@e.ntu.edu.sg

Abstract

The incidence of diabetes and cancer has increased significantly in recent years. Furthermore, there are many common risk factors for both diabetes and cancer, such as obesity, sedentary lifestyle, smoking, and ageing. A large body of epidemiological evidence has indicated that diabetes is considered as an independent risk factor for increased rates of heterogeneous types of cancer occurrence and death. The incidence and mortality of various types of cancer, such as pancreas, liver, colorectal, breast, endometrial, and bladder cancers, have a modest growth in diabetics. However, diabetes may work as a protective factor for prostate cancer. Although the underlying biological mechanisms have not been totally understood, studies have validated that insulin/insulin-like growth factor (IGF) axis (including insulin resistance, hyperinsulinemia, and IGF), hyperglycemia, inflammatory cytokines, and sex hormones provide good circumstances for cancer cell proliferation and metastasis. Insulin/IGF axis activates several metabolic and mitogenic signaling pathways; hyperglycemia provides energy for cancer cell growth; inflammatory cytokines influence cancer cell apoptosis. Thus, these three factors affect all types of cancer, while sex hormones only play important roles in breast cancer, endometrial cancer, and prostate cancer. This minireview consolidates and discusses the epidemiological and biological links between diabetes and various types of cancer.

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Core tip: The incidence of diabetes and cancer has increased significantly in recent years. The incidence and mortality of various types of cancer, such as pancreas, liver, colorectal, breast, endometrial, and bladder cancers, have a modest growth in diabetics. However, diabetes may work as a protective factor for prostate cancer. This minireview consolidates and discusses the epidemiological and biological links between diabetes and various types of cancer.

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INTRODUCTION

Both diabetes and cancer are serious and prevalent diseases which are increasing rapidly worldwide. Diabetes is a kind of metabolic disease whereby the patients have high levels of blood sugar. Worldwide, the number of people with diabetes was 422 million in 2014 and a new study has projected that the number of cases will increase to at least 592 million in 2035[1]. Meanwhile, cancer has been considered as a metabolic disease by most medical researchers, and the World Health Organization estimated that the number of global cancer patients would increase from 14 million in 2012 to 22 million in 2032[2].

The most common types of diabetes are type 1 and type 2. On the one hand, the autoimmune impairment of insulin-producing beta cells, causing absolute insulin deficiency, leads to type 1 diabetes mellitus (T1DM) and it accounts for about 5% to 10% of all diabetes cases. On the other hand, T2DM is associated with metabolic disorders, by which cells become insensitive to insulin and hence manifest relative insulin deficiency[3,4]. Several studies have found that although T1DM and T2DM are associated with increased risks for cancer, T2DM has a stronger link with cancer both epidemiologically and biologically[5]. The potential explanation is that cancer and T2DM share risk factors, such as obesity, smoking, and ageing. Therefore, diabetes (primarily type 2) has been closely linked to many forms of cancer, including cancers of the pancreas, liver, colorectal, breast, endometrium, bladder, and prostate[6]. The underlying mechanisms for the association of diabetes and the incidence of cancer are still unclear. However, several lines of evidence have indicated that insulin/insulin-like growth factor (IGF) axis, hyperglycemia, inflammatory cytokines, and sex hormones could be the possible reasons[7,8]. Therefore, this minireview aims to illustrate the correlations between diabetes and cancer and the underlying mechanisms.

ASSOCIATION BETWEEN DIABETES AND PANCREATIC CANCER

Pancreatic cancer (PC) is one of the deadliest malignant diseases, with a 5-year survival rate less than 10%. Currently, PC is the tenth most common cancer and the fourth lethal cause in the United States[9]. The positive relationship of diabetes with PC has been noted for nearly 200 years[10], and recently, there are two hypotheses about the correlation of these two diseases. On the one hand, epidemiological studies have demonstrated that the incidence of PC in diabetics is significantly higher than that in non-diabetics, thus, diabetes is a risk factor for PC. On the other hand, many studies have also proved that new-onset diabetes is a sign of PC, which is caused by PC[10-13]. A prospective study was conducted in China to find out the association between diabetes and PC. The study recruited 512000 people aged 30-79 years from ten different regions of China between 2004 and 2008. After an 8-year follow-up, 595 cases of PC were recorded. It has been shown that diabetes was associated with a 1.87-fold

increase in the risk of PC [adjusted hazard ratio (HR) = 1.87, 95% confidence interval (CI): 1.48-2.37], proving that diabetes is a risk factor for PC[14]. A multiethnic cohort study was carried out in African Americans and Latinos to reveal the correlation between new-onset diabetes and PC. It is illustrated that new-onset diabetes was associated with a 2.3-fold higher increase in the risk of PC than long-term diabetes, supporting that new-onset diabetes is a sign of PC[15]. More studies have indicated that the association between diabetes and PC is bidirectional, and there is an inverse duration-dependent risk of diabetes and PC. In the first 2 years after diagnosis of diabetes, there is a remarkable rate of PC occurrence, and the rate will have a modest decrease as time goes by. For those who suffer diabetes for more than 5 years, the risk of PC decreases significantly[16,17]. Therefore, we can conclude that, long-term diabetes is a risk factor for PC, and new-onset diabetes is a sign of PC.

ASSOCIATION BETWEEN DIABETES AND LIVER CANCER

Primary liver cancer, also known as hepatocellular carcinoma (HCC), has emerged globally as the fifth most common malignancy in men as well as the seventh one in women, and its incidence is especially high in oriental Asia and Africa[18]. This neoplasm is also regarded as a highly fatal disease. Recent studies have suggested that diabetes is strongly associated with HCC, pointing out an independent risk factor for HCC. Before elucidating the relationship between diabetes and HCC, we need to take note that persistent infections by hepatitis B virus and hepatitis C virus (HCV), aflatoxin exposure, and non-alcoholic fatty liver disease (NAFLD) are three important risk factors for the development of HCC. Hence, diabetes and HCC are closely linked because of their correlation with hepatitis viruses and NAFLD[18,19]. A perspective cohort study investigated the association of diabetes and HCC in Taiwan with a high prevalence of hepatitis virus infections. Fifty-four thousand nine hundred seventy-nine subjects were screened, and 5732 subjects were diabetics who were followed until they were diagnosed with HCC. That study found that the effect of diabetes in increasing the risk of HCC is more significant in patients who were HCV negative than in those who were HCV positive[20]. NAFLD includes various progressive hepatic diseases, ranging from pure steatosis to steatohepatitis. Furthermore, more than 70% of diabetics have NAFLD due to insulin resistance[20,21], which means that people with diabetes are more susceptible to severe hepatic diseases, such as HCC. Several systematic reviews and meta-analyses also have indicated that NAFLD is a spotlight of the correlation of diabetes and HCC[22,23]. As a result, diabetes is a modifiable risk factor and its association with an increased rate of HCC cannot be ignored.

ASSOCIATION BETWEEN DIABETES AND COLORECTAL CANCER

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of death in the United States. Moreover, CRC-specific mortality rate is about 33% in the developed countries[24]. The correlation of diabetes and an elevated risk of CRC has been verified in many studies that have displayed that there are many common risk factors between diabetes and CRC, such as age, obesity, sedentary lifestyle, and smoking. Meanwhile, diabetes serves as an independent risk factor for CRC. Furthermore, a higher mortality has been found in CRC patients with diabetes[25]. Interestingly, sex differences have been strongly reported in many studies, which have demonstrated only a small increased risk in women with diabetes, while a significantly growing risk of diabetics among men[26]. In a cohort study, 73312 men and 81663 women were successfully followed, and 1567 men (227 with diabetes) and 1242 women (108 with diabetes) were diagnosed with CRC. There was a 1.24-fold increased risk of incident CRC in men with diabetes [RR (relative risk) = 1.24; 95%CI: 1.08-1.44]. However, among women, there was no association with the risk of incident CRC (RR = 1.22, 95%CI: 1.04-1.45)[27]. And in another Swedish study, the authors showed that men with diabetes had a 49% increased risk of CRC with all subsites in the colorectum[28]. Last but not least, diet is also an important factor in the incidence of diabetes and CRC, but research has revealed that only women but not men have the ability to lower the risk of CRC, even if both woman and men have a similarly healthy diet[29].

ASSOCIATION BETWEEN DIABETES AND BREAST CANCER

Breast cancer is the foremost carcinoma in women in developed countries and with the popularity of Western lifestyle, its incidence is rapidly growing in developing countries as well. Diabetes, as a metabolic disorder, is robustly associated with an increased risk of breast cancer[30]. Large amounts of epidemiological evidence have indicated that diabetes contributes to higher incidence and mortality rates of breast cancer. Additionally, a meta-analysis has suggested that the correlation between diabetes and breast cancer seems to be confined to post-menopausal women[31]. However, this result is inconsistent with another study showing that the increased risk of breast cancer in pre-menopausal women is attributed to diabetes[32]. Moreover, in a study investigating the relation of diabetes and breast cancer among Asian-American women, the authors found that after adjusting body mass index and waist to hip ratio, the incidence of breast cancer still increased. This indicated that the history of diabetes has an intense relation with breast cancer[33]. Besides, there are two studies that had similar conclusions, introducing that diabetes may interfere with focus to other health problems and cause a low rate of diagnosis of breast cancer. Moreover, diabetes may promote the growth of tumors. A retrospective cohort study assessed the impact of diabetes on stages of breast cancer, and among 38407 women with breast cancer, 6115 (15.9%) were diabetics, who had more advanced breast cancer stages than their nondiabetics counterparts - Stage II [adjusted odds ratio (aOR) = 1.14, 95%CI: 1.07-1.22], Stage III (aOR = 1.21, 95%CI: 1.11-1.33), and Stage IV (aOR = 1.16, 95 % CI: 1.01-1.33) *vs* Stage I breast cancer[34]. In another study, the impact of pre-existing diabetes on breast cancer prognosis was examined. Compared to nondiabetic women, the overall mortality had a remarkable increase among women who suffered diabetes (HR = 1.57, 95%CI: 1.23-2.01). Radiation therapy was difficult to carry out on diabetic women[35]. Therefore, diabetes accounts for a delayed diagnosis and limited treatment choices, thus leading to a more aggressive breast cancer and a higher mortality.

ASSOCIATION BETWEEN DIABETES AND ENDOMETRIAL CANCER

Endometrial cancer (EC) is the fourth most common cancer in women in the United States and the most common type of gynecological cancer. Compared to other types of cancer, EC often has an earlier diagnosis and a better prognosis. However, the death rate of EC rose significantly during the past 20 years. This phenomenon could be explained by longer life expectancy and lifestyle changes as ageing and physical activities are linked to diabetes[36,37]. Therefore, diabetes is associated with EC, which has been consistently supported by cohort study, case-control study, and meta-analysis. These studies have demonstrated that diabetes leads to a higher mortality of EC as an independent risk factor. A cohort study, conducted in Sweden, assessed the incidence of EC among 80005 women with diabetes, with the standardized incidence ratios as 1.8 and CI as 1.6-2.0, and the results indicated that diabetes elevates the incidence of EC[38]. Besides, a case-control study in Washington illustrated that irrespective of other present risk factors, diabetes is strongly related to EC (OR = 1.7, 95%CI: 1.2-2.3), and new-onset diabetics (< 5 years) have a 2-fold increased odds of EC compared with those with a more distant diagnosis (≥ 5 years)[39]. Furthermore, a systematic review and meta-analysis of cohort studies summarized 29 cohort studies and revealed the morbidity of EC in women with *vs* without diabetes. The summary RR was 1.89 (95%CI: 1.46-2.45; $P < 0.001$) and the summary incidence rate was 1.61 (95%CI: 1.51-1.71; $P < 0.001$), once again confirming that diabetes is an independent risk factor for the increased EC incidence. However, the correlation of diabetes and EC-specific mortality remains to be validated by more studies[40].

ASSOCIATION BETWEEN DIABETES AND BLADDER CANCER

Bladder cancer (BC) is one of the most prevalent malignancies in the world, and its morbidity and mortality are expected to be associated with age, smoking, and occupational exposure[41]. Recently, researchers have paid attention to deducing the effect of diabetes on BC. A meta-analysis of 36 observational studies has demonstrated that most studies were carried out in Western countries, and only one study was performed in Korea[42]. Therefore, the current results cannot fully represent

global correlation of diabetes and BC. Moreover, this meta-analysis also pointed out that there is a negative relation of BC and diabetic duration, and people with diabetes less than 5 years have a higher risk of BC[42]. But a case-control study has a totally different result, which has suggested that the risk of BC increases with diabetic duration (OR = 1.92 for 1-5 years, 1.63 for 5-10 years, 2.39 for 10-15 years, and 2.58 for ≥ 15 years)[43]. Furthermore, a cohort study has confirmed a positive association between diabetes and BC in women[44]. However, a meta-analysis indicated that the relation of diabetes and increased risk of BC or cancer mortality in women requires further explorations[45]. Findings from epidemiological studies are controversial, nevertheless, most meta-analyses support that diabetes is a risk factor for BC, and both incidence and death rates of BC increase in diabetics[41,46-48].

ASSOCIATION BETWEEN DIABETES AND PROSTATE CANCER

The latest study performed by the American Cancer Society has reported that the number of new prostate cancer cases is the highest in the United States, and prostate cancer is also the second leading cause of cancer death in American males[49]. Although diabetes appears to be a risk factor for many types of cancer, studies have, however, elucidated an inverse association between diabetes and prostate cancer[50]. A meta-analysis, including 45 studies (29 cohort and 16 case–control studies) with 8.1 million participants and 132331 prostate cancer cases, has provided strong evidence to verify the association of diabetes with a reduced risk of prostate cancer[51]. Besides, two cohort studies have expressed the underlying reason for the inverse relationship: The likelihood of receiving a prostate screening test increases with diabetes comorbidity, thus, the incidence of early stage prostate cancer is reduced[52,53]. However, the incidence of advanced stage is irrelevant with diagnosis of diabetes, which has been mentioned in several studies[52]. Furthermore, a mate-analysis has illustrated that the inverse association between diabetes and prostate cancer is limited to incidence but not mortality, and prostate cancer patients with diabetes have a worse prognosis[54]. In spite of the negative consequences reported in many studies, a different conclusion has been declared in a Swedish cohort study showing that after eliminating the confused risk factors, there is no association between diabetes and prostate cancer[55]. Therefore, further investigations need to be carried out to draw a consistent conclusion.

In short, the links between diabetes and various types of cancers are apparent. Table 1 provides a non-exhaustive list of association studies between diabetes and cancers in the past 5 years.

BIOLOGICAL LINKS BETWEEN DIABETES AND CANCER

Insulin/IGF axis

Insulin is a peptide hormone which can regulate carbohydrate and fat metabolism by improving glucose absorption. However, insulin loses the function to enhance cellular glucose uptake and utilization in diabetics, which is defined clinically as insulin resistance. Therefore, beta cells secret more insulin to compensate, resulting in hyperinsulinemia[56]. Also, the high level of insulin is a hallmark of hyperinsulinemia, which stimulates the liver cells to produce IGF-1 when insulin binds to the insulin receptor on the surface of target cells. IGF-1 binds to IGF 1 receptor (IGF-1R), a receptor tyrosine kinase, to activate several metabolic and mitogenic signaling pathways to regulate cancer cell proliferation, differentiation, and apoptosis[6,57]. After numerous downstream targets, phosphoinositide-3-kinase-protein kinase B and rat sarcoma-mitogen-activated protein kinase/extracellular signal regulated kinase signaling pathways are activated[58,59]. Phosphoinositide-3-kinase-protein kinase B signaling pathway leads to cancer cell survival and migration, whereas rat sarcoma-mitogen-activated protein kinase/extracellular signal regulated kinase signaling pathway governs cancer cell metabolism and proliferation[60]. Therefore, patients with diabetes are associated with higher levels of IGF-1, which makes it more susceptible to an increased risk of developing many types of cancer such as colorectal, breast, and prostate cancers. Besides, many studies have revealed that IGF-1 is more frequently expressed in breast cancer cells than other cancer types[61,62], and the reason is related to the location where IGF-1 is expressed: The stromal cells beside normal epithelial cells of the breast. An experiment used a mouse model of HER2-mediated breast cancer in a condition of hyperinsulinemia to investigate the effect of increased levels of insulin on HER2 mediated primary tumor growth and lung metastasis. It has

Table 1 Non-exhaustive summary of representative association studies between diabetes and various types of cancers in the past 5 years (2015-2019)

Cancer	Ref.	Design	Findings
Pancreatic Cancer	Setiawan *et al*[15], 2019	Cohort study	Positive association between diabetes and pancreatic cancer
	Chen *et al*[89], 2017	Cohort study	
	Pang *et al*[14], 2017	Meta-analysis of 22 cohort studies	
	Tan *et al*[90], 2017	Systematic review and meta-analysis	
	Dankner *et al*[91], 2016	Cohort study	
	Song *et al*[92], 2015	Meta-analysis	
	Ogunleye *et al*[93], 2009	Cohort study	
	Gupta *et al*[16], 2006	Cohort study	
Liver cancer	Li *et al*[94], 2017	Case-control study	Increased risk of liver cancer in diabetes
	Wang *et al*[95], 2017	Metaanalysis	
	Chen *et al*[96], 2015	Meta-analysis of 21 cohort studies	
	El-Serag *et al*[23], 2006	Systematic review	
	Wang *et al*[22], 2014	Systematic review and meta-analysis	Diabetes is independently associated with a poorer survival in HCC patients
	Lai *et al*[20], 2006	Cohort study	Diabetes increases risk of HCC in HCV negative individuals
Colorectal cancer	Zhu *et al*[97], 2017	Meta-analysis	Positive correlation of diabetes with colorectal cancer
	Guraya *et al*[98], 2015	Meta-analysis of 8 cohort studies	
	Larsson *et al*[28], 2005	Cohort study	
	Amshoff *et al*[25], 2018	Cohort study	Pre-existing T2DM has no influence on disease-specific and all-cause survival among CRC patients
	Jacobs *et al*[29], 2016	Cohort study	The aMED score is related to lower mortality only in African-American women
	Campbell *et al*[27], 2010	Cohort study	Modest association between T2DM and CRC among men, but not among women
Breast cancer	Luo *et al*[35], 2015	Cohort study	Pre-existing diabetes increases the risk of total mortality among women with breast cancer
	Lipscombe *et al*[34], 2015	Cross-sectional study	Diabetes may predispose to more aggressive breast cancer
	Alokail *et al*[32], 2009	Cohort study	
	Boyle *et al*[31], 2012	Meta-analysis	Risk of breast cancer is increased by 27% in diabetic women
Endometrial cancer	Saed *et al*[99], 2019	Systematic review and meta-analysis	Diabetes increases the risk of endometrial cancer in women
	Saltzman *et al*[39], 2008	Systematic review of case-control study	
	Lindemann *et al*[37], 2015	Cohort study	Diabetes, but not BMI, is associated with an increased risk of all-cause death and death from EC
Bladder cancer	Xu *et al*[45], 2017	Meta-analysis of 21 cohort studies and case–control studies	Diabetes increases the risk of bladder cancer
	Turati *et al*[43], 2015	Case–control study	
	Zhu *et al*[42], 2013	Meta-analysis of 36 observational studies	
	Prizment *et al*[44], 2013	Cohort study	Positive association between diabetes and bladder cancer risk among White post-menopausal women
Prostate cancer	Häggström *et al*[55], 2018	Cohort study	An inverse association between diabetes and prostate cancer
	Lee *et al*[54], 2016	Metaanalysis	
	Dankner *et al*[52], 2016	Cohort study	
	Khan *et al*[100], 2016	Cross-sectional, case-only study	
	Fall *et al*[101], 2013	Case-control study	

BMI: Body mass index; HCC: Hepatocellular carcinoma; HCV: Hepatitis C virus; T2DM: Type 2 diabetes mellitus; CRC: Colorectal cancer; EC: Endometrial cancer.

revealed that tumor mass grew and IR and IGF-1R had higher phosphorylation levels, demonstrating that hyperinsulinemia contributes to the elevated growth of mammary tumors through the insulin/IGF axis[63]. Another epidemiological study assessed the correlation between hyperinsulinemia and increased cancer mortality in both obese and non-obese people. The study successfully followed 3060 obese participants (2303 with hyperinsulinemia) and 6718 non-obese participants (2057 with hyperinsulinemia). The overall cancer mortality was remarkably higher in those with hyperinsulinemia than in their counterparts (adjusted HR = 2.04, 95%CI: 1.24-3.34, P = 0.005)[64]. Therefore, the insulin/IGF-1 axis (hyperinsulinemia, IR, and IR signaling pathway) promotes cancer cell growth and metastasis.

Hyperglycemia

It is necessary to provide energy for cell growth and proliferation. Generally, cells obtain energy through tricarboxylic acid cycle, whereas cancer cells shift to glycolysis, leading to an easier glucose uptake which is known as the Warburg Effect[65]. Thus, hyperglycemia of diabetics provides cancer cells great condition to survive and proliferate. Meanwhile, the synthesis of tumor protein and DNA is associated with glucose metabolism. Therefore, a high level of blood glucose affects tumor growth and metastasis[66]. Studies have also indicated that hyperglycemia accelerates mitochondrial dysfunction and the generation of free radicals and other reactive molecules, such as reactive oxygen species (ROS), triggering the formation of advanced glycation end products (AGEs) and activating protein kinase C isomers[67]. ROS can not only directly damage DNA, inducing genetic mutation, but regulate mitogen activated protein kinases and p21 activated kinase, promoting tumor metastasis. Moreover, ROS are able to oxygenate protein kinase C and protein tyrosine phosphatase, which are the key molecules that are involved in the invasion of cancer cells and help cancer cells to adapt the adverse environment[68]. AGEs receptor exists in many types of cancer cells, such as immune cells, neurons, osteoblasts, activated endothelial cells, and vascular smooth muscle cells. Furthermore, it can be triggered by AGEs, leading to chronic inflammation which links to many cancer-related signaling pathways[69], eventually increasing cell genetic mutation and evolution and resulting in advanced stages of cancer[5,58,70]. However, since hyperglycemia and hyperinsulinemia simultaneously exist in most diabetic patients and it is difficult to distinguish the independent role of each abnormality, there is no congruent opinion on whether hyperglycemia is an independent factor to promote tumor growth and metastasis.

Inflammatory cytokines

Diabetes has a strong connection with obesity and both hyperinsulinemia and visceral adiposity can augment the production of inflammatory cytokines. With the increase in the production of inflammatory cytokines, chemicals of acute phase such as C-reactive protein and plasminogen activator inhibitor-1 increase as well, promoting the formation of inflammatory network at the early stage of diabetes. With the development of diabetes, inflammatory network spreads[71]. Although a plenty of inflammatory cytokines are associated with the development of cancer, interleukin-6 (IL-6) and tumor necrosis factor α (TNFα) secreted by adipose tissue have been verified as the major inflammatory cytokines related to diabetes and cancer at the same time[70]. In breast cancer, IL-6 can activate nuclear factor-κB and increase cyclin D1, and therefore, neoplastic transformation develops. Besides, IL-6 can cause cells to isolate from each other but remain alive by activating the process of epithelial-to-mesenchymal transition, which leads to cancer metastasis[72]. Normally, TNF-α is an important mediator of anti-tumor immune responses, but chronic exposure to TNF-α can activate a series of signaling pathways, such as nuclear factor-κB, mitogen activated protein kinase, and Jun kinase, thus preventing cancer cell apoptosis and accelerating cancer cell growth and metastasis[73]. An animal experiment has demonstrated that the blockade of TNF-α prevents the expression of programmed cell death ligand 1 in cancer cells, thereby preventing tumor proliferation[74]. Moreover, researchers have found that despite higher basic levels of inflammatory cytokines in diabetics, the production of cytokines is impaired during immune defense. Also, complement dependent phagocytic activities and chemotactic phagocytosis of macrophages are inhibited, resulting in immune dysfunction, which causes easier infection and provide tumor a better place to survive[75,76]. Table 2 summarizes the three main biological links between diabetes and cancer as mentioned above.

Sex hormones

Basically, sex hormone binding globulin (SHBG) and albumin are capable of binding to circulating sex hormones such as androgens and estrogens to regulate the levels of free sex hormones and their bioavailability. However, SHBG has a higher affinity to

Table 2 Biological links between diabetes and cancer

Characteristic of diabetes	Consequences which promote cancer
High blood sugar level	DNA damage
	ROS production
	Chronic inflammation
	Promote cancer cell proliferation
	Promote cancer cell growth
	Promote cancer cell metastasis
	Provide alternative energy source for cancer cell survival
High blood insulin level (as in T2DM)	Increase level of IGF-1
	Promote cancer cell proliferation
	Promote cancer cell differentiation
	Promote cancer cell survival
	Promote cancer cell migration
	Promote cancer cell growth
	Promote cancer cell metastasis
Inflammation	Promote cancer cell proliferation
	Accelerate cancer cell growth
	Accelerate cancer cell metastasis
	Promote EMT
	Promote cancer cell survival
	Inhibit certain immune responses

ROS: Reactive oxygen species; T2DM: Type 2 diabetes mellitus; IGF-1: Insulin-like growth factor-1; EMT: Epithelial-to-mesenchymal transition.

sex hormones than albumin, and the affinity to testosterone is twice that of estradiol and distinct between gender[77]. Recently, more and more studies have indicated that high blood glucose and insulin are associated with low levels of circulating SHBG, which affects the maintenance of glucose homeostasis[78,79]. A nested case-control study investigated the correlation between SHBG and the risk of diabetes on 718 postmenopausal women (359 with newly diagnosed type 2 diabetes and 359 controls) and suggested that low circulating levels of SHBG are strongly associated with the risk of diabetes. Moreover, the same result was found in an independent cohort study of 340 men (170 with newly diagnosed type 2 diabetes and 170 controls)[79]. Therefore, the synthesis of SHBG decreases indirectly with increased levels of blood glucose and serum insulin, which promotes free estrogen and testosterone synthesis. High levels of free estrogen and testosterone are associated with higher risks of many types of cancer, such as breast, endometrial, and prostate cancers[6,80]. Studies have found that both biologically available estrogen and testosterone are elevated in diabetic women[81], while total testosterone concentrations are lower in diabetic men than in nondiabetic men[82,83]. Although the mechanism remains unclear, it is probably attributed to the different affinities to SHBG[77,84]. This is the main reason why diabetes may play an important role in protecting patients from prostate cancer.

BIOMARKERS

There are many diabetes-related biomarkers, such as fasting glucose, glycated hemoglobin, glycated albumin, adiponectin, serum insulin, and C-peptide, among which the increased levels of serum insulin and C-peptide are regarded as associated biomarkers of several types of cancer. However, further studies are still needed to figure out the mutual biomarkers of diabetes and cancer[62,85].

CONCLUSION

Cancer can be a metabolic disease resulting from both internal factors and external factors[86-88]. The association between diabetes and increased cancer incidence and

mortality has been well demonstrated in many studies. Also, the incidence of both diabetes and cancer has a rapid growth worldwide because of lifestyle changes and longer life expectancy. Therefore, precautionary measures such as physical exercise and regular cancer screening are necessary to improve both diabetes and cancer outcomes. Moreover, diabetes and cancer are global problems, and international health experts or organizations should develop guidelines on the prevention, diagnosis, and treatment of diabetes and cancer to reduce the social burden. As the intrinsic heterogeneity of both diabetes and cancer makes studies difficult to conduct, there are still many unanswered questions: Do T1DM and T2DM affect cancer in a same way? How should we define the general and specific cancer risks in each individual? Also, how can we fully understand the underlying biological mechanisms? More studies should be carried out to answer these questions in order to provide more preventive and therapeutic choices for diabetes and cancer patients.

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ORIGINAL ARTICLE

Basic Study

CD47 decline in pancreatic islet cells promotes macrophage-mediated phagocytosis in type I diabetes

Jing Zhang, Su-Bee Tan, Zhi-Gang Guo

ORCID number: Jing Zhang (0000-0002-4082-9994); Su-Bee Tan (0000-0002-7394-530X); Zhi-Gang Guo (0000-0001-7771-1829).

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Jing Zhang, Zhi-Gang Guo, Jiangsu Key Laboratory for Molecular and Medical Biotechnology, College of Life Sciences, Nanjing Normal University, Nanjing 210097, Jiangsu Province, China

Jing Zhang, Laboratory of Molecular Gerontology, National Institute on Aging, National Institutes of Health, Baltimore, MD 21224, United States

Su-Bee Tan, National Key Laboratory for Biochemistry, College of Life Sciences, Nanjing University, Nanjing 210093, Jiangsu Province, China

Corresponding author: Zhi-Gang Guo, PhD, Professor, Senior Research Fellow, Jiangsu Key Laboratory for Molecular and Medical Biotechnology, College of Life Sciences, Nanjing Normal University, 1 Wenyuan Road, Nanjing 210097, Jiangsu Province, China. guozgang@gmail.com

Abstract

BACKGROUND

Type I diabetes (T1D) is characterized by insulin loss caused by inflammatory cells that excessively infiltrate and destroy the pancreas, resulting in dysregulation of tissue homeostasis, mechanobiological properties, and the immune response. The streptozotocin (STZ)-induced mouse model exhibits multiple features of human T1D and enables mechanistic analysis of disease progression. However, the relationship between the mechanochemical signaling regulation of STZ-induced T1D and macrophage migration and phagocytosis is unclear.

AIM

To study the mechanochemical regulation of STZ-induced macrophage response on pancreatic beta islet cells to gain a clearer understanding of T1D.

METHODS

We performed experiments using different methods. We stimulated isolated pancreatic beta islet cells with STZ and then tested the macrophage migration and phagocytosis.

RESULTS

In this study, we discovered that the integrin-associated surface factor CD47 played a critical role in immune defense in the STZ-induced T1D model by preventing pancreatic beta islet inflammation. In comparison with healthy mice, STZ-treated mice showed decreased levels of CD47 on islet cells and reduced interaction of CD47 with signal regulatory protein α (SIRPα), which negatively

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regulates macrophage-mediated phagocytosis. This resulted in weakened islet cell immune defense and promoted macrophage migration and phagocytosis of target inflammatory cells. Moreover, lipopolysaccharide-activated human acute monocytic leukemia THP-1 cells also exhibited enhanced phagocytosis in the STZ-treated islets, and the aggressive attack of the inflammatory islets correlated with impaired CD47-SIRPα interactions. In addition, CD47 overexpression rescued the pre-labeled targeted cells.

CONCLUSION
This study indicates that CD47 deficiency promotes the migration and phagocytosis of macrophages and provides mechanistic insights into T1D by associating the interactions between membrane structures and inflammatory disease progression.

Key words: Type I diabetes; Immune defense; CD47; Migration; Phagocytosis; Cell-cell interaction

Core tip: Type I diabetes (T1D) has caused worldwide public health concerns. The mechanochemical regulation of the disease-induced immune response raised more considerations. We provide mechanistic insights into T1D, associating interactions between membrane structures and inflammatory disease progression. The immune response could be a novel section for preventing the T1D progression.

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DOI: https://dx.doi.org/10.4239/wjd.v11.i6.239

INTRODUCTION

Infiltration of inflammatory cells into pancreatic islets and selective destruction of insulin-secreting cells are characteristics of type I diabetes[1,2]. A similar process occurs in autoimmune diabetes, as well as in multiple low-dose streptozotocin (STZ)-treated mice[3,4]. Macrophages play a critical role in the development and pathogenesis of autoimmune or inflammatory disease. Macrophage recruitment strongly correlates with the progression of autoimmune diabetes, as these are the first immune cells to infiltrate the pancreatic islet, where they act as antigen-presenting and effector cells[5-9]. To maintain tissue integrity, tissue macrophages must prevent phagocytosis of healthy endogenous cells. By differentiating "self" and "non-self" cells, macrophages exert their phagocytic function. Immunogenic proteins play critical roles in this process. CD47-signal regulatory protein α (SIRPα) interaction-mediated inhibition is a critical mechanism that prevents macrophages from phagocytizing healthy endogenous cells[10-13]. CD47 is an integrin-associated molecule that is an essential marker of ''self''[14]. The inhibitory receptor SIRPα is an extracellular ligand of CD47. In this mechanism, CD47 acts as a marker of self, along with SIRPα, and inhibits signaling in macrophages related to migration and phagocytosis of abnormal cells or other antigens[13,15]. Through its extracellular IgV-like loops, SIRPα binds to CD47, which induces phosphorylation of the SIRPα immunoreceptor tyrosine-based inhibitory motifs (ITIMs), leading to association with the SH2 domain–containing protein tyrosine phosphatases SHP-1 or SHP-2. Then, negative signaling cascades are initiated, resulting in the inhibition of macrophage function[16,17]. The end result of CD47-SIRPα-mediated signaling is the inhibition of inappropriate phagocytosis of endogenous cells[18,19]. Previous studies have reported the CD47-SIRPα inhibition mechanism in red blood cell (RBC) transfusion experiments, which demonstrated that wild-type mice rapidly eliminate syngeneic CD47-null RBCs through erythrophagocytosis in the spleen. The lack of tyrosine phosphorylation in SIRPα ITIMs was associated with macrophage aggressiveness[20,21]. Later, other experiments showed that CD47-deficient circulating cells were rapidly cleared by splenic

macrophages. A lack of this inhibitory signaling promoted blood cell binding to macrophages and was sufficient to trigger a phagocytic signal[22,23]. Consistent with the CD47-SIRPα interaction inhibiting macrophage phagocytosis, studies of cancer pathogenesis indicated that increased CD47 expression commonly occurred on tumor cells and acted as a pathway to evade immunological eradication[24-26]. However, perturbation of the CD47-SIRPα interaction provides opportunities for cancer eradication, especially in conjunction with therapeutic anticancer antibodies[27-31]. Other studies showed that by binding to SIRPα, lung factors, such as surfactant protein A (SP-A) and surfactant protein D (SP-D), act as surveillance molecules to suppress macrophage phagocytic function and lung inflammation[32,33]. Recent research indicated that both the CD47-SIRPα interaction and IL-10 constrain inflammation-induced macrophage phagocytosis of healthy endogenous cells[10]. Multiple low-dose STZ (MLD-STZ) treatment induces infiltration of macrophages in the islets and then leads to insulitis and diabetes[34]. Thus, the core question remains: What is the mechanism that initiates macrophage infiltration and phagocytosis of endogenous cells under inflammatory stimulation? In this mouse model, the results revealed that CD47 expression by pancreatic islet beta cells was reduced, leading to increased interest in discovering whether CD47 downregulation induces macrophage recruitment to pancreatic islets. As a protective factor, CD47 expression in pancreatic islet beta cells prevents macrophage phagocytic function when inflammatory lesions occur[35,36]. Ablating CD47 might be sufficient to contribute to autoimmune disease progression. Enhancing the expression of CD47 might improve the survival of pancreatic islet beta cells in the development of autoimmune diabetes.

MATERIALS AND METHODS

Antibodies and chemicals

The primary antibody against insulin was obtained from Cell Signaling Technology (Boston, CA, United States). Primary antibodies against CD47 and GAPDH were obtained from Santa Cruz BioTechnology (San Diego, CA, United States). The anti-F4/80 primary antibody was purchased from eBioscence (San Diego, CA, United States). STZ was purchased from Sigma. The insulin ELISA kit was purchased from BD Biosciences. Carboxy fluorescein succinimidyl ester (CFSE) was purchased from Invitrogen. RAW264.7 and Min6 cells were purchased from the China Cell Culture Center (Shanghai, China). The cells were cultured in low-glucose RPMI 1640 supplemented with 10% fetal bovine serum (FBS) (Gibco), penicillin, and streptomycin in a water-saturated atmosphere with 5% CO_2.

Mice and STZ diabetes mouse model

Male C57BL/6J mice (7-8 wk old, weighing 20-25 g) were purchased from the Model Animal Research Center of Nanjing University (Nanjing, China) and were maintained in a pathogen-free animal facility on a 12 h light/dark cycle. STZ-induced murine diabetes was established as previously described. Briefly, to establish diabetes, the mice received five daily intraperitoneal injections of STZ (40 mg/kg body weight) dissolved in citrate buffer, pH 4.5. Control mice were given equal volumes of citrate buffer. The mice were monitored for blood glucose and body weight changes.

Immunohistochemistry and flow cytometry analysis

To detect pancreatic islet CD47 protein expression and macrophage infiltration, 5 mm sections of frozen pancreas were labeled with anti-insulin, anti-CD47, and anti-F4/80 primary antibodies. The corresponding fluorescent secondary antibodies were used to label the primary antibodies. Fluorescence microscopy was then used for imaging. Min6 cells were labeled with a CD47 primary antibody and subsequently with a secondary FITC antibody. The labeled Min6 cells were detected by flow cytometry to evaluate CD47 expression changes.

In vitro phagocytosis assay

Macrophage activation and *in vitro* phagocytosis assays were performed as previously described. In brief, lipopolysaccharide (LPS) was added to the medium to stimulate macrophage activation for 8 h. Min6 cells, treated with and without STZ, were labeled with CFSE and co-incubated with activated macrophages for 2 h, after which phagocytosis was analyzed by fluorescence microscopy.

Pancreatic islet isolation and insulin secretion detection

The mice were anesthetized with chloral hydrate and euthanized. Pancreatic islets were isolated by collagenase digestion and were hand-picked according to the method described above. The islets were cultured in RPMI 1640 medium containing

5.5 mmol/L glucose and supplemented with 1% penicillin-streptomycin, 10% fetal bovine serum (all from Gibco/BRL, Burlington, ON), and 10 mmol/L HEPES (Sigma). Serum insulin concentrations were assessed using specific insulin ELISA kits according to the manufacturer's instructions.

All animal experiments were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and were approved by the Ethics Committee on the Care and Use of Laboratory Animals of Nanjing Normal University.

Western blot analysis

Min6 cell lysates were analyzed by Western blot to detect changes in CD47 expression after treatment with STZ. Western blot analysis was conducted using an antibody specific for CD47. The antigen was visualized using an ECL plus detection system (Amersham Pharmacia Biotech). Normalization was performed by probing the same samples with an anti-GAPDH antibody. Student's *t*test was used for comparisons.

RESULTS

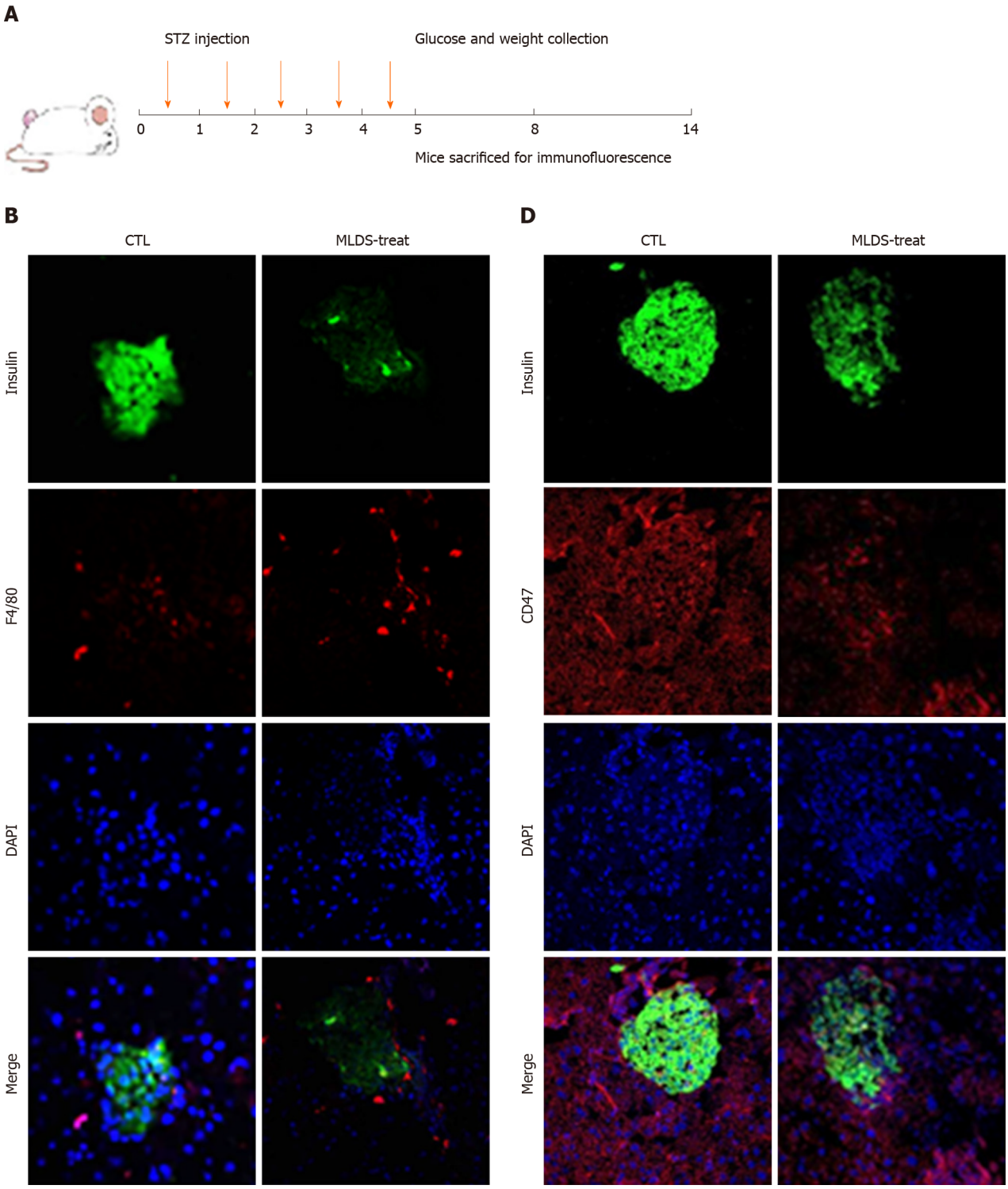
Increased macrophage migration to pancreatic islet cells with reduction of CD47 expression under STZ-inflammation condition

A diabetic mouse model was established by MLD-STZ treatment as previously described[37]. Seven- to eight-wk-old male C57/BL6 mice received five daily intraperitoneal injections of STZ (40 mg/kg body weight), which was dissolved in citrate buffer (pH 4.5) (Figure 1A). Control animals received equal volumes of citrate buffer. Daily blood samples were taken from the tail vein for glucose detection. Then, any changes in blood glucose were tested with a glucometer. The results revealed that plasma glucose values in STZ-injected mice were significantly elevated after the fourth STZ injection (mean plasma glucose value of 13.6 mmol/L, $n = 10$) compared to those of the citrate buffer group (mean plasma glucose value of 8.7 mmol/L, $n = 10$), and a substantially high level was maintained for the subsequent 9 d (Supplementary Figure 1A). Additionally, the body weights were recorded. The control group displayed a normal body weight, while the STZ-treated mice showed slower growth (Supplementary Figure 1B).

To determine macrophage infiltration, pancreatic tissue was fixed and labeled for F4/80[38,39]. As shown in Figure 1B and 1D, a large number of macrophages surrounded and infiltrated the islets, accompanied by reduced insulin secretion in STZ-treated mice. The statistical analysis is shown in Figure 1C and 1D. Significant insulin reduction was associated with pancreatic islet beta cell necrosis and pancreatic architecture damage. The anti-CD47 antibody was used to detect CD47 expression in pancreatic islet cells. CD47 expression on pancreatic islets was significantly reduced after five daily doses of STZ (Figure 1D). These results clearly highlight that macrophage activation and invasiveness were increased with a reduction in pancreatic islet cell CD47 expression in the STZ-treated group.

In vitro studies of macrophage phagocytosis

The use of Min6 cells that were treated with STZ further confirmed the effect of STZ on CD47 expression, as well as macrophage phagocytosis. For these experiments, Min6 cells were stimulated with 1 mmol/L STZ for 18 h. As expected, CD47 expression on the Min6 cell surface strongly decreased after STZ treatment, as measured by a FAC scan flow cytometer (Figure 2A and 2B). These results further confirmed that STZ affected CD47 expression both *in vitro* and *in vivo*. To determine the function of Min6 cells after STZ treatment, we incubated Min6 cells with 1 mmol/L STZ for 1 h. After a 24-h recovery, insulin secretion was detected under 5 mmol/L or 25 mmol/L glucose conditions. Insulin secretion was reduced under both low and high glucose conditions in STZ-treated cells (Figure 2C). STZ impaired Min6 cell function with CD47 expression reduction. These results suggest that the reduction in CD47 is a critical factor in the process of macrophage accumulation in pancreatic islet cells, resulting in a series of immune responses, as well as in the clinical development and pathogenesis of autoimmune diabetes. To detect CD47 expression-mediated regulation of the phagocytic function of macrophages, Min6 cells were labeled with CFSE and subsequently cocultured with LPS-activated macrophages. Accelerated Min6 cell phagocytosis was observed under STZ treatment compared with that of the control group. The results revealed that macrophages had a greater tendency to phagocytose CFSE-labeled Min6 cells, and the STZ-induced downregulation of CD47 vastly improved macrophage phagocytic activity (Figure 3D).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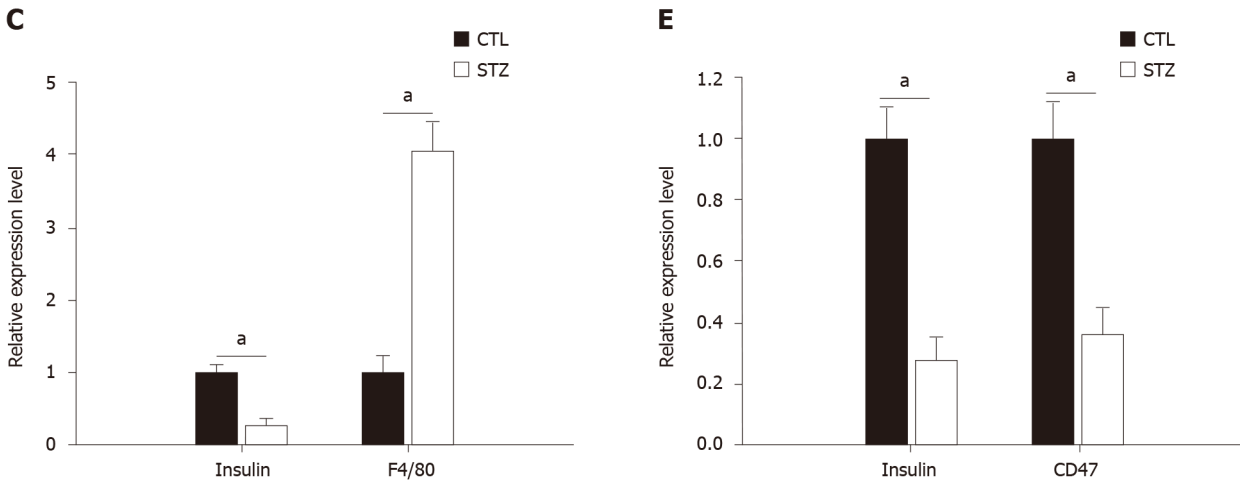


Figure 1 Increased macrophage migration to pancreatic islet cells with the reduction of CD47 expression under streptozotocin treatment. A: The experimental design. Mice were treated by five daily intraperitoneal injections of streptozotocin (STZ) to construct a diabetes model; B: Macrophage infiltration into pancreatic islet cells which was indicated by increased F4/80 labeling accompanied by decreased insulin secretion in STZ treated cells; C: Statistical data; D and E: CD47 expression decreased under STZ condition. Student's *t*-test was performed. $^{a}P < 0.01$ *vs* CTL. CD47: Cluster of differentiation 47; STZ: Streptozotocin; CFSE: Carboxy fluorescein succinimidyl ester.

To imitate a similar situation and study the direct effect of STZ on pancreatic islet beta cells, mouse pancreatic islet cells were isolated as previously described[40]. Then, the islet cells were cultured in dishes with or without 1 mmol/L STZ stimulation for 12 h. Consistent with the *in vitro* test, we found that CD47 expression in pancreatic islet beta cells was significantly reduced under STZ treatment (Supplementary Figure 2A and B). Insulin secretion was also detected at 5 mmol/L or 25 mmol/L glucose. There was a similar result as that of treatment of Min6 cells, and insulin secretion was greatly reduced by STZ stimulation (Supplementary Figure 2C). These results indicate that the effect of STZ on pancreatic islet beta cells and macrophages might be related to the reduction in CD47 expression, which may provide a new mechanism of diabetes pathogenesis.

Signaling mechanisms that regulate macrophage phagocytosis upon CD47-SIRPα interaction

To confirm the direct effect of CD47 in regulating macrophage phagocytosis, we transfected Min6 cells with CD47 siRNA, followed by coculture of CFSE-labeled Min6 cells and LPS-activated macrophages to detect macrophage phagocytic activity. As shown in Figure 3A and 3B, relative CD47 expression was significantly downregulated with siCD47 transfection compared with siCTL transfection. Correspondingly, enhanced macrophage phagocytic activity was observed with CD47 siRNA transfection (Figure 3C). The CD47 open reading frame (ORF) was also transfected to further confirm that CD47-SIRPα negatively mediates phagocytosis. The CD47 expression level was tested by Western blot (Figure 3D and 3E). As shown in Figure 3F, cells transfected with the CD47 ORF displayed decreased macrophage phagocytosis compared to those treated with STZ alone. This demonstrates that the CD47-SIRPα interaction plays a key inhibitory role in the process of pancreatic islet beta cell clearance. These results confirmed that the absence of CD47-SIRPα-mediated inhibition improved macrophage phagocytic activity, and stronger inhibitory signaling triggered by CD47 ligation under STZ conditions is needed to effectively block macrophage phagocytosis.

CD47-regulated macrophage phagocytosis signaling

Figure 4 shows the hypothetical model of CD47-SIRPα-regulated macrophage phagocytosis in pancreatic islets with or without STZ stimulation. CD47-SIRPα-mediated inhibition is relevant and indispensable when phagocytosis occurs toward the "self". Under normal conditions, the CD47-SIRPα interaction provides inhibitory signals that prevent macrophage phagocytosis. In inflammatory conditions, such as STZ stimulation, macrophage phagocytosis is activated due to weakened CD47-SIRPα interactions. Reduced SIRPα might promote macrophage phagocytosis of CD47-low target cells, such as STZ-induced pancreatic islet beta cells.

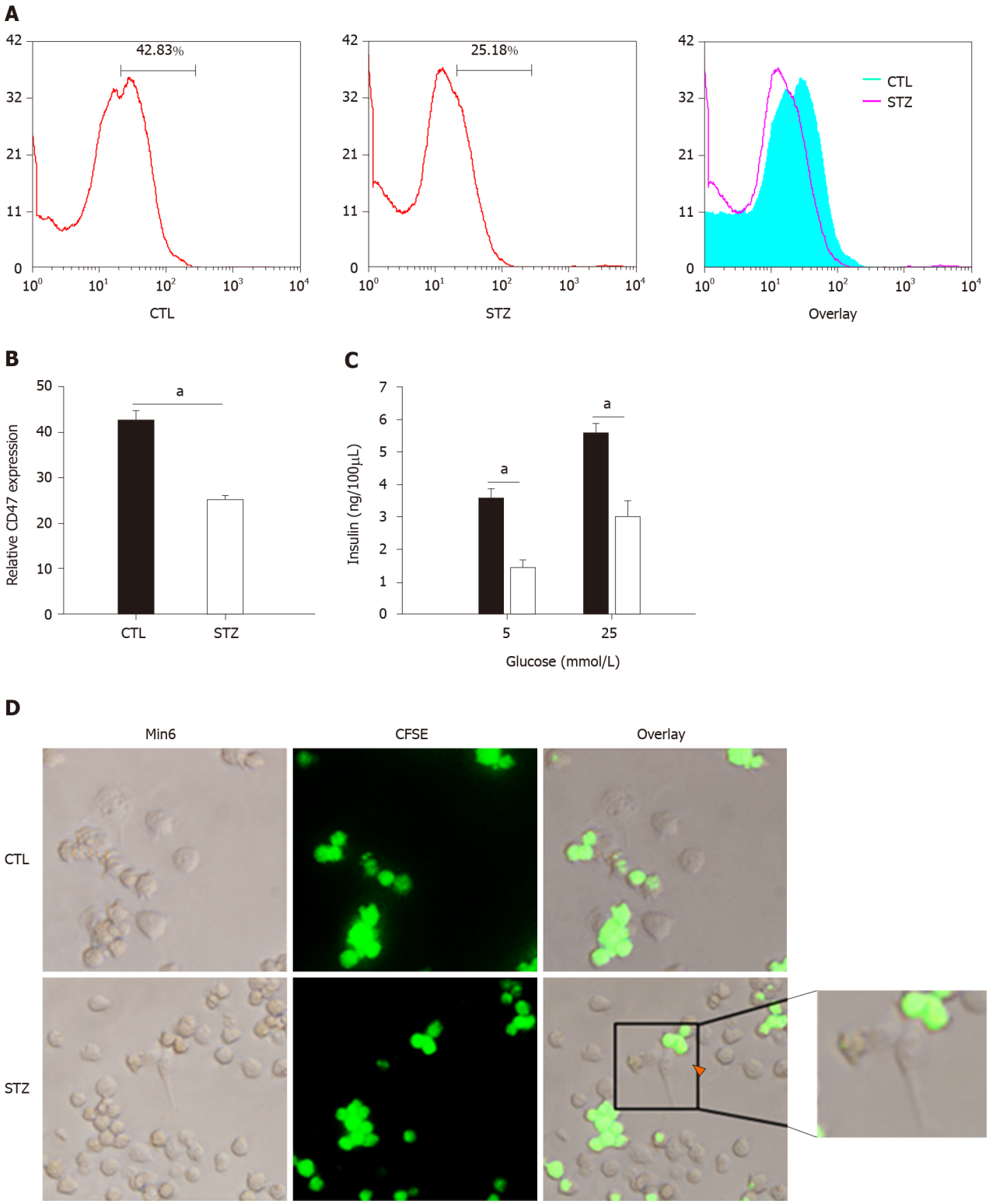
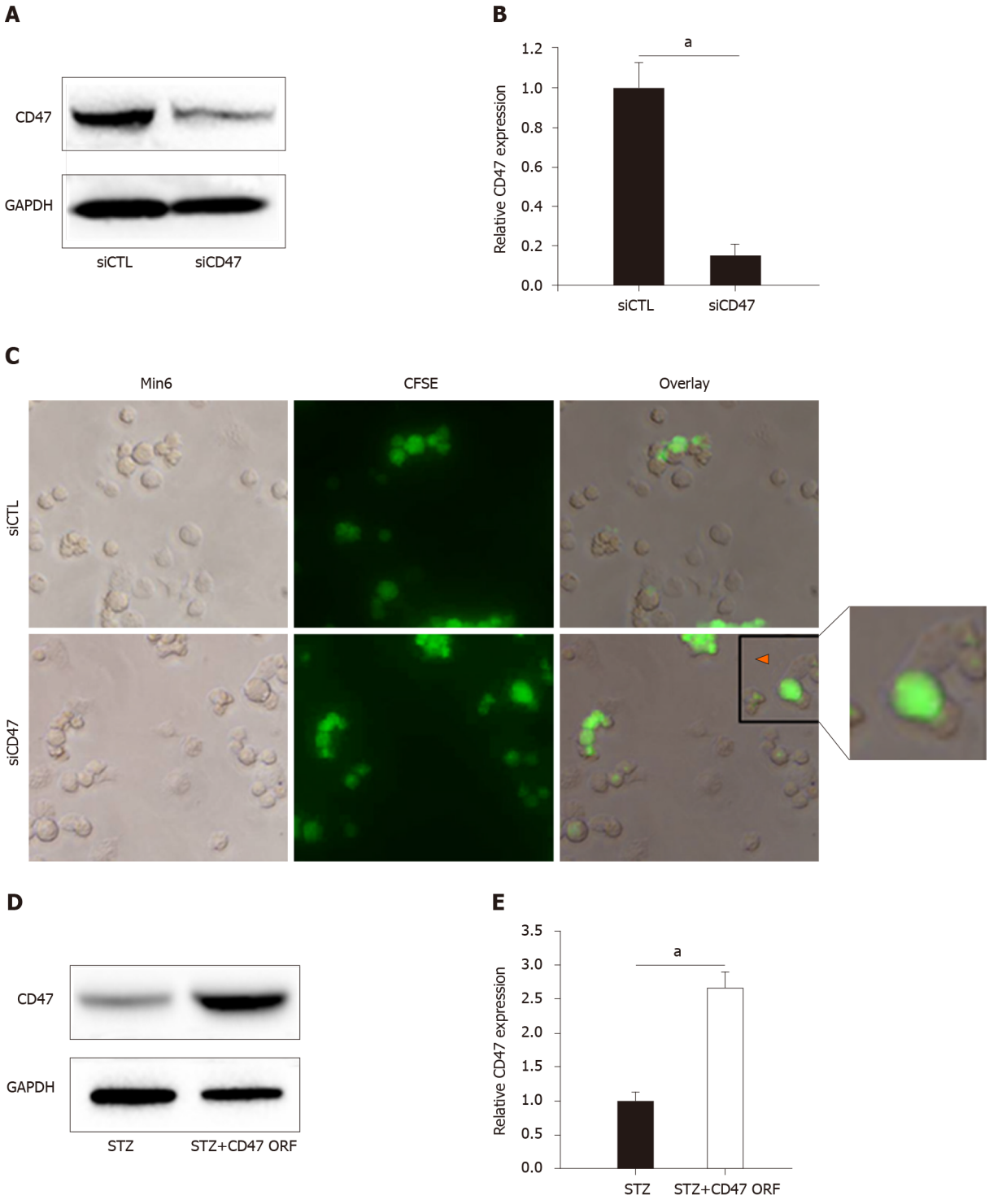


Figure 2 Macrophage phagocytosis assay *in vitro*. A and B: Flow cytometry results displayed declined CD47 expression of Min6 cells. C: Insulin secretion decreased with STZ stimulation. D: More LPS activated macrophages were recruited to phagocyte CD47 down-regulated Min6 cells. Arrows indicate phagocytosis. Student's *t*-test was performed. $^{a}P < 0.01$ *vs* CTL. CD47: Cluster of differentiation 47; STZ: Streptozotocin; CFSE: Carboxy fluorescein succinimidyl ester.

DISCUSSION

Macrophages are critical in the development and pathogenesis of autoimmune disease. They are the first immune cells to infiltrate the pancreatic islet when an "eat me" signal is present[3,7,41]. The balance between activating and inhibitory signals[42,43] regulates macrophage activation. CD47 is one of the inhibitory signals through its interaction with SIRPα, which is expressed on the surface of macrophages and other immune cells. Cells that express CD47 are recognized as "self"; otherwise, they will be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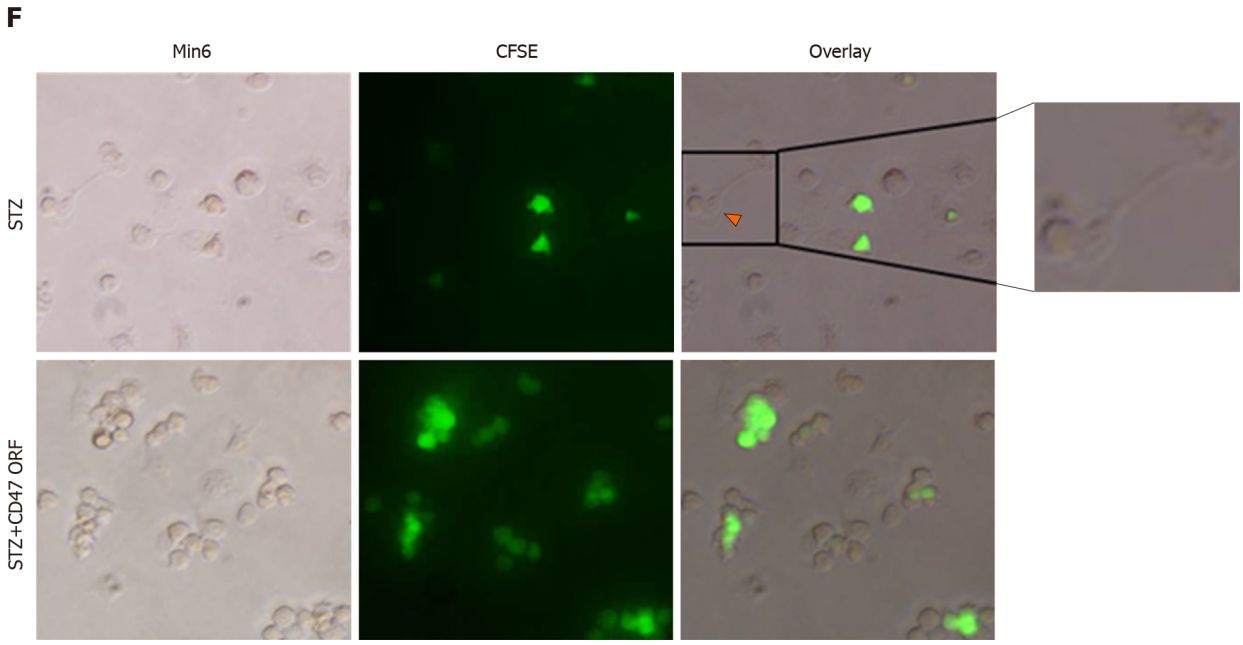

Figure 3 Macrophage phagocytosis is increased by CD47 siRNA transfection while recovered with CD47 overexpression. A and B: Western blot analysis revealing CD47 relative protein expression with CD47 siRNA transfection and statistical data; C: Macrophage phagocytosis was enhanced when Min6 cells were transfected with CD47 siRNA; D and E: Western blot analysis indicating CD47 relative protein expression when transfection with CD47 open reading frame (ORF; CD47 overexpression) and statistical data; F: Macrophage phagocytosis was impaired by CD47 ORF transfection under STZ condition. GAPDH served as a loading control. Western blot analysis represents the results of three independent experiments. Student's *t*test was performed. $^{a}P < 0.01$ *vs* CTL. CTL: Control. CD47: Cluster of differentiation 47.

eliminated as "non-self" targets[23]. Although the CD47-SIRPα mechanism may be dispensable under normal conditions, it becomes extremely important under inflammatory conditions and infection, during which macrophages enhance phagocytosis toward endogenous cells[44]. Findings from SIRPα-/- and CD47-/- mice show that the animals rapidly develop anemia under inflammatory challenges, which suggests that the lack of SIRPα or CD47 significantly reduces the threshold of this condition[45,46]. As reported previously[47,48], SIRPα expression in macrophages decreased following LPS stimulation, suggesting the dynamic nature of CD47-SIRPα-mediated inhibition, especially in inflammation and infection. In addition, data presented in recent studies showed that CD47-SIRPα-mediated inhibition controls not only phagocytic target selection but also the phagocytic robustness of the chosen target[10].

In the present study, we report for the first time that pancreatic islet beta cell surface CD47 reduction plays a critical role in pancreatic islet beta cell depletion in STZ-induced diabetes. This conclusion was supported by the data derived from both *in vivo* and *in vitro* experiments. First, concurrent pancreatic islet beta cell depletion and reduction in CD47 expression was observed in STZ-injected mice compared with citrate buffer-treated mice. Macrophage infiltration in pancreatic islets was also increased, as determined by F4/80 labeling. The reduction in CD47 expression was specific to pancreatic islet beta cells, since there was no change in CD47 surface expression in other cells in the pancreas after STZ treatment. This might explain why STZ specifically attacks pancreatic islet beta cells and leads to diabetes. Second, we confirmed the direct effect of STZ on pancreatic islet beta cells *in vitro*. After STZ treatment, both Min6 cells and isolated pancreatic islet beta cells displayed reduced CD47 expression levels and reduced insulin secretion. Enhanced phagocytosis of STZ-stimulated Min6 cells was also observed in an *in vitro* phagocytosis experiment. In addition, the enhanced macrophage phagocytosis of cells with downregulated CD47 expression was confirmed by direct transfection of CD47 siRNA. These results confirm our hypothesis that macrophages phagocytize pancreatic islet beta cells by recognizing CD47 signaling in the MLD-STZ-induced diabetes mouse model, which might provide an explanation of the mechanism of STZ-induced diabetes. CD47 is a novel therapeutic factor aimed at attenuating and preventing macrophage-regulated target cell depletion[49]. Moreover, these findings also encourage us to prevent the progression of diabetes or other autoimmune and inflammatory diseases clinically by improving CD47 expression. Further studies are needed to define the mechanism that controls receptor-mediated macrophage phagocytic recognition of endogenous cells.

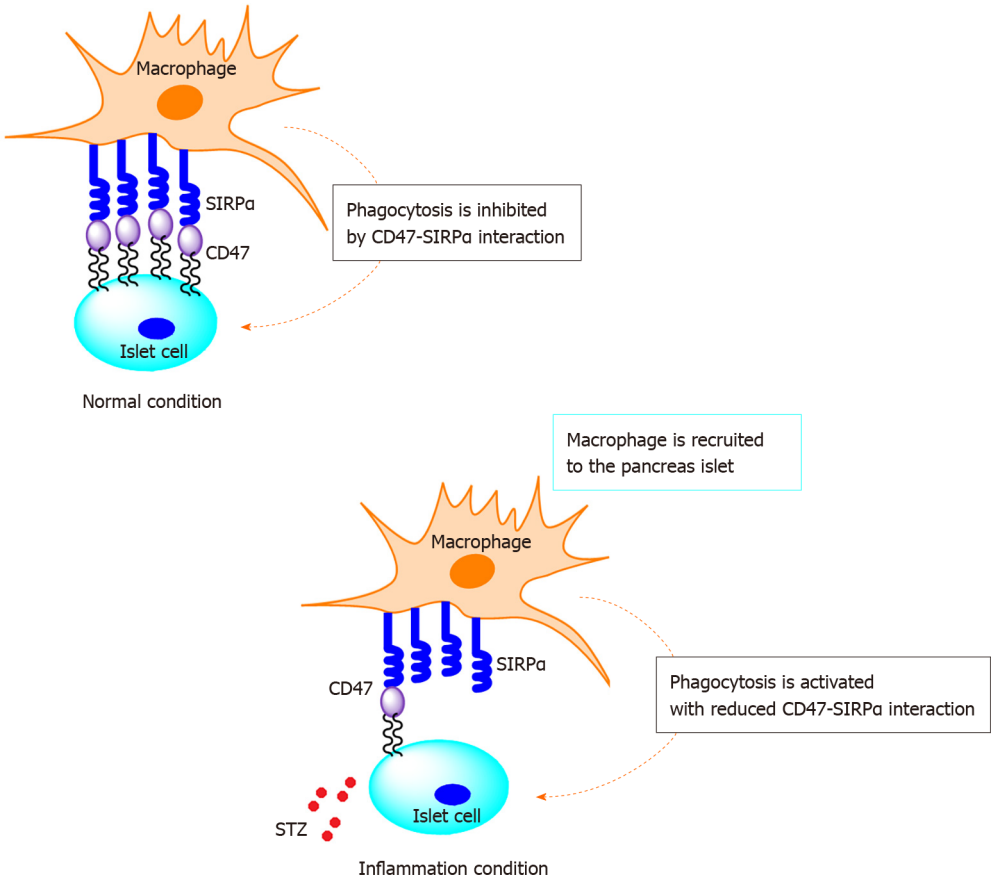

Figure 4 Hypothetical model of CD47-SIRPα-regulated inhibition phagocytosis in STZ-induced diabetes. Normally, CD47 is universally expressed on pancreatic islet beta cells. CD47-SIRPα interaction effectively governs macrophage phagocytosis toward healthy self-cells by a "not attach-self" default mode. With the stimulation of STZ, macrophages infiltrate into the pancreatic islet and phagocytose cells when CD47-SIRPα interaction could not be maintained under inflammation condition. "Eat me" signal is transferred with declined expression of CD47 on pancreatic islet cells. CD47: Cluster of differentiation 47; SIRPα: Signal regulatory protein α.

ARTICLE HIGHLIGHTS

Research background

Type I diabetes (T1D) is characterized by insulin loss, accompanied by excessive inflammatory cell infiltration like macrophages and the destruction of the pancreas. Regarding the mechanochemical signaling regulation of T1D, the relationship between macrophage migration and phagocytosis is still unclear. In this study, we provided a new insight into the immune response occurring in the pancreas.

Research motivation

We try to provide a new insight into the mechanism of immune response occurring in the pancreas of T1D patients.

Research objectives

Our aim was to provide a new strategy to prevent T1D progression.

Research methods

This study was performed both *in vivo* and *in vitro*. Macrophage migration and infiltration were assayed to study the mechanism of T1D immune response. The statistical analysis was performed using SPSS statistical software (version 16.0).

Research results

In this study, we found a significant decrease of CD47 in pancreatic beta islet cells stimulated with STZ and enhanced migration and infiltration of macrophages. As an integrin-associated surface factor, CD47 expression level is strongly related to the microphage immune response to inflamed pancreas beta islet.

Research conclusions

Our study shows a new mechanistic insight into T1D from view of immune response.

Research perspectives

This study could provide a new strategy to prevent the progression of T1D.

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ORIGINAL ARTICLE

Clinical and Translational Research

Do different bariatric surgical procedures influence plasma levels of matrix metalloproteinase-2, -7, and -9 among patients with type 2 diabetes mellitus?

Wen-Chi Wu, Wei-Jei Lee, Tzong-His Lee, Shu-Chun Chen, Chih-Yen Chen

ORCID number: Wen-Chi Wu (0000-0003-1383-0460); Wei-Jei Lee (0000-0001-7091-3006); Tzong-His Lee (0000000225003844); Shu-Chun Chen (0000-0002-4129-0273); Chih-Yen Chen (0000-0003-0937-0596).

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Wen-Chi Wu, Department of Medicine, Taipei Veterans General Hospital, Taipei 11217, Taiwan

Wei-Jei Lee, Department of Surgery, Min-Sheng General Hospital, Taoyuan 330, Taiwan

Wei-Jei Lee, Taiwan Society for Metabolic and Bariatric Surgery, Taipei 11031, Taiwan

Tzong-His Lee, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Far Eastern Memorial Hospital, New Taipei City 220, Taiwan

Shu-Chun Chen, Department of Nursing, Chang-Gung Institute of Technology, Guishan, Taoyuan 333, Taiwan

Chih-Yen Chen, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, Taipei 11217, Taiwan

Chih-Yen Chen, Faculty of Medicine and Institute of Emergency and Critical Medicine, National Yang-Ming University School of Medicine, Taipei 11221, Taiwan

Chih-Yen Chen, Association for the Study of Small Intestinal Diseases, Guishan, Taoyuan 33305, Taiwan

Chih-Yen Chen, Chinese Taipei Society for the Study of Obesity, Taipei 110, Taiwan

Corresponding author: Chih-Yen Chen, AGAF, MD, PhD, Attending Doctor, Professor, Division of Gastroenterology and Hepatology, Department of Medicine, Taipei Veterans General Hospital, 201, Sec. 2, Shih-Pai Road, Taipei 11217, Taiwan. chency@vghtpe.gov.tw

Abstract

BACKGROUND

Bariatric surgery is an efficient strategy for body weight and type 2 diabetes mellitus (T2DM) management. Abnormal lipid deposition in visceral organs, especially the pancreas and liver, might cause beta-cell dysfunction and insulin resistance. Extracellular matrix (ECM) remodeling allows adipose expansion, and matrix metalloproteinases (MMPs) play essential roles in ECM construction. MMP-2 and MMP-9 are the substrates of MMP-7. Different studies have reported that MMP-2, -7, and -9 increase in patients with obesity and metabolic syndromes or T2DM and are considered biomarkers in obesity and hyperglycemia patients.

AIM

written consent about personal and medical data collection prior to study enrolment.

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To prospectively investigate whether MMP-2, MMP-7, and MMP-9 differ after two bariatric surgeries: Gastric bypass (GB) and sleeve gastrectomy (SG).

METHODS
We performed GB in 23 and SG in 19 obese patients with T2DM. We measured body weight, waist circumference, body mass index (BMI), and serum concentrations of total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood sugar (FBS), hemoglobin A1c (HbA1c), C-peptide, homeostasis model assessments of insulin resistance, and MMP-2, MMP-7, and MMP-9 levels at baseline and at 3, 12, and 24 mo post-operation.

RESULTS
Twenty-three patients aged 44.7 ± 9.7 years underwent GB, and 19 patients aged 40.1 ± 9.1 years underwent SG. In the GB group, BMI decreased from 30.3 ± 3.4 to 24.4 ± 2.4 kg/m^2, HbA1c decreased from 9.2% ± 1.5% to 6.7% ± 1.4%, and FBS decreased from 171.6 ± 65.0 mg/dL to 117.7 ± 37.5 mg/dL 2 years post-operation ($P < 0.001$). However, the MMP-2, MMP-7, and MMP-9 levels pre- and post-GB were similar even 2 years post-operation ($P = 0.107$, 0.258, and 0.466, respectively). The SG group revealed similar results: BMI decreased from 36.2 ± 5.1 to 26.9 ± 4.7 kg/m^2, HbA1c decreased from 7.9% ± 1.7% to 5.8% ± 0.6%, and FBS decreased from 138.3 ± 55.6 mg/dL to 95.1 ± 3.1 mg/dL ($P < 0.001$). The serum MMP-2, -7, and -9 levels pre- and post-SG were not different ($P = 0.083$, 0.869, and 0.1, respectively).

CONCLUSION
Improvements in obesity and T2DM induced by bariatric surgery might be the result of MMP-2, -7, or -9 independent pathways.

Key words: Matrix metalloproteinases; Extracellular matrix; Obesity; Type 2 diabetes mellitus; Gastric bypass; Sleeve gastrectomy

Core tip: Bariatric surgery is a very effective strategy for managing obesity patients and those with type 2 diabetes mellitus. Matrix metalloproteinases play roles in extracellular matrix remodeling which consequently results in insulin resistance. Some authors reported higher levels of matrix metalloproteinases (MMP)-2, -7, and -9 in obese or diabetic patients. We measured plasma MMP-2, -7, and -9 concentrations in obese patients before and after bariatric surgeries; however, we did not identify any statistical differences in the MMP levels. We suggested that bariatric surgery reduces obesity and diabetes through MMP-2, -7, or -9 independent pathways.

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INTRODUCTION

Type 2 diabetes mellitus (T2DM) and obesity raise concerns among global health issues[1-4]. Bariatric surgical procedures, including gastric bypass (GB) and sleeve gastrectomy (SG), have been generally acknowledged as some of the most effective methods to manage body weight and glycemic control in obese patients[5-8]. Matrix metalloproteinases (MMPs) are calcium-dependent and zinc-containing proteases involved in extracellular matrix (ECM) synthesis, basement membrane degradation, and growth factor stimulation[9,10], which further affect adipogenesis and adipose tissue growth[11]. MMPs are classified into six groups based on their substrate and homology: Collagenases, such as MMP-1 and MMP-8; gelatinases, such as MMP-2, and -9; stromelysins, such as MMP-3 and -11; matrilysins, including MMP-7 and -26;

membrane type MMPs; and other MMPs[12]. In 2001, Bouloumié *et al*[13] first reported that human adipocytes and pre-adipocytes secrete MMP-2 and MMP-9, and in turn, these two MMPs serve as potential essential regulators in adipocyte differentiation.

MMPs have been recognized as biomarkers of several disorders such as coronary artery diseases and heart failure. Plasma levels of MMPs have been reported to be significantly higher in obesity and T2DM patients[11]. MMP-2 and MMP-9 have both been reported to promote inflammation in high coronary risk events and plaque instability[14,15]. Both have also been reported to increase in obese patients, those with metabolic syndromes, and even patients with diabetes[16,17]. MMP-7 targets various substrates for ECM function, including MMP-2 and MMP-9[12,18]. Elevated MMP-7 levels in obese patients were reported to facilitate adipocyte differentiation[19]. Some authors considered MMP-7 as a marker for obesity, fat cell diameters, and obesity-related metabolic traits[20,21].

We hypothesized that having bariatric surgery would result in a decrease of plasma levels of MMP-2, -7, and -9. If correct, then those MMPs might represent biomarkers of the efficacy of bariatric surgeries. Furthermore, bariatric surgery might improve glycemic control through MMP-2, -7, or -9 independent pathways, and those MMPs could be novel therapeutic targets and prognostic biomarkers for obese patients with T2DM.

MATERIALS AND METHODS

We conducted a prospective observational study using a hospital-based design. Overweight or obese patients with T2DM receiving either GB or SG surgery were enrolled in the study. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board (IRB approval number: MSIRB2016006).

Eligible patients had been diagnosed with T2DM for more than 6 mo previously with a hemoglobin A1c (HbA1c) level > 8% and were receiving regular medical treatment, including therapeutic nutritional therapy, oral anti-diabetic agents, or insulin. The body mass index (BMI) in these patients ranged from 27.5-35 kg/m^2, and these patients were willing to undergo additional treatment with lifestyle modifications, accepted follow-up visits, and provided written informed consent documents.

Patients with cancer within the last 5 years, human immunodeficiency virus infection, active pulmonary tuberculosis, cardiovascular instability within the previous 6 mo, pulmonary embolisms, serum creatinine levels > 2.0 mg/dL, chronic hepatitis B or C, liver cirrhosis, inflammatory bowel disease, acromegaly, organ transplantation, history of another bariatric surgery, alcoholic disorders, or drug abuse, or those who were uncooperative were excluded from the study.

Clinical anthropometry and routine laboratory assessments were performed on the day before surgery as baseline (M0) and at 3 mo (M3), 12 mo (M12), and 24 mo (M24) postoperatively. The participants were required to fast overnight prior to each blood sample collection. The samples were taken from the median cubital vein between 8 and 11 o'clock in the morning. Laboratory assessments included serum levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood sugar (FBS), hemoglobin A1c (HbA1c), C-peptide, homeostasis model assessments of insulin resistance, and MMPs-2, -7, and -9. Anthropometry measurements included body weight, waist circumference (WC), and BMI. The homeostasis model assessments of insulin resistance was calculated as plasma glucose (mmol/L) × insulin (μU/mL)[22].

Overall, there were 23 patients who received GB, and 19 patients who underwent SG in this study. There were 6 men and 17 women aged 44.7 ± 9.7 years in the GB group. There were 14 men and 5 women aged 40.1 ± 9.1 years in the SG group. The duration of T2DM was 4.0 ± 2.7 and 2.6 ± 2.8 years in the GB and SG groups, respectively (Table 1).

The blood samples were promptly injected into aprotinin-containing tubes (500 U/mL) once taken. After standardized centrifugation at 300 *g* and storage at −20 °C, the plasma was aliquoted into polypropylene tubes. Validated enzyme immunoassays for MMPs-2, -7, and -9 (QuickZyme Biosciences B.V., CK Leiden, The Netherlands) performed in a single batch and in a blinded fashion was used to measure the concentrations of MMP-2, -7, and -9.

The comparison of baseline and postoperative variables was conducted using the Wilcoxon signed-rank test. Friedman's one-way repeated measures analysis of variance on ranks and a post-hoc test were performed to analyze the difference in plasma levels of MMP-2, -7, and -9 at M0, M3, M12, and M24. Spearman's correlation

Table 1 Baseline characteristics of the two groups

Baseline characteristics	Gastric bypass	Sleeve gastrectomy
Patient numbers	23	19
Male	6	14
Female	17	5
Age (yr)	44.7 ± 9.7	40.1± 9.1
Duration of type 2 diabetes mellitus (yr)	4.0 ± 2.7	2.6 ± 2.8

analysis was used to test the correlations between two parameters. The statistical package for Social Science, version 12.0 (SPSS, Inc., Chicago, Illinois, IL, United States) was used for all analyses.

RESULTS

In the GB group, WC, BMI, HbA1c, and FBS were significantly decreased at 2 years postoperatively. WC decreased from 103.2 ± 10.3 to 84.2 ± 7.1 cm; BMI decreased from 30.3 ± 3.39 to 24.4 ± 2.4 kg/m^2; HbA1c decreased from 9.2% ± 1.5% to 6.7% ± 1.4%; and FBS decreased from 171.6 ± 65.0 to 117.7 ± 37.5 mg/dL; and all were statistically significant ($P < 0.001$). However, the MMP-2, MMP-7, and MMP-9 levels were similar before and after GB even 2 years postoperatively ($P = 0.107$, 0.258, and 0.466, respectively) (Table 2).

The SG group revealed similar results. WC decreased from 109.4 ± 10.5 to 87.7 ± 11.3 cm; BMI decreased from 36.2 ± 5.1 to 26.9 ± 4.7 kg/m^2; HbA1c decreased from 7.9% ± 1.7% to 5.8% ± 0.6%; and FBS decreased from 138.3 ± 55.6 mg/dL to 95.1 ± 3.1 mg/dL; and all were statistically significant ($P < 0.001$), although serum MMP-2, -7, and -9 levels before and after SG were not statistically significant ($P = 0.083$, 0.869, and 0.1, respectively) (Table 3). The serum MMP-2, MMP-7, and MMP-9 concentration trends of GB and SG are shown in Figure 1.

DISCUSSION

Obesity results from more lipid storage in adipose tissues causing further ECM accumulation[23]. ECM remodeling and reshaping are necessary to allow for new adipose tissue to grow[24]. In obesity, oxidative stress such as hypoxia and inflammation leads to pathological expansion of the ECM, macrophage aggregation, and collagen expression. Collagen accumulation might further induce lipid deposition[25]. Excessive ECM in white adipose tissue causes necrosis and apoptosis, cell death, accumulation of macrophages, and, consequently, insulin resistance[26]. Ectopic lipid deposition in the liver and pancreas might further result in beta-cell dysfunction and additional insulin resistance[27,28]. ECM changes in adipose tissue are considered to be related to T2DM[29].

Molecules other than MMPs such as integrins, collagens, a disintegrin and metalloproteinase domain-containing proteins, osteopontin, and tissue inhibitors of metalloproteinases are crucial players in ECM remodeling and adipose tissue rearrangement[30]. Integrins are the major adhesion receptors of the ECM, which transduce signals across the cell membrane and influence intracellular signaling[31]. Rodent studies have demonstrated that integrins might modulate glucose transporter 4 in adipose tissue, impair skeletal muscle glucose uptake, and aggravate insulin resistance[32,33]. Integrins take part in mechanical stimulation of insulin signaling, membrane insulin receptor localization, and insulin sensitivity[34]. Integrin subgroup β2 impacts glucose balance under high fat consumption by activating the immune system, increasing neutrophil growth, and allowing infiltration of leukocytes into the tissue, which improves insulin resistance[35]. This mechanism was corroborated in a study by Roumans *et al*[36] who demonstrated changes in integrin gene activity and ECM remodeling in obesity patients whose therapy was diet-control.

Collagens affect cell adhesion, migration, and differentiation in adipose tissue[37], and their accumulation results in the formation of adipose tissue and insulin resistance[38]. In patients with obesity, collagen V1 was suppressed in adipose tissue and surgery-induced weight loss increased collagen VI in subcutaneous tissue[39]. Other authors found that plasma osteopontin was significantly elevated in T2DM patients. They also concluded that osteopontin might serve a key role in insulin

Table 2 Body mass index, hemoglobin A1c, fasting blood sugar, matrix metalloproteinas-2, -7, and -9 levels at baseline, 3 mo, 12 mo, and 24 mo after gastric bypass

	BMI (kg/m^2)		Waist circumference (cm)		HbA1c (%)		FBS (mg/dL)		MMP-2 (ng/mL)		MMP-7 (ng/mL)		MMP-9 (ng/mL)	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
M0	30.3	3.4	103.2	10.3	9.2	1.5	171.6	65.0	9.22	1.9	2.5	1.2	21.7	22.3
M3	26.0	2.8	90.4	8.0	7.1	1.6	127.0	46.7	9.28	2.0	2.1	1.1	18.8	12.8
M12	24.2	2.2	82.3	5.3	6.5	1.2	114.1	31.1	10.65	4.3	2.5	1.2	20.6	16.2
M24	24.4	2.4	84.2	7.1	6.7	1.41	117.7	37.5	10.59	3.5	1.5	1.2	19.1	22.4
P	< 0.001[1]		< 0.001[1]		< 0.001[1]		< 0.001[1]		0.107		0.258		0.466	

SD: Standard deviation; BMI: Body mass index; HbA1c: Hemoglobin A1c; FBS: Fasting blood sugar; MMP: Matrix metalloproteinases; M0: The baseline prior to surgery; M3: 3 mo postoperatively; M12: 12 mo postoperatively; M24: 24 mo postoperatively.
[1]Statistically significant.

resistance and help to predict 3-year diabetic remission rates in patients undergoing bariatric surgery[40-42].

Although some studies demonstrated higher levels of MMP-2 and MMP-9 in patients with obesity, metabolic syndrome, or diabetes compared to controls[16], other studies showed no difference in the levels of MMP-2 and -9 in patients with similar disorders[43]. Additionally, two studies have shown that MMP-2 and MMP-9 activity decreased in white adipose tissue, but not in the plasma from animals with insulin resistance[44,45]. According to the 2019 report by García-Prieto *et al*[46], MMP-2 activity, measured by gelatin zymography, was initially similar in both obesity and non-obesity patients, but then decreased significantly after bariatric surgery. Similarly, although MMP-9 levels were higher in obesity patients than in non-obesity control patients, it decreased after bariatric surgery[46]. Boumiza *et al*[47] found that *MMP-7* polymorphisms had only a non-significant association with BMI, and both systolic and diastolic blood pressures, triglycerides, total cholesterol, and high-density lipoprotein cholesterol plasma levels were not influenced by *MMP-7* polymorphisms.

Metabolically unhealthy people with normal body weight are susceptible to cardiovascular diseases and DM due to hyperinsulinemia, insulin resistance, and hypertriglyceridemia[23,48]. Therefore, the mechanism of how bariatric surgery improves DM might not be related to its ability to control weight. Furthermore, a previous study also demonstrated that while long-term aerobic training attenuated MMP-2 levels, it also increased MMP-9 levels[12]. The interactions and associations among MMP-2, MMP-7, MMP-9, and weight management are still ambiguous and require additional research.

Our study has some limitations. First, the study population was relatively small. Second, more women received GB than men and more men received SG than women. Third, a type-2 statistical error might occur due to the selected study populations. Furthermore, neither the MMP levels in adipose tissue nor their activities in plasma or adipose tissue were measured. Lastly, the study was conducted in a single-center and was open-labeled.

In the present study we investigated the effects of two bariatric surgeries, GB and SG, on MMP-2, -7, and -9 plasma concentrations. The plasma levels of the three MMPs did not differ before and after the two surgeries. We suggested that bariatric surgery helps improve glucose in obese patients with T2DM *via* the MMP-2, -7, and -9 independent pathways, and that it might be the adipose tissue, rather than the plasma concentrations of MMP-2, -7, and -9, or the plasma and adipose tissue MMP activities, that influences T2DM. Our results augment the current evidence of how bariatric surgery affects glycemic control in obesity and T2DM patients. Further trials determining whether MMPs could be potential markers for the efficacy of bariatric surgeries and how bariatric surgeries can affect diabetic control in obese patients are warranted.

Table 3 Body mass index, hemoglobin A1c, fasting blood sugar, matrix metalloproteinas-2, -7, and -9 levels at baseline, 3 mo, 12 mo, and 24 mo after sleeve gastrectomy

	BMI (kg/m^2)		Waist circumference (cm)		HbA1c (%)		FBS (mg/dL)		MMP-2 (pg/mL)		MMP-7 (pg/mL)		MMP-9 (pg/mL)	
	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD	mean	SD
M0	36.2	5.1	109.4	10.5	7.9	1.7	138.3	55.6	15.4	10.8	2.3	1.3	12.1	9.4
M3	30.6	4.6	92.5	9.9	5.9	0.5	91.0	2.2	16.3	12.9	2.1	1.2	16.4	12.2
M12	26.8	4.4	87.1	12.7	5.7	0.5	90.6	3.5	14.4	10.9	2.3	1.2	12.3	7.6
M24	26.9	4.7	87.7	11.3	5.8	0.6	95.1	3.1	27.0	12.0	1.6	1.4	12.1	8.3
P	< 0.001[1]		< 0.001[1]		< 0.001[1]		< 0.001[1]		0.083		0.869		0.100	

[1]Statistically significant. SD: Standard deviation; BMI: Body mass index; HbA1c: Hemoglobin A1c; FBS: Fasting blood sugar; MMP: Matrix metalloproteinases; M0: The baseline prior to surgery; M3: 3 mo postoperatively; M12: 12 mo postoperatively; M24: 24 mo postoperatively.

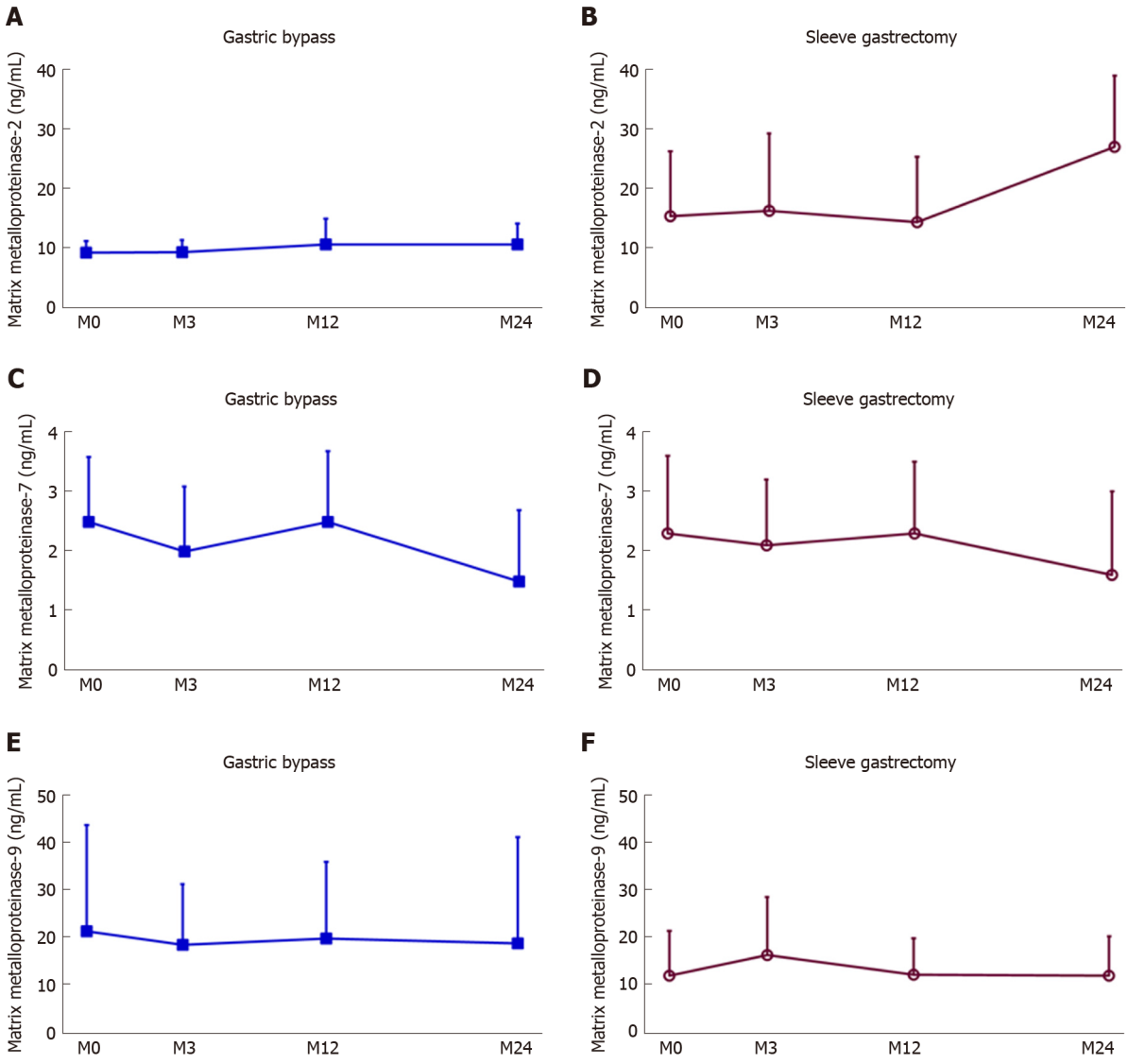

Figure 1 Matrix metalloproteinas-2, -7, and -9 plasma levels at the baseline, 3 mo, 12 mo, and 24 mo after gastric bypass and sleeve gastrectomy. A: Matrix metalloproteinase (MMP)-2 levels in GB (gastric bypass) group; B: MMP-2 levels in SG (sleeve gastrectomy) group; C: MMP-7 levels in GB group; D: MMP-7 levels in SG group; E: MMP-9 levels of GB; F: MMP-9 levels of SG. M0: The baseline prior to surgery; M3: 3 mo postoperatively; M12: 12 mo postoperatively; M24: 24 mo postoperatively; GB: Gastric bypass; SG: Sleeve gastrectomy.

ARTICLE HIGHLIGHTS

Research background

Bariatric surgeries, including gastric bypass and sleeve gastrectomy, are generally accepted to be effective in controlling body weight and blood glucose in obese patients. Researchers have found matrix metalloproteinases (MMPs) as biomarkers in many disorders. The levels of MMPs were reported to be increased in obese and type 2 diabetes mellitus (T2DM) patients.

Research motivation

Previous research reported decreased MMPs, along with reduced body weight, in the exercise group rather than the control group. We hypothesized that the MMP-2, -7, -9 levels would decrease in patients who underwent bariatric surgeries and further explained the mechanism of body weight loss and blood sugar control caused by bariatric surgeries.

Research objectives

The results disclosed that the MMP-2, -7, and -9 levels did not differ before or after bariatric surgery. Bariatric surgeries are helpful for weight loss and blood sugar control without significantly affecting MMP-2, -7, and -9 levels. How bariatric surgeries regulate body weight and blood sugar in obese T2DM patients needs further investigation. Whether MMPs other than MMP-2, -7, and -9 play roles demands further study.

Research methods

Overall, 6 men and 17 women who received gastric bypass (GB), and 14 men and 5 women who received sleeve gastrectomy (SG) were included. All of the above subjects had a hemoglobin A1c (HbA1c) level > 8% under regular medication by endocrinologists and a body mass index (BMI) ranging from 27.5-35 kg/m^2. We measured their clinical anthropometry and serum levels of total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, fasting blood sugar, HbA1c, C-peptide, homeostasis model assessments of insulin resistance, and MMPs-2, -7, and -9 on the day before surgery as the baseline (M0 and at 3 mo (M3), 12 mo (M12), and 24 mo (M24) postoperatively. We use the validated enzyme immunoassays (QuickZyme Biosciences B.V., CK Leiden, The Netherlands) for the concentration of MMPs-2, -7, and -9. The procedure was performed in a blinded manner. For data analyses, the statistical package for Social Science, version 12.0 (SPSS, Inc., Chicago, Illinois, IL, United States) was used. The statistical methods included the Wilcoxon signed-rank test, Friedman's one-way repeated measures analysis of variance on ranks followed by a post-hoc test, and Spearman's correlation analysis.

Research results

In both the GB and SG groups, waist circumference, BMI, HbA1c, and fasting blood sugar were significantly decreased 2 years postoperatively. However, serum MMP-2, -7, and -9 levels did not significantly change after both surgeries. Our study added on the knowledge about the relationship between the biomarkers MMP-2, -7, and -9 and GB and SG surgeries.

Research conclusions

Our study demonstrated that the MMP-2, -7, and -9 levels did not differ before or after the bariatric surgeries, which indicated that bariatric surgeries might be helpful for body weight and glucose management without altering MMP-2, -7, and -9 levels. The mechanism of weight loss and glucose management by bariatric surgeries in obese T2DM patients needs more exploration.

Research perspectives

The study population was relatively small, and there were more women than men who received GB, and more men than women who received SG. Also, neither of the MMP levels nor their activities in adipose tissue were measured. In future studies, the sex ratio should be kept balanced in both groups. Furthermore, the MMP levels and activities in adipose tissue should be taken into consideration.

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ORIGINAL ARTICLE

Case Control Study

Effects of lifestyle interventions on rural patients with type 2 diabetes mellitus

Bo Wang, Xiao-Li Mu, Juan Zhao, Hai-Ping Jiang, Shan-Shan Li, Ge Yan, Ying-Ying Hua, Xue-Yi Ren, Li-Xia Xing, Yan Liang, Shu-Dong Zhang, Yu-Chi Zhao

ORCID number: Bo Wang (0000-0001-9355-5176); Xiao-Li Mu (0000-0001-6123-268X); Juan Zhao (0000-0002-3076-0452); Hai-Ping Jiang (0000-0002-3209-3403); Shan-Shan Li (0000-0002-7581-4573); Ge Yan (0000-0003-3437-3481); Ying-Ying Hua (0000-0001-9159-8893); Xue-Yi Ren (0000-0001-8785-0961); Li-Xia Xing (0000-0003-0172-4345); Yan Liang (0000-0002-4985-0327); Shu-Dong Zhang (0000-0001-8003-1357); Yu-Chi Zhao (0000-0002-4776-1419).

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Bo Wang, Xiao-Li Mu, Juan Zhao, Hai-Ping Jiang, Shan-Shan Li, Ge Yan, Ying-Ying Hua, Xue-Yi Ren, Li-Xia Xing, Yan Liang, Shu-Dong Zhang, Department of Internal Medicine, Yantaishan Hospital, Yantai 264025, Shandong Province, China

Yu-Chi Zhao, Department of Osteoarthropathy, Yantaishan Hospital, Yantai 264025, Shandong Province, China

Corresponding author: Yu-Chi Zhao, MD, Chief Doctor, Department of Osteoarthropathy, Yantaishan Hospital, No. 91, Jiefang Road, Zhifu District, Yantai 264001, Shandong Province, China. zhaoyuchizyc@163.com

Abstract

BACKGROUND

The prevalence of type 2 diabetes mellitus (T2DM) is rising rapidly in rural areas, and lifestyle interventions can effectively reduce the blood glucose levels of patients with T2DM. However, current dietary and exercise guidelines are still at experimental stages and are difficult for subjects to understand and implement. The Human Metabolism Analyzer provides real life interventions for the prevention and treatment of T2DM, and our pilot research has demonstrated its effectiveness and good compliance.

AIM

To investigate the effect of and compliance with lifestyle interventions in rural patients with T2DM.

METHODS

A total of ten rural villages were randomly selected in Chaoshui Township, Penglai City, Shandong Province, China, to conduct health screening among residents aged 50 years or older. Each rural village represented a group, and 12 patients with T2DM were randomly selected from each group (total: 120) to participate in this study and receive real life lifestyle interventions and medication guidance. Lifestyle interventions included changing the meal order (A), postprandial activities (B), resistance exercise (C), and reverse abdominal breathing (D). Diabetes education was conducted at least once a month with a weekly phone follow-up to monitor exercise and diet. Waist circumference, blood pressure, body mass index (BMI), motor function, body composition, fasting blood glucose, and glycated hemoglobin (HbA1c) were analyzed before and 3 mo after the intervention. Moreover, patient compliance and adjustments of hypoglycemic drugs were evaluated.

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RESULTS

A total of 109 subjects completed the study. The compliance rates for lifestyle interventions A, B, C, and D were 57.79%, 60.55%, 64.22%, and 75.23%, respectively. Among the subjects who received hypoglycemic drugs, the dose was reduced 2 to 3 times based on blood glucose in 54 (67.50%) subjects and was tapered and discontinued in 5 (6.25%) subjects within 3 mo, with no significant fluctuations in blood glucose after dose reduction and withdrawal. After lifestyle interventions, waist circumference, BMI, fasting blood glucose, and HbA1c significantly decreased ($P < 0.001$); motor function and body composition also significantly improved ($P < 0.001$).

CONCLUSION

For patients with T2DM, compliance to real-life lifestyle interventions is good, and the interventions significantly improve metabolic indicators such as waist circumference, BMI, blood pressure, HbA1c, body composition, and motor function. Some patients are able to taper or discontinue hypoglycemic drugs.

Key words: Type 2 diabetes mellitus; Lifestyle interventions; Body mass index

Core tip: The prevalence of type 2 diabetes mellitus (T2DM) is rising rapidly in rural areas, and lifestyle interventions can effectively reduce the blood glucose levels of patients with T2DM. However, current dietary and exercise guidelines are still at experimental stages and are difficult for subjects to understand and implement. The Human Metabolism Analyzer can accurately detect and analyze the effects of food types, sequence of food intake, activity or exercise pattern, and time on blood glucose production and consumption, providing a simple and effective lifestyle intervention for patients with type 2 diabetes. In this study, we analyzed the precise data obtained by the Human Metabolism Analyzer, demonstrating that this method has good effectiveness and compliance, and provides a new method for the prevention and treatment of diabetes.

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INTRODUCTION

Regular activity and exercise reduce glycated hemoglobin (HbA1c) levels, improve insulin resistance[1], reduce cardiovascular risk factors, and improve the quality of life[2,3] of patients with type 2 diabetes mellitus (T2DM). T2DM is an independent risk factor for decreased muscle strength[4] and causes a rapid decline in muscle strength and muscle performance[5]. Exercise and strict diet management prevent or delay the progression of T2DM[6,7].

Existing exercise and diet management regimens are associated with two problems: Unclear exercise methods and schedule can lead to exercise injuries, hypoglycemia, and poor results; and poor compliance can lead to poor long-term hypoglycemic effects and incomplete correction of glucose metabolism disorders. Therefore, it is urgent to refine diet and exercise programs and improve their effectiveness and patient compliance.

A human metabolism data acquisition and processing system (Human Metabolism Analyzer) built and implemented by the General Administration of Sport of China in 2018 has fundamentally solved the problems above. The Human Metabolism Analyzer accurately analyzes the effects of food types, food intake sequence, and activity/exercise mode and schedule on the production and consumption of blood glucose, thereby providing simple and effective interventions for patients with T2DM.

To date, few studies have been conducted in China or other countries to investigate the effect of Human Metabolism Analyzer-based lifestyle interventions on metabolic

indicators of patients with T2DM. Our research group has been conducting clinical and preclinical studies on the prevention and treatment of DM for the past few years and has participated in the research on chronic diseases sponsored by the General Administration of Sport. Our small clinical observation pilot study demonstrated good clinical efficacy of real-life lifestyle interventions on T2DM, as well as on pre-type 2 DM, simple obesity, and polycystic ovary syndrome. The next step is to include more subjects to further validate the effectiveness of and patient compliance with lifestyle interventions.

MATERIALS AND METHODS

We randomly selected ten rural villages in Chaoshui Township, Penglai City, Shandong Province, China to conduct T2DM screening among permanent residents aged 50 years or older. Each rural village represented a group, and 12 patients with T2DM were randomly selected from each group to participate in this study. The exclusion criteria were as follows: Severe cardiopulmonary insufficiency, swallowing difficulty or physical impairment, acute or chronic infections, long-term use of glucocorticoids, malignant tumors, or body mass index (BMI) < 25 kg/m^2.

All participants signed an informed consent form and completed T2DM questionnaires. General information such as height, weight, waist circumference, systolic blood pressure, and diastolic blood pressure was recorded. BMI was calculated as weight (kg)/height (m^2). A Huayi glucose meter (EZ-8, Beijing Huayi Jingdian Biotechnology Co., Ltd., China) was used to measure fasting blood glucose[8,9]; an Alere Afinion™ AS100 Analyzer (Alere Technologies AS, United States) was used to measure HbA1c; an MES-01S20 muscle performance analyzer (Beijing Mai Dakang Medical Device Manufacturing Co., Ltd., China) was used to evaluate motor function (lower extremity neural response rate and lower extremity reaction time) and body composition (lower extremity muscle distribution coefficient, fat percentage, and fat distribution). To measure waist circumference, the subject was instructed to stand as usual, with his or her feet 30-40 cm apart, and an inelastic tape measure with 1 mm increments was placed around the middle line between the upper edge of the ileums and the line connecting the lower edge of the twelfth rib; the measurement was taken at the end of normal exhalation.

Lifestyle interventions included changing the meal order (A), *i.e.*, eating in the following order: Vegetables, meat and eggs, and carbohydrates, with no limitation on the amount of carbohydrates and food variety; adjustment of activity schedule (B), *i.e.*, indoor activities from 30 min to 120 min after a meal, such as household chores and slow walking; resistance exercise (C), *i.e.*, resistance exercise, including squatting, standing on heels, standing on toes, resistance band exercise, and plank (8 to 10 times each), 3 to 5 times a week under the guidance of a rehabilitation specialist; and reverse abdominal breathing (D), *i.e.*, inhaling slowly *via* the nose while sucking in the abdomen, holding the breath for 3 to 5 s, and then exhaling slowly *via* the mouth while relaxing the abdomen; the technique was repeated after 2 to 3 rounds of normal breathing, with 10 to 15 cycles per session, 3 to 5 times per day. After 3 mo of intervention, fasting blood glucose, waist circumference, blood pressure, BMI, body composition, and motor function were measured and recorded.

Given the risk of hypoglycemia in subjects receiving insulin or oral hypoglycemic drugs after lifestyle interventions, we tapered medication based on the daily blood glucose readings and reduced the dose by approximately 20% (rounded) when fasting blood glucose levels were lower than 6 mmol/L or postprandial blood glucose levels were lower than 8 mmol/L. The process continued if blood glucose remained at stable level, until withdrawal (if possible).

Statistical analysis

SPSS17.0 was used for statistical analyses. Preintervention and postintervention waist circumference, BMI, blood glucose, HbA1c, blood pressure, motor function, and body composition were analyzed by paired *t*-test. $P < 0.05$ was considered statistically significant.

RESULTS

A total of 109 of the 120 subjects completed the study. The patient compliance rates for the four lifestyle interventions (A, B, C, and D) were 57.79%, 60.55%, 64.22%, and 75.23%, respectively. Among the 109 subjects, 80 received oral hypoglycemic drugs or insulin, and 28 did not use any hypoglycemic drugs. Among the subjects who

received hypoglycemic drugs, the dose was adjusted (reduced by approximately 20%) 2 to 3 times based on blood glucose in 54 (67.50%) patients and was tapered and discontinued in 5 (6.25%) patients within 3 mo, with no significant fluctuations in blood glucose after dose reduction and withdrawal.

After lifestyle interventions, various metabolic indicators such as waist circumference, BMI, fasting blood glucose, and blood pressure were significantly reduced ($P < 0.001$) (Table 1). Moreover, after lifestyle interventions, body composition (Table 2) and motor function (Table 3) improved significantly ($P < 0.001$).

DISCUSSION

With aging and lifestyle changes in China, DM has now become epidemic, and its prevalence increased from 0.67% in 1980[10] to 10.4% in 2013[11]. With the acceleration of urbanization, the improvement in living standards in rural areas, less physical activity due to mechanized planting, numerous risk factors for obesity and dyslipidemia due to unbalanced diets and poor lifestyles, and limited health resources and low levels of awareness in rural areas, the prevalence of DM is rising rapidly in rural areas. We conducted chronic disease screening in permanent rural residents aged 50 years or older from ten rural villages of Chaoshui Township from May to August 2019 (n = 896) and found that the prevalence of T2DM and pre-type 2 DM was 21.75%, the diagnosis rate was 60.03%, the undiagnosed rate was 39.97%, and the on-target rate was only 16.9%.

Several randomized controlled studies have shown that appropriate lifestyle interventions may delay or prevent T2DM in individuals with impaired glucose tolerance (IGT)[12-15]. After 10 years of follow-up, the benefits of DM prevention have been shown to remain despite some weight gain in the lifestyle intervention group[16].

The absorption of nutrients and the glycemic index (GI) are related to meal order, and high GI foods are associated with a more significant increase in postprandial blood glucose levels and more sustained hyperglycemia, which contribute to postprandial hyperglycemia and high insulin levels. Therefore, individualized diets based on digestive ability (pattern of gastric acid secretion) can ensure adequate nutrition and a low GI, while guiding meal order (vegetables and animal proteins first, followed by carbohydrates). Blood glucose starts to increase at 30 min after a meal, peaks at approximately 60 min after a meal, and then gradually decreases to the baseline level at 120 min after a meal. Therefore, any indoor or outdoor activity 30-120 min after a meal helps reduce postprandial blood glucose, fat synthesis, and glycogen storage through glucose consumption. By activating the nerve reflex pathway, reverse abdominal breathing increases visceral fat metabolism, and a reduction in visceral fat in liver cells and the greater omentum improves insulin resistance. Resistance exercise increases the quantity and strength of muscles, expels fat from muscles, and improves insulin resistance. Adult diabetes patients should engage in resistance exercise 2 to 3 times (on nonconsecutive days) per week[17], with no strict restriction on the duration of strength training, the effect of which is determined by the load. Resistance exercise with a heavier load is more effective for improving blood glucose levels and strength; however, it is recommended that individuals should engage in resistance exercise (any intensity) throughout their lifetime to enhance strength, balance, and self-care[18].

The existing diet and exercise guidelines and medication adjustment standards are still at experimental stages and difficult to understand and implement. In this study, we "translated" these methods into plain language and content that is easy to implement in daily life. For example, we did not use medical terms such as energy (calorie), gastrointestinal, glucose load, exercise intensity, and heart rate changes; instead, we used easy-to-understand guidelines, such as food types (vegetables, carbohydrates, meat, egg, and milk), intake order, postprandial household chores and free outdoor activities, and a medication dose reduction of 20% in the presence of stable plasma glucose levels. Our 3-year pilot study demonstrated the effectiveness of and good patient compliance with this method.

This is the first study to apply real-life lifestyle interventions to real-world patients to investigate the effects of this method on waist circumference, blood glucose, and motor function in overweight DM patients aged 50 years or older. The results showed that the patient compliance rates for the four lifestyle interventions were 57.79%, 60.55%, 64.22%, and 75.23%, respectively. Among the 80 subjects who received hypoglycemic drugs, the dose was reduced 2 to 3 times to 40% to 60% of the original dose in 54 (67.5%) patients and was discontinued in 5 (6.25%) patients within 3 mo, with no significant fluctuations in blood glucose after dose reduction and withdrawal. After the intervention, fasting blood glucose and HbA1c were significantly reduced ($P < 0.001$). This study showed that real life lifestyle interventions significantly reduced

Table 1 Measurement and comparison of waist circumference, body mass index, blood pressure, fasting blood glucose, and glycosylated protein before and after lifestyle interventions

Value	Before intervention	After intervention	Paired *t*-test	
			t	*P* value
Waist circumference (cm)	97.83 ± 7.81	96.99 ± 7.65	10.02	< 0.001
BMI (kg/m^2)	29.20 ± 3.64	28.52 ± 3.21	5.82	< 0.001
SBP (mmHg)	150.53 ± 21.07	141.15 ± 17.49	6.03	< 0.001
DBP (mmHg)	87.14 ± 13.52	84.36 ± 10.55	1.84	< 0.001
Fasting blood glucose (mmol/L)	11.22 ± 2.78	8.40 ± 1.81	6.21	< 0.001
Glycosylated hemoglobin (%)	8.94 ± 1.92	8.06 ± 1.32	5.87	< 0.001

BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure.

blood glucose and the use of hypoglycemic drugs and improved lifestyle, with good patient compliance.

This study showed that after lifestyle interventions, waist circumference, BMI, fat percentage, and fat distribution changed significantly ($P < 0.001$), suggesting that interventions reduced visceral fat and fundamentally improved insulin resistance due to abdominal obesity. Moreover, the lower extremity nerve response rate and lower extremity response time changed significantly ($P < 0.001$), suggesting that the interventions improved muscle strength and mass, which helped to improve insulin resistance and enhance cardiopulmonary function.

In this study, lifestyle interventions were based on precise data from the Human Metabolism Analyzer and were easy to implement with significant effects, including a decrease in potential risks of high-intensity exercise and improvement in quality of life, without hunger associated with a ketogenic diet. This is the first study in which reverse abdominal breathing was applied as an intervention for abdominal obesity and to prevent and treat T2DM, with good patient compliance.

Further research is needed on the lifestyle interventions used in this study to investigate the molecular mechanism of improved insulin resistance and the duration of improved insulin resistance, in order to provide more evidence to fundamentally resolve insulin resistance in patients with T2DM.

Table 2 Measurement and comparison of body composition before and after lifestyle interventions

Value	Before intervention	After intervention	Paired *t*-test	
			t	*P* value
Lower limb muscle distribution coefficient (Phantom ratio)	0.92 ± 0.24	1.07 ± 0.23	-10.64	< 0.001
Fat distribution/ calculation (g/cm)	171.37 ± 50.62	167.43 ± 49.99	3.88	< 0.001
Percentage/calculation of fat (%)	36.28 ± 8.23	35.57 ± 8.50	4.63	< 0.001

Table 3 Measurement and comparison of nerve and body reaction velocity before and after lifestyle interventions

Value	Before intervention	After intervention	Paired *t*-test	
			t	*P* value
Nerve response velocity of left lower limb (s)	0.24 ± 0.15	0.23 ± 0.14	4.84	< 0.001
Nerve response velocity of right lower limb (s)	0.25 ± 0.09	0.24 ± 0.09	6.76	< 0.001
Body reaction speed of left lower limb (s)	0.44 ± 0.16	0.39 ± 0.14	9.56	< 0.001
Body reaction speed of right lower limb (s)	0.45 ± 0.17	0.41 ± 0.14	9.30	< 0.001

ARTICLE HIGHLIGHTS

Research background

The prevalence rate of type 2 diabetes mellitus (T2DM) in rural areas is increasing rapidly, and lifestyle interventions can effectively reduce blood glucose in patients with T2DM, but the current diet and exercise guidance remains at the laboratory level, which is difficult for subjects to understand and operate. Existing exercise and diet management regimens are associated with two problems: Unclear exercise methods and schedule can lead to exercise injuries, hypoglycemia, and poor results; and poor compliance can lead to poor long-term hypoglycemic effects and incomplete correction of glucose metabolism disorders. It is urgent to refine diet and exercise programs and improve their effectiveness and patient compliance. The Human Metabolism Analyzer accurately analyzes the effects of food types, food intake sequence, and activity/exercise mode and schedule on the production and consumption of blood glucose, thereby providing simple and effective interventions for patients with T2 DM. Our small clinical observation pilot study demonstrated good clinical efficacy of real-life lifestyle interventions on T2DM, as well as on pre-type 2 DM, simple obesity, and polycystic ovary syndrome.

Research motivation

To turn the scientific data provided by the Human Metabolism Analyzer into life-oriented intervention measures, and apply the life-oriented intervention measures to the prevention and treatment of T2DM to observe its effectiveness and compliance, so as to provide effective and continuous intervention measures for the prevention of T2DM in rural residents.

Research objectives

The main goal was to observe the effect of life-style interventions on the metabolic indexes of rural patients with T2DM, and the secondary goal was to observe the compliance with this method.

Research methods

Ten natural villages in Chaoshui Town, Penglai City, Shandong Province were randomly selected to screen the villagers over 50 years old. In the natural village as a group, 12 patients with type 2 DM were randomly selected from each group as the study subjects, and all the subjects were given lifestyle interventions and medication guidance. Lifestyle interventions included changing meal order (A), postprandial activity (B), anti-resistance exercise (C), and anti-abdominal breathing (D). DM education was carried out at least once a month, and a weekly telephone follow-up was conducted to supervise exercise and diet. Before and 3 mo after intervention, the differences of waist circumference, blood pressure, body mass index (BMI), motor function, body composition, blood glucose, and glycosylated glycosylated protein were compared, and the compliance of patients and the adjustment of hypoglycemic drugs were evaluated. All the data were processed with SPSS17.0 statistical software, and the data of waist circumference, BMI, blood glucose, HbA1c, blood pressure, motor function, and body composition before and after intervention were analyzed by paired *t*-test. Compared with the current lifestyle intervention methods for the treatment of T2DM, this study has achieved innovative breakthroughs in the following four aspects: (1) The way T2DM patients ate was defined. Based on each person's digestive ability (gastric acid secretion pattern), the diet structure that each subject was suitable for was determined, and the diet order of the subjects

was guided at the same time. It not only ensured that the subjects did not have to go on a diet and had adequate nutrition, but also ensured the stability of postprandial blood glucose and the reduction of fat synthesis; (2) The activity and movement mode was defined. One hundred and twenty minutes of indoor and outdoor activities after a meal is the most effective activity or exercise time to reduce postprandial blood sugar and control fat synthesis. Anti-resistance exercise not only increases the number and strength of muscles, but also expels fat from muscles, which is the main measure to reduce insulin resistance; (3) The quantitative principle of gradually reducing the dose of insulin and other drugs was clarified. The subjects were instructed to reduce the drug dose step by step based on the blood glucose values monitored every day, so as to achieve the goal of gradually reducing the drug dose or even stopping the drug under the condition of stable blood glucose; and (4) Scientific methods were used in daily life. In this study, all these methods were transformed into life language and content that were easy to operate in daily life. The current pre-research work has proved the effectiveness and good compliance of this method.

Research results

One hundred and eight subjects completed the experiment. The compliance rates of A, B, C, and D lifestyle interventions were 57.79%, 60.55%, 64.22% and 75.23%, respectively. Fifty-four (67.50%) subjects who received hypoglycemic drugs reduced their blood sugar 3 times within 3 mo according to their blood sugar, and five (6.25%) cases gradually stopped using hypoglycemic drugs, and there was no significant fluctuation in blood sugar after drug reduction and withdrawal. After lifestyle intervention, the waist circumference, BMI, fasting blood glucose, and HbA1c decreased significantly ($P < 0.001$), and the motor function and body composition improved significantly ($P < 0.001$). The lifestyle intervention measures used in this study come from the accurate data obtained by the Human Metabolism Analyzer, which is effective, simple, and easy, without the hunger of ketogenic diet, and reduces the harm that high-intensity exercise may bring. For the first time, anti-abdominal breathing was used in the intervention of abdominal obesity and the prevention and treatment of DM with high compliance. Further research on the lifestyle intervention measures used in this study is still needed to clarify the molecular mechanism of improving insulin resistance and the duration of insulin resistance improvement, so as to provide more evidence for the fundamental solution of insulin resistance in patients with T2DM.

Research conclusions

In the past, the lifestyle intervention measures for the prevention and treatment of T2DM only stayed in the laboratory stage, which was difficult for patients to master and their compliance was not high. This study uses the scientific data provided by the Human Metabolism Analyzer to transform all these methods into life language and content that are easy to operate in daily life. Specifically, it includes defining the diet, activity and exercise patterns, and the quantitative principle of gradually reducing the dose of insulin and other drugs, so as to truly achieve the daily life of scientific data. It is assumed that this method can effectively control the metabolic indexes of patients with T2DM, reduce the use of hypoglycemic drugs, and improve the compliance of patients. The results showed that lifestyle intervention could significantly improve the metabolic indexes such as waist circumference, BMI, blood pressure, HbA1c, body composition, exercise function and so on. Some patients could gradually reduce or stop using hypoglycemic drugs, and lifestyle intervention in T2DM had good compliance. This study realized the experimental hypothesis and provided effective and simple lifestyle intervention measures for rural T2DM patients.

Research perspectives

The lifestyle intervention measures used in this study come from the accurate data obtained by the Human Metabolism Analyzer, which is effective, simple, and easy, without the hunger of ketogenic diet, and reduces the harm that high-intensity exercise may bring. For the first time, anti-abdominal breathing was used in the intervention of abdominal obesity and the prevention and treatment of DM with high compliance. Further research on the lifestyle intervention measures used in this study is still needed to clarify the molecular mechanism of improving insulin resistance and the duration of insulin resistance improvement, so as to provide more evidence for the fundamental solution of insulin resistance in patients with T2DM.

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