Clinics 81 (2026) 100904

CLINICS
OFFICIAL SCIENTIFIC JOURNAL OF FACULDADE DE MEDICINA AND HOSPITAL DAS CLÍNICAS
UNIVERSIDADE DE SÃO PAULO - SÃO PAULO, BRAZIL

Contents lists available at ScienceDirect

Clinics

journal homepage: www.elsevier.com/locate/clinsp

Original articles

Lack of effect of short-term interval training on kidney function in obese adolescent females

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ARTICLE INFO

Edited by José Maria Soares Junior

Keywords:
High-intensity interval training
Adolescent obesity
Renal function
Estimated glomerular filtration rate
Body composition
Electrolytes
Overweight females

ABSTRACT

Objective: Obesity is a major independent risk factor for chronic kidney disease. High-Intensity Interval Training (HIIT) is recognized as an interesting therapeutic strategy in managing obesity and related disorders. However, there is still a lack of knowledge about its impact on kidney function. The study aimed to evaluate the impact of the HIIT program on kidney function and erythrocyte parameters in overweight/obese women.
Methods: Thirty-three overweight/obese young women (age, 17.0 ± 1.15 yrs.; body mass index, 33.3 ± 4.77 kg/m^2) were allocated into HIIT (n = 17) or control (n = 16) groups. The HIIT program was performed 3 times a week for nine weeks. Body composition parameters, blood creatinine, blood urea, estimated Glomerular Filtration Rate (eGFR), serum electrolytes (i.e., sodium, potassium, chloride, calcium, phosphorus, and magnesium), and red blood cell parameters (i.e., red blood cell count, hematocrit, hemoglobin and mean corpuscular volume) were collected before the start and after the completion of the training.
Results: Nine weeks of HIIT significantly improved ($p < 0.01$) body mass index, body fat, and waist circumference, but the auhtors found no statistically significant changes in blood creatinine, urea, eGFR, and red blood cell parameters ($p > 0.05$). No variable changed in the control group.
Conclusions: HIIT improved body composition; however, no significant changes in renal function parameters were detected in this underpowered study.

Introduction

The pervasiveness of obesity worldwide has increased dramatically over the last several decades. It has tripled since 1975, rising from 4.6 % to 14 % between 1980 and 2019,[1] with new data predicting that, by 2030, more than half of the world's population will be obese.[2] Obesity is strongly related to a wide variety of illnesses, including Type 2 diabetes mellitus and hypertension, which are important risk factors for kidney diseases. It plays an important role in the development and progression of kidney diseases, including Chronic Kidney Disease (CKD), glomerulopathy, nephrolithiasis, and renal cancer.[3] Overweight and obese patients have a higher risk of developing kidney diseases, reaching 38 %.[4] Data from the Swedish National Population Register showed that being overweight at age 20 was associated with risk for CKD compared to participants with a Body Mass Index (BMI) ≤ 25 kg/m.[25] Vivante et al.[6] showed that overweight and obesity were precarious factors for renal failure in adolescents. The mechanism by which obesity initiates and/or is involved in the progression of kidney diseases can be inflammation.[7] The primary biochemical marker indicator of inflammation is complete blood count, playing an important role in the release of inflammatory cytokines and autoantibodies, contributing to tissue destruction and kidney diseases that can evolve into renal failure.[7] Changes in hemogram parameters, including Red Blood Cell (RBC) count, Hematocrit (HCT), Hemoglobin (HGB), and Mean Corpuscular Volume (MCV), have

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https://doi.org/10.1016/j.clinsp.2026.100904
Received 5 August 2025; Received in revised form 13 December 2025; Accepted 27 December 2025
Available online 21 March 2026

been recognized as an important component of the systemic inflammatory response, playing an important part in predicting kidney disease.[8] Immune dysfunction and chronic inflammation, progressing with loss of kidney function, are the leading causes of cardiovascular disease and infections, two significant contributors to mortality among people with kidney diseases.[8] Kidney function is routinely assessed by measuring nitrogen compounds (creatinine, urea, and uric acid), estimated Glomerular Filtration Rate (eGFR), and electrolytes.[9] Sodium, potassium, chloride, calcium, phosphorus, and magnesium are the most common electrolytes related to kidney function; their disorders can cause serious health problems, including vascular calcification, bone demineralization, and even death.[9] Early interventions to monitor kidney function to prevent/reduce the risk of kidney failure are a major public health concern. Recent research investigated the role of medications and therapies in managing the early stages of CKD, emphasizing that despite potential benefits, all medicines cause unwanted side effects.[10] Exercise intervention presents the first-line approach to improve outcomes in patients with kidney disease, an inexpensive and riskless option.[11] Recent evidence from an umbrella review and narrative reviews has consolidated that different exercise modalities significantly improve key clinical and physiological parameters in patients with CKD, including eGFR, serum creatinine, blood pressure, electrolyte balance, and markers of metabolic and inflammatory status.[11-13] Beyond clinical outcomes, it has been proposed that physical exercise may act as a "polypill" against CKD by simultaneously improving cardiovascular, metabolic, and renal pathways.[13]

However, little is known about the effects of exercise on kidney function markers in the overweight/obese population. Aerobic training improves eGFR and leads to preventing or delaying the progression of CKD in overweight/obese persons.[14] Recently, high-intensity interval training (HIIT) has been the main focus of researchers.[15] Systematic review with meta-analysis and a scoping review have indicated that HIIT produces health-related benefits in various high-risk populations, including individuals with obesity and patients with renal conditions.[16,17] Specifically, Lovatto et al.[17] explored the use of HIIT as an adjunct to physical rehabilitation in renal populations, such as kidney transplant recipients, suggesting that HIIT can improve cardiovascular fitness, functional capacity, and kidney function. However, the effects of HIIT on renal function in overweight/obese adolescents have not been investigated. In this study, the auhtors evaluated, for the first time, the effect of a 9-week HIIT program on kidney function in young, overweight/obese women. It was hypothesized that: 1) Interval training would manage obesity and reduce body composition parameters. 2) Markers of renal function, such as nitrogen composition, eGFR, electrolyte levels, or erythrocyte parameters, would result in significant improvement over a 9-week intervention period.

Methods

Ethical approval

Informed written parental consent was obtained from each participant after informing on the benefits and potential risks of participation in the study. The study has been examined and approved by the local Ethics Committee of the High Institute of Sports and Physical Education of Kef (ISSEPK-04/2019), and all procedures were conducted in accordance with the Helsinki Declaration. The procedures of this study followed the CONSORT statement.

Study protocol

The study was conducted from March to May 2019 under the following environmental conditions: temperature between 14 °C and 19 °C and humidity from 64 % to 71 %. Participants followed the HIIT program for nine weeks. Anthropometric measurement, blood pressure, maximal aerobic speed, and biochemical parameters were evaluated before and after the training program. Body mass, Body Fat percentage (BF), and Muscular Mass (MM) were measured using a TANITA scale (Tanita BC-533, Tokyo, Japan). A stadiometer determines height to calculate BMI (kg/m^2) = body weight/body $height^2$. Girls with a BMI between the 85^{th} and 95^{th} percentile, and a BMI above the 95^{th} percentile, were classified as having overweight and obesity, respectively. Waist Circumference (WC) was measured at the midpoint between the inferior rib margin and the superior border of the iliac crest with non-deformable tape. Systolic (SBP) and Diastolic (DBP) blood pressure were measured using an automatic sphygmomanometer (Omron BP652, Omron Healthcare Inc., Vernon Hills, IL, USA). A graded exercise test was performed to determine Maximal Aerobic Speed (MAS) until exhaustion as previously described.[15]

Participants

Sample size estimation was performed using G*Power software (version 3.1, Germany). Considering a partial effect size of 0.55, a power level of 0.95, and an α value of 0.05 for a two-group, two-time point design, the analysis suggested that 14 subjects per group would be required, as reported by Abassi et al.[18] The auhtors enrolled 49 female participants aged 15–18 years with a BMI > 85^{th} percentile. Girls with medical contraindication to intensive physical exercise and/or cardiometabolic disorders and those receiving nutritional intervention were excluded. Thirty-six participants were randomly assigned to the training or non-training control group (n = 16). Three participants dropped out, and 33 continued the protocol: 17 girls in the HIIT group and 16 girls in the control group. The process adopted for the enrollment, allocation, and drop-out of participants is shown in Fig. 1. All girls participated in school-based only physical education classes twice a week, for 60 min each time.

Training program

The exercise training was in accordance with the HIIT guidelines.[15,19,20] The training group underwent 3 HIIT sessions per week for nine weeks. Before the exercise training, they did 15 min of warm-up and stretching as previously described.[20] The training group executed 2 sets of 6 repetitions of 30 s runs at 100 %–105 %, interspersed with 30 s of active rest at 50 % of MAS between repetitions and 5 min of passive recovery between sets. The number of repetitions and the intensity increased from the 4^{th} and 7^{th} weeks, respectively. The details of the prescribed training are included in Table 1.

Blood samples

Fasting blood samples (5 mL) were obtained from the antecubital vein from 7 am to 8 am, before and after the completion of the training intervention. Serum was separated by centrifugation at 2000 rpm for 25 min for biochemical analysis. Kidney function markers (serum creatinine and urea) and plasma electrolytes (sodium, potassium, calcium, chloride, magnesium, and phosphorus) were measured using an automated immunoassay system (AU480 Chemistry Analyzer; Beckman Coulter, Brea, CA). A Sysmex XN450 automated blood cell counter was used to determine red blood cell indices, including RBC count, HCT, HGB, and MCV. The eGFR was estimated using the Schwartz formula[21] as follows: eGFR ($mL/min/1.73\ m^2$) = 0.413 × (height/serum creatinine).

Statistical analysis

Analysis was performed using SPSS software (SPSS version 22.0 Inc., Chicago, IL, USA). The normality of all variables was assessed and confirmed using the Kolmogorov-Smirnov test. The homogeneity of variance was verified using Levene's test. Data are presented as mean and standard deviation. Comparisons between groups were carried out

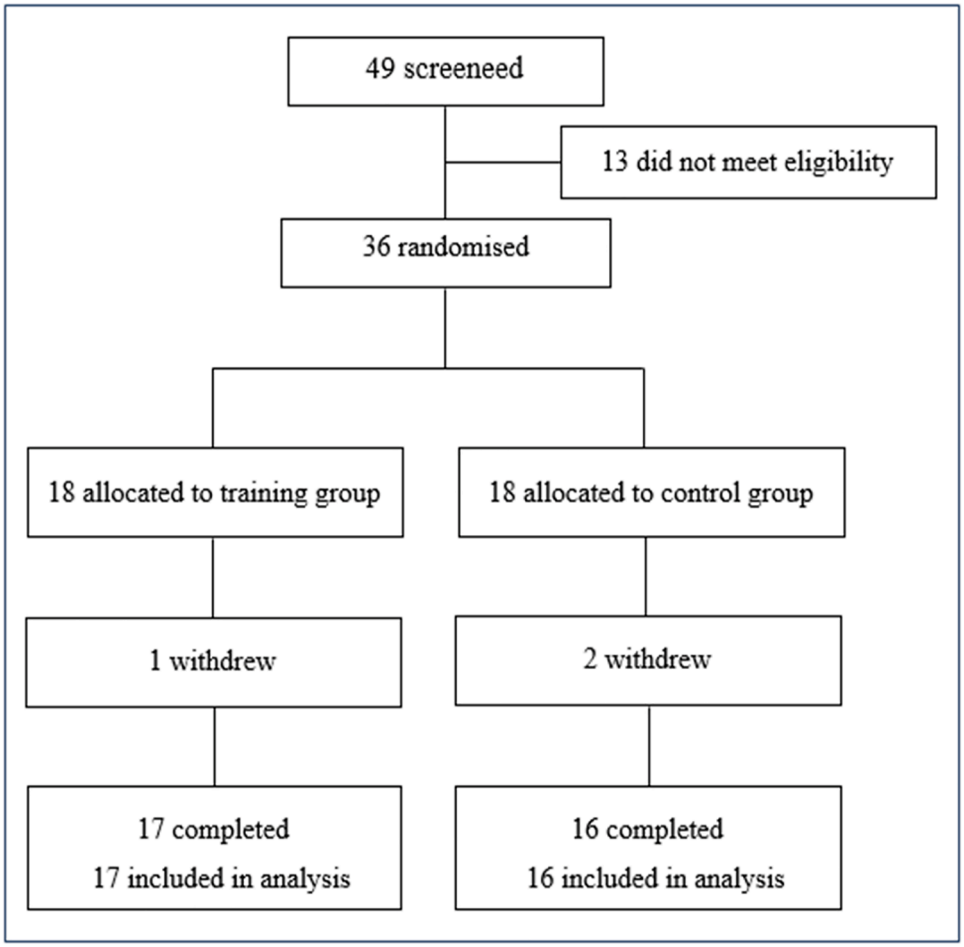

Fig. 1. Flow chart of the study participants.

Table 1
High-Intensity Interval Training (HIIT) description.

	Week 1–3	Week 4–6	Week 7–9
Number of sets	2	2	2
Number of races per sets	6	8	8
Run/active recuperation time, s	30/30	30/30	30/30
Percent of MAS (run/active recuperation)	100/50	100/50	105/50
Passive recovery time, min	5	5	5

MAS, Maximal Aerobic Speed.

using *t*-tests for independent samples. Two-way mixed analyses of variance (ANOVA) with repeated measures (2 groups × 2 time points: pre- and post-intervention) were used to test the interaction effect of group by time on the outcome variables. Effect size (ES) was tested based on Cohen's classification. The effect was considered small ($0.00 < d < 0.49$), medium ($0.50 < d < 0.79$), and large ($d < 0.80$).[22] A two-sided p-value < 0.05 was considered significant.

Results

Body composition and cardio-respiratory fitness

Pre- and post-training values are presented in Table 2. Before the intervention, no statistically significant differences were detected between the HIIT and control groups in body composition parameters, blood pressure, and MAS. The repeated two-way ANOVA analyses revealed significant interactions (all $p < 0.05$) for body mass, BMI, BF, WC, SBP, and MAS. No significant interactions were found in MM and DBP. Post-hoc analyses found that the HIIT group revealed a significant decrease in body mass ($p < 0.001$, ES = 0.25), BMI ($p = 0.001$; ES = 0.29), BF ($p < 0.001$, ES = 0.52), WC ($p = 0.003$, ES = 0.37), and SBP ($p = 0.011$, ES = 0.80), and a significant increase in MAS ($p = 0.035$, ES = 0.54). Between-group analyses indicated that HIIT significantly increased post-intervention MAS ($p = 0.010$, ES = 0.99) compared to the control groups.

Biochemical parameters

Table 3 displays changes in hematological, kidney function markers, and electrolyte levels in the HIIT and control groups before and after the intervention. No significant between-group differences were detected for the baseline measures. No significant time × group interactions ($p > 0.05$) were observed for blood creatinine, eGFR, urea, and electrolytes. In the between-group comparison, HIIT showed a significant decrease in blood sodium ($p = 0.047$; ES = 0.75) and chloride ($p = 0.045$; ES = 0.74) levels compared to the control group. Additionally, no significant groupv× time interactions were observed for the RBC, HBG, HCT, and MCV levels.

Discussion

The findings indicate that despite weight loss and body composition enhancement, no significant changes were detected in nitrogen compounds (creatinine and urea), estimated glomerular filtration rate, electrolyte levels, or erythrocyte parameters after a 9-week HIIT

Table 2
Participant characteristics at baseline (Pre) and post-intervention (Post) in the training and control groups.

	Control group ($n = 16$)		Training group ($n = 17$)		Baseline comparison	Interaction (time × group)		
	Pre	Post	Pre	Post	p	F	p	η_p^2
Age (year)	17.3 ± 1.10		16.7 ± 1.32		–	–	–	–
Height (cm)	159 ± 8.33		160 ± 7.05		–	–	–	–
Body mass (kg)	84.0 ± 9.74	85.9 ± 9.24	85.1 ± 11.4	82.3 ± 11.0[c]	0.782	14.6	0.001	0.32
BMI (Kg/m²)	33.6 ± 5.45	34.3 ± 4.83	33.1 ± 4.18	32.0 ± 3.81[c]	0.765	13.2	0.001	0.30
Body fat (%)	32.7 ± 2.76	33.3 ± 2.88	34.5 ± 3.87	32.7 ± 3.16[c]	0.149	14.7	0.001	0.32
Muscular mass (Kg)	29.7 ± 4.83	29.1 ± 4.05	29.4 ± 3.36	30.3 ± 3.93	0.818	3.01	0.093	0.08
WC (cm)	101 ± 8.47	101 ± 7.82	107 ± 10.4	104 ± 8.34[b]	0.061	8.49	0.007	0.22
SBP (mmHg)	125 ± 3.40	125 ± 3.91	125 ± 2.74	123 ± 2.71[b]	0.809	4.92	0.034	0.14
DBP (mmHg)	77.4 ± 3.18	77.3 ± 3.76	78.1 ± 4.19	77.0 ± 3.88	0.636	1.45	0.237	0.05
MAS (km/h)	10.8 ± 1.24	10.4 ± 1.03	10.9 ± 1.64	11.8 ± 1.74[a,d]	0.709	5.77	0.022	0.16

Data are expressed as mean ± SD; BMI, Body Mass Index; WC, Waist Circumference; SBP, Systolic Blood Pressure; DBP, Diastolic Blood Pressure; MAS, Maximal Aerobic Speed.
[a] $p < 0.05$.
[b] $p < 0.01$.
[c] $p < 0.001$ (compared to the pre-intervention value in the group).
[d] $p < 0.01$ (compared to the post-intervention value in the control group.

Table 3
Red blood cell parameters, renal function parameters, and electrolytes at baseline (Pre) and post-intervention (Post) in the training and control groups.

	Control group ($n = 16$)		Training group ($n = 17$)		Baseline comparison	Interaction (time × group)		
	Pre	Post	Pre	Post	p	F	p	η_p^2
Red blood cells (10^6/μL)	4.65 ± 0.30	4.73 ± 0.42	4.75 ± 0.31	4.55 ± 0.40	0.355	3.353	0.077	0.098
Hemoglobin (g/dL)	12.9 ± 0.63	12.9 ± 0.77	12.8 ± 0.93	12.2 ± 1.28	0.739	2.882	0.100	0.085
Hematocrit (%)	38.8 ± 1.91	39.3 ± 2.09	38.5 ± 2.48	38.1 ± 2.32	0.701	2.344	0.136	0.070
MCV (fL)	83.1 ± 5.20	83.6 ± 5.98	82.5 ± 6.35	81.4 ± 7.03	0.758	1.046	0.314	0.033
Creatinine (mg/dL)	0.56 ± 0.06	0.56 ± 0.07	0.54 ± 0.05	0.52 ± 0.04	0.438	2.632	0.115	0.078
eGFR (mL/min/1.73 m²)	119.2 ± 13.3	119.5 ± 15.8	123.6 ± 14.2	128.9 ± 16.0	0.360	2.332	0.137	0.070
Urea (mmoL/L)	3.46 ± 0.72	3.64 ± 0.80	3.68 ± 0.71	3.47 ± 0.70	0.372	3.497	0.071	0.101
Phosphorus (mmoL/L)	1.22 ± 0.18	1.21 ± 0.20	1.48 ± 0.25	1.47 ± 0.22	0.092	0.007	0.936	0.000
Sodium (mmoL/L)	138.2 ± 0.84	138.5 ± 1.96	137.4 ± 1.38	136.9 ± 2.51[a]	0.060	1.461	0.236	0.045
Potassium (mmoL/L)	4.51 ± 0.27	4.56 ± 0.31	4.44 ± 0.41	4.37 ± 0.43	0.567	1.682	0.204	0.051
Calcium (mmoL/L)	2.43 ± 0.09	2.44 ± 0.05	2.40 ± 0.05	2.38 ± 0.06	0.214	0.451	0.507	0.014
Magnesium (mmoL/L)	0.75 ± 0.06	0.76 ± 0.03	0.72 ± 0.07	0.71 ± 0.07	0.143	0.328	0.571	0.010
Chloride (mmoL/L)	104.2 ± 1.63	104.4 ± 2.14	103.7 ± 1.41	103.1 ± 1.44[a]	0.348	0.833	0.368	0.026

Data are expressed as mean ± SD.
[a] $p < 0.05$ (compared to the control group); eGFR, estimated Glomerular Filtration Rate; MCV, Mean Corpuscular Volume.

program in overweight/obese young women with normal renal function.

In the present study, the authors' first hypothesis has been confirmed. Thus, after 9-weeks of intervention, subjects in the HIIT group achieved significant weight loss and reduction in BMI, body fat, MM, and WC. These results are in accordance with previous observations, showing that HIIT has a similar impact on body composition in overweight/obese young women.[15,19,20] The proposed physiological mechanisms underlying improved body composition after HIIT are the release of catecholamines and the decreased appetite after exercise that promotes tissue lipolysis.[23]

Referring to the second hypothesis, the auhtors found no statistically significant changes in serum creatinine and eGFR after 9-weeks of HIIT. Few studies have investigated the effects of HIIT on creatinine and eGFR. The effects of other training types on eGFR and blood creatinine are controversial. A 16-week moderate-intensity aerobic exercise did not affect eGFR in obese women.[24] Twelve-week endurance and endurance-strength training increased serum creatinine and decreased eGFR in obese women.[25] In the current study, no significant change was detected in urea levels in overweight/obese girls following HIIT. Currently, there is limited evidence regarding the effect of HIIT on serum urea in overweight/obese individuals. However, one study reported an increase in urea concentrations following HIIT in youth athletes.[26] Evidence suggests that increases in eGFR and decreases in urea are associated with improved kidney function in overweight women with normal renal function.[27] In obese individuals, weight loss is necessary to improve kidney function.[28] In this study, no significant changes were detected in urea and eGFR despite significant weight loss. Long-term HIIT programs with adequate intensity may be necessary to improve kidney function in obese subjects with normal kidney function.

The study showed no significant changes in serum phosphorus after 9-week HIIT. Little is known about the HIIT effect on phosphorus. The present findings align with the study of Miele et al.[24] who showed that 16-weeks of moderate-intensity aerobic exercise caused no changes in phosphorus levels in obese women. However, an 8-week aerobic training intervention decreased serum phosphorus in hemodialysis patients.[29] The lack of an effect on serum phosphorus is compatible with the study of Fallahi et al.,[30] suggesting that more time and/or exercise intensity are necessary to induce a noticeable change in phosphorus levels. Previous studies reported that phosphorus is generated from skeletal muscle after exercise training. The lack of post-training phosphorus change might be explained by phosphorus being used to replenish energy stores.[31]

During the 9-week HIIT, no significant change was found in serum sodium. Regarding the limited evidence on sodium response after HIIT, these findings are matched by those of Miele et al.[24] showing that 16-weeks of moderate-intensity aerobic exercise three times per week does not induce changes in serum sodium in obese women. However, a significant increase in sodium levels was observed in overweight and obese subjects after moderate-intensity prolonged exercise.[32] These discrepancies may stem from differences in exercise training duration.

The auhtors also found no statistically significant change in serum

chloride. At the same time, no significant change in chloride levels was found after marathon running in youth athletes.[33] In this study, although post-hoc analyses revealed small but statistically significant reductions in sodium and chloride levels in the HIIT group, these changes remained within the normal physiological range and were not supported by the primary time × group interaction analysis. Therefore, they are unlikely to reflect a clinically meaningful effect of HIIT and should be interpreted with caution. Most authors have found that serum sodium and chloride responses to exercise training usually correlate, demonstrating that during exercise, hyponatremia is accompanied by a reduction in serum chloride, as sodium and chloride are the main constituents of sweat in the salt form.[34]

Moreover, the auhtors found no statistically significant effect of HIIT on serum calcium. Researchers reported increased serum calcium after high-intensity karate training in karateka women.[35] To date, reports on the effect of HIIT on calcium are scarce, while other training protocols are more available. The present study confirmed previous observations that reported no significant change in serum calcium after 8-week aerobic training in hemodialysis patients.[29] The most likely factor accounting for the increased serum calcium is the excessive reduction of adenosine triphosphate after high-intensity exercise training, which disrupts the function of the calcium pump and increases the calcium ion inside the cell.[35]

No significant changes were detected in serum potassium after 9-weeks of HIIT. There is a lack of reports on the HIIT effect on potassium levels. A previous study suggested that 4-months of aerobic exercise increased potassium levels in hemodialysis patients.[36] Some evidence suggests that the improved serum potassium after training is related to the increased activation of Na/K pumps during exercise training.[37] The auhtors found no statistically significant change in serum magnesium. Respecting the poor available literature on magnesium response to HIIT, Rose et al.[38] reported no change in magnesium levels after marathon running.[33] Furthermore, a previous study indicated that prolonged submaximal exercise is accompanied by hypomagnesemia due to the increase in glycolysis, which leads to an increase in the absorption of glucose in the kidney, blocking the reabsorption of divalent cations and rising magnesium diuresis.

The present results suggest that in overweight/obese subjects with normal kidney function, short-term HIIT interventions may not be sufficient to produce measurable changes in electrolytes, despite improvements in body composition. No significant changes were observed in erythrocyte parameters after the 9-week HIIT intervention. These findings are consistent with a study showing no significant change in HGB and HCT after 6-weeks of HIIT in overweight/obese young men.[39] In contrast, the present results are inconsistent with findings that demonstrated HCT and HGB increases after 8-weeks of HIIT in young normal-weight men.[40] Differences in exercise intensity and duration, and subjects' trainability might explain the study discrepancy.

The present study did not observe significant changes in renal markers following the HIIT intervention, despite the improvements in body composition. The null findings may be attributed to the short intervention duration, which may have been insufficient to elicit measurable adaptations in renal function, which often require longer-term exposure to exercise stimuli. Also, the small sample size may have reduced the statistical power, increasing the likelihood of type II error. At the same time, the relatively healthy baseline status of participants could have limited the potential for improvement, as their renal function was already preserved.

This study has limitations that should be considered in future research. Firstly, the sample size of this study was relatively small, which has underpowered the study. Therefore, the observed null results should be interpreted with extreme caution, as type II errors (false negatives) are highly probable. Secondly, the homogeneity of the cohort, young obese but otherwise healthy Tunisian females with normal baseline renal function, restricts the generalizability of the results to other populations, including males, different age groups, ethnicities, and especially individuals with impaired kidney function. Thirdly, dietary intake was not controlled, which is a major potential confounder for body composition, electrolytes, and urea levels. It is therefore possible that the slight improvement is partly explained by unmeasured dietary changes. Finally, the duration of the intervention may have been too short to elicit detectable changes in renal outcomes such as eGFR in a young population with preserved kidney function.

Conclusions

This study showed no significant changes in renal function markers and erythrocyte parameters after a 9-week HIIT intervention in overweight/obese young women. Long-term HIIT programs of adequate intensity may be necessary to improve renal function. Additionally, a proper diet along with the training program may be required to improve kidney function in obese individuals.

Abbreviations

BF, Body Fat; BMI, Body Mass Index; CKD, Chronic Kidney Disease; DBP, Diastolic Blood Pressure; eGFR, estimated Glomerular Filtration Rate; ES, Effect Size; HCT, Hematocrit; HGB, Hemoglobin; HIIT, High-Intensity Interval Training; MCV, Mean Corpuscular Volume; MM, Muscular Mass; RBC, Red Blood Cell; SBP, Systolic Blood Pressure; WC, Waist Circumference.

Data availability statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Funding

This study was not supported by any specific grant from public, commercial, or non-profit funding entities. All resources utilized were provided by the authors' respective institutions.

CRediT authorship contribution statement

Wissal Abassi: Conceptualization, Methodology, Supervision, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Nejmeddine Ouerghi:** Conceptualization, Methodology, Supervision, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Omar Feki:** Conceptualization, Methodology, Supervision, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Martine Duclos:** Conceptualization, Methodology, Supervision, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Anissa Bouassida:** Conceptualization, Methodology, Supervision, Investigation, Data curation, Formal analysis. **Moncef Feki:** Conceptualization, Methodology, Supervision, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing. **Thomas Rosemann:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Katja Weiss:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing. **Beat Knechtle:** Conceptualization, Methodology, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

The authors are indebted to all the girls and their parents for their

wholehearted support and cooperation in completing the study.

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