Role of Klotho in Hyperglycemia

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Hyperglycemic conditions (HG), at early stages of diabetic nephropathy (DN), cause a decrease in podocyte numbers and an aberration of their function as key cells for glomerular plasma filtration. Klotho protein was shown to overcome some negative effects of hyperglycemia. Klotho is also a coreceptor for fibroblast growth factor receptors (FGFRs), the signaling of which, together with a proper rate of glycolysis in podocytes, is needed for a proper function of the glomerular filtration barrier.

Keywords: Klotho protein ; diabetes mellitus ; diabetic nephropathy ; hyperglycemia ; fibroblast growth factor receptors

1. Introduction

The selective filtration of plasma is performed in the cortex of the kidney in the glomerulus of the nephron. Endothelial cells of blood arteries that enter the glomerulus, a glomerular basement membrane (GBM) between them and podocytes, and podocytes themselves form the glomerular filtration barrier (GFB). Podocytes are highly specialized cells that are dedicated to plasma filtration. They consist of a cell body and major and foot processes. Foot processes branch out from major processes and tightly cover blood arteries in the glomerulus. Between neighboring foot processes, a cell–cell junction is present, forming slit diaphragms that form a size-selective barrier for the excretion of proteins that is critical for proper kidney filtration [1].

Diabetes mellitus (DM) affected 8.5% of adults worldwide in 2014 [2]. The prevalence of this chronic disorder is increasing. Type 2 diabetes is more common than the autoimmune type 1 form of the disease and consists of 90–95% of DM cases [3]. It is characterized by high blood glucose levels (hyperglycemia), aberrant insulin production, and a decrease in the sensitivity of cells to this hormone [4][5]. Up to 40% of patients with DM develop kidney dysfunction, such as diabetic nephropathy (DN). During the course of DN, many metabolic and histological changes occur. Hyperglycemia results in the generation of reactive oxygen species and oxidative stress that damage DNA, proteins, and lipids in tissues that are affected by the disease [6]. Changes in glycemia and the rate of glycolysis can also lead to a reduction in the formation of foot processes by podocytes, a decrease in their migratory ability, and the induction of apoptosis. This partly results from the fact that glycolysis is the source of adenosine triphosphate (ATP) production in foot processes of podocytes [7] and that hyperglycemic conditions decrease the dependence of podocytes on oxidative phosphorylation and increase the dependence of podocytes on glycolysis [8]. During the course of DN, podocytes start to detach from the GBM [9]. The number of podocytes and slit diaphragms decrease, together with an increase in glycemia and proteinuria, a hallmark of kidney dysfunction [10][11]. Hyperglycemia also leads to the inflammation of renal tissue and its fibrosis. These pathological changes that occur in DN resemble premature cellular senescence [11][12].

Klotho is an anti-aging molecule. Upon its discovery, Klotho was shown to extend its lifespan in mice by 30% and protect them from many disorders, especially disorders of renal tissue [13][14]. Klotho is a transmembrane molecule that can be cleaved to its soluble form by a disintegrin and metalloproteinase domain-containing protein 10 (ADAM-10) as well as ADAM-17, β-secretase 1, and other unknown proteases [13]. Klotho is expressed mostly in the kidneys and brain [13]. Klotho expression was detected in mouse podocytes, cells of the proximal and distal tubules of the nephron, and human glomeruli [15][16]. Moreover, kidney cells were found to be the main source of the soluble form of Klotho, which is considered to be a hormone that exerts beneficial effects on target tissues [17]. This form of the protein was detected in both serum and urine, but reports of Klotho levels in these bodily fluids in renal disorders are rare and sometimes conflicting [13][14][18].

Klotho has frequently been reported to decrease inflammation through suppression of the activation of numerous proinflammatory cytokines, chemoattractants, and receptors. Moreover, Klotho inhibits tissue fibrosis [13][19]. Therefore, it can mitigate some pathological changes that occur in diabetes that are caused by hyperglycemia. In mice with streptozotocin-induced type 1 diabetes, Klotho treatment suppressed cardiac inflammation, lowered oxidative stress, and prevented cardiac cell apoptosis [20]. However, only a few studies have investigated its effects on renal tissue under

hyperglycemic conditions. Klotho decreases hyperglycemia-induced oxidative stress, with resulting podocyte injury and apoptosis, through the inhibition of various signaling pathways, including insulin-like growth factor 1, protein kinase-1/2, and p38 mitogen-activated protein kinase [21]. Klotho may also prevent protein kinase C-mediated podocyte injury in DN and alleviate glomerular hypertrophy [21][22].

Both membrane-bound and soluble Klotho can bind to fibroblast growth factor (FGF) receptors 1-4 (FGFR1-4), serving as a coreceptor protein for FGF23. Klotho alters the structure of these receptors and increases their binding affinity for FGF23 twenty-fold. FGFRs are widespread throughout the body [23]. Studies in rats and mice have shown that FGFRs are expressed in renal tissue, and FGFR1-3 are expressed in glomeruli [24][25]. However, to our knowledge, no studies have investigated the expression of FGFRs in human podocytes. The function of FGFRs influences the control of phosphate and vitamin D metabolism [14][17][23], the regulation of immune system responses, tissue repair, and tissue regeneration [23][26]. Fibroblast growth factor signaling is also important for cytoskeletal reorganization in podocytes and the formation of their actin-based processes [27]. It is also suggested to be required for podocyte recovery after glomerular injury [28].

The present study analyzed levels of Klotho expression in renal tissue and its levels in serum and urine under both standard and hyperglycemic conditions. Additionally, we investigated whether Klotho influences FGFR1-4 expression and glucose metabolism in podocyte cells that are cultured in media with standard glucose (SG) or high glucose (HG) concentrations. Finally, we investigated whether Klotho protein influences albumin permeability of the GFB. In brief, we found that the decrease in the urinary excretion of Klotho might be an early biomarker of DN and that Klotho administration may have several beneficial effects on renal function in DN.

2. Discussion

In the present study, we found a significant decrease in the membrane expression of Klotho in glomeruli and renal tissue in diabetic rats. These findings are consistent with the fact that, in patients with chronic kidney disease (CKD), low levels of calcitriol are found, which is an activator of Klotho expression [29]. We found that the decrease in renal Klotho expression was accompanied by the lower urine excretion of soluble Klotho in early diabetic rats, which accumulated inside the body and increased in serum. Conflicting findings of plasma and urine levels of Klotho have been reported in individuals with DN. Such disparate findings have been reported by studies that included various groups with different stages of DN [18][30][31]. Kacso et al., also reported a decrease in urinary levels of Klotho protein in a group of patients with DN. However, similar to the study of Bob et al., the group of patients had different stages of nephropathy [30]. Bob et al., reported that the increase in serum levels of soluble Klotho was linked to a rapid annual decline of kidney function [31]. According to van Ark et al., circulating levels of Klotho protein were not disrupted in serum from patients with type 2 diabetes without nephropathy, suggesting that circulating Klotho protein levels might be a hallmark of DN [32]. Cho et al., reported that individuals with low urinary Klotho levels, similar to the diabetic rats in the present study, were significantly more prone to have foot process effacement, whereas high serum Klotho levels were associated with a lower risk of interstitial fibrosis and segmental glomerulosclerosis [33]. This would reflect pathological changes that are observed during initial stages of DN that may be biomarkers of the disease, which is consistent with our aforementioned findings in diabetic rats 14 days after diabetes induction by STZ.

Kim et al., reported the presence of Klotho in human glomeruli [15]. To our knowledge, the present study is the first to report the presence of Klotho in human podocytes. The mRNA and total protein expression of Klotho were unaltered under hyperglycemic conditions. However, we found that the level of the membrane form of Klotho significantly decreased under hyperglycemic conditions, together with an increase in soluble Klotho shedding. This could be explained by the increased level of serum ADAM10 and the elevated kidney expression of ADAM17 in diabetic models, which are both Klotho-shedding metalloproteinases [34][35]. This was also consistent with our finding of the increase in soluble Klotho levels in serum in diabetic rats and the previous finding that the majority of Klotho shedding occurs in the kidneys [17]. The lower level of membrane-bound Klotho under hyperglycemic conditions was previously reported for distal convoluted tubules of the nephron but not for podocytes [36]. This may be correlated with the previously reported aggravation of diabetes-induced oxidative stress, inflammation, podocyte injury, and apoptosis, resulting in proteinuria, that are caused by Klotho deficiency [13][22].

We also found that all four FGFRs were present in human podocytes at both the mRNA and protein levels. Under hyperglycemic conditions, we observed a significant decrease in the protein levels of FGFR1-4 and the mRNA expression of *FGFR1* and *FGFR2*. We also found that the addition of recombinant Klotho to the cell medium increased the mRNA expression of *FGFR1* and *FGFR2* under SG conditions, with an upward tendency under hyperglycemic conditions. This tendency accelerated at the protein level, in which the addition of Klotho significantly increased the expression of both FGFR1 and FGFR2 in podocytes that were grown in HG, which was also confirmed by immunofluorescent staining.

Studies of the level and function of FGFRs in renal tissue in diabetic individuals are scarce. Consistent with the present findings, Taylor et al., reported a decrease in the protein level of FGFR4 in mice with CKD [37]. Cheng et al., reported a decrease in the expression of FGFRs in the kidneys in diabetic rats, which can be due to an increase in the presence of ADAM10/17 metalloproteinases, which have been recently proven to cleave FGFRs [38][39]. Chen et al., however, found no effect of Klotho on FGFR expression, like we did [38]. Klotho upregulated FGFR levels in the present study, which may reflect a beneficial effect against DN. According to Wu et al., the activation of FGFR1 by an antibody that mimicked FGF21 ameliorated hyperglycemia in type 2 diabetes [40]. FGFR2 was found to be important in protection against the apoptosis of tubular cells in acute kidney injury, partly by stimulating the activation of extracellular signal-regulated kinase 1/2 (Erk1/2; also called mitogen-activated protein kinase 3/1) [41]. Cheng et al., suggested that the restoration of FGFR levels in the kidneys in diabetic rats can protect against fibrosis [38].

In the present study, Klotho increased glycolysis and glycolytic capacity in human podocytes under both standard and hyperglycemic conditions. To our knowledge, the only studies that investigated the influence of Klotho protein at the level of glycolysis were performed under aerobic conditions and with organs other than the kidneys. In the brain, full-length Klotho protein participates in supplying nutrients to neurons by astrocytes. Klotho stimulates a rapid increase in aerobic glycolysis and lactate release from astrocytes, which is needed for energy production by neurons [42]. However, as reported by Bringkoetter et al., podocytes primarily rely on anaerobic glycolysis and, to a lesser extent, on the β-oxidation of lipids [43]. In the present study, both aerobic and anaerobic glycolysis were increased by Klotho in podocytes, in which the upregulation of glycolytic capacity by Klotho mirrored anaerobic glycolysis conditions and oxidative phosphorylation was halted by an injection of oligomycin [42][44][45]. As mentioned above, ATP deficiency in podocytes results in a decrease in the formation of foot processes, a decrease in the migratory ability of the cells, and the induction of apoptosis [7], which can lead to defective glomerular filtration and nephropathy. Therefore, the increase in glycolytic parameters that is induced by Klotho might enable podocytes to withstand the damaging effects of hyperglycemia. As revealed in adipocytes, glycolysis produces metabolites for lipogenesis and directs fatty acids from excessive oxidation to the synthesis of triglycerides, thereby reducing oxidative stress. Such a beneficial function of glycolysis is consistent with the function of Klotho protein [13][46].

Our research group previously found that HG conditions increase albumin permeability in rat glomeruli and cultured rat podocytes, accompanied by F-actin redistribution to cortical regions of podocytes [47][48][49]. However, to our knowledge, the present study is the first report of an analogous effect of hyperglycemia on human podocytes. We also found that the incubation of rat glomeruli and a monolayer of human podocytes with recombinant Klotho significantly decreased albumin permeability, especially under hyperglycemic conditions. This may be linked to our observation that Klotho reversed the HG-induced redistribution of F-actin filaments, the organization of which is critical for proper glomerular filtration [15]. Consistent with our findings, Klotho ameliorated ATP-induced reorganization of the actin cytoskeleton in mouse podocytes and decreased proteinuria by targeting transient receptor potential channel 6 (TRPC6) [15]. Moreover, a previous study reported that Klotho caused functional and histological improvements of renal tissue [50]. Thus, the addition of Klotho may prevent proteinuria and restore function of the GFB in DN.

To strengthen the findings of the current study, future analyses should concern testing of human serum and/or urine samples for Klotho level assessment. These analyses could also show results of iv vivo-based studies of FGF receptors levels, glycolytic parameters and albumin permeability of glomeruli and podocytes after Klotho supplementation in diabetic rats.

3. Conclusions

In conclusion, we observed significantly higher serum levels of soluble Klotho and a decrease in its urinary excretion, which may be considered early biomarkers of DN. We found that Klotho improved the function of renal tissue through effects on the restoration of FGFRs, improved glycolysis, and lowered albumin permeability under hyperglycemic conditions. Our findings indicate that Klotho should be investigated further with regard to its potential role in reducing the pathological effects of DN.

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