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ARTICLE

Effects of β-glucan and Vitamin D Supplementation on Inflammatory Parameters in Patients with Diabetic Retinopathy

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ABSTRACT

The objective of this article is to evaluate the potential effects of beta-glucan and vitamin D supplementation in patients with diabetic retinopathy. We evaluated the levels of several parameters of inflammatory reactions (C-reactive protein [CRP], serum amyloid A [SAA], and interleukin- [IL-] 6), leptin, and vitamin D. Using a 3-month interval, we divided the patients into three groups: (1) supplemented with beta-glucan and vitamin D, (2) supplemented with vitamin D and placebo, and (3) supplemented with vitamin D alone. By this division, we aim not only to observe whether beta-glucan can increase the effects of vitamin D, but also to eliminate the potential effects of placebo. The doses of vitamin D corresponded to phototype, weight, age, and sex of the individual. Fifty-two diabetic retinopathy patients were selected for our study. We found significant vitamin D deficits in all cases, even after three months of supplementation with vitamin D. Significant changes in levels of CRP were observed in the beta-glucan–supplemented group; levels of SAA and IL-6 were not changed. Leptin levels were significantly lowered in the beta-glucan–supplemented group and increased in the other groups. More detailed studies and/or longer supplementation is necessary.

KEYWORDS

beta-glucan; CRP; IL-6; leptin; vitamin D

Introduction

Diabetic retinopathy (DR) is a classic microvascular complication of diabetes mellitus (DM). DR is caused by specific morphological changes resulting from a metabolic disorder in patients with type 1 or 2 diabetes. DM is the fifth most common cause of preventable blindness and a highly common cause of several vision deteriorations (Lee, Wong, & Sabanayagam, 2015). The most common DR manifestation is diabetic macular edema, which lowers vision sharpness. Clinically significant diabetic macular edema is found in 6%–10% of patients with DM (Pickup, 2004). Possible local ophthalmological treatments of clinically significant diabetic macular edema include laser photocoagulation (thermal burn in retinal tissue by laser-generated light), intravitreal application of vascular endothelial growth factor blockers or corticosteroids, and pars plana vitrectomy (vitreous humor gel that fills the eye cavity is surgically removed to provide better access to the retina). Laser treatment performed by classical photocoagulation often results in retinal scarring. Depending on the diabetic

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macular edema type, focal or mesh photocoagulation is used. Another possibility is using subliminal photocoagulation (laser therapy based on a stimulation concept using extremely short pulses followed by cooling periods), which is without the risk of scarring and can be repeated as necessary (Luttrull & Dorin, 2012).

The most important clinical risk factors of disease progression are length of disease, hypertension, and hyperglycemia. Additional DR risk factors include profession (blue collar), smoking, dyslipidemia, and obesity. We have recently begun studying the effects of inflammatory reactions on DR. Aspects of chronic systemic low-level inflammation (pathophysiological parainflammation) are induced by products of oxidative stress involving not only acute inflammation proteins (C-reactive protein [CRP], serum amyloid A [SAA], interleukin [IL-] 6, tumor necrosis factor [TNF] alpha/beta, IL-8, and other cytokines) but also induction of proteins related to a complement cascade (C3a, C5a, C5, C5b–C9, CFH, CD35, and CD46) (Gruys, Toussaint, & Niewold, 2005; Marzi et al., 2013; Nita, Grzybowski, Ascaso, & Huerva, 2014). The correlation between elevated inflammatory parameters and development of DR has been clearly established (Meleth, Agron, & Chan, 2005; Roy, Janal, Crosby, & Donnelly, 2013; Semeraro, Cancarini, & dell'Omo, 2015).

Hypoxia, in addition to hyperreactivity of the complement system with inflammation, results in disorder of proangiogenic/antiangiogenic balance (Nita et al., 2014). Inflammatory reactions, together with activation of innate immune reactions, are loosely related to pathogenesis of type 2 DM. However, it is necessary to clearly establish whether they represent the primary inductor or are only the response to hyperglycemia, obesity, atherosclerosis, metabolic syndrome, or other diseases (Pickup, 2004; Solomon et al., 2017).

Obesity is the most common condition of DM. In 2015, the World Health Organization proposed that there are at least 3 billion obese or overweight people. Obesity leads to dysregulation of immunological parameters and an increase of fat cell–derived proteins, adipokines. Adipokines are cytokines secreted by adipose tissue. Adipocyte-produced proteins are hormones produced by adipose tissue. They can increase (adiponectin) or decrease (resistin) effects of insulin. Leptin (first adipokine discovered) acts as an endogenic factor regulating relations between metabolism and immune reactions. In the obese population, we can detect its elevation relating to proinflammatory effects. Leptin is a weight regulator with promising potential as an obesity treatment (Meek & Morton, 2016). In addition, leptin is a well-known regulator of immune responses, being mostly involved in enhancing immune functions such as inflammatory cytokine production, chemotaxis, and increased Th17 proliferation (Naylor & Petri, 2016). It is important to note, however, that its application might result in damage to the immune functions due to its proinflammatory effects. Thus, it is important to discuss the importance of vitamin D levels and the possibility of supplementing the individual to adjust inflammatory reactions in DM and other diseases (Mousa, Misso, Teede, Scragg, & de Courten, 2016). Vitamin D deficiency has been implicated in the pathophysiology of various inflammatory diseases such as Crohn disease and rheumatoid arthritis. It is documented that adding vitamin D lowers the risk of developing DM, which led to recommendations of vitamin D supplementation as DM prevention (Pickup, 2004). Vitamin D significantly affects glucose metabolism, regulates exocytosis of insulin, directly affects stimulation of insulin receptors, improves intake of glucose in peripheral cells, and regulates insulin resistance (Bajaj et al., 2014). Vitamin D insufficiency directly relates to DM severity (Alcubierre et al., 2015). Authors seeking recent information on the role of vitamin D in DM and DR should seek these excellent studies (Luo, Gao, & Qin, 2017; Nakashima, Yokoyama, Yokoo, & Urashima, 2016).

The possible regulation of energetic metabolism, obesity, and metabolic syndrome is gaining attention. The relation between these reactions and beta-glucan supplementation is the

subject of numerous studies. Studies have shown that adding beta-glucan to food helps prevent or treat metabolic syndrome and decreases insulin resistance, dyslipidemia, hypertension, and obesity (Stier, Ebbeskotte, & Gruenwald, 2014; Wang et al., 2016). It has been suggested that beta-glucan assists in balancing gut microbiota, particularly in altering the ratio between bacteroides (Gram-negative bacteria such as *Bacteriodes fragilis*) and firmicutes (mostly Gram-positive bacteria such as *Clostridia* and *Bacilli*) (Wang et al., 2016). Detailed studies of beta-glucan effects, possible relationships between function and purity, or physicochemical structure are currently under way.

Materials and methods

Beta-glucan

Yeast-derived insoluble beta-glucan #300 (> 85% dry w/w basis) was purchased from Transfer Point (Columbia, SC, USA). This beta-glucan contains 96% carbohydrates and 2.1% proteins. Neutral sugar analysis confirmed 91.3% glucose and 8% mannose.

Protocol

We explained the experimental protocol and obtained consent forms from all participating patients. This study was Institutional Review Board approved, 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 52 patients and divided them into three groups: (1) Group A consisted of patients supplemented with beta-beta-glucan and vitamin D; (2) Group B consisted of patients supplemented with vitamin D and placebo; and (3) Group C consisted of patients supplemented with vitamin D only. Of these 52 patients, 30 were male, ranging in age from 49 to 76 years (average 64.5 years), and 22 were female, ranging in age from 48 to 87 years (average 67.3 years). Individual groups of DR patients were supplemented for three months (one dose per day), in addition to normal treatment. The beta-glucan dose was 500 mg/day; the placebo consisted of pills in the same design, shape, and color. By this division, we aimed not only to observe whether beta-glucan can increase the effects of vitamin D, but also to eliminate the potential effects of placebo. The tests were performed at the beginning and the end of the experiment.

Vitamin D

Vitamin D (colecaciferol, D3, Vigantol) was manufactured by Merck (Darmstadt, Germany). One milliliter of solution contains 20,000 IU of vitamin D3; one drop contains 500 IU. We based individual patient doses on their phototype, sex, age, and weight. All patients were instructed to ingest vitamin D with fat-containing food.

Tests

Vitamin D levels were measured by an enzyme-linked immunosorbent assay (ELISA) assay using standards recommended by the manufacturer (DRG Instruments, Germany). Plasma levels of IL-6 were measured using Immulite immunoassay system (Siemens, Germany) with diagnostics and standards provided by the manufacturer. The sensitivity of this system is 2 pg/ml. CRP and SAA were measured using nephelometer Siemens BM II (Siemens

Healthcare, Diagnostics, Germany) as recommended by the manufacturer. Levels of leptin were measured using enzymoimmunoassay purchased from Mediagnost (Germany) using calibrated WHO international standards NIBSC Code 97/594. Anthropometric evaluation was part of the physical evaluation at the beginning of the study. Weight and height were measured, and body mass index (BMI) levels were calculated.

Statistical analysis

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

Results

Anthropometric measurement findings were not optimistic, as BMI values were significantly higher than those of corresponding age groups in the Czech Republic. BMI values to 25 kg/m^2 were found in only 13.6%, to 30 kg/m^2 in 29.6%, to 35 kg/m^2 in 29.6%, and over 35 kg/m^2 in 27.2% of tested patients. Approximately 45% of healthy populations of people in the Czech Republic have a normal BMI index (Čapková et al., 2017). Average BMIs in individual groups were 32.58 (SEM 28.9–36.2) in Group A, 30.6 (SEM 28.1–33.0) in Group B, and 31.3 (SEM 27.7–34.9) in Group C. In healthy populations, this value is 27.5 (SEM 26.4–28.5).

According to the manufacturer's information, average values of vitamin D 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 and 29 ng/ml, and normal levels range between 30 and 100 ng/ml.

Figure 1 shows effects of tested supplements on levels of vitamin D. We found the values at the beginning of the study to be 15.3 ng/ml (SEM 12.8–17.9) in Group A, 12.4 ng/ml (SEM 10.4–14.4) in Group B, and 15.4 ng/ml (SEM 10.2–20.5) in Group C. Vitamin D deficiency (i.e., levels below 30 ng/ml) was found in 70% with an additional 4% of patients having higher, but still suboptimal, values of 31–38 ng/ml. Ninety days of supplementation increased

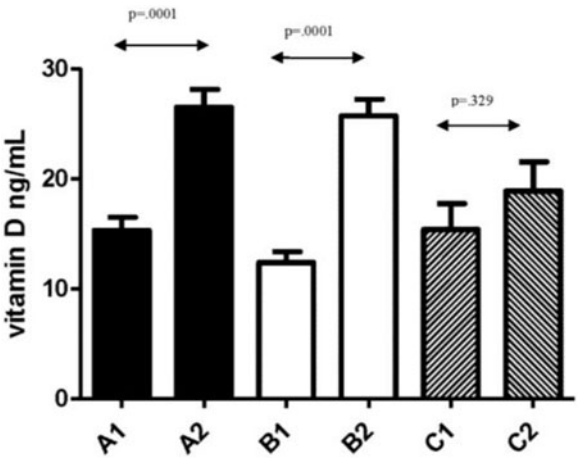

Figure 1. Effects of supplementation on levels of vitamin D in patients with diabetic retinopathy at the (1) start and (2) end of the study. A1, A2: vitamin D and beta-glucan supplementation; B1, B2: vitamin D and placebo supplementation; C1, C2: vitamin D supplementation.

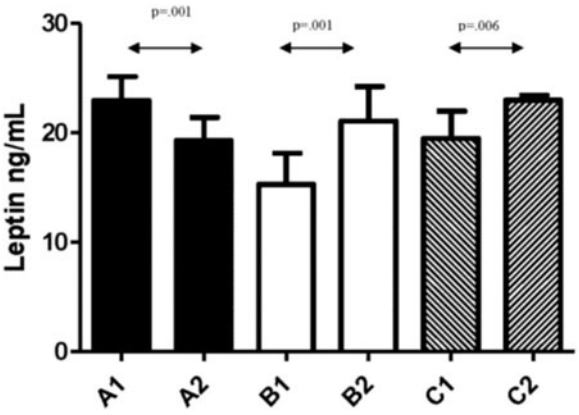

Figure 2. Effects of supplementation on levels of leptin in patients with diabetic retinopathy at the (1) start and (2) end of the study. A1, A2: vitamin D and beta-glucan supplementation; B1, B2: vitamin D and placebo supplementation; C1, C2: vitamin D supplementation.

the levels of vitamin D, but significant correlations between plasma levels of vitamin D and patient weight remained. The changes in Group A and Group B were statistically significant.

Figure 2 shows elevated levels of leptin in all tested groups. In Group A (vitamin D and beta-beta-glucan), we observed a statistically remarkable decrease of leptin levels from 22.96 ± 2.17 mg/ml to 19.28 ± 2.12 mg/ml. Group B (vitamin D and placebo) demonstrated significant increase from 15.28 ± 2.85 mg/ml to 21.08 ± 3.16 mg/ml, and Group C (vitamin D only) showed significant increase from 19.49 ± 2.49 mg/ml to 22.99 ± 0.45 mg/ml.

IL-6 levels were not significantly changed by any of the tested supplements. Figure 3 shows minimal increase from 2.49 to 2.54 pg/ml in Group A. IL-6 levels were higher in Group B, from 2.29 ± 0.51 pg/ml to 4.71 ± 7.91 pg/ml, but after eliminating extreme values caused by strong inflammation in one patient, the increase to 3.92 ± 0.68 ($p = .032$) was not significant. In Group C, the increase from 2.3 ± 0.65 pg/ml to 2.97 ± 1.21 pg/ml was also not significant.

Vitamin D and beta-glucan supplementation significantly lowered the levels of CRP from 6.09 ± 1.9 mg/ml to 3.37 ± 1.81 mg/ml (Figure 4). Group B was not significant, but had

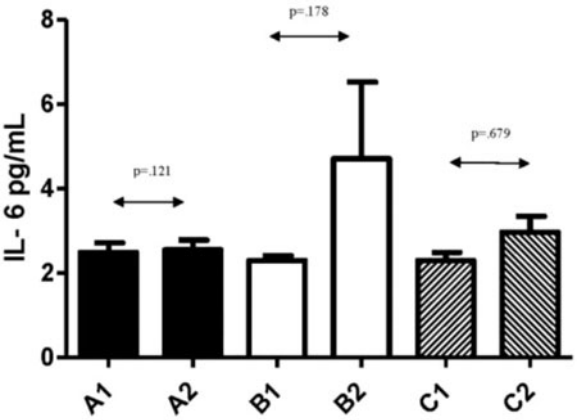

Figure 3. Effects of supplementation on levels of interleukin-6 (IL-6) in patients with diabetic retinopathy at the (1) start and (2) end of the study. A1, A2: vitamin D and beta-glucan supplementation; B1, B2: vitamin D and placebo supplementation; C1, C2: vitamin D supplementation.

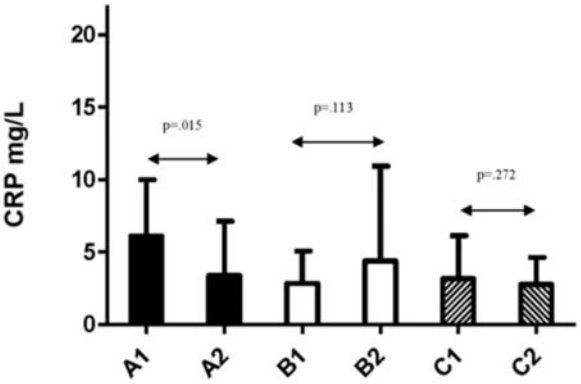

Figure 4. Effects of supplementation on levels of C-reactive protein (CRP) in patients with diabetic retinopathy at the (1) start and (2) end of the study. A1, A2: vitamin D and beta-glucan supplementation; B1, B2: vitamin D and placebo supplementation; C1, C2: vitamin D supplementation.

markedly increased of levels from 2.83 ± 2.2 mg/ml to 4.39 ± 2.92 mg/ml. The decrease from 3.17 ± 2.9 mg/ml to 2.78 ± 1.8 mg/ml in Group C was again not significant.

Levels of serum SAA are shown in Figure 5. It is clear that all levels show slight inflammatory conditions, common for patients with metabolic syndrome or with its initialization by type 2 diabetes. No changes were significant.

Discussion

Following the discovery of leptin in 1994, major research efforts offered better understanding of the cellular and molecular mechanisms underlying the biological effects of this hormone. Interestingly, leptin exerts potent antidiabetic actions that are independent of its effects on body weight and food intake. In particular, leptin can correct diabetes in animal models of either DM type 1 or DM type 2. It might be important to note that depression is a common comorbid manifestation of types 1 and 2 diabetes (Hood et al., 2012). Despite recent studies suggesting the possibility of a biological correlation between depression and diabetes, the knowledge of metabolic inflammation factors remains inadequate. Significant correlation

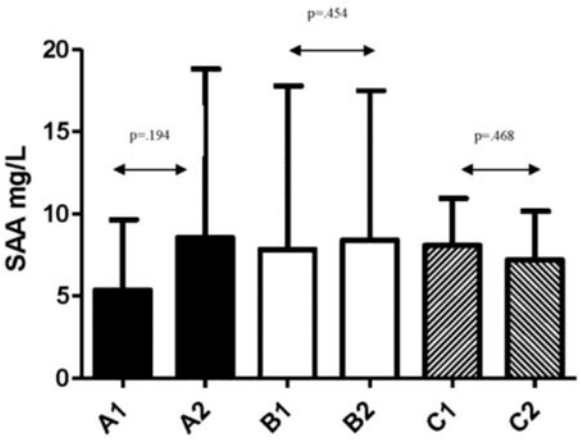

Figure 5. Effects of supplementation on levels of serum amyloid A (SAA) in patients with diabetic retinopathy at the (1) start and (2) end of the study. A1, A2: vitamin D and beta-glucan supplementation; B1, B2: vitamin D and placebo supplementation; C1, C2: vitamin D supplementation.

of Center of Epidemiological Depression Studies (CES-D) with gradation changes in some inflammatory proteins and fat metabolism indicators has been established (Hood et al., 2014). Our findings of changes of leptin levels correspond with this report.

A different situation exists in the case of CRP. Our results show that vitamin D and beta-glucan supplementation significantly lowered the levels of CRP from 6.09 ± 1.9 mg/ml to 3.37 ± 1.81 mg/ml. On the other hand, in Group B we found strong but insignificant increase of CRP levels from 2.83 ± 2.2 mg/ml to 4.39 ± 2.92 mg/ml. Clearly, addition of beta-glucan makes a strong difference. The significant changes in CRP levels with the strong decrease of leptin levels (Group A) were, however, surprising. The levels of vitamin D improved in all groups, which was expected, as each group was supplemented with vitamin D. The reduction of serum leptin in Group A despite achieving almost normalization of vitamin D level is particularly interesting and clearly must be the effect of addition of beta-glucan.

Besides energetic homeostasis regulation, another significant role of leptin is in control of glucose metabolism via effects on the central nervous system. Dysfunction or decreased leptin levels help to therapeutically influence diabetes (Meek & Morton, 2016). In support of this, rodent models of leptin deficiency are characterized by insulin resistance and diabetes, and leptin treatment lowers blood glucose and insulin levels independent of changes in food intake and in body weight. However, the mechanism that mediates the glucose-lowering effects of leptin in diabetes remains to be fully elucidated and is an area of active investigation. At the same time, lower levels of leptin are reflected in fat deposit decreases, which subsequently result in changes of acute inflammatory reactive protein levels followed by lower risk of cardiovascular disease (Gruys et al., 2005).

Significant weight increase commonly follows diabetes and clearly results in high risk of metabolic syndrome induction. Obesity is a problem affecting over 3 billion people (Andrade-Oliveira et al., 2015). It results in dysregulation of immune mechanisms and in changes in production and release of fat cell–derived proteins, which subsequently increase (adiponectin) or decrease (TNF-beta, interleukin beta, and others) the effects of insulin. Obesity and reduction of physical activity result in progressively decreased vitamin D levels. Decreased vitamin D levels can also result from low exposure to sun, aging, and changes in diet. We observed a significantly low level of vitamin D in our study, which in many cases reached critical levels. Low levels of vitamin D are known to be involved in the pathophysiology of numerous diseases, including rheumatoid arthritis, kidney disease, Crohn disease, and DM. This deficiency is also seen in health conditions such as inflammation, obesity, and cardiovascular diseases. However, a systematic review of vitamin D supplementation effects on inflammation is still lacking (Mousa et al., 2016).

Three-month supplementation with vitamin D resulted in significant improvements in the vitamin D deficiencies. However, optimal levels were still not reached. This could be the result of not adhering to the recommended protocol or because of insufficient dosage, which was calculated based on phototype, age, weight, physical load, alcohol intake, and smoking. It is clear that to see significant improvements, it is important to influence the lifestyle for a longer period (Mehmood & Papandreou, 2016). Our study results concur with those published by (Rabenberg et al., 2015), who found similar levels in healthy adult German populations. Longer supplementation will be tested in a subsequent study.

Our study showed that normalization of vitamin D levels is followed by improvements of systemic inflammation and reduction of leptin levels as mentioned before (Garcia-Bailo et al., 2011; Nita et al., 2014). Leptin is an inflammatory molecule that is capable of activating both adaptive and innate immunities. It can increase the production of proinflammatory cytokines and inhibit CD4 cell differentiation (Naylor & Petri, 2016). Numerous studies have confirmed that long-term leptin-replacement therapy is well tolerated and dramatically

improves glycemic control, insulin sensitivity, and plasma triglycerides in patients with severe insulin resistance due to lipodystrophy. Together, these results have spurred enthusiasm for the use of leptin therapy to treat humans suffering from DM (Coppari and Bjorbaek, 2012). Reduction of leptin levels by the beta-glucan/vitamin D supplementation found in our study is therefore clearly beneficial.

A correlation between vitamin D deficiency and diabetes has been suggested, but its effects on hemoglobin regulation and insulin resistance regulation are not unequivocal (Rebello, Burton, Heiman, & Greenway, 2015). However, clinical findings suggest an important correlation of clinical values of diabetic nephropathy and retinopathy (Bonakdaran and Shoeibi, 2015). Correlation between gradation of these changes and increased prevalence of microvascular impairments is clear, but some studies do not endorse these findings (Bajaj et al. 2014; Bonakdaran and Shoeibi, 2015). It is clearly necessary to perform more experimental and perspective research to study this problem in full detail (Alcubierre et al., 2015).

Beta-glucans are plant immunomodulators with clearly defined mechanisms of action. Being the only evolutionary fully conserved immunomodulator acting across the entire animal kingdom, beta-glucan is the most studied natural immunomodulator, with more than 20,000 published studies. Beta-glucan supplementation is based not only on established significant improvements of the immunological mechanisms but also mostly on the established positive effects of the psychological state (Richter, Kral, & Stiborova, 2015; Richter, Kral, & Vetvicka, 2016; Talbott & Talbott, 2012; Vetvicka & Vetvickova, 2016). This was clear in our patients after short-term supplementation. A moderate weight decrease represents a positive effect, which affects, among other factors, the mental state of patients. In addition, beta-glucan as a nutritional fiber has positive and preventive effects on metabolic syndrome (El Khoury et al., 2012; Galisteo et al., 2008). These effects are probably due to the changes of intestinal microbiota, which falls outside the scope of this report (Cloetens et al., 2012). Readers inquiring for more information on this subject should read a comprehensive report by (Wang et al., 2016).

In conclusion, our data suggest that supplementation with materials combining bioactive molecules, such as inulin or polyphenols, with beta-glucan might positively influence the health conditions of patients with DR (Rebello et al., 2015). In addition, the combination of beta-glucan with selenium could offer improvements in the current conditions and inhibition of cancer growth (Vetvicka & Vetvickova, 2016). According to studies showing synergy between various bioactive compounds, it is possible that supplementation with materials combining bioactive molecules such as inulin or polyphenols with beta-glucan might positively influence the health conditions of patients with DR. Cleary, supplementation of the diet with beta-glucan and vitamin D offers a simple, safe, and cost-effective way of increasing leptin levels. Taken together with current suggestions of using leptin in treatment of DM, we believe that our study might open a new window for future medical practice.

Declaration of interest

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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