*Khwaja Yunus Ali Univ. J. Vol. 3, Issue 1, December 2018*

### Review Article

Autophagy: An Important Cellular Mechanism Implicated in Diabetes Mellitus

***Md. Rezaul Karim 1****,#,\*,* ***Zinat Tamannaa 1****,#,* ***Md. Foyzur Rahman 1, Md. Rezanur Rahman 1***

## 1 Department of Biochemistry and Biotechnology, Khwaja Yunus Ali University, Sirajganj-6751, Bangladesh.

#These two authors made equal contribution.

***\*Correspondence to:***

*E-mail:* [*rezaul929@gmail.com*](mailto:rezaul929@gmail.com)

***Abstract:***

***Autophagy is involved in clearance of redundant or dysfunctional components.* To *maintain physiological functions properly and promoting survival, autophagy acts as a molecular mechanism. Dysfunction in autophagy causes many diseases such as neuro-degeneration, cancer and diabetes mellitus (DMJ, infectious diseases and aging. Inadequate or ineffective insulin or both are the main causes of diabetes mellitus. In T2DM, autophagy provides nutrients* to *uphold cellular energy at fasting and also removes injured organelles, lipids and miss-folded proteins. In addition, autophagy plays a key role* to *prevent dysfunction of pancreatic beta cell and insulin resistance. In this review, we stated the functions of autophagy in diabetes mellitus.***

***Keywords: Autophagy; Type2 diabetes mellitus; Pancreatic !3-cells; Insulin resistance.***

**Introduction:**

Autophagy is the natural regulated mechanism of the cell that disassembles unnecessary or dysfunctional components (Klionsky 2008). Now­ a-days the frequency of diabetes mellitus (DM) is increasing globally. The major contributing factors in the pathogenesis of diabetes (Calcutt et.al., 2009) may be the increased plasma glucose levels secondary to insulin resistance. The pancreatic beta cells dysfunction occurred due to increasing the metabolic disorder that causes of the succession of diabetes. However, DM is traditionally introduced as a non-immune disorder. Evidence showed that the main pathways in the progression and pathogenesis of

# 01

## this chronic metabolic disease are inflammatory mechanisms, apoptosis, autophagy and endoplasmic reticulum stress (Su et. al., 2013). Autophagy which is denoted as a stress­ responsive intracellular system is thought that the disturbance of this machinery is involved in the pathogenesis of age and diabetes related diseases (Gonzalez et.al., 2011; Mizushima et.al., 2008) The damaged intracellular proteins and organelles are degraded by autophagy that is a part of the catabolic processes (Hartleben et.al., 2010). Autophagy has also a defensive role against kidney dysfunction induced by aging (Kume et.al, 201O; Kimura et. al, 2011), hypoxia (Jiang et.al, 201O; Takahashi et.al., 2012) and anticancer drugs autophagy in diabetic mellitus.

**Autophagy:**

## Autophagy is one kind of cellular degradation process that involves the fusion of autophagosomes and lysosomes (Yang et.al., 2008). It is a tightly regulated lysosomal pathway and critical for homeostasis, development and survival of cell Levine (Kroemer et.al., 2008). Autophagy, a programmed cell death became popular in the 1990s by the discovery of autophagy-related genes (Levine et.al., 2004). Autophagy becomes activated in a single-cell organism if no food is available to digest. As autophagy takes place in both cell survival and death in humans so this process is more complicated to understand. Autophagy may have a central role in the integrated pathways including apoptosis and mammalian target of rapamycin (mTOR) signaling which are also

keystone of cell homeostasis (Tanaka et.al., 2012; Kroemer et.al., 2010). However, eukaryotic cells must adjust to various detrimental effects of external stimuli including ultraviolet light, microbial pathogens, starvation and fluctuations of conditions such as temperature, ion concentration, pH, cytokines and hormones (Kroemer et.al., 2010). Eukaryotic cells undergo

autophagosomes with lysosomes. In the case of vesicle nucleation, Beclin-1 interacts with Atg14L, Bcl2, Rubicon, p150 and Pl3Kinase class Ill proteins. After binding regulators such as Bcl-2 protein (anti-apoptotic protein) and Rubicon bind Beclin-1 inhibit the vesicle nucleation stage of autophagy.

Pl3K-1/Akt MAPK/ERK

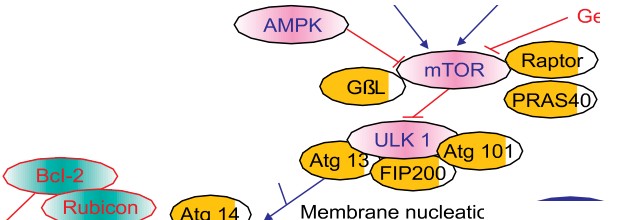
pathway pathway

rapid changes to protect themselves against detrimental attacks and can fight with sub-lethal stress. In this stress-induced adaptation, autophagy plays a major role by eliminating

(B)Nucleation

ATP AMP

ER stress



l

notoxic Stress

(A) Induction

Upstream signaling processes

**(D)** Termination

n

damaged or harmful components through

Apopt Sequestration *[Rd\*

Autophagosomal

mechanism including lysosome-associated digestion (He et.al., 2009). Thus, exaggerated or exiguous autophagy can be harmful to cells. For recycling of essential amino acids autophagy is required (Mizushima et.al., 201O). A specific gene family called autophagy-related genes is involved with initiation, formation and maturation of autophagosomes. These autophagosomes later fuse with lysosomes for hydrolysis or degradation of enwrapped materials by the process of autophagy (Figure 1).

**LC3-II** ►

**AUTOPHAGOSOMES**

*>* **LYSOSME**

**ATG16L1 ATG12 ATG5**

►

**AUTOPHAGOSOMES**

**Figure 1:** Molecular machinery of autophagy.

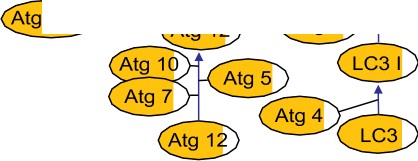
**The molecular mechanisms of autophagy:** Autophagy is consisted of four stages: (A) induction, (B) vesicle nucleation, (C)

autophagosome membrane elongation and (D)

termination/ fusion and degradation I (Figure 2) (Salminen et.al., 2016; Kume et.al., 2015). Recent evidence suggests that mTORC1 complex is also regulated by some signaling pathway such as, Pl3K-1/Akt, MAPK/ ERK and AMPK. And, autophagy is initiated by the activation of AMPK phosphorylates Raptor and inhibition of mTOR (Cetrullo et.al., 2015; Dunlop et.al., 2014; Sridharan et.al., 2011). Beclin-1 complex (Pl3Kinase class 111, p 150, Beclin-1 and Atg14) is essential for vesicle nucleation which promotes the synthesis of

Ph Autoph:gosome *§g* formation

PE Autophagolysosome



16

**Atg**

(C) Elongation ----

@

Autophagy

**Figure 2:**There are four stages in the autophagic process: (A) induction, (B) nucleation, (C) elongation and

(D) termination. (Courtesy:Yang et al., 2017)

Autophagosome membrane arrangement is performed by the Atg12 and LC3 ubiquitin-like conjugation systems: (1) Atg12 ubiquitin-like conjugation system: ubiquitin-like Atg12 is coupled to Atg5, Atg7 and Atg10. Atg10 known as the E2 enzyme. The Atg5-Atg12/Atg16L complex is balanced by the Beclin-1 complex and assigns to the convex surface of the isolation membrane.(2) LC3 ubiquitin-like conjugation system: LC3 is splited by the Atg4 cysteine protease, consecutively processed by Atg7 and Atg3 and then combined to the membrane lipid phosphatidylethanolamine (the conjugated form is termed LC3-II). The Atg5-Atg12/Atg16L1 complex is important to develop the modification of LC3-I to LC3-II. Thus autophagy allows the sequential humiliation and reprocess ion of cellular components. Quality control of organelles and proteins are the main objectives of autophagy and protection of intracellular homeostasis in stress and nutrient efficiency (Yang et.al., 2017).

### Type 2 diabetes mellitus {T2DM):

Type 2 diabetes mellitus (T2DM) is commonly known as diabetes, which is a metabolic and chronic disease all over the world (Hou et.al., 2016; Chen et.al., 2016). The patients have hyperglycemia over a prolonged period. The

character in diabetes mellitus is a relative or absolute lack of insulin, causing hyperglycemia (Middleton et.al., 2016). Frequent urination , thirst and increased hunger are the symptoms of hyperglycemia.The Acute symptomps of DM can include nonketotic hyperosmolar coma, diabetic ketoacidosis and death. Serious complications of DM include cardiovascular disease, stroke, chronic kidney failure, nephropathy, foot ulcers, neuropathy and damage to the eyes (Adeshara et.al., 2016; Zatalia et.al., 2013; ResI et.al., 201O; Hahr et.al., 2010). According to World Health Organization (WHO) report in 2014, approximately 422 million people were diagnosed with DM (Balakumar et.al., 2016; Nowotny et.al., 2015). There are three main types of diabetes mellitus: (1) Type 1 diabetes (T1D): also called insulin-dependent, juvenile or childhood-onset diabetes.Tl D is specified by deficient insulin production in the body. The pathology in T1D is described as an autoimmune disease because the pancreatic beta cells (insulin­ producing tissue) are shattered in the islets of Langerhans (Boldison et.al., 2016). T1D is diagnosed most in children and young adults. T1D patients require daily supervision of insulin to regulate the amount of glucose in their blood (Kesavadev 2016). Environmental factors and genetic influence play a key role in T1D. (Zou et.al., 2016; Hotta-lwamura et.al., 2016). (2) Type 2 diabetes (T2D): formerly called non-insulin­

(hyperinsulinemia). The pancreatic beta cells severely secrete insulin and then slowly decline. T2D at late stage is characterized by insufficient secretion of insulin from the pancreatic beta cells, conjugated with impaired insulin action in target tissues such as muscle, liver and fat. Hyperglycemia results when insulin secretion is inadequate to repay for insulin resistance (Tian et.al., 2017; Garabadu et.al., 2017; Eaton et.al., 2017; Wong et.al., 2012; Yang et.al., 2004). Mechanisms in the development and pharmacological treatments of T2D are summarized in Figure 3, 4.

Ethnicity

Insulin resistance

Family history

Increasing age

Physical inactivity

Poor diet

Obesity

Impaired insulin Secretion

Type 2 Diabetes (T2D)

**Figure 3:** Etiology of T2D. Two major physiological defects associated with T2D are reduced insulin sensitivity, insulin resistance and combined with impaired insulin secretion. Obesity, poor diet, physical inactivity, increasing age, family history and ethnicity lead to a higher risk ofT2D. (Yang et. al., 2017).

**The mechanisms of Type 2 diabetes mellitus (T2D)**

dependent (NIDDM) or adult onset diabetes. T2D is the most common type of diabetes widespread in Bangladesh in which cells fail to respond to and uptake of insulin. In the body T2D begins with insulin resistance (Sakai et.al., 2016;

Honardoost et.al., 2016; Rezai et.al., 2016). Insulin

resistance can be increased by weight reduction

Early stage

Sulfonylurea Non-SA: Meqlitinide

Increase insulin secretion

Late stage

Insulin resistance in peripheral tissue

Insulin production in pancreatic beta cells

Dipeptidy1 peptidase 4 inhibitor (DPP-4 inhibitor)

DPP-4 inhibition and lncretins activation

Metformine, Thiazolidinediones (TZD) Enhances insulin sensit

Hyperinsulinemia (Insulin t)

* Dipeptid•yl pep tidase 4

Metformine, Glycogen hydrolysis and Gluconeogenesis inhibition

Pancreatic beta cells dysfunction

(OPP-4)!

Impaired insulin secretion (lnsulinJ) .. lncretinsJ

Metformine

and exercise (Arias-Loste et.al., 2014). (3)

Gestational diabetes: pregnant women without a previous history of diabetes develop high blood

1. Glycogen hydrolysis
2. Gluconeogenesis
3. Carbohydrate absorption and ... decomposition

Hyperglycemia (glucose in blooc:t )

Thiazol (TZD) Enhances insulin sensitivity

.. Insulin resistance in peripheral tissue

sugar levels (Viecceli et.al., 2017; Logan et.al., 2017). On the other hand, the defective or mutant insulin receptor may be caused no response to

insulin in body tissues. And, the patients with T2D

a-glu**t**cos1daset

Reactive oxygen species (ROS) production

Cellular cytotoxicity and damage

a-Glucosidase inhibitor Carbohydrate absorption and decomposition inhibition

Cardiovascular disease Stroke

Nephropathy Foot ulcers Neuropathy Retinopathy

in the early stage often have a normal or high bone mineral density (BMD), associated with obesity and hyperinsulinemia,and altered level of insulin. The pancreatic beta cells produce more and more insulin, When cells are insensitive to insulin (or insulin resistance), which leads to the higher insulin concentration in blood

**Figure 4:** Mechanisms in the development and pharmacological treatments ofT2D. (Yang et. al., 2017).

### Autophagy and type 2 diabetes:

Autophagy has close link to the progression of type 2 diabetes mellitus as it regulate the function of pancreatic beta cells and insulin

target tissues (skeletal muscle, liver and adipose tissue) of our body (Marrif et.al., 2016; Lee 2014; Wang et.al., 2013; Hur et.al., 2010). Upon insulin resistance, hyperinsulinemia occurs to compensate for hyperglycemia on the early onset of T2D (Figure 5). On the late onset of T2D, in contrast, the number of pancreatic cells progressively diminished through apoptotic cell death (Marrif et.al., 2016; Montane et.al., 2014; Quan et.al., 2013; Lee et.al., 2012). Studies suggest that enhanced autophagy acts as a protective mechanism against oxidative stress in pancreatic beta cells (Hur et.al., 2010; Montane et.al., 2014; Quan et.al., 2013; Lee et.al., 2012; Rivera et.al,. 2014). In vivo studies demonstrated that Atg7- deficient mice showed a decrease in the number of pancreatic beta cells, impairment of glucose tolerance and reduction in insulin secretion (Kim et.al., 2014). The insulin resistant mice (beta-cell­ specific Atg7 knockout mice) model has been shown that autophagy plays a vital role in the development of diabetes and in preserving the structure and function of pancreatic beta cells. Accumulation of autophagosomes in the pancreatic beta cell has been demonstrated in db/db mouse model (Las et.al., 2010; Fujitani et.al., 2009) showed that reduction in insulin secretion was associated with pancreatic beta cell disintegration and impaired glucose in autophagy-deficient mice. However, constitutively activated autophagy has deleterious effects on pancreatic beta cells and chronic activation of autophagy causes autophagic cell death (Las et.al., 2010; Demirtas et.al., 2016; Pabon et.al., 2016; Wang et.al., 2013; Bartolome et.al., 2012;

Masini et.al., 2009).

**Autophagy and Insulin resistance:** Dysregulated autophagy in addition to beta-cell dysfunction, may possibly be involved in insulin

resistance as well, because ER stress has been

implicated not only in beta-cell dysfunction but also in insulin resistance (Ozcan et.al., 2004). Because autophagy deficiency could lead to abnormal ER stress or ER stress response, impaired autophagy may affect insulin resistance. A recent paper reported that autophagy is deficient in the liver of obese mice and over expression of Atg7 restored insulin sensitivity

together with alleviated expression of ER stress markers (Yang et.al., 2010). Recently, autophagy was reported to participate in the down­ regulation of insulin receptors and ER stress­ mediated insulin resistance as an adaptive process in ER stresses (Zhou et.al., 2009). Conversely, insulin resistance has been reported to suppress autophagy (Liu et.al., 2009). Although these findings suggest that autophagy may be related to insulin resistance, direct causal relationship between them would require further investigation.

### Conclusion and future perspective:

We know that obesity is one of the risk factors for diabetes. But not all human or experimental animals with obesity develop diabetes. Our survey suggests that in case of deficiency of beta­ cell, autophagy could be an preventing factor in the progression from obesity to diabetes. With respect to the confirmation of pathogenetic role of dysregulated autophagy in the development of natural human diabetes a new class of drugs will be possible to discover on a new principle. Metformin is generally used in the treatment of T2D that can defend pancreatic beta cells from damage by activating autophagy through AMPK pathway. We precis the function of autophagy in diabetes mellitus. New medicine would be expected to develop and more effective agents are targeted in autophagy for the therapy of T2D. In our study we found not so strong evidence about the relationship of autophagy with type 1 diabetes. So, future experiments are needed to explore this relationship.

**Conflict of interest:** The authors declare "no conflict of interest".

**Acknowledgement:** The authors would like to thank Prof. Dr. Hossain Reza, Vice-Chancellor of Khwaja Yunus Ali University for his helpful suggestions on the improvement of the manuscript. We also would like to express our gratitude to our dear colleagues in the departments for their suggestions on improvement of the manuscript.

**References:**

Adeshara, A. K., G Diwan, A., & S Tupe, R. (2016). Diabetes and complications: cellular signaling pathways, current understanding and targeted therapies. Current drug targets, 17(11), 1309-1328.

Arias-Loste, M., Ranchal, I., Romero-Gomez, M., & Crespo, J. (2014). lrisin, a link among fatty liver disease, physical inactivity and insulin resistance. International journal of molecular sciences, 15(12), 23163-23178.

Balakumar, P., Maung-U, K., & Jagadeesh, G. (2016). Prevalence and prevention of cardiovascular disease and diabetes mellitus. Pharmacological research, 113, 600-609.

Bartolome, A., Guillen, C., & Benito, M. (2012). Autophagy plays a protective role in endoplasmic reticulum stress-mediated pancreatic 13 cell death. Autophagy, 8(12), 1757-1768.

Boldison, J., & Wong, F. S. (2016). Immune and pancreatic 13 cell interactions in type 1 diabetes. Trends in Endocrinology & Metabolism, 27(12), 856-867.

Calcutt, N. A., Cooper, M. E., Kern,T. S., & Schmidt, A.

M. (2009). Therapies for hyperglycaemia-induced diabetic complications: from animal models to clinical trials. Nature Reviews Drug Discovery, 8(5), 417.

Cetrullo S, D'Adamo S, Tantini B, Cetrullo, S., D'Adamo, S., Tantini, B., Borzi, R. M., & Flamigni, F. (2015). mTOR, AMPK, and Sirtl: key players in metabolic stress management. Critical Reviews™ in Eukaryotic Gene Expression, 25(1).

Chen, S. Y., Hsu, Y. M., Lin, Y. J., Huang, Y. C., Chen, C.

J., Lin, W. D., ... & Yang, J. S. (2016). Current concepts regarding developmental mechanisms in diabetic retinopathy in Taiwan. Biomedicine, 6(2).

Demirtas, L., Guclu, A., Erdur, F. M., Akbas, E. M.,

Ozcicek, A., Onk, D., & Turkmen, K. (2016). Apoptosis, autophagy & endoplasmic reticulum stress in diabetes mellitus. The Indian journal of medical research, 144(4), 515.

Dunlop, E. A., & Tee, A. R. (2014, December). mTOR and autophagy: a dynamic relationship governed by nutrients and energy. In Seminars in cell & developmental biology (Vol. 36, pp. 121-129).

Academic Press.

Eaton, S. B., & Eaton, S. B. (2017). Physical inactivity, obesity, and type 2 diabetes: an evolutionary perspective. Research quarterly for exercise and sport, 88(1), 1-8.

Ebato, C., Uchida, T., Arakawa, M., Komatsu, M., Ueno, T., Komiya, K., ... & Kawamori, R. (2008). Autophagy is important in islet homeostasis and compensatory increase of beta cell mass in response to high-fat diet. Cell metabolism, 8(4), 325-332.

Fujitani, Y., Kawamori, R., & Watada, H. (2009). The role of autophagy in pancreatic ?-cell and diabetes. Autophagy, 5(2), 280-282.

Garabadu, D., & Krishnamurthy, S. (2017). Metformin attenuates hepatic insulin resistance in type-2 diabetic rats through Pl3K/Akt/GLUT-4 signalling independent to bicuculline-sensitive GABAA receptor stimulation. Pharmaceutical biology, 55(1), 722-728.

Gonzalez, C. D., Lee, M. S., Marchetti, P., Pietropaolo, M., Towns, R., Vaccaro, M. I., ... & Wiley, J. W. (2011). The emerging role of autophagy in the pathophysiology of diabetes mellitus. Autophagy, 7(1), 2-11.

Hahr, A. J., & Molitch, M. E. (201O). Diabetes, cardiovascular risk and nephropathy. Cardiology clinics, 28(3), 467-475.

Hartleben, B., Godel, M., Meyer-Schwesinger, C., Liu, S., Ulrich, T., Kobler, S., ... & Cohen, C. D. (2010). Autophagy influences glomerular disease susceptibility and maintains podocyte homeostasis in aging mice. The Journal of clinical investigation, 120(4), 1084-1096.

He, C., & Klionsky, D. J. (2009). Regulation mechanisms and signaling pathways of autophagy. Annual review of genetics, 43.

Honardoost, M., Arefian, E., Soleimani, M., Soudi, S., & Sarookhani, M. R. (2016). Development of insulin resistance through induction of miRNA-135 in C2C12 cells. Cell Journal (Yakhteh), 18(3), 353.

Hotta? lwamura, C., & Tarbell, K. V. (2016). Type 1 diabetes genetic susceptibility and dendritic cell function: potential targets for treatment. Journal of leukocyte biology, 100(1), 65-80.

Hou WH, Li CY, Chen LH, Wang LY, Kuo KN, Shen HN, et al. (2016). Prevalence of hand syndromes among patients with diabetes mellitus in Taiwan: A population-based study. Journal of diabetes, 9(6), 622-627.

Jiang, M., Liu, K., Luo, J., & Dong, Z. (2010). Autophagy is a renoprotective mechanism during in vitro hypoxia and in vivo ischemia-reperfusion injury. The American journal of pathology, 176(3), 1181-1192.

Jung, H. S., Chung, K. W., Kim,J. W., Kim,J., Komatsu,

M., Tanaka, K., ... & Jeong, Y. T. (2008). Loss of autophagy diminishes pancreatic ? cell mass and function with resultant hyperglycemia. Cell metabolism, 8(4), 318-324.

Kim, J., Cheon, H., Jeong, Y. T., Quan, W., Kim, K. H.,

Cho, J. M., ... & Lee, M. K. (2014). Amyloidogenic peptide oligomer accumulation in autophagy­ deficient ? cells induces diabetes. The Journal of clinical investigation,124(8), 3311-3324.

Kimura, T., Takabatake, Y., Takahashi, A., Kaimori, J. Y., Matsui, I., Namba, T., ... & Rakugi, H. (2011). Autophagy protects the proximal tubule from degeneration and acute ischemic injury. Journal of the American Society of Nephrology, 22(5), 902-913.

Klionsky, D. J. (2008). Autophagy revisited: a conversation with Christian de Duve. Autophagy, 4(6), 740-743.

Kroemer, G., Marino, G., & Levine, B. (2010). Autophagy and the integrated stress response. Molecular cell, 40(2), 280-293.

Kume, S., & Koya, D. (2015). Autophagy: a novel therapeutic target for diabetic nephropathy. Diabetes & metabolism journal, 39(6), 451-460.

Kume, S., Uzu, T., Horiike, K., Chin-Kanasaki, M.,

lsshiki, K., Araki, S. I., ... & Koya, D. (2010). Calorie restriction enhances cell adaptation to hypoxia through Sirtl-dependent mitochondrial autophagy in mouse aged kidney. The Journal of clinical investigation,120(4), 1043-1055.

Las, G., & Shirihai, 0. S. (201O). The role of autophagy in !3-cell lipotoxicity and type 2 diabetes. Diabetes, Obesity and Metabolism, 12, 15-19.

Lee, M. S. (2014). Role of islet !3-cell autophagy in the pathogenesis of diabetes. Trends in Endocrinology & Metabolism, 25(12), 620-627.

Lee, M. S., Kim, K. A., & Kim, H. S. (2012). Role of pancreatic !3-cell death and cell death-associated inflammation in diabetes. Current molecular medicine, 12(10), 1297-1310.

Levine, B., & Klionsky, D. J. (2004). Development by self-digestion: molecular mechanisms and biological functions of autophagy. Developmental cell, 6(4), 463-477.

Levine, B., & Kroemer, G. (2008). Autophagy in the pathogenesis of disease. Cell, 132(1), 27-42.

Levine, B., & Yuan, J. (2005). Autophagy in cell death: an innocent convict?.The Journal of clinical investigation, 115(10), 2679-2688.

Liu, H. Y., Han, J., Cao, S. Y., Hong, T., Zhuo, D., Shi, J.,

... & Cao, W. (2009). Hepatic autophagy is suppressed in the presence of insulin resistance and hyperinsulinemia inhibition of FoxOl­ dependent expression of key autophagy genes by insulin. Journal of Biological Chemistry, 284(45), 31484-31492.

Logan, K. M., Gale, C., Hyde, M. J., Santhakumaran, S., & Modi, N. (2017). Diabetes in pregnancy and infant adiposity: systematic review and meta­ analysis. Archives of Disease in Childhood-Fetal and Neonatal Edition, 102(1), F65-F72.

Marrif, H. I., & AI-Sunousi, S. I. (2016). Pancreatic 13-

cell mass death. Frontiers in pharmacology, 7, 83

Middleton, P., Crowther, C. A., & Simmonds, L. (2016). Different intensities of glycaemic control for pregnant women with pre-existing diabetes. Cochrane Database of Systematic Reviews, (5).

Mizushima, N., Levine, B., Cuervo, A. M., & Klionsky,

D. J. (2008). Autophagy fights disease through cellular self-digestion.nature, 451(7182),1069.

Mizushima, N., Yoshimori, T., & Levine, B. (2010). Methods in mammalian autophagy research. Cell, 140(3), 313-326.

Montane, J., Cadavez, L., & Novials, A. (2014). Stress and the inflammatory process: a major cause of pancreatic cell death in type 2 diabetes. Diabetes, metabolic syndrome and obesity: targets and therapy, 7, 25.

Nowotny, K., Jung, T., Hohn, A., Weber, D., & Grune,

T. (2015). Advanced glycation end products and oxidative stress in type 2 diabetes mellitus. Biomolecules, 5(1), 194-222.

Ozcan, U., Cao, Q., Yilmaz, E., Lee, A. H., lwakoshi, N.

N., Ozdelen, E., ... & Hotamisligil, G. S. (2004). Endoplasmic reticulum stress links obesity, insulin action, and type 2 diabetes. Science, 306(5695), 457-461.

Pabon, M. A., Ma, K. C., & Choi, A. M. (2016).

Autophagy and obesity-related lung disease. American journal of respiratory cell and molecular biology, 54(5), 636-646.

Periyasamy-Thandavan,S., Jiang, M., Wei, Q., Smith, R., Yin, X. M., & Dong, Z. (2008). Autophagy is cytoprotective during cisplatin injury of renal proximal tubular cells. Kidney international, 74(5), 631-640.

Quan, W., Jo, E. K., & Lee, M. S. (2013). Role of pancreatic (3-cell death and inflammation in diabetes. Diabetes, Obesity and Metabolism, 15(s3), 141-151.

Resl M., Clodi, M. (2010). Diabetes and cardiovascular complications. Wien Med Wochenschr.; 160: 3-7.

Rezai, S., LoBue, S., & Henderson, C. E. (2016). Diabetes prevention: Reproductive age women affected by insulin resistance. Women's Health, 12(4),427-432.

Rivera, J. F., Costes, S., Gurlo,T., Giabe, C. G., & Butler,

P. C. (2014). Autophagy defends pancreatic (3-cells from human is let amyloid polypeptide-induced toxicity. The Journal of clinical investigation, 124(8), 3489-3500.

Rubinsztein, D. C., Marino, G., & Kroemer, G. (2011). Autophagy and aging. Cell, 146(5), 682-695.

Sakai, S.,Tanimoto, K., lmbe, A., Inaba, Y., Shishikura, K., Tanimoto, Y., ... & Hanafusa, T. (2016). Decreased (3-cell function is associated with reduced skeletal Muscle mass in Japanese subjects without diabetes. PloS one, 11(9), e0l 62603.

Salminen, A., Kaarniranta, K., & Kauppinen, A. (2016). AMPK and HIF signaling pathways regulate both longevity and cancer growth: the good news and the bad news about survival mechanisms. Biogerontology,17(4), 655-680.

Sridharan, S., Jain, K., & Basu, A. (2011). Regulation of autophagy by kinases. Cancers, 3(2), 2630-2654.

Su,J., Zhou, L., Kong, X., Yang, X., Xiang, X., Zhang, Y.,

... & Sun, L. (2013). Endoplasmic reticulum is at the crossroads of autophagy, inflammation, and apoptosis signaling pathways and participates in the pathogenesis of diabetes mellitus. Journal of diabetes research, 2013.

Takahashi, A., Kimura, T., Takabatake, Y., Namba, T., Kaimori, J., Kitamura, H., ... & Yoshimori, T. (2012). Autophagy guards against cisplatin-induced acute kidney injury. The American journal of pathology, 180(2), 517-525.

Tanaka, Y., Kume, S., Kitada, M., Kanasaki, K., Uzu, T., Maegawa, H., & Koya, D. (2011). Autophagy as a therapeutic target in diabetic nephropathy. Experimental diabetes research, 2012.

Tian, J., Lian, F., Yang, L., & Tong, X. (2018). Evaluation of the C hinese herbal medicine J inlida in type 2 diabetes patients based on stratification: Results of sub-group analysis from a 12-week trial.Journal of diabetes, 10(2), 112-120.

Viecceli, C., Remonti, L. R., Hirakata, V. N., Mastella,

L. S., Gnielka, V., Opperman, M. L. R., ... & Reichelt, A.

J. (2017). Weight gain adequacy and pregnancy outcomes in gestational diabetes: a meta­ analysis. Obesity reviews, 18(5), 567-580.

Wang, S., Sun, Q. Q., Xiang, B., & Li, X. J. (2013).

Pancreatic is let cell autophagy during aging in rats. Clinical and Investigative Medicine, E72-E80.

Wang, Y., Li, Y. B., Yin, J. J., Wang, Y., Zhu, L.B., Xie, G.

Y., & Pan, S. H. (2013). Autophagy regulates inflammation following oxidative injury in diabetes. Autophagy, 9(3), 272-277.

Wong, P., Weiner, M. G., Hwang, W. T., & Yang, Y. X. (2012). Insulin therapy and colorectal adenomas in patients with diabetes mellitus. Cancer Epidemiology and Prevention Biomarkers, 21(10), 1833-1840.

Yang, C., Kaushal, V., Shah, S. V., & Kaushal, G. P. (2008). Autophagy is associated with apoptosis in cisplatin injury to renal tubular epithelial cells. American Journal of Physiology-Renal Physiology, 294(4), F777-F787.

Yang, C., Kaushal, V., Shah, S. V., & Kaushal, G. P. (2008). Autophagy is associated with apoptosis in cisplatin injury to renal tubular epithelial cells. American Journal of Physiology-Renal Physiology, 294(4), F777-F787.

Yang, J. S., Lu, C. C., Kuo, S. C., Hsu, Y. M., Tsai, S. C.,

Chen, S. Y., ... & Lin, W. D. (2017). Autophagy and its link to type II diabetes mellitus. Biomedicine, 7(2).

Yang, L., Li, P., Fu, S., Calay, E. S., & Hotamisligil, G. S. (2010). Defective hepatic autophagy in obesity promotes ER stress and causes insulin resistance. Cell metabolism, 11(6),467-478.

Yang, Y. X., Hennessy, S., & Lewis, J. D. (2004). Insulin therapy and colorectal cancer risk among type 2 diabetes mellitus patients. Gastroenterology, 127(4), 1044-1050.

Zatalia, S. R., & Sanusi, H. (2013). The role of antioxidants in the pathophysiology, complications, and management of diabetes mellitus. Acta medica lndonesiana, 45(2), 141-147.

Zhou, L., Zhang, J., Fang, Q., Liu, M., Liu, X., Jia, W., ... & Liu, F. (2009). Autophagy-mediated insulin receptor down-regulation contributes to endoplasmic reticulum stress-induced insulin resistance. Molecular pharmacology, 76(3), 596-

603.

Zou, D., Ye, Y., Zou, N., & Yu, J. (2017). Analysis of risk factors and their interactions in type 2 diabetes mellitus: A cross?sectional survey in Guilin, China. Journal of diabetes investigation,8(2), 188-194.