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Physical Fitness and Its Relationship to Plasma Leptin, Leptin Soluble Receptor, and Free Leptin Index in a Saudi Population: A Comparison Between Diabetic and Non-Diabetic Individuals

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Low physical activity is considered to be a risk factor for type 2 diabetes mellitus (T2DM). One theory suggest that leptin resistance is involved in the pathophysiology of impaired glucose metabolism. In this study we aimed to assess the correlation of physical fitness scores (PFS) with serum total leptin (TL), serum leptin soluble receptor (LSR), and free leptin index (FLI) in a group of Saudi patients with T2DM.

Material/Methods: This cross-sectional study involved 115 subjects: 52 healthy control subjects and 63 patients with T2DM. All subjects underwent body composition analysis. Blood samples were analyzed for fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), serum total leptin (TL), and serum leptin soluble receptor (LSR). Based on ideal body composition and our previous studies, physical fitness scores (PFS) were recorded for each subject.

Results: In patients with T2DM, levels of LSR were positively correlated with PFS ($r=0.281$, $p=0.025$), while the levels of TL ($r=-0.425$, $p=0.001$) and FLI ($r=-0.439$, $p=0.001$) were negatively correlated with PFS. In control subjects, TL and FLI levels were negatively correlated ($r=-0.612$, $p=0.001$ and $r=-0.543$, $p=0.001$ respectively) with PFS. In linear regression analysis, after adjustment for age and BMI, TL and FLI were independent predictors of PFS.

Conclusions: Serum TL and FLI were negatively correlated while LSR was positively correlated with PFS in patients with T2DM. Therefore, they may be important biomarkers for predicting the outcomes of physical fitness and exercise programs.

MeSH Keywords: **Adiposity • Physical Fitness • Receptors, Leptin**

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Background

The lifestyle changes associated with urbanization are characterized by high calorie intake due to increased dependence on fast food as a main meal, as well as reduced consumption of vegetables and fruits. In addition, the modern lifestyle with increasing use of technology most of the day encourages different age groups to practice sedentary behaviors. In 2010 the World Health Organization (WHO) identified physical inactivity as the fourth leading risk factor for global mortality due to its correlation with the prevalence of non-communicable diseases, such as being the root cause of 27% of cases of diabetes [1]. The combination of high calorie intake and inactivity disturb the energy balance and lead to increase incidence of overweight and obesity, which is a leading cause of type 2 diabetes mellitus.

The regulation of body weight involves both central and peripheral factors. Leptin and ghrelin are 2 important hormones that have a central role in the regulation of food intake and body weight [2]. Leptin, discovered in 1994, is a 16kDa protein encoded in humans by a gene located in chromosome 7q31.3, translated into 167 amino acids protein, and circulated in the blood as 146 amino acid residues [3]. The main tissue that synthesizes leptin is fatty tissue, which regulates body fat stores through a feedback mechanism to inform the brain about the body fat mass [4]. Most research in humans has found that the expression of leptin was greater in subcutaneous fat than in omental fat. One study showed that subcutaneous fat tissue secretes higher amounts of leptin than the omental fat tissue, perhaps due to the larger cell size and increased expression of the leptin gene in subcutaneous fat [5]. Similarly, another study concluded that leptin expression is lower in omental than in subcutaneous adipose tissue, possibly due to differences in fat cell size and/or sympathetic innervation [6].

The correlation between plasma leptin level and physical activity has been investigated and the results showed that the predictors of circulating leptin levels were physical activity in women and peak oxygen uptake in men [7]. Similarly, a study conducted on 5-year-old children reported a positive correlation between fasting plasma leptin level and physical activity [8]. It has been reported that plasma leptin level can be reduced following changes in diet and physical activity [9].

In this study we aimed to assess the correlation of physical fitness scores (PFS) with serum total leptin (TL), serum leptin soluble receptor (LSR), and free leptin index (FLI) in a group of Saudi patients with type 2 diabetes mellitus (T2DM).

Material and Methods

This cross-sectional study was conducted in the Department of Physiology, College of Medicine and King Saud university Medical City. Ethics approval was obtained from the institutional review board of the College of Medicine. All subjects were recruited after they signed the consent form typed both in Arabic and English languages. A total of 115 subjects were selected (59 males and 56 females). Fifty-two were control subjects and 63 were patients who were diagnosed as having T2DM. The control individuals had no history of cardiovascular, renal, or neuropathic diseases. Patient with T2DM were in stable metabolic condition and were free from acute diabetic states like diabetic ketoacidosis and hyperosmolar coma. A detailed history was taken from all the subjects and demographic data was recorded. All patients underwent body composition analysis. We used InBody 3.0 for body composition analysis. InBody uses the principal of bio impedance analysis with an 8-point tactile electrode system (contact at the hands and feet). Based on ideal body composition and our previous studies, physical fitness scores (PFS) were recorded for each subject [10,11]. The maximum fitness score is 100. All body composition assessments were performed in light clothing in early morning in fasting state with bladder empty for uniformity in all subjects. The subject was asked to first wipe the sole of the feet with a wet tissue and then stand over the electrodes of the machine, and results were ready in 3–5 min. Parameters recorded included height, body weight, body surface area, BMI, obesity degree, protein mass, muscle mass, fat mass, body fat percentage, fat control, muscle control, and fitness scoring based on the target values for ideal body fitness. Segmental analysis can calculate slight differences by sex, age, and race without using empirical estimation. The technique uses multiple frequencies to measure intracellular and extracellular water separately. The frequency at 50 kHz measures the extracellular water, while the frequency above 200 kHz measures the intracellular water.

Fasting venous blood samples were also collected to measure fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), serum total leptin (TL), and serum leptin soluble receptor (LSR). Leptin and SLR immunoassays were performed by quantitative standard sandwich ELISA technique using monoclonal antibody specific for these parameters with kits supplied by R&D Systems (Abingdon, United Kingdom). Free leptin index (FLI) was calculated by dividing TL by LSR levels.

Statistical analysis

The data were analyzed using the SPSS version 20 (Chicago, IL, USA). Descriptive characteristics and the lipid profile of the study patients are expressed as mean \pm SD (standard deviation). Kolmogorov-Smirnov^a and Shapiro-Wilk tests were used to determine if data were normally distributed. Those parameters

Table 1. Comparison of demographic data and body composition indices between control and type 2 diabetes meletus (DM) patients.

Variables	Control N=52 (M/F: 27/25)	Diabetic N=63 (M/F: 32/31)	P value
Age (years)	47.22±7.73	50.02±9.99	0.790
Height (cm)	162.94±8.50	158.73±8.04	0.005
Weight (kg)	76.80±12.43	79.08±15.20	0.354
Body mass index	28.9±4.22	31.43±5.7	0.005
Body fat %	34.89±8.18	37.7±7.42	0.043
Fasting blood sugar (mmol/L)	5.02±.46	7.9±2.55	0.001
HbA1c (%)	5.00±.47	8.4±8.7	0.003
Intracellular fluid/L	24.9±4.95	24.10±3.91	0.319
Extracellular fluid/L	11.95±2.93	11.76±1.94	0.676
Total body water	36.65±7.15	35.86±5.76	0.494
Protein mass/kg	10.0±2.0	9.64±1.56	0.255
Soft lean mass	46.6±9.12	45.5±7.32	0.453
Mineral mass/kg	3.36±1.05	3.18±.415	0.211
Lean body mass	49.9±9.64	48.7±7.74	0.454
Fat mass/kg	26.64±8.46	30.17±10.6	0.040
Body fat %	34.5±8.80	37.6±7.4	0.032
Body fat mass distribution			
Right arm	2.07±.52	2.1±.44	0.812
Left arm	2.04±.51	2.1±.44	0.702
Trunk	17.5±3.22	17.3±2.74	0.753
Right leg	5.64±1.2	5.3±1.01	0.072
Left leg	5.62±1.13	5.3±1.05	0.076
Fitness score	66.8±6.5	65.9±6.71	0.467

HbA1c – glycosylated hemoglobin. Data is expressed as mean ±SD. not following normal distribution were analyzed by the non-parametric Mann-Whitney test. For continuous data with normal distribution, we used the *t* test. Correlations were determined by Pearson’s correlation analysis for serum TL, LSR, and FLI. We also performed linear regression analysis with fitness score as the dependant variable and TL, LSR, and FLI as independent variables after adjustment for age and BMI. Serum TL, LSR, and FLI at different tertiles of PFS were determined and compared by one-way analysis of variance (ANOVA).

Results

Table 1 expresses the comparison of demographic data and body composition indices between control and type 2 DM

patients. When we compared the body composition parameters between these 2 groups, the difference was not significant for body weight ($p=0.378$), Measure intracell Fluid/L ($p=0.319$), Measure Extracellular Fluid ($p=0.676$), Total Body Water ($p=0.494$), Measure Protein Mass/kg ($p=0.255$), Soft Lean Mass Measure ($p=0.453$) Mineral Mass/kg ($p=0.211$), and Lean body Mass ($p=0.454$). BFM and BF% were significantly higher in patients with diabetes compared to control ($p=0.040$ and 0.032 , respectively). The difference in average fitness score between controls ($66.8±6.5$) and patients with diabetes ($65.9±6.71$) was non-significant ($P=0.467$). In patients with type 2 DM (Figure 1), serum TL levels were negatively correlated with physical fitness scores ($r=-0.425$, $p=0.001$), while the levels of LSR ($r=0.281$, $p=0.025$) showed a positive correlation. On the other hand, FLI was negatively correlated with PFS ($r=-0.439$, $p=0.001$). In non-diabetic control

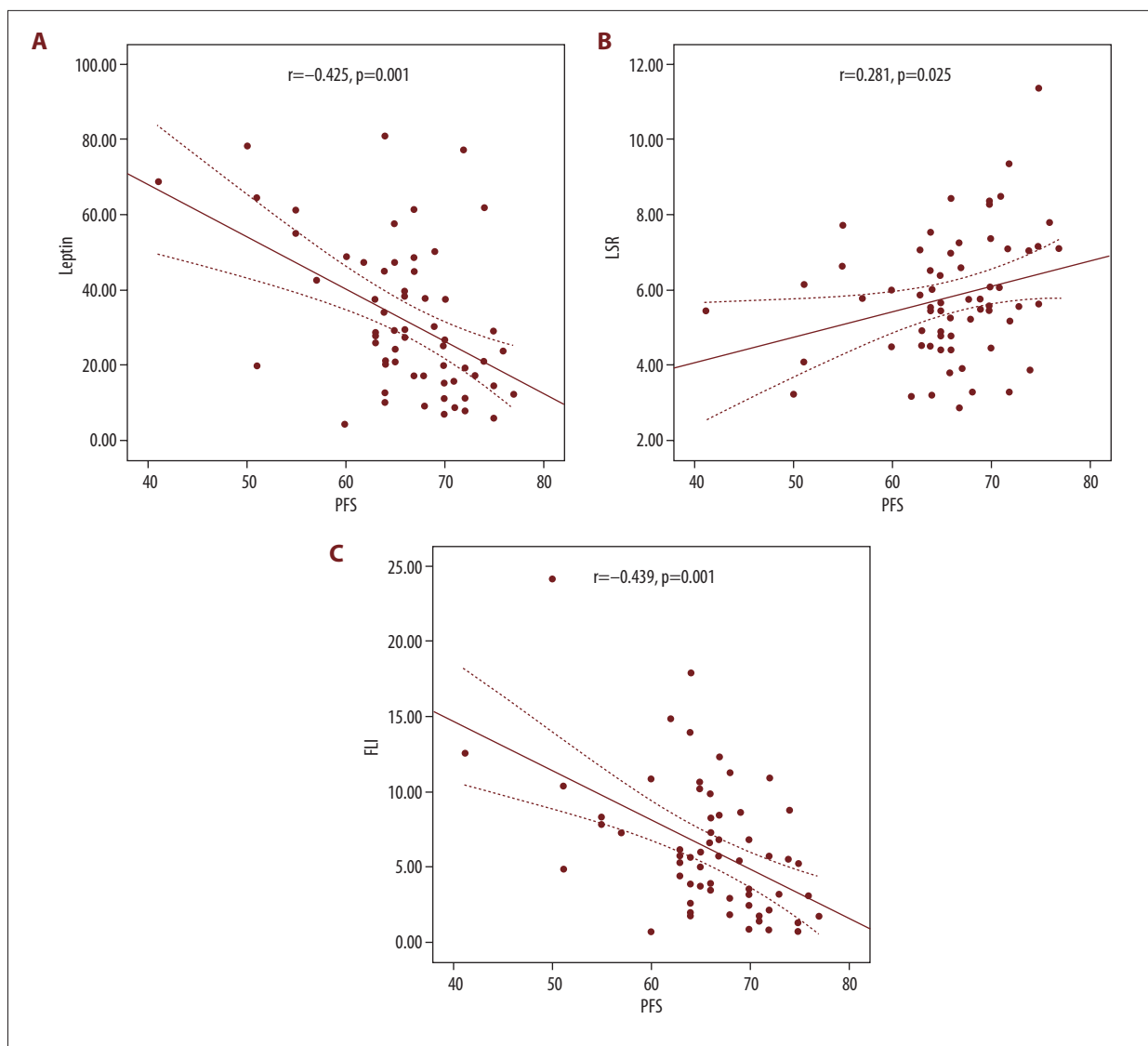


Figure 1. Correlation of serum total leptin (A), leptin soluble receptor (LSR) (B), and free leptin index (FLI) (C) with physical fitness scores (PFS) in patients with type 2 diabetes mellitus (T2DM).

subjects (Figure 2), serum TL levels were negatively correlated ($r=-0.612$, $p=0.001$) with physical fitness scores. The correlation of LSR with PFS was not significant ($r=0.075$, $p=0.594$). FLI was negatively correlated with PFS ($r=-0.543$, $p=0.001$). Figure 3 shows serum TL, LSR, and FLI at different tertiles of PFS in all subjects, showing significant differences for TL ($p=0.043$), SLR ($p=0.051$), and FLI ($p=0.036$), supporting the results of correlation analysis. In linear regression analysis after adjustment for age and BMI, TL and FLI were the only independent predictors of PFS in control subjects but these became non-significant in patients with T2DM (Table 2).

Discussion

It is well known that serum leptin level relates to the adiposity level and that it is involved in regulation of appetite, metabolism, and energy balance. Our findings in the present study showed that in control subjects and patients with T2DM, leptin level decreases with higher fitness score. In line with our findings, Plonka et al. reported that, in girls, the level of serum leptin was inversely correlated with the level of physical activity, and the study findings showed that girls performing higher physical activity have the lowest serum leptin level [12]. Previous studies found a negative correlation between leptin and physical fitness [13]. According to Martinez-Gomez et al., individuals with high levels of cardiorespiratory fitness or muscle fitness or those who participated in physical activity

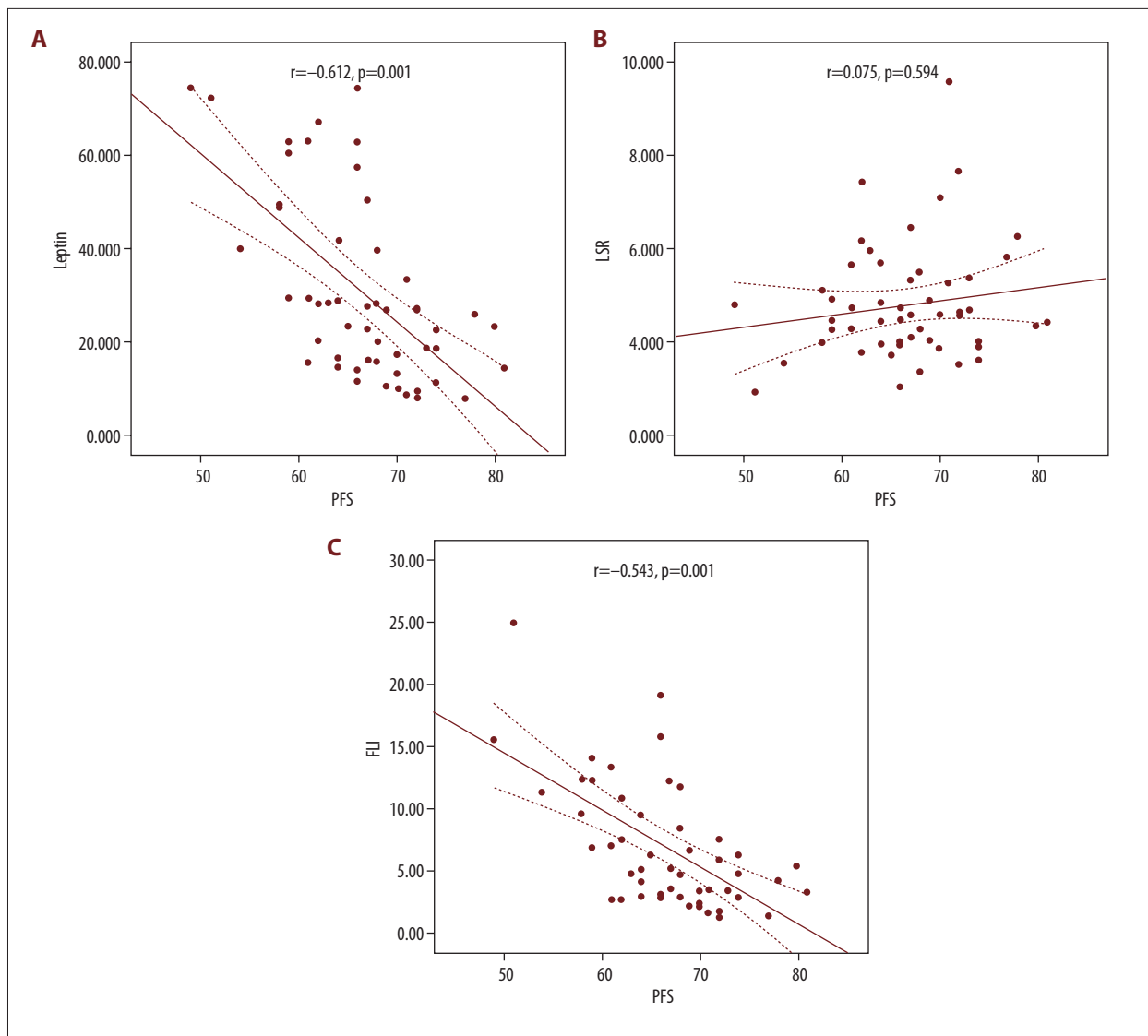


Figure 2. Correlation of serum total leptin (A), leptin soluble receptor (LSR) (B), and free leptin index (FLI) (C) with physical fitness scores (PFS) in control subjects.

tend to have increased insulin sensitivity and decreased insulin release, which could lead to decreased leptin levels [14]. Miyatake et al. (2014) found that, in clinical practice, reduced circulating leptin levels can be promoted by physical fitness in men and physical activity in women [7].

A group of investigators reported lower fitness level among patients with gestational diabetes when compared with pregnant women having normal blood glucose levels. The same study found that after adjustment for BMI and body fat mass, there was a significant negative correlation between physical fitness and serum leptin level in the whole study cohort [15]. Regular exercise, which is known to increase plasma epinephrine, is necessary to achieve and maintain physical fitness. Epinephrine increases transportation of leptin across the blood brain barrier,

which might explain the negative correlation between physical fitness level and blood leptin concentration [16]. A previous study showed that men who were addicted to exercise have low levels of leptin [17]. It has been hypothesized that, as an adaptation to enhance the pursuit and procurement of food, falling leptin levels increase stamina and the rewarding effects of running. Recently, a group of researchers found that when there is food restriction and low leptin level, there is a relationship between increased physical activity and reduced LepR-STAT3 signaling in midbrain dopaminergic neurons [18]. Another study conducted on a group of patients with non-alcoholic fatty liver, showed that resistance exercise resulted in decreased intramyocellular lipids, insulin resistance, and blood levels of free fatty acids and leptin [19]. Recently, a meta-analysis study confirmed that, even without diet or major loss of

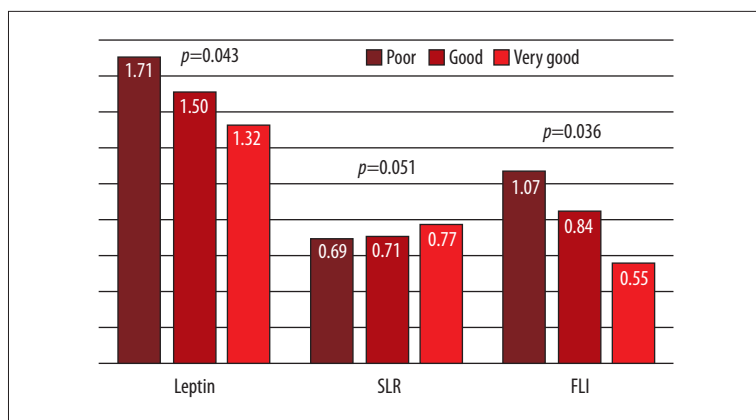


Figure 3. Serum total leptin, leptin soluble receptor (LSR), and free leptin index (FLI) at different tertiles of physical fitness scores (PFS) in all subjects, based on physical fitness categories.

Table 2. Linear regression analysis with fitness scores as dependent variable and TL, LSR, and FLI as independent variables (adjusted for age and BMI).

	B	S.E. (E)	P
Control			
Leptin	-0.294	0.042	0.023
LSR	0.052	0.553	0.620
FLI	-0.292	0.151	0.017
T2DM			
Leptin	-0.071	0.036	0.498
LSR	0.092	0.352	0.290
FLI	-0.071	0.158	0.506

weight, resistance training was strongly associated with reduction of serum leptin level [20]. A recent study used computerized tomography (CT) scanning to measure abdominal subcutaneous and visceral obesity in a large, multi-ethnic sample of men and women, reporting a strong negative association between higher levels of moderate-to-vigorous physical activity and serum leptin levels [21]. Although leptin plays an important role in stimulating fatty acid oxidation and inhibiting fat storage in skeletal muscles, it has been demonstrated that leptin has a negative association with muscle mass and function [22]. Another study demonstrated that a 6-week strength-training program that increased lean body mass and reduced fat mass did not cause significant changes in serum leptin concentration; however, the LSR was increased at the end of the training while the FLI remained unchanged [23].

In the current study we found a significant positive correlation between serum LSR levels and physical fitness only in diabetic patients. Similarly, Yang et al. reported a significantly higher level of LSR concentration after short-duration exercise [24]. LSR is the main molecule that regulates and monitors leptin

action, and low levels might indicate the development of leptin resistance in obesity [9].

In our study the free leptin index (FLI), which represents the ratio between the levels of leptin and LSR, was multiplied by 100, showing a strong negative association with fitness score in patients with diabetes and in healthy controls. In line with our findings, Herrick et al. reported a reduction in fat mass, circulating leptin, and free leptin index in response to a diet and physical activity lifestyle intervention, which may suggest an improvement in leptin action [9]. The FLI could be a more potent predictor of developing T2DM than other traditional biomarkers, since it was found to be associated with metabolic abnormalities [25]. Interestingly, another group of researchers concluded that in a naturally existing mixed population, insulin resistance in obese and non-obese subjects was associated with TL levels and FLI, but not LSR; however, this association disappeared in isolated obese or lean cohorts [26].

A recently prospective study involving 2519 participants aged 60 years and above reported that, independent of the estimated body fat, there was a strong positive association between high leptin level and the risk of impairment in mobility, lower-extremity function, agility, and overall physical performance [27].

Conclusions

We found that, in patients with T2DM, serum TL and FLI were negatively correlated and LSR was positively correlated with physical fitness scores. Therefore, they might be important biomarkers for predicting the outcomes of physical fitness and exercise programs.

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