The Effects of 12-Weeks Combined Exercises on Cost, Dosage of Insulin, and Glycemic Indices in Type 2 Diabetic Patients

Mahmoud Hakami[1,2], **Hossein Chiti**[3*], **Tahereh Mohammadi**[4]

1. *National Center for Health Insurance Research, Tehran, Iran*
2. *Department of Physical Education, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*
3. *Zanjan Metabolic Diseases Research Center, Health and Metabolic Diseases Research Institute, Zanjan University of Medical Sciences, Zanjan, Iran*
4. *Center for Health Insurance Research, Zanjan, Iran*

Article Info

10.61186/jambr.32.152.191

Received: 2023/08/21;
Accepted: 2024/07/03;
Published Online: 27 Sep 2024;

Corresponding Information:
Hossein Chiti, Zanjan Metabolic Diseases Research Center,Health and Metabolic Diseases Research Institute, Zanjan University of Medical Sciences ,Zanjan,Iran

E-Mail: H.chiti@yahoo.com

ABSTRACT

Background & Objective: As the prevalence of type 2 diabetes is growing worldwide, the need to use insulin and the resulting costs are progressively increasing. Exercise can be an effective way to reduce the insulin dose and its cost. This study investigates the effects of 12 weeks combined exercises on cost, dosage of insulin, and glycemic indices in type 2 diabetic patients.

Materials & Methods: Sixty-eight patients, aged 40 to 60 years, with type 2 diabetes and acceptable conditions to perform targeted exercises, were recruited in a randomized clinical trial. All of them had been on treatment with a combination of short-acting and long-acting insulins. Participants were randomly divided into control and case groups with matched gender and age (17 women and 17 men). In addition to the standard exercise recommendations given to both groups, the case group also received the supervised aerobic and resistance exercises three sessions a week for 12 weeks reaching the defined maximum heart rate percentage. The dose of short- and long-acting insulins used during the study was recorded and the resulting cost change along with FBS, 2hpp and HbA1clevel alterations were calculated.

Results: The cost and dosage of long-acting and short-acting insulins in the trained group were significantly reduced by 50% and 39.67%, respectively, compared to the control group ($p=0.00$). The values of HbA1c (21.5%), 2hpp-BS (24.68%), and FBS (13.89%) also decreased in the trained group ($p=0.00$), while all the mentioned values increased in the control group.

Conclusion: The effect of 12 weeks combined exercises was remarkable on reducing the dose of injectable insulins, better glycemic control of patients, and reducing the cost of treatment. Providing the necessary arrangements for supervised exercise in diabetic patients can be economical and beneficial.

Keywords: : Exercise, Insulin, Type 2 diabetes, Cost-effectiveness

Introduction

Insulin is a peptide hormone secreted by the beta cells of the pancreatic islets. This hormone maintains the blood glucose level in a normal state by facilitating the cellular absorption of glucose **(1)**.The process of type 2 diabetes in majority of patients begins with insulin resistance, followed by the destruction of beta cells and finally, a decline in insulin secretion **(2, 3)**. Diabetic patients are prone to microvascular and macrovascular complications, which are considered the most important factors in their morbidity and mortality **(4-6)**, With the progress of type 2 diabetes, the function and secretion of insulin becomes further impaired, which ultimately necessitates the injection of insulin by patients **(7)**.With the increase in the prevalence of this disease worldwide, the use of injectable insulins has also increased. In this regard, an estimate suggested that insulin use will grow from 516.1 million 1000-unit vials (95% CI: 409.0, 658.6 million) to 633.7 million vials (95% CI: 500.5, 806.7 million) between 2018 and 2030 **(8)**.

Many factors are involved in the amount of insulin consumption and its cost. The quantity of insulin consumed is primarily influenced by the availability of insulin and the number of insulin-dependent diabetic patients. In the African regions with the lowest access to insulin, it is estimated that only 1.8% of individuals with type 2 diabetes will receive insulin treatment by 2030. In contrast, the United States has the highest level of insulin usage, with 15.5% **(9)**. Secondly, many studies show that about 30% or one person out of four type 2 diabetes patients are dependent on insulin **(10)**. Note that Insulin consumption is also influenced by various treatment protocols, so that, if the percentage of diabetic patients receiving basal insulin drops from 75% to 70% or rises to 80%, the quantity of vials used will fall or grow by 2%respectively **(8).**

Studies on the costs of insulin users reveal that the insulin market is a high-volume, profitable and highly exclusive market. According to a research study published by Custom Market Insights, the global human insulin market size was valued at approximately USD 44 billion in 2021 and USD 46.9 billion in 2022, and is expected to reach USD 70.68 billion by 2030. Also, the global insulin market is expanding at a compound annual growth rate (CAGR) of approximately 8% during the forecast period 2022 to 2030 **(9).**

The cost of insulin accounts for a large part of the costs of diabetic patients. It can vary significantly depending on factors such as country, brand, and type of insulin, dose, and health care system. Insulin cost in the United States is higher than in other countries. In countries such as Canada, the United Kingdom, and many European countries with government-controlled health care systems, the cost of insulin is generally lower than in the United States **(11)**.

In addition to global factors affecting insulin prices, in Iran, especially in the current crisis, the price of insulin has been affected by international sanctions on oil, banking, goods transfer and commercial insurance, which causes a further increase in the cost of insulin. Currently, there are about 6 million known diabetics in Iran, which is expected to reach more than 9 million in 2030. Assuming that 30% of these 9 million populations have access to insulin, 2,700,000 people will need insulin daily. This issue will impose a huge cost on the country **(12).**

It seems that different tools should be used to reduce the high costs of insulin. One of these tools is targeted physical exercises. Extensive studies have been conducted on the role of different types of physical exercises for the management of type 2diabetes. **(7)**. Regular exercise produces health benefits beyond improvements in cardiovascular fitness. These include enhanced glycemic control, insulin signaling, and blood lipids, as well as reduced low-grade inflammation, improved vascular function, and weight loss **(8)**. Newly, we know that combined aerobic and resistance exercises are the most effective physical exercises for enhancing insulin sensitivity and better glucose absorption in prediabetic (IFG, IGT) and diabetic patients **(13, 14)**.

Nowadays, there are few studies about the effect of targeted physical exercises on the amount and cost of injectable insulin consumption. The aim of this study was to evaluate the effects of 12-weeks combined exercises on the cost, dosage of insulin, and glycemic indices in type 2 diabetic patients.

Materials and Methods

This study was conducted in the northwest of Iran, Zanjan. Sixty-eight type-II diabetic patients aged 40-60 treated by a combination of long and short acting injectable insulins participated in a randomized clinical trial to examine the effects of 12 weeks combined aerobic and resistance exercises. Anthropometric indices, serum level of FBS, 2hpp-BS, Hb-A1C, insulins doses and their imposed cost were registered at the baseline and end of study. Diabetic patients requiring high doses of insulin (more than 1 IU/Kg/Day) to control their blood sugar, and whose Hb-A1C level was at most 2-3% higher than normal values, were included in the study. Patients who were absent from the exercise program for a continuous week or three alternating sessions, or were unable to continue exercise due to any physical or clinical limitations were excluded from the study.

At the beginning of the study, the total sample size, including the control and the case groups, was calculated to be 60 diabetic patients. With the possibility that some patients would not be able to cooperate until the end of the study, 68 patients participated. The participants were randomly divided into control and case groups with matched gender and age (17 women and 17 men aged 40-60 years old). The control group was advised to perform the standard exercise recommendations, but the case group received the supervised aerobic and resistance exercises three sessions a week for 12 weeks to reach the defined maximum heart rate percentage.

The exercise protocol was selected based on American College of Sports Medicine (ACSM) and the American Diabetes Association (ADA) recommendations **(15)**. The training protocol has been summarized in Tables 1 and 2. Each training session included three parts: warm-up, the main program, and a cool-down phase in the gym. If the patient needed any advice during sessions, he or she would consult with his or her coach face to face or via his or her smart phone to receive the necessary guidance.

In the resistance exercises section (Table 1), the patients participated in a maximum repetition test after a week of familiarization with the correct execution of the exercise movements.

In the aerobic training section, (Table 2), the patients participated in an aerobic program suiting their physical and clinical conditions such as running and walking, treadmill, elliptical, step and spinning (indoor cycling). The maximum heart rate using the formula (age-220) was the criterion for measuring the intensity of exercise. The intensity of aerobic exercises in the initial sessions was 50% of the maximum heart rate for at least 20 to 25 minutes, which gradually increased to 70% of the maximum heart rate for 60 minutes. The heart rate of the participants was controlled by a heart rate monitor.

The initial dumbbell weight that each patient chose at the beginning was based on his or her ability to move it. After performing the most repetitions of the movement for the target muscles, the maximum weight and repetitions were recorded by the assistant coach. We used the formula:[number of repetitions ÷30+ 1 × the amount of dumbbell weight] for estimate a one repetition maximum (1RM) **(16, 17)**. Movements used for the workout included: ankle flexion and extension, knee flexion and extension, arm flexion and extension, chest press, abdominal muscle exercises and a modified sit-up.

Clinical issues were considered before, during and after each exercise session. Food and insulin were used 1 to 3 hours before training and blood glucose level measured before training. If the blood glucose level was higher than 250 mg/dL, the participants were not allowed to do exercise and referred for urinary ketone evaluation. During training, energy and water supplements were used every 30 minutes and blood glucose level was controlled to prevent significant hypo- or hyperglycemia. Patients were educated about the insulin dose adjustment and the amount of food intake based on their self-monitoring of blood glucose and insulin management strategies for exercise in diabetes **(18)** at home, 12-24 hours post-exercise.

Equipment used in this study included the following: Breuer model accurate smart scale and its attached height gauge, Micolife professional sphygmomanometer and heart rate monitor, Personal glucometers with accessories, 7 cm foam step, Promaster club treadmill, elliptical machine (space skiing), JK Fitness stationary bike, standard barbell and dumbbells, standard chest press, standard knee flexor and extender, standard ankle flexor and extender. We used American Monobind kit for insulin, Iranian Pars Azmoun kits for blood sugar, LDL and HDL and Spanish Biosystem kit for HbA1c evaluation.

Blood sample was drown from the antecubital vein, on the first morning of the training session, after 12-h overnight fasting. A questionnaire including, biographical, anthropometrics and physical fitness information, the amount of short and long-acting insulins usage and their costs along with a 24-hour food recall form was filled by an expert registrar. It was emphasized that the participants should not have physical exercises on non-training days and follow the recommended diet. Environmental conditions such as temperature and humidity were kept stable during exercise training. The amounts of short-acting and long-acting insulins consumed and their costs were also recorded between training sessions and at the end of the study. Exercises were prescribed according to the physical and clinical conditions of participants. Consumed insulins included: Asparat (Novorapid), Glulisine (Apidra), Human Regular, Isophan (NPH), Premix Aspart70-30 (Novomix), Human Biphasic Isophan70-30, Glargin (Lantus), and Detemir (Levemir). According to the physician advice and based on the extents of blood glucose changes after the exercises, the participants modified the amount of consumed insulin.

The proposal of this study approved by the ethics committee of Zanjan University of Medical Sciences under number IR.ZUMS.REC.1400.135 and recorded in IRCT with code: IRCT20180530039909N1.

Table 1. **12-weeks resistance training protocol**

Muscles under training	Weeks	Intensity	Rest
Resistance exercises include Anterior and posterior muscles of the forearm, Anterior and posterior thigh muscles, pectoral muscles, ankle flexors and extensors and abdominal muscles.	Weeks 1-2	%50 (1RM)●	3minutes rest between sets
	Week 3-4	%60 (1RM)	
	Week 5-6	%70 (1RM)	
	Week 7-8	%80 (1RM)	
	Week 9-12	%85 (1RM)	

●

1Repetition Maximum

Table 2. 12-weeks metabolic training protocol

Types of aerobic training	Weeks	The intensity and duration of each session	Sessions per week
Running and walking, treadmill, elliptical, step, exercise program with body weights and spinning selected according to the athlete's clinical condition	Week1	One repetition, 20minutes, 50(٪HRmax)	Three sessions a week
	Week2	one repetition, 20minutes, ٪50(HRmax)	
	Week3-4	two repetitions of 20minutes, ٪55(HRmax)	
	Week5-6	two repetitions of 20minutes, ٪60(HRmax)	
	Week7-8	three repetitions of 20minutes, ٪70(HRmax)	
	Week9-12	three repetitions of 20minutes, ٪75(HRmax)	

●Heart rate Maximum

Results

Sixty eight type II diabetic patients matched in terms of gender (17 men and 17 women in each group) and age (40-60 years old) were included in two groups of case and control. Gender specific characteristics of participants are summarized in (Table3).

Table 3. Gender specific baseline characteristics of participants in the two groups

Variables \ Gender	Men		Women	
	Cases(N=17) (Mean±SD)	Controls(N=17) (Mean±SD)	Cases(N=17) (Mean±SD)	Controls(N=17) (Mean±SD)
Body Weight (Kg)	77±8	78±8	69.9±7.3	69.5±8.2
Height (cm)	168±9	169±8	157.6± 6.1	158.7 ±5.5
FBS (mg/dl)	160.28±58.54	154.67±6201	148.52.41	143.78±48.90
2hpp-BS (mg/dl)	280.38±78.82	252.01±87.92	274.64±72.98	258.72±86.52
Hb-A1C (%)	7.29±2.18	7.18±1.93	6.92±1.98	6.70±2.01
Total energy intake (Kcal/day)	1840.6±527.2	1849.8±543.8	1652 ±68.8	1658 ±74.4
Protein intake (gr/day)	63.5±12.2	65.5±36.2	61.5±24	65.5±20
Carbohydrate intake (gr/day)	249 ±76.1	261 ±72.8	229.6±55.1	233.5±56.34
Fat intake (gr/day)	57.1±20.1	51.1±22.9	46.7±15.8	43.1±17.6
P-Value	NS		NS	

During the study, 2 patients (1 man and 1 woman) out of 34 subjects from case group and 4 patients (2 men and 2 women) out of 34 subjects from control group were excluded due to non-cooperation.

After 12-weeks exercise training of case group, the consumption of short-acting as well as long- acting insulins diminished significantly compared to the control group. The average percentage dosage reduction in short-acting and long- acting insulins was about %50 and %40 respectively. The values of Hb-A1c, 2hpp-BS, and FBS also dropped in the trained group compared to the control group (Table 4).

Table 4. **Comparison of glycemic indices and insulin dosage before and after intervention**

Variable \ Group		Cases (Mean±SD)	Controls (Mean±SD)	P-Value*
FBS (mg/dl)	Pre-test	152.28±54.62	148.43±48.01	0.148
	Post-test	120.97±38.04	178.70±66.45	0.000
	% Change	-13.89	+25.53	0.000
	P-Value**	0.001	0.000	-
2hpp (mg/dl)	Pre-test	290.72±76.29	242.00±90.00	0.518
	Post-test	209.81±51.07	260.53±98.17	0.026
	% Change	-24.68	+23.89	0.000
	P-Value**	0.000	0.000	-
HbA1c (%)	Pre-test	7.11±2.08	6.60±1.99	0.455
	Post-test	5.29±1.05	8.74±2.53	0.001
	% Change	-21.57	+15.95	0.000
	P-Value**	0.000	0.000	-
Short or rapid- acting insulin (IU)	Pre-test	26.47±16.97	23.47±20.25	0.09
	Post-test	12.50±11.56	28.77±22.30	0.000
	% Change	-50.02	+2.86	0.000
	P-Value**	0.000	0.085	-
Medium or long- acting insulin (IU)	Pre-test	27.72±10.99	25.17±15.94	0.039
	Post-test	14.56±8.35	26.67±14.82	0.000
	% Change	-39.67	+1.91	0.000
	P-Value**	0.000	0.302	-

: Between groups difference** *: Intra group difference**

Figures1 and 2 clearly demonstrate that 12-weeks combined exercises can significantly lower the short and long-acting insulin needs respectively in type II diabetic patients. Based on the obtained information, our first hypothesis of the clear effect of 12-weeks combined exercise on reducing the need of diabetic patients consuming short-acting and long-acting insulins is proven.

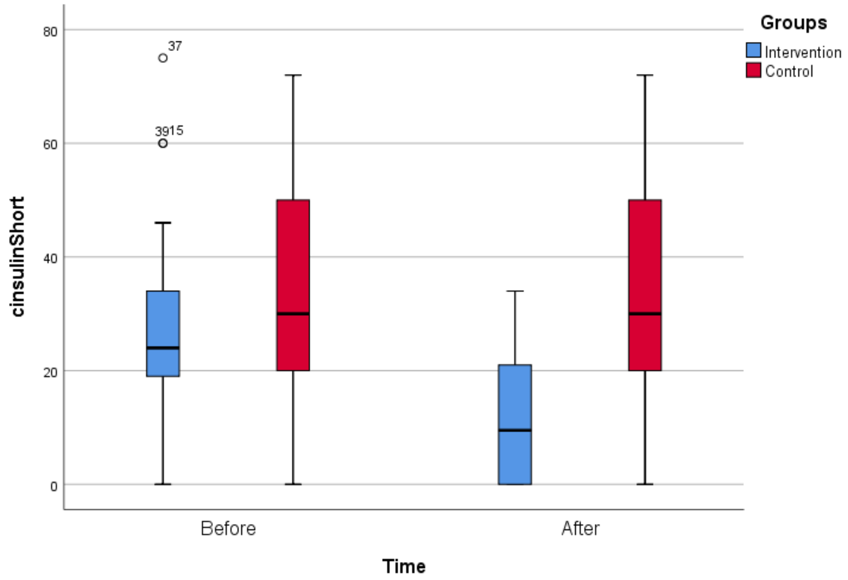

Figure 1. **Effects of 12-weeks combined exercises on short-acting insulin needs**

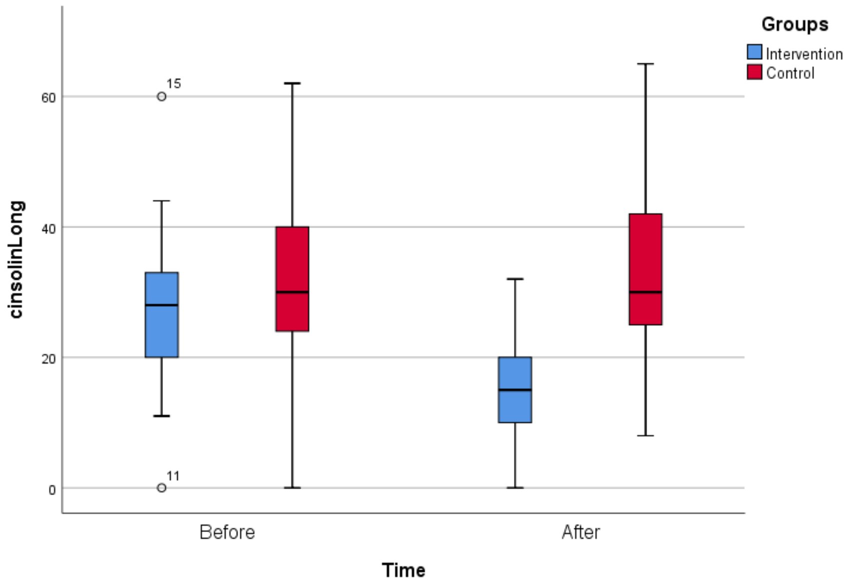

Figure 2. **Effects of 12-weeks combined exercises on long-acting insulin needs**

In our study, the patients who did supervised exercise were able to reduce their need for short-acting and long-acting insulins by 50% and almost 40% respectively, but in those who did not exercise, the need for short-acting and long-acting insulin increased by 3% and 2%, respectively.

Three months of combined exercises could reduce the average dose of short-acting insulin from 794 units to 357 and long-acting insulin from 832 units to 437. The price of each 300-unit pen of insulin in Iran with foreign currency subsidy is about 5.35 USD, 90% of which is paid by the insurance ($4.815) and 10% by the patient ($0.535). Taking into account the access of 20% of 6 million diabetic patients to insulin in Iran, the total average saving of cost attributed to its dose reduction after exercise will be 7.41×1200000= $8,892,000 per month for short-acting insulins and 7.05×1200000= $8,460,000 per month for long-acting insulins. The average cost saving for the insurance organization will be $8,002,800 per month about short-acting insulins and $7, 614,00 about long-acting insulins. The total cost savings for all short and long-acting insulins will be $208,080.000 per year.

An increased consumption of short-acting insulins by 3% and long-acting insulins by 2% in the control group led to total average cost increase of $1, 128000 per month (Table5).

The average cost of exercise in the gym is about $4 per month for each insulin-dependent diabetic patient in Iran. According to this estimation, the total annual cost of participating in exercise for all insulin-dependent diabetics will be about $48 million. It is clear that paying $48 million a year for 1,200,000 insulin-dependent diabetics is far more cost-effective than spending more than $200 million for injectable insulins.

Table 5. Final effects of combined exercises compared to routine care on the dose and cost of insulin

Variable / Group	Type of insul in		Averae daily insulin dose (IU)	Average percent change in insulin dose (%)	Insulin saved per day (IU)	Insulin saved per month (IU)	Insulin saved per year (IU)	Average monthly cost of insulin($)	Average cost of insulin saved (-) / wasted (+) per month($)	Average cost of insulin saved(-) /wasted(+)annua lly($)	Annual cost saving(-) /wastage(+)in the country ($)	
Cases	Short-acting	Pre-Test	26.47	-%50	-13.97	-419.1	-5029	14.17	-7.41	-88.8	-106,560,000	-208,080.000
		Post-test	12.50					6.77				
	Long-acting	Pre-Test	27.72	-%40	-13.16	-394.8	-4737.6	14.85	-7.05	-84.6	-101,520,000	
		Post-test	14.56					7.80				
Controls	Short-acting	Pre-Test	23.47	+%2.86	+5.3	+159	+1908	13.11	+0.16	+1.92	+2,304,000	+13,536,000
		Post-test	28.77					13.27				
	Long-acting	Pre-Test	25.17	+%1.91	+1.5	+45	+540	11.90	+0.78	+9.36	+11,232000	
		Post-test	26.67					12.68				

Discussion

The results obtained from this study revealed that 12-week combined exercises in type 2 diabetic patients could reduce the consumed dose of short and long-acting insulins by 50% and 40%, respectively. This reduction in insulin dose means a cost reduction equivalent to about $208,080.000 per year in our country.

A microsimulation analysis concerning global insulin use for type 2 diabetes states that two factors are effective on the amount of insulin consumption: demographic changes such as prevalence of disease as well as crowding and the amount of access to insulin. Demographic changes alone can augment the insulin consumption from 516.1 million vials of 1000 units to 633.7 million vials per year between 2018 and 2030. This consumption will be less in the African region due to low access to medicine and low prevalence of type 2 diabetes and highest in the Americas region due to higher insulin use and higher prevalence of type 2 diabetes. Of course, the number of insulin vials required in the Oceanic region will be the lowest at 4.2 million vials in 2030 and the highest in Asia at 321.6 million vials in 2030 due to the population size. If access to insulin is improved until the year 2030, the percentage of diabetic patients using insulin is expected to grow from 7.4% to 15.5%. According to this estimate, insulin consumption will increase by 7.1 times in Africa and 26 million people will be added to insulin users in Asia **(8)**.

With this perspective, we should try to minimize insulin consumption with appropriate interventions such as nutritional supports and programmed exercises.

There are several studies that emphasize the cost-effectiveness of diet and exercise programs on non-insulin-dependent **(19)** and insulin-dependent type 2 diabetic patients **(5, 20-22)**, all of which confirm the results of the present study.

Regarding the type of effective exercises chosen for treatment of diabetic patients, Coyle et al. determined that combined resistance and metabolic exercises are more effective and economical than other exercise methods **(23)**. Exactly for this reason, we used this type of exercise in the present study.

Ana Barbosa, in a systematic review which included 3000 studies, emphasized exercise as a worthwhile investment for the management of type 2 diabetes **(21)**.

Concerning the cost-utility of diet and exercise interventions in non-insulin-dependent type-2 diabetes mellitus, Arrow et al. estimated that the programmed diet and exercises produced 0.092 good years per participant. The total cost of program per participant calculated about US$1,000 and the cost-benefit ratio was US$1000 / 0.092 = US$10,870 per year **(19)**.

The study of Askarian et al. showed that regular exercise for three months not only improves the quality of life in type 2 diabetic patients, but also reduces the cost of treatment directly and indirectly with a significant impact on the economy of the family and the government **(20)**. The direct and indirect cost reduction in this study was about 40% and 50% respectively, which was similar to the results obtained from our study.

In another study, Jalilian et al. investigated the hospital and non-hospital economic burden of type 2 diabetes in Iran. The non-hospital cost of the patients ($9757) was about 2.5 times the hospital cost ($3517), most of which was related to insulin ($3087). Managed exercises were able to lower the consumed insulin dose and cost by 55% (P=0.000), which resulted in saving 1693 dollars out of 3087 dollars **(24)**.

Di Loreto et al. surveyed long-term effects of different amounts of physical activity in type 2 diabetes. They showed that programmed exercises can induce significant reductions in body weight, body mass index, waist circumference, fasting plasma glucose, glycosylated hemoglobin, systolic and diastolic blood pressure, heart rate, as well as total and LDL cholesterol and triglycerides, similar to what happened in our study. They also noticed a 3% reduction in the 10-year risk of coronary heart disease along with a significant increase in HDL cholesterol. Improvements in glycemic control and cardiovascular risk factors were associated with significant reductions in medical and social costs, saving a total of $855 per person **(25)**.

Regarding the level of exercise, a cost-effectiveness study in type 2 diabetic patients has stated that a daily 3-mile walk reduces drug costs by $550, other medical costs by $700, indirect social costs by $1,100, and total costs by $2,000, though it increases the direct social costs up to $400. After 24 months of study, the number of patients treated with insulin dropped by 25% and there was a significant inverse correlation between level of exercise based on METs per hour per week and daily units of insulin ($p \leq 0.0001$). The results of this study, as in our study, indicated the effects of planned and supervised physical exercises on the amount of insulin consumed as well as other glycemic indicators related to diabetes **(26)**.

Conclusion

The effect of 12 weeks combined exercises was remarkable on reducing the dose of injectable short and long-acting insulins, better glycemic control of patients, and reducing the cost of treatment. Due to the progressive prevalence of type-2 diabetes along with the economic problems of patients and insufficient access to support systems, providing the necessary arrangements for supervised exercise in diabetic patients can be economical and beneficial.

Acknowledgments

The authors sincerely thank all the participants in this research, Especially from Dr. Alireza Shoghli, Dr Farzaneh Ahmadi for statistical analysis, diabetic athletes and Iranian Health Insurance Management and their colleagues.

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding

This study was financially supported by National Center for Health Insurance Research,Tehran,Iran

Ethics Approval and consent to participate

The proposal of this study approved by the ethics committee of Zanjan University of Medical Sciences under number IR.ZUMS.REC.1400.135 and recorded in IRCT with code: IRCT20180530039909N1

Authors' Contributions

H.C, and M.H conceptualization and designed the study, TM data provided collection and verification. M.H and H.C contributed to the writing and revision of the manuscript. M.H supervised methodology design and implementation. All authors read and approved the final version of the manuscript.

References:

1. Alibegovic AC, Sonne MP, Højbjerre L, Bork-Jensen J, Jacobsen S, Nilsson E, et al. Insulin resistance induced by physical inactivity is associated with multiple transcriptional changes in skeletal muscle in young men. Am J Physiol Endocrinol Metab. 2010;299(5):E752-E63. https://doi.org/10.1152/ajpendo.00590.2009

2. Aoyama-Sasabe S, Fukushima M, Xin X, Taniguchi A, Nakai Y, Mitsui R, et al. Insulin secretory defect and insulin resistance in isolated impaired fasting glucose and isolated impaired glucose tolerance. J Diabet Res. 2016;2016. https://doi.org/10.1155/2016/1298601

3. Blackburn DF, Wilson TW. Antihypertensive medications and blood sugar: theories and implications. Canadian J Cardiol. 2006;22(3):229-33. https://doi.org/10.1016/S0828-282X(06)70902-3

4. Bloem CJ, Chang AM. Short-term exercise improves β-cell function and insulin resistance in older people with impaired glucose tolerance. J Clin Endocrinol Metab. 2008;93(2):387-92. https://doi.org/10.1210/jc.2007-1734

5. Subías-Perié J, Navarrete-Villanueva D, Gómez-Cabello A, Vicente-Rodríguez G, Casajús JA. Health economic evaluation of exercise interventions in people over 60 years old: A systematic review. Experiment Gerontol. 2022;161:111713. https://doi.org/10.1016/j.exger.2022.111713

6. Aranda-Reneo I, Albornos-Muñoz L, Rich-Ruiz M, Cidoncha-Moreno MÁ, Pastor-López Á, Moreno-Casbas T, et al. Cost-effectiveness of an exercise programme that provided group or individual training to reduce the fall risk in healthy community-dwelling people aged 65-80: a secondary data analysis. Health Care. 2021;9(6)714. https://doi.org/10.3390/healthcare9060714

7. Lakhtakia R. The history of diabetes mellitus. Sultan Qaboos Univ Med J. 2013;13(3):368. https://doi.org/10.12816/0003257

8. Basu S, Yudkin JS, Kehlenbrink S, Davies JI, Wild SH, Lipska KJ, et al. Estimation of global insulin use for type 2 diabetes, 2018-30: a microsimulation analysis. Lancet Diabet Endocrinol. 2019;7(1):25-33. https://doi.org/10.1016/S2213-8587(18)30303-6

9. Gale E. The Market in Insulin. Life in the Age of Insulin: A Brief History: Springer; 2024. p. 237-49. https://doi.org/10.1007/978-3-031-47190-2_17

10. Control CfD, Prevention. Age-adjusted percentage of adults with diabetes using diabetes medication, by type of medication, United States, 1997-2011. National Center for Health Statistics, Division of Health Interview Statistics Retrieved from https://www cdc gov/diabetes/statistics/meduse/fig2 htm. 2013.

11. Mulcahy AW, Schwam D, Edenfield N. Comparing insulin prices in the United States to other countries. Rand Corporation. 2020. https://doi.org/10.7249/RRA788-1

12. Javanbakht M, Mashayekhi A, Baradaran HR, Haghdoost A, Afshin A. Projection of diabetes population size and associated economic burden through 2030 in Iran: evidence from micro-simulation Markov model and Bayesian meta-analysis. PloS one. 2015;10(7):e0132505. https://doi.org/10.1371/journal.pone.0132505

13. Maiorana A, O'Driscoll G, Goodman C, Taylor R, Green D. Combined aerobic and resistance exercise improves glycemic control and fitness in type 2 diabetes. Diabet Res Clin Pract. 2002;56(2):115-23. https://doi.org/10.1016/S0168-8227(01)00368-0

14. Damirchi A, Chiti H, Faghihzadeh S, Hakmai Zanjani M. The effect of eight weeks of combined aerobic and resistance exercise on impaired fasting glucose (IFG), impaired glucose tolerance (IGT) and HbA1c in pre-diabetic patients. J Adv Med Biomed Res. 2017;25(113):13-23.

15. Colberg SR, Sigal RJ, Fernhall B, Regensteiner JG, Blissmer BJ, Rubin RR, et al. Exercise and type 2 diabetes: the American College of Sports Medicine and the American Diabetes Association: joint position statement. Diabetes care. 2010;33(12):e147-e67. https://doi.org/10.2337/dc10-9990

16. Kirwan JP, Sacks J, Nieuwoudt S. The essential role of exercise in the management of

type 2 diabetes. Clev Clin J Med. 2017;84(7 Suppl 1):S15. https://doi.org/10.3949/ccjm.84.s1.03

17. Julio UF, Panissa VLG, Franchini E. Prediction of one repetition maximum from the maximum number of repetitions with submaximal loads in recreationally strength-trained men. Sci Sport. 2012;27(6):e69-e76. https://doi.org/10.1016/j.scispo.2012.07.003

18. Zaharieva DP, Riddell MC. Insulin management strategies for exercise in diabetes. Canadian J Diabet. 2017;41(5):507-16. https://doi.org/10.1016/j.jcjd.2017.07.004

19. Kaplan RM, Atkins CJ, Wilson DK. The cost-utility of diet and exercise interventions in non-insulin-dependent diabetes mellitus. Health Promot Int. 1987;2(4):331-40. https://doi.org/10.1093/heapro/2.4.331

20. Askarian F, Akhtari Shoja E, Malekmohammadfam N. A study of changes in medical expenses of type 2 diabetes patients following 3 months of regular exercise. Sport Physiol Manag Investig. 2018;10(1):144-55.

21. Barbosa A, Whiting S, Ding D, Brito J, Mendes R. Economic evaluation of physical activity interventions for type 2 diabetes management: a systematic review. Europ J Pub Health. 2022;32(Supplement_1):i56-i66. https://doi.org/10.1093/eurpub/ckac074

22. Brun JF, Bordenave S, Mercier J, Jaussent A, Picot MC, Préfaut C. Cost-sparing effect of twice-weekly targeted endurance training in type 2 diabetics: a one-year controlled randomized trial. Diabet Metab. 2008;34(3):258-65. https://doi.org/10.1016/j.diabet.2008.01.010

23. Coyle D, Coyle K, Kenny GP, Boulé NG, Wells GA, Fortier M, et al. Cost-effectiveness of exercise programs in type 2 diabetes. Int J Technol Assess Health Care. 2012;28(3):228-34. https://doi.org/10.1017/S0266462312000256

24. Jalilian H, Heydari S, Imani A, Salimi M, Mir N, Najafipour F. Economic burden of type 2 diabetes in Iran: A cost-of-illness study. Health Sci Report. 2023;6(2):e1120. https://doi.org/10.1002/hsr2.1120

25. Di Loreto C, Fanelli C, Lucidi P, Murdolo G, De Cicco A, Parlanti N, et al. Make your diabetic patients walk: long-term impact of different amounts of physical activity on type 2 diabetes. Diabet Care. 2005;28(6):1295-302. https://doi.org/10.2337/diacare.28.6.1295

26) Mendes MdA, Da Silva I, Ramires V, Reichert F, Martins R, Ferreira R, et al. Metabolic equivalent of task (METs) thresholds as an indicator of physical activity intensity. PloS one. 2018;13(7):e0200701. https://doi.org/10.1371/journal.pone.0200701