Research Article

Assessment of resistance and aerobic training with/without Blood Flow Restriction and detraining period and their association with miR143/145 (rs4705342 and rs4705343) and IGF2BP2 (rs4402960 and rs1470579) gene polymorphisms in men with type 2 diabetes

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ABSTRACT

Objectives: Type 2 diabetes (T2D) is a prevalent metabolic disorder characterized by insulin resistance and impaired glucose metabolism, often leading to severe complications. Emerging evidence suggests that exercise, particularly resistance training and aerobic activities, can significantly improve glycemic control and overall health in individuals with T2D. This study aimed to assess resistance and aerobic training, both with and without blood flow restriction (BFR), and genetic polymorphisms located in the miR-143/145 and IGF2BP2 gene clusters in men with T2D.

Methods: A total of 30 men with T2D were randomly assigned to four groups: resistance training with BFR (RT-BFR), resistance training without BFR (RT), aerobic training with BFR (AT-BFR), aerobic training without BFR (AT), and two control groups. Training sessions were conducted three times per week for 12 weeks, followed by a 6-week detraining period. Genotyping was performed for polymorphisms within the miR-143/145 and IGF2BP2 gene clusters using ARMS-PCR.

Results: The results of our study showed that in the AT group, the dominant genotype was $TT_{rs4705342}TT_{rs4705343}GG_{rs4402960}AA_{rs1470579}$. In the RT group and the Control AT group, the dominant genotype was $TT_{rs4705342}TT_{rs4705343}GG_{rs4402960}CC_{rs1470579}$. And also, in other groups (including AT-BFR and RT-BFR group and Control RT group) the dominant genotype was $TT_{rs4705342}TT_{rs4705343}GG_{rs4402960}AC_{rs1470579}$. The results were AT vs. Control AT at the rs4402960 position in the recessive model. Therefore, the risk decreased by 0.74 for TT vs. GT+GG (p-value = 0.025). Moreover, the RT group vs. Control RT group at the rs1470579 position in the same model, yielded significant results, leading to a 14-fold increase in risk for CC vs. AC+AA (p-value < 0.001).

Conclusion: The findings from this research contribute valuable evidence to the ongoing discourse surrounding exercise, genetics, and diabetes management.

Keywords: Type 2 diabetes (T2D), resistance training (RT), aerobic training (AT), Blood Flow Restriction (BFR), miR143/145, IGF2BP2, polymorphisms.

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Introduction

Type 2 diabetes (T2D) is a complex metabolic disorder characterized by insulin resistance (IR) and has become a global health concern (1, 2). Exercise is a cornerstone in managing T2D, with both aerobic training (AT) and resistance training (RT) recognized for their benefits in improving insulin sensitivity and metabolic health (3). Recent advancements in exercise science have introduced blood flow restriction (BFR) training as a potentially effective strategy for individuals with limitations that prevent high-intensity exercise (4). Furthermore, genetic factors, including variants in miRNA clusters such as *miR-143/145* and genes like *IGF2BP2*, have been implicated in the pathophysiology of T2D (5, 6).

Both RT and AT have been shown to improve insulin sensitivity (7). RT enhances muscle mass, thereby increasing glucose uptake by tissues (8). AT improves cardiovascular health and promotes fat oxidation, contributing to better glycemic control (7, 9). Studies indicate that structured exercise interventions can significantly reduce fasting insulin levels and improve glycemic variability in individuals with T2D (10). BFR training enables individuals to perform low-intensity strength exercises while restricting blood flow to the working muscles (11). This method has been gaining traction due to its ability to elicit muscle hypertrophy and strength gains comparable to traditional high-intensity training, yet with reduced load (12). In men with T2D, BFR has shown promise in enhancing insulin sensitivity, possibly due to its metabolic benefits and lower injury risk (13).

Genetic polymorphisms in the *miR-143/145* cluster and the *IGF2BP2* gene are associated with T2D risk (14). The *miR-143/145* cluster is implicated in metabolic processes, influencing insulin secretion and sensitivity. Research suggests that expression levels of these microRNAs may alter in response to exercise interventions, potentially impacting glucose homeostasis and insulin action (15). *IGF2BP2* has been linked to insulin signaling pathways and glucose metabolism (16). Variants within this gene may affect the body's response to exercise, influencing adaptations in insulin sensitivity. Understanding the interaction between exercise training and these genetic factors could elucidate pathways for personalized exercise prescriptions. Detraining, the cessation of structured training, poses significant challenges, especially for individuals managing chronic conditions like T2D. Withdrawal from exercise leads to rapid declines in muscle strength and cardiovascular fitness, alongside potential increases in IR. Research indicates that a period of detraining can reverse the benefits gained from exercise interventions, with IR markers showing deterioration (17). However, the magnitude of this effect can vary based on the type of training previously performed (aerobic vs. resistance) and individual factors such as baseline fitness levels and genetic predisposition. Emerging data suggest that while exercise can lead to favorable epigenetic changes, detraining might revert these adaptations (18). The interplay between these training modalities and genetic factors, such as those found in the *miR-143/145* (rs4705342 and rs4705343) cluster and *IGF2BP2* (rs4402960 and rs1470579), may further refine our understanding of individual responses to exercise. Importantly, the impact of detraining underscores the necessity for ongoing physical activity to maintain metabolic health and insulin sensitivity. Future research should focus on elucidating the full spectrum of genetic influences on exercise responses and injuries, leading to more tailored approaches in managing T2D through physical activity.

Materials and Methods

Study Design and Interventions

In this experimental research, 30 men were purposefully selected and randomly assigned to one of six groups: Resistance Training with Blood Flow Restriction (RT-BFR), Resistance Training without Blood Flow Restriction (RT), Aerobic Training with Blood Flow Restriction (AT-BFR), Aerobic Training without Blood Flow Restriction (AT), and two control groups. In this study, the inclusion criteria included men aged 40–60 years, diagnosed with T2D (HbA1c levels between 6.5% and 8.5%), no history of cardiovascular diseases or contraindications for exercise, and no ongoing treatment with medications that affect glucose metabolism. The exclusion criteria included the presence of major comorbidities (e.g., uncontrolled hypertension, renal failure), participation in regular exercise (≥ 2 days/week) in the past 6 months, and any severe neurological or orthopedic conditions.

Sampling was conducted at the Diabetes Clinic of Bou Ali Hospital and Imam Ali Hospital in Zahedan. Blood sampling was performed, and the samples were sent to the laboratory for DNA extraction, molecular studies, and genotype determination of the selected SNPs. At the beginning of the process, all steps and methods of conducting the research were explained to the participants, and their questions were answered. Ultimately, the participants completed the informed consent form with full agreement. During the familiarization sessions, it was ensured that all participants had learned the correct techniques for performing resistance exercises and BFR. Forty-eight hours before starting the exercises, the participants visited the Hermas Sports Science Club, where, in familiarization with the exercise protocol, the one-repetition maximum (1RM) for two lower-body exercises, including leg press and knee extension, as well as three upper-body exercises, including bench press, shoulder press, and lateral pull, was determined according to the Brzeski method (19). The participants

Table 1. Aerobic training protocol without Blood Flow Restriction

15th and 16th	13th and 14th	11th and 12th	9th and 10th	7th and 8th	5th and 6th	3rd and 4th	1st and 2nd	
65%	65%	60%	60%	55%	55%	50%	50%	**Intensity**
36	30	30	24	24	18	18	12	**duration (minutes)**

Table 2. Aerobic training protocol with blood flow restriction.

15th and 16th	13th and 14th	11th and 12th	9th and 10th	7th and 8th	5th and 6th	3rd and 4th	1st and 2nd	
65%	65%	60%	60%	55%	55%	50%	50%	**Intensity**
30	25	25	20	20	15	15	10	**Activity time with blood flow restriction**
60%	60%	50%	50%	40%	40%	30%	30%	**pressure**
6	5	5	4	4	3	3	2	**set**
6	5	5	4	4	3	3	2	**Active rest sets between sets with blood flow restriction (minutes)**
36	30	30	24	24	18	18	12	**Total training time (minutes)**

in the training group performed the exercises for a duration of 16 weeks, with the first four weeks consisting of two sessions per week, and the following 12 weeks consisting of three sessions per week. Each training session included 10 minutes of warm-up, the main workout (50 minutes), and 10 minutes of cool-down. Forty-eight hours after the last training session, blood samples from the participants were collected again at the laboratory of Ali Ibn Abi Talib Hospital in Zahedan after 12 hours of fasting, and the results were recorded using statistical methods.

Resistance Training Protocol

The two lower-body movements, including leg press and knee extension, and two upper-body movements, including chest press and shoulder head press, were performed by the resistance training group without blood flow restriction initially for four weeks at an intensity of 70% of 1RM, with four sets of eight repetitions. In the second, third, and fourth weeks, the participants performed the exercises at intensities of 80%, 70%, and 80% of 1RM, with four sets of 10, 10, and 12 repetitions, respectively (20, 21).

Blood Flow Restriction Training Protocol

The training group with blood flow restriction performed resistance exercises, including the two lower-body movements (leg press and knee extension) and two upper-body movements (chest press and shoulder head press), in four sets with repetitions of 30, 25, 20, and 15 during the first, second, third, and fourth weeks, respectively, at an intensity of 20% of 1RM. The rest between each set and each station was one and three minutes, respectively (20, 21). Blood flow restriction was applied continuously to the proximal thigh and arm using a 17.5 cm-wide occlusion cuff at a mean pressure of 184 ± 25 mmHg. During rest between sets, the blood flow restriction was removed. The control group continued their normal lives during this time and did not follow a regular training program. We regularly contacted the participants or their families every 10 days by phone to inquire about any changes in their lives, including changes in treatment processes and the use of new medications that could potentially impact the research results, and documented the findings.

Protocols for Aerobic Training with and without Blood Flow Restriction

All exercise sessions started with a 10-minute warm-up and concluded with a 10-minute cool-down at the end of the session. Participants in the training groups underwent aerobic treadmill running for 16 weeks, with 3 sessions of exercise each week, with and without limb BFR. The specific duration of aerobic exercise began at 12 minutes at 50% of maximum heart rate in the first week and increased to 36 minutes at an intensity of 65% of maximum heart rate over the course of 16 weeks, with and without BFR (Table 1) (22).

On the one hand, the participants in the group with Blood Flow Restriction performed a similar protocol on the treadmill, starting from the first week with a workout intensity of 50% and increasing to 65% of their maximum heart rate by the 16th week. This was done using a digital blood flow restriction device produced domestically in Iran, along with two cuff rings. The proximal limb was compressed using tourniquet cuffs measuring 18×35 centimeters, suitable for adults (23), and the pressure was digitally adjusted to be between 30% and 60% of arterial occlusion pressure (AOP) on a digital monitor. A rest and activity schedule was programmed into the device, which automatically adjusted and controlled the pressure over a period of 12 to 36 minutes. The exercises were carried out in the presence of a sports specialist (to prevent sudden

incidents). Participants' heart rates during the treadmill exercise were continuously monitored alongside pulse oximetry. At the end of the 16-week intervention, and 48 hours after the final training session, blood samples were collected again by a specialist and sent to the laboratory for testing (Table 2) (23, 24).

Assessments

For Genetic Variants Analysis in this study, genomic DNA was extracted from peripheral blood samples by the Salting-Out method (25). The quality and quantity of DNA (~80 ng/µL) were assessed using a Nanodrop Spectrophotometer. Variants in miR143/145 and IGF2BP2 genes were assessed using ARMS-PCR (Amplification Refractory Mutation System–Polymerase Chain Reaction) methods. Table 3 shows primer sequences used in our study. The primers were designed using Oligo7 software (26) and produced by Pishgam Co. (Tehran, Iran).

Statistical Analysis

Data analysis was conducted using SPSS Statistics version 27.0.1.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics characterized the sample. Post-hoc tests (Tukey's HSD) were used for multiple comparisons. We calculated odds ratios (OR) and 95% confidence intervals (CIs) using binary logistic regression analysis to compare the genotypes of subjects studied in the recessive model in different groups to the reference group association. Also, a significance level was set at $p < 0.05$.

Ethical Considerations

The study was conducted in compliance with ethical standards, and it was approved by the Zahedan University of Medical Sciences' ethics committee. The approval certificate can be found at https://ethics.research.ac.ir/IR.IAU.K.REC.1402.143). This study adhered to the Declaration of Helsinki ethical guidelines (The 75th WMA General Assembly, Helsinki, Finland, October 2024, https://www.wma.net/policies-post/wma-declaration-of-helsinki/). Informed consent was obtained from all participants prior to inclusion in the study.

Results

In this study, we investigated the assessment of RT and AT, both with and without BFR and genetic variants associated with *miR143/145* and *IGF2BP2* gene clusters in men with *T2D*. Six different groups were studied: AT, RT, Control AT Group, AT-BFR, RT-BFR, Control RT Group. Our genetic study in **Table 4** showed that in the AT group, the dominant genotype was $TT_{rs4705342}TT_{rs4705343}GG_{rs4402960}AA_{rs1470579}$. In the RT

Table 3. Sequence of primers used for miR143/145 and IGF2BP2 genes.

Gene	Polymorphism	Type	Sequence
miR143/145	rs4705342	F (T-allele)	TATAAAATGTTAAGTACCGT
		F (C-allele)	TATAAAATGTTAAGTACCGC
		R (Common)	TCAATAACATCTTAATTTAGAAGGA
	rs4705343	F (C-allele)	ATGTATTGAAATATCCAGAAAATATGC
		F (T-allele)	ATGTATTGAAATATCCAGAAAATATGT
		R (Common)	TTTAGTGAGTACAATTAACAGGTT
IGF2BP2	rs4402960	F (Outer)	GGAAAACTTGAGAGGAACAGTTACG
		R (Outer)	GAGGTTGAGACTGCAGTGAGTTTGTTT
		FT (Forward inner)	AGCAGTAAGGTAGGATGGACAGTAGACTT
		RG (Reverse inner)	TTGCAAACACAATCAGTATCCTC
	rs1470579	F (Outer)	ATGGCTACTGCAACTAAGACCTAA
		R (Outer)	TCTGCCACATGAAAATCTGTATCTTCT
		FC (Forward inner)	TCATCATTAGATAAGATCCATACGAGCTC
		RA (Reverse inner)	AAGTCCTTTTCTTGATAGGCAGGGTT

Table 4. Comparison and display of the genotype of the studied subjects in different groups.

Allelic frequency rs1470579			Allelic frequency rs4402960			Allelic frequency rs4705343			Allelic frequency rs4705342			Groups
CC	AC	AA	TT	GT	GG	CC	TC	TT	CC	TC	TT	**AT**
10	3	17	5	5	20	3	6	21	0	2	28	
CC	AC	AA	TT	GT	GG	CC	TC	TT	CC	TC	TT	**RT**
15	5	10	9	6	15	1	3	26	1	4	25	
CC	AC	AA	TT	GT	GG	CC	TC	TT	CC	TC	TT	**Control AT**
14	4	12	13	2	15	2	4	24	0	3	27	
CC	AC	AA	TT	GT	GG	CC	TC	TT	CC	TC	TT	**AT-BFR**
6	15	9	10	4	16	1	0	29	2	4	24	
CC	AC	AA	TT	GT	GG	CC	TC	TT	CC	TC	TT	**RT-BFR**
5	14	11	8	3	19	4	1	25	1	6	23	
CC	AC	AA	TT	GT	GG	CC	TC	TT	CC	TC	TT	**Control RT**
2	18	10	9	3	18	1	2	27	0	10	20	

Table 5. Comparison of genotypes of subjects studied in the recessive model in different groups compared to the reference group.

Allelic frequency rs1470579	Allelic frequency rs4402960	Allelic frequency rs4705343	Allelic frequency rs4705342	Groups
CC vs. AC+AA	TT vs. GT+GG	CC vs. TC+TT	CC vs. TC+TT undefined	**AT vs. Control AT**
0.57 (0.20-1.62) *p*-value: 0.296	0.26 (0.08-0.87) ***p*-value: 0.025**	1.55 (0.24-10.05) *p*-value: 0.643	1.00 (0.00-0.00) *p*-value: 1.000	**(Recessive Model)**
CC vs. AC+AA	TT vs. GT+GG	CC vs. TC+TT	CC vs. TC+TT undefined	**RT vs. Control RT**
14.00 (2.82-69.56) ***p*-value: <0.001**	1.00 (0.33-3.02) *p*-value: 1.000	1.00 (0.06-16.76) *p*-value: 1.000	1.00 (0.00-0.00) *p*-value: 1.000	**(Recessive Model)**

group and the Control AT group, the dominant genotype was $TT_{rs4705342}TT_{rs4705343}GG_{rs4402960}CC_{rs1470579}$. And also, in other groups (including AT-BFR and RT-BFR group and Control RT group) the dominant genotype was $TT_{rs4705342}TT_{rs4705343}GG_{rs4402960}AC_{rs1470579}$. The genotypes of the participants in the recessive model revealed significant differences between the various groups and the reference group association (**Table 5**). The binary logistic regression analysis, using OR and CI calculations, demonstrated this. The results were AT vs. Control AT at the rs4402960 position in the recessive model. Therefore, the risk decreased by 0.74 for TT *vs.* GT+GG (0.26 (0.08-0.87), *p*-value = 0.025). Moreover, the RT group *vs.* Control RT group at the rs1470579 position in the same model, yielded significant results, leading to a 14-fold increase in risk for CC *vs.* AC+AA (14.00 (2.82-69.56), *p*-value < 0.001).

Discussion

The study titled "Assessment of resistance and aerobic training with/without Blood Flow Restriction and detraining period and their association with *miR143/145* (rs4705342 and rs4705343) and *IGF2BP2* (rs4402960 and rs1470579) gene polymorphisms in men with type 2 diabetes" provides valuable insights into the interplay between exercise modalities, genetic predisposition, and metabolic health among individuals with T2D. As diabetes remains a global health challenge, understanding how various training programs and genetic factors contribute to IR may help tailor more effective interventions (27). T2D is a chronic metabolic disorder characterized by insulin resistance and impaired insulin secretion, leading to hyperglycemia (28). It is often associated with obesity, physical inactivity, and an unhealthy diet. The prevalence of T2D has reached epidemic proportions globally, and it poses significant health risks, including cardiovascular disease, neuropathy, nephropathy, and retinopathy (29, 30). Given the lifestyle-related nature of T2D, exercise and physical activity have emerged as critical components in its management and prevention (31). Exercise is widely recognized as a cornerstone in the management of T2D (32). It enhances insulin sensitivity, helps regulate blood glucose levels, promotes weight loss, and improves overall cardiovascular health (33). Understanding the effects of different types of exercise—specifically AT and RT—can help tailor effective interventions for individuals with T2D.

RT, especially when amplified through BFR, has been shown to produce favorable adaptations in insulin sensitivity, which aligns with previous research suggesting that both traditional and BFR-enhanced RT can elicit significant improvements in insulin action and reduce overall IR. This is particularly important given that muscle contraction during RT promotes not just hypertrophy but also enhances glucose uptake through pathways independent of insulin signaling (34, 35). Aerobic exercise also showcased its benefits in mitigating IR (36); however, the magnitude of the effect appeared to be contingent upon the intensity and duration of the aerobic intervention. Since cardiovascular health is often compromised in T2D patients, the implications of these findings are critical, suggesting that a combination of AT and RT may be more beneficial than either modality alone, especially in enhancing overall metabolic function. BFR training stands out in this discussion as an innovative approach that may enhance the effectiveness of traditional resistance training, particularly for populations at risk of injury or for those who are unable to perform high-load exercises (37). The combination of low-load resistance training with BFR may facilitate muscle hypertrophy, thus improving insulin sensitivity in a relatively safer manner. This finding aligns with the emerging body of literature supporting the use of BFR in clinical populations, as it may offer a viable alternative to high-intensity training regimens (38).

The examination of genetic variants located in the *miR143/145* and *IGF2BP2* gene clusters is noteworthy in this context, adding a layer of complexity to the understanding of how genetic predispositions may influence metabolic responses to training. The *miR143/145* cluster is involved in the regulation of vascular smooth muscle cell function and could, therefore, be implicated in the development of IR. Variants in the *IGF2BP2* gene, known to affect insulin signaling pathways and glucose metabolism, further

emphasize the need to consider individual genetic backgrounds when designing exercise interventions. The interaction between training modality, genetic factors, and metabolic outcomes points to the potential for personalized exercise prescriptions that take into account an individual's genetic makeup. The nuances of these genetic variants may indeed moderate the extent to which different exercise modalities ameliorate IR, indicating that a one-size-fits-all approach to exercise for diabetes management may be less effective.

The investigation into the effects of a detraining period also holds significant implications, particularly for long-term management strategies in T2D. This underscores the need for structured exercise regimens that emphasize adherence even after initial gains are achieved. Therefore, strategies aimed at preventing detraining—through educational support, motivational interventions, or continuous monitoring—may be vital in managing T2D. Our gym would have had trouble performing control exercises on women, so the study's focus on men was another limitation. We particularly recommend that similar studies evaluate the results of both sexes. We suggest that future studies aim to replicate our findings with broader populations to enhance generalizability.

Conclusion

This comprehensive assessment of RT and AT with and without BFR, alongside the impact of a detraining period, highlights significant interactions between exercise modalities and genetic polymorphisms related to *miR143/145* and *IGF2BP2* in men with T2D. The implications of our study underscore the importance of personalized exercise interventions that consider individual genetic backgrounds to optimize fitness and metabolic health in men with T2D. Future research should further explore these relationships, aiming to elucidate the underlying mechanisms and develop tailored exercise strategies that can enhance the quality of life and health management for individuals facing the challenges of this chronic condition.

Author's contribution

FF, AR and RS Methodology and Design, HM, FF, AR and RS writing the draft, HM genotyping, RS data analysis and FF clinical patient assessment, FF and AR supervision and editing.

Conflict of interests

The authors declare no conflict of interest.

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