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MINI REVIEW

Review: The Commonality of Energy Metabolism of Starvation, Disorders of Glucose-Lipid Metabolism, Diabetes Mellitus and Cachexia

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ABSTRACT

Diabetes mellitus, pathoglycemia, dyslipidemia, non-alcoholic fatty liver, overweight, hypertension, and atherosclerosis are common diseases endangering human health. Cachexia is a life-threatening disease condition. Cachexia is associated with increased mortality. Cancer patients with cachexia are less tolerant and have a decreased response to chemotherapy and radiation. Do these diseases have a common pathogenesis? We will discuss the commonality of energy metabolism in starvation, disorders of glucose-lipid metabolism, diabetes mellitus and cachexia, and how the stress response alters the pattern of energy metabolism.

INTRODUCTION

Diabetes mellitus, pathoglycemia, dyslipidemia, non-alcoholic fatty liver, overweight, hypertension, and atherosclerosis are common diseases endangering human health. There were 424 million people worldwide suffered from diabetes mellitus in 2020, and the number is expected to increase to 552 million by 2030 [1]. Cachexia is a state of poor nutrition associated with increased mortality [2], weight loss and decreased skeletal muscle mass are characteristic symptoms of cachexia. Cachexia affects the majority of cancer patients [3,4], but cachexia is not unique to cancer patients. Cachexia also occurs in late stage of many benign diseases, such as chronic heart failure, chronic renal failure, and autoimmune diseases. Cancer patients with cachexia are less tolerant and have a decreased response to chemotherapy and radiation [5]. Cancer cachexia encompasses distinct stages of pre-cachexia, cachexia, and refractory cachexia been validated in the clinical setting [6,7], and cachexia cannot be reversed by nutritional support. In this review, we will discuss the common biological metabolic mechanism in starvation, disorders of glucose-lipid metabolism, diabetes mellitus and cachexia, and explore potential therapeutic options for disorders of glucose-lipid metabolism, diabetes mellitus and cachexia.

The commonality of energy metabolism of starvation, disorders of glucose-lipid metabolism, diabetes mellitus and cachexia

Energy metabolism in starvation state: In starvation state, firstly hepatic glycogen is converted into glucose to replenish blood sugar, then amino acids are converted into glucose in liver, and fat is decomposed into fatty acid and ketone

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body. When fat is exhausted, the energy supply depends on decomposition of protein [8-11]. When the protein exhausted more than 40% of total body, the life is threatened.

The brain is a vital organ of the body. Brain cells rely on glucose or ketone body for energy. The metabolism in brain is very active, 20-25% of total oxygen and 20% of total glucose is consumed in brain, even in starvation state, the brain needs an adequate supply of energy. The red blood cells only depend on the energy from glycolysis.

The biological energy materials include carbohydrate, fat, and protein. When food is abundant, insulin promotes cells to convert glucose into glycogen reserved in the liver and muscles, fatty acid into triglyceride stored in fat cells, and amino acids into protein reserved in muscles. When there are no food available, hyperglycemic hormones promote cells to convert hepatic glycogen into glucose to replenish blood sugar, and initiate gluconeogenesis to convert amino acids into glucose in liver, and initiate lipid mobilization to decompose fat into fatty acid and ketone body. Insulin is the only hormone to promote organismic cells to store energy. On the contrary, there are many hyperglycemic hormones to promote organism to use the energy stored in cells.

1.1.1. Prolonged starvation triggers stress response to alter pattern of energy metabolism. Stress response is non-specific reaction of organism to various stressors. Stress response coordinates functions of systems to overcome risk status. The core of stress response is the axis of hypothalamus, pituitarium and adrenal cortex. Stress response is characterized by a large amount of adrenal cortical hormone. Adrenal corticosteroids resist the function of insulin, and work with hyperglycemic hormones to initiate gluconeogenesis and lipid mobilization. Adrenal corticosteroid alters the pattern of energy metabolism that prevents tissues except brain from consuming glucose, and ensures the adequate supply of glucose for the brain and adequate fatty acid supply for other tissues in starvation state. Without external energy supplement, the quantity of fat determines the survival time of starvation.

Energy metabolism in disorders of glucose-lipid metabolism, diabetes mellitus and cachexiaManifestation: Hyperglycemia, essential hypertension and coronary heart disease are the main manifestations of disorders of glucose-lipid metabolism. Insulin resistance is the common pathological basis of essential hypertension, coronary heart disease and hyperlipidemia [12-15]. The inhibitory effect of insulin on lipolysis is weakened by insulin resistance, free fatty acids are released into circulation [16]. The free fatty acids stimulate liver cells to synthesize and release triglycerides leading to low-density lipoprotein increase and high-density lipoprotein decrease, and the formation of hypertriglyceridemia [17]. The effect of insulin stimulating hemangiectasis through nitric oxide release is weakened by insulin resistance [18,19], and on the contrary, the effect of insulin promoting reabsorption of sodium salts and stimulating proliferation of vascular smooth muscle cell and angiotensin producing is significantly enhanced by insulin resistance [20] leading to high blood pressure.

Hyperglycemia and lipid mobilization are main manifestations of diabetes mellitus. Insulin resistance plays an important role in diabetes mellitus [21,22]. As insulin resistance outlasts compensatory ability of pancreatic beta cells, glucose intolerance and hyperglycemia occur [23].

Weight loss, especially with decreasing skeletal muscle mass, is manifestation of cachexia [24,25]. The 2008 consensus of cachexia emphasized that cachexia is an energy metabolic syndrome affecting glucose, lipid, protein [26]. Insulin resistance plays an important role in cancer cachexia [21,22]. The skeletal muscle is a highly plastic tissue with the ability to adapt its structure and metabolism in response to different physiological stimuli. Only when fat is exhausted, the energy supply depends on decomposition of protein. When the protein exhausted more than 40% of total body, the life is threatened. Adipose tissue has white and brown adipose tissue. White adipose tissue and brown adipose tissue are different in distribution, morphology and function. White adipose tissue mainly serves as energy storage organ; brown adipose tissue is used for thermogenesis in colder conditions, inflammation and other critical state. Brown adipose tissue found in cachectic mice and patients [27,28] indicates the body in a serious critical condition.**Causes:** Insulin resistance, as a physiological adaptive response, is a significant feature in the setting of fasting, exercise, acute stress, and pregnancy [29]. Insulin resistance ensures vital organs the brain an adequate glucose supply in a crisis situation. The physiological mechanism behind insulin resistance is the stress response. The stress response alters energy metabolism patterns through insulin resistance.

Stress response is non-specific reaction to various stressors, many stressors, such as starvation, inflammation and physical or psychic trauma, can induce stress response. The chronic systemic inflammatory response is one of important causes of stress response in disorders of glucose-lipid metabolism, diabetes mellitus and cachexia. Chronic inflammatory responses lead to insulin resistance, various metabolic abnormalities and glucolipid metabolic diseases [30-32]. Immunological and neuroendocrinological abnormalities play an important role in Cachexia [33,34]. Insulin resistance in cancer cachexia has been attributed to chronic exposure of pro-inflammatory cytokines including Tumor Necrosis Factor (TNF)-a, Interleukin (IL)-6, and Insulin-Like Growth Factor (IGF) binding protein [35]. The level of growth hormone, epinephrine, glucagon, and adrenocorticotropic hormone and corticotropin releasing factors is high in patients with cancer cachexia [36]. These studies observed a relationship between inflammatory response and insulin resistance, but ignored the intermediate link between them, the stress response (Table 1).

Table 1: Process of energy expenditure caused by insulin resistance.

	Glycogen conversion	gluconeogenesis	lipid mobilization	Protein decomposition
Short-Term Starvation	√	√		
Long-Term Starvation			√	√
Disorders of Glucose-Lipid Metabolism			√	
Diabetes Mellitus			√	
Cachexia				√

CONCLUSION

Stress response coordinates functions of systems organism to overcome risk state. Stress response is non-specific reaction, many factors, such as inflammation, physical or psychic trauma can induce stress response. Stress hormones alter the pattern of energy metabolism by insulin resistance to ensure the brain adequate glucose supply in risk condition.

Although the causes are different, there is commonality of energy metabolism in starvation, disorders of glucose-lipid metabolism, diabetes mellitus and cachexia. Disorders of glucose-lipid metabolism and diabetes mellitus are characterizing by overconsumption of lipid. Cachexia is characterizing by overconsumption of protein. Disorders of glucose-lipid metabolism, diabetes mellitus and cachexia are manifestations in different stages of the altered energy metabolism. To return the altered energy metabolism to normal energy metabolic process, it is necessary to eliminate the stressors and to calm the stress responses. The treatment directed at underlying endocrine dysfunctions may lead to potential therapeutic options for disorders of glucose-lipid metabolism, diabetes mellitus and cachexia.

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