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The diagnostic and prognostic roles of serum irisin in bladder cancer

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ABSTRACT

Background: Egypt is among the countries with the highest incidence of bladder cancer (BC). Adipokines involved in BC development. This study aimed to examine the diagnostic and prognostic roles of irisin in BC through its function as an adipokine. *Patients and methods*: This study included 150 subjects; 75 patients newly diagnosed as BC and 75 apparently healthy subjects. Serum irisin levels were quantified by enzyme-linked immunosorbent assay. *Results*: Serum irisin levels exhibited significantly lower levels in BC patients compared to controls (1.07 [0.51-1.96] and 1.8 [0.5-2.44] μg/mL), respectively ($P < 0.001$). Serum irisin was positively correlated with BMI ($r = 0.386$, $P = 0.001$) and negatively correlated with serum cholesterol ($r = -0.58$, $P < 0.0001$). Irisin had 74.7% sensitivity and 90.7% specificity at a cutoff point of ≤1.2 μg/mL. Serum irisin levels reduction can predict the BC stages, when adjusted for BMI and serum cholesterol level, serum irisin had an adjusted odds ratio of 14 ($P = 0.001$). Low serum irisin patients had a higher mortality rate when compared to those with high levels (38.2% vs 5%). *Conclusion*: BC patients had significantly lower levels of serum irisin. Serum irisin showed acceptable performance criteria in BC diagnosis. It had a limited role in BC grading but showed a decreasing trend in different BC stages. Serum irisin seems to be an excellent diagnostic and prognostic marker for BC.

Abbreviations: AJCC, American Joint Committee on Cancer; AUC, area under curve; BC, bladder cancer; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; ROC, receiver operating characteristic; TG, triglycerides; WHO, World Health Organization.

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Introduction

Egypt is among the areas with the highest prevalence of schistosomiasis and therefore is likewise among the countries with the highest incidence of bladder cancer (BC),[1-3] besides a high frequency of tobacco smoking in men.[4]

Irisin is a newly described myokine with some adipokine features, which assumes a role in the transformation of white adipose tissue to brown one.[5] Irisin is modulated by peroxisome proliferator-activated receptor-g coactivator 1. The precursor protein (fibronectin type III domain containing protein 5) is exposed to proteolytic cleavage then the irisin is released to the circulation.[6]

Irisin was initially examined as an exercise hormone and then studied in obesity and metabolic diseases.[7-9] Obesity was considered a risk factor for numerous diseases, including the malignant ones.[10,11] The association between obesity and BC are evident.[12,13] Obesity is accompanied by high production of insulin that leads to increase the free insulin-like growth factor-I[14] which enhances cancer growth by modifying the angiogenesis and the apoptosis processes.[15] Additionally, obesity associated with chronic low-grade inflammation resulting in alterations of cytokines and adipokines levels,[16] which may play a role from bladder cancer development.[17,18]

The aim of this study was to examine the role of irisin in BC. In order to evaluate its diagnostic and prognostic values, this study evaluated the irisin ability to predict BC diagnosis, staging and outcome.

Subjects and methods

In this case-control study, 150 subjects were enrolled (75 patients newly diagnosed as BC by histopathological examination of cystoscopic bladder biopsy and 75 apparently healthy subjects). Both groups are matched regards the age and the sex. BC follow-up patients and patients with other cancer origins were excluded. From April 2017 to December 2018, this study was carried out in Clinical Pathology and Urology Departments, Zagazig University Hospitals. The Institutional Review Board of the Faculty of Human Medicine, Zagazig University validates this study ethically. All participants accept to share and sign acceptance consent.

All BC patients were subjected to full history and clinical examination. BC patients were graded and staged according to the World Health Organization (WHO) and the American Joint Committee on Cancer (AJCC) criteria, respectively. During the follow-up period (1 year), survival was evaluated every month.

After 12-hour fasting, blood samples were collected in 2 BD Vacutainer® plastic plain tubes. After 15-30 minutes of collection, tubes were centrifuged at 1200 × g for 10 minutes. The serum of the first tube used to measure glucose, cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) using Cobas 8000/C702 Analyzer (Roche, Germany). The serum of the second tube was separated in 1.5 microcentrifuge tube and stored at −80° C until irisin analysis. Serum irisin levels were measured by enzyme-linked immunosorbent assay (ELISA) kits (BioVendor Laboratory Medicine, Brno, Czech Republic) [Catalog No.: RAG018R]. The steps were performed as recommended by the manufacturer. By Sunrise™ absorbance reader (Tecan Trading AG, Männedorf, Switzerland), the plates were read at 450 nm and the results were expressed as (μg/mL).

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Table 1
Demographic and clinical characteristics of the studied groups.

Parameter	Control (No. = 75)	Bladder cancer (No. = 75)	*P*
Age (years)	62 (37-76)	63 (42-79)	0.37
Sex: Male/ Female	67/8 (89.3/10.7)	63/12 (84/16)	0.34
BMI (Kg/m^2)	27.4 (21.6-31.2)	27.6 (22.3-39)	0.03*
History of diabetes mellitus	0 (0)	4 (5.3)	0.13
Family history of carcinoma	7 (9.3)	5 (6.7)	0.54
Tumor grade (G):			
G1	—	16 (21.3)	
G2	—	42 (56)	
G3	—	17 (22.7)	
TNM staging:			
Stage 0a	—	13 (17.3)	
Stage 1	—	21 (28)	
Stage 2	—	16 (21.4)	
Stage 3	—	7 (9.3)	
Stage 4	—	18 (24)	
Mortality in 1 year	—	22 (29.3)	

No., number of subjects; BMI, body mass index.
Data are presented as No. (%) or median (range).
* Significant.

Statistical analysis

Continuous data had a nonparametric distribution. The Kruskal–Wallis H test, Mann Whitney U test, and Chi-squared test were applied when appropriate. The Spearman's correlation and the binary logistic regression analysis were utilized to clarify the association. The receiver operating characteristic (ROC) curve was analyzed to detect the cutoff value. To survey the survival, the Kaplan–Meier curve and the log-rank test were used. Statistical analysis was performed by SPSS® version 19.0 (SPSS Inc., Chicago, IL). The *P*-value <0.05 is the statistical significant point.

Results

Table 1 presents the baseline characteristics of BC patients and healthy controls. The 2 groups had no significant differences regarding age, sex, history of diabetes mellitus, and family history of carcinoma. Significant differences were observed in body mass index (BMI), BC patients values were higher compared to those of the controls ($P = 0.03$).

Regards the laboratory parameters, no significant differences were observed in fasting glucose, TG, HDL-C and LDL-C between BC patients group and control group. But cholesterol was significantly lower in BC patients when compared with controls ($P = 0.03$). Serum irisin levels exhibited significantly lower levels in BC patients compared to controls ($P < 0.001$) (Table 2).

The correlation between serum irisin and significant calculated and measured variables in BC patients was studied by Spearman's test. All showed insignificant correlations ($P > 0.05$) except BMI and serum cholesterol. Serum irisin was positively correlated with BMI ($r = 0.39$, $P = 0.001$) and negatively correlated with cholesterol ($r = -0.58$, $P < 0.0001$).

ROC curve analysis was used to evaluate the effectiveness of serum irisin in BC diagnosis. At a cutoff level of irisin of $\leq$ 1.2 µg/mL, ROC-area under curve was 0.914 (95% confidence interval: 0.859-0.968; $P < 0.001$) (Fig. 1). At this cutoff, sensitivity and specificity were 74.7% and 99.7%, respectively. The positive and negative predictive values were 84.8% and 78.2%, respectively. Irisin had a diagnostic accuracy of 82.7%.

The associations between serum irisin levels and BC characteristics were investigated. Irisin levels were significantly differed between tumor grades ($P = 0.017$). The serum irisin level was significantly lower in G3 compared to G1 ($P = 0.032$), but no significant difference between G1 and G2 ($P = 0.17$) or G2 and G3 ($P = 0.46$) (Fig. 2).

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Table 2
Laboratory finding of controls and bladder cancer patients.

Laboratory test	Control (No. = 75)	Bladder cancer (No. = 75)	*P*
Cholesterol (mg/dL)	117.7 (76-190.3)	102.8 (70-199]	0.03*
Triglycerides (mg/dL)	82.5 (52.3-162.3)	88.6 (32.8-183.2)	0.38
HDL-C (mg/dL)	45.2 (22.1-60.8)	44.3 (32.9-59.3)	0.25
LDL-C(mg/dL)	57.9 (33-120.2)	64.3 (57.5-129.6)	0.57
Fasting glucose (mg/dL)	79.2 (71.6-95)	79.6 (73.4-93.6)	0.11
Irisin (μg/mL)	1.8 (0.5-2.44)	1.07 (0.51-1.96)	< 0.001*

No., number of subjects; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol.
Data are presented as median (range).
* Significant.
Conversion for cholesterol, LDL-C and HDL-C from mg/dL to SI (in mmol/L): multiply by 0.0259.
Conversion for triglyceride and glucose from mg/dL to SI units (in mmol/L): multiply by 0.0113 and 0.0555, respectively.
Conversion for irisin from μg/mL to SI units (in mmol/L): multiply by 0.046; with molecular weight 22 KDa.

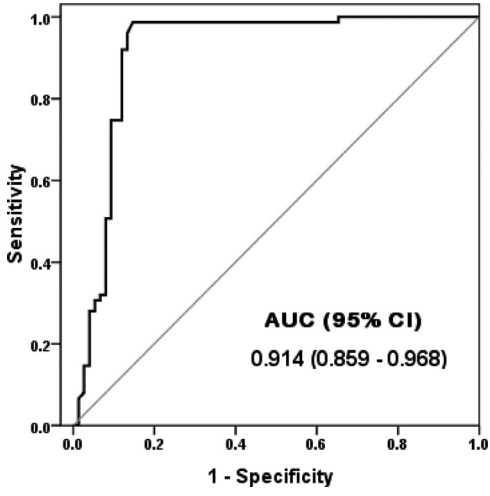

Fig. 1. ROC curves of irisin in cancer bladder.

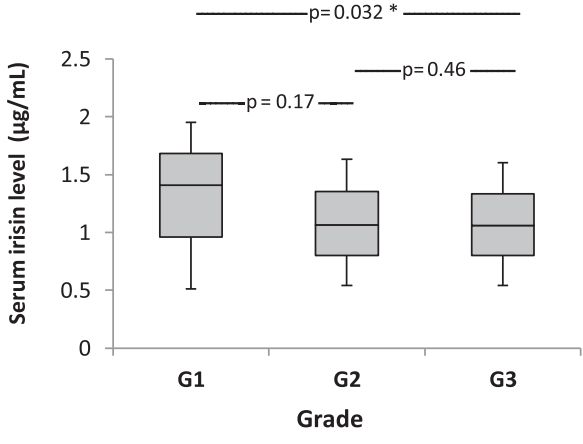

Fig. 2. Serum irisin level in BC patients with different grades.

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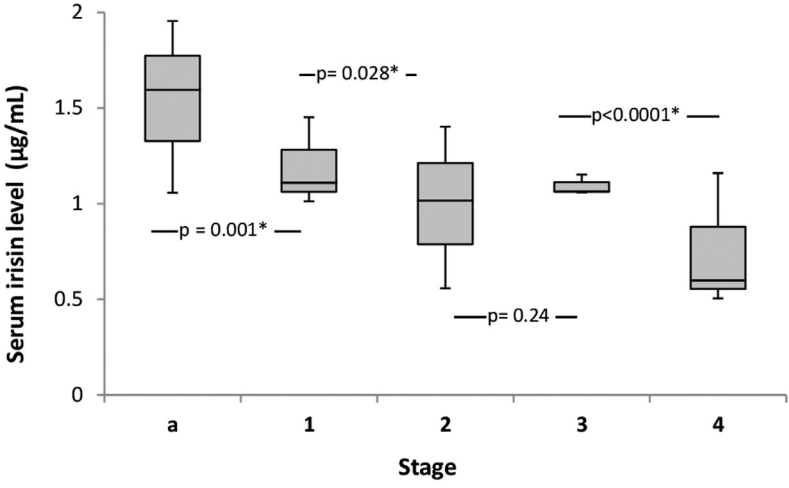

Fig. 3. Serum irisin level in BC patients with different Stages.

There was a statistically significant difference in serum irisin between BC stages ($P < 0.001$). Serum irisin levels showed a significant decreasing trend in all BC stages, but no significant difference was detected between stage II and stage III ($P = 0.24$) (Fig. 3). In the univariate binary logistic regression analysis, serum irisin levels reduction can predict significantly the BC stages, serum irisin had a significant odds ratio of 9.5 (95% confidence interval: 2.9-30.9) ($P < 0.0001$). In the multivariate logistic regression test, it was adjusted for BMI and serum cholesterol level, serum irisin had an adjusted odds ratio of 14 (95% confidence interval: 2.8-68.6) ($P = 0.001$).

The mortality rate was assessed in a 1-year period; patients with high-serum irisin levels had a 5% mortality rate, whereas it was 38.2% in patients with low irisin levels. BC patients with high-serum irisin level had significantly longer survival than those with low levels ($P = 0.02$) (Fig. 4).

Discussion

According to the International Agency for Research on Cancer data, the incidence rank of BC among all cancers is number 7 in males and number 11 in both sexes.[19] BC is still the most common cancer among males in Egypt and some African and Middle East countries.[20] So, searching for markers to screen BC is the objective of our study.

Obesity is possibly associated with BC progression, recurrence and poor survival rate.[21] Our study revealed significantly higher BMI in BC patients when compared to healthy controls. This result confirms the previous result of Samanic et al[22]; Holick et al[23]; and Koebnick et al.[24] In contrast, Housa et al[25] found a decreased risk while others reported no significant association.[26-28] Our study revealed a significantly lower level of serum cholesterol in BC patients. Despite no accordant relation was detected between low cholesterol levels and cancer occurrence.[29,30]

Skeletal muscle is considered an endocrine organ.[31] Irisin is secreted by skeletal muscles in response to exercise and enhances energy expenditure.[32] Ever after the discovery of irisin, its role in metabolic diseases was investigated.[33-35] At the same time, irisin was evaluated in chronic kidney diseases and heart diseases.[36]

Irisin role in cancer caught the attention of the researchers. The cytotoxic effects of irisin on prostate cancer cells were proved by Tekin et al.[37] Kuloglu et al[38] determine high irisin expression levels in human breast, ovarian, and cervical cancer tissues. Provatopoulou et al[39] found

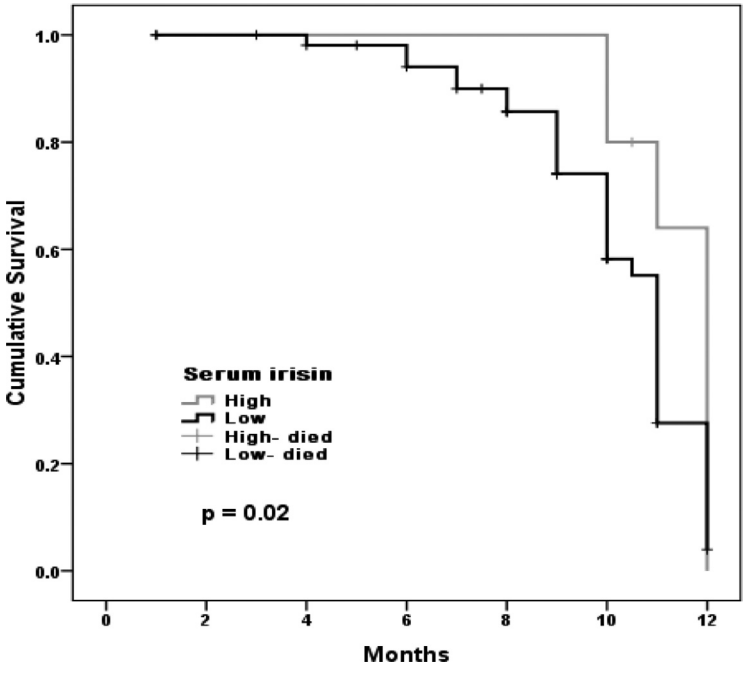

Fig. 4. Kaplan–Meier survival curves according to the different levels of serum irisin in BC patients

the role of serum irisin in breast cancer diagnosis. High irisin expression in gastrointestinal cancer tissues was also proved.[40] Irisin suppresses the epithelial-to-mesenchymal transition which inhibits the growth and spread of lung cancer cells[41] and osteosarcoma cells.[42] Irisin was evaluated as a renal cancer diagnostic marker.[43] So, this study aimed to investigate its potential role in human BC.

To our knowledge, the present study is the first evaluation of the potential diagnostic and prognostic roles of irisin in BC. Our study revealed lower levels of irisin in BC patients when compared to healthy controls. ROC curve analysis revealed that irisin can discriminate between BC patients and healthy individuals with acceptable performance criteria.

This study found that serum irisin was positively correlated with BMI. This result confirms the previous results of Huh et al,[44] Stengel et al,[45] and Pardo et al.[46] A significant negative correlation was detected between serum irisin and total cholesterol. In line with our findings, Gouni-Berthold et al,[47] and Oelmann et al,[48] reported an inverse relation of irisin with total cholesterol.

This study investigated the relationship between serum irisin level and the tumor grade. Irisin was significantly higher in G3 when compared with G1 with no other significant differences between either G1 and G2 or G2 and G3. Serum irisin levels showed a significant decreasing trend in all BC stages, but no significant difference between stage II and stage III. Serum irisin levels reduction can predict significantly the BC stages even with adjustment to BMI and serum cholesterol level. This study found that high serum irisin levels were associated with longer survival rates.

Further studies are necessary to determine the role of irisin in BC carcinogenesis. Further studies with a larger number of participants are required to confirm the role of irisin in the diagnosis, grading, staging, and prognosis of BC. Confirmed role of irisin in BC will help for developing a new protective and treatment modalities.

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Conclusion

BC patients had significantly lower levels of serum irisin. Serum irisin showed acceptable performance criteria in BC diagnosis. It had a limited role in BC grading but showed a decreasing trend in different BC stages. Serum irisin seems to be an excellent diagnostic and prognostic marker for BC.

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