

# Vitamin D and $\beta$ -glucan supplementation affects levels of leptin, apolipoproteins and general nutrition state in patients with diabetic retinopathy

Josef Richter, Martina Závorková, Vaclav Vetvicka, Ivana Liehneová, Vlastimil Král, Ivana Stiborova

## ABSTRACT

**Aims:** Diabetic retinopathy is a common complication in Type 1 and Type 2 diabetes. A global pandemic increase in diabetes has led to the search for new preventative, diagnostic and curative methods. We aimed to evaluate levels of vitamin D, apolipoproteins A and B, and leptin after vitamin D/glucan supplementation. **Methods:** Using a collection of 52 patients with diabetic retinopathy, we evaluated levels of vitamin D, apolipoproteins A and B, and leptin, we compared this data with effects of food supplementation with vitamin D and  $\beta$ -glucan. We correlated our findings with a group of 20 healthy individuals. **Results:** There was a statistically relevant reduction of vitamin D levels in all tested groups, but more so in the diabetic group. The group supplemented with both vitamin D and  $\beta$ -glucan had suppressed levels of leptin, whereas supplementation with vitamin D caused an increase of leptin levels. **Conclusion:** Based on these findings, we conclude the importance of vitamin D and  $\beta$ -glucan supplementation in patients with diabetic retinopathy.

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## INTRODUCTION

Diabetes mellitus (DM) is a disease with high glucose levels over a prolonged period of time resulting in secondary complications. It represents a group of metabolic disorders characterized by an absolute or relative deficit of insulin or inability to react to insulin, hyperglycemia, dyslipidemia, and neurovascular impairment. This disease can impact every organ, lower the quality of life, significantly disrupt the entire health system and potentially disrupt the socioeconomic situation [1]. As of 2015, an estimated 415 million people had diabetes worldwide, with type 2 DM comprising ~90% of cases. This represents 8.3% of the adult population.

Diabetic retinopathy (DR) is a common complication of type 1 and type 2 diabetes, and affects approximately one-third of the diabetic population. It is one of diabetes complications that affects eyes. It's caused by damage to the blood vessels of the light-sensitive tissue at the back of the eye. It is manifested by visual impairments

often leading to blindness, and can occur secondary to specific living and working conditions. Risk of blindness is 25x higher in diabetic patients compared to healthy individuals, yet with appropriate medical and ophthalmic care, 90% of cases can be prevented [1, 2]. Social conditions can lead to an increase in diabetes cases; 75% of diabetic patients are in low-income countries [3]. As DR remains asymptomatic until the pathology is significantly advanced, early screening is necessary. Several circulating biomarkers, such as collagen IV and laminin, are possible markers of early and advanced stages of DR [4].

Problems with DM need to be monitored from two main perspectives: 1) Lifestyle and understanding of effects of diabetes induction on the molecular level [3]; 2) The second perspective involves a broad range of problems. Diabetic retinopathy, which is a microvascular complication of DM, is both a vascular and a neural disease. Affected persons are at high risk for further developing vascular complications, including diabetic nephropathy and various heart diseases. These impairments can be related to the immune system's condition, hyperglycemia, dyslipidemia, obesity, smoking, and lifestyle [1]. In our study, we focused on several biomarkers established in patients with diabetic retinopathy and known to support the development of disease.

We also evaluated the possible association between vitamin D and serum lipid levels, and the possible role of supplementation with vitamin D and/or  $\beta$ -glucan [5]. We aimed to measure if this supplementation affects not only metabolic syndrome and obesity of patients, but parameters of lipid metabolism and subsequent reduction of heart disease risk [5-9]. A correlation between apolipoproteins A and B and risks of prediabetes and diabetes are well known. It is assumed that an APO B/APO A1 ratio is particularly important; there is stronger connection of apolipoproteins A1 and B with diabetic retinopathy than with traditional lipids [10-12]. In patients with diabetic retinopathy, this represents a significant indication of cardiovascular problems [13].

Research conducted in the last decade has demonstrated a clear link between obesity and vitamin D. Studies report that obesity (so called low-grade inflammation reactions) affects vitamin D levels and subsequently results in several immune function disruptions. Correlation between obesity and levels of vitamin D and leptin is currently being tested. Leptin is a regulatory hormone with multiple roles in the immune system. Via signaling, leptin affects several aspects of immune dysregulation observed in malnutrition, obesity and autoimmunity [14]. Vitamin D supplementation leads to increased leptin levels [8, 15]. A preventative strategy should focus on improving modifiable factors such as ensuring a healthy cardiovascular system and adequate supply of vitamin D [16, 17]. There is close correlation between serum lipids, vitamin D levels and atherogenic index of plasma. Vitamin D deficiency can be connected to a higher risk of dyslipidemia, particularly

in men [5]. Levels of vitamin D are lower in diabetics compared with the normal population. These levels are significantly lower in patients with proliferative DR [18]. In addition, medications, such as Rifampin, Phenytoin, or Phenobarbital, might disrupt vitamin D metabolism [18]. Vitamin D is a micronutrient, which is nonessential due to its endogenous production via UV light. However, due to the current common deficit of this vitamin, it is an indispensable part of nutrition [3, 7, 8].

Short-term (3–8 weeks) supplementation with oat  $\beta$ -glucan improved glycemia control, but did not influence sensitivity to insulin [19]. Soluble dietary fibers, particularly  $\beta$ -glucan, help to reduce cholesterol and insulin levels, have positive effects on gut microflora and help to reduce levels of risk factors for cardiovascular diseases. The FDA recommends four daily doses of fibers [1]. Research suggests that  $\beta$ -glucan supplementation reduces cardiovascular disease risk factors and offers significant medical effects in diabetic treatment. The mechanisms of action are still not completely clear [19]. Gut microbiome changes are one suggested intervention that results in a physiological switch in the gastrointestinal tract and its immune mechanisms [20]. This study represents a part III of our continuous investigation of the role of glucan and vitamin D supplementation in diabetic treatment and/or prevention.

## MATERIALS AND METHODS

### Glucan

Yeast-derived insoluble Glucan #300 (>85% dry w/w basis) was purchased from Transfer Point (Columbia, SC, USA). This glucan contains 96% carbohydrates and 2.1% proteins. Neutral sugar analysis confirmed 91.3% glucose and 8% mannose. Glucan was ingested on an empty stomach, followed by 100 ml of water and a 30-minute rest prior to any food intake. Simultaneous use with nonsteroid compounds (NSAIDs) was not recommended.

### Vitamin D

Vitamin D (coleciferol, D<sub>3</sub>, Vigantol) was manufactured by Merck (Darmstadt, Germany). One ml of solution contains 20,000 IU of vitamin D<sub>3</sub>, one drop contains 500 IU. All patients were instructed to ingest vitamin D with fat-containing food. The dose was changed according to the season; from November to February, the dose doubled. No negative side effects were observed; three patients breached conditions (elimination of fats from food).

### Protocol

We explained the experimental protocol and obtained consent forms from all participating patients. This study was Institutional Review Board (Regional Masaryk

University) approved and performed in full agreement with the Helsinki declaration (revised version 2000.09.01) and in full compliance with the Czech Republic's clinical testing rules.

We reviewed and randomly divided 72 individuals into four groups: 1) Group A consisted of 20 diabetic patients supplemented with  $\beta$ -glucan and vitamin D; 2) Group B consisted of 20 diabetic patients supplemented with vitamin D and placebo; 3) Group C consisted of 12 diabetic patients supplemented with vitamin D only; 4) Group D represented 20 healthy patients getting no supplementation. Tested diabetic groups consisted of 30 males and 22 females.

Individual groups of DR patients were supplemented for three months (one dose per day), in addition to normal treatment. The glucan dose was 500 mg/day, in the morning, before any food intake. Vitamin D dosage was based on age, weight and season. The placebo consisted of pills in the same design, shape, and color. Tests were performed at the beginning and the end of the experiment, in each case after fasting for 12 hours.

## Tests

Patients were established by skin photo type, weight, height, BMI and starting levels of vitamin D [21-23]. Apolipoproteins A1 and B were tested using a kit from Siemens Health Care Diagnostic (Newark, DE). Levels of leptin were evaluated by enzymatic immunoassay (Mediagnost, Germany) using calibrated WHO standards EIBSCode 97/599.

Vitamin D levels were measured by an ELISA assay using standards recommended by the manufacturer (DRG Instruments, Germany). Based on the manufacturer's information, average values for a healthy common 58-year-old Caucasian population are 26.1 ng/ml in males and 30.2 ng/ml in females. A vitamin D deficit is considered when levels are below 10 ng/ml, insufficient levels range between 10–29 ng/ml, and normal levels range between 30–100 ng/ml. Samples were taken in the morning on an empty stomach. Anthropometric evaluations were part of the initial medical examinations. Weight, height, waistline and hipline were measured; BMI levels were also calculated.

## Statistical analysis

Paired t test statistical significance was evaluated (GraphPad Prism 5.04; GraphPad Software, USA). An average and standard deviation was evaluated after determining standard value composition (D'Agostino, Pearson). In case of nonstandard composition, values were converted into logarithms.

## RESULTS

We studied a group of 52 individuals diagnosed with DR and 20 healthy individuals of the same age category (Table 1). The participants were randomly divided into the following subgroups: A) supplemented with vitamin D and  $\beta$ -glucan; B) supplemented with vitamin D and placebo; C) supplemented with vitamin D alone; D) without any supplementation. Age of individuals did not differ among these groups (range, 62.1–67 years).

BMI values among Groups A, B, and C were statistically identical, but were significantly different when compared to Group D. As can be concluded from Table 1, normal weight could be found only in up to 15.8% of people with diabetes and in 5% of normal population. A share of obese individuals was extremely high and was influenced by socioeconomic composition of our tested sample (95% of blue-collar workers).

Levels of vitamin D are shown in Table 1, which shows significant differences between groups with diabetes and control population. Individual diabetic groups have different values compared to control group (Figure 1), particularly Group A vs. Group D ( $P < 0.0001$  level), Group B against Group D ( $P < 0.0001$  level). There was no significant difference between Groups C and D, probably due to the lower number of individuals in Group C.

Application of vitamin D in doses related to sex, BMI and phototype of tested individual and a season of application, resulted in increase of vitamin D levels in all tested groups (Figure 1). After supplementation, the normal recommended serum levels (30–100 ng/ml) were not seen in any group. In some cases, this might be a result of ignoring recommended dosage or application without lipids. In Groups A and B, we found increase of average values up to 16.5 ng/ml, the increase in Group C was minimal.

Leptin levels (Figure 2) showed significant decrease, from 23 ng/ml to 19.3 ng/ml, in the group supplemented with vitamin D and  $\beta$ -glucan (Group A). In Group B, we found a statistically significant increase ( $P < 0.001$  level); in Group C, we found an increase to 23 ng/ml.

Apolipoprotein A levels were the same in all groups and reached normal laboratory levels (1.25–2.15 mg/ml). In supplemented groups, there were no changes even after 90 days supplementation, but the decrease in control group was statistically significant (Table 2). Table 3 summarizes changes in levels of apolipoprotein B. At the beginning of the study, the levels of apolipoprotein B corresponded with normal laboratory levels (0.55–1.25 mg/ml); the situation was not changed after experimental supplementation. Table 4 shows APO B/APO A ratio. No significant changes between supplemented groups were found, but this index was significantly lower in control Group D.

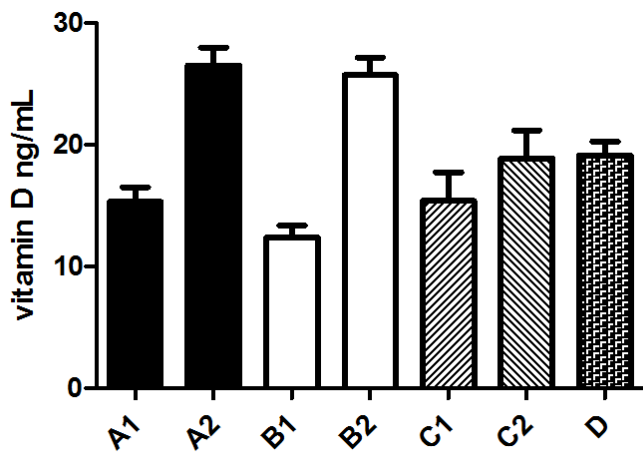


Figure 1: Effect of glucan and vitamin D supplementation of vitamin D levels in Individual groups.

Group A: Vitamin D and β-glucan evaluated at the start (A1) and end (A2) of the 3 month supplementation; Group B: Vitamin D and placebo supplementation evaluated at the start (A1) and end (A2) of the 3 month supplementation; Group C: Vitamin D supplementation evaluated at the start (A1) and end (A2) of the 3 month supplementation; Group D: control group of healthy individuals evaluated at the start (A1) and end (A2) of the 3 month supplementation. Results are given as mean ± SD.

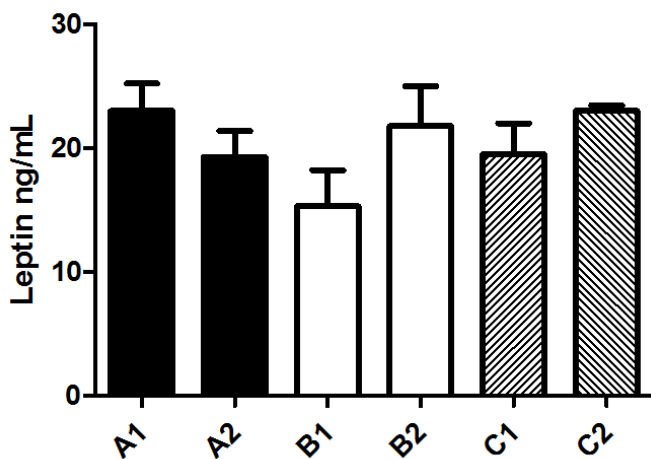


Figure 2: Effect of glucan and vitamin D supplementation of leptin levels.

Group A: Vitamin D and β-glucan evaluated at the start (A1) and end (A2) of the 3 month supplementation; Group B: Vitamin D and placebo supplementation evaluated at the start (A1) and end (A2) of the 3 month supplementation; Group C: Vitamin D supplementation evaluated at the start (A1) and end (A2) of the 3 month supplementation; Group D: control group of healthy individuals evaluated at the start (A1) and end (A2) of the 3 month supplementation. Results are given as mean ± SD.

## DISCUSSION

Diabetes and obesity currently represents a significant problem for almost every country of the world. DR represents a major complication of diabetes. Monitoring of risk factors, such as glycemia, lipid metabolism (lipids,

Table 1: Basic characteristics of tested individuals

	A	B	C	D
n	20	20	12	20
Age	64.6	66.1	67	62.14
BMI	34.2	30.56	31.29	29.96
Underweight %	0	0	0	0
Normal weight %	12.5	15.8	0	5
Overweight %	18.7	31.6	50	55
Obesity %	68.8	52.6	50	40
Vitamin D (ng/ml)	15.34	12.41	15.35	19.09

Basic information about the physiological characteristics pertinent for our study

Group A: Vitamin D and β-glucan – evaluated at the start of the study; Group B: Vitamin D and placebo supplementation; Group C: Vitamin D supplementation; Group D: control group of healthy individuals - evaluated at the start and end of the 3 month period

Table 2: Effects of supplementation on apolipoprotein A levels

Group	Start	End	P
A	1.53 ± 0.29	1.55 ± 0.28	0.699
B	1.58 ± 0.27	1.53 ± 0.25	0.964
C	1.65 ± 0.34	1.87 ± 0.44	0.357
D	1.63 ± 0.33	1.55 ± 0.32	0.037

Levels of apolipoprotein A at the beginning and end of the study in individual groups

Group A: Vitamin D and β-glucan – evaluated at the start and end of the 3 month supplementation

Group B: Vitamin D and placebo supplementation

Group C: Vitamin D supplementation

Group D: control group of healthy individuals - evaluated at the start and end of the 3 month period.

Results are given as mean ± SD.

Table 3: Effects of supplementation on apolipoprotein B levels

Group	Start	End	P
A	0.921 ± 0.265	0.948 ± 1.718	0.0681
B	0.968 ± 0.307	0.880 ± 0.273	0.263
C	0.803 ± 0.215	0.724 ± 0.193	0.763
D	0.905 ± 0.271	0.843 ± 0.226	0.142

Levels of apolipoprotein B at the beginning and end of the study in individual groups

Group A: Vitamin D and β-glucan – evaluated at the start and end of the 3 month supplementation; Group B: Vitamin D and placebo supplementation; Group C: Vitamin D supplementation

Group D: control group of healthy individuals - evaluated at the start and end of the 3 month period. Results are given as mean ± SD.



Table 4: Effects of supplementation on APO B/APO A index

Group	Start	End	P
A	1.727 ± 0.352	1.717 ± 0.453	0.577
B	1.821 ± 0.756	1.909 ± 0.747	0.263
C	2.180 ± 0.650	2.611 ± 0.542	0.303
D	1.052 ± 0.796	1.033 ± 0.764	0.331

Levels of an APOB/APO A index at the beginning and end of the study in individual groups.

Group A: Vitamin D and β-glucan – evaluated at the start and end of the 3 month supplementation; Group B: Vitamin D and placebo supplementation; Group C: Vitamin D supplementation Group D: control group of healthy individuals - evaluated at the start and end of the 3 month period. Results are given as mean ± SD.

blood pressure, weight), age, ethnicity and smoking, is important for prevention or reduction of diabetes severity [24]. Clinical biochemical and molecular factors, together with genetic and epigenetic factors, contribute to the risk of developing DR. A detailed understanding of current and new biomarker effects should help to improve diagnosis, prognosis and treatment of diabetes and its complications.

Understanding of new biomarkers and mediators of DR, particularly those connected to inflammatory processes and those mediating angiogenesis, is of extreme importance. It offers possibilities of new treatments (corticoids or intravitreal macular inhibitors of growth factor VEGFC intravitreal anti-vascular endothelial growth factor inhibitor). It is important to remember, however, that despite using wide spectrum of various treatments, including laser photocoagulation, intraocular application of steroids, NRGF, fenofibrate and PPAR-alpha agonists, a majority of patients still suffer from the lack of progress [9]. The ever-increasing incidence of diabetes and related complications are directly linked to the limited scope of preventative actions, particularly those able to affect the population in further worsening the progress of the disease (e.g., smoking, obesity, low physical activity).

The already high prevalence of obesity in the Czech Republic is steadily increasing, particularly among lower education populations where obesity, metabolic syndrome, and other complications are commonly observed. The most pronounced occurrence of these problems is among Roma populations. Among the Roma population in the Slovak Republic, the prevalence of obesity-related diabetes is virtually identical: 30% Roma vs 10% in non-Roma population. High occurrence of smoking (95% of adult Roma population compared to 30% in blue-collar workers) is probably the highest risk factor, followed by low physical activity. When we compared populations with low level of education and low

level of physical activity, we found the same correlation throughout central Europe [25]. Published data, together with our study results, confirm that lowering obesity is a major requirement for reduction of diabetes type 2 and subsequent health complications. At the same time, it is important not to forget additional influences, particularly genetic [16]. Several risk factors are preventable and their prevention in some countries have already shown positive results [16]. Countries that severely limit smoking, lower social differences, or increase health interest and knowledge can serve as an example.

Occurrence of low or deficient levels of vitamin D is indirectly related to obesity, mostly as a result of low physical activity [1]. Additional causes include inadequate exposure to sunlight (as reported in the Czech Republic secondary to severe pollution), urbanization and nutrition. Compared to European countries, the use of fish meat in the Czech Republic is significantly lower and reaches only 6 kg/year. Vitamin D deficiency is one of the risk factors during induction of diabetes type 2. In addition, in case of further deepening deficit, it is a possible inductor of DR, particularly its proliferative form [9].

The role of glucan in diabetes is less studied; however, some studies report strong and dose-dependent effects in the control of blood glucose levels in diabetic patients [26]. Glucans improve metabolic and anthropometric variables in diabetic patients [27]. Findings in this study seem to support this older data.

Evaluation of leptin levels found a surprising decrease in Group A supplemented with both vitamin D and β-glucan. Leptin is considered to be a risk factor for insulin resistance in relation to weight and sexual dimorphism [8]. Our experience suggests β-glucan has a significant role; it affects not only glycemia in patients, but also reduces inflammatory reaction [3, 18]. There is high probability that these effects are manifested via changes of intestinal microbiome, as changes in ratio of lactobacilli population, particularly a decrease of bacteroides, was observed after β-glucan supplementation. Glucan also plays an important role in cholesterol regulation, probably via interaction with lipids and biliary salt in the bowel [28]. β-glucan supplementation results in significant risk reduction of atherogenesis and cardiovascular diseases [6, 7, 19, 20]. Also important is the significant weight decrease in Group A patients, which correlated with decrease of leptin (linear regression leptin/BMI is  $P < 0.0014$ ). The fact that leptin plays an important role in homeostatic regulation of energy is well established, and attention is currently focused on its role in glycemia control. These new findings suggest using leptin as supplement in diabetes treatment [15]. Based on our data, we suggest that simultaneous use of β-glucan and vitamin D might be used in complex treatment of diabetic retinopathy [29].

## CONCLUSION

Simultaneous supplementation with vitamin D and  $\beta$ -glucan resulted in positive changes in apolipoprotein A1 metabolism. In addition, this supplementation caused a significant decrease of leptin levels, accompanied by weight reduction of tested patients.

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Josef Richter – Substantial contributions to conception and design, Analysis and interpretation of data, Drafting the article, Final approval of the version to be published

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Vaclav Vetvicka – Analysis and interpretation of data, Revising it critically for important intellectual content, Final approval of the version to be published

Ivana Lihneová – Substantial contributions to conception and design, Acquisition of data, Drafting the article, Final approval of the version to be published

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**Guarantor of Submission**

The corresponding author is the guarantor of submission.

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None

**Consent Statement**

Written informed consent was obtained from the patient for publication of this study.

**Conflict of Interest**

Authors declare no conflict of interest.

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