

# Research Progress on the effect of High altitude and hypoxia on Mitochondrial function in Obesity

Ying Liu<sup>1</sup>, Baoning Qi<sup>1\*</sup>, Wenbin Zhang<sup>2\*</sup>, Yifan Zhang<sup>3</sup>, Wenqing Wei<sup>1</sup>

1. Shaanxi University of Chinese Medicine Xianyang, Shaanxi, 712046, China

2. Military Medical University of the Air Force, Xi'an 710038, China.

3. Department of Occupational and Environmental Health, Fourth Military Medical University, Qinghai Provincial People's Hospital, Xining 810007, China.

---

**Abstract:** Obesity is one of the diseases that threaten human health at present, and it can lead to the increasing prevalence of related complications, such as Insulin resistance, Non-alcoholic fatty liver diseases NAFLD and Type 2 diabetes mellitus and so on. In the whole world, the prevalence rate of obesity is on the rise. Insulin resistance is one of the most common complications of obesity. More and more studies have shown that there is a close relationship between mitochondrial dysfunction and insulin resistance. Skeletal muscle is an important target organ of insulin. Skeletal muscle mitochondrial dysfunction can lead to abnormal glucose and lipid metabolism and further affect the signal pathway of energy metabolism. The new epidemiological survey shows that the prevalence of obesity in high altitude areas is significantly lower than that in plain areas, and the prevalence of overweight and obesity is negatively correlated with altitude. This paper discusses the relationship between high altitude hypoxia and mitochondrial metabolism.

**Keywords:** High Altitude; Hypoxia; Obesity; Insulin; Skeletal Muscle; Mitochondrial Metabolism

---

## 1. Introduction

Obesity has become one of the diseases affecting public health. It increases the risk of insulin resistance (IR), Non-alcoholic fatty liver diseases (NAFLD), Type 2 diabetes mellitus (T2DM), cardiovascular disease, hypertension and some malignant tumors such as breast cancer, rectal cancer and renal cancer [1-3]. Obesity refers to the accumulation of excessive fat in organisms, which is affected by many factors, such as behavioral factors, socio-economic factors, environmental factors, heredity, metabolism and microbiota. In contemporary society, changes in people's lifestyle, such as long-term intake of high-calorie foods, sedentary inactivity and other factors are the most common causes of obesity [4-5]. Sherpa L Y et al. [6] found that there was a negative correlation between BMI and sea pull by comparing the body mass index (Body weight index, BMI) of residents living at different elevations of 1200 m, 2900 m and 3600 m (Nepal and Qinghai-Tibet Plateau). Lippel et al. [7] scholars have shown that living at high school altitude can reduce the weight of obese patients and improve their metabolic function.

## 2. Effects of High altitude hypoxia on body weight, Insulin sensitivity and Lipid Metabolism in obese mice

IR is one of the metabolic characteristics of obesity [8]. IR is a response to the weakening of the effect of insulin, which can lead to a decrease in glucose uptake by muscle and adipose tissue fine cells, a decrease in liver glycogen production, and an increase in intrahepatic glucose production [9-10]. Obesity seriously affects the biological function and function of insulin target tissues including skeletal muscle, liver and adipose tissue. Obesity is considered to be the main risk factor for IR, and IR is the most common metabolic disorder of obesity. They interact and influence each other. The long-term interaction of genetic and environmental factors leads to the occurrence of IR. Genetic factors refer to the susceptibility to insulin resistance. At present, studies are mainly focused on gene mutations, such as insulin receptor, glucose transporter 4 (GLUT-4) and insulin signal pathway. At the same time, aging, nutritional imbalance, lack of exercise and stress are all environmental factors that cause IR, among which overnutrition, especially high-fat diet is one of the most common causes of IR in daily life.

Hill NE et al. [11] showed that insulin resistance improved gradually with the increase of altitude (3600-5120m). Nirmal Aryal et al. [12] reported that with the increase of altitude, triglyceride and low density lipoprotein decreased, while the content of high density lipoprotein

increased.

Compared with residents living below 500m above sea level, healthy residents living between 3000 m and 4500 m above sea level had lower fasting blood glucose<sup>[13]</sup>. The related literature reports further suggest that the median fasting plasma glucose concentration of healthy male residents living above 3000 m is 81.6 mg/dl, while the median fasting plasma glucose concentration of non-pregnant women at low altitude is 91.2 mg/dl; above 3000 m, the median fasting plasma glucose concentration is 71.7 mg/dl, while the blood glucose concentration of low altitude is 85.9 mg/dl<sup>[14]</sup>. Compared with people living at sea level, the analysis of blood glucose in 12 hours found that people living at 3200 m above sea level had lower blood sugar<sup>[15]</sup>.

### **3. Effects of hypoxia at high altitude on mitochondria and insulin signal pathway in obese skeletal muscle**

One of the recognized metabolic characteristics. Skeletal muscle is an important target organ of insulin, and skeletal muscle plays a central role in systemic insulin resistance and metabolic syndrome related to high-fat diet, obesity and aging [16-17]. Skeletal muscle accounts for about 45% of the human body, and is an important tissue involved in human glucose metabolism. Under normal circumstances, 60-70% of the glucose in the blood is metabolized in the skeletal muscle and stored in the form of glycogen, and when needed, the body decomposes into glucose for the benefit of the machine, forming a dynamic balance<sup>[18]</sup>. When obesity, the balance is broken, in order to control elevated blood sugar, the body will secrete more islet, aggravating IR<sup>[19]</sup>.

Mitochondrial dysfunction is associated with the occurrence of insulin resistance [16,20-22]. Mitochondria are the platform for the production and supply of cellular energy ATP<sup>[23]</sup>. Mitochondrial function can be evaluated by changes in mitochondrial-related m-RNA levels, protein levels, activities of key mitochondrial enzymes, mitochondrial size and shape, and substrate oxidation levels. When mitochondrial dysfunction occurs, it can affect glucose metabolism and lipid metabolism and induce glycolipid toxicity<sup>[24]</sup>. Aging is accompanied by the decrease of mitochondrial biomass function, which leads to the decrease of glucose and lipid metabolism, and glycolipid accumulation induces glycolipid toxicity further affect the energy metabolism signal pathway and cause mitochondrial function damage. Increased ROS production, decreased mitochondrial biosynthesis or changes in some mitochondrial-related proteins may impair mitochondrial function, and these factors are also the inducements of insulin resistance[25-26].

Adenosine monophosphate activated protein kinase (AMPK) is a serine / threonine protein kinase in eukaryotic cells. Its function is to regulate energy metabolism and maintain mitochondrial homeostasis as an energy sensor<sup>[27]</sup>. According to the literature, the biological function of mitochondria in skeletal muscle decreased after the knockout of AMPK genes in mice<sup>[28]</sup>. A large number of studies have shown that lipid accumulation in skeletal muscle can reduce insulin sensitivity. Intracellular lipid adenosine monophosphate activated protein kinase (AMPK) is a serine / threonine protein kinase in eukaryotic cells. Its function is to regulate energy metabolism and maintain mitochondrial homeostasis as an energy sensor<sup>[27]</sup>.

Previous studies have confirmed that in the skeletal muscle tissue of patients with IR, the expression of PGC-1 protein decreased significantly, and the number of mitochondria in muscle tissue decreased. The increase of NRFs and Tfam can promote the transcription and replication of mitochondrial DNA and improve the function of mitochondrial biosynthesis[29-30]. A large number of studies have shown that lipid accumulation in skeletal muscle can reduce insulin sensitivity. Intracellular lipid adenosine monophosphate activated protein kinase (AMPK) is a serine / threonine protease in eukaryotic cells. Its function is to regulate energy metabolism and maintain mitochondrial homeostasis as an energy sensor<sup>[27]</sup>.

### **4. Conclusion**

To sum up, high altitude hypoxia can reduce the body weight of obese mice induced by high fat diet, enhance insulin sensitivity, and reduce the contents of free fatty acids and triglycerides in serum. Mitochondria are the main place of energy metabolism. Skeletal muscle and liver contain a large amount of mitochondria. Under high altitude and hypoxia environment, by improving the biosynthesis function of skeletal muscle mitochondria, the content of mitochondria and the level of mitochondrial oxidized phosphate, it can reduce the deposition of lipids in skeletal muscle cells, improve fat decomposition, decrease the content of ceramide and improve the expression of AKT in insulin signal

pathway.

## References

- [1] Chandler M, Cunningham S, Lund E M, et al. Obesity and Associated Comorbidities in People and Companion Animals: A One Health Perspective[J]. *J Comp Pathol*, 2017, 156(4): 296-309.
- [2] Saltiel A R, Olefsky J M. Inflammatory mechanisms linking obesity and metabolic disease[J]. *J Clin Invest*, 2017, 127(1): 1-4.
- [3] Rahtu-Korpela L, Karsikas S, Horkko S, et al. HIF prolyl 4-hydroxylase2 inhibition improves glucose and lipid metabolism and protects against obesity and metabolic dysfunction[J]. *Diabetes*, 2014, 63(10): 3324-33.
- [4] Crichton G E, Alkerwi A. Physical activity, sedentary behavior time and lipid levels in the Observation of Cardiovascular Risk Factors in Luxembourg study[J]. *Lipids Health Dis*, 2015, 14: 87.
- [5] Jezewska-Zychowicz M, Gebiski J, Guzek D, et al. The Associations between Dietary Patterns and Sedentary Behaviors in Polish Adults (LifeStyle Study) [J]. *Nutrients*, 2018, 10(8)
- [6] Sherpa L Y, Deji, Stigum H, et al. Obesity in Tibetans aged 30-70 living at different altitudes under the north and south faces of Mt. Everest[J]. *Int J Environ Res Public Health*, 2010, 7(4): 1670-80.
- [7] Lippel F J, Neubauer S, Schipfer S, et al. Hypobaric hypoxia causes body weight reduction in obese subjects[J]. *Obesity (Silver Spring)*, 2010, 18(4): 675-81.
- [8] Molnar D, Schutz Y. The effect of obesity, age, puberty and gender on resting metabolic rate in children and adolescents[J]. *Eur J Pediatr*, 1997, 156(5): 376-81.
- [9] Meex R C R, Watt M J. Hepatokines: linking nonalcoholic fatty liver disease and insulin resistance[J]. *Nat Rev Endocrinol*, 2017, 13(9): 509-520.
- [10] Zhao R R, O'Sullivan A J, Fiatarone Singh M A. Exercise or physical activity and cognitive function in adults with type 2 diabetes, insulin resistance or impaired glucose tolerance: a systematic review[J]. *Eur Rev Aging Phys Act*, 2018, 15: 1.
- [11] NE H, K D, J M, et al. Continuous Glucose Monitoring at High Altitude-Effects on Glucose Homeostasis[J]. *Medicine and science in sports and exercise*, 2018, 50(8): 1679-1686.
- [12] Aryal N, Weatherall M, Bhatta Y K D, et al. Lipid Profiles, Glycated Hemoglobin, and Diabetes in People Living at High Altitude in Nepal[J]. *Int J Environ Res Public Health*, 2017, 14(9)
- [13] Woolcott O O, Ader M, Bergman R N. Glucose homeostasis during short-term and prolonged exposure to high altitudes[J]. *Endocr Rev*, 2015, 36(2): 149-73.
- [14] Holden J E, Stone C K, Clark C M, et al. Enhanced cardiac metabolism of plasma glucose in high-altitude natives: adaptation against chronic hypoxia[J]. *J Appl Physiol (1985)*, 1995, 79(1): 222-8.
- [15] Castillo O, Woolcott O O, Gonzales E, et al. Residents at high altitude show a lower glucose profile than sea-level residents throughout 12-hour blood continuous monitoring[J]. *High Alt Med Biol*, 2007, 8(4): 307-11
- [16] Putti R, Migliaccio V, Sica R, et al. Skeletal Muscle Mitochondrial Bioenergetics and Morphology in High Fat Diet Induced Obesity and Insulin Resistance: Focus on Dietary Fat Source[J]. *Front Physiol*, 2015, 6: 426.
- [17] Lark D S, Fisher-Wellman K H, Neuffer P D. High-fat load: mechanism(s) of insulin resistance in skeletal muscle[J]. *Int J Obes Suppl*, 2012, 2(Suppl 2): S31-S36
- [18] Crossland H, Skirrow S, Puthuchery Z A, et al. The impact of immobilisation and inflammation on the regulation of muscle mass and insulin resistance: different routes to similar end-points[J]. *J Physiol*, 2019, 597(5): 1259-1270.
- [19] Perez-Schindler J, Philp A. Regulation of skeletal muscle mitochondrial function by nuclear receptors: implications for health and disease[J]. *Clin Sci (Lond)*, 2015, 129(7): 589-99.
- [20] Montgomery M K, Turner N. Mitochondrial dysfunction and insulin resistance: an update[J]. *Endocr Connect*, 2015, 4(1): R1-R15.

- [21] Garcia-Roves P M. Mitochondrial pathophysiology and type 2 diabetes mellitus[J]. Arch Physiol Biochem, 2011, 117(3): 177-87.
- [22] Lewis M T, Kasper J D, Bazil J N, et al. Quantification of Mitochondrial Oxidative Phosphorylation in Metabolic Disease: Application to Type 2 Diabetes[J]. Int J Mol Sci, 2019, 20(21)
- [23] Rovira-Llopis S, Banuls C, Diaz-Morales N, et al. Mitochondrial dynamics in type 2 diabetes: Pathophysiological implications[J]. Redox Biol, 2017, 11: 637-645.
- [24] Varga N A, Pentelenyi K, Balicza P, et al. Mitochondrial dysfunction and autism: comprehensive genetic analyses of children with autism and mtDNA deletion[J]. Behav Brain Funct, 2018, 14(1): 4.
- [25] Parish R, Petersen K F. Mitochondrial dysfunction and type 2 diabetes[J]. Curr Diab Rep, 2005, 5(3): 177-83.
- [26] Civitarese A E, Ravussin E. Mitochondrial energetics and insulin resistance[J]. Endocrinology, 2008, 149(3): 950-4.
- [27] Herzig S, Shaw R J. AMPK: guardian of metabolism and mitochondrial homeostasis[J]. Nat Rev Mol Cell Biol, 2018, 19(2): 121-135.
- [28] Lantier L, Fentz J, Mounier R, et al. AMPK controls exercise endurance, mitochondrial oxidative capacity, and skeletal muscle integrity[J]. FASEB J, 2014, 28(7): 3211-24.
- [29] Kelly D P, Scarpulla R C. Transcriptional regulatory circuits controlling mitochondrial biogenesis and function[J]. Genes Dev, 2004, 18(4): 357-68.
- [30] Ekstrand M I, Falkenberg M, Rantanen A, et al. Mitochondrial transcription factor A regulates mtDNA copy number in mammals[J]. Hum Mol Genet, 2004, 13(9): 935-44.