Review

# Impaired function of fibroblast growth factor 23 / Klotho protein axis in prediabetes and diabetes mellitus: Promising predictor of cardiovascular risk

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## ARTICLE INFO

## ABSTRACT

The discovery of clear molecular mechanisms of early cardiac and vascular complications in patients with prediabetes and known diabetes mellitus are core element of stratification at risk with predictive model creation further. Previous clinical studies have shown a pivotal role of impaired signaling axis of fibroblast growth factor 23 (FGF23), FGF23 receptor isoforms and its co-factor Klotho protein in cardiovascular (CV) complications in prediabetes and diabetes. Although there were data received in clinical studies, which confirmed a causative role of altered function of FGF-23/Klotho protein axis in manifestation of CV disease in prediabetes and type 2 diabetes mellitus (T2DM), the target therapy of these diseases directing on improvement of metabolic profiles, systemic and adipokine-relating inflammation by beneficial restoring of dysregulation in FGF-23/Klotho protein axis remain to be not fully clear. The aim of the review was to summarize findings regarding the role of impaired FGF-23/Klotho protein axis in developing CV complications in patients with prediabetes and type 2 diabetes mellitus. It has been elucidated that elevated levels of FGF-23 and deficiency of Klotho protein in peripheral blood are predictors of CV disease and CV outcomes in patients with (pre) diabetes, while predictive values of dynamic changes of the concentrations of these biomarkers require to be elucidated in detail in the future.

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## 1. Introduction

The prevalence of type 2 diabetes mellitus (T2DM) has rapidly attained epidemic level worldwide that shaped the disease one of the global public health challenges with extremely high economic burden [1]. During last two decades the number of patients with known T2DM has doubled and over next 20 years as it is expected increase in prevalence of the disease will affect all ages and various populations of people that make the number of diabetics in 4-fold more than nowadays [2]. Although there are well-established strategies regarding prevention and treatments of T2DM and it complications [3], most T2DM patients have yielded for short-term period at least one serious complication, such as cardiovascular (CV) event and/or disease, which are potentially direct causes of increased morbidity and mortality [4,5]. Indeed, contemporary global CV risk management in T2DM, which is based on lifestyle modification and personifying strategy of daily use of multiple drugs, appears to be successful in prediction rather macro vascular complications than micro vascular events, while they influenced at least 65% of deaths in T2DM patients [6]. In fact, strong association of metabolic disorders in diabetics with CV disease requires much more integrated approach further. In this context, discover new molecular targets, which are responsible for manifestation and advancing CV co-morbidity and impaired endogenous compounds regulating food intake, energy metabolism and energy expenditure in abdominal obesity, prediabetes and T2DM, is promising.

There is large body of evidence reading a pivotal role of impaired signaling axis of fibroblast growth factor 23 (FGF-23), FGF-23 receptor isoforms and its co-factor Klotho protein (alpha and beta isoforms) in CV complications in abdominal obesity and obesity-associated diseases, such as T2DM [7–9]. Several animals and clinical studies have yielded a positive metabolic effect of FGF-23, which are affected improvements in plasma lipids and fasting glucose, prevention of body weight gain and resistance to insulin

[10,11]. Therefore, Klotho protein was determined as key regulator of calcium and phosphorus homeostasis, circuit of vitamin D and transmembrane ion channels [12–14]. Additionally, beneficial protective impact of FGF23 and Klotho protein on numerous tissues (myocardium, vessels, kidney, brain, and retina) was found in vitro and animal experiments, as well as in clinical settings [15–17]. Moreover, Klotho protein is considered as the anti-aging hormone [18]. Although there were data received in clinical studies, which confirmed a causative role of altered function of FGF-23/Klotho protein axis in manifestation of CV disease in prediabetes/T2DM and abdominal obesity [19,20], the target therapy of these diseases directing on improvement of metabolic profiles, systemic and adipokine-relating inflammation by beneficial restoring of dysregulation in FGF23/Klotho protein axis remain to be not fully clear. Yet, there was not understood whether deficiency of serum Klotho protein, receptors for FGF-23 are diagnostic and predictive biomarkers for CV disease and events in prediabetes/T2DM and abdominal obesity [21]. The aim of the review was to summarize findings regarding the role of impaired FGF-23/Klotho protein axis in developing CV complications in patients with prediabetes and type 2 diabetes mellitus.

## 2. The FGF-23/Klotho signaling system

The FGF-23 is multifunctional metabolic regulator (firstly described as hepatokine) that belongs to type-I transmembrane protein family, which in human is predominantly synthesized by the osteoblasts/osteocytes and hepatocytes. The FGF-23 is secreted in a circulation, when it is measured in low concentrations under physiological circumstances [22]. Other sites of primarily production of FGF-23 are adipocytes, skeletal muscle, and pancreatic cells, but they become a source for synthesis and releasing of FGF-23 in pathological conditions [23,24].

The primary triggers for FGF-23 secretion are non-specific stimuli, such as cold, and numerous diets, such as fasting, starvation, high fat and carbohydrate diets, diet enriched ketogenic compounds, low amino acid and protein diets. Therefore, over expression of FGF-23 was found in target cells in hepatosteatosis, steatohepatitis, abdominal obesity and diabetes mellitus [22,25]. The FGF-23 is substrate for disintegrating impact of the ADAMs (a disintegrin and metalloprotease) −10 and ADFAM-17, which belong to metalloproteases family [26,27]. Additionally, FGF-23 might be shedded by several soluble secretases, such as BACE1 (β-Amyloid Precursor Protein cleaving enzyme-1) and γ-secretase, the main biological role of them is a regulation of intramembrane proteolysis and a control for membrane expression of numerous proteins including FGF-21, Notch, L-selectin, transforming growth factor alpha, and tumor necrosis factor-alpha [28].

In physiological condition the FGF-23 mediates mineral metabolism through suppression of reabsorption of phosphates from the urine and synthesis of the 1α,25-dihydroxyvitamin D3 (1,25(OH) 2D3) in the kidney [29,30]. Additionally, in pathological states the FGF23 also regulates mineral, lipid and glucose metabolism in target organs (brain, kidney, lung, heart, muscles and adipose tissue), which is mediated by FGF receptor isoforms (predominantly FGFR1c and FGFR3c) and high-affinity binding of both alpha and beta co-factor Klotho proteins [22]. The FGF-23 is responsible for osteopenia/osteomalacia, inflammation, fibroblast cell growth and differentiation, vascular and myocardial hypertrophy, cardiac and kidney fibrosis and accumulation of extracellular matrix, vascular calcification, accelerating atherosclerosis, endothelial dysfunction [31–34]. The exact cellular and molecular mechanisms mediating these effects are poorly understood. The principal mechanisms, which are embedded into the FGF-23/Klotho protein signaling pathway, are reported in Fig. 1.

Klotho is a low molecular (120−135 kDa) type-I transmembrane protein, which is representing in two membrane-associated isoforms (Klotho protein-alpha and Klotho protein-beta) as a result of alternate splicing [35]. In human physiological condition Klotho protein is predominantly expressed in distal convoluted tubules of nephron and in certain brain regions, such as pituitary, hippocampus and probably the choroid plexus [36]. Down-expression of Klotho protein was established in numerous pathological states, such as diabetes mellitus, abdominal obesity, heart failure, whereas changing in circulating levels of Klotho was a result of rather increased degradation than impaired synthesis. In fact, the serum levels of soluble form of Klotho, which were substrate for ADAMs like FGF-23, might be related to systemic inflammation, an effect of transcription factors (Wnt/beta-catenin), calcium-dependent proteases (μ-calpain), a as well as genetic predisposition (disruption in 5′-flanking promoter region of the Klotho gene) to lowered synthesis [37].

Klotho protein binds several molecular targets and thereby appears an ability to induce variable metabolic effects and cellular responses [38]. For instance, it has found that Klotho protein exhibited anti-apoptotic capacity acting as a specific suppressor of p53/21 and p16 pro-apoptotic proteins [39]. The next molecular targets for FGF-23/Klotho protein signaling pathway could be tyrosine-kinase receptors, AMP-activated protein (AMPK) kinase/ sirtuin 1/peroxisome proliferator-activated receptor-γ coactivator-1α (Pgc1α) and ERK1/2 [40]. Therefore, stimulation of transcriptional activity in the target tissues may have supported by growth hormone through mediating a resistance to FGF-23 [41]. Indeed, FGF-23 exerted beneficial metabolic impact on the levels of free fatty acids (FFAs) and lipid metabolism, augmentation of glucose transport via up-regulation of glucose transporter (GLUT-4), and insulin sensitivity in liver cells and skeletal muscle cells through ERK1/2 intracellular pathway and AMPK/acetyl-CoA carboxylase axis [40–42]. However, this effect did not require the inhibitory interaction of AMPK with acetyl-CoA carboxylase in white (WAT) and brown adipose tissue (BAT) [40,41]. Indeed, FGF-23 interacts directly with the extracellular domain of the membrane bound co-factor Klotho protein in the FGF23-Klotho protein beta-FGFR complex to activate FGFR substrate 2α and subsequently induce ERK1/2 and AMPK phosphorylation [43]. Interestingly, adaptive response to nutrient deprivation and led to elevated levels of endogenous FGF23 and down regulation of expression of Klotho protein in target cells including hepatocytes and WAT/BAT adipocytes [44].

Constitutively, tissue-specific expression of Klotho protein-beta depended on endogenous activity of FGF-23 [45], whereas peripheral tissue resistance to FGF-23 related to altered expression and affinity of FGF receptor 1c as well as uncoupling of FGF receptor 1c/Klotho protein-beta complex was associated with abdominal obesity and T2DM [46,47]. Foltz IN et al. (2012) [46] reported that deletion of FGFR1 was associated with an abrogation of FGF23-related transcriptional activity in WAT/BAT. Moreover, animal model has been shown that mice with FGFR1deletion did not yielded FGF21-mediated lowering of serum levels of fasting glucose, insulin, triglycerides, adipokines, and elevated caloric expenditure, whereas an ability to reduce FFSs in circulation and in hepatocytes was remained to be significant [46,47]. On contrary, animals with neuronal loss of FGFR1 have been not found significant changes in the metabolic activity of FGF-23 [48]. Previous studies have shown that rather peripheral metabolic effects of FGF-23 than central response can directly occur through a regulation of synthesis and releasing of several adipocytokines, including adiponectin, visfatin and leptin, and tissue sensitivity to them [48–50].

In fact, FGF-23/Klotho protein signaling pathway is one of the
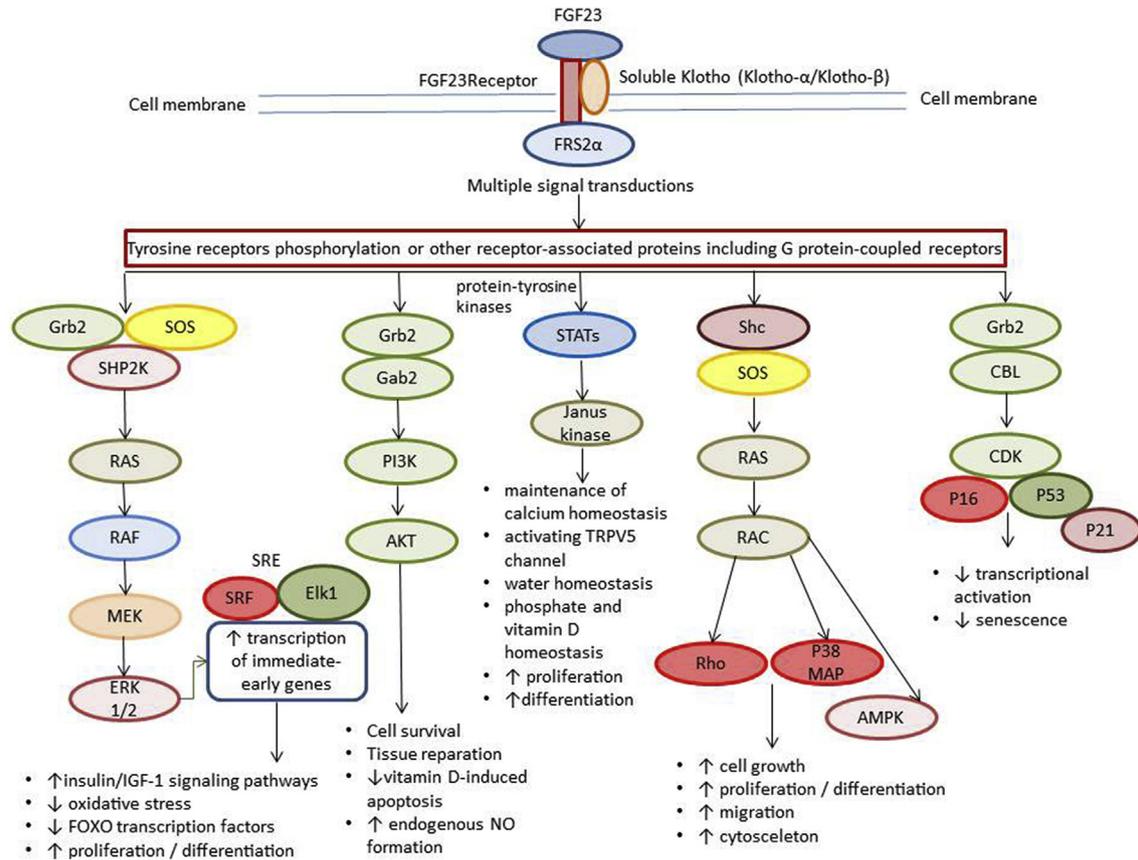
**Fig. 1.** FGF23/Klotho protein-beta signaling pathway. FGF23 interacts with specific FGFRs and Klotho protein and activates multiple intracellular signal transductions. Abbreviations: FGFR, FGF-receptor; Grb2, growth factor receptor bound protein 2; Gab2, GRB2 associated binding protein 2; SOS, super oxides; SHP2K, Src homology region 2, phosphatase 2; RAS, a family of small GTP-binding proteins; RAF, protein-serine/threonine kinase; Rab, small GTP-binding protein that regulate vesicle traffic; MEK, mitogen-activated protein kinase/ERK kinase; ERK, extracellular signal-regulated kinase; IGF-1, insulin-like growth factor-1; PI3K, phosphoinositol-3 kinase; AKT, RAC-alpha serine/threonine-protein kinase; NO, nitric oxide; STAT, signal transducers and activators of transcription; CBL, E3 ubiquitin-protein ligase; CDK, cyclin dependent kinase; RAC, Ras-related C3 botulinum toxin substrate 1; Rho, rhodopsin protein; AMPK, AMP-activated protein; AMP, adenosine-monophosphate; SRE, serum response element; SRF, serum response factor; Elk-1, nucleus transcription factor.

most powerful endogenous regulating mechanisms that are embedded onto control for metabolism of glucose and lipids, insulin tolerance, dynamic changes in WAT and BAT and caloric expenditure (Fig. 2). Interestingly, FGF23/Klotho protein signaling directly attenuates a regulation of adipose tissues during cold that is dispensable for effective thermoregulation, whereas central effects of FGF-23 signaling is essential for maximal sympathetic impact on BAT to support thermoregulation during cold. Noted that there is a large number of metabolic effects of FGF-23/Klotho protein, which have sufficient difference depending on physiological and pathological conditions. Although previously it has been suggested that hepatic induction of FGF23 was limited to acute metabolic stress in liver, further investigations have shown that FGF23 appeared to be more general metabolic regulator occurring in the pathogenesis of CV disease. However, FGF-23/Klotho protein signaling complex was found to be potentially regulated by other regulatory interactions, including galectins, the extracellular matrix, and co-expression of suppressor of tumorigenicity-2 [48,50]. Finally, Klotho protein-related functions were found as anti-aging reactions in humans due to suppression of insulin/IGF-1 and sirtuin-1 signaling pathways, renin-angiotensin-aldosteron system activity, anti-oxidative modalities and ability to prevent vascular injury and dysfunction ameliorating growth, survival and differentiation of endothelial progenitor cells [51,52].

## 3. Impaired FGF-23/Klotho protein signaling system in prediabetes/T2DM

Previous clinical studies have revealed that lowered serum Klotho protein levels were down-regulated in patients with impaired fasting glucose, abdominal obesity and manifestation of T2DM [53], whereas FGF-23 as a protector against T2DM was found in significantly increased concentration in abdominal obese patients and diabetics compared with healthy volunteers [54,55]. In fact, serum Klotho protein levels were positively associated with the glomerular filtration rate, and inversely correlated with the urinary albumin to creatinine ratio and randomly sampled serum levels of creatinine, blood urea nitrogen, and blood glucose [51], while circulating FGF-23 levels were positively correlated with homeostasis model assessment of insulin resistance [52]. Interestingly, there were opposite changes in Klotho protein expression in fat and liver that reflected tissue-specific alterations in the responsiveness to FGF-23/Klotho protein axis in prediabetes and T2DM. For instance, the hepatic expression of FGF-23 was increased. Therefore, Klotho protein transcript levels in visceral fat and Klotho protein levels in subcutaneous and visceral fat were significantly reduced in obese patients, whereas hepatic levels for Klotho protein, FGFR1 and FGFR3 transcripts were significantly increased. In fact, overexpression of FGF-23 in BAT together
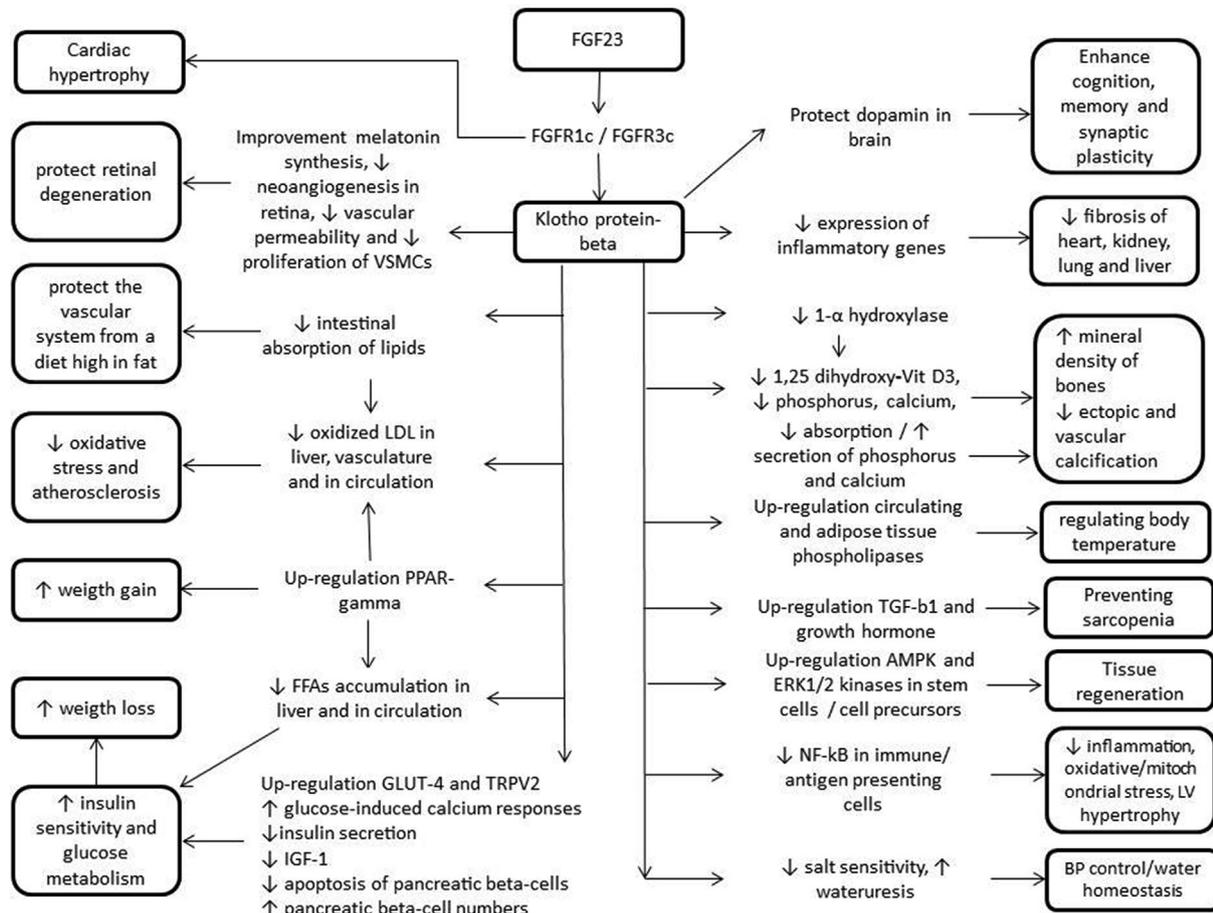
**Fig. 2.** FGF23/Klotho protein-beta relating condition. Abbreviations: FGFR, FGF-receptor; LDL, low density protein; VSMCs, vascular smooth muscle cells; TGF, transforming growth factor; AMPK, AMP-activated protein; NF-kB, nuclear factor kappa-beta; ERK, extracellular signal-regulated kinase; FFAs, free fatty acids; PPAR, Peroxisome proliferator activated receptor; TRPV2, transient receptor potential cation channel subfamily V member 2.

lowered expression of Klotho protein is considered as molecular clock, which attenuate diet-induced abdominal obesity and corresponds to peripheral tissue response, especially affecting an inflammation in adipose tissue. Indeed, pre-adipocytes/adipocytes, and macrophages have been implicated in initiating adipose tissue inflammation and this process is under particular control of FGF23 [56]. Additionally, there were significant associations between dysregulation of FGF23/Klotho protein axis in diabetics and altered cell growth, oxidative stress activity, impaired calcium intracellular signaling, and vascular inflammation, which have been implicated tissue reparation, senescence, vascular damage and age-associated CV disease [57]. However, FGF-23/Klotho protein-beta/FGFR1c and AMPK/sirtuin 1/Pgc1α signaling pathways are embedded in the prevention of developing diabetes-induce kidney disease via maintain of vascular reparation [15]. Deficiency of serum Klotho protein levels in circulation and lowered expression of Klotho protein-beta in endothelial cells of glomeruli and in epithelial cells in tubule of nephron were closely associated with kidney fibrosis, vascular inflammation, oxidative stress, and renal morphological abnormalities that were corresponded to advanced diabetic proliferative nephropathy [15]. Moreover, impaired axis of FGF-23/Klotho protein-beta/FGFR1c in kidney was reported as strong predictor of kidney fibrosis independently from altered glucose homeostasis and dyslipidemia in diabetics [57]. Thus, beyond important physiological role of the FGF-23/Klotho protein axis in the regulation of energy and mineral metabolism, bone mineralization, adipose tissue paracrine activity, endogenous reparation

and vitamin D synthesis, its alteration has been related to various processes associated with cardiac and vascular damages.

## 4. FGF-23/Klotho protein as biomarkers of CV complications of prediabetes and T2DM patients

Because altered FGF-23/Klotho protein axis was reported to be associated with metabolic factors that predispose to an increased CV risk, it has been postulated that elevated serum level of FGF-23 and lowered Klotho protein in circulation may be potentially modifiable predictors for CV disease as well as vascular and kidney complications in T2DM and abdominal obese patients [58—60]. Indeed, deficiency Klotho protein in serum and elevated circulating levels of FGF-23 were found as predictors for diabetic foot syndrome (DFS) in T2DM patients [61]. Although lowered serum levels of Klotho protein and increased concentrations of FGF-23 had been reported having close inversely association with C-reactive protein and interleukin-6, the independent negative predictive probability for DFS was identified for deficiency levels of Klotho protein, whereas higher serum FGF23 was associated with a higher risk for this complication. There is evidence regarding that elevated levels of FGF-23 have been positively associated with CV events and CV mortality in abdominal obesity patients regardless of T2DM, while their dynamic changes under the effect of the interventions, such as blood pressure lowering, lipid lowering drugs, were not independently associated with any CV outcome [62,63]. In contrast, gastric bypass, or laparoscopic sleeve gastrectomy compared with

nonsurgical obesity management were able to decrease all-cause mortality, but not CV mortality in abdominal morbid obesity and T2DM patients and this beneficial outcome was related to decrease in FGF-23 serum levels [63,64]. The Ludwigshafen Risk and Cardiovascular Health Study has shown that serum levels of FGF-23 was not just associated with conventional CV risk factors (dyslipidemia, hypertension, abdominal obesity, T2DM), but other mineral metabolic factors and bone biomarkers (calcium, parathyroid hormone, alkaline phosphatase, vitamin D, and serum phosphate) among 2974 patients suspected atherosclerosis and underwent coronary angiography [65]. Interestingly, age- and sex-adjusted regression has revealed that the fourth quartile compared to the first quartile of FGF23 were independently associated with all cause (odds ration [OR] = 2.54; 95% confidence interval [CI] = 2.09—3.09; p < 0.001) and CV mortality (OR = 2.56; 95% CI = 1.99—3.28; p < 0.001) over 9.9 years of follow-up [65]. Thus, increased FGF-23 levels can indicate a negative impact of metabolically induced atherosclerosis on survival regardless of conventional CV risk factors and serum phosphate. However, recent clinical studies have yielded that elevated serum levels of FGF23 exerted deleterious impact on CV events independently of Klotho protein [66,67].

Previously, vascular Klotho protein deficiency was reported in close relation to early atherosclerosis, plaque formation, vascular calcification and presence and severity of coronary artery disease (CAD) [68—70]. Patients with known T2DM having lowered circulating levels of Klotho protein were considered to be resistant to FGF-23 [68], while they had higher risk of CAD [70]. Although both circulating levels and endogenous vascular gene Klotho protein expression are related to severity of inflammation that corresponds to vascular intima lipid infiltration and advanced atherosclerosis in T2DM [71], Klotho protein gene polymorphisms were found to be powerful factors contributing susceptibility to vascular complications in T2DM [72,73]. However, preliminary assumption, which was based on the results received in animal and preclinical studies regarding that lowered Klotho protein levels regardless of FGF-23 expression corresponded to endothelial dysfunction, has confirmed in clinical settings in pre-diabetics/T2DM [74—76]. Noted that interrelation between serum Klotho protein levels and CV disease had been defined in patients in conventional CV risk factors, including dyslipidemia, hypertension, smoking, and abdominal obesity [77,78]. Whether impaired actions of FGF-23/Klotho protein axis in diabetics appears independent predictor of cardiac and vascular complications, it is not fully clear, while FGF-23/Klotho protein system binds early metabolic abnormalities suitable for prediabetes and T2DM with micro vascular inflammation and endothelial dysfunction. This issue has found a confirmation in the results of the Framingham heart study, which were reported an association of cerebral small vessel disease, poor cognition and elevated levels of FGF-23 [79]. It was intriguing because flawlessly executed proportional-hazards regression analysis, adjusted for age, sex, education, systolic blood pressure, use of antihypertensive drugs, prevalent CV disease, T2DM, smoking and apoE ε4 carrier status, had revealed that increased serum FGF-23 levels were strongly associated with high risk of newly incidences of vascular dementia. Additionally, FGF-23 concentrations, which were found to be elevated in T2DM patients with moderate-to-severe chronic kidney diseases required to be treated with chronic hemodialysis in the HEMO Study, predicted well all-cause mortality [80]. Moreover, trend to changes of FGF-23 serum levels was better prognosticator for mortality that peak FGF-23 concentrations at baseline. Yet, there are interesting data regarding the relationship between the FGF-23/Klotho protein serum levels and management of the diabetics, duration of the disease, severity of insulin resistance, and developing CV complications [81]. However these findings appear to be

controversies. The first controversy affects an impact of sodium glucose cotransporter 2 (SGLT-2) inhibitor dapagliflozin on circulating levels of FGF-23 in T2DM patients. Occasionally dapagliflozin led to increase in serum phosphate levels, plasma parathyroid hormone levels, and FGF-23 concentration [82]. This effect was independent of concomitant changes in estimating GFR and 24-h albumin excretion that requires to be clearly explained further, because dapagliflozin previously had demonstrated a positive effect on CV mortality and prevention of renal injury [83,84]. Unexpectedly increased levels of FGF-23 in T2DM patients treated with dapagliflozin were associated with beneficial effect on target organ damage. The next controversy regards assumption that continuous monitoring of changes of the FGF-23/Klotho protein concentrations could better predict a risk of CV events in non-known CV disease diabetics than individuals with established CV disease. Finally, FGF-23/Klotho protein levels can be biomarker of early vascular complications in (pre)-diabetics despite sufficient improvements in glucose and lipid homeostasis, because elevated FGF-23 levels appears prior to fasting glucose abnormality and corresponds frequently to a risk of T2DM in general population [85]. Interestingly, the MESA Study results have shown that higher levels of FGF-23 were associated with an increased risk of heart failure (HF) in hypertensive patients, but the risk did not distinguish by treatment with ACE inhibitors or angiotensin-II receptor blockers (ARBs) [86]. Authors, however, have concluded that FGF-23 may be a useful biomarker for HF risk in hypertensive populations [86]. This is intriguing result, because chronic blockade or renin-angiotensin system in T2DM is established factor attenuating CV risk and improving survival. Although increased serum levels of FGF023 in T2DM patients corresponds strongly to insulin resistance (IR) and resisting concentrations [87], it is difficult to explain whether elevation of FGF-23 in peripheral blood in diabetics treated with dapagliflozin is beneficial effect, whereas therapy with other antidiabetic drugs including insulin and metformin and ACI inhibitors/ARBs was associated with declining in FGF-23 and increasing in Klotho protein levels [88]. Perhaps, relationships of IR and FGF-23 in prediabetes and T2DM do not draw strict similarity and can depend on other factors that did not yet determine [89]. However, the C-terminal of FGF-23 being a competing antagonist of FGF-23-related signaling pathway has exhibited a beneficial therapeutic effect regarding preventing advance of T2DM-induced nephropathy and suppressing inflammation [90]. Thus, altered function of FGF-23/Klotho protein axis in prediabetes and T2DM is considered as predictor of CV events and CV disease, although it is not fully clear whether FGF-23/Klotho protein—guided therapy is powerful tool for improvement of clinical outcomes in this patient population. Further large clinical studies are required to elucidate the role of altered function of the FGF-23/Klotho protein system in the development and progression of CV complication in prediabetes and established diabetes mellitus.

**In conclusion**, manifestation and development of prediabetes and diabetes mellitus are associated with metabolic disturbances, severity of which is under control of several auto- and paracrine mechanisms. One of important of them is the FGF-23/Klotho protein system that mediates energy and mineral metabolism and has cardioprotective effects. Elevated levels of FGF-23 and deficiency of Klotho protein in peripheral blood are established predictors of CV disease and CV outcomes in patients with (pre) diabetes, while predictive values of dynamic changes of the concentrations of these biomarkers require to be elucidated in detail in the future.

## Conflict of interests

Not declared.

## Acknowledgments

## Abbreviations

| | |
|---|---|
| ACE | angiotensin-converting enzyme |
| AKT | RAC-alpha serine/threonine-protein kinase |
| AMP | adenosine-monophosphate |
| AMPK | AMP-activated protein |
| ARBs | angiotensin-II receptor blockers |
| BAT | brown adipose tissue |
| CAD | coronary artery disease |
| CBL | E3 ubiquitin-protein ligase |
| CDK | cyclin dependent kinase |
| CI | confidence interval |
| CV | cardiovascular |
| Elk-1 | nucleus transcription factor |
| ERK | extracellular signal-regulated kinase |
| FFAs | free fatty acids |
| FGF23 | fibroblast growth factor 23 |
| FGFR | FGF-receptor |
| Gab2 | GRB2 associated binding protein 2 |
| Grb2 | growth factor receptor bound protein 2 |
| IGF-1 | insulin-like growth factor-1 |
| MAP | mitogen-activated protein kinases |
| MEK | mitogen-activated protein kinase/ERK kinase |
| NO | nitric oxide |
| OR | odds ratio |
| Pgc1$\alpha$ | peroxisome proliferator-activated receptor-$\gamma$ coactivator-1$\alpha$ |
| PI3K | phosphoinositol-3 kinase |
| PPAR | peroxisome proliferator activated receptor |
| Rab | small GTP-binding protein that regulate vesicle traffic |
| RAC | Ras-related C3 botulinum toxin substrate 1 |
| RAF | protein-serine/threonine kinase |
| RAS | a family of small GTP-binding proteins |
| Rho | rhodopsin protein |
| SHP2K | Src homology region 2 phosphatase 2 |
| SOS | super oxides |
| SRE | serum response element |
| SRF | serum response factor |
| STAT | signal transducers and activators of transcription |
| T2DN | type 2 diabetes mellitus |
| TRPV2 | transient receptor potential cation channel subfamily V member 2 |
| WAT | white adipose tissue |

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