Int J Clin Exp Med 2019;12(7):9116-9121
www.ijcem.com /ISSN:1940-5901/IJCEM0082049

Original Article

Serum concentration of autophagy-related protein 7 is correlated with non-alcoholic fatty liver disease in Chinese adults

Pu Zhang, Luping Ren, Guangyao Song, Lin Zhang, Yang Li, Guangsen Hou, Shuchun Chen

Department of Endocrinology, General Hospital of Hebei, Shijiazhuang 050051, Hebei, P. R. China

Received July 3, 2018; Accepted January 9, 2019; Epub July 15, 2019; Published July 30, 2019

Abstract: In the current study, we evaluated the serum levels of the autophagy indicators, autophagy-related protein 7 (Atg7) and Beclin-1, and the possible association of these indicators with lipid and glucose metabolic components in patients with non-alcoholic fatty liver disease (NAFLD). A total of 176 individuals were involved in the study. Eighty-eight healthy individuals were randomly selected as the control group, and 88 patients with NAFLD were recruited to the NAFLD group. Blood lipids, blood glucose and other parameters were measured, with serum levels of Atg7 and Beclin-1 measured by enzyme-linked immunosorbent assay. Compared with the control group, the blood triglyceride, fasting plasma insulin, and 2-h post-challenge insulin levels were higher in the NAFLD group ($P < 0.05$), as was the homeostasis model assessment of insulin resistance ($P = 0.001$) and Atg7 serum levels ($P < 0.05$). Although serum Beclin-1 levels tended to be higher in the NAFLD group than the control group, there was no significant difference. While serum Atg7 was negatively associated with age, waist: hip ratio, total cholesterol, triglycerides, high-density lipoprotein cholesterol, apolipoprotein B, fasting blood glucose, postprandial blood glucose, and 2-h post-challenge insulin, it was positively correlated with body mass index, low-density lipoprotein cholesterol, fasting plasma insulin and homeostasis model assessment of insulin resistance. Serum Beclin-1 was positively correlated with body mass index and triglycerides. An increase in the autophagy indicators, Atg7 and Beclin-1, in patients with NAFLD provides evidence that autophagy may play a role in the pathogenesis of NAFLD.

Keywords: NAFLD, autophagy, Atg7, Beclin-1

Introduction

It is widely known that the prevalence of obesity and metabolic syndrome is rising dramatically [1]. Metabolic syndrome is a clustering of obesity, diabetes, dyslipidemia and hypertension, which may cause alterations in hepatic glucose and lipid metabolism and is closely associated with the pathophysiologies of non-alcoholic fatty liver disease (NAFLD) [2]. NAFLD is characterized by lipid accumulation within hepatocytes and may progress to non-alcoholic steatohepatitis (NASH), and even hepatic cirrhosis. Although the pathological mechanism of NAFLD is not yet fully understood, many studies suggest that metabolic stress, inflammation, endoplasmic reticulum stress, and autophagy are all involved [3, 4].

Autophagy is a major intracellular degradative process which delivers cytoplasmic materials to the lysosome for degradation and is required for the homeostasis of biomacromolecules [5]. It can be induced by different metabolic stresses, including nutrient deprivation, hypoxia, and the accumulation of protein or lipids [6]. Once the autophagy balance is disrupted, it can affect many diseases, including type 2 diabetes, cancer, aging, and neurological diseases [7-9]. Recently, it has been reported that autophagy is important in the regulation of lipid metabolism and may play a role in the pathogenesis of NAFLD [10, 11].

However, research into the association between autophagy and NAFLD in vivo is rare, and the results of previous in vivo and in vitro studies are inconsistent [12]. Investigations focusing on autophagy in humans are probably scarce because human studies are limited by experimental restrictions or the ability to perform consecutive biopsies. Therefore, in this study, we

evaluated the correlation between autophagy and NAFLD by measuring the serum levels of the autophagy indicators, autophagy-related protein 7 (Atg7) and Beclin-1, in patients with NAFLD.

Materials and methods

Setting and participants

This study was conducted in the Health Examination Center of Hebei Province General Hospital from January to April 2015. A total of 176 individuals were recruited for the study. Eighty-eight healthy individuals (28 men, 60 women), with a mean age of 52.30±11.23 years, were randomly selected as the control group, and 88 individuals (38 men, 50 women) with NAFLD (mean age, 50.95±12.08 years) were enrolled in the NAFLD group. According to the *EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease* [13], we formulated corresponding standards. Patients in the NAFLD group met the following conditions: (1) no history of drinking, or alcohol consumption < 210 g per week for men and < 140 g per week for women; (2) imaging or histology showed steatosis; (3) no abnormal liver function; and (4) no history of viral hepatitis. The exclusion criteria for all participants were: history of excessive drinking, drug-induced hepatitis, viral hepatitis, autoimmune hepatitis, severe infection or other diseases that may cause fatty liver disease, malignant tumor, hematological diseases, or obstructive sleep apnea; and for women: polycystic ovary syndrome, pregnancy, lactation or taking oral contraceptives.

Laboratory analyses

Blood lipids, blood glucose (BG) and other parameters were analyzed using an automatic biochemical analyzer (Hitachi 7600 Automatic Biochemical Analyzer, Hitachi Corporation, Tokyo, Japan) or an electrochemical luminescence method (Roche Cobas e 601 Electrochemical Luminescence Instrument, Roche, Mannheim, Germany). All these laboratory analyses were performed by a qualified physician. The homeostasis model assessment of insulin resistance (HOMA-IR) was used to evaluate IR, and it was calculated using the following formula: fasting BG (mmol/L) × fasting insulin (mU/L)/22.5.

Enzyme-linked immunosorbent assay

According to the product instructions, the serum levels of Atg7 and Beclin-1 were measured by enzyme-linked immunosorbent assay kits for Atg7 and Beclin-1, respectively (Cloud-Clone Corp. Houston, TX).

Statistical analysis

All statistical analyses were carried out using the statistical software package, SPSS version 21.0 (Chicago, IL). Normal distribution of the data was verified with the Shapiro-Wilk test. Variables are presented as the mean ± standard deviation or, in the case of non-Gaussian distribution, as the median (interquartile range). The comparisons of variables between groups were performed using the independent samples *t* test, and the non-parametric rank sum test was adopted for comparing the groups with a non-Gaussian distribution. The Pearson correlation and the Spearman correlation coefficients were utilized to assess the correlation between the variables. All the tests are two-sided. A *P*-value < 0.05 was regarded as significant.

Results

The study results are depicted in **Table 1**. There was no significant difference in age (NAFLD, 50.95±12.08; control, 52.30±11.23 years; P = 0.59) or thyroid hormones between the NAFLD and control groups. Compared with the control group, the NAFLD group had a larger body mass index (BMI; 24.05±3.15 vs. 27.55±3.56 kg/m^2, respectively; P < 0.001) and a higher waist: hip ratio (0.86 (0.81, 0.89) vs. 0.90 (0.86, 0.93), respectively; P = 0.002). The NAFLD group also had higher levels of serum triglyceride (TG), fasting plasma insulin (FINS), and 2-h post-challenge insulin than the control group (P < 0.05), but the levels of high-density lipoprotein cholesterol and apolipoprotein A1 were lower in the NAFLD group than the control group. Furthermore, the NAFLD group had increased HOMA-IR compared to the control group (P = 0.001).

The results of the comparison of serum Atg7 and Beclin-1 levels are depicted in **Figures 1** and **2**. Compared with the control group, the serum level of Atg7 was significantly higher in the NAFLD group (P < 0.05). Although serum

Table 1. Characteristics of the study participants

	Control	NAFLD	P
n	88	88	
Age (y)	52.30±11.23	50.95±12.08	0.591
BMI (kg/m^2)	24.05±3.15	27.55±3.56	< 0.001
WHR	0.86 (0.81, 0.89)	0.90 (0.86, 0.93)	0.002
TC (mmol/L)	4.62±0.78	4.64±0.87	0.901
TG (mmol/L)	0.98 (0.64, 1.36)	1.23 (0.92, 1.37)	0.003
HDL-C (mmol/L)	1.59 (1.36, 1.91)	1.29 (1.14, 1.49)	< 0.001
LDL-C (mmol/L)	2. 43±0.64	2. 72±0.82	0. 068
APOA1 (g/L)	1.42±0.23	1.27±0.21	0.002
APOB (g/L)	0.65 (0.55, 0.76)	0.69 (0.62, 0.81)	0.087
FBG (mmol/L)	5.21±0.37	5.30±0.41	0.292
PBG (mmol/L)	5.94 (5.29, 6.65)	5.98 (5.47, 6.93)	0.637
HBA_{1c} (%)	5.70 (5.40, 5.80)	5.65 (5.40, 5.82)	0.804
FINS (uU/mL)	6.89 (5.06, 9.83)	10.85 (6.60, 17.06)	0.001
2hINS (uU/mL)	30.05 (19.41, 44.35)	41.51 (25.36, 66.51)	0.017
HOMR-IR	1.50 (1.22, 2.40)	2.64 (1.56, 4.14)	0.001
TT3 (nmol/L)	1.70 (1.58, 1.90)	1.85 (1.65, 2.14)	0.097
TT4 (nmol/L)	103.60±22.61	105.44±20.98	0.693
TSH (uIU/mL)	2.55 (1.61, 3.57)	2.31 (1.05, 3.01)	0.433
Atg7 (ng/mL)	2.29 (0.82, 4.98)	3.58 (1.70, 10.60)	0.029
Beclin1 (ng/mL)	4.44 (2.13, 5.70)	4.64 (2.95, 5.89)	0.710

Values are the mean ± standard deviation or the median (interquartile range). Abbreviations: NAFLD, non-alcoholic fatty liver disease; BMI, body mass index; WHR, waist: hip ratio; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APO, apolipoprotein; FBG, fasting blood glucose; PBG, postprandial blood glucose; HbA_{1c}, glycated hemoglobin A_{1c}; FINS, fasting plasma insulin; 2hINS, 2-h post-challenge plasma insulin; HOMA-IR, homeostasis model assessment of insulin resistance; TT3, total triiodothyronine; TT4, total thyroxine; TSH, thyroid-stimulating hormone; Atg7, autophagy-related protein 7.

Beclin-1 levels in the NAFLD group tended to be higher than in the control group, there was no significant difference between the two groups ($P > 0.05$).

As shown in **Table 2**, the association between the serum Atg7 level and metabolic risk factors was analyzed using the Spearman correlation coefficient. The results showed that serum Atg7 was positively correlated with BMI, low-density lipoprotein cholesterol, FINS and HOMA-IR. In addition, an analysis using the Spearman correlation coefficient showed that serum Beclin-1 levels were also positively correlated with BMI and TG. These findings are presented in **Table 3**.

Discussion

Nowadays it is generally accepted that autophagy may play a role in hepatic lipid metabolism. In this study, we found that the serum level of Atg7 in the NAFLD group was higher in comparison to the control group. Serum Beclin-1 levels in the NAFLD group also tended to be higher than in the control group, without reaching statistical significance. These findings support the hypothesis that autophagy may play a role in the development of NAFLD. Several previous studies have indicated a lipogenic function of autophagy in the liver. Rather than being involved in the breakdown of lipid droplets (LDs), autophagy is necessary for the genesis of LDs [14], and the LC3 conjugation system plays a key role in the formation of both LDs and autophagosomes. Furthermore, several studies have shown that fasting-induced steatosis was relieved in adult mice with a deficiency in hepatic autophagy and fed a control diet [15, 16]. Moreover, lipid accumulation does not increase after feeding a high-fat-diet to autophagy-deficient mice. The gene expression of proteins involved in fatty acid and TG synthesis, including FAS and SCD1, are also decreased in autophagy-deficient mice compared to control mice. These findings indicate a role of autophagy in lipogenesis. However, there is controversy regarding the exact role of autophagy in lipid metabolism. Indeed, some research has suggested a lipolytic function of autophagy. Pharmacological inhibition or knockdown of autophagy (by targeting Atg5) in hepatocytes can lead to increased hepatocyte TG accumulation and a decrease in the oxidation of free fatty acids [6]. In *ob/ob* mice, autophagy induction via liver-specific overexpression of Atg7 can reduce liver steatosis [11]. Our findings are the first to prove that serum levels of autophagy markers increase in individuals with fatty liver disease, supporting an association of autophagy with fatty liver disease in humans, although they are non-conclusive about the lipogenic or lipolytic function of autophagy. The role of autophagy in hepatic lipid metabolism requires further studies.

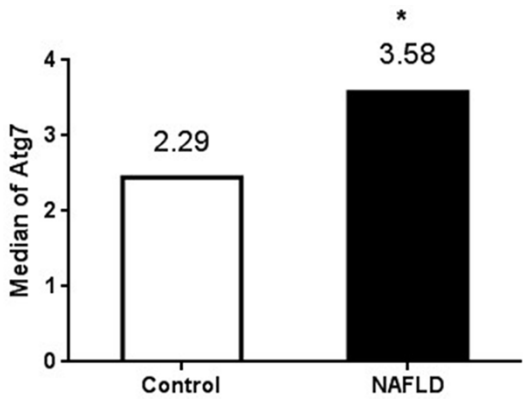

Figure 1. Serum level of autophagy-related protein 7 (Atg7), expressed as the median, in the non-alcoholic fatty liver disease (NAFLD) group (n = 88) and the control group (n = 88). *P < 0.05, compared with control group.

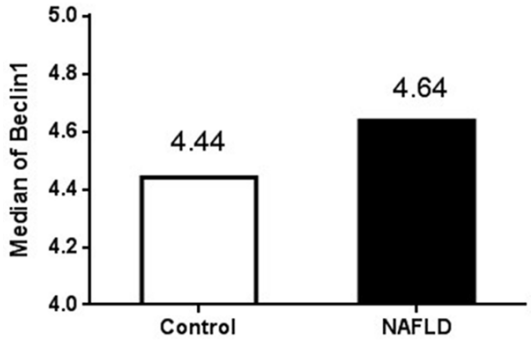

Figure 2. Serum level of Beclin-1, expressed as median, in the non-alcoholic fatty liver disease (NAFLD) group (n = 88) and the control group (n = 88). P = 0.71, NAFLD vs. control.

In our study, the serum Atg7 level was positively correlated with BMI and low-density lipoprotein cholesterol, while the serum Beclin-1 level was positively correlated with BMI and TG. These findings suggest an interaction between autophagy, obesity, and IR. A previous study revealed that the HOMA-IR score is associated with hepatocyte apoptosis in NAFLD patients [17]. Patients with greater IR show higher values of cytokeratin-18 fragments, which is a major intermediate protein in the liver and can induce apoptosis of hepatic cells. Decreased autophagy has been reported in dietary and genetic mouse models of obesity, whereas the overexpression of Atg7 has some beneficial metabolic effects [18]. Overexpression of Atg7 in mice results in a decreased fat mass and protection from diet-induced obesity and IR [18]. Moreover, insulin sensitivity and glucose tolerance are improved in obese mice with overexpression of Atg7. However, other studies have shown that suppression of Atg7 expression in lean mice fails to alter lipid accumulation in the liver or alter serum TG or free fatty acid levels. These contradictory results might be attributable to the different study designs and animal models used in the studies [11].

Moreover, our study found that the serum Atg7 level was positively correlated with FINS and HOMA-IR. It is well established that autophagy is suppressed by insulin during the satiety state; in contrast, autophagy is activated during starvation [19]. When plasma insulin is low and plasma glucagon is high, autophagy is also activated. Thus, autophagy activity fluctuates along with food intake and fasting every day. This fluctuation is necessary for cell survival and health. In the presence of IR and hyperinsulinemia, this function may be impaired because of the continuously increased insulin concentration in the blood [20]. As a result, the autophagy level may be increased in the presence of IR and hyperinsulinemia. Reduced autophagy has been also linked to IR in studies using high-fat-diet and ob/ob mice [18], where IR is not the cause but the result of decreased autophagy. The knockdown of autophagy in lean mice induces severe IR, while overexpression of Atg7 in obese mice improves insulin sensitivity and glucose tolerance, therefore decreasing steatosis. Further investigations are needed to clarify the association of autophagy with IR.

Consistent with previous studies, our present study shows that patients with NAFLD have higher levels of serum TG, FINS, and 2-h postchallenge insulin than the control individuals; likewise, HOMA-IR is also increased in patients with NAFLD. Another interesting finding of the present study is that there is no significant difference in fasting or postprandial BG between the NAFLD and control individuals, despite the liver playing a primary role in glucose metabolism. Impaired insulin signaling is an important feature of NAFLD [21]. In addition, other research has revealed that liver autophagy contributes to the maintenance of BG and amino acids [22]. In liver-specific autophagy (Atg7)-deficient mice, BG levels continue to decrease in contrast to wild-type mice, indicating that

Table 2. Associations between serum total Atg7 level and metabolic risk factors

	r	P		r	P
Age (y)	0.155	0.149	APOB (g/L)	0.181	0.091
BMI (kg/m^2)	0.222	0.038	FBG (mmol/L)	0.088	0.415
WHR	0.133	0.228	PBG (mmol/L)	-0.024	0.827
TC (mmol/L)	0.100	0.356	HBA1c (%)	0.038	0.741
TG (mmol/L)	0.155	0.148	FINS (uU/mL)	0.224	0.036
HDL-C (mmol/L)	-0.168	0.117	2hINS (uU/mL)	0.115	0.288
LDL-C (mmol/L)	0.229	0.032	HOMR-IR	0.228	0.033
APOA1 (g/L)	-0.166	0.122	Beclin1	0.143	0.184

Abbreviations: r, correlation coefficient; BMI, body mass index; WHR, waist: hip ratio; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APO, apolipoprotein; FBG, fasting blood glucose; PBG, postprandial blood glucose; HbA_{1c}, glycated hemoglobin A_{1c}; FINS, fasting plasma insulin; 2hINS, 2-h post-challenge plasma insulin; HOMA-IR, homeostasis model assessment of insulin resistance.

Table 3. Associations between serum total Beclin-1 level and metabolic risk factors

	r	P		r	P
Age (y)	-0.11	0.917	APOB (g/L)	0.138	0.200
BMI (kg/m^2)	0.215	0.045	FBG (mmol/L)	0.029	0.791
WHR	0.173	0.116	PBG (mmol/L)	0.050	0.644
TC (mmol/L)	0.122	0.258	HBA1c (%)	-0.071	0.533
TG (mmol/L)	0.244	0.036	FINS (uU/mL)	0.095	0.381
HDL-C (mmol/L)	-0.156	0.148	2hINS (uU/mL)	-0.053	0.621
LDL-C (mmol/L)	0.101	0.351	HOMR-IR	0.102	0.345
APOA1 (g/L)	-0.097	0.369	Beclin1	0.143	0.184

Abbreviations: r, correlation coefficient; BMI, body mass index; WHR, waist: hip ratio; TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; APO, apolipoprotein; FBG, fasting blood glucose; PBG, postprandial blood glucose; HbA_{1c}, glycated hemoglobin A_{1c}; FINS, fasting plasma insulin; 2hINS, 2-h post-challenge plasma insulin; HOMA-IR, homeostasis model assessment of insulin resistance; Atg7, autophagy-related protein 7.

insulin plays a dominant role over glucagon in controlling liver autophagy. Nevertheless, for lipid metabolism, the exact interaction between the effect of insulin and autophagy is still not entirely clear [23].

There are some limitations in the current study. Firstly, the cross-sectional design of this study can prove an association but not the causality between autophagy and fatty liver. Moreover, our sample size was relatively small. Another limitation of this study was that the NAFLD group was not divided into subgroups according to disease stage. Since autophagy is a process of dynamic change in the body, it cannot be ruled out that autophagy has different roles in the different stages in the development of NAFLD. Lastly, because the role of autophagy is site-specific and the effect of autophagy varies in different tissues, the exact role of autophagy in whole-body metabolism is unclear. Further research is clearly needed to elucidate the exact role of autophagy in NAFLD.

In conclusion, serum levels of the autophagy indicator Atg7 were increased in patients with NAFLD. Serum Atg7 levels were positively associated with NAFLD, indicating autophagy may play a role in the pathogenesis of NAFLD. However, the pathophysiological mechanism and possible clinical implications require further investigation.

Acknowledgements

The study was supported by the Natural Science Foundation of Hebei Province (no. H2015307034).

Disclosure of conflict of interest

None.

Address correspondence to: Luping Ren and Guangyao Song, Department of Endocrinology, General Hospital of Hebei, Shijiazhuang 050051, Hebei, P. R. China. Tel: 18730121599; Fax: +86-21-57643271; E-mail: renluping@hotmail.com (LPR); sguangyao2@163.com (GYS)

References

[1] Bray GA. Contemporary diagnosis and management of obesity and the metabolic syndrome. 4th edition. Longboat Key, FL: Handbooks in Health Care; 2011. pp. 314.

[2] Byrne CD, Wild SH. The metabolic syndrome. 2nd edition. Chichester, West Sussex: Wiley-Blackwell; 2011. pp. 366.

[3] Sun C, Fan JG, Qiao L. Potential epigenetic mechanism in non-alcoholic fatty liver disease. Int J Mol Sci 2015; 16: 5161-5179.

[4] Ren LP, Chan SM, Zeng XY, Laybutt DR, Iseli TJ, Sun RQ, Kraegen EW, Cooney GJ, Turner N, Ye JM. Differing endoplasmic reticulum stress response to excess lipogenesis versus lipid over-

supply in relation to hepatic steatosis and insulin resistance. PLoS One 2012; 7: e30816.
[5] Jiang P, Mizushima N. Autophagy and human diseases. Cell Res 2014; 24: 69-79.
[6] Singh R, Kaushik S, Wang Y, Xiang Y, Novak I, Komatsu M, Tanaka K, Cuervo AM, Czaja MJ. Autophagy regulates lipid metabolism. Nature 2009; 458: 1131-1135.
[7] Quan W, Lim YM, Lee MS. Role of autophagy in diabetes and endoplasmic reticulum stress of pancreatic beta-cells. Exp Mol Med 2012; 44: 81-88.
[8] Autophagy: cancer, other pathologies, inflammation, immunity, infection, and aging. In: Hayat MA, editor. Cambridge, MA: Academic Press; 2014.
[9] Autophagy of the nervous system: cellular self-digestion in neurons and neurological diseases. In: Yue Z, Chu CT, ediotrs. Singapore: World Scientific Publishing; 2012.
[10] Bechmann LP, Hannivoort RA, Gerken G, Hotamisligil GS, Trauner M, Canbay A. The interaction of hepatic lipid and glucose metabolism in liver diseases. J Hepatol 2012; 56: 952-964.
[11] Dong H, Czaja MJ. Regulation of lipid droplets by autophagy. Trends Endocrinol Metab 2011; 22: 234-240.
[12] Kaur J, Debnath J. Autophagy at the crossroads of catabolism and anabolism. Nat Rev Mol Cell Biol 2015; 16: 461-472.
[13] European Association for the Study of the Liver (EASL); European Association for the Study of Diabetes (EASD); European Association for the Study of Obesity (EASO). EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64: 1388-1402.
[14] Shibata M, Yoshimura K, Furuya N, Koike M, Ueno T, Komatsu M, Arai H, Tanaka K, Kominami E, Uchiyama Y. The MAP1-LC3 conjugation system is involved in lipid droplet formation. Biochem Biophys Res Commun 2009; 382: 419-423.
[15] Ma D, Molusky MM, Song J, Hu CR, Fang F, Rui C, Mathew AV, Pennathur S, Liu F, Cheng JX, Guan JL, Lin JD. Autophagy deficiency by hepatic FIP200 deletion uncouples steatosis from liver injury in NAFLD. Mol Endocrinol 2013; 27: 1643-1654.
[16] Kim KH, Jeong YT, Oh H, Kim SH, Cho JM, Kim YN, Kim SS, Kim DH, Hur KY, Kim HK, Ko T, Han J, Kim HL, Kim J, Back SH, Komatsu M, Chen H, Chan DC, Konishi M, Itoh N, Choi CS, Lee MS. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing Fgf21 as a mitokine. Nat Med 2013; 19: 83-92.
[17] Civera M, Urios A, Garcia-Torres ML, Ortega J, Martinez-Valls J, Cassinello N, del Olmo JA, Ferrandez A, Rodrigo JM, Montoliu C. Relationship between insulin resistance, inflammation and liver cell apoptosis in patients with severe obesity. Diabetes Metab Res Rev 2010; 26: 187-192.
[18] Yang L, Li P, Fu S, Calay ES, Hotamisligil GS. Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. Cell Metab 2010; 11: 467-478.
[19] Barlow AD, Thomas DC. Autophagy in diabetes: beta-cell dysfunction, insulin resistance, and complications. DNA Cell Biol 2015; 34: 252-260.
[20] Liu HY, Han J, Cao SY, Hong T, Zhuo D, Shi J, Liu Z, Cao W. Hepatic autophagy is suppressed in the presence of insulin resistance and hyperinsulinemia: inhibition of FoxO1-dependent expression of key autophagy genes by insulin. J Biol Chem 2009; 284: 31484-31492.
[21] Torres DM, Williams CD, Harrison SA. Features, diagnosis, and treatment of nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 2012; 10: 837-858.
[22] Ezaki J, Matsumoto N, Takeda-Ezaki M, Komatsu M, Takahashi K, Hiraoka Y, Taka H, Fujimura T, Takehana K, Yoshida M, Iwata J, Tanida I, Furuya N, Zheng DM, Tada N, Tanaka K, Kominami E, Ueno T. Liver autophagy contributes to the maintenance of blood glucose and amino acid levels. Autophagy 2011; 7: 727-736.
[23] Kwanten WJ, Martinet W, Michielsen PP, Francque SM. Role of autophagy in the pathophysiology of nonalcoholic fatty liver disease: a controversial issue. World J Gastroenterol 2014; 20: 7325-7338.