VITAMIN D AMELIORATIVE EFFECT ON SOME IMMUNOLOGICAL ASPECTS OF TYPE 2 DIABETES MELLITUS IN RAT MODEL

Ahmed M. Sh. Ibrahim[(1,2)]; Moustafa H. Ragab[(1)]; Amany S. Elwakkad[(2)]; Howida S. Abou-Seif [(2)]; Marwa Tarek [(3)]

1) Faculty of Graduate Studies and Environmental Research, Ain Shams University 2) Medical Physiology Department, National Research Center 3) Biochemistry and Molecular Biology Department, Faculty of Medicine, Ain Shams University

ABSTRACT

Type 2 Diabetes and its complications is a worldwide epidemic and a significant cause of illness and death. The specific relation between vitamin D level and immunity status in Diabetes is still poorly understood. This research may help create new potential therapies to prevent diabetic complications. To find out the impact of vitamin D dietary supplementation on Type 2 diabetes immunological aspects, an experimental randomized prospective study was carried out in the Medical Physiology Department, Medical division, National Research Center on thirty albino male rats. Three groups—negative control, positive diabetic control, and diabetic group with intramuscular injections of 20,000 IU/kg Vitamin D3 were included in the study. Insulin, fasting blood glucose (FBG), homeostasis model assessment for insulin resistance (HOMA-IR) and inflammatory markers were measured in all groups. HOMA-IR, nuclear factor kappa B (NF-KB), tumor necrosis factor-α (TNF-α), Interleukin 1B (IL-1B), C reactive protein (CRP) and immunoglobulin A (IgA), were considerably lower in treated group than positive control group. After treatment, glucose was significantly lowered in the group treated with vitamin D3. As a result, vitamin *D3 i.m* administration may enhance glycemic management in those animals with type 2 diabetes mellitus.

Keywords: Type 2 Diabetes Mellitus, Vitamin D3, Insulin, C-Reactive Protein , IL-1B, NF-KB, IgA.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) was one of several non-skeletal conditions with inadequate vitamin D that had been reported in recent years. Being overweight, older, and inactive were risk factors for T2DM and low vitamin D levels (Alvarez., 2010). There were links between vitamin D insufficiency and conditions like cardiovascular disease, metabolic syndrome, and osteoporosis. Vitamin D insufficiency had been linked to T2DM in several research studies (Pathania *et al.,* 2023). Yaribeygi *et al.* (2020) demonstrated that vitamin

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Print ISSN 1110-0826
Online ISSN 2636 - 3178

D's impacts on insulin sensitivity and production might be a factor in glucose tolerance. Subjects with T2DM had significantly reduced levels of 25-(OH) D in their blood circulation than do healthy controls. Additionally, compared to women, who were more likely to have vitamin D insufficiency, older males with vitamin D deficiency release more insulin after consuming glucose. (Akter *et al.,* 2020).

Studies on animals had demonstrated the importance of vitamin D as a fundamental element for healthy insulin production. Vitamin D lowers insulin resistance most likely via up-regulating the insulin receptor gene and impacting calcium and phosphorus metabolism. Vitamin D supplementation enhanced insulin sensitivity by 54% in one trial of 5,677 individuals with poor glucose tolerance. Additional research had revealed that elevating consuming insulin sensitivity was increased by vitamin D (Baynes *et al.,* 1997 and Takishi *et al.,* 2012).

Chiu *et al.,* (2004) revealed a clear correlation between insulin sensitivity and 25-(OH)D levels as well as a deleterious impact of vitamin D insufficiency on pancreatic beta-cell activity. A 20-year follow-up research on 4,843 T2DM patients found consuming Vitamin D was linked to a lower incidence of the disease (Ozfirat and Chowdhury, 2010).

Diabetes mellitus (DM) patients were more likely to have infections. Diabetic people were more prone than non-diabetic patients to experience several of these illnesses with a difficult course. For instance, 75% of the time, an infection causd or aggravated diabetic ketoacidosis. Patients who had both an infection and ketoacidosis have a 43% death rate (Akash *et al.,* 2020). It was reported that type 1 diabetes exhibited elevated serum levels of complement factor 4 (C4) that were below the normal range (Kulak, 2021). Diabetic patients had elevated resting compared to non-diabetic controls. There was a decreased response to stimulation and increased concentrations of IL-6, IL-8, and TNF-K. Patients with type 1 or type 2 diabetes had been reported to have significantly less chemotaxis than controls (Erener, 2020).

Almost all immune cells show the Vitamin D receptor (VDR), which suggested that vitamin D may have an impact on their metabolism. Additionally, a number of immune cells that can

convert 25-hydroxyvitamin D (25(OH)D) into the active 1,25-hydroxyvitamin D **(**1,25(OH)2D) include monocytes, dendritic cells, macrophages, B cells, and T cells. As a result, the active form can be controlled locally at the site of inflammation (Medrano *et al.*, 2018).

In the cell nucleus, the complex formed by the active 1,25(OH)2D binding to the VDR can affect the expression of hundreds of genes, including those involved in the production of cytokines. *In vitro* studies revealed that vitamin D played a role in enhancing pathogen clearance mechanisms (Hewison, 2012).

Numerous studies implied that vitamin D aids the body's defense against viral infections. There was a link between vitamin D deficiency and influenza infections (Zhixin Zhu *et al.*, 2022). Vitamin D levels were found to be linked with the risk of RTIs (respiratory tract infections) in a major cross-sectional survey of British people (Berry *et al.*, 2011).

The outcomes of intervention trials remained debatable. There had been several published meta-analyses, some of which revealed supplemental vitamin D had no effects (Fares *et al.*, 2015) whereas some display modesty (Martineau *et al.,* 2016, Jolliffe *et al.,* 2016) or weak supporting evidence (Pojsupap *et al.,* 2015) of a constructive nature, while other reported indisputable association (Martens *et al.*, 2020). Therefore, it was yet unknown how vitamin D supplementation affects immunological components, particularly in T2DM.

MATERIALS AND METHODS

The present randomized experimental study was carried out in the Medical Physiology Department, Medical division, National research center. The ethical committee at National research center approved the study protocol (number 350 dated 07/14/2020), which complies with the "Guide for the Care and Use of Laboratory Animals.", 8th edition, National Research Council Committee on the Update of the Guide for the Care and Use of Laboratory Animals (US), 2011].

Animals

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Print ISSN 1110-0826
Online ISSN 2636 - 3178

Thirty male Albino rats in total were purchased from the Egyptian Organization for Biological Products and Vaccines, Cairo, Egypt. Rats had grown up and weighed 250±20 g having normal vital signs and baseline laboratory testing at the beginning of the experiment. Rats were kept in conventional housing conditions in stainless steel litters for 10 days for acclimatization before the study began so they could get adjusted to the new surroundings (25±2°C and a 12-hour cycle of light and gloomy). Rats were given a supper of rodent chow (El-Nasr Pharmaceuticals and Chemicals Industry, Egypt) at this moment and were allowed unlimited access to distilled water.

Induction of diabetes mellitus

Rats in diabetic groups were given a diet high in fat in order to cause experimental diabetes. Eight weeks later, a single intraperitoneal injection was administered of 40 mg/kg of streptozotocin (STZ) **R** (40 mg/kg), (Sigma Aldrich Chemicals Co., St. Louis, MO., USA), freshly dissolved in cold 0.1 M citrate buffer (pH 4.5) and rats with diabetes were identified as having fasting blood glucose levels more than 250 mg/dL measured by (Accucheck Active Performa, Roche Germany) from blood obtained from the tail vein **(Furman, 2015)**. Control rats (Group 1) received standard diet and were given an intraperitoneal injection of citrate buffer.

Administration of vitamin D3 (Group 3)

On the first and fourteenth days after the onset of diabetes, 20,000 IU/kg of vitamin D3-intramuscular shots were given (Calcijex intramuscular injections, Avara Liscate Pharmaceutical service,Italy) **(Derakhshanian *et al.*, 2019)**.

Blood sampling

At the end of the study, rats were fasted for the night and given free access to water. Samples of blood from retro-orbital veins were collected in tubes without anticoagulants from anesthetized animals, The blood was spun down at 3000 rpm for 10 minutes, and the serum was frozen at -20° C for later analysis. The serum was utilized immediately for the determination of glucose and insulin levels, and measuring FBG, insulin, HOMA-IR, CRP,

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Print ISSN 1110-0826
Online ISSN 2636 - 3178

inflammatory markers measurement (Tumor Necrosis Factor -α Nuclear Factor -κB, Interlukin1B), immunoglobulin A, and vitamin D3 levels.

Statistical analysis

The SPSS version 18 (USA) software was used to analyze the data. Results were expressed as mean ± SD. One-way ANOVA was used for the statistical comparisons, followed by the Tukey's test. The degree of significance was determined at $P<0.05$

RESULTS

Vitamin D levels were substantially greater in the non-diabetic control group than in the diabetic control group while there was no significant difference after vitamin D administration. Also, it was significantly lower in diabetic control group compared to vitamin D treated group (Table 1).

Table 1: Level of serum vitamin D3 among the studied groups

Vitamin D conc.	**Group 1 N=10**	**Group 2 N=10**	**Group 3 N=10**
Mean ± SD	**87.8 ± 5.1**	**47.1 ± 6.3**	**114.9 ± 13.3**
***P* Value**	**<0.0001***		
***P* value of LSD vs control**		**0.02**	**0.26**
***P* value of LSD vs group 2**			<0.0001*

The data are evaluated using one-way ANOVA and Tukey's test. *: highly significant

There was no significant difference among the studied groups regarding glucose (Initial). Glucose (after induction of DM) was significantly lower in control group than diabetic control group and after administration of vitamin D. There was no significant difference between diabetic control group and vitamin D. Glucose (after treatment) was significantly lower in control group than diabetic control group and after administration of vitamin D. Also, it was significantly higher in diabetic control group compared to vitamin D group (Table 2).

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Print ISSN 1110-0826
Online ISSN 2636 - 3178

Table 2: Level of fasting glucose (mg/dl) (Initial, after induction of DM and post treatment with vitamin D3) among the studied groups

	Group 1 N=10	**Group 2 N=10**	**Group 3 N=10**
Fasting blood glucose (initial)			
Mean ± SD	**87.8 ± 3.16**	**96.3 ± 4.22**	**85.3 ± 4.66**
***P* Value**	**0.15**		
***P* value of LSD vs control**		**0.56**	**0.99**
***P* value of LSD vs group 2**			**0.3**
Glucose conc. (after induction of DM)			
Mean ± SD	**87 ± 4.12**	**396.7 ± 26.9**	**329.8 ± 25.7**
***P* Value**	<0.0001*		
***P* value of LSD vs control**		<0.0001*	<0.0001*
***P* value of LSD vs group 2**			**0.21**
Glucose (After treatment with vitamin D3)			
Mean ± SD	**85.6 ± 2.45**	**416.6 ± 16.4**	**192.4 ± 7.4**
***P* Value**	<0.0001*		
***P* value of LSD vs control**		<0.0001*	<0.0001*
***P* value of LSD vs group 2**			<0.0001*

Data are analyzed using one way ANOVA followed by Tukey's test. *: highly significant

Insulin was significantly higher while HOMA-IR was significantly lower in control group than diabetic positive control group and after administration of vitamin D. Also, insulin and HOMA-IR were significantly higher in the diabetic control group compared to vitamin D treated group. (Table 3).

Table 3: Level of blood insulin and HOMA-IR among the studied animal groups

	Group 1 N=10	**Group 2 N=10**	**Group 3 N=10**
Insulin (mIU/ml)			
Mean ± SD	**6.5 ± 0.28**	**3.9 ± 0.18**	**5.1 ± 0.23**
***P* Value**	<0.0001*****		
***P* value of LSD vs control**		<0.0001*	**0.02**
***P* value of LSD vs group 2**			**0.03**
HOMA-IR			
Mean ± SD	**1.4 ± 0.08**	**4.07 ± 0.27**	**2.48 ± 0.17**
***P* Value**	<0.0001*		
***P* value of LSD vs control**		<0.0001*	**0.0008**
***P* value of LSD vs group 2**			<0.0001*

Data were analyzed using one way ANOVA followed by Tukey's test. *: highly significant

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Print ISSN 1110-0826
Online ISSN 2636 - 3178

NF-KB, IgA, TNF-α, IL-1B and CRP were significantly lower in control group than diabetic control group. Also, they were significantly higher in diabetic control group compared to vitamin D treated group. (Table 4).

Table 4: Level of inflammatory markers among the studied groups

	Group 1 N=10	**Group 2 N=10**	**Group 3 N=10**
NF-KB			
Mean ± SD	**0.39 ± 0.09**	**1.16 ± 0.06**	**0.56 ± 0.09**
***P* Value**	<0.0001*****		
***P* value of LSD vs control**		**0.0002**	**0.82**
***P* value of LSD vs group 2**			**0.005**
IGA			
Mean ± SD	**74.07 ± 11.15**	**187.1 ± 28.4**	**64.8 ± 7.3**
***P* Value**	<0.0001*		
***P* value of LSD vs control**		<0.0001*	**0.99**
***P* value of LSD vs group 2**			<0.0001*
TNF-α			
Mean ± SD	**60.9 ± 10.3**	**179.6 ± 14.9**	**63.6 ± 11.9**
***P* Value**	<0.0001*****		
***P* value of LSD vs control**		<0.0001*****	**0.99**
***P* value of LSD vs group 2**			<0.0001*
IL-1B			
Mean ± SD	**16.7 ± 0.64**	**38.4 ± 1.79**	**16.1 ± 0.91**
***P* Value**	<0.0001*****		
***P* value of LSD vs control**		<0.0001*****	**0.99**
***P* value of LSD vs group 2**			<0.0001*
CRP			
Mean ± SD	**229.1 ± 10.2**	**1299 ± 153.9**	218.5 ± 14.5
***P* Value**	<0.0001*****		
***P* value of LSD vs control**		<0.0001*	**0.99**
***P* value of LSD vs group 2**			<0.0001*

The data are statistically evaluated using one-way ANOVA and Tukey's test. *: highly significant

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Print ISSN 1110-0826
Online ISSN 2636 - 3178

DISCUSSION

Recently, vitamin D has come under scrutiny as a possible diabetes risk reducer. Recent investigations have demonstrated that vitamin D receptor is expressed in non-skeletal cells like pancreatic beta cells and other tissues like brain, breast and prostate, emphasizing its importance and potentially major extra-skeletal beneficial effects (Abugoukh *et al.,* 2022).

According to studies, vitamin D may lower the incidence of type 2 diabetes, and this effect is likely mediated through vitamin D's effects on beta cell activity, insulin sensitivity, and systemic inflammation (Khudayar *et al.,* 2022).

It has been noted that vitamin D insufficiency (VDD) is a major issue in the field of public health. According to estimates, 80% of people with chronic renal disease (CKD) have VDD. Beyond playing a crucial function in maintaining the balance of calcium and phosphorus, vitamin D also modulates important biological processes like redox balance and the system of renin, angiotensin, and aldosterone. Vitamin D has a major impact on innate acquired immunity and endothelial homeostasis (Franca Gois *et al.,* 2018).

According to research, insulin resistance is all that high-fat diet-fed rats show; they do not actually have diabetes or genuine hyperglycemia. Type 2 diabetes is largely caused by insulin resistance; hence it is hypothesized that the high fat diet (HFD) may be a more effective method to start it (Lang *et al.,* 2019, Reilly *et al.,* 2022). Streptozotocin (STZ) was currently utilized extensively to cause cell death through DNA alkylation in both insulin-dependent and non-insulin-dependent forms of diabetes mellitus (Zhu, 2022).

Despite the fact that large intake of Low-dose of STZ has been shown to cause a mild reduction of insulin production, that is similar to the feature of the later stage of type 2 diabetes. While STZ significantly impairs insulin secretion, type 1 diabetes is developed. Researchers have begun to create a rat model that closely reflects the metabolic features of type 2 diabetes in humans by feeding the rat a high-fat diet followed by low doses of STZ. Events in the disease's natural course, such as insulin resistance and cell malfunction, will be closely modeled in the rat model. A successful implementation of such a strategy would make the investigation and testing of numerous drugs in order to treat type 2 diabetes more

affordable, accessible, and useful. Although the combination. In nongenetic, outbred rats, the HFD feeding and low dose STZ treatments caused the establishment of the type 2 diabetes pattern; however, the STZ injection dose and its methods were inconsistent in those investigations (Naimi *et al.,* 2017, Chen *et al.,* 2022).

Insulin resistance has been always described as the main pathology in T2DM. The diabetic rats showed significant increase by the insulin resistance measurement tool HOMA-IR (homeostatic model assessment of insulin resistance). The HOMA-IR test's ability to measure research into insulin resistance is extensive (Antunes *et al.,* 2016).

Successful induction of T2DM in the studied groups was proved by maintaining high serum glucose, insulin and increased insulin resistance for 1 week after STZ injection. The significant improvement in serum glucose and insulin levels as well as insulin resistance assessed by HOMA-IR after administration of vitamin D is not a new finding. It may be through direct action of Vitamin D by up-regulating the expression of insulin receptors enhancing insulin responsiveness for glucose transport or indirectly through ensuring normal calcium influx through cell membranes (Rafiq and Jeppesen, 2021).

According to our research, vitamin D supplementation helps male rats with T2DM and HOMA-IR maintain better glycemic control and lessen insulin resistance. It also enhanced the immune response in diabetic rats fed a high-fat diet.

Rats with metabolic syndrome caused by a high-fat diet also showed comparable results (Mostafa *et al.,* 2016). In agreement with our study, in experimental models of diabetes mellitus, a prior study demonstrated that cholecalciferol can successfully lower blood glucose levels (Hu *et al.,* 2019).

Chronic oral vitamin D administration (for 70–80 days) significantly reduced insulin resistance in diabetic obese mice (Guareschi *et al.,* 2019), these results are in line with our study.

According to several researches, the insulin gene promoter region of islets may contain a VDRE, or vitamin D response element which could be the source of the vitamin D's ability to boost insulin secretion (Szymczak-Pajor *et al.,* 2020). Derakhshanian et al. (2017)

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demonstrated that vitamin D raises insulin levels in the studied rats. In their investigation, STZ was utilized to induce diabetes at a high dose (45 mg/kg). Their findings were explained by the effects of STZ when administered alone being reversible or by vitamin D's anti-inflammatory properties.

In addition, a previous study that done by Guareschi ZM *et al*. (2019) diabetic rats were given oral vitamin D supplementation (1000 IU and 2000 IU) for successive 45 days showed better glycemic control and insulin resistance.

Impaired insulin production has been linked to vitamin D deficiency and secretion, according to an earlier study, pancreatic beta cells possess the vitamin D receptor. Furthermore, it has been proposed that vitamin D may improve glycemic management (Enciso *et al.*, 2015). Deficit of vitamin D also raises parathyroid hormone levels, which raises the risk of hypertension and hyperglycemia as well as additional insulin resistance (Lee *et al.*, 2018).

In the current study, NF-KB compared to the diabetic control group and vitamin D levels were noticeably lower in the control group in the current study. When compared to the vitamin D-treated group, it was also remarkably greater in the diabetic control group. TNF was significantly lower in the control group than in the group of those with diabetes, while there was no significant difference after administration of vitamin D. This can be explained as the macrophages are cells with a large capacity for cytokine production, especially TNF-α. TNF-α gene activation is largely dependent on NF-KB (Baker *et al.*, 2011). 1,25-dihydroxy vitamin D was found to up-regulates nuclear factor of Kappa polypeptide in B-cell inhibitor (IKB) which inhibit NF-KB by decreasing IKB phosphorylation. (Merav *et al.*, 2006).

In agreement with our study, Haddad Kashani *et al.* (2018) found similar benefits of vitamin D which were seen in persons with diabetics receiving hemodialysis on inflammatory markers. Dadrass *et al.* (2019) investigated the effect of resistance training on the diabetic population's response to vitamin D's anti-inflammatory properties. They could provide evidence of how vitamin D therapy alone affected IL-6 but not TNF.

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In another study regarding effect of vitamin D on CRP, Krajewska *et al.* (2022) discovered the favorable effects of vitamin D supplementation on populations that are overweight or obese. Supplementing with vitamin D seems to have an anti-inflammatory impact mostly through lowering CRP levels and safeguarding stable values of IL-10. Binding of Vitamin D to its receptors in monocytes lead to reducing pro-inflammatory cytokines This can be why Vitamin D decrease CRP level and systemic inflammation (Foroughi *et al.,* 2014).

The rat study by Gomma *and* El-Aziz (2017) indicated that compared to HFD-rats that did not receive vitamin D supplementation, vitamin D treatment significantly reduced body weight gain, decreased blood CRP levels, and significantly increased serum IL-10 levels, these results agree with our study.

In addition, Mousa *et al.* (2018) based on 20 trials with 1,270 people, who offered a thorough study and meta-review stated that patients who received vitamin D treatment had decreased erythrocyte sedimentation rate (ESR), CRP, and TNF- levels than the control individuals.

Results of Adelani *et al.* (2020) were in line with our study that claim vitamin D has the ability to reduce inflammation by lowering inflammatory cytokine concentrations, including IL-1 and TNF-α.

Yu *et al.* (2018) discovered no statistically significant correlation between vitamin D supplementation and any of the outcomes of our investigation and their impact on TNF- and IL-6 levels. This difference may be due to different sample size. There are two known systemic inflammatory biomarkers: TNF- and IL-6. Clinical studies have revealed that taking vitamin D supplements lowers levels of circulating biomarkers in type 2 diabetics (TNF, IL-6). It has been shown that TNF- production is decreased by vitamin D3 and to decrease NF-B activity by upregulating IKB expression. However, it appeared that the data from the human studies were conflicting (Tabesh *et al.,* 2014, Ghavamzadeh *et al.,* 2014).

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In the current investigation, there was no noticeable difference after vitamin D treatment; however, IgA levels in the control group were considerably lower than in the diabetic control group. Additionally, it was significantly higher in the diabetic group compared to the vitamin D-treated group.

Vitamin D's anti-inflammatory qualities aid in protecting the kidneys (Kim and Kim, 2014). When glucocorticoids or immune suppressants failed to work, the addition of active vitamin D, as achieved with the use of the drug valsartan, is notably beneficial in IgAN patients who have moderate proteinuria. (Xiaowei *et al.*, 2020). Additionally, Li *et al.* (2021) demonstrated that effect s of vitamin D and hydroxychloroquine treatment on Toll-like receptor 4 (TLR4) expression in the kidney of IgAN rats showed protective benefits. A longer-term, quantitative evaluation of kidney glomerular damage in response to these treatments will therefore be required. These findings may have significant clinical implications since they imply that patients with IgAN may benefit from a combined hydroxychloroquine (HCQ) and Vitamin D treatment.

However, in Ahmed *et al.* (2019) study, this difference was not statistically significant. Compared to diabetic patients with negative tTG (IgA) antibodies, those with positive tTG (IgA) antibodies had lower vitamin D levels.

CONCLUSION

HOMA-IR, NF-KB, TNF-α, IL-1B, CRP and IgA was substantially lower in the vitamin D-treated group than in the diabetic group. After therapy, the group receiving vitamin D had significantly reduced blood sugar levels. Therefore, wise vitamin D treatment has advantageous aspects for the management of type 2 diabetes.

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Print ISSN 1110-0826
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تأثير فيتامين (د) التحسيني على بعض الجوانب المناعية لمرض السكري من النوع الثاني في نموذج الفئران

أحمد محمد شاكر إبراهيم [2،1]– مصطفى حسن رجب [1]– أمانى صلاح الدين الوقاد[2]
هويدا سيد أبو سيف [2]– مروة طارق[3]

1) كلية الدراسات العليا والبحوث البيئية، جامعة عين شمس 2) المركز القومى للبحوث 3) كلية الطب، جامعة عين شمس

المستخلص

يعد مرض السكري من النوع الثاني ومضاعفاته وباءً عالميًا وسببًا مهمًا للمرض والوفاة. وبما أن العلاقة الدقيقة بين مستوى فيتامين (د) والحالة المناعية لدى مرضى السكري لا تزال غير معروفة، فقد يساعد هذا البحث في إنشاء علاجات محتملة جديدة لمنع مضاعفات مرض السكري ولمعرفة تأثير فيتامين (د) كمكمل غذائي على الجوانب المناعية لمرض السكري من النوع الثاني ؛ أجريت الدراسة التجريبية العشوائية الحالية في قسم الفسيولوجيا الطبية، القسم الطبي بالمركز القومي للبحوث على ثلاثين من ذكور الجرذان البيضاء؛ تم تقسيمهم لثلاث مجموعات: مجموعة ضابطة سلبية، ومجموعة ضابطة إيجابية تم فيها التحريض لحدوث مرض السكري من النوع الثانى، ومجموعة العلاج تم فيها التحريض لحدوث مرض السكري من النوع الثانى مع الحقن العضلي لـ 20000 وحدة دولية / كغ من فيتامين (د). فى كل المجموعات تم قياس الأنسولين ومستوى الجلوكوز فى الدم فى حالة الصيام وتقييم نموذج التوازن لمقاومة الأنسولين وتم قياس علامات الالتهاب: عامل نخر الورم، العامل النووى، البروتين التفاعلى والجلوبيولين المناعى وكانت النتائج إيجابية حيث كان مستوى الجلوكوز وعلامات الالتهاب أقل بشكل كبير فى المجموعة المعالجة عن المجموعة الضابطة الإيجابية، ولذلك قد يؤدي تناول فيتامين د إلى تعزيز إدارة نسبة الجلوكوز في الدم لدى المصابين بمرض السكري من النوع الثانى وتقليل المضاعفات.

الكلمات المفتاحية: مرض السكرى، فيتامين (د)، الأنسولين، البروتين التفاعلى، معامل نخر الورم، العامل النووى، الجلوبيولين المناعى.

Vol. (53); No. (4); April 2024
Print ISSN 1110-0826
Online ISSN 2636 - 3178