Prediabetes is Characterized by Higher FGF23 Levels and Higher Prevalence of Vitamin D Deficiency Compared to Normal Glucose Tolerance Subjects

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ABSTRACT

In the last years there is an increasing interest towards the bone as an endocrine organ and the role of bone and calcium-phosphate metabolism markers in a range of metabolic disturbances. The aim of the present study is to assess the changes of calcium phosphate metabolism markers in patients with prediabetes compared to normogycemic controls and their link to glucose disturbances and cardiovascular risk factors. In this study, 80 patients with mean age 50.4 ± 10.6 years were included, divided into 2 age- and BMI-matched groups – group 1 with obesity without glycemic disturbances (n = 41) and group 2 with obesity and prediabetes (n = 39). Oral glucose tolerance test (OGTT) with measurement of immunoreactive insulin was performed in all participants and levels of PTH, 25(OH)D, FGF23, and Klotho were measured. We found significantly higher levels of FGF23 in patients with prediabetes compared to normal glucose tolerance subjects (10.4 ± 10.7 vs. 5.8 ± 7.3 pg/ml; p = 0.03). FGF23 showed a weak positive correlation to fasting blood glucose (r = 0.224; p = 0.048) but not to blood glucose on the first and second hour of oral glucose tolerance test or insulin levels. There was extremely high prevalence of vitamin D deficiency in both groups. Lower levels of 25(OH)D were observed in prediabetes group, although without statistical significance (p = 0.57). Patients with prediabetes have higher FGF23 levels and higher prevalence of vitamin D deficiency compared to normal glucose tolerance subjects. Elevated FGF23 levels seem to be correlated more to elevated fasting blood glucose levels than to insulin resistance state of the patients.

Introduction

Prediabetes is a metabolic condition, situated between normal glucose homeostasis and diabetes and includes impaired fasting glucose (IFG) and impaired glucose tolerance (IGT). Patients with prediabetes have increased risk of developing type 2 diabetes in the future [1–3]. Insulin resistance is a typical characteristic of prediabetic patients and plays a role in the increased cardiovascular risk. Because of the fact that the risk of cardiovascular disease and macrovascular complications is increased long before diabetes diagnosis, many authors point out the components of the metabolic syndrome as main factors for increased cardiovascular risk in prediabetes. Impaired glucose regulation (diabetes, IFG, IGT) is part of the last IDF definition of metabolic syndrome in combination with abdominal obesity, hypertension, hypertriglyceridemia, and reduced HDL-cholesterol [4].

In the last years, there is an increasing interest towards the bone as an endocrine organ and the role of bone and calcium phosphate metabolism markers in a range of metabolic disturbances. Vitamin D has a critical role in calcium phosphate metabolism and bone formation, but in the last decade it became clear that vitamin D deficiency may be associated also with a range of diseases, including

cancer, cardiovascular disease, and type 2 diabetes [5]. Vitamin D increases glucose-mediated insulin secretion, increases the expression of the insulin receptor and enhances insulin-mediated glucose transport [6, 7]. In Vitamin D deficient patients with prediabetes, treatment with vitamin D improves insulin resistance and glycemic parameters [8] and reduces the risk of progression to diabetes.

Initially it was thought that vitamin D and PTH are the sole regulators of calcium phosphate metabolism. Nowadays it is known that FGF23 and Klotho also play an important role and these regulators form the so called bone-kidney-endocrine axis [9–12]. FGF23 is a phosphaturic hormone that reduces the number of sodium-phospatecotransporter2a (NaPi-2a) number on the proximal renal tubule membrane. It suppresses the synthesis and stimulates the degradation of 1,25-dihydroxyvitamin D3, which reduces intestinal phosphate and calcium absorption. 1,25-Dihydroxyvitamin D3 on the other hand upregulates FGF23 gene expression and closes the negative feedback loop [11]. FGF23 exerts its effects through binding to its receptors (FGF-R) in the presence of membrane protein called Klotho, acting as a co-receptor [13]. FGF23 levels are elevated in patients with chronic kidney disease [14, 15] and its higher levels are associated with increased mortality and cardiovascular risk [16–18].

Recent animal studies show that Klotho can act as a renoprotective factor [19, 20]. Klotho expression is downregulated by angiotensin II and upregulated by peroxisome proliferator-activated receptor gamma (PPARγ) agonists and 1,25(OH)$_2$D3 [21–23]. Vitamin D deficiency and elevated FGF23 levels can decrease Klotho expression. Recent studies show reduced kidney Klotho expression in diabetic patients with normal kidney function compared to non-diabetic subjects. This suggests that reduced Klotho levels can be an early marker of diabetic nephropathy and microvascular complications in patients with diabetes [24, 25].

There is no data about the levels of FGF23 and Klotho in patients with prediabetes and their link to insulin resistance and glucose homeostasis.

The aim of the present study is to assess the changes of calcium-phosphate metabolism markers in patients with prediabetes compared to normogycemic controls and their link to glucose disturbances and cardiovascular risk factors.

The study was approved by the University ethics committee for clinical projects and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. All patients included in the study signed an informed consent for participation in the study.

Patients and Methods

Participants in the study were recruited from hospitalized patients in University hospital Endocrine clinic. In the present study, those patients were included who met the following including and excluding criteria:

Inclusion criteria

- Age 35–74 years
- IGT (glucose on 120 min of OGTT between 7.8 and 11.0 mmol/l) and/or IFG (fasting glucose between 6.1 and 6.9 mmol/l) with obesity (BMI ≥ 30 kg/m^2), or
- Normal glucose tolerance (NGT) and obesity (BMI ≥ 30 kg/m^2)

Exclusion criteria

- Metformin or any other antidiabetic drug treatment during the last 3 months prior to study entry
- Previous cardiovascular or cerebrovascular accident (myocardial infarction, angioplasty, stenting, ischemic stroke)
- Severe renal (GFR < 60 ml/min/1.73 m^2), or liver disease (AST and/or ALT levels 3 times above the upper limit of reference range), heart failure (NYHA class III or IV)
- Malignancies

The following study methods were used:

1. Anthropometric measurements

- Height (cm)
- Weight (kg)
- BMI calculation (weight in kilograms divided by height in meters squared)
- Waist circumference (WC) – measurement was made midway between the 8th rib and the iliac crest
- Hip circumference (HC) – measurement was made at the level of the greater trochanter
- Calculation of waist-to-hip ratio (WHR)
- Calculation of the waist-to-stature ratio (WSR)
- Calculation of visceral adiposity index (VAI) = [WC/(36.58 + (1.89 × BMI)] × (TG/0.81) × (1,52/HDL)
- Body Composition Analysis by means of Body Impedance Analyzer (TANITA™ TBF-215GS)
- Blood pressure measurement. Arterial hypertension was assumed if BP ≥ 140/90 mmHg or if the patient was taking antihypertensive medications

2. Evaluation of carbohydrate metabolism

- An oral glucose tolerance test (OGTT) with measurement of glucose and immunoreactive insulin (IRI) on 0, 60, and 120 min. For measuring IRI electrochemiluminiscence (ECLIA) method was used by analytics Elecsys 2010 Measuring range: 0.2–1000 μU/ml
- HOMA index ((fasting glucose X fasting immunoreactive insulin)/22.5) was calculated
- Insulin resistance was assumed if: Fasting IRI > 17 mU/l and/or IRI 60 min > 130 mU/l and/or IRI 120 min > 80 mU/l and/or HOMA index > 2.6 [26–27]

3. Laboratory tests

- Blood count, ESR, ASAT, ALAT, GGT, total cholesterol (TC), TG, HDL, LDL, VLDL, creatinine, uric acid

4. Metabolic syndrome (MetS)

This was diagnosed according to the IDF and AHA/NHLBI criteria – 3 out of 5 risk factors – increased waist circumference (> 80 cm), increased TG (> 1.7 mmol/l), decreased HDL (< 1.3 mmol/l), increased BP (> 130/85 mmHg), and increased fasting blood glucose (> 5.5 mmol/l).

5. Measurement of bone markers

Measurement of FGF 23 was performed by enzyme-linked immunosorbent assay (MYBIOSOURCE) – Repeatability: Coefficient of variation < 10 %. Measurement of Klotho was performed by enzyme-linked immunosorbent assay (MYBIOSOURCE) - Intra-assay Precision (Precision within an assay): CV % < 8 %; Inter-assay Precision (Precision between assays): CV % < 10 %. 25(OH)D was measured by electrochemiluminescence immunoassay (Roche Elecsys

2010 Chemistry Analyzer), based on competition principle (Vitamin D total, Roche Diagnostics GmbH, 68305 Mannheim, Germany). Blood for all measurements was taken after overnight fasting, was immediately centrifuged for 15 min at 4000 rpm and the serum was stored at (−80 °C) until the test was performed.

Subjects were categorized by their vitamin D status on the basis of their 25(OH)D levels as follows:

- optimal ≥ 75 nmol/l (≥ 30 ng/ml);
- insufficient 50–74.9 nmol/l (20.0–29.9 ng/ml); and
- deficient < 49.9 nmol/l (< 20.0 ng/ml [28]).

Statistical methods

The data were processed using the statistical package SPSS 16.0 (IMB™). The level of significance for rejecting the null hypothesis was $p < 0.05$. The following statistical methods were applied: descriptive analysis, variation analysis, Kolmogorov–Smirnov's one sample nonparametric test, Student's t-test for 2 independent samples, Mann–Whitney's nonparametric test for 2 independent samples, one-way analysis of variance between-groups ANOVA, correlation analysis. Data are presented as mean ± SD.

Results

In the present study, we included 80 patients with mean age 50.4 ± 10.6 years, divided into 2 groups – group 1 (control group) with obesity without glycemic disturbances (NGT) (n = 41; 6 males, 35 females) and group 2 with prediabetes (n = 39; 6 males, 33 females). The characteristics of the 2 groups are presented in ▶ **Table 1**. The 2 groups were similar in age, body weight, fat %, BMI, WHR, WSR, and VAI. There was no significant differences between serum creatinine levels and eGFR in both groups (75.9 ± 12.2 µmol/l vs. 79.9 ± 14.7 µmol/l; $p = 0.182$ and 125.2 ± 35.6 ml/min vs. 124.5 ± 39.8 ml/min; $p = 0.941$ respectively).

The prevalence of the classical cardiovascular risk factors determined in the study is shown on ▶ **Table 2**. There was no difference in the prevalence of hypertension and dyslipidemia between the groups.

Patients with prediabetes had higher levels of IRI on 0 and 120 min of OGTT and higher HOMA index although similar rates of hyperinsulinemia/insulin resistance were observed between the 2 groups (▶ **Table 3**). The patients with prediabetes also had higher prevalence of metabolic syndrome and a higher number of components of MetS (3.3 ± 1.19 vs. 2.8 ± 1.07; $p = 0.04$) compared to the patients without carbohydrate disturbances.

We found significantly higher levels of FGF23 in patients with prediabetes compared to normal glucose tolerance subjects (10.4 ± 10.7 vs. 5.8 ± 7.3 pg/ml; $p = 0.03$) (▶ **Table 4**). Patients with insulin resistance also had higher FGF23 levels compared to controls (9.5 ± 10.1 vs. 5.2 ± 7.3 pg/ml) with borderline statistical significance ($p = 0.05$). FGF23 showed a weak positive correlation to fasting blood glucose ($r = 0.224$; $p = 0.048$) but not to blood glucose on the first and second hour of oral glucose tolerance test. No correlation was found to the markers of insulin resistance.

There was extremely high prevalence of vitamin D deficiency in both groups. Lower levels of 25(OH)D were observed in prediabetes group, although without statistical significance ($p = 0.57$). There was no correlation between vitamin D levels and patients' age, anthropometric indices, carbohydrate indices, and cardiovascular risk factors.

▶ **Table 2** Cardiovascular risk factors.

	Group 1 Obesity	Group 2 Prediabetes
Systolic BP (mmHg)	138.5 ± 16.7	131.9 ± 17.0
Diastolic BP (mmHg)	85.4 ± 10.0	84.2 ± 9.8
Arterial hypertension (%)	65.9	59.0
Total cholesterol (mmol/l)	5.9 ± 1.2	5.4 ± 1.1
LDL cholesterol (mmol/l)	3.9 ± 1.1	3.4 ± 1.1
HDL cholesterol (mmol/l)	1.2 ± 0.4	1.1 ± 0.3
Triglycerides (mmol/l)	1.8 ± 1.5	1.9 ± 0.8
Dyslipidemia (%)	65.0	65.8
Smoking (%)	46.3	23.7

All differences are not significant.

▶ **Table 1** Anthropometric characteristics of the study groups.

	Group 1 Obesity + NGT	Group 2 Obesity + Prediabetes (IGT and/or IFG)
Age (years)	50.6 ± 9.7	50.3 ± 11.5
Weight (kg)	97.3 ± 17.9	99.6 ± 20.3
BMI (kg/m²)	36.6 ± 5.2	37.7 ± 6.1
% Fat tissue	44.2 ± 4.7	44.6 ± 6.5
WHR	0.90 ± 0.08	0.92 ± 0.07
WSR	0.66 ± 0.07	0.68 ± 0.08
VAI	3.2 ± 4.0	3.4 ± 2.0

All differences are not significant.

▶ **Table 3** Markers of insulin resistance.

	Group 1 Obesity	Group 2 Prediabetes
IRI 0 min (mU/l)	16.7 ± 7.4	21.9 ± 13.4*
IRI 60 min (mU/l)	128.2 ± 81.8	123.8 ± 69.8
IRI 120 min (mU/l)	66.0 ± 64.0	121.2 ± 83.3**
HOMA index	3.7 ± 1.7	5.5 ± 3.4**
Prevalence of insulin resistance (%)	67.5	78.4

* $p < 0.05$; ** $p < 0.01$.

Table 4 Calcium phosphate metabolism parameters.

	Group 1 Obesity	Group 2 Prediabetes
Parathormone (pmol/l)	5.1 ± 2.3	5.1 ± 2.0
25(OH)D (nmol/l)	35.3 ± 19.3	28.0 ± 13.5
Vitamin D deficiency (%)	87.5	94.7
FGF-23 (pg/ml)	5.8 ± 7.3	10.4 ± 10.7 * (p = 0.03)
Klotho (pg/ml)	935.8 ± 338.5	845.1 ± 309.2

± p < 0.05.

Klotho levels were lower in patients with prediabetes, again without statistical significance. There was no PTH levels difference between the groups.

Discussion

The role of vitamin D, FGF23, and Klotho in bone metabolism and the pathogenesis of osteoporosis is well established. Recent data, however, show that they can be linked to vascular and metabolic disturbances, especially in patients with chronic kidney disease.

Vitamin D deficiency has been reported as a risk factor for developing both type 1 [29] and type 2 diabetes [30–32], while vitamin D supplementation or higher levels seem to be protective [33]. A recent meta-analysis shows that for individuals in the top third vs. those in the bottom third of total baseline vitamin D levels, adjusted for age, diabetes risk factors and seasonality, have relative risk for metabolic syndrome and insulin resistance 0.86 (95 % CI 0.80, 0.92), while the risk of developing diabetes was 0.81 (95 % CI, 0.71, 0.92) [34]. The data on vitamin D levels in patients with prediabetes compared to controls are inconsistent. Some studies show similar 25(OH)D levels in patients with prediabetes and controls and only hypovitaminosis D combined with high parathyroid hormone concentrations was associated with glycemic dysregulation in elderly patients [35], while others find lower levels of 25(OH)D in prediabetes vs. controls [36, 37]. Vitamin D deficiency however seems to be related to insulin resistance in prediabetic patients [36, 38], but not in normoglycemic subjects [39]. In our study, we found only a tendency towards lower levels of 25(OH)D in patients with prediabets but no relationship to insulin resistance state. Recently, we showed that obese women with PCOS have lower levels of 25(OH)D compared to lean PCOS patients [40]. There was no correlation between 25(OH)D levels and indices of glucose metabolism, but patients with optimal vitamin D levels had much lower rate of insulin resistance compared to the other 2 groups with insufficiency and deficiency. The precise mechanism of action of vitamin D on glucose homeostasis and insulin sensitivity is not clearly understood, but there are data that it is involved in beta-cell function and insulin secretion, intracellular calcium levels and postreceptor insulin signaling or autocrine/paracrine role of vitamin D in insulin target tissues [41].

FGF23 is thought to be a novel risk factor for cardiovascular morbidity and mortality not only in advanced chronic kidney disease [42–44], but also in patients in the early stages of CKD and in the general population [45], independently from calcium, phosphate, and vitamin D levels. It is hypothesized that FGF23 could have direct negative effect on cardiovascular function. Most of the studies show elevated levels of circulating FGF23 in the individuals with type 2 diabetes [46, 47]. Serum FGF23 levels are also much higher in subjects with a first-degree family history of diabetes than in those without [48, 49]. Not much is known about the levels of FGF23 in patients with early stages of glucose disturbances (insulin resistance and prediabetes). Our study shows significantly higher FG23 levels in patients with prediabetes compared to normal glucose tolerance subjects with similar age, BMI and cardiovascular risk factors. Its levels were higher also in patients with insulin resistance compared to those without but the levels correlated only to fasting blood glucose and not insulin resistance measures. This indicates that the main factor for FGF23 elevation is the impaired fasting glucose. A recent basic research study showed, however, that insulin signaling and the activity of sympathetic nervous system have a role in FGF23 production [50]. It is possible that early disturbances in glucose metabolism similar to overt type 2 diabetes act through the same mechanism in elevating FGF23 levels. This is supported to some extent by the elevated levels seen in relatives of type 2 diabetes patients, where mild insulin resistance with no glucose disturbances is usually observed.

To our knowledge this is the first study that evaluates FGF23 and Klotho levels in patients with prediabetes.

Conclusions

The levels of FGF23 are elevated in patients with prediabetes compared to normal glucose tolerance subjects and in insulin resistance compared to controls. FGF23 shows a weak positive correlation to fasting blood glucose but not to blood glucose on the first and second hour of oral glucose tolerance test and no correlation to the markers of insulin resistance was found. Klotho levels are lower in patients with prediabetes, but without statistical significance.

Author Contributions

Antoaneta Gateva performed the study, collected the data, and wrote the paper. Yavor Assyov performed the study and collected the data. Adelina Tsakova performed the laboratory tests. Zdravko Kamenov designed the study and reviewed the final paper.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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