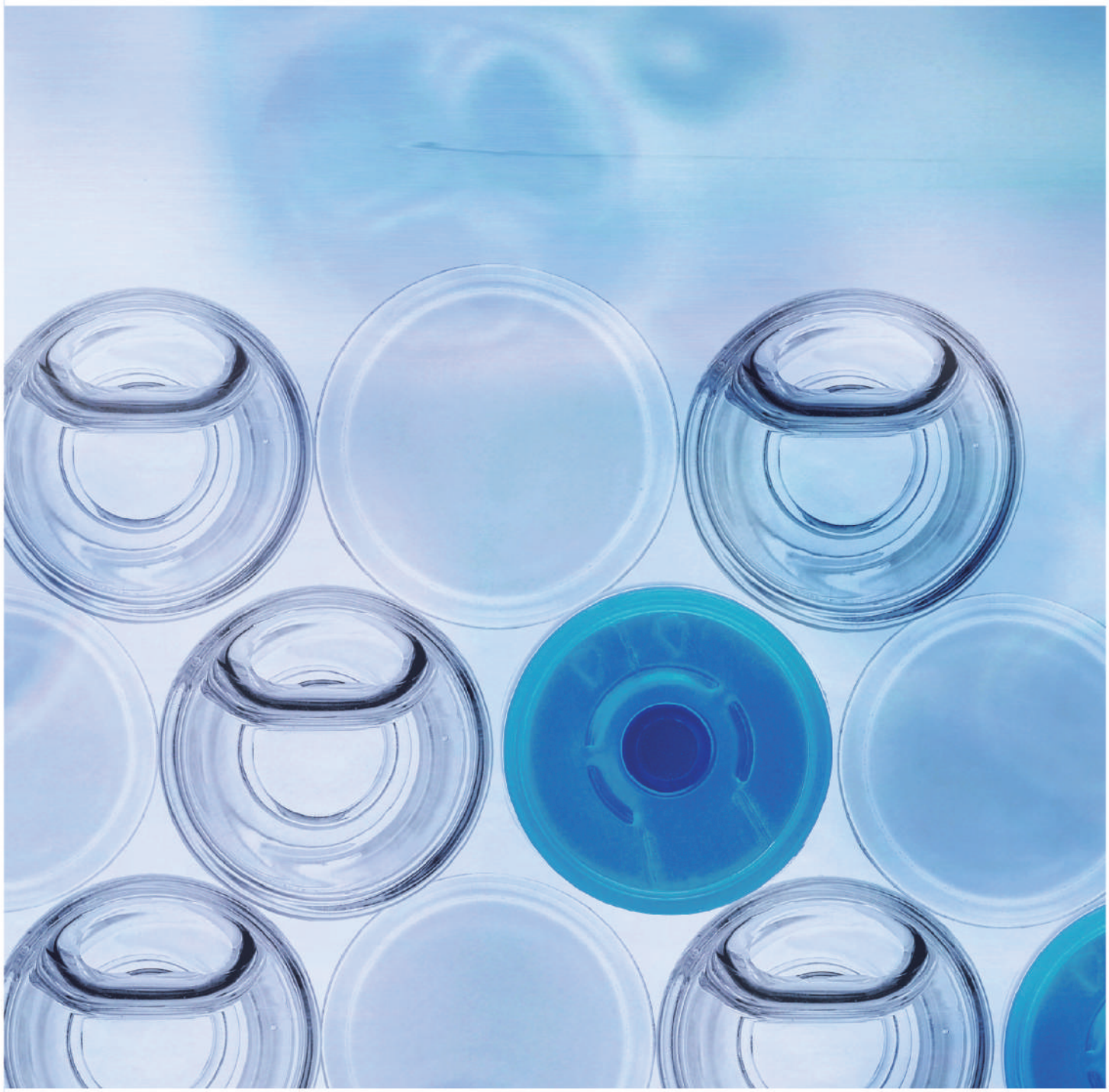
Journal of Endocrinology Research

Volume 1 | Issue 1 | 2019 April | ISSN 2630-5224 (Online)



BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Volume 1 Issue 1 • April 2019 • ISSN 2630-5224 (Online)

Journal of Endocrinology Research

BILINGUAL PUBLISHING CO.

Pioneer of Global Academics Since 1984

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Volume 1 | Issue 1 | April 2019 | Page 1-32
Journal of Endocrinology Research

Contents

Article

8 **Phosphorylation of Protein Kinase Akt by Mtorc2 in Peripheral Blood Mononuclear Cells of Patients with Cancer and Diabetes**
Ya Li, Weiguo Ma, Jiao Bai, Chuanqing Xie, Yuanyuan Huo

16 **Managing diabetes mellitus in underserved subjects of Western China using a telemedicine system— A clinical trial**
Manuel Ojea Rúa

25 **An Analysis of Clinical Characters of Inpatients with Infection in the Department of Endocrinology**
Jianying Zhang

Review

1 **An Updated Mini Review of Acute and Chronic Responses to Exercise Training-induced Irisin in Browning of White Fat**
Sílvia Rocha-Rodrigues, Bruno Silva

13 **Application Analysis of Diabetes Health Education in Endocrinology Nursing**
Yu Tao

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

REVIEW

An Updated Mini Review of Acute and Chronic Responses to Exercise Training-induced Irisin in Browning of White Fat

Sílvia Rocha-Rodrigues[1,2*] Bruno Silva[1,3]

1. Polytechnic Institute of Viana do Castelo, School of Sport and Leisure, Melgaço, Portugal
2. Laboratory of Metabolism and Exercise, Research Centre in Physical Activity, Health and Leisure (CIAFEL), Faculty of Sport Sciences, University of Porto, Portugal
3. Research Center in Sports Sciences, Health and Human Development (CIDESD), Vila Real, Portugal

ARTICLE INFO

Article history
Received: 20 March 2019
Accepted: 23 April 2019
Published Online: 30 April 2019

Keywords:
Hormones
Exercise
PGC-1α
UCP1

ABSTRACT

Nowadays, is well established that the benefits induced by exercise training (ET) affects not only skeletal muscle, but also other non-contractile organs over time. One potential mechanism underlying this crosstalk is the synthesis and secretion of several biological active factors, such as irisin, by muscle contractile activity. This hormone has been described to be able to induce a brown adipocyte-like phenotype in white adipose (WAT), increase whole-body metabolic rate, and therefore prevent and/or treat obesity-related metabolic diseases. Thus, the modulatory impact of ET on WAT may also occur through skeletal muscle - adipose organ axis. In this review, we summarize the acute and chronic adaptations to ET-induced irisin synthesis and secretion on the development of browning of white fat and, thus, providing an overview of the potential preventive and therapeutic role of ET on the obesity-related underlying pathways.

1. Introduction

Exercise training (ET) represents an important part in the increase of energy expenditure in active humans, stimulates fat mass loss and helps to maintain lean mass, besides promoting positive effects on the physiological function of hormones [1]. Accumulating evidence show that distinct ET modalities, such as endurance, strength and high-intensity interval training (HIIT), have a significant effect on reducing visceral fat accumulation [2-5] as well as adipocyte disturbances induced by obesity. Thus, contributing to systemic metabolic improvements through a favorable dynamics changes in white adipose tissue (WAT) morphology and metabolism [6-9], including a brown adipocyte-like phenotype [10-12]. This phenotype has been characterized by a greater capacity for thermogenic stimulation, as demonstrated by elevated uncoupled protein 1 (UCP1) expression and other brown adipocyte-specific genes [10-11, 13], converting these cells into more metabolically active cells, which in turn, burn more calories[14]. The presence of this type of cells opens attractive perspectives to treat obesity and related metabolic disorders.

Based on current state of knowledge, ET stimulates the production and secretion of several biological factors in skeletal muscle, such as irisin, whose effects can be local and/or far-reaching organs/tissues, like white adipose tis-

**Corresponding Author:*
Sílvia Rocha-Rodrigues,
Escola Superior Desporto e Lazer; Complexo Desportivo e de Lazer Comendador Rui Solheiro, 4960-320 Melgaço, Viana do Castelo, Portugal;
Email: silviadarocharodrigues@gmail.com

 DOI: https://doi.org/10.30564/jer.v1i1.570

sue (WAT), liver, heart, and brain in distinct animal models [15-17]. Thus, skeletal muscle has been recognized as endocrine organ. The present review highlights the prominent role of skeletal muscle-induced irisin in browning of white fat in response to acute and chronic adaptations induced by ET to better understand its regulation in skeletal muscle and its possible systemic and tissue modulatory effects on WAT and its potential application in combating metabolic diseases.

2. Exercise Training-regulated Myokines to Induce Browning of White Fat

Mechanistically, muscle contractile activity induces local paracrine-mediated actions on several signaling pathways involved on its structure and metabolism and also produces and secretes myokines, which act in an endocrine-like fashion on distant organs and tissues, including WAT [18]. Particularly, some myokines alter the metabolic phenotype of WAT by inducing browning, fatty acid oxidation and improving insulin sensitivity [10, 12-13, 19-20]. Therefore, myokines likely provide a conceptual basis to understand, at least in part, the modulatory impact of ET on WAT, e.g. the cross-talk between skeletal muscle and adipose organ axis, which is of particular interest in the context of obesity and metabolic disorders. Evidence have been supported that ET stimulates several myokines secretion by skeletal muscle, including β-aminoisobutyric acid (BAIBA) [21], brain-derived neurotrophic factor (BDNF) [22], IL-6 [17], meterion-like [23] or irisin [10]. Once released into the bloodstream, they can operate upon distant organs in a hormone-like fashion and may drive important *stimuli* ultimately leading to browning of white fat. Roberts and colleagues [21] identified BAIBA as a myokine able to increase the expression of brown adipocyte–specific genes in white adipocytes *in vitro* and *in vivo* by a peroxisome proliferator-activated receptor α-dependent mechanism. This myokine also improved glucose homeostasis in mice and induced a brown adipose–like phenotype in human pluripotent stem cells [21]. Meteorin-like is mainly induced in response to strength training and peroxisome proliferator-activated receptor gamma coactivator 1α (PGC-1α)4 overexpression, which promotes activation of M2 macrophages and catecholamines production from these cells to induce browning effects [23] and sustain adaptive thermogenesis [24]. An overexpression of the *Il6* mediated by ET increased the UCP1 gene and protein expression in rat brown and white adipose tissue [17, 25]. Moreover, the ET-induced increase in skeletal muscle IL-6 levels was strongly correlated with brown adipocyte-like phenotype markers expression and its regulators in obese rats [26]. Despite de potential role of these myokines mediating the beneficial effects of ET, irisin is the one that has received more attention in literature due to its physiological functions and potential applications in health and in a variety of metabolic diseases. Irisin is derived from fibronectin type III domain-containing protein 5 (FNDC5), membrane-spanning protein highly expressed in skeletal muscle, proteolytically cleaved and released into circulation as a powerful messenger reaching other distant organs, such as WAT [15-16]. Indeed, several studies have been supported that irisin induces skeletal muscle hypertrophy [27], energy expenditure by stimulating the brown-like phenotype in WAT [11-12], and improved glucose homeostasis by reducing insulin resistance [28-29]. In the original study, Bostrom *et al*[10] reported that *in vivo* and *in culture* brown adipocyte-like phenotype were mediated *via* the activation of the main metabolic regulator, PGC-1α, a well-known player on skeletal muscle adaptive response to ET [30-32]. As an important transcriptional coactivator involved in energy metabolism, elevated levels of PGC-1α has been associated with an increased mitochondrial content [11], fatty acid oxidation as well as brown adipocyte-like phenotype development in WAT [12, 33]. Moreover, the Sirtuin 1 (SIRT1), a NAD^+-dependent type III metabolic sensor, also seems to be closely involved in the regulation of these processes [30]. The SIRT1 binds to PPARγ and represses the transcriptional activation of PPARγ by binding to nuclear co-receptor/silencing mediator of retinoid and thyroid hormone receptor complex, resulting in the reduction of fat accumulation in WAT and higher level of non-esterified fatty acids (NEFA) in blood [34]. SIRT1-dependent deacetylation of Lys268 and Lys293 is required to recruit the brown adipose tissue (BAT) program activation and repression of visceral WAT genes associated with insulin resistance [35]. In response to 8-wks of ET, higher levels of SIRT1 was found associated to a brown-like phenotype development in WAT from obese rats [36].

2.1 Acute Skeletal Muscle Adaptations

Animal-based studies reported an increased skeletal muscle FNDC5 expression in response to acute bout of exercise [10, 37-38] while some found no alterations [39-42]. The study of Dehghani and colleagues [37], whose objective was to analyse the distinct types of muscle contractions, demonstrated that one bout of both concentric and eccentric exercises increased skeletal muscle PGC-1α and FNDC5 mRNA expression in skeletal muscle of BALB/C mice. Moreover, the eccentric exercised group benefited from a greater impact on PGC-1α and FNDC5 genes than the concentric exercised group, suggesting that a single bout of eccentric exercise has a notable impact

DOI: https://doi.org/10.30564/jer.v1i1.570

on myokines secretion and their regulators. This effect was attributed to muscular microscopic damage and the greater production of reactive oxygen species, in comparison with the concentric exercises [43]. After an acute exercise session, was reported no changes immediately and after 3h from acute submaximal bout of exercise at 70% maximal running velocity in *tibialisanterior* muscle [39]. While [40] and [42] showed that *gastrocnemius* FNDC5 mRNA expression decreased immediately after exercise session and remained unchanged 3h after submaximal and maximal treadmill running. On the other hand, mice *quadriceps femoris* and *triceps surae* muscles FNDC5 values displayed high levels 24 hours after cessation of ET bout [37]. Czarkowska-Paczek and colleagues [40] showed an increase of circulating irisin levels 3h after the end of treadmill running session with no alterations on FNDC5 levels. Other studies with rodents supported this idea revealing that circulating irisin levels were acutely overexpressed immediately after one bout of exercise [41, 44]. This acute response was possibly attributed to the commonly described ET-induced oxidative stress. Oxidative stress is known to stimulate p38 MAPK and the extracellular regulated protein kinase (ERK) [45-46], which in turn activates PGC-1α in skeletal muscle, an important regulator of FNDC5.

Evidence from human studies showed that FNDC5 mRNA expression was increased in endurance-trained athletes males with maximal oxygen consumption (VO_2 max) higher than 55 $mL^{-1}.kg^{-1}.min^{-1}$[47]. In response to an acute bout of high-intensity exercise [48] and strength exercises (5 sets of 10 repetitions until failure) [49], skeletal muscle FNDC5 and PGC-1α mRNA levels increased in healthy individuals.Although an increased FNDC5 has been detected without any changes in circulating irisin after ET [47, 49], acute increases in irisin levels have been widely reported in physically inactive individuals[10, 50-56]. In this line, Kraemer *et al* [54] found that plasma irisin levels increased during the course of a 90 min (60% of VO_2 max) treadmill running, reaching the peak values at 54 min while returned to baseline levels immediately post-exercise. Moreover, Norheim *et al*[56] reported a peak concentration of irisin after 45 min cycling without a concomitant increase in *Fndc*5 gene expression, which suggests that increases on irisin levels during acute exercise may be associated with protein *post-translational* modifications. Actually, the type, duration, and particularly the intensity of the ET sessions seems to influence the expression of circulating irisin. In fact, high-intensity exercise at 80% VO_2max for 20 min promoted greater irisin response comparatively to low-intensity exercise at 40% VO_2max for 40 min under similar energy consumption conditions [50]. Thus, circulating irisin levels increased when the muscle adenosine triphosphate (ATP) levels acutely dropped, but remain unchanged when muscle ATP content is restored, suggesting that irisin may contribute to ATP homeostasis [57]. Based on this hypothesis, the lack of irisin changes in some studies may be explained by the intensity as short-term low-to-moderate intensity ET induces low ATP depletion [57]. In this line, plasma irisin levels seem to be progressively elevated in response to increasing ET workloads as physically active individuals with higher VO_2max showed greater concentrations of irisin during maximal workload ET [50, 53, 55]. Collectively, data suggest that circulating irisin levels seem to be increased in response to acute intense ET in humans; however new insights into irisin regulation during ET are clearly needed. However, some inconsistencies may be related to interactions between irisin and other cytokines and hormones, for example IL-6, BDNF or adiponectin [58-60]. Moreover, other tissues, such as cardiomyocytes and purkinje cells of cerebellum [13, 59, 61], have been described to interfere with irisin metabolism/regulation, and should also be considered in future studies.

2.2 Chronic Skeletal Muscle Adaptations

In animal models, several studies have confirmed that chronic ET programs induced FNDC5 synthesis and subsequently release irisin into circulation that have impact on browning of white fat [10-13, 62]. Whereas some studies have not been able to recognize a consistent increase in the expression of FNDC5 mRNA [63] or plasma irisin levels [49, 64] after long-term ET program. Tiano et al 2015 [12] studied the contribution of distinct models of exercise, such as running, countercurrent swimming and voluntary running wheel, on irisin secretion and browning of white fat. For the treadmill and swimming models, mice showed a ~35% increase in serum irisin levels at 2nd week along with an increase in the area under the curve (AUC) over the 3rd week; however a voluntary running wheel model had no impact on irisin concentration. In the same study, only the treadmill-exercised mice showed an increased FNDC5 mRNA and protein expression in skeletal muscle. In response to 2-wks of treadmill running [12], the browning-related markers, such as PGC-1α; its downstream target UCP1, the major protein responsible for nonshivering thermogenesis; and PR domain containing 16, the transcriptional regulator of BAT differentiation [65] were increased in both subcutaneous and visceral fat depots. Moreover, a strength exercise program increased serum irisin and *soleus* FNDC5 levels in mice performed ladder climbing with tail weight 3 days *per* week for 12 weeks [66]. Xiong and colleagues [67] created a mouse model of *Fndc*5 mutation through transcription activator-like effec-

 DOI: https://doi.org/10.30564/jer.v1i1.570

tor nuclease-mediated DNA targeting. In response to 8-wks of treadmill running (60min.day^{-1}, 10% slope at constant 18min.m^{-1} velocity), the *Fndc*5 mutant mice exhibit lower VO_2max and attenuate ET-induced browning of white fat when compared with exercised wild-type mice, providing genetic evidence that *Fndc*5 is required for exercise-induced browning of WAT in mice.

Several studies reported that irisin remained stable after an ET program, but the duration of high levels after exercise remains unresolved [38, 40, 68]. Another aspects that need further investigation are the effects of different types and intensities of exercise on muscle metabolism and disruption at distinct ways, and in turn, on irisin concentrations [69-70]. Nevertheless, data from studies performed with humans are not so consistent. Some studies showed that chronic ET, strength or the combination of both models did not affect skeletal muscle FNDC5 [48-49] or circulating irisin [49, 63, 71] levels in sedentary healthy individuals or in children with obesity [72]. In contrast, other studies revealed an increased FNDC5 and PGC1α expression in response to 12-wks of combined endurance and strenght exercises [56]. A study using Gene Set Enrichment Analysis method showed that ET promoted several alterations on genes involved in metabolism, mitochondrial biogenesis, oxidative stress and signaling, membrane transport, cell stress, proteolysis, apoptosis, and replication [33], underlining the degree of plasticity of WAT and its prominent role in physiological whole-body adaptions to ET. Moreover, ET-induced browning of white fat is possibly associated with other myokines synthesis and secretion, including IL-6, BAIBA, BDNF, meteorin-like and others. Altogether, data suggest that irisin levels seem to be increased acutely and chronically in response to ET; however new understandings into irisin regulation during ET are clearly needed.

3. Conclusions

In summary, acute and chronic response to ET seems to have a crucial role in the synthesis and secretion of irisin from skeletal muscle to stimulate the browning of white fat and its main regulators (figure 1), which are determinant for improving metabolic function and energy expenditure, and, thus, preventing and/or counteracting obesity-related metabolic disorders.

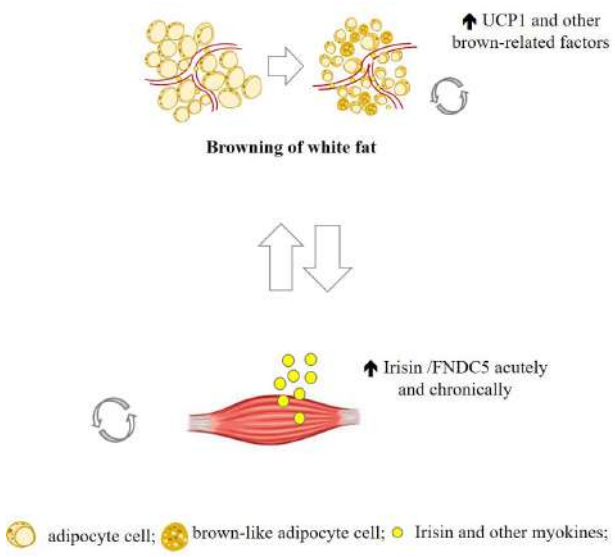


Figure 1: Summary of acute and chronic adaptations to ET-induced irisin secretion in browning of white fat.

Legend: FNDC5, fibronectin type III domain-containing protein 5; UPC1, uncoupled protein 1; © increase

References

[1] Hoffmann, C. and C. Weigert. Skeletal Muscle as an Endocrine Organ: The Role of Myokines in Exercise Adaptations. Cold Spring Harb Perspect Med, 2017, 7(11).

[2] Zhang, H., et al.. Comparable Effects of High-Intensity Interval Training and Prolonged Continuous Exercise Training on Abdominal Visceral Fat Reduction in Obese Young Women. J Diabetes Res, 2017, 5071740.

[3] Fatouros, I.G., et al.. Leptin and adiponectin responses in overweight inactive elderly following resistance training and detraining are intensity related. J Clin Endocrinol Metab, 2005, 90(11): 5970-7.

[4] Klimcakova, E., et al.. Dynamic strength training improves insulin sensitivity without altering plasma levels and gene expression of adipokines in subcutaneous adipose tissue in obese men. J Clin Endocrinol Metab, 2006, 91(12): 5107-12.

[5] Maillard, F., et al.. High-intensity interval training reduces abdominal fat mass in postmenopausal women with type 2 diabetes. Diabetes Metab, 2016.

[6] Dietz, P., et al.. Influence of exclusive resistance training on body composition and cardiovascular risk factors in overweight or obese children: a systematic review. Obes Facts, 2012, 5(4): 546-60.

[7] Bajer, B., et al.. Exercise associated hormonal signals as powerful determinants of an effective fat mass

DOI: https://doi.org/10.30564/jer.v1i1.570

loss. Endocr Regul, 2015, 49(3): 151-63.

[8] Leggate, M., et al.. Determination of inflammatory and prominent proteomic changes in plasma and adipose tissue after high-intensity intermittent training in overweight and obese males. J Appl Physiol, 2012, 112(8): 1353-60.

[9] Marcinko, K., et al.. High intensity interval training improves liver and adipose tissue insulin sensitivity. Mol Metab, 2015, 4(12): 903-15.

[10] Bostrom, P., et al.. A PGC1-alpha-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. Nature, 2012, 481(7382): 463-8.

[11] Rocha-Rodrigues, S., et al.. Effects of physical exercise on myokines expression and brown adipose-like phenotype modulation in rats fed a high-fat diet. Life Sci, 2016, 165: 100-108.

[12] Tiano, J.P., et al.. SMAD3 negatively regulates serum irisin and skeletal muscle FNDC5 and peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1alpha) during exercise. J Biol Chem, 2015, 290(12): 7671-84.

[13] Roca-Rivada, A., et al.. FNDC5/irisin is not only a myokine but also an adipokine. PLoS One, 2013, 8(4): e60563.

[14] Pardo, M., et al.. Association of irisin with fat mass, resting energy expenditure, and daily activity in conditions of extreme body mass index. Int J Endocrinol, 2014, 857270.

[15] Mo, L., et al.. Irisin Is Regulated by CAR in Liver and Is a Mediator of Hepatic Glucose and Lipid Metabolism. Mol Endocrinol, 2016, 30(5): 533-42.

[16] Shanaki, M., et al.. Lower circulating irisin is associated with nonalcoholic fatty liver disease and type 2 diabetes. Diabetes Metab Syndr, 11 Suppl 1, 2017: S467-s472.

[17] Knudsen, J.G., et al.. Role of IL-6 in exercise training- and cold-induced UCP1 expression in subcutaneous white adipose tissue. PLoS One, 2014, 9(1): e84910.

[18] Rodríguez, A., et al.. Cross-talk between adipokines and myokines in fat browning. Acta Physiol (Oxf), 2016.

[19] Lee, P., et al.. Irisin and FGF21 are cold-induced endocrine activators of brown fat function in humans. Cell Metab, 2014, 19(2): 302-9.

[20] Wu, M.V., et al.. Thermogenic capacity is antagonistically regulated in classical brown and white subcutaneous fat depots by high fat diet and endurance training in rats: impact on whole-body energy expenditure. J Biol Chem, 2014, 289(49): 34129-40.

[21] Roberts, L.D., et al.. beta-Aminoisobutyric acid induces browning of white fat and hepatic beta-oxidation and is inversely correlated with cardiometabolic risk factors. Cell Metab, 2014, 19(1): 96-108.

[22] Cao, L., et al.. White to brown fat phenotypic switch induced by genetic and environmental activation of a hypothalamic-adipocyte axis. Cell Metab, 2011, 14(3): 324-38.

[23] Rao, R.R., et al.. Meteorin-like is a hormone that regulates immune-adipose interactions to increase beige fat thermogenesis. Cell, 2014, 157(6): 1279-91.

[24] Nguyen, K.D., et al.. Alternatively activated macrophages produce catecholamines to sustain adaptive thermogenesis. Nature, 2011, 480(7375): 104-8.

[25] Li, G., et al.. Induction of uncoupling protein 1 by central interleukin-6 gene delivery is dependent on sympathetic innervation of brown adipose tissue and underlies one mechanism of body weight reduction in rats. Neuroscience, 2002, 115(3): 879-89.

[26] Rocha-Rodrigues, S., et al.. Effects of physical exercise on myokines expression and brown adipose-like phenotype modulation in rats fed a high-fat diet. Life Sci, 2016.

[27] Reza, M.M., et al.. Irisin is a pro-myogenic factor that induces skeletal muscle hypertrophy and rescues denervation-induced atrophy. Nat Commun, 2017, 8(1): 1104.

[28] Lopez-Legarrea, P., et al.. Higher baseline irisin concentrations are associated with greater reductions in glycemia and insulinemia after weight loss in obese subjects. Nutr Diabetes, 2014, 4, e110.

[29] Ronn, T., et al.. Extensive changes in the transcriptional profile of human adipose tissue including genes involved in oxidative phosphorylation after a 6-month exercise intervention. Acta Physiol (Oxf), 2014, 211(1): 188-200.

[30] Canto, C. and J. Auwerx. PGC-1alpha, SIRT1 and AMPK, an energy sensing network that controls energy expenditure. Curr Opin Lipidol, 2009, 20(2): 98-105.

[31] Ringholm, S., et al.. PGC-1alpha is required for exercise- and exercise training-induced UCP1 up-regulation in mouse white adipose tissue. PLoS One, 2013, 8(5): e64123.

[32] Thirupathi, A. and C.T. de Souza. Multi-regulatory network of ROS: the interconnection of ROS, PGC-1 alpha, and AMPK-SIRT1 during exercise. J Physiol Biochem, 2017, 73(4): 487-494.

[33] Stanford, K.I., et al.. A novel role for subcutaneous adipose tissue in exercise-induced improvements in glucose homeostasis. Diabetes, 2015, 64(6): 2002-14.

[34] Picard, F., et al.. Sirt1 promotes fat mobilization in

 DOI: https://doi.org/10.30564/jer.v1i1.570

white adipocytes by repressing PPAR-gamma. Nature, 2004, 429(6993): 771-6.

[35] Qiang, L., et al.. Brown remodeling of white adipose tissue by SirT1-dependent deacetylation of Ppargamma. Cell, 2012, 150(3): 620-32.

[36] Rocha-Rodrigues, S., et al.. Physical exercise remodels visceral adipose tissue and mitochondrial lipid metabolism in rats fed a high-fat diet. Clin Exp Pharmacol Physiol, 2016.

[37] Dehghani, M., et al.. A comparative study on the effects of acute and chronic downhill running vs uphill running exercise on the RNA levels of the skeletal muscles PGC1-alpha, FNDC5 and the adipose UCP1 in BALB/c mice. Gene, 2018, 679: 369-376.

[38] Liu, J., et al.. Effects of high-intensity treadmill training on timeliness and plasticity expression of irisin in mice. Eur Rev Med Pharmacol Sci, 2015, 19(12):2168-73.

[39] Lally, J.S., et al.. Skeletal muscle AMPK is essential for the maintenance of FNDC5 expression. Physiol Rep, 2015, 3(5).

[40] Czarkowska-Paczek, B., et al.. One session of exercise or endurance training does not influence serum levels of irisin in rats. J Physiol Pharmacol, 2014, 65(3): 449-54.

[41] Brenmoehl, J., et al.. Irisin is elevated in skeletal muscle and serum of mice immediately after acute exercise. Int J Biol Sci, 2014, 10(3): 338-49.

[42] Quinn, L.S., et al.. Circulating irisin levels and muscle FNDC5 mRNA expression are independent of IL-15 levels in mice. Endocrine, 2015.

[43] Stupka, N., et al.. Cellular adaptation to repeated eccentric exercise-induced muscle damage. J Appl Physiol (1985), 2001, 91(4): 1669-78.

[44]Samy, D.M., et al.. Circulating irisin concentrations in rat models of thyroid dysfunction -- effect of exercise. Metabolism, 2015, 64(7): 804-13.

[45] Sanchis-Gomar, F. and C. Perez-Quilis. The p38-PGC-1alpha-irisin-betatrophin axis: Exploring new pathways in insulin resistance. Adipocyte, 2014, 3(1): 67-8.

[46] Zhang, Y., et al.. Irisin stimulates browning of white adipocytes through mitogen-activated protein kinase p38 MAP kinase and ERK MAP kinase signaling. Diabetes, 2014, 63(2): 514-25.

[47] Vosselman, M.J., et al.. Low brown adipose tissue activity in endurance-trained compared with lean sedentary men. Int J Obes (Lond), 2015.

[48] Nygaard, H., et al.. Irisin in blood increases transiently after single sessions of intense endurance exercise and heavy strength training. PLoS One, 2015, 10(3): e0121367.

[49] Pekkala, S., et al.. Are skeletal muscle FNDC5 gene expression and irisin release regulated by exercise and related to health? J Physiol, 2013, 591(Pt 21): 5393-400.

[50] Tsuchiya, Y., et al.. High-intensity exercise causes greater irisin response compared with low-intensity exercise under similar energy consumption. Tohoku J Exp Med, 2014, 233(2): 135-40.

[51] Miyamoto-Mikami, E., et al.. Endurance training-induced increase in circulating irisin levels is associated with reduction of abdominal visceral fat in middle-aged and older adults. PLoS One, 2015, 10(3): e0120354.

[52] Jedrychowski, M.P., et al.. Detection and Quantitation of Circulating Human Irisin by Tandem Mass Spectrometry. Cell Metab, 2015.

[53] Huh, J.Y., et al.. Exercise-induced irisin secretion is independent of age or fitness level and increased irisin may directly modulate muscle metabolism through AMPK activation. J Clin Endocrinol Metab, jc20141437, 2014.

[54] Kraemer, R.R., et al.. A transient elevated irisin blood concentration in response to prolonged, moderate aerobic exercise in young men and women. Horm Metab Res, 2014, 46(2): 150-4.

[55] Daskalopoulou, S.S., et al.. Plasma irisin levels progressively increase in response to increasing exercise workloads in young, healthy, active subjects. Eur J Endocrinol, 2014, 171(3): 343-52.

[56] Norheim, F., et al.. The effects of acute and chronic exercise on PGC-1alpha, irisin and browning of subcutaneous adipose tissue in humans. FEBS J, 2014, 281(3): 739-49.

[57] Egan, B. and J.R. Zierath. Exercise metabolism and the molecular regulation of skeletal muscle adaptation. Cell Metab, 2013, 17(2): 162-84.

[58] Pedersen, B.K. and M.A. Febbraio. Muscles, exercise and obesity: skeletal muscle as a secretory organ. Nat Rev Endocrinol, 2012, 8(8): 457-65.

[59] Wrann, C.D., et al.. Exercise induces hippocampal BDNF through a PGC-1alpha/FNDC5 pathway. Cell Metab, 2013, 18(5): 649-59.

[60] Comassi, M., et al.. Acute effects of different degrees of ultra-endurance exercise on systemic inflammatory responses. Intern Med J, 2015, 45(1): 74-9.

[61] Raschke, S. and J. Eckel. Adipo-myokines: two sides of the same coin--mediators of inflammation and mediators of exercise. Mediators Inflamm, 2013, 320724.

[62] Guilford, B.L., et al.. Increased FNDC5 is associated with insulin resistance in high fat-fed mice. Physiol Rep, 2017, 5(13).

DOI: https://doi.org/10.30564/jer.v1i1.570

[63] Timmons, J.A., et al.. Is irisin a human exercise gene? Nature, 488(7413), p. E9-10; discussion E10-1, 2012.

[64] Wu, J., et al.. Beige adipocytes are a distinct type of thermogenic fat cell in mouse and human. Cell, 2012, 150(2): 366-76.

[65] Seale, P., et al.. PRDM16 controls a brown fat/skeletal muscle switch. Nature, 2008, 454(7207): 961-7.

[66] Kim, H.J., et al.. Resistance exercise training increases the expression of irisin concomitant with improvement of muscle function in aging mice and humans. Exp Gerontol, 2015, 70: 11-17.

[67] Xiong, Y., et al.. Fndc5 loss-of-function attenuates exercise-induced browning of white adipose tissue in mice. Faseb j, fj201801754RR, 2019.

[68] Seo, D.Y., et al.. Effects of aged garlic extract and endurance exercise on skeletal muscle FNDC-5 and circulating irisin in high-fat-diet rat models.Nutr Res Pract, 2014, 8(2): 177-82.

[69] Huh, J.Y., et al.. Irisin in response to exercise in humans with and without metabolic syndrome.J Clin Endocrinol Metab, 2015, 100(3): E453-7.

[70] Bostrom, P.A., et al.. Irisin in humans: recent advances and questions for future research.Metabolism, 2014, 63(2): 178-80.

[71] Hecksteden, A., et al.. Irisin and exercise training in humans - results from a randomized controlled training trial.BMC Med, 2013, 11: 235.

[72] Palacios-Gonzalez, B., et al.. Irisin levels before and after physical activity among school-age children with different BMI: a direct relation with leptin.Obesity (Silver Spring), 2015, 23(4): 729-32.

 DOI: https://doi.org/10.30564/jer.v1i1.570

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

ARTICLE

Phosphorylation of Protein Kinase Akt by Mtorc2 in Peripheral Blood Mononuclear Cells of Patients with Cancer and Diabetes

Vatseba T.S. Sokolova L.K. Pushkarev V.V. Kovzun O.I. Pushkarev V.M.* Guda B.B. Tronko M.D.

SI "V.P. Komisarenko Institute of endocrinology and metabolism of NAMS of Ukraine", Kyiv, Vyshgorodska st, 69, 04114, Ukraine

ARTICLE INFO

Article history
Received: 20 March 2019
Accepted: 23 April 2019
Published Online: 30 April 2019

Keywords:
Akt, mTORC2
P70S6K1
Peripheral blood mononuclear cell
Cancer
Diabetes

ABSTRACT

Akt/mTOR/p70S6K1 signaling pathway plays an important role in the pathogenesis of cancer and diabetes. Macrophages and lymphocytes are involved in the pathogenesis of diabetes, diabetic atherosclerosis, formation of insulin resistance as well as immune response to cancer and tumor maintenance. The aim of the study was to determine the Akt activation by mTORC2 in peripheral blood mononuclear cell (PBMC) of patients with type 2 diabetes and cancer. The following groups were studied: control group, patients with type 2 diabetes, cancer patients and patients with both cancer and diabetes. The amounts of phospho-Akt (p-S473) and phospho-p70S6K1 (p-T389) were determined using ELISA kits. The amount of phosphorylated Akt significantly increases in PBMC of patients with cancer. There was no effect in PBMC from patients with type 2 diabetes and significant decrease in the amount of phospho-Akt in PBMC of the patients group both with cancer and diabetes. p70S6K1 activation was observed in PBMC of the groups 2 and 3 patients. Thus, chronic diseases such as type 2 diabetes and cancer can affect the signaling mechanisms in blood cells. The state of Akt phosphorylation in leukocytes can indicate the activity of mTORC1 and its substrates, which may be important for the evaluation of the pathological process and the efficacy of the drugs.

1. Introduction

Protein kinase Akt (v-act murine thymoma viral oncogene homolog) plays a key role in regulation of cell growth, homeostasis, survival, proliferation and metabolism [1]. Akt is activated by PDK1 via T308 phosphorylation in the T-loop of the catalytic domain and by rapamycin-insensitive mTORC2 through S473 phosphorylation in the hydrophobic region on the C-tail. Akt enhances insulin-dependent translocation of GLUT-4 and glucose transport, and activates downstream protein kinases mTORC1 and p70S6K that control protein synthesis and biogenesis of ribosomes. Dysregulation of the PI3K/Akt/mTOR/p70S6K signaling lead to severe diseases such as cancer, obesity and type 2 diabetes (T2D).

The peripheral blood mononuclear cell (PBMC) include several types of cells that play a significant role in the development of pathological conditions such as diabe-

**Corresponding Author:*
Pushkarev V.M.,
SI "V.P. Komisarenko Institute of endocrinology and metabolism of NAMS of Ukraine", Kyiv, Vyshgorodska st, 69, 04114, Ukraine;
E-mail: pushkarev.vm@gmail.com

DOI: https://doi.org/10.30564/jer.v1i1.674

tes and cancer [2-4]. The pathway PI3K/Akt is involved in the activation of macrophages and lymphocytes, secretion of cytokines, initiation of inflammatory processes and immune surveillance failure [5].

The serine/threonine kinase mTOR forms two different signaling complexes, mTORC1 and mTORC2, by binding several proteins. mLST8, DEPTOR, and Tti1/Tel2 complex are contained in both mTORC1 and mTORC2. RAPTOR and PRAS40 are specific to mTORC1, and RICTOR, mSin1 and PROCTOR 1/2 are specific to mTORC2. These kinase complexes interact with specific substrates and initiate various signaling events that modulate cellular functions. mTORC1 controls the main cellular anabolic processes, linking them to the availability of nutrients; mTORC2 phosphorylates and activates Akt, controlling cellular metabolism, survival and organization of the cytoskeleton. The actions of mTORC1, mTORC2 and Akt are closely intertwined in some contexts. Thus, in growing and proliferating cells, Akt is a critical activator of mTORC1, and activated mTORC1 mediates by feedback inhibition of mTORC2 and Akt. Therefore, mTORC1, mTORC2 and Akt constitute a key metabolic signaling network that coordinates many of the metabolic processes in growing, proliferating cells and metabolic tissues [6, 7].

The aim of the work was to determine the activation of Akt, the main effector kinase of PI3K/Akt/mTORC/p70S6K cascade, in PBMC of patients with T2D and cancer.

2. Materials and methods

The study was conducted in the diabetology department of the Institute. All patients signed informed consent to conduct further diagnostic and research study. Immediately after collection, the blood was layered on histopaque 1077 (Sigma, USA), centrifuged at 500 g (RT) for 15 min in the 15 ml conical Falcon™ tubes, the PBMC collected were washed in PBS and frozen at -80 °C until use. For determination of phospho-Akt1/2/3 (p-S473) and phospho-p70S6K1 (p-T389) amounts ELISA kits 85-86046 and 85-86053 respectively (Invitrogen, USA) were used. The studies were carried out in triplets. The cells were lysed in the extraction buffer with inhibitors of proteases and phosphatases from the kits. The protein concentration in the lysate was determined using BCA protein assay kit (Novagen, USA). The measurements were carried out on a microplate reader (Bio-tek Instruments, USA) at a wavelength of 450 nm.

The OD values of samples obtained are located on the calibration curve satisfactorily coinciding with a theoretical line that indicates no scattering of the data.

The results of the study are presented as M ± SD, n = 6 - 15. To compare the data groups One-Way ANOVA and Student's *t*-test (with statistical module of Origin 7.0 software) were used. Values of $P \leq 0.05$ were considered as significant.

The following groups were investigated: 1 – control group (n = 6) – healthy people, representative by age; 2 – patients with T2D (n = 12); 3 – cancer patients (n = 15); 4 – patients with both cancer and T2D (n = 7). Patients with T2D used combined treatment with insulin and metformin. Patients with diabetes (groups 2 and 4) have HbA1c level – 7.4-9.2%. The patients of groups 3 and 4 have uterine, breast and bowel cancers. All examined patients belonged to the Caucasian race, age was in range from 46 to 72. Gender and BMI characteristics of the patients are shown in the Table 1. The patients and a control group were selected with close age and body mass index.

3. Results and Its Discussion

The PBMC include monocytes/macrophages and lymphocytes (T-cell, B-cell, NK) involved in the processes of cellular and humoral immunity. PI3K/Akt/mTOR is a signaling cascade that largely determines the functioning of these blood cells in diabetes and malignant neoplasm [2-4, 8].

As shown in Figure 1"2", the content of Akt phosphorylated by mTORC2 does not differ from the control in the group of patients with diabetes.

Table 1. Gender and BMI characteristics of the patients

	I group		II group		III group		IV group	
	Men (n=3)	**Women (n=3)**	**Men (n=6)**	**Women (n=6)**	**Men (n=5)**	**Women (n=10)**	**Men (n=3)**	**Women (n=4)**
Age (years)	57.0±1.70	60.0±3.71	60.17±2.94	57.50±1.17	60.4±5.8	59.2±2.19	61.3±2.12	55.5±1.9
BMI (кg/m2)	27.39±2.37	30.22±1.13	32.44±1.25	32.12±1.49	30.75±1.46	32.47±0.93	32.8±1.6	29.2±1.8

 DOI: https://doi.org/10.30564/jer.v1i1.674

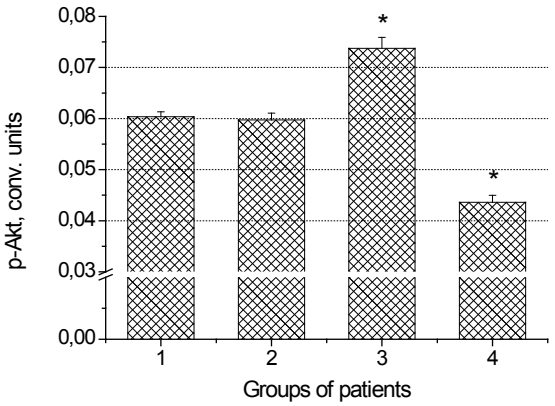


Figure1. Amount of phospho-Akt1/2/3 (p-S473) in peripheral blood mononuclear cell of patients with cancer and diabetes

PBMC cells were isolated from the blood, lysed in the extraction buffer with inhibitors of proteases and phosphatases and phospho-Akt1/2/3 amounts was determined using of ELISA kits.

All patients belonged to the Caucasian race with age in range from 46 to 72. The patients and a control group were selected with close age and body mass index.

1 - control (n = 6); 2 - patients with type 2 diabetes (n = 12); 3 - cancer patients (n = 15); 4 patients with both diabetes and cancer (n = 7). To compare the data groups One-Way ANOVA and Student's *t*-test were used. M ± SD, * - the difference from the control group is significant, P <0,05.

It is known that in tissues of patients with T2D, as a result of prolonged exposure to high doses of insulin, the activity of Akt and its downstream kinases, mTORC1 and p70S6K, is enhanced, resulting in phosphorylation of key adapter protein IRS-1 (S307 and other amino acid residues), its degradation, impaired insulin signaling and, consequently, insulin resistance [9]. The level of phosphorylated Akt in PBMC of patients with T2D is probably determined by the ratio of metformin and insulin effects. Metformin activates the AMPK and inhibits mTORC1 activity, but improves insulin signaling. Insulin activates the signaling cascade of PI3K/Akt/mTORC1 and inhibits the activation of AMPK by metformin [10]. The final result of the interaction of these drugs and the signaling mechanisms induced is the state of Akt activity.

At the same time, in PBMC of patients with T2D we observed 143.4±18.9% (M±SD) enhancement of p70S6K1 phosphorylation (p-T389), indicating the activity of the PI3K/Akt/mTORC1/p70S6K1 pathway. Obviously, mTORC2 does not participate in the activation of Akt in this context.

It has been shown earlier that PBMC of patients with systemic insulin resistance express matrix metalloproteinase 9, hypoxia-induced factor 1α, split AMPKα, IRS-1 phosphorylated on S312, Akt phosphorylated on T308, and TLR4 [11, 12]. TLR4 activation in macrophages caused increased expression of scavenger receptors via mTORC2/Akt/mTORC1 signaling cascade which accelerates oxLDL uptake and foam cell formation – key event in the pathogenesis of atherosclerosis [13].

In PBMC of cancer patients enhancement of Akt phosphorylation (p-S473) was observed (Figure 1.3). The phosphorylation level of p70S6K is also increased to 120.6±9.17 %. Thus, mTORC2 may contribute in activation of mTORC1 and its downstream targets.

It is well established that the PI3K/Akt pathway is frequently dysregulated in cancer [14]. Unlike mTORC1, the regulation of mTORC2 and its functional contribution to cancerogenesis remain poorly understood. Recent studies demonstrate that an intact mTORC2 is required for the activation of Akt *in vitro* and *in vivo* [15]. mTORC2 combines the effects of extracellular growth factors and survival signals with pathways controlling cell growth and proliferation. mTORC2 binds extracellular signals (such as growth and cytokine factors) with mTORC1 activation, cell proliferation and survival through direct phosphorylation of the protein kinase Akt on Ser473 in its hydrophobic C-tail that is required for its maximum activation [16]. Both complexes control each other, since the Akt regulates the phosphorylation of PRAS40, which disinhibits the activity of mTORC1, while p70S6K regulates Sin1 to modulate the activity of mTORC2 [17].

It has been shown that loss of mTORC2 in macrophages suppresses tumor growth. The mTORC2-mediated pathway comprising PI3K and Akt, is important for the accented glucose metabolism, promotes the activation of M2 macrophages (alternatively activated macrophages) and involves M-CSF as an upstream activator. M2 macrophages function in constructive processes, such as wound healing and tissue repair, and disable the activation of the damaging immune system by the secretion of anti-inflammatory cytokines such as IL-10 [18]. It is also known that macrophage M2 polarization – a key pro-tumoral phenomenon [19]. mTORC2 activity was found to be elevated in glioma cell lines and primary tumors as compared with normal brain tissue. Xenograft studies also supported a role for increased mTORC2 activity in tumorigenesis and enhanced tumor growth [20].

There was estimated a strong link between diabetes (especially T2D) and cancer. Hyperinsulinemia enhances the expression of insulin and IGF receptors that causes a cumulative mitogenic effect. Hyperglycemia provides cancer cells with excess of glucose [21]. Therefore somewhat

DOI: https://doi.org/10.30564/jer.v1i1.674

unexpected was the decrease in the amount of phospho-Akt (Figure1"4") in the PBMC of patients group both with cancer and diabetes. The level of phosphorylation of p70S6K is also reduced to 89.7 ± 6.27% of the control level and more than 30% compared to the cancer group (Figure 1"3"). Consequently, in the PBMC of group 4 patients the activity of Akt, mTORC1 and p70S6K is significantly suppressed, as compared to the group of cancer patients.

Probable explanation for such inhibition may be competition for common signaling mechanisms. It is also possible the participation of tumor suppressors, such as TRIB3 (Tribbles pseudokinase 3), which suppress activation of Akt by mTORC2 in tumors [22]. The involvement of IKKα, a subunit of the IKK complex that controls NF-κB activation, is also not excluded. IKKα regulates the mTORC2 kinase activity directed to Akt on S473 and Akt-mediated phosphorylation of FOXO3a and GSK-3β, but not other Akt-associated targets such as TSC2 and PRAS40, which control the mTORC1/p70S6K activity [23]. TLR4 expression in macrophages mentioned above could activate NF-κB signaling [24].

It should be noted that we did not observe a significant difference in the activity of both kinases in the PBMC between patients with different types of cancer within groups 3 and 4. We also did not observe gender differences.

4. Conclusion

Thus, chronic diseases such as type 2 diabetes and cancer may have a systemic effect on signaling mechanisms in different tissues of the body, including blood cells. The state of Akt phosphorylation in PBMC can indicate the activity of mTORC1 and its substrates, which may be important for the evaluation of the pathological process and the efficacy of the drugs.

References

[1] Manning BD, Toker A. AKT/PKB Signaling: Navigating the Network [J]. Cell. 2017, 169: 381-405.

[2] de Oliveira CE, Oda JM, Losi Guembarovski R, de Oliveira KB, Ariza CB, Neto JS, Banin Hirata BK, Watanabe MA. CC chemokine receptor 5: the interface of host immunity and cancer [J]. Dis Markers. 2014, 2014: 126954.
DOI: 10.1155/2014/126954

[3] Senovilla L, Vacchelli E, Galon J, Adjemian S, Eggermont A, Fridman WH, Sautès-Fridman C, Ma Y, Tartour E, Zitvogel L, Kroemer G, Galluzzi L. Trial watch: Prognostic and predictive value of the immune infiltrate in cancer [J]. Oncoimmunology. 2012, 1(8): 1323-1343.

[4] Tronko ND, Pushkarev VM, Sokolova LK, Pushkarev VV, Kovzun OI. Molecular mechanisms of pathogenesis of diabetes and its complications [M]. K.: Publishing house Medkniga, 2018: 264 (In Russian).

[5] Dituri F, Mazzocca A, Giannelli G, Antonaci S. PI3K functions in cancer progression, anticancer immunity and immune evasion by tumors [J]. Clin Dev Immunol. 2011, 2011: 947858.
DOI: 10.1155/2011/947858

[6] Covarrubias AJ, Aksoylar HI, Horng T. Control of macrophage metabolism and activation by mTOR and Akt signaling [J]. Semin Immunol. 2015, 27(4): 286-296.
DOI: 10.1016/j.smim.2015.08.001

[7] Covarrubias AJ, Aksoylar HI, Yu J, Snyder NW, Worth AJ, Iyer SS, Wang J, Ben-Sahra I, Byles V, Polynne-Stapornkul T, Espinosa EC, Lamming D, Manning BD, Zhang Y, Blair IA, Horng T. Akt-mTORC1 signaling regulates Acly to integrate metabolic input to control of macrophage activation [J]. Elife. 2016, 5: e11612.
DOI: 10.7554/eLife.11612

[8] Kim LC, Cook RS, Chen J. mTORC1 and mTORC2 in cancer and the tumor microenvironment [J]. Oncogene. 2017, 36(16): 2191-2201.
DOI: 10.1038/onc.2016.363

[9] Puskarev VM, Sokolova LK, Pushkarev VV, Tronko ND. The role of AMPK and mTOR in the development of insulin resistance and type 2 diabetes. The mechanism of metformin action [J]. Probl Endocr Pathol. 2016, 3: 77-90. (In Russian).

[10] Sokolova LK, Pushkarev VM, Belchina YB, Pushkarev VV, Tronko ND. Effect of combined treatment with insulin and metformin on 5′AMP-activated protein kinase activity in lymphocytes of diabetic patients [J]. Rep Nat Acad Sci Ukr. 2018, 5: 100-104.
DOI: https://doi.org/10.15407/dopovidi2018.05.100

[11] Zhang Z, Amorosa LF, Coyle SM, Macor MA, Birnbaum MJ, Lee LY, Haimovich B. Insulin-dependent regulation of mTORC2-Akt-FoxO suppresses TLR4 signaling in human leukocytes: relevance to type 2 diabetes [J]. Diabetes. 2016, 65(8): 2224-2234.
DOI: 10.2337/db16-0027

[12] Zhang Z, Amorosa LF, Coyle SM, Macor MA, Lubitz SE, Carson JL, Birnbaum MJ, Lee LY, Haimovich B. Proteolytic cleavage of AMPKα and intracellular MMP9 expression are both required for TLR4-mediated mTORC1 activation and HIF-1α expression in leukocytes. J Immunol [J]. 2015, 195(5): 2452-2460.
DOI: 10.4049/jimmunol.1500944

[13] Banerjee D, Sinha A, Saikia S, Gogoi B, Rathore AK, Das AS, Pal D, Buragohain AK, Dasgupta S. Inflammation-induced mTORC2-Akt-mTORC1 signaling promotes macrophage foam cell formation [J]. Biochimie. 2018, 151: 139-149.
DOI: 10.1016/j.biochi.2018.06.001

[14] Fruman DA, Rommel C. PI3K and cancer: lessons, challenges and opportunities [J]. Nat Rev Drug Discov. 2014, 13: 140-156.

[15] Xu Z, Hu J, Cao H, Pilo MG, Cigliano A, Shao Z, Xu M, Ribback S, Dombrowski F, Calvisi DF, Chen X. Loss of Pten synergizes with c-Met to promote hepatocellular carcinoma development via mTORC2pathway [J]. Exp Mol Med. 2018, 50(1): e417.
DOI: 10.1038/emm.2017.158

[16] Ebner M, Sinkovics B, Szczygieł M, Ribeiro DW, Yudushkin I. Localization of mTORC2 activity inside cells [J]. J Cell Biol. 2017, 216(2): 343-353
DOI: 10.1083/jcb.201610060

[17] Jhanwar-Uniyal M, Amin AG, Cooper JB, Das K, Schmidt M, Murali R. Discrete signaling mechanisms of mTORC1 and mTORC2: Connected yet apart in cellular and molecular aspects [J]. Adv Biol Regul. 2017, 64: 39-48.
DOI: 10.1016/j.jbior.2016.12.001

[18] Huang SC, Smith AM, Everts B, Colonna M, Pearce EL, Schilling JD, Pearce EJ. Metabolic reprogramming mediated by the mTORC2-IRF4 signaling axis is essential for macrophage alternative activation [J]. Immunity. 2016, 45(4): 817-830.
DOI: 10.1016/j.immuni.2016.09.016

[19] Shrivastava R, Asif M, Singh V, Dubey P, Ahmad Malik S, Lone MU, Tewari BN, Baghel KS, Pal S, Nagar GK, Chattopadhyay N, Bhadauria S. M2 polarization of macrophages by Oncostatin M in hypoxic tumor microenvironment is mediated by mTORC2 and promotes tumor growth and metastasis [J]. Cytokine. 2018: S1043-4666(18)30118-2.
DOI: 10.1016/j.cyto.2018.03.032

[20] Altomare DA, Testa JR. FRAP1 (FK506 binding protein 12-rapamycin associated protein 1) [J]. Atlas Genet Cytogenet Oncol Haematol. 2009, 13(5); 348-353.

[21] Pushkarev VM, Sokolova LK, Pushkarev VV, Tronko MD. Biochemical mechanisms connecting diabetes and cancer. Effects of metformin [J]. Endokrynologia. 2018, 23(2): 167-179. (In Russian).

[22] Salazar M, Lorente M, García-Taboada E, Gómez EP, Dávila D, Zúñiga-García P, Flores JM, Rodríguez A, Hegedus Z, Mosén-Ansorena D, Aransay AM, Hernández-Tiedra S, López-Valero I, Quintanilla M, Sánchez C, Iovanna JL, Dusetti N, Guzmán M, Francis SE, Carracedo A, Kiss-Toth E, Velasco G. TRIB3 suppresses tumorigenesis by controlling mTORC2/AKT/FOXO signaling [J]. Mol Cell Oncol. 2015, 2(3): e980134.
DOI: 10.4161/23723556.2014.980134

[23] Dan HC, Antonia RJ, Baldwin AS. PI3K/Akt promotes feedforward mTORC2 activation through IKKα [J]. Oncotarget. 2016, 7(16): 21064-21075.
DOI: 10.18632/oncotarget.8383

[24] Korneev KV, Atretkhany KN, Drutskaya MS, Grivennikov SI, Kuprash DV, Nedospasov SA. TLR-signaling and proinflammatory cytokines as drivers of tumorigenesis [J]. Cytokine. 2017, 89: 127-135.
DOI: 10.1016/j.cyto.2016.01.021

DOI: https://doi.org/10.30564/jer.v1i1.674

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

REVIEW

Application Analysis of Diabetes Health Education in Endocrinology Nursing

Yu Tao*

Nanjing Jiangning Hospital, Nanjing, Jiangsu, 210000, China

ARTICLE INFO

Article history
Received: 27 March 2019
Accepted: 28 April 2019
Published Online: 30 April 2019

Keywords:
Diabetes
Health education
Endocrinology care
Application

ABSTRACT

Objectives: To explore the clinical value of applying diabetes health education to endocrinology care. **Methods:** A total of 122 patients with diabetes admitted to our department from October 2016 to October 2017 were selected. After consulting patients, they were randomly divided into two groups, with 61 cases in each group. The control group performs routine care, and the experimental group provides patients with diabetes-specific health education. After three months, the compliance of the two groups of patients was compared. The ADL scores of the two groups of patients before and after treatment were compared. **Results:** Experimental group had significantly higher compliance rate than control group in all aspects. The difference was statistically significant (P<0.05). The ADL scores of both groups were significantly improved. The effects before and after the care were compared. The difference was statistically significant (P<0.05). The score of experimental group increased more significantly than that of the control group. The difference was statistically significant (P<0.05). **Conclusions:** In the endocrinology care, the implementation of diabetes special health education for patients can improve patient compliance and improve patients' daily living ability, which is an ideal nursing measure. It is worth promoting.

1. Introduction

Clinically, diabetes is a chronic metabolic disease with high morbidity. The causes are mainly genetic factors, mental factors and personal physique[1]. Because the blood sugar level of diabetic patients is in a high state for a long time, serious damage has occurred in many systems of the body. If the blood sugar control effect is not satisfactory, it will cause many complications, such as diabetic nephropathy and diabetic eye disease. In this regard, the intensity of clinical care for diabetic patients needs to be strengthened. This article aims to explore the clinical application value of diabetes health education[2].

2. Materials and Methods

2.1 General Information

122 patients with diabetes admitted to the secretory department of our hospital from October 2016 to October 2017 were selected. With the consent of the patient, the grouping was randomly determined by drawing lots. There were 61 cases in the control group, including 33 males and 28 females, aged 47 to 72 years, with an average age of (61.23±3.75) years. The course of the disease was 4

**Corresponding Author:*
Yu Tao,
Nanjing Jiangning Hospital, Nanjing, Jiangsu, 210000, China;
E-mail: taoyu@gmail.com

 DOI: https://doi.org/10.30564/jer.v1i1.694

months to 12 years, with an average (5.64±1.31) years. There were 61 cases in the experimental group, including 34 males and 27 females, aged 46 to 73 years, with an average age of (61.32±3.67) years. The course of the disease was 6 months to 11 years, with an average (5.59±1.27) years. The patient has no other major basic diseases, no mental system diseases, can successfully understand the nursing guidance, and has no severe disability or dysfunction. Research conforms to medical ethics. The informed consent of the patient shall be signed by the patient himself.

2.2 Research Method

The control group is given regular care. (1) Dietary guidance: Help patients make a scientific diet plan, avoid eating stimulating or high-sugar food, tell patients not to eat coffee and other meals that may affect sleep; (2) Medication nursing: Inform the patient of the specific method and dose of the relevant drugs, and supervise the patient to take the medicine on time; (3) Blood glucose monitoring: To guide patients and their families in the correct method of blood glucose measurement, measure the blood glucose level of patients on a regular basis, master the patient's blood glucose control, and report to the doctor to adjust the treatment plan accordingly.

On the basis of control group, diabetes health education was conducted for patients in experimental group. (1) Education of disease-related knowledge: Through brochures, video, lectures and other means, the pathogenesis and inducing causes of diabetes were explained to the patients and their families, and the influence of related bad daily habits was informed. Diabetes is not curable, but it can be effectively controlled. Medical staff should help patients establish a sense of health, so that patients can actively cooperate with treatment and nursing, pay attention to regulate their own behavior, and strengthen self-care consciousness[3]. (2) Drug related knowledge: Medical staff shall explain the efficacy, property, indications, contraindications, precautions for medication, and possible adverse reactions of the relevant hypoglycemic drugs to the patients, and make sure that the patients and their families have an accurate understanding and master them. Patients should take medicine on time and in accordance with the amount and in a scientific way to prevent the occurrence of missed or repeated medication. (3) Life behavior and habit intervention: Medical staff help patients establish awareness of healthy behaviors. Behaviors that are not conducive to disease control, such as diet, activity and rest, are told to patients to make them aware of the harm of bad behaviors. In combination with the patient's own behavioral patterns, targeted improvement programs were developed. (4) Continuing health education: After the patient leaves the hospital, the doctor regularly conducts telephone and door-to-door follow-up to understand the reasons that affect the patient's blood sugar control effect and help correct it. WeChat, weibo and other platforms are used to push relevant knowledge and other contents to patients through the establishment of public accounts to help them solve their doubts[4].

2.3 Observation Standard

The compliance of patients was evaluated from aspects of diet control, living behavior norms and medication. All aspects of compliance were compared between the two groups. ADL score was evaluated before and after nursing and the results were compared.

2.4 Statistical Treatment

SPSS19.0 statistical software was used to process the data. The ADL score is expressed as x ± s. A t test was applied. Compliance is expressed in (%).The x^2 test is applied. The results are compared with reference to the P value. 0.05 is the reference value. If the result is lower than this value, it is statistically significant[5].

3. Results

3.1 Comparison of Compliance between the Two Groups

The compliance rate of experimental group patients in diet, medication and life behavior was significantly higher than that of control group. The difference was statistically significant ($P < 0.05$) (Table 1).

Table 1. Comparison of compliance between the two groups [n(%)]

Group	Cases	Diet	Medication	Life behavior
Control group	61	53(86.89)	54(88.52)	51(83.61)
Experimental group	61	59(96.72)	60(98.52)	58(95.08)
x^2		3.921	4.816	4.219
P		0.048	0.028	0.040

3.2 Comparison of ADL Scores before and after Care in the two Groups of Patients

After treatment, the ADL score of control group patients increased from (53.17±4.79) to (75.79±5.03) points. The ADL score of experimental group patients increased from (53.21±4.73) to (87.99±5.17) points. The ADL scores of both groups were significantly improved compared with

DOI: https://doi.org/10.30564/jer.v1i1.694

those before treatment. The difference was statistically significant (t values were 25.435 and 38.766, respectively, $P < 0.05$). Comparing the two groups, the patient score of the experimental group increased more significantly. The difference was statistically significant ($t=13.210$, $P<0.05$) [3].

4. Discussion

In the past, the endocrinology department had obvious deficiencies in health education for patients with type 2 diabetes, including the following aspects: (1) The content and method of health education is too simple; (2) Health education failed to grasp the key points; (3) The self-learning ability of patients and their families has not been mobilized. For chronic disease management, self-management capabilities are important [5].

To this end, the hospital has carried out intensive health education to improve the pertinence of health education. Patients in the observation group had significantly higher knowledge scores when they left the hospital. At the same time, after leaving the hospital, the quality of disease management was better in three months, and the blood sugar control rate reached 80.0%. The implementation rate of nursing care such as foot care is high, and the level of secondary management is finally improved, which is of great significance for the prevention of complications such as diabetic foot [2]. The new health education has the following advantages: (1) At admission, patients' knowledge is assessed and on-demand health education is conducted to meet individual needs; (2) Suitable health education objects and personnel are selected. Through the construction of harmonious nurse-patient relationship, the quality of daily education is improved; (3) The teaching methods were enriched to match the individual knowledge level and self-learning ability of patients and their families. The mission is more interesting, profound and hierarchical. Personal examples can enhance the authenticity of the mission. Patient activities can play a mutually supportive role, improve the quality of out-of-hospital education, and provide more social support.

References

[1] Li Li. Application of 120 Cases of Diabetes Health Education in Endocrinology Nursing [J]. Cardiovascular Disease Journal of Integrated Traditional Chinese and Western Medicine, 2017, 5(13):112-113.

[2] Yan Xu. Application of Diabetes Health Education in Endocrinology Nursing [J]. Journal of Practical Gynecologic Endocrinology, 2017, 4(04): 82+84.

[3] Ying Sun. Application of Diabetes Health Education in Endocrinology Nursing. Diabetes New World. 2016, 19(1): 163-165. [4] Yao Guo. Analysis of the Application of Diabetes Health Education in Endocrinology Nursing. Diabetes New World. 2015, 18(11): 216-217. [5] Chunxia Zhang, Rong Fu. Observation on the Application of Diabetes Health Education in Endocrinology Nursing. Medical Information. 2015, 28(52): 294.

 DOI: https://doi.org/10.30564/jer.v1i1.694

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

ARTICLE

Managing diabetes mellitus in underserved subjects of Western China using a telemedicine system— A clinical trial

Ya Li* **Weiguo Ma** **Jiao Bai** **Chuanqing Xie** **Yuanyuan Huo**

Department of endocrinology, The First Affiliated Hospital of Xi'an Medical University, Xi'an 710077, China

ARTICLE INFO

Article history
Received: 21 March 2019
Accepted: 1 April 2019
Published Online: 30 April 2019

Keywords:
Clinical trial
Diabetes care
Insulin resistance
Glycaemic control
Type 2 diabetes

ABSTRACT

Objective: To evaluate the effectiveness of Internet and telephone-based telemedicine system managing on patients' glycemic index, blood pressure, and lipid level control in underserved subjects with type 2 diabetes in Western China. **Research designs and methods:** In a 3 years, randomized, controlled, single-blind, parallel-group treat-to-target study, 412 subjects with type 2 diabetes were randomized to telemedicine (Tel; n =208) group and usual care (control; n =204) group. We evaluated the effects of the intervention on blood sugar, blood pressure, and lipid levels at 1, 2, 3 years point, and investigated the cause of the loss during follow-up by phone call. **Results:** Intra-group comparison: in the Tel group, the FBS, 2HPG, HbA1c, and SBP at 1, 2, 3 years and DBP, TC, TG, BMI at 2, 3 years were significantly decreased compared with baseline level ($P<0.05$). Moreover, the Tel group had an obvious better control of their HbA1c at 2 and 3 years and 2HPG at 3 years of follow-up respectively compared with the outcomes at 1 year ($P<0.05$).Inter-group comparison: the FBS, 2HPG, and HbA1c of Tel group decreased significantly from the baseline to the 1 year more than those of control group ($P<0.05$ or $P<0.01$). In this analysis, all clinical measures of Tel group had a significant downward compared with the outcomes of Control group at 2 years, the FBS, HbA1c and BMI ($P<0.001$), the 2HPG and SBP ($P<0.01$) and DBP, TC, and TG ($P<0.05$) were statistically significant respectively. Logistic regression analysis showed that the subject loss during follow-up was associated with worse diabetes management (OR=3.842), low income (OR=3.201), low education level (OR=0.923), and greater distance to the hospital (OR=0.921).**Conclusions:** The study results indicated that the telemedicine may be a useful tool for managing diabetes mellitus.

1. Introduction

The increased incidence of type 2 diabetes (T2DM) and associated increases in mortality are important challenges facing the world [1]. Diabetes can damage the heart, blood vessels, eyes, kidneys and nerves, leading to foot amputation and related deaths. The World Health Organization predicts that diabetes-related mortality will double between 2005 and 2030 [2]. In China, the study found that the overall prevalence of diabetes in adults is estimated at 11.6%; of these, 12.1% of men and 11.0% of women [3]. The pre-diabetes prevalence rate of Chinese adults was 50.1%: 52.1% for men and 48.1% for women. It is worth noting that the pre-diabetes prevalence

**Corresponding Author:*
Ya Li,
Department of endocrinology, The First Affiliated Hospital of Xi'an Medical University, Xi'an 710077, China;
Email: yaliya19@163.com

DOI: https://doi.org/10.30564/jer.v1i1.671

rate of rural residents is slightly higher than that of urban residents, especially men. In addition, pre-diabetes are more prevalent in economically underdeveloped areas and overweight and obese people. These studies suggest that the incidence of diabetes may reach alert levels among Chinese adults, and diabetes can lead to major epidemics of related complications, including cardiovascular disease, stroke and chronic kidney disease. If the Chinese government does not adopt effective state interventions, diabetes will be a serious problem in the near future. [3].

Diabetes patient education and interventions can improve patients' self-care activities, maintain metabolic stability, improve quality of life, and prevent or delay the development of complications [4]. In a systematic review of 41 studies involving 48,000 patients, the researchers described the effectiveness of professional guidance, organizational transformation, and patient-centered interventions for health professionals [5]. However, most of these studies have been selected in cities with good health care. In contrast, many patients, particularly the underserved do not attain these recommended levels of care, due to poverty, economic backwardness, and poor insurance. A lot of people with uncontrolled Type 2 diabetes do not achieve recommended targets including blood sugar, blood pressure, and lipid levels. Presently, diabetes management is seldom reported in underserved subjects of the economically underdeveloped area. We, therefore, implemented a telephone and internet-based system for offering professional care management for an underserved type 2 diabetes patients with or without medical insurance in poor areas of Western China.

2. Research Design and Methods

2.1. Patients

The study protocol was approved by an independent ethics committee at each center, based on the Helsinki Declaration and Clinical Practice Guidelines. All volunteers provided written consent before the study [6]. We conducted a randomized, controlled, single-blinded, paralleled-group study to test the hypothesis that an internet and telephone-based communication systems of diabetes care will allow more patients to reach individualized target blood glucose level when compared with usual care. Each patient obtained an ID using a computer-based random number generator on internet system, and then had adequate allocation concealment using serially numbered sealed opaque envelopes. Statistical outcomes were interpreted blindly by a statistician. There are five basic elements in research design: education and behavioral guidance, development of treatment plans, care management, team care methods, and physician leadership. Develop all the details of the study, including clinic staff and leadership training, patient process protocols and a detailed description of the budget.

2.2. Inclusion and Exclusion Criteria

Population of people from ten counties and districts of remote areas in the West of China were studied. Volunteers were recruited from county-level hospitals, community activity centers, medical affiliated hospitals, and medical centers. The inclusion criteria are: a. Diagnose patients with T2DM, b. Adults between the ages of 20 and 65, c. Ability to live independently, d. Ability to complete the questionnaire independently, e. Informed and agreed to participate in the study and sign an informed consent form.. The exclusion criteria were: a. patients who were pregnant, planning a pregnancy, or currently lactating during the study, b. patients with severe diabetic complications and c. patients with liver and kidney dysfunction. Eventually the eligible 412 subjects were randomly divided into two groups based on telemedicine: telemedicine (Tel) group with 208 people and control group with 204 people (usual care).

2.3. Organization Training

Patients in telemedicine management (telephone group) receive diabetes-related care management, including diabetes education, self-management, and medication guidance, which consists of nurse administrators and doctors at research centers. In addition, telemedicine subjects have received training in telemedicine use. Control subjects (control group) were provided with data from their baseline assessment and instructed to contact their primary caregiver for further care. No further intervention was provided for the control subjectsDue to local funding needs and the willingness of employees to participate in diabetes quality improvement training, intervention clinics and follow-ups were purposefully selected. All costs from baseline to final follow-up of biochemical and serological tests for the eligible 412 subjects relied on the local funding. The cost of drug and other tests from baseline to final follow-up relied on medical insurance or fee-paying.

2.4. Follow-up

412 patients were followed up, each telemedicine patient was followed up once every three months by the professional nurse and once every six months by the professional physician alternately, excluding the exit patients. While the nurse called patient via telemedicine system to provide diabetic care, the physician gave instruction on

 DOI: https://doi.org/10.30564/jer.v1i1.671

the treatment, the nurse ask physician for help. Overview of care for people with diabetes, such as medication use, diet planning, exercise, blood glucose monitoring, dietary restrictions, medication adherence, foot care and smoking cessation[7]. Diabetes and quality of life, such as diabetes condition control, treatment satisfaction, social life and sexual function[8]. Subsequently each patient was seen at a follow-up visit at least once every 1 year and the indicator for further observation was completed at the research center. The clinical goals of the telemedicine program include raising hemoglobin A1c levels to 7.0%, blood pressure (BP) to below 140/90 mmHg, and triglyceride (TG) levels to below 150 mg/dL. When the patient's hemoglobin A1c, blood pressure and TG levels are higher than the clinical target, the doctor will increase the patient's medication regimen, including current medication metrology adjustments and new oral medications or insulin.

2.5. Data Entry

Each patient receives an ID from a random number generator on the Internet. The staff then collected the patient's experimental data using standard procedures at baseline, 1 year, 2 years, and 3 years. Includes demographic characteristics such as age, gender, insurance, duration of diabetes, height, weight (calculated BMI), and blood pressure. Blood samples were obtained by venipuncture and fasting blood glucose was measured using standard laboratory procedures, hemoglobin A1c, total cholesterol, triglycerides, low density lipoprotein (LDL), high density lipoprotein (HDL), aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatinine. 2h-post-meal plasma glucose (2hPG) was performed after the meal.

2.6. Statistical Analysis

The analysis was performed by SAS 8.1 (SAS Institute Inc., Cary, NC) and GraphPad Prism 5 (GraphPad Software, Inc., San Diego, USA). Results were presented as mean ± SD. Chi-square tests were adopted for comparing differences among the groups. Logistic regression was used to estimate the odds ratio (OR) and 95% confidence interval (CI) of the reason for the loss during follow-up , including diabetes management, income level, education level, and the distance to the hospital. A P value of less than 0.05 was considered statistically significant.

The study may have lost follow-up, and if some random participants are not within the scope of the analysis, the estimated intervention may be biased. This kind of missing imbalance between groups may indicate bias. Intent-to-treat (ITT) analysis aims to randomly include all participants in the trial, regardless of what happens next. In this study, the "last observation" was implemented to assume that no changes occurred; ITT and each protocol (PP) analysis were performed.

3. Results

3.1. Clinical Outcomes

The study was conducted over a 3-year period and we recruited 450 subjects. Out of the total number of the subject recruited, 26 declined to participate in the study after screening process and 12 did not complete screening process. Figure 1 showed a flow diagram of the recruiting process. The sugar, fat, blood pressure and BMI metabolic parameters of four groups were observed at 1, 2, and 3 years. Because of the loss in number of control group exceeded 15%, it was a failure comparison in 3 years.

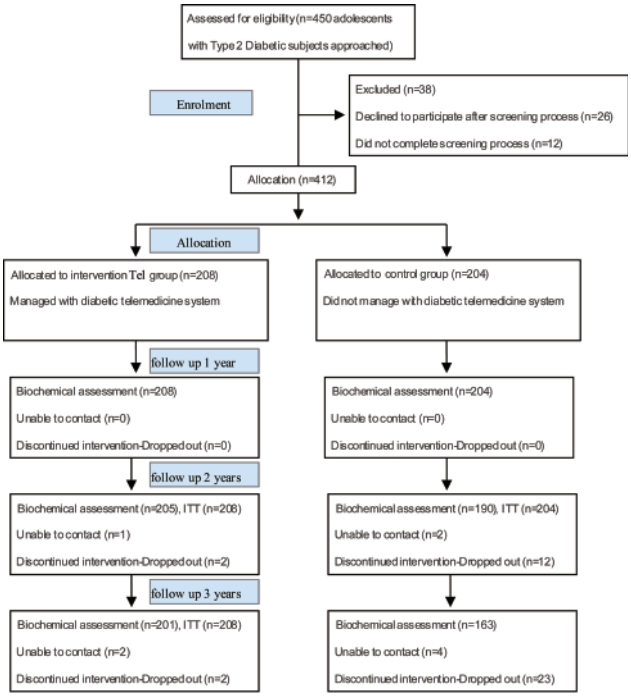


Figure 1. Subject flow diagram. The number of patients at baseline, the frequency of follow-up visits, reasons for withdrawal,number of patients completing the study and the number of ITT. ITT, intention to treat analysis.

As shown in Table 1, there were no statistical significant differences in demographic characteristics or mean clinical parameters at baseline between patients in the intervention and control practices. Sixty-one percent were male, more than 77% had low family incomes at or near the poverty level, and 25% completed high school. Diabetic patients using insulin constituted 13% of the study subjects.

DOI: https://doi.org/10.30564/jer.v1i1.671

Table 1. Baseline characteristics of participants by group

Characteristics	Tel group (n=208)	Control group(n=204)	P
Age, years	50.0 (14.9)	51.1 (14.2)	0.5615
Sex			
Male	128	122	
Female	80	82	
Diabetes duration, years	6.1 (5.0)	6.0 (4.9)	0.7612
Height, cm	165.0 (11.2)	168.0 (10.8)	0.0536
Weight, kg	70.6 (10.5)	71.0 (10.7)	0.2906
BMI, kg/ m2	25.1 (2.5)	25.0 (2.6)	0.4261
Systolic blood pressure, mmHg	132.8 (17.2)	130.9 (19.0)	0.1833
Diastolic blood pressure, mmHg	79.0 (8.5)	78.3(9.0)	0.8356
Fasting plasma glucose, mg/dL	146.3 (38.4)	145.0 (39.2)	0.9244
Postprandial 2-h glucose, mg/dL	230.5 (66.6)	227.8 (67.4)	0.7578
A1C, %	8.4 (1.5)	8.4 (1.6)	0.5093
Total cholesterol, mg/dL	165.6 (37.7)	163.5(39.2)	0.2832
Triglyceride, mg/dL	145.2 (58.0)	146.7(57.1)	0.2870
HDL cholesterol, mg/dL	51.4 (10.5)	51.1 (9.7)	0.2204
LDL cholesterol, mg/dL	107.5(25.5)	106.7(23.9)	0.5503
Aspartate aminotransferase, IU/L	22.6 (9.1)	22.3 (8.5)	0.2934
Alanine aminotransferase, IU/L	25.7 (13.1)	25.3 (11.9)	0.7761
Serun creatinine, mg/dL	1.16 (0.25)	1.13 (0.20)	0.1228
Medication for glucose control			
None, n (%)	13(6.3)	13(6.4)	0.7993
Sulfonylurea, n (%)	81(38.9)	77(37.7)	0.7097
Metformin, n (%)	100(48.1)	99(48.5)	0.5037
Thiazolidinedione, n (%)	18(8.7)	19(9.3)	0.3580
a-Glucosidase inhibitor, n (%)	41(19.7)	37(18.1)	0.6306
Dipeptidyl peptidase 4, n (%)	11(5.3)	12(5.9)	0.7921
Insulin, n (%)	22(10.6)	21(10.3)	0.8737
Education level			0.9250
Primary school, n (%)	59(28.4)	65(32.0)	
Junior high school, n (%)	95(45.7)	94 (46.2)	
High school, n (%)	54(25.9)	45(21.8)	
Income			0.9791
low income, n (%)	162 (77.8)	165 (80.8)	
medium income, n (%)	38(18.5)	31(15.30)	
high income, n (%)	8(3.7)	8(3.9)	

Note: Data are presented as mean (SD) or number of participants (%).

 DOI: https://doi.org/10.30564/jer.v1i1.671

Anthropometric and biochemical parameters after 1, 2, and 3 years of follow-up are summarized in Table 2.

3.2. Intra-group Comparison

In the Tel group, FBS, 2HPG, HbA1c, and SBP (Figure 2 A, B, C, and D) decreased significantly at 1, 2, and 3 years of follow-up, and DBP, TC, TG, BMI (Figure 2E,F,G, and H) also reduced significantly at 2 and 3 years compared with baseline level ($P<0.05$). Moreover, the Tel group had an obvious better control of their

Table 2. Change of clinical measures at 1, 2 and 3 years follow up by group

Clinical Parameters	Tel group	Control group
FPG (mg/dL) 0 years	146.3 (38.4) (n=208)	145.0 (39.2) (n=204)
1 years	138.1 (34.0) (n=208)	146.1 (38.5) (n=204)
2 years	133.1 (27.0) (n=205) /133.2 (27.1) (n=208,ITT)	147.3(39.0) (n=190) /147.0(38.9) (n=204,ITT)
3 years	132.3(26.9) (n=201) /132.5 (26.8) (n=208,ITT)	- (n=163)
2HPG(mg/dL) 0 years	230.5 (66.6) (n=208)	227.8 (67.4) (n=204)
1 years	216.1 (53.0)(n=208)	230.1 (68.6) (n=204)
2 years	208.9(45.5) (n=205) /202.0(43.6) (n=208,ITT)	230.0 (69.5) (n=190) /229.2(69.5) (n=204,ITT)
3 years	202.2(41.2) (n=201) /203.3(41.6) (n=208,ITT)	- (n=163)
A1C (%) 0 years	8.4 (1.5) (n=208)	8.4 (1.6) (n=204)
1 years	8.0 (1.0) (n=208)	8.4(1.5) (n=204)
2 years	7.6 (0.9) (n=205) /7.7 (0.9) (n=208,ITT)	8.4(1.6) (n=190) /8.5(1.5) (n=207,ITT)
3 years	7.5 (0.8) (n=201) /7.6 (0.8) (n=208,ITT)	- (n=163)
SBP (mmHg) 0 years	132.8 (17.2) (n=208)	130.9 (19.0) (n=204)
1 years	128.8 (17.0) (n=208)	131.1 (19.8) (n=204)
2 years	126.3 (16.4) (n=205) /126.7 (16.3) (n=208,ITT)	131.0 (19.6) (n=190) /131.1(20.2) (n=204,ITT)
3 years	125.1(15.6) (n=201) /125.2(15.7) (n=208,ITT)	- (n=163)
DBP (mmHg) 0 years	79.0 (8.5) (n=208)	78.3(9.0) (n=204)
1 years	78.4 (8.0) (n=208)	78.1 (9.8) (n=204)
2 years	76.1 (7.6) (n=205) /76.3 (7.6) (n=208,ITT)	78.3 (9.9) (n=190)/78.2 (9.8) (n=204,ITT)
3 years	75.3(7.6) (n=201) /75.5(7.6) (n=208,ITT)	- (n=163)
TC(mg/dL) 0 years	165.6 (37.7) (n=208)	163.5(39.2) (n=204)
1 years	162.1 (35.0) (n=208)	164.1 (39.0) (n=204)
2 years	156.7 (30.5) (n=205) /156.9 (30.6) (n=208,ITT)	163.7 (39.1) (n=190) /163.8(39.1) (n=204,ITT)
3 years	155.3(29.9) (n=201) /156.0(29.8) (n=208,ITT)	- (n=163)
TG (mg/dL) 0 years	145.2 (58.0) (n=208)	146.7(57.1) (n=204)
1 years	138.5 (52.4) (n=208)	147.1 (57.8) (n=204)
2 years	132.7 (45.5) (n=205) /133.0(45.6) (n=81,ITT)	145.0 (56.9) (n=190) /145.5(57.0) (n=204,ITT)
3 years	130.3(43.0) (n=201) /130.5(43.1) (n=81,ITT)	- (n=163)
BMI (kg/m^2) 0 years	25.1 (2.5) (n=208)	25.0 (2.6) (n=204)
1 years	24.7 (2.6) (n=208)	25.1 (2.5) (n=204)
2 years	24.3(2.5) (n=205) /24.2 (2.5) (n=208,ITT)	25.2(2.5) (n=190) /25.2(2.4) (n=204,ITT)
3 years	23.9(2.5) (n=201) /24.0(2.5) (n=208,ITT)	- (n=163)
Results are expressed as the mean ± SD. - no statistical data (Loss of follow-up rate was more than 20%). ITT: intention to treat		
Analysis (last observation carried forward). FPG , fasting plasma glucose;2HPG , postprandial 2-h glucose; HbA1c, hemoglobin A1c;		
SBP , systolic blood pressure; DBP , diastolic blood pressure; TC, total cholesterol; TG, triglyceride; BMI, body mass index.		

DOI: https://doi.org/10.30564/jer.v1i1.671

HbA1c (Figure2C) at 2 and 3 years and 2HPG (Figure2B) at 3 years of follow-up respectively compared with the outcomes at 1 year (P<0.05).

In addition, the FBS, 2HPG, HbA1c, SBP, DBP, TC, TG, and BMI (Figure2A,B,C,D,E,F,G, and H) of Control group had a slight upward trend from baseline to 2 years, however, this was not statistically significant (P>0.05).

All ITT and PP analysis revealed similar results in Figure 2 (Intention to treat -last observation carried forward data set).

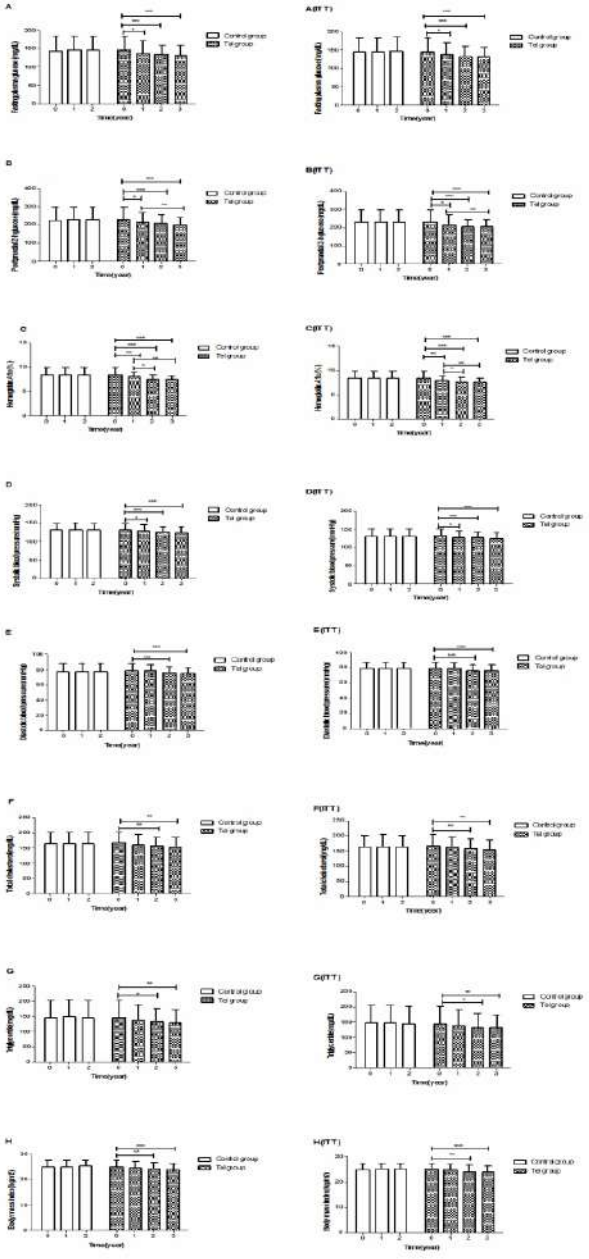


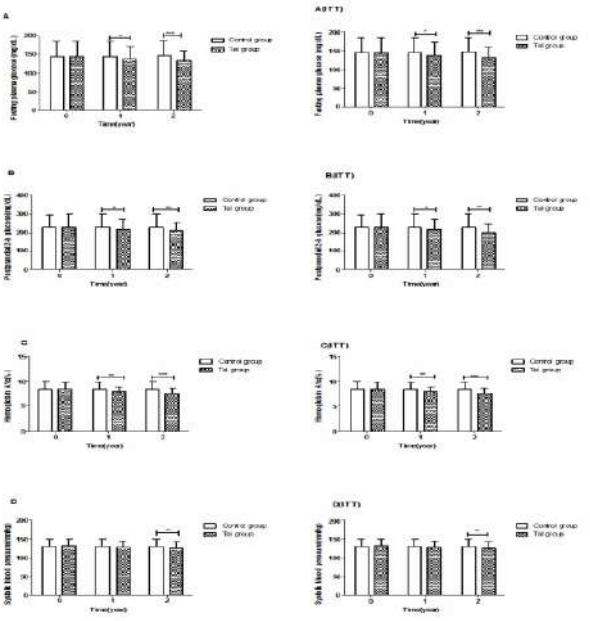
Figure 2. Intra-group comparison of different follow-up times

Note: A: FPG levels of four groups at different follow-up times; B: 2HPG levels of four groups at different follow-up times; C: HbA1c levels of four groups at different follow-up times; D: SBP levels of four groups at different follow-up times; E: DBP levels of four groups at different follow-up times; F: TC levels of four groups at different follow-up times; G: TG levels of four groups at different follow-up times; H: BMI levels of four groups at different follow-up times. A(ITT), B(ITT), C(ITT), D(ITT), E(ITT), F(ITT), G(ITT), and H(ITT): Corresponding index levels of four groups at different follow-up times by ITT. ITT-LOCF: intention to treat analysis-last observation carried forward. Results ara expressed as the mean ± SD. * P<0.05, **P<0.01, ***P<0.001 for comparisons between conditions.

3.3. Inter-group Comparison

As shown in Figure3, the FBS, 2HPG, and HbA1c (Figure 3A,B, and C) of Tel group decreased significantly from the baseline to the 1 year more than those of control group (P<0.05 or P<0.01). In this analysis, all clinical measures (Figure3A,B,C,D,E,F,G, and H) of Tel group had a significant downward compared with the outcomes of Control group at 2 years, the FBS, HbA1c and BMI (Figure 3A, C and H, P<0.001), the 2HPG and SBP (Figure 3B and D, P<0.01) and DBP, TC, and TG (Figure 3E, F and G, P<0.05) of the Tel group decreased more than those of the control group at 2 years, and it were statistically significant respectively.

All ITT and PP analysis revealed similar results in Figure 3 (Intention to treat-last observation carried forward data set).



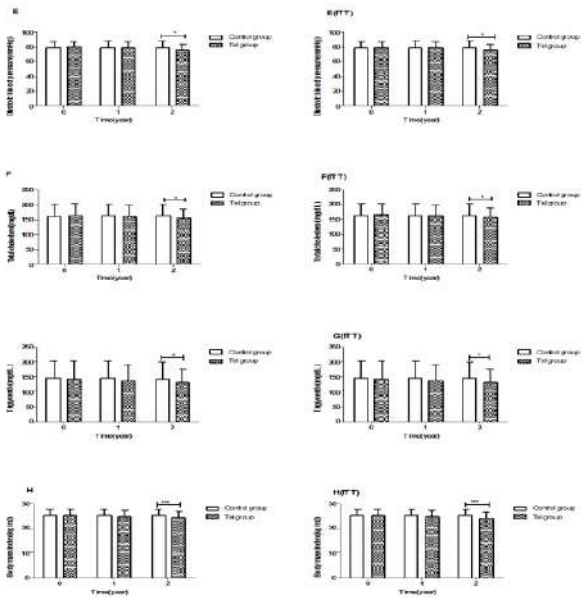


Figure 3. Inter-group comparison of same follow-up times

Note: A: FPG levels of four groups at same follow-up times; B: 2HPG levels of four groups at same follow-up times; C: HbA1c levels of four groups at same follow-up times; D: SBP levels of four groups at same follow-up times; E: DBP levels of four groups at same follow-up times; F: TC levels of four groups at same follow-up times; G: TG levels of four groups at same follow-up times; H: BMI levels of four groups at same follow-up times. A(ITT), B(ITT), C(ITT), D(ITT), E(ITT), F(ITT), G(ITT), and H(ITT): Corresponding index levels of four groups at same follow-up times by ITT. ITT-LOCF: intention to treat analysis-last observation carried forward. Results ara expressed as the mean ± SD. * P<0.05, **P<0.01, ***P<0.001 for comparisons between conditions.

3.4. Logistic Regression Results

The results of the logistic regression model are given in Table 3, which examines the changes from baseline to final follow-up and the probability of loss. In this analysis, the reason for the loss in follow-up was associated with worse diabetes management (OR=3.842), low income (OR=3.201), low education level (OR=0.923), and greater distance to the hospital (OR=0.921).

Table3. Logistic regression results

Effect	regression coefficient	Odds ratio	95% Wald confidence limits		P-value
No diabetes management	1.171	3.842	1.741	1.957	0.009
Low income	1.163	3.201	1.074	9.533	0.037
Education level	–0.079	0.923	0.875	0.977	0.006
The distance to the hospital	–0.083	0.921	1.18	1.50	0.001

Notes: The reason of the lost to follow-up N =48.

4. Discussion

This study is a 3-year RCT that examined a telephone and Internet- based diabetes education intervention for diabetes control in a underserved population of Western China. Studies have shown that there are significant barriers to achieving good care and good clinical outcomes in low-income patients[9, 10]. Parchman et al[11]and Stange[12] how primary care physicians are struggling to cope with competitive demands when attempting to address elevated levels of hemoglobin A1c. Our redesign studies have shown that diabetes care can be effectively managed even in resource-constrained settings.. Because the use of cell phone is ubiquitous, most of the subjects preferred it as a means of communication. Each telemedicine patient was followed up once every three months by the professional nurse and once every six months by the professional physician alternately, excluding the exit patients. The nurse provided diabetic care, the physician gave instruction on the treatment by telemedicine system. Bray et al. For African-American patients who have established diabetes interventions, they are provided with professional care strategies that can ideally control blood glucose based on rural primary care service charges[13]. Our research shows that chronic diabetes management can be done through a professional team and long-term follow-up. In this study, we found that redesigning diabetes care to combine professional care management resulted in significant improvements in blood sugar, blood lipids, and blood pressure. These findings were consistent with those of Johansson et al[14, 15] and Glazier et al[16]. A recent study showed that diabetes and its complications in patients with type 2 diabetes in Taiwan have a combined effect on antidiabetic drugs, lifestyle adjustments, and social and psychological support, as well as diabetes education, compared with a 12.5% drop in HbA1c levels in the control group. The group fell by 26.7%. This indicates the significant role of education and related care in patients with type 2 diabetes [17]. However, these studies did not mention further concern about the reason for the loss in follow-up.

The analysis comparing intervention group to control group patients showed striking differences in response. The telemedicine management can decreased significantly blood sugar, blood pressure and blood lipid compared with control group. The results demonstrated that the telemedicine management was effective in glycemic index, blood pressure, and lipid level control in underserved subjects with type 2 diabetes in Western China. The results of the study are consistent with the benefits of telemedicine, especially among Hispanic Americans, which have the dual qualifications of Medicare and Medicaid, so drug

DOI: https://doi.org/10.30564/jer.v1i1.671

costs should not be a problem compared to other populations [18]. However, the Austrian disease management plan implemented through statutory health insurance can improve the quality of the process and increase weight, but it does not significantly improve the metabolic control of patients with type 2 diabetes [19]. The reason for opposite result could be some risk of bias remains. we tried to achieve a study design free of bias, and worked out a randomized, controlled, single-blind, parallel-group treat-to-target study. Meanwhile, perfect diabetes management was a prerequisite for good quality health care delivery, and it could enable more diabetic patients to obtain blood sugar, blood pressure, and blood lipids to standard [20]. Ngo-Metzger et al. found that there is an economic burden for the treatment of diabetes, and because of cost reasons, patients are likely to not adhere to medication. Poor drug compliance is directly related to poor control of diabetes, such as an increase in HbA1c. However, having health insurance does reduce the economic pressure on health care [21]. Therefore, the results of telemedicine management could be more reliable.

In this study, BMI was significantly lower at 2 years than at baseline level in the Tel group, and it was statistically significant($P<0.05$). In addition, the BMI of Tel group decreased more than those of control group at 2 years ($P<0.05$). These findings were consistent with those of Mohamed et al [22] and Delahanty et al [23]. The American Association of Diabetes Educators recommends seven self-care behaviors as new examples of diabetes education, including healthy eating, physical exercise, monitoring, adherence to drugs, problem solving, mitigation and risk reduction [17]. The subjects of Tel group showed weight loss through healthy eating and physical activity, which also reduced the blood sugar. However, BMI of control group had a slight upward trend , but have no prominent difference($P>0.05$). This further proved the telemedicine management is effective to metabolic control.

In addition, 412 patients were followed up, a small number of subjects were lost during the 2 years follow- up period, and ITT and PP analysis revealed similar results, consequently, drawing the conclusion that it was reliable. However, because the lost subjects in control group exceeded 15%, it was failure comparison in 3 years, but the lost subjects of Tel group was less than 5%. Further investigation on the cause of the loss during follow-up by phone-call showed that the four main reasons were referring to worse diabetes management, lower income, lower education level, and greater distance to the hospital; this population with poor sugar control was especially vulnerable to disengagement. West China is regarded as the poorest with the backward areas， subjects have less economic development as they live on low income for a longtime, with poor diabetes care and lower education level. These might be the major cause of loss of subjects during follow-up. Furthermore, these results suggested that it was important to note that increasing the telemedicine management coverage for more subjects received point-of-care diabetes education, self-management coaching, and medication adjustment. Therefore, perfect diabetes telemedicine management might optimize glycemic control and improve compliance leading to reduction of diabetes complications, decreased rates of hospitalization, and mortality.

5. Conclusions

In conclusion, diabetes telemedicine management intervention can decrease blood sugar, blood pressure and blood lipid compared with usual care , and may still improve compliance to reduce the loss during follow-up. Consequently, diabetes telemedicine may be a useful tool for managing diabetes mellitus.

Acknowledgements

We would like to thank the patients and investigators of the study group for participating in this trial. This work was supported by the Natural Science Foundation of Shanxi Province, China (Grant No. 2012sp2-08). We want to express our immeasurable thanks to Prof Taixiang Wu (Chinese Cochrane Center, Chinese Evidence-Based Medicine Center & Regional Clinical Epidemiology Re, West China Hospital, Sichuan University, Chengdu, China) for his assistance with statistical data analysis.

Author Contributions

Conceived and designed the experiments: YL . Performed the experiments: YL WGM CQX JB YYH . Analyzed the data: YL JB WGM .Contributed reagents/materials/analysis tools: YL WGM CQX JB YYH. Wrote the manuscript: YL .

Competing Interests

There are no conflicts of interest which it is considered would have been likely to influence the content of this paper.

References

[1] Zimmet, P., et al., Diabetes mellitus statistics on prevalence and mortality: facts and fallacies. Nature Reviews Endocrinology, 2016. 12(10): 616.

[2] Whiting, D.R., et al., IDF diabetes atlas: global es-

 DOI: https://doi.org/10.30564/jer.v1i1.671

timates of the prevalence of diabetes for 2011 and 2030. Diabetes research and clinical practice, 2011. 94(3): 311-321.

[3] Ning, G., W. Zhao, and W. Wang, Study evaluates prevalence of diabetes among adults in China Chicago. JAMA, 2013. 10: 161-163.

[4] Beck, J., et al., 2017 National standards for diabetes self-management education and support. The Diabetes Educator, 2018. 44(1): 35-50.

[5] Renders, C.M., et al., Interventions to improve the management of diabetes in primary care, outpatient, and community settings: a systematic review. Diabetes care, 2001. 24(10): 1821-1833.

[6] Blonde, L., et al., Patient-directed titration for achieving glycaemic goals using a once-daily basal insulin analogue: an assessment of two different fasting plasma glucose targets-the TITRATETM study. Diabetes, Obesity and Metabolism, 2009. 11(6): 623-631.

[7] Association, A.D., Standards of medical care in diabetes—2016 abridged for primary care providers. Clinical diabetes: a publication of the American Diabetes Association, 2016. 34(1): 3.

[8] Hwang, C., et al., Development and validation of a Chinese version of the diabetes-39 to measure diabetes quality of life in Taiwan. Taiwan J Public Health, 2009. 28: 218-31.

[9] Mendenhall, E., et al., Non-communicable disease syndemics: poverty, depression, and diabetes among low-income populations. The Lancet, 2017. 389(10072): 951-963.

[10] Mullin, B., B.S. Cervantes, and J. Billimek, Material Need Insecurity and Its Concurrent Barriers to Diabetes Management Among Low-Income Latino Adults Receiving Medical Care. Diabetes care, 2019. 42(3): e31-e33.

[11] Parchman, M.L., et al., Competing demands or clinical inertia: the case of elevated glycosylated hemoglobin. The Annals of Family Medicine, 2007. 5(3): 196-201.

[12] Stange, K.C., Is 'clinical inertia'blaming without understanding? Are competing demands excuses? The Annals of Family Medicine, 2007. 5(4): 371-374.

[13] Byers, D., et al., Facilitators and barriers to Type 2 diabetes self-management among rural African American adults. Journal of Health Disparities Research and Practice, 2016. 9(1): p. 9.

[14] Johansson, T., et al., Effectiveness of a peer support programme versus usual care in disease management of diabetes mellitus type 2 regarding improvement of metabolic control: a cluster-randomised controlled trial. Journal of diabetes research, 2016, 2016.

[15] Wright, A.K., et al., Life expectancy and cause-specific mortality in type 2 diabetes: a population-based cohort study quantifying relationships in ethnic subgroups. Diabetes Care, 2017. 40(3): 338-345.

[16] Glazier, R.H., et al., A systematic review of interventions to improve diabetes care in socially disadvantaged populations. Diabetes care, 2006. 29(7): 1675-1688.

[17] Powers, M.A., et al., Diabetes self-management education and support in type 2 diabetes: a joint position statement of the American Diabetes Association, the American Association of Diabetes Educators, and the Academy of Nutrition and Dietetics. The Diabetes Educator, 2017. 43(1): 40-53.

[18] Izquierdo, R.E., et al., Case management with a diabetes team using home telemedicine: acceptance of treatment recommendations by primary care providers in IDEATel. Telemedicine and e-Health, 2015. 21(12): 980-986.

[19] Weinstock, R.S., et al., Glycemic control and health disparities in older ethnically diverse underserved adults with diabetes: five-year results from the Informatics for Diabetes Education and Telemedicine (IDEATel) study. Diabetes care, 2011. 34(2): 274-279.

[20] Association, A.D., 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. Diabetes care, 2018. 41(Supplement 1): S13-S27.

[21] Berkowitz, S.A., et al., Material need insecurities, control of diabetes mellitus, and use of health care resources: results of the Measuring Economic Insecurity in Diabetes study. JAMA internal medicine, 2015. 175(2): 257-265.

[22] Mohamed, H., et al., Culturally sensitive patient-centred educational programme for self-management of type 2 diabetes: a randomized controlled trial. Primary Care Diabetes, 2013. 7(3): 199-206.

[23] Delahanty, L.M., et al., Design and participant characteristics of a primary care adaptation of the Look AHEAD Lifestyle Intervention for weight loss in type 2 diabetes: The REAL HEALTH-diabetes study. Contemporary clinical trials, 2018. 71: 9-17.

DOI: https://doi.org/10.30564/jer.v1i1.671

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research
https://ojs.bilpublishing.com/index.php/jer

ARTICLE

An Analysis of Clinical Characters of Inpatients with Infection in the Department of Endocrinology

Jianying Zhang*

The Township Hospital of Nancai Town, Shunyi District, Beijing, 101300, China

ARTICLE INFO

Article history
Received: 4 April 2019
Accepted: 17 April 2019
Published Online: 30 April 2019

Keywords:
Department of endocrinology
Infection
Inpatient
Clinical analysis

ABSTRACT

Objective: To analyze the clinical characters of 812 inpatients with infection in the Department of Endocrinology. **Methods:** Retrospective exhibition of these patients' clinical characters included undergoing diseases, infectious organs, history illness, blood glucose and glycosylated hemoglobin (HbA1C), biochemical indicators, pathogens training description and results, medical imagines, antibiotic utilization, length of stay and hospital costs, final diagnosis and situations. **Results:** Non-diabetic patients accounted for 176 (21.67%), who were the cases of untreated well hyperthyroidism, mainly suffered with respiratory tract infection. Diabetic patients accounted for 636 (78.33%). In the type2 diabetes patients 376 (59.12) suffered with urinary tract infection. 192 (30.19%) suffered with respiratory system infection, 124 (19.50%) were accompanied with diabetic foot infection, which had 74 (59.67%) patients with HbA1C>9.0%.Statistical comparisons showed that the days of antibiotic use and average length of stay in hospital per capita in patients with HbA1C≥8% were more than ones with HbA1C<8% in those with diabetic infections (P<0.01) . The days of antibiotic use per capita in patients with HbA1C>9% were more than ones with HbA1C<7% in those with diabetic foot infections (P<0.01). **Conclusion:** Endocrine diseases lack rigid and effective long-term control, which may result in the complications involved with urinary tract, respiratory tract and infections in other organs. The time of hospitalization per capita and the duration of antibiotic use rise are longer in diabetic patients with poor blood sugar control and diabetic foot infection.

1. Introduction

Patients with endocrinology have immune dysfunction. If chronic underlying diseases cannot be effectively monitored for a long time, infectious diseases of different systems will continue to occur. The pathogenesis, age, average length of hospital stays, and per capita cost of patients with endocrine diseases who are susceptible to infection, pathogens, and the most common endocrine diabetic population are summarized and compared with diabetes management to attract clinicians' attention. The clinical features of infection in different populations were recognized. This not only provides a possible reference for the early prevention and treatment of infectious diseases, but also helps to strengthen the education of patients, improve

**Corresponding Author:*
Jianying Zhang,
The Township Hospital of Nancai Town, Shunyi District, Beijing, 101300, China;
Email: cindyjianying@yahoo.com

 DOI: https://doi.org/10.30564/jer.v1i1.729

the quality of life of patients, shorten the length of hospitalization and reduce the cost of treatment.

2. Objects and Methods

2.1 Research Object

Clinical analysis was conducted on 812 patients admitted to the Department of Endocrinology of the Second People's Hospital of Yunnan Province with concurrent infection from March 2015 to March 2018.There were 341 males and 471 females. The age is 12 ~ 86 years old, with an average of (59.16±10.21) years old. The course of the underlying disease ranged from 10 d ~ 33 a with an average of (104.97 ± 85.44) months.

2.2 Research Method

The clinical data of each patient was entered into the Excel table, including general demographic data, underlying disease course, concomitant disease, time of infection, site of infection, past medical history, diabetes type of diabetes, and management of blood glucose, admission of glycated hemoglobin HbA1C, biochemical metabolic indicators, pathogen culture name and results, ultrasound or X-ray or CT or MRI imaging data, antibiotic use, length of hospital stay, hospitalization expenses, discharge diagnosis, etc. Further statistical analysis was performed.

2.3 Statistical Treatment

SPSS statistical software was used to process the data. The enumeration data are expressed in constituent ratio. Measurement data are expressed as mean ± standard deviation (±s).Independent sample t test was used for intragroup comparison. One-way ANOVA was used for comparison between groups.P <0.05 was considered statistically significant.

3. Results

3.1 Major Diseases and Associated Infection Sites

Among the 812 infected patients, 176 were non-diabetic patients with concurrent infection. There were 75 males and 101 females. These are mainly endocrine diseases such as hyperthyroidism and methylene inflammation. The main infection sites are shown in Table 1.The number of patients with concomitant diabetes was 636.There were 266 males and 370 females. The age was(60.08 ± 13.61) years old. The course of diabetes is (102.54 ± 86.14) months. The main infection sites are shown in Table 2.

Table 1. Major diseases and associated infection sites in non-diabetic patients with concurrent infection

Disease and associated infection site	*n*	Composition ratio (%)
Hyperthyroidism		
Complicated with upper respiratory tract infection	39	22.16
Severe pulmonary infection secondary to agranulocytosis	26	14.77
Urinary tract infection	12	6.82
Complicated with digestive tract infection	11	6.25
Methylene inflammation with respiratory infection	38	21.59
Thyroid-associated ophthalmopathy with respiratory or urinary tract infections	18	10.23
Thyroid nodules with respiratory or urinary tract infections	9	5.11
Hypothyroidism with respiratory tract infection	8	4.55
Gouty arthritis with skin infection	6	3.41
Climacteric syndrome with respiratory or urinary tract infections	4	2.27
Cushing's syndrome with pneumonia	2	1.14
Pituitary crisis with pneumonia	1	0.57
Sheehan syndromewith bronchitis	1	0.57
Primary aldosteronism with upper respiratory tract infection	1	0.57

Table2. The main site of infection in diabetic patients with infection

Disease and associated infection site	*n*	Composition ratio (%)
Type 1 diabetes (n=22)		
Male	6	
Female	16	
Combined respiratory infection (n=18)		2.83
Male	8	
Female	10	
Combined urinary tract infection (n=10)		1.57
Male	4	
Female	6	
Combined acute enteritis (n=2)		0.31
Female	2	
Hidden autoimmune diabetes in adults (n = 4)		
Male	3	
Female	1	

DOI: https://doi.org/10.30564/jer.v1i1.729

Combined ketosis and respiratory infection (n=4)	4	0.63
Male	3	
Female	1	
Type 2 diabetes (n=610)		
Male	257	
Female	353	
Combined urinary tract infection (n=376)		59.12
Male	149	
Female	227	
Combined respiratory infection (n=192)		30.19
Male	106	
Female	86	
Combined digestive system infection (n=37)		5.82
Male	26	
Female	11	
Inflammation associated with oral and maxillofacial space infection (n=7)		1.10
Male	5	
Female	2	
Combined orbital and intraocular inflammation (n = 5)		0.79
Male	2	
Female	3	
Diabetic foot infection (n = 124)		19.50
Male	83	
Female	41	

3.2 Diabetes Mellitus Patients with Multiple Systemic Infections, Repeated Hospitalizations with Infections and Nosocomial Infections

3.2.1 Patients with multiple systemic infections

A total of 51 patients were infected with two or more systemic infections. Among them, 8 cases (4.55%) were nonglycosuria, and 43 cases (6.76%) were diabetes.

3.2.2 Recurrent Hospitalization of Diabetic Patients with Infection

A total of 44 patients (7.21%) with type 2 diabetes mellitus were hospitalized repeatedly within 3 years. Among them, 17 cases (38.64%) were diabetic foot complicated with infection. The patients with diabetes who were repeatedly hospitalized for 3 times or more with concurrent infection were 7 cases (15.91%).3 cases (13.64%) with type 1 diabetes mellitus were hospitalized repeatedly within 3 a.

3.2.3 Nosocomial Infection

In 3a, 121 cases (14.90%) had nosocomial infection. 5 cases (0.62%) were non-diabetic. Among them, 3 cases were secondary respiratory tract infection caused by hyperthyroidism, and 2 cases were urinary tract infection.116 cases (14.29%) were diabetes. This included 54 cases of upper respiratory tract infection (46.55%), 37 cases of painless urinary tract infection (31.90%), 7 cases of gastrointestinal tract infection, and 18 cases of secondary intestinal, oral or urinary tract infection (15.52%) after antibiotics.

3.3 Pathogenic Test Results and Selection of Antibiotics

3.3.1 Etiology Test Results

In accordance with the principles of antibiotic use, patients admitted to the hospital with infectious symptoms, signs or examination data suggest that the infected person should be examined for relevant etiology before using antibiotics, such as swabs of pharynx or culture of sputum, urine, feces, blood and broken secretions. The inspection rate of the specimen is 100%. A total of 304 cases (37.44%) of the pathogenic bacteria were cultivated in infected patients. The main results of the pathogenic bacteria cultured in different specimens were as shown in Table 3.

Table 3. The main results of the pathogenic bacteria cultured in different specimens (n)

Main pathogen name	Urine	Foot secretion	Sputum and throat swab	Blood	Foreskin secretion	Maxillofacial space exudate	Eye secretions
Escherichia coli	117	12	4	14	1		
Klebsiella pneumoniae	11	8	24	6			
Staphylococcus aureus		22				2	
Proteus mirabilis		7					
Enterobacter cloacae		6					
Acinetobacter baumannii		6	4	4			
Streptococcus pneumoniae							
Salmonella							
Streptococcus agalactiae							1

 DOI: https://doi.org/10.30564/jer.v1i1.729

3.3.2 Developed Resistant Bacteria

A total of 95 resistant bacteria were cultured, accounting for 31.25% of the pathogenic bacteria. Among them, 53 cases of drug-resistant bacteria were cultured in urine, accounting for 17.43% of the pathogenic bacteria. There were 49 cases of multi-drug resistant bacteria, including 44 cases of escherichia coli, 4 cases of klebsiella pneumoniae, 1 case of proteus singularity, and 4 cases of pandrug-resistant escherichia coli. Twenty cases of multiple drug-resistant bacteria were cultured from foot secretions, including 14 cases of escherichia coli, 3 cases of klebsiella pneumoniae, 2 cases of staphylococcus aureus, 1 case of streptococcus haemolyticus, and 4 cases of pandrug-resistant bacteria, all of which were acinetobacter baumannii.6 cases of multi-drug resistant bacteria were cultured from sputum and pharyngeal swabs, including 3 cases of escherichia coli, 3 cases of klebsiella pneumoniae and 5 cases of pandrug-resistant bacteria, all of which were acinetobacter baumannii.Three cases of escherichia coli with multiple drug resistance were cultured in blood. 4 cases of pandrug-resistant bacteria included 2 cases of mrsa and 2 cases of acinetobacter baumannii.

3.3.3 Selection of Antibiotics

Antibiotics are mainly selected or replaced based on the results of drug susceptibility testing. However, some patients have been taking oral antibiotics for a long time before admission, or injecting antibiotics at local clinics, and they are unable to produce pathogenic bacteria. Therefore, the antibiotics can only be selected empirically according to the clinical judgment of community-acquired infection or nosocomial infection to observe the clinical efficacy. Infection indicators such as blood routine, urine routine, procalcitonin, chest radiographs or CT and other imaging data were monitored and adjusted in time, and the drugs were administered according to the grading management system of antimicrobial drugs in the hospital as far as possible. The frequency of antibiotics from high to low was pentahydrate cefazoline, cefmenoxime, cefdiazine, ceftian, levofloxacin, metronidazole, tinidazole, penicillin, azithromycin, piperacillin, tazobactam, cefoperazone/sulbactam, meropenem, imipenem and vancomycin, respectively.The comparison between glycated hemoglobin and age, duration of disease, days of antibiotic use, length of hospital stay, and cost in patients with diabetes mellitus and diabetic foot infection are shown in Tables 4 and 5.

Table 4. The comparison of age, course of disease, days of antibiotic use, length of hospital stay and costs between diabetic patients with infections with HbA1C<8% and those with HbA1C≥8%

Item	HbA1C<8%	HbA1C≥8%	*t*	*P*
Age	61.13±15.05	59.68±13.01	1.156	0.249
Duration of diabetes(month)	93.84±82.93	106.18±87.10	-1.686	0.092
Per capita days of antibiotic use (d)	1.53±3.79	10±4.53	-3.424	0.001
Per capita hospitalization days (d)	11.17±3.67	12.49±4.51	-3.461	0.001
Per capita hospitalization expenses (RMB)	12 647.77±7 847.64	14 324.14±6 312.31	-2.801	0.005

Table 5. The comparison of age, course of disease, days of antibiotic use, length of hospital stay and costs between diabetic patients with infections with HbA1C<7%, ones with HbA1C from 7% to 9% and those withHbA1C> 9%

Item	HbA1C<7%	HbA1C 7%~9%	HbA1C> 9%	F	P
Age	66.24±15.41	61.76±11.55	61.03±11.19	1.021	0.363
Duration of diabetes(month)	111±85.03	119.97±87.53	111.26±84.33	0.139	0.0871
Per capita days of antibiotic use (d)	7.18±3.22	11.5±4.59	12.95±4.90	9.063	0.000
Per capita hospitalization days (d)	9.58±2.35	13.82±6.89	13.70±5.30	2.937	0.057
Per capita hospitalization expenses (RMB)	12211.77± 2920.27	18792.98± 10795.06	18163.94± 7685.47	2.928	0.057

4. Discussion

Among the 812 patients with coinfection in the Department of Endocrinology of The Second People's Hospital of Yunnan Province from March 2015 to March 2018, the basic diseases of coinfection were mainly common endocrine diseases.176 cases (21.67%) were non-diabetic, and the number of females is more than males. Patients with hyperthyroidism are often in a state of high metabolism and are prone to malnutrition. In particular, hyperthyroidism was not treated or controlled in time, and autoimmune disorders were associated

DOI: https://doi.org/10.30564/jer.v1i1.729

with increased risk of various infections and severe infections. However, at present, insufficient attention has been paid to various infections in patients with hyperthyroidism, and relevant research reports are lacking[1]. In this study, 88 cases of hyperthyroidism were associated with infection, including 39 cases (22.16%) with upper respiratory tract infection and 26 cases (14.77%) with severe granulocytosis. In addition, endocrine disorders with autoimmune disorders were also prone to co-infection, such as subthyroiditis combined with respiratory tract infection in 38 cases (21.59%). Other thyroid related diseases, climacteric syndrome, gout, adrenal and pituitary diseases are also associated with different organ infections. If patients with diabetes do not timely control sugar, long-term high blood sugar will cause serious damage to the function of the body's white blood cells and reduce the immunity of various body organs, which is conducive to the invasion and reproduction of bacteria. In particular, patients with poor glycemic control are associated with stress-induced ketosis or acidosis, which leads to increased difficulty in controlling infection during treatment, and the patient's condition may worsen or even severe infection [2]. In this study, 636 patients (78.33%) with diabetes were older and had a longer course of diabetes. The number of females is more than males.

The prevalence of diabetes mellitus associated with urinary tract infection in women is high, which is related to the structure of the female urinary tract. The amount of estrogen secretion in menopausal women is significantly reduced, the urethra is prone to atrophy, and the vaginal flora is dysregulated. In patients with poor long-term glycemic control, the ability of white blood cells, mononuclear cells, megakaryocyte chemotaxis and phagocytosis are all affected, which increases the incidence and extent of infection. It is often manifested as urinary tract infection or acute pyelonephritis [3-4].In the study of type 2 diabetes, 458 patients (72.01%) were HbA1C > 8.0%.There were 376 cases of urinary tract infections, which accounted for 59.12%. Similarly, the incidence of women is higher than that of men (149 males and 227 females).Hyperglycemia can result in hypertrophy of basement membrane of capillaries in lung tissue and prolonged diffusion distance of blood oxygen. As the pulmonary capillary bed becomes less, the pulmonary surfactant decreases, the glycosylated protein increases, and oxygen dissociation is difficult. Moreover, the ventilatory/blood flow ratio imbalance and oxygen carrying capacity are significantly reduced, which leads to tissue hypoxia and is more prone to pulmonary infection [5].In the 22 cases of type 1 diabetes in the study (6 males and 16 females), the most common ones were respiratory tract infection (n = 18) and urinary tract infection (n = 10).Ketosis and respiratory tract infection occurred in all 4 cases (3 males and 1 female) of occult autoimmune diabetes mellitus in adults.192 cases of type 2 diabetes mellitus (30.19%) were accompanied by respiratory tract infection, and the number of males is more than females (106 males and 86 females).Age is also a risk factor for diabetic foot, and the incidence increases with age [6]. Foreign studies [7] suggest that the incidence of diabetic foot in men is higher than that in women. Because men work a lot, it is more likely to cause changes in foot pressure or secondary infections. Among the patients with diabetes mellitus, 124 (19.50%) were diabetic foot infections, and the number of males is more than females (83 males and 41 females).The older, the longer the course of diabetes.HbA1C> 9% of patients were 74 cases (59.67%), and HbA1C< 7% was 12 cases (9.68%).

Diabetic patients have abnormal metabolism of glucose, lipid and protein, and are often associated with hypoproteinemia, which increases the risk, frequency and degree of infection and mortality of multiple organ infections [8].Among the patients with multiple systemic infections in this study, 8 (4.55%) were non-diabetic, and 43 (6.76%) were diabetic. A total of 44 patients with type 2 diabetes who were repeatedly hospitalized with infection in 3a were mostly associated with hypertension, dyslipidemia, diabetic neuropathy and vascular disease, nephropathy, eye disease and hypoproteinemia. Among them, diabetic foot infection accounted for 38.64%; diabetes patients with repeated hospitalization ≥3 times or more had 15.91%.4 cases were diabetic foot infection. The four cases were examined at HbA1C 8.0% to 12.5%. One female patient was 65 years old and had a diabetes course of 13 a. The male patients were aged 45, 59 and 66 years old, and the duration of diabetes was 7, 10, 20 a, respectively. Diabetes mellitus is often complicated with neurogenic bladder and urinary retention, which leads to recurrent urinary tract infection in patients with diabetes mellitus. In this study, 3 patients with type 1 diabetes were repeatedly hospitalized and infected.1 case was a 16-year-old male, whose course of diabetes was 11a. He was complicated with cataract in both eyes, diabetic neuropathy, recurrent urinary tract infection secondary renal insufficiency and urinary retention. The patient was admitted to the urology department for cystostomy with continuous indwelling catheter for 4 times within 3 a and left the hospital.

In the hospital, 121 patients (14.90%) were infect-

 DOI: https://doi.org/10.30564/jer.v1i1.729

ed with nosocomial infections: non-diabetic patients were mainly secondary respiratory infection caused by hyperthyroidism. The main causes of diabetes were painless urinary tract infection (31.90%), secondary intestinal, oral mucosa or urinary tract infection (15.52%), and upper respiratory tract infection (46.55%).The results were similar to those reported in diabetic patients with nosocomial infections [9].

Urinary tract infections are mainly Gram-negative bacterial infections, which are mainly Escherichia coli. Adhesion of the bacteria is an important cause of retrograde infection. When the immunity of diabetes declines, endogenous infection will occur in the body, and drug sensitivity test shows that escherichia coli has high drug resistance. In this study, 151 cases of pathogenic bacteria were cultured in urine, of which 117 cases were mainlyEscherichia coli. A total of 53 resistant bacteria were cultured in urine, accounting for 17.43% of pathogenic bacteria, and 49 cases were multi-drug resistant bacteria, which were still mainly Escherichia coli. Diabetic patients are often associated with asymptomatic bacteriuria. Whether early drug intervention is needed is still controversial [10].In view of the increase of multiple drug-resistant bacteria infections, it is necessary to regularly monitor and timely analyze the drug resistance, rationally select antibiotics, and effectively prevent and control the emergence of drug-resistant bacteria. There are many kinds of pathogenic microorganisms in patients with diabetic foot infection. They are mainly drug-resistant bacterial infections or mixed bacterial infections, and it is difficult to treat diabetic foot infection clinically [11].In this study, 77 cases of pathogenic bacteria were cultured in the foot secretions, which were mainly Staphylococcus aureus. Among them, there were 24 cases resistant bacteria and 20 cases multi-drug resistant bacteria, which were mainly Escherichia coli.Klebsiella pneumoniae, one of the important opportunistic pathogens, is usually colonized in the respiratory tract and intestinal tract of normal people.It is usuallyhospital-acquired infection. The increased risk of infection is associated with low patient immunity, such as diabetes, malignant tumors, renal failure, glucocorticoids, radiotherapy and chemotherapy, etc. [12].With the large-scale application of lactam antibiotics, especially the third-generation cephalosporins, extended-spectrum lactam-resistant bacteria have also been induced [13].In this study, 44 cases of pathogenic bacteria were cultured in throat swabs, which were mainly 24 cases of Klebsiella pneumoniae. There were 6 cases of multi-drug resistant bacteria, including 3 cases of Escherichia coli and 3 cases of Klebsiella pneumoniae. 5 cases of pan-resistant bacteria were Acinetobacter baumannii.

For the general diabetic population, the control target HbA1C < 7% is required[14].Diabetic patients with long course of disease and older age often have more complications and fail to reach the standard. By referring to domestic and foreign literatures, it can be appropriately adjusted to 8.0% ~ 8.5% [15].According to the latest Chinese guidelines, HbA1C < 8% may be more suitable for patients with significant vascular complications or severe comorbidities with a shorter life expectancy [14].Therefore, in this study, HbA1C < 8% and ≥ 8% were used to compare the difference between the number of days of per capita antibiotic use, the length of hospital stays, and the per capita hospitalization cost.The results showed that the number of days of antibiotic use per person and the number of days of hospitalization per capita were significantly higher in patients with HbA1C≥8% diabetes infection than those with HbA1C<8% ($P < 0.01$).This indicates that patients with poor glycemic control have a long period of antibiotic use during hospitalization and prolonged per capita hospitalization. For diabetic foot patients, strictly speaking, when HbA1C < 7%, the incidence of foot ulcers and infections can be reduced, and the risk of amputation can be reduced [16].American scholars suggest that if the quality of life is poor and the expected survival period is short, the control target can be adjusted to HbA1C < 9% [15].Therefore, in this study, HbA1C < 7%, HbA1C7% ~ 9% and HbA1C> 9% were selected to divide the combined infection of 3a diabetic foot. The statistical results showed that the number of days of antibiotic use per capita was significantly higher in HbA1C>9% diabetic foot infection patients than in HbA1C <7% ($P < 0.01$).This indicates that patients with poor glycemic control of diabetic foot complicated with infection spend a long time in hospital on antibiotics.

Medicine is a multidisciplinary knowledge group, as is the endocrinology profession. In particular, diabetes, which can be associated with multiple systemic diseases, requires specialized cooperation in addition to specialized treatments. Among the study cases, 6 cases were successfully transferred to the laminar flow ward of the hematology department due to the aggravation of respiratory tract infection secondary to hyperthyroidism combined with granulocyte deficiency. Nine patients were transferred to ICU for treatment of diabetes complicated with severe respiratory failure or heart failure and unstable vital signs. Two cases died of ineffective rescue. After diabetes was admitted to hos-

DOI: https://doi.org/10.30564/jer.v1i1.729

pital, 4 patients were diagnosed with tuberculosis, and the symptoms of tuberculosis poisoning were obvious. They were transferred to the provincial center for disease control and prevention for treatment. There were 5 cases of diabetic foot infection secondary to sepsis, the condition was extremely critical. They were transferred to ICU for treatment, and 2 cases died of ineffective rescue.3 cases were treated with osteomyelitis and 3 cases were treated with vascular occlusion and vascular surgery. Three patients with diabetes mellitus with persistent high fever were referred to hepatobiliary surgery for diagnosis and treatment after hepatic abscess combined with imaging. Two patients with diabetes mellitus complicated with endophthalmitis and infection of periorbital space were transferred to ophthalmology. Two patients with diabetes complicated with oral and maxillofacial space infection were transferred to maxillofacial surgery. The remaining patients were all in the endocrinology department of the Second People's Hospital of Yunnan Province, and if necessary, they were timely invited to consult relevant departments such as respiratory, urinary, digestive, renal, blood, pharmaceutical and nutrition departments to adjust the diagnosis and treatment plan. Eventually, when the disease is relatively stable, the patient can leave the hospital.

In the face of the long-term and comprehensive and effective management needs of many chronic diseases, such as endocrine system diseases, primary hospitals or grade hospitals should do their best to supervise basic diseases as early as possible, so as to reduce the occurrence and progress of associated diseases, such as infectious diseases. Patients with infections that may have been induced or have been associated are identified and early standardized examination is performed. Rational drug selection and multidisciplinary cooperative treatment may shorten the hospitalization period and reduce the cost of treatment, which is conducive to improving the quality of life of patients.

References

[1] Cui W, Deng B,Wang W,et al. Graves hyperthyroidism accompanied with acute hepatitis B virus infection: an extra hepatic manifestation [J]. Virology Journal,2016,13(9): 80-81.

[2] Gyssens I C. Efficacy and safely of IV/PO moxifloxacinand IV piperacillin/ tazobactam followed by PO amoxicillin/clavulanic acid in the treatment of diabetic foot infections: Results of the Relief study[J]. Infection, 2013, 1 (1): 125.

[3] Sorensen S M, Schcnheyder H C, Nielsen H. The role of imaging of the urinary tract in patients with urosepsis [J]. Int J Infect Dis, 2013, 17 (5) :299-303.

[4] Arrellano-Valdez F, Urrutia-Osorio M, Ar-royo C, et al. A comprehensive review of urologic complications in patients with diabetes [J]. Springer Plus, 2014, 11 (3): 54-59.

[5] Yi Zou, Shuyu Huang, Yimin Yan. Clinical Analysis of Elderly Patients with Type 2 Diabetes Mellitus Complicated with Pulmonary Infection [J]. Journal of Practical Diabetology. 2015, 11(1): 36-37.

[6] Dubsky M, Jirkovská A, Bem R, et al. Risk factors for recurrence of diabetic foot ulers: prospective follow-up analysis in the Euro diale subgroup [J]. Int Wound J, 2013, 10 (5): 555-561.

[7] Neto A M, Zantut-Wittmannn D E, Fernandes T D, et al. Risk factors for ulceration and amputation in diabetic foot: study in a cohort of 496 patients[J]. Endcrine, 2013, 44 (1): 119-124.

[8] Hongxia Sun, Xianrong Liu, Chuanbo Zhou. Etiology and Drug Resistance of Pulmonary Infection in Diabetic Patients [J]. Chinese Journal of Nosocomiology, 2016, 26(2): 332-334.

[9] Ling Li, Rong Shen, Xinrong Wang, Distribution and Drug Resistance of Common Pathogens in Hospital Infection of Inpatients with Respiratory Diseases [J]. Chinese Journal of Nosocomiology, 2015, 35(3): 531-533.

[10] Nicolle L E. Asymptomatic bacteriuria[J]. Curr Opin Infect Dis, 2014, 27 (1):90-96.

[11] Lan Yao. Analysis of Pathogen Distribution and Drug Resistance in 95 Patients with Diabetic Foot Infection [J]. Acta Academiae Medicinae Wannan, 2015, 34(5): 464-468.

[12] Hsiang C W, Liu C H, Fan H L, et al. Clinical features and computed tomography characteristics of non-Klebsiella pneumoniae liver abscesses in elderly (>65 years) and nonelderly patients [J]. Yonsei Med J, 2015, 56 (2): 519-528.

[13] Boyle D P, Zembower T R. Epidemiology and management of emerging drug-resistant gram-negative bacteria: Extended-spectrum IL lactamases and beyond[J]. Urol Clin North Am, 2015, 42 (4): 493-505.

[14] Chinese Diabetes Society. Guidelines for the Prevention and Treatment of Type 2 Diabetes in China (2013 edition) [J]. Chinese Journal of Endocrinology and Metabolism, 2014, 30 (10): 893-942.

[15] Jing Dai, Lixin Guo. Interpretation of the 2013 International Diabetes Federation Management Guidelines for Type 2 Diabetes in the Elderly [J]. Chinese Journal of the Frontiers of Medical Sci-

 DOI: https://doi.org/10.30564/jer.v1i1.729

ence. 2014, 6(2): 98-102.
[16] Diabetic Foot Disease Society of China International Exchange and Promotion Association for Medical and Healthcare. Chinese Diabetes Foot Treatment Guide [J]. National Medical Journal of China. 2017, 97(4): 251-258.

DOI: https://doi.org/10.30564/jer.v1i1.729

Author Guidelines

This document provides some guidelines to authors for submission in order to work towards a seamless submission process. While complete adherence to the following guidelines is not enforced, authors should note that following through with the guidelines will be helpful in expediting the copyediting and proofreading processes, and allow for improved readability during the review process.

Ⅰ. Format

- Program: Microsoft Word (preferred)
- Font: Times New Roman
- Size: 12
- Style: Normal
- Paragraph: Justified
- Required Documents

Ⅱ. Cover Letter

All articles should include a cover letter as a separate document.

The cover letter should include:

- Names and affiliation of author(s)

The corresponding author should be identified.

Eg. Department, University, Province/City/State, Postal Code, Country

- A brief description of the novelty and importance of the findings detailed in the paper

Declaration

v Conflict of Interest

Examples of conflicts of interest include (but are not limited to):

- Research grants
- Honoria
- Employment or consultation
- Project sponsors
- Author’s position on advisory boards or board of directors/management relationships
- Multiple affiliation
- Other financial relationships/support
- Informed Consent

This section confirms that written consent was obtained from all participants prior to the study.

- Ethical Approval

Eg. The paper received the ethical approval of XXX Ethics Committee.

- Trial Registration

Eg. Name of Trial Registry: Trial Registration Number

- Contributorship

The role(s) that each author undertook should be reflected in this section. This section affirms that each credited author has had a significant contribution to the article.

1. Main Manuscript
2. Reference List
3. Supplementary Data/Information

Supplementary figures, small tables, text etc.

As supplementary data/information is not copyedited/proofread, kindly ensure that the section is free from errors, and is presented clearly.

Ⅲ. Abstract

A general introduction to the research topic of the paper should be provided, along with a brief summary of its main results and implications. Kindly ensure the abstract is self-contained and remains readable to a wider audience. The abstract should also be kept to a maximum of 200 words.

Authors should also include 5-8 keywords after the abstract, separated by a semi-colon, avoiding the words already used in the title of the article.

Abstract and keywords should be reflected as font size 14.

Ⅳ. Title

The title should not exceed 50 words. Authors are encouraged to keep their titles succinct and relevant.

Titles should be reflected as font size 26, and in bold type.

Ⅳ. Section Headings

Section headings, sub-headings, and sub-subheadings should be differentiated by font size.

Section Headings: Font size 22, bold type

Sub-Headings: Font size 16, bold type

Sub-Subheadings: Font size 14, bold type

Main Manuscript Outline

Ⅴ. Introduction

The introduction should highlight the significance of the research conducted, in particular, in relation to current state of research in the field. A clear research objective should be conveyed within a single sentence.

Ⅵ. Methodology/Methods

In this section, the methods used to obtain the results in the paper should be clearly elucidated. This allows readers to be able to replicate the study in the future. Authors should ensure that any references made to other research or experiments should be clearly cited.

Ⅶ. Results

In this section, the results of experiments conducted should be detailed. The results should not be discussed at length in

this section. Alternatively, Results and Discussion can also be combined to a single section.

Ⅷ. Discussion

In this section, the results of the experiments conducted can be discussed in detail. Authors should discuss the direct and indirect implications of their findings, and also discuss if the results obtain reflect the current state of research in the field. Applications for the research should be discussed in this section. Suggestions for future research can also be discussed in this section.

Ⅸ. Conclusion

This section offers closure for the paper. An effective conclusion will need to sum up the principal findings of the papers, and its implications for further research.

Ⅹ. References

References should be included as a separate page from the main manuscript. For parts of the manuscript that have referenced a particular source, a superscript (ie. [x]) should be included next to the referenced text.

[x] refers to the allocated number of the source under the Reference List (eg. [1], [2], [3])

In the References section, the corresponding source should be referenced as:

[x] Author(s). Article Title [Publication Type]. Journal Name, Vol. No., Issue No.: Page numbers. (DOI number)

Ⅺ. Glossary of Publication Type

J = Journal/Magazine

M = Monograph/Book

C = (Article) Collection

D = Dissertation/Thesis

P = Patent

S = Standards

N = Newspapers

R = Reports

Kindly note that the order of appearance of the referenced source should follow its order of appearance in the main manuscript.

Graphs, Figures, Tables, and Equations

Graphs, figures and tables should be labelled closely below it and aligned to the center. Each data presentation type should be labelled as Graph, Figure, or Table, and its sequence should be in running order, separate from each other.

Equations should be aligned to the left, and numbered with in running order with its number in parenthesis (aligned right).

Ⅻ. Others

Conflicts of interest, acknowledgements, and publication ethics should also be declared in the final version of the manuscript. Instructions have been provided as its counterpart under Cover Letter.

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Journal of Endocrinology Research

Aims and Scope

Journal of Endocrinology Research is an international peer-reviewed journal operating under the open-access publishing model. The journal is focused on the promotion of research of the endocrine system, a vital component of the body's self-regulatory function.

The scope of the Journal of Endocrinology Research includes, but is not limited to:

- Endocrine structure
- Endocrine glands
- Endocrine cells
- Hormones (reproduction/metabolism/growth/etc.)

Bilingual Publishing Co. (BPC)

Tel:+65 65881289

E-mail:contact@bilpublishing.com

Website:www.bilpublishing.com

About the Publisher

Bilingual Publishing Co(BPC) is an international publisher of online, open access and scholarly peer-reviewed journals covering a wide range of academic disciplines including science, technology, medicine, engineering,education and social science. Reflecting the latest research from a broad sweep of subjects, our content is accessible worldwide – both in print and online.

BPC aims to provide an analytics as well as platform for information exchange and discussion that help organizations and professionals in advancing society for the betterment of mankind. BPC hopes to be indexed by well-known databases in order to expand its reach to the science community, and eventually grow to be a reputable publisher recognized by scholars and researchers around the world.

BPC adopts the Open Journal Systems, see on http://ojs.s-p.sg

Database Inclusion

National Library, Singapore

Asia & Pacific area Science Citation Index

China National Knowledge Infrastructure

Creative Commons

Google Scholar

Crossref

J-Gate

My Science Work

National Library of Singapore

NLB manages the National Library, 26 Public Libraries and the National Archives.

NLB promotes reading, learning and information literacy by providing a trusted, accessible and globally-connected library and information service through the National Library and a comprehensive network of Public Libraries. By forging strategic partnerships to cultivate knowledge sharing, the libraries also encourage appreciation and awareness of Singapore's history through their wide range of programmes and collection on Singapore and regional content. The National Archives of Singapore oversees the collection, preservation and management of public and private archival records, including government files, private memoirs, maps, photographs, oral history interviews and audio-visual materials.

Established on 1 September 1995 as a statutory board, NLB is an agency under the Ministry of Communications and Information (MCI).

Bilingual Publishing Co. is a company registered in Singapore in 1984, whose office is at 12 Eu Tong Sen Street, #08-169, Singapore 059819, enjoying a high reputation in Southeast Asian countries, even around the world.

BILINGUAL PUBLISHING CO.
Pioneer of Global Academics Since 1984

Tel: +65 65881289
E-mail: contact@blipublishing.Com
Website: www.Blipublishing.Com

ISSN 2630-5224 01
9 772630 522191