CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

https://doi.org/10.5281/zenodo.5447766

Online at: http://www.iajps.com *Research Article*

ASSOCIATION OF SERUM FETUIN-A WITH β -CELL DYSFUNCTION IN FIRST DEGREE RELATIVES OF TYPE 2 DIABETICS

[1]Nazia Shahzadi, [2]Rukhshan Khurshid, [3]Maira Mahmood, [4]Huma Ashraf, [5]Imran Abdullah, [6] Rehan Abdullah

[1]Department of Biochemistry, Services Institute of Medical Sciences, Lahore, Pakistan
Nazia78y@gmail.com

[2]Department of Biochemistry, Shalamar Medical and Dental College, Lahore, Pakistan
Rakhshan99@yahoo.com

[3]Department of Biochemistry, FMH College of Medicine and Dentistry, Lahore, Pakistan
drmairamahmood@gmail.com

[4]Department of Biochemistry, CMH Medical College & Institute of Dentistry, Lahore, Pakistan
Huma.monim.zat.ash@gmail.com

[5]Institute Of Nuclear Medicine & Oncology (INMOL), Lahore, Pakistan
Abdullah_dr2003@yahoo.com

[6]Institute Of Nuclear Medicine & Oncology (INMOL), Lahore, Pakistan
rehanpmc@gmail.com

Article Received: July 2021 **Accepted:** July 2021 **Published:** August 2021

Abstract:

Objectives: *To determine the relationship between serum Fetuin-A and β cell function in adolescents with family history of type 2 diabetes mellitus (T2DM)*

Background: *Increased level of circulating Fetuin-A, may alter both maturity and adaptive ability of β cells in response to glucose and increase the progression of T2DM. Genetic factors may have a role in the formation of immature β cells resulting in altered functioning of β cells.*

Methods: *The study population included adolescents with family history of T2DM. The study variables included age, sex, fasting blood sugar (BSF), serum insulin and serum Fetuin-A. 70 adolescents first degree relatives (FDR) of diabetics and 50 controls aged 18 to 20 years were included. Insulin resistance and β-cell function were examined by using a homeostatic model assessment. Data was statistically analyzed by student's 't' test and Pearson Correlation Coefficient.*

Results: *Significantly increased level of Fetuin-A was related with increased level of BSF, serum insulin and insulin resistance in both male as well as female study subjects. Similarly, it is also associated with decreased β cell function in both genders (indirect correlation).*

Conclusion: *This study highlights the significance of Fetuin-A as a predictor of β cell functionality in non-diabetics with positive family history.*

Keywords: *Type 2 Diabetes Mellitus (T2DM) , Fetuin-A, β cells function , Fasting blood sugar(BSF)*

Corresponding author:
Dr Maira Mahmood,
Associate Professor,
Department of Biochemistry,
FMH College of Medicine and Dentistry, Lahore, Pakistan
Drmairamahmood@gmail.com
Orcid Id: https://orcid.org/0000-0002-0459-2598

Please cite this article in press Nazia Shahzadi et al., ***Association Of Serum Fetuin-A With β -Cell Dysfunction In First Degree Relatives Of Type 2 Diabetics..****, Indo Am. J. P. Sci, 2021; 08(08).*

INTRODUCTION:

Endocrine diseases are persistent and a worldwide challenge leading to a fast decline in the quality of lifestyle and is related with intake of extra sugary starchy foods, cumulative body weight, and sedentary life style [1]. T2DM is a multifaceted disease distinguished by failure of β cell function leading to insulin resistance in adipose tissues and muscles. Its progression is related with different changes in β-cells like oxidative stress, altered redox signaling, lipotoxicity and glucotoxicity [2].

In neonatal stage of life, the β cells of pancreas firmly control the of process maturation via increase in the receptors of transcriptional factors, parts of secretory system, cell-cell interactions and their communication with extracellular matrix (ECM), along with inhibitors of cell cycle [3,4]. The main function of pancreatic β cells is to secrete proper amount of insulin in response of glucose. Homeostasis of glucose is well maintained by proper functioning of β cells, it's associated signaling of insulin in β cells and its coordinated balance with glucose recipient tissues. However, the proper response of β cells to glucose may be reduced with metabolic stress or ageing, causing deficiency of insulin, which may result in DM. In primary stages of this ailment, the β cells adjust insulin resistance by increasing its mass and function as a response mechanism of the human body. However, continuous consumption of excessive starchy and energy rich food results in hyperglycemia and increased free fatty acids production that may give negative impact on the functioning of pancreatic β cells [5,6].

Insulin is secreted by pancreatic β cells in response to increased postprandial blood glucose levels in order to prevent hyperglycemia as well as to inhibit the secretion of insulin under fasting state as a protective action against hypoglycemia. At birth, these β cells do not have this functional capability and this glucose-stimulated insulin secretion (GSIS) is acquired later during the neonatal period. There is a role of DNA methylation for the procurement of pancreatic β cell functionality. Genetic factor may therefore , play a role in the formation of immature β cells resulting in an impaired functioning of β cells [7]. This dysfunction of β cells and insulin resistance can activate the pathogenesis of DM. Moreover, it can also induce hyperglycemia leading to increased insulin demand. With insulin resistance, the defect in insulin signaling pathways results in defective response of insulin in tissues recipient to glucose and hence hyperglycemia. Both pathological states (β cell dysfunction and insulin resistance) mutually stimulate each other and synergistically aggravate DM [8]. It has been proved that insulin resistance and metabolic stress limit not only endocrine capability but also adaptive β cell proliferation [5,6].

During adulthood, fatty liver causes increased levels of circulating serum Fetuin-A, which may alter both maturity and the adaptive ability of β cells in response to increased blood glucose, thereby increase the progression of T2DM. Increased circulating serum Fetuin-A eliminates the responsiveness of pancreatic β islets to increased serum glucose levels. Additionally, it is found that elevated level of Fetuin-A and liver steatosis can also alter maturation and functioning of β cells, leading to significantly decreased adjustable proliferation [9,10].

Different studies have found different variations in serum Fetuin-A levels in obesity, DM, females with polycystic ovarian syndrome (PCOS), cardiovascular disease, metabolic syndrome and fatty liver. There is conflicting evidence in regards to its relationship with altered glucose tolerance as well as insulin resistance [11,12]. These variable findings on the association between Fetuin-A, β cell function and insulin resistance need more research studies.

The correct assessment of pancreatic β cells functioning requires a concomitant quantification of insulin secretion and sensitivity. For better understanding of the pathogenic mechanisms that take part in the development of T2DM in individuals,

other markers are needed in concomitance to evaluation of β cell functions.

A prospective observational study was designed to find out the relationship between serum Fetuin-A and β cell functions in adolescents with family history of DM.

METHODS:

Study designs and patient details

This study was a cross sectional comparative study carried out in the Services Institute of Medical Sciences, Lahore. The duration of study was 2018 to 2019. Participants of both genders were recruited in the study which was carried out in Biochemistry Department, Services Institute of Medical Sciences, (SIMS), Services Hospital, Lahore. About 3.0 ml of blood sample was drawn and collected in EDTA tubes for estimation of blood glucose level using SWISS Max analyzer. For estimation of serum insulin and serum Fetuin-A levels, the blood sample was centrifuged for 15 minutes at 3000rpm at 2 - 8°C and plasma was stored at -20°C until use. Their levels were estimated by ELISA (ALPCO, US). Insulin resistance was estimated using Homeostatic Model Assessment for Insulin Resistance (HOMA IR), and β cell functions were examined by using a homeostatic model assessment (HOMA 2).

Definitions

According to the National Human Genome Research Institute (NHGRI) of the US, FDR may be defined as the members of family who share about 50 % of their genes with a specific person in a family. These may be parents, full siblings and off springs .

Data collection and follow-up

Convenient sampling technique was used for selection of study subjects. 70 non diabetic FDR adolescents including both males and females, aged 18 to 20 years, were included. They had a BMI ≤ 25Kg/m^2 and were free of any neoplastic or major illness. Subjects with a family history of cardiovascular diseases, hypertension, and renal disease were excluded from the study. 50 adolescents including both genders and falling in the same age range without family history of T2DM were taken as controls. Informed consent was obtained from the participants and the procedure explained in detail.

Statistical analysis

Data analysis was performed with Statistical Analysis Software (SAS) version 9.4 and SPSS version 25.0 (IBM Corp., Armonk, NY, USA).Qualitative data was expressed as frequency. Quantitative variables were expressed as mean ± SD. Independent student's 't' test was used for the determination of variables which included age, body mass index (BMI), BSF. Serum insulin and serum Fetuin-A levels were also estimated during fasting both in patients as well as healthy controls. Pearson Correlation Coefficient was used to find the correlation between Fetuin A and β cell function. P< 0.05 was taken as statistically significant.

RESULTS:

Demographics and patient features

The demographic variables in male and female adolescents are presented. The mean age group was 19 years with a BMI 23.09 Kg/m^2 for females and 25.14 Kg/m^2 in males. In majority of both genders, the life style was sedentary with middle socioeconomic class. Both genders used vegetarian and non-vegetarian diet along with junk food. Majority, of the adolescents were residing in hostels (Table 1).

Table 1: Demographic Variables in female and male FDR Adolescents

Variables	Female FDR adolescents of Type 2 Diabetics (n=35)	Male FDR adolescents of Type 2 Diabetics (n=35)
Age (years)	19.25±2.26	19.17±2.24
BMI (Kg/m^2)	23.08±1.71	24.14±1.6
Life style	27 Sedentary (78%) 8 Active (22%)	20 Sedentary (57.0 %) 15 Active (43%)
Socioeconomic status	Upper class = 20 Middle class = 15	Upper class =18 Middle class = 17
Dietary Pattern	Rice-meat food / Sweet to fast food	Rice-meat food / Sweet to fast food
Present residence	Day scholar = 15 (42.8%) Hostel = 20 (57.1%)	Day scholar = 10 (28.5%) Hostel = 25 (71.4%

BSF, insulin and Fetuin-A

Levels of BSF, serum insulin and serum Fetuin-A were raised in male FDR of type 2 diabetics as compared to their controls. A significant difference was only observed in case of serum Fetuin-A. Values of insulin resistance were increased and β cell functions were decreased in male adolescents with family history of T2DM in comparison to their controls. Similarly in female FDR of type 2 diabetics, the levels of BSF and serum Fetuin-A were increased when compared to their controls, but a significant difference (P<0.01) was only observed in case of serum Fetuin-A. Values of serum insulin and insulin resistance were same in both groups. However, the values of β cell function were decreased in female adolescents with family history of diabetes in comparison with their controls (Table 2).

Table 2: Variations in the Level of Fasting Blood Sugar (BSF), Serum Insulin and Serum Fetuin-A in Male and Female FDR Adolescents with and without Family History of T2DM.

Values are expressed as mean ± SD

Variables	Male FDR adolescents with family history of T2DM (35)	Male adolescents without familial diabetic background (25)	Female FDR adolescents with family history of T2DM (35)	Female adolescents without familial diabetic background (25)
BSF(mg/dl)	93.51±7.36	87.23±7.37	95.31±6.98	94.32± 7.83
Serum Insulin (mIU/L)	5.99±2.3	5.85±3.61	7.21±3.31	7.22±4.5
Serum Fetuin-A(ng/ml)	195.17±188.16**	157.26±138.82	843.34±811.21**	296.38±272.8
Insulin resistance	0.99	0.76	0.90	0.96
β cell function	74.88±4.09	84.4±32.84	78.8±4.09	83.3±33.84

**P <0.001 highly significant

Correlations

In both male and female adolescents with family history of T2DM, a weak indirect correlation of serum Fetuin-A with beta cell function was observed with r value -0.28 and -0.12 respectively (Figure 1, 2).

Figure 1: Correlation of β Cell Function with Serum Fetuin-A (r = -0.12) in Female FDR Adolescents having familial diabetic background.

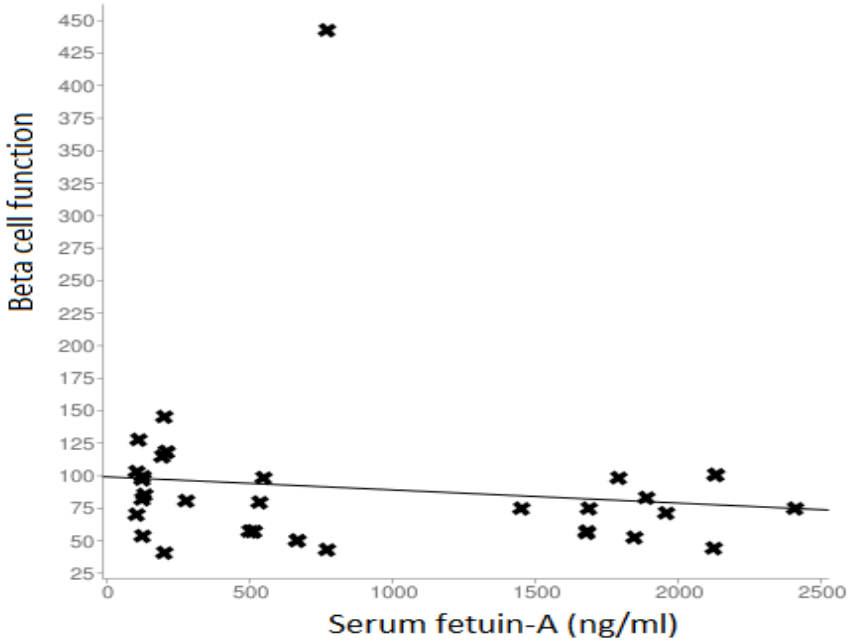
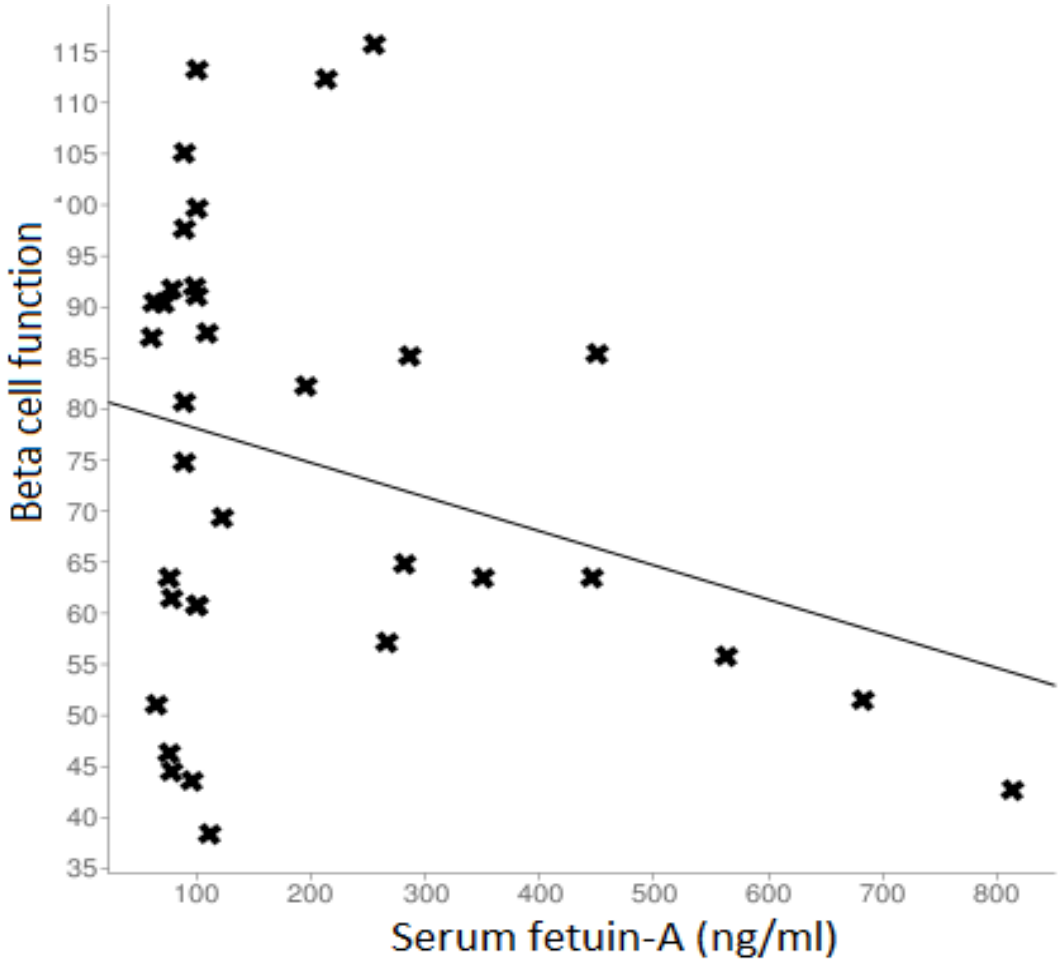


Figure 2: Correlation of Beta Cell Function with Serum Fetuin-A (r = - 0.28) in male FDR Adolescents having familial diabetic background.



DISCUSSION:

To the best of our understanding and knowledge, ours is the first study of its kind on serum Fetuin-A levels and insulin resistance amongst non-obese, non-diabetic FDR male and female adolescents, belonging to age group 18 to 20 years, with positive family history. Our study included adolescents of both genders with family history of DM, with mean age 18-20 years and normal BMI (18.5-24.5kg/m^2). Majority of them were students residing in hostels, had sedentary lifestyle and a diet mainly composed of sugary, processed and junk food. According to a research study also found that junk food or poor nutritional diet along with sedentary life style in youth may have a role in progression of T2DM [13]. A fractional loss of the phenotype of pancreatic β cells may have a role in reducing their mass and increase the progression of T2DM. Increased secretion of the heptokine Fetuin-A blocks the secretion of insulin from pancreatic β cells [14]. Many studies have reported reduced the association of decreased functional β-cells along with impaired glucose tolerance and the development of T2DM. It has been demonstrated that β-cell functions begins to decline due to continuous hyperglycemia [15]. It is also suggested that raised number of dysfunctional β-cells is related to poor glycemic control and hence ultimately contributing to failure of treatment [16]. It is also reported that altered BSF may reflect diverse metabolic sub-phenotypes of pre form of T2DM that may be one of the factors of disparate chances of metabolic consequences. Besides, alterations in the concentration of adipocytes including Fetuin A and cytokines are also observed in the state of impaired glucose tolerance and may indicate the dysfunction of adipose tissues as an early predictor for the development of T2DM [17]. Hyperglycemia during fasting is mainly due to reduced ability of pancreatic

β-cells to secrete serum insulin, and hence contributes to the development of T2DM [18]. The association between Fetuin-A and insulin resistance is well established and it may further decrease the secretion of insulin. All these events finally disturb homeostasis of glucose, especially in individuals who have altered function of pancreatic β-cells [19,20]. Our results were also in accordance with these findings. Many studies report elevated levels of Fetuin A in pre-diabetics as well. In addition to this, their raised level in non-diabetics indicates a 23 to 24% risk of developing T2DM [21]. Another study reported that increased values of serum Fetuin-A may be a powerful indicator of progression of T2DM [22]. It has also been demonstrated that the hepatokine Fetuin-A is not only a powerful marker of insulin resistance and a well-established risk factor for development of T2DM, but it also impairs the secretion of insulin from pancreatic β-cells [23]. On the contrary some studies have also reported *no* correlation *between Fetuin*-A *and* risk of developing T2DM [24]. In our research study a weak indirect correlation of serum Fetuin-A with pancreatic β cell function was observed. Our results were in accordance with another study which reported a positive correlation of serum Fetuin-A with the functional capacity of pancreatic β cells, fasting levels of serum insulin as well as HOMA-IR, which are the primary and key indicators of insulin resistance in T2DM. It can be hence emphasized that Fetuin-A alters the maturation and adaptive proliferation of pancreatic β cells and may be a factor for development of overt DM [25]. It is also proposed that Fetuin-A halts the glucose sensitivity of pancreatic islets via inhibition of cell signaling of transforming growth factor β (TGFBR) peptide and decreases the maturity of pancreatic islet cells. Additionally, Fetuin-A is also an adverse modulator of proliferation and function of β cells. Moreover, chronic fatty liver also stimulates increased level of circulating Fetuin-A, altering its functional maturity and the tendency to decrease the mass of β cells, thereby increasing the risk of development of T2DM [9].

CONCLUSION:

Although setup in a tertiary care hospital, this was a single centered study with limited sample size. The lack of repetitive estimations may result in underestimation of association between serum Fetuin-A and pancreatic β cell function. Moreover, this study had a smaller sample size, since this was a pilot study of its kind. Data should be recorded in multiple age groups and also in pre-diabetics in addition to non-diabetics to increase the authenticity of the study. In spite of limitations, results of our study showed a weak indirect correlation of serum Fetuin-A with pancreatic β cells in both male and female FDR adolescents of type 2 diabetics as compared to healthy controls. They may prove to be a good novel predictor of identifying the subjects who are especially prone to develop pre-diabetes or overt diabetes in the future, especially in FDR and may be an early alternative biomarker for the screening of asymptomatic individuals from an adolescent age. Hence it can play a vital role for the prevention of T2DM and progression to diabetic complications. Moreover, proper functional capability of pancreatic β-cells may play a protective role in adolescents who are categorized by normal BSF from the harmful effects of high levels of circulating Fetuin-A.

Disclosure

The authors declare no conflict of interest.

Ethical approval

Ethical approval for this cross-sectional comparative study was obtained from the Institutional Review Board of SIMS, Lahore with study number: IRB/2019/505/SIMS. A written informed consent was taken from the participants.

Acknowledgments

This research did not receive any funding or financial grant from agencies in the public, commercial, or not-for-profit sectors.

REFERENCES:

[1] Shao A, Drewnowski A, Willcox DC, Krämer L, Lausted C, Eggersdorfer M, et al. Optimal nutrition and the ever-changing dietary landscape: a conference report. Eur J Nutr 2017;56:1–21.

[2] Ježek P, Jabůrek M, Plecitá-Hlavatá L. Contribution of oxidative stress and impaired biogenesis of pancreatic β-cells to type 2 diabetes. Antioxid Redox Signal 2019;31:722–51.

[3] Huang C, Walker EM, Dadi PK, Hu R, Xu Y, Zhang W, et al. Synaptotagmin 4 regulates pancreatic β cell maturation by modulating the Ca2+ sensitivity of insulin secretion vesicles. Dev Cell 2018;45:347–61.

[4] Alessandra G, Algerta M, Paola M, Carsten S, Cristina L, Paolo M, et al. Shaping pancreatic β-cell differentiation and functioning: the influence of mechanotransduction. Cells 2020;9:413.

[5] Kushner JA. The role of aging upon β cell turnover. J Clin Invest 2013;123:990–5.

[6] Henquin J, Nenquin M. Immaturity of insulin secretion by pancreatic islets isolated from one human neonate. J Diabetes Investig 2018;9:270–

3.
[7] Dhawan S, Tschen S-I, Zeng C, Guo T, Hebrok M, Matveyenko A, et al. DNA methylation directs functional maturation of pancreatic β cells. J Clin Invest 2015;125:2851–60.
[8] Cerf ME. Beta cell dysfunction and insulin resistance. Front Endocrinol (Lausanne) 2013;4:37.
[9] Gerst F, Kemter E, Lorza-Gil E, Kaiser G, Fritz A-K, Nano R, et al. The hepatokine fetuin-A disrupts functional maturation of pancreatic beta cells. Diabetologia 2021;64:1358–74.
[10] Gerst F, Wagner R, Kaiser G, Panse M, Heni M, Machann J, et al. Metabolic crosstalk between fatty pancreas and fatty liver: effects on local inflammation and insulin secretion. Diabetologia 2017;60:2240–51.
[11] Khadir A, Kavalakatt S, Madhu D, Hammad M, Devarajan S, Tuomilehto J, et al. Fetuin-A levels are increased in the adipose tissue of diabetic obese humans but not in circulation. Lipids Health Dis 2018;17:1–13.
[12] Liu S, Hu W, He Y, Li L, Liu H, Gao L, et al. Serum Fetuin-A levels are increased and associated with insulin resistance in women with polycystic ovary syndrome. BMC Endocr Disord 2020;20:1–7.
[13] Cree-Green M, Triolo TM, Nadeau KJ. Etiology of insulin resistance in youth with type 2 diabetes. Curr Diab Rep 2013;13:81–8.
[14] Guo VY, Cao B, Cai C, Cheng KK, Cheung BMY. Fetuin-A levels and risk of type 2 diabetes mellitus: a systematic review and meta-analysis. Acta Diabetol 2018;55:87–98.
[15] DeFronzo RA, Eldor R, Abdul-Ghani M. Pathophysiologic approach to therapy in patients with newly diagnosed type 2 diabetes. Diabetes Care 2013;36:S127–38.
[16] Saisho Y. β-cell dysfunction: Its critical role in prevention and management of type 2 diabetes. World J Diabetes 2015;6:109.
[17] Li Y, Feng D, Esangbedo IC, Zhao Y, Han L, Zhu Y, et al. Insulin resistance, beta-cell function, adipokine profiles and cardiometabolic risk factors among Chinese youth with isolated impaired fasting glucose versus impaired glucose tolerance: the BCAMS study. BMJ Open Diabetes Res Care 2020;8:e000724.
[18] Galicia-Garcia U, Benito-Vicente A, Jebari S, Larrea-Sebal A, Siddiqi H, Uribe KB, et al. Pathophysiology of type 2 diabetes mellitus. Int J Mol Sci 2020;21:6275.
[19] Petersen MC, Shulman GI. Mechanisms of insulin action and insulin resistance. Physiol Rev 2018;98:2133–223.
[20] Yin L, Cai W, Chang X, Li J, Su X, Zhu L, et al. Association between fetuin-A levels with insulin resistance and carotid intima-media thickness in patients with new-onset type 2 diabetes mellitus. Biomed Reports 2014;2:839–42.
[21] Roshanzamir F, Miraghajani M, Rouhani MH, Mansourian M, Ghiasvand R, Safavi SM. The association between circulating fetuin-A levels and type 2 diabetes mellitus risk: systematic review and meta-analysis of observational studies. J Endocrinol Invest 2018;41:33–47.
[22] Bourebaba L, Marycz K. Pathophysiological implication of Fetuin-A glycoprotein in the development of metabolic disorders: a concise review. J Clin Med 2019;8:2033.
[23] Ward K, Mulder E, Frings-Meuthen P, O'Gorman DJ, Cooper D. Fetuin-A as a potential biomarker of metabolic variability following 60 days of bed rest. Front Physiol 2020;11.
[24] Jensen MK, Bartz TM, Djoussé L, Kizer JR, Zieman SJ, Rimm EB, et al. Genetically elevated fetuin-A levels, fasting glucose levels, and risk of type 2 diabetes: the cardiovascular health study. Diabetes Care 2013;36:3121–7.
[25] Song A, Xu M, Bi Y, Xu Y, Huang Y, Li M, et al. Serum fetuin-A associates with type 2 diabetes and insulin resistance in Chinese adults. PLoS One 2011;6:e19228.