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Klotho Protein and Type 2 Diabetes Mellitus

Klotho Proteini ve Tip 2 Diabetes Mellitus

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Abstract

Diabetes mellitus (DM) is considered an epidemic disease by many countries and shown as one of the leading causes of death in western societies. In the development of the disease, the underlying pathophysiological mechanisms are complex and multifactorial. The frequency of DM increases with age, and the severity of events such as oxidative stress and inflammation increases in patients diagnosed with DM. The Klotho (KL) protein, defined as a new anti-aging protein as a result of the studies on aging mechanisms and it has an important functions on glucose homeostasis and insulin secretion. In this review study, the relationship between KL protein and DM is explained by compiling the information in the articles published in PubMed indexed journals between 2002-2020. In conclusion, a decrease in KL levels plays a role in type 2 DM and the development of nephropathy and vascular diseases caused by type 2 DM.

Keywords: Type 2 Diabetes mellitus, Klotho, Oxidative stress, Inflammation

Özet

Diabetes Mellitus (DM), birçok ülke tarafından epidemik bir hastalık olarak kabul edilmekte ve batı toplumlarında en önde gelen ölüm nedenlerinden biri olarak gösterilmektedir. Hastalığın gelişiminde altta yatan patofizyolojik mekanizmalar kompleks ve multifaktöriyeldir. DM sıklığı yaş ile artmakta ve bununla birlikte oksidatif stres, inflamasyon gibi olayların şiddeti de DM tanılı hastalarda artmaktadır. Yaşlanma mekanizmaları üzerinde yapılan araştırmalar sonucu yeni bir anti-aging protein olarak tanımlanan klotho (KL) proteini glukoz homeostazı ve insulin salgılanmasında önemli fonksiyonlara sahiptir. Bu derleme çalışmasında, 2002-2020 yılları arasında PubMed'de taranan dergilerde yayınlanan makalelerdeki bilgiler derlenerek KL proteini ile DM arasındaki ilişki anlatılmıştır. Sonuç olarak, KL düzeylerindeki azalma tip 2 DM ve buna bağlı olarak gelişen nefropati ve vasküler hastalıklarda önemli rol oynar.

Anahtar Kelimeler: Tip 2 Diabetes mellitus, Klotho, Oksidatif stres, İnflamasyon

Abbreviations: Diabetes mellitus (DM); Klotho (KL); α-Klotho (KLA); β-Klotho (KLB); γ-Klotho (KLG); Fibroblast growth factors (FGFs); Insulin-like growth factor-1 (IGF-1); Insulin receptor substrate (IRS); Transforming growth factor-β1 (TGF-β1); 1,25-dihydroxyvitamin D_3 (1,25(OH)2VD3); Reactive oxygen species (ROS); Superoxide dismutase (SOD)

1. INTRODUCTION

With the adoption of a sedentary lifestyle and a type of nutrition with a high glycemic index, chronic diseases with high morbidity and mortality rates are rapidly increasing worldwide. Diabetes mellitus (DM) is considered an epidemic disease by many countries and shown as one of the leading causes of death in western societies (Özdemir et al., Whiting et al., 2011). DM is described by hyperglycemia resulting from certain or relative insufficiency of insülin secretion because of pancreatic β-cell dysfunction or reduction of insulin sensitivity. DM is a chronic disease that influences quality of life and lifetime negatively owing to micro and macro complications (Dokumacioglu et al., 2018; Ighodaro, 2018).

Different pathogenic stage are related in the development of DM. These range from autoimmune demolition of the β-cells of the pancreas with result insulin hormone insufficiency to abnormalities that consequent in resistance to insulin action. DM is a group of metabolic disorders of carbohydrate, lipid and protein metabolism characterized by hyperglycemia (ADA, 2012). Hyperglycaemia is associated with both inadequate insulin secretion and insulin resistance. Reduction of insulin hormone secretion and flaws in insulin action constantly coexist in the same patient, and it is often uncertain which abnormality, if either alone, is the basic reason of the high levels of glucose (Kahn, 2003). Due to the increase in mortality and morbidity rates resulting from diabetes and its negative effects on all organ systems, identification of the molecules playing a role in the pathogenesis of the disease and development of effective treatment strategies are of extreme importance. In the development of the disease, the underlying pathophysiological mechanisms are complex and multifactorial. DM and aging are in close interaction with each other. The frequency of DM increases with age, and the severity of events such as oxidative stress and inflammation increases in patients diagnosed with DM (Banday et al., 2020; Domingueti et al., 2016).

The KL protein, defined as a new anti-aging protein as a result of the studies on aging mechanisms, was named after Klotho, who was one of the three goddesses of destiny and spun the thread of life according to Greek mythology (Kuro-o, 2008). It has been reported that in

case of a mutation or dysfunction in the KL protein expressed in various tissues and organs, mice in which early aging symptoms appeared and the expression of the KL protein was inhibited had short lives. Information indicating the relationship between the KL protein, glucose hemostasis, and insulin secretion in the literature shows that these proteins can be effective in the occurrence of insulin resistance and diabetes (Kuro-o, 2008). In this review study, the information in the literature was compiled, and the relationship between the KL protein and diabetes was explained. Additionally, the relationship between KL protein and DM is explained by compiling the information in the articles published in PubMed indexed journals between 2002-2020.

2. KLOTHO PROTEINS AND BIOLOGICAL FUNCTIONS

The KL gene, first discovered in 1997, is located on the q arm of chromosome 13 in the genome. The human KL gene consists of 5 exons and 4 introns and is located in a region of approximately 50 kbp on chromosome 13 (Arking et al., 2002; Matsumura et al., 1998). The KL protein is almost 130 kDa with a putative signal sequence at the N-terminus, a single transmembrane domain near the C-terminus and a short cytoplasmic domain (Razzaque et al., 2012). KL is a single-pass trans-membrane protein secreted in the brain, kidney, eye, testis, ovary, pancreas, pituitary and parathyroid gland tissues (Kuro-o, 2010; Moos et al., 2020). The KL protein family has three members: alpha, beta and gamma. α-Klotho (KLA) was shown to be an antiaging molecule (Zhang et al., 2017). Mice that exhibited KL insufficiency offered a premature aging phenotype, whereas KL over expression spreaded their lifetime by up to 30% and conserved them against many pathological phenotypes, particularly renal disease (Kuro-o, 2018; Zou et al., 2018). β-Klotho (KLB) is mostly secreted in the liver, but it exists in the kidney, pancreas, adipose tissue, and spleen and regulates bile acid production (Ito et al., 2000; Ito et al., 2005). γ-Klotho (KLG) is expressed in the kidney, testis, and skin. In literature indicated that KLG has a major role in prostate tumorigenesis and it may become a new biomarker for diagnosis and/or a therapeutic target in patients with prostate cancer (Onishi et al., 2020). The KL proteins are compulsory components of fibroblast growth factors (FGFs) receptor complexes and these proteins form a unique endocrine system that manages various metabolic processes in mammals (Kuro-o, 2019; Kurosu et al., 2009). FGF23 synthesized in the bone, particularly in osteocytes, is also produced by the heart, lymph nodes, liver, and thymus. Although FGF23, FGF21, and FGF19 belong to the FGF ligand superfamily, they are collectively named endocrine FGFs. The reason why they are named so is that they function as endocrine factors, contrary to other classic FGFs working as paracrine and autocrine factors

(Degirolamo et al., 2016; Yamashita et al., 2000). FGF23 and FGF21 need the Klotho proteins to show their metabolic activity. This enabled the Klotho proteins to be defined as cofactors to show their effects by binding to the receptors of FGF23 and FGF21 (Nishimura et al., 2000; Stubbs et al., 2007).

KL proteins are determined as having the activity of endocrine, autocrine, and paracrine hormone (Olejnik et al., 2018). KL proteins have been found to arrange energy metabolism, utilize anti-oxidative and anti-inflammatory effects and modulate calcium homeostasis by the restriction of insulin/insulin-like growth factor-1 (IGF-1) and transforming growth factor-β1 (TGF-β1) signaling pathways (Haipeng et al., 2017; Yamamoto et al., 2005). KL proteins have also been reported in vascular disease and various studies propose that KL has a cardioprotective effect (Martin-Nunez et al., 2014). Additionally, KL proteins seems to modulate tissue inflammatory responses to damage or interact with inflammatory mediators (Maekawa et al., 2009; Xie et al., 2012). KL is affected by numerous physiological and pathological terms. Decreased KL level is remarkably changed with numerous physiological processes. For example, KL level decreases in the heart sinoatrial node and the liver with aging (Cararo-Lopes et al., 2017; Jia et al., 2019). KLA is a circulating hormone that can lead to phosphaturia on its own, independently of FGF-23, and exhibit renal-cardio efficacy through endothelial protection (Maltese et al., 2012).

2.1. Klotho Protein Role in Type 2 Diabetes

DM is a general health problem worlwide. This disease having harmful influences on all tissues and causing increased mortality and morbidity levels. At the present time, researchers investigate on identifying molecules that play a role in the pathogenesis of DM (Dokumacioglu et al., 2019). KL protein defends cells against expedited aging and destruction during the course of DM. The oxidative stress, inflammation, degradation of phosphate and calcium metabolism and an increase in the ratio of β-cell and adipocyte loss through apoptosis can be consequence in pathologies of DM (Buchanan et al., 2020; Buendía et al., 2016). Oxidative stress develops as a result of the deterioration of the balance between oxidants and antioxidants. Increased oxidative stress in diabetes leads to loss of membrane integrity, structural or functional changes in proteins, and genetic mutations (Rehman & Akash, 2017). Hepatic glucose production also has a major role in maintaining glucose metabolism (Ohnishi et al., 2011). In the literature, it has been reported that KLA and KLB levels are low in patients with type 2 DM. Nie et al. (2017) found significantly lower α-KL levels in diabetics than in healthy controls, and suggested that such a decrease in α-KL levels could be involved in the pathological mechanism

of type 2 diabetes. It has been underlined that this decrease in the levels of KL proteins negatively influences the physiological processes of diabetic nephropathy and coronary artery diseases caused by DM (Nie et al., 2017). In a study conducted on people above the age of 65, an aging-related decrease in serum KL levels was reported. Moreover, it was stated that this decrease in KL levels would increase the rate of encountering new diabetes cases in this age group (Semba et al., 2011).

KLA is induced by 1,25(OH)2VD3 and restricted by FGF-23 thereby creating an endocrine loop, as circulating KL can stimulate FGF-23-FGFR signaling (Silva et al., 2017; Urakawa et al., 2006). In many clinical studies of chronic kidney disease has been defined has a state of FGF-23 resistance owing to endocrine and renal KL insufficiency (Hu et al., 2013; Ribeiro et al., 2020). There are various opinions on the effect of KL protein on diabetes. KL insufficiency induced the apoptosis of insulin-producing β-cells, which were defended against this process after KL overexpression (Kim et al., 2016; Olauson et al., 2014). Also, KL increased the β-cell function and prevented the progress of type 2 DM (Typiak et al., 2021). Dokumacioglu et al. (2019) put forward that the KL protein levels are a promising bio-indicator in various cases of type 2 diabetes pathology.

Oxidative stress could fast-track the incidence of clinical manifestation of DM. Oxidative stress is playing a major role in the etiology and pathophysiology of DM (Harani et al., 2012). This is because prolonged exposure of both human and animal tissues to hyperglycaemia is recognised to result in non-enzymatic glycation of proteins and the end products such as schiff base and culminates in the generation of free radicals (Hojs et al., 2016). Hyperglycaemia is recognised to be accountable for the damage of DNA, lipids and proteins and the degree of damage has been linked to the degree of hyperglycaemic-induced production of ROS and consequently oxidative stress (Butkowski et al., 2017). KL protein enhances counteraction to oxidative stress at the cellular and organismal level in mammals. KL protein mobilizes the FoxO transcription factors that are unfavorable arranged by insulin/IGF-1 signaling, thereby inducing expression of superoxide dismutase (SOD). In this way facilitates rustication of ROS and prevents oxidative stress (Figure 1) (Kazemi et al., 2021; Lim et al., 2019). Therefore, overexpress of KL levels have higher levels of MnSOD and decreased oxidative stress as demonstrated by lower levels of DNA damage. Secretion of KL can decrease the levels of peroxide induced apoptosis, SOD production and mitochondrial DNA fragmentation (Guo et al., 2018; Ma et al., 2021).

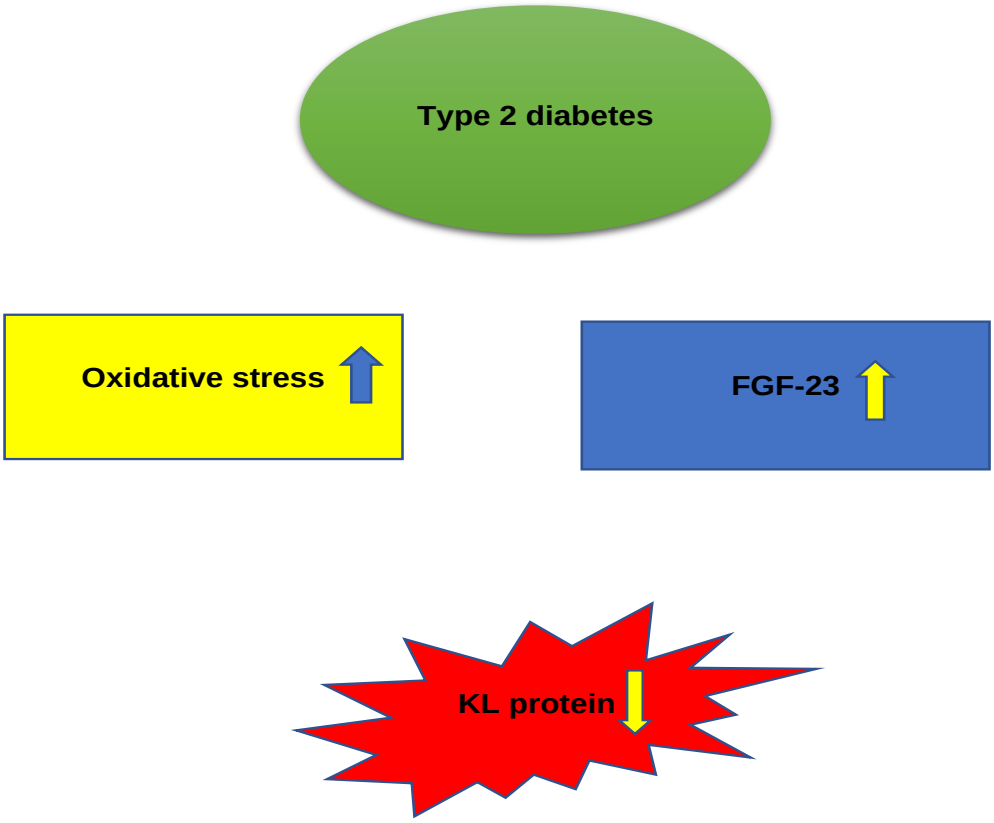

Figure 1. KL/FGF-23/Oxidative stress in Type 2 Diabetes

Inflammation is a significant factor in the progression of DM. Elevated serum levels of various inflammatory cytokines, as well as infiltration of the vascular tissue by immune cells, are features of a low-grade inflammation which can behavior as substrate for the initiation and progression of DM (Oguntibeju, 2019; Tsalamandris et al., 2019). Many researchs on human and animal models ensured further supporting proof for the role of inflammation in the development of DM. Numerous scientific resource reports that activation of pro-inflammatory markers in target cells of insulin action may conduce to obesity, insulin resistance and involved metabolic damages including DM (León-Pedroza et al., 2003; Marques-Vidal et al., 2012).

Inflammatory cytokines can down-regulate KL levels whereas, in the reverse direction, KL is able to modulate inflammation by inhibiting central signaling pathways and the expression of inflammatory involved molecules (Buendía et al., 2015; Maekawa et al., 2009). Some immunotherapeutic treatment protocols for type 1 and type 2 DM, diabetic nephropathy, and other kidney disorders have been suggested. In the literatüre, KL have indicated its possible beneficial as an early biomarker for DM initiation and progression (Hu et al., 2012; Liu et al., 2014). KL proteins may serve as a potential, safe and powerful agent in immunotherapy of DM and its complications. KL protein was newly indicated to function as a hormone that restricts

insulin/insulin-like growth factor-1 (IGF-1) signaling (Rubinek et al., 2016). In the literature, KL knockout mice have declined insulin production with increased insulin sensitivity. Additionally, mice have less energy storage and consumption than controls. KL can restrict IGFRs and insulin receptor substrate (IRS) through indirect pathways (Hasannejad et al., 2019; Utsugi et al., 2000).

3. CONCLUSION

Diabetes mellitus imposes a significant burden on patients due to the loss of working capacity and extremely high treatment costs. It is known that early diagnosis and treatment of type 2 DM are of great significance to delay or prevent the emergence of diabetic complications (Marshall & Flyvbjerg, 2006). It is clear that any new finding that could be an indicator of early diagnosis will be critically important in respect of the diagnosis, follow-up, and treatment of patients. To this end, there is a need for ideal biomarkers for the protection of health, early diagnosis, evaluation of treatment efficacy, and prognosis. The KL proteins are shown as promising markers in many diseases. A decrease in Klotho levels plays a role in type 2 DM and the development of nephropathy and vascular diseases caused by type 2 DM. A decrease in the KL proteins identified at an early stage will contribute to the prevention of diseases caused by type 2 DM and cessation of their progression.

DECLARATIONS

All authors declare that they have no conflicts of interest.

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