Circulating CXCL16 in type 2 diabetes mellitus Egyptian patients

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is an international health concern. The C-X-C chemokine ligand 16 (CXCL16) functions as a scavenging cell surface receptor. Vitamin D3 has vital effects on inflammation and insulin homeostasis.

Purpose: To investigate the significance of serum CXCL 16 and vitamin D3 in T2DM patients to understand disease pathophysiology.

Materials and Methods: The current work was performed as a cross-sectional study. The study included 60 participants, 30 patients with T2DM attending the national institute of diabetes clinics and 30 age and sex-matched healthy controls. Participants underwent the following: Serum CXCL16 by enzyme-linked immunosorbent assay (ELISA), vitamin D3 by radio-immuno assay(RIA), glycosylated hemoglobin (HbA1c), fasting blood sugar(FBS), thyroid stimulating hormone (TSH), liver and kidney functions.

Results and discussion: Serum CXCL16 levels were significantly higher and serum vitamin D3 levels were significantly lower in T2DM patients compared to controls (p < 0.00001). Serum CXCL16 levels correlated negatively with vitamin D3 levels (r = −0.377 and p = 0.00001) while a negative correlation was recognized between vitamin D3 levels and HbA1c % in patients (r = −0.609 and p = 0.0035).

Conclusion: Serum CXCL16, vitamin D3 and HbA1c may be important parameters in monitoring T2DM and predicting complications.

1. Introduction

Type 2 Diabetes mellitus (T2DM) is a quickly growing clinical problem in Egypt with a great impact on morbidity and mortality. Currently, the prevalence of type 2 diabetes Mellitus (T2DM) in Egypt is approximately 15.6% of adults aged between 20 to 80. The International Diabetes Federation (IDF) has categorized Egypt as the eighth ranking state worldwide as regards the prevalence of T2DM (Hegazi et al., 2015).

Physiological regulation of glucose metabolism is determined by a feedback loop mechanism involving the pancreatic islets of Langerhans β-cells and insulin sensitive tissues. Blood glucose levels increase when β-cells are unable to secrete adequate insulin in the presence of insulin resistance. Although β-cellular dysfunction has a strong genetic etiology, environmental factors may be involved. Recent studies have emphasized the importance of hexoses, amino acids, fatty acids in the shaping of insulin resistance and β-cells disorders (Kahn et al., 2014).

Current findings have suggested that inflammation plays a role in the pathogenesis of T2DM. Many reviews have established that low grade inflammation and activation of intrinsic immunity are two of the principle mechanisms of the pathogenesis of T2DM (Herder et al., 2005).

Vitamin D plays many significant physiological roles since most tissues such as brain, breast, prostate, colon, pancreatic tissue, white blood cells carry vitamin D receptors (Wang et al., 2012). Vitamin D appears to have dynamic effects on insulin production, secretion and action (Alvarez & Ashraf, 2010) as well as inflammation (Del Pinto et al., 2017) all of which may have an effect on the pathophysiology of T2DM. A protein called C-X-C chemokine ligand 16 (CXCL16) has been isolated, which combines scavenger receptor functions with the properties of an inflammatory chemokine. This transmembrane protein consists of an extracellular chemokine domain attached to a transmembrane mucin stalk (Adamski et al., 2017). This chemokine domain acts as a recruiter for cells expressing the CXCR6 receptor and a scavenger facilitating the uptake of oxidized low-density lipoprotein (ox-LDL). Pro-inflammatory stimuli enhance CXCL16 expression increasing the uptake of ox-LDL and hastening foam cell formation in the vascular endothelium (Xia et al., 2013). Recent evidence has also shown that CXCL16 promotes cancer (Mir et al., 2019), fatty liver (Ma et al., 2018), kidney damage (Elewa et al., 2016) and coronary artery disease (Xing et al., 2018).

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The role of CXCL16 in type 2 diabetes mellitus per se has not been widely investigated. The objective of the present study was to examine whether serum CXCL16, HbA1c and active vitamin D could be of value in assessing glycemic control, monitoring T2DM patients as well as better understanding the pathophysiology of this disease.

2. Subjects and methods

The current work was carried out as a cross-sectional study conducted at the National Institute of Diabetes and Endocrinology (NIDE) in the period from October to December 2018. The study was performed on 30 patients visiting the diabetes and internal medicine outpatient clinic (12 males/16 Females) with diagnosed type 2 diabetes mellitus (T2DM) receiving either oral medications or injectable insulin. The mean duration of diabetes for T2DM in cases was 12.3 ± 4.3 years, and their mean age was 47.6 ± 13.4. Exclusion criteria included patients with thyroid disease, current or previous intake of vitamin D or multivitamins, pregnant women, patients with chronic kidney disease, heart disease, fatty liver patients or patients with malabsorptive intestinal diseases, hepatitis B, hepatitis C or HIV. The control group comprised 30 age and sex matched healthy subjects (14 males/16 females) whose mean age was 45.4 ± 15.6. They attended their routine appointments at the preventive health care service clinic on the same day that patients attended their follow-up appointments. They were healthy volunteers with normal fasting blood glucose, vitamin D3, liver and kidney functions. All participants were subjected to full history taking and a detailed clinical examination.

Fasting blood samples were collected from all participants using suitable vacutainers. Sera and plasma were separated as the preferred schedule and kept at −20° C till the time of assay. Fasting blood sugar, urea, creatinine, total cholesterol, triglycerides, ALT, AST, were measured using routine methods on Hitachi 971 instrument (Roche Diagnostics GmbH, D, 68,298 Mannheim). Glycosylated hemoglobin (HbA1c) was done by quantitative chromatographic spectrophotometric determination using a kit provided by Biosystem reagents and instruments, Barcelona (Spain) (Roberts et al., 2005). Thyroid stimulating hormone (TSH) was done by coat-A count TSH-IRMA provided by diagnostics products co-operation ISO13485:2003, catalog number IKT5 (Chen & Heminger, 1984) (Roche Diagnostics GmbH, D, 68,298 Mannheim). Serum vitamin D3 levels (1, 25 Dihydro-Cholecalciferol) was measured using a standard Radioimmunoassay Technique (RIA) by using 25(OH) D125 I RIA kit (DiaSource S.A., Belgium) (Zerwekh, 2008). Serum CXCL16 Levels were measured using a suitable ELISA kit specific for recombinant and natural Human C-X-C motif chemokine 16 N0: e0771 h, provided by Wuhan Elaab Science Co., Ltd, China according to the manufacturer’s instructions on Infinite F50 TECAN ELISA instrument.

All collected data in this work was expressed as mean ± standard deviation. Correlations between Serum CXCL16, Vitamin D3, HbA1c as well as other variables were evaluated by Pearson’s Correlation test. Comparisons between the means of the two groups were evaluated using Student’s two tailed t-test. A p-value less than 0.05 was considered to be significant. All statistical analysis was carried out using Macintosh statistical software.

3. Results

Serum CXCL16 levels and HbA1c % were shown to be significantly higher in T2DM cases joining in the study compared to the controls (p < 0.00001). On the other hand, serum vitamin D3 levels were found to be significantly lower in the cases in comparison with the controls (p < 0.00001). Total cholesterol levels were significantly higher in the cases compared to the controls (p < 0.000068). However, no statistically significant differences were observed in the cases compared to the controls as regards the remaining parameters’ levels which were measured such as serum triglycerides, TSH, ALT and AST as well as urea and creatinine (Table 1). Serum CXCL16 levels correlated negatively with vitamin D3 levels in patients and the correlation was considered to be statistically significant

(r = −0.837, p = 0.00001). Furthermore, a highly significant negative correlation was recognized between vitamin D3 levels and HbA1c in patients

(r = −0.609, p = 0.00035). These correlations are demonstrated in Figures 1 and 2. The above-mentioned significant correlations were not observed in the control group participants as evident from Figures 3 and 4.

4. Discussion

Type 2 Diabetes Mellitus is considered to be one of the most important growing public health concerns in Egypt. Its high incidence continues to rise as a result of a host of factors such as abdominal obesity, sedentary lifestyle, unhealthy eating habits and the increased prevalence of hepatitis C (Hegazi et al., 2015). Type 2 diabetes mellitus (T2DM) is an international health issue affecting people of diverse ages and socioeconomic backgrounds leading to various complications. The longer duration of the disease, poor glycemic and lipid control as well as an early age of onset comprise a group of risk factors causing the patient to develop several microvascular and macrovascular complications such as kidney, eye and heart disease (Grant & Kirkman, 2015).
Table 1. Laboratory investigations of the studied groups.

| Parameters                  | Mean ± SD Controls n = 30 | Mean ± SD Cases n = 30 | T value (two tailed t-test) | P-value | Significance (p < 0.05) |
|-----------------------------|----------------------------|------------------------|-----------------------------|---------|-------------------------|
| CXCL16 (pg/ml)              | 48.10 ± 6.19               | 107 ± 53.90            | 5.94                        | <0.00001| Significant              |
| Fasting Glucose (mg/dl)     | 75 ± 3.60                  | 134.7 ± 46.50          | 7                           | <0.0001 | Significant              |
| Post -Prandial Glucose (mg/dl) | 92 ± 7.50                | 158 ± 52               | 6.88                        | <0.0001 | Significant              |
| HbA1 c (%)                  | 4.75 ± 0.40                | 6.61 ± 2.10            | 4.72                        | 0.000015| Significant              |
| Vitamin D3 (ng/ml)          | 42.56 ± 7.71               | 17.87 ± 6.10           | -13.78                      | <0.00001| Significant              |
| Cholesterol (mg/dl)         | 163.53 ± 2.30              | 202.50 ± 42.70         | 4.29                        | 0.000068| Significant              |
| Triglycerides (mg/dl)       | 127.83 ± 14.4              | 148.36 ± 59.70         | 1.82                        | 0.072457| Not Significant          |
| TSH (mU/L)                  | 1.80 ± 0.60                | 1.7 ± 0.60             | 0.60                        | 0.550606| Not Significant          |
| ALT (IU/L)                  | 21.10 ± 2.80               | 22.83 ± 5.20           | 1.59                        | 0.116393| Not Significant          |
| AST (IU/L)                  | 22.70 ± 4.10               | 23.16 ± 4.80           | 0.17                        | 0.859216| Not Significant          |
| Urea (mg/dl)                | 23.70 ± 5.90               | 26.16 ± 10.30          | 1.12                        | 0.263635| Not Significant          |
| Creatinine (mg/dl)          | 0.79 ± 0.10                | 0.83 ± 0.10            | 1.20                        | 0.23439 | Not Significant          |

Figure 1. Pearson’s Correlation between Serum CXCL16 Levels (pg/ml) and Vitamin D3 Levels (ng/ml) in Patients.

Figure 2. Pearson’s Correlation between HbA1 c (%) and Vitamin D3 Levels (ng/ml) in Patients.

The significance of vitamin D in human physiology was seriously investigated after the discovery of vitamin D receptors in pancreatic and immune cells. It has been affirmed that subjects with vitamin D deficiency are prone to developing T2DM (Chiu et al., 2004). Vitamin D has numerous effects on glucose metabolism pathways and several authors have emphasized that vitamin D deficiency contributes to the
pathogenesis of T2DM and its related complications. In the current study, the mean level of vitamin D3 in T2DM patients (17.87 ± 6.10 ng/ml) was significantly lower compared to that of healthy participants (42.56 ± 7.71 ng/ml). The level of vitamin D3 in T2DM patients correlated negatively with HbA1c in participating patients and the correlation was found to be significant (r = −0.609, P = 0.00035). The results validate previous research findings ascertaining that vitamin D and its metabolites appear to have major effects on the aptitude of beta cells to convert proinsulin to insulin and subsequently insulin secretion by the pancreatic islets (Mackawy & Badawi, 2014). Vitamin D stimulates insulin receptors in a direct manner thus increasing insulin response to glucose by binding of its active circulating form to its receptor in beta cells. Indirectly, vitamin D acts through reducing insulin resistance by regulating intracellular and extracellular calcium ion content. Calcium has been accepted as an indispensable component for the sound activity of cellular glucose transporters (Nikooeyeh et al., 2011). Reduced serum vitamin D levels could be considered as a risk factor for T2DM patients to progress to diabetes complications including retinopathy (Payne et al., 2012), microvascular complications (Bajaj et al., 2014), metabolic syndrome (Chiu et al., 2004), cardiovascular diseases (Kheiri et al., 2018), inflammatory bowel diseases (Nielsen et al., 2019) and multiple sclerosis (Berezowska et al., 2019).

The results observed in the present study validate previous research findings ascertaining that vitamin D and its metabolites appear to have major effects on the aptitude of beta cells to convert proinsulin to insulin and subsequently insulin secretion by the pancreatic islets (Zoppini et al., 2013) and active vitamin D could be regarded as being a metabolic biomarker that could reflect the inflammatory and immunologic conditions of the body. It is also worth noting that (Yousefi Rad et al., 2014) revealed that vitamin D supplementation had beneficial effects in decreasing HbA1c in type 2 diabetes mellitus patients. Therefore, vitamin D is considered to be an important nutrient benefiting glucose homeostasis (Lin et al., 2019).

CXCL16 is a recognized chemokine that is usually expressed in both dendritic cells and macrophages. It plays a fundamental role in the recruitment of T cells
and NK cells (Chandrasekar et al., 2004). The inflammatory cytokines TNF-alpha and IFN-gamma enhance the expression of CXCL16 (Abel et al., 2004). Although considerable information is known about CXCL16 from animal-based studies, very little is known about CXCL16 in terms of human-based studies particularly in patients with T2DM. Alterations in the levels of serum CXCL16 have not yet been fully examined in T2DM patients without complications such as heart disease and chronic kidney disease. Therefore, the present study was dedicated to probing changes that occur in serum concentrations of CXCL16 and its early diagnostic value in type 2 diabetes mellitus patients. Moreover, the present study was a trial to find a relationship between vitamin D3 and CXCL16 levels in diabetic patients for a better understanding of the pathophysiology of type 2 diabetes mellitus.

Data of the present study revealed that mean serum CXCL16 levels were significantly higher in T2DM patients (107 ± 53.90 pg/ml) compared to those of the healthy controls (48.10 ± 6.19 pg/ml). These results are in concurrence with a similar study (Zhou et al., 2016) that investigated CXCL16 levels in patients suffering from T2DM with or without coronary artery disease and they found that CXCL16 levels were higher than the controls in both diabetic patient groups. Similar results were obtained from a study carried out on cases with gestational diabetes mellitus. Significantly higher serum CXCL16 levels were found in these cases compared to those of the controls (Lekva et al., 2017). On the other hand, another study (Elewa et al., 2016) did not find any significant differences in serum CXCL16 levels between healthy controls and T2DM Caucasian diabetic patients. Also, a study carried out on Chinese diabetic patients didn’t show significant changes in serum CXCL16 levels of diabetic patients when compared to the controls (Zhao et al., 2014). However, the mechanism responsible for the elevation of CXCL16 concentration and its role in the pathophysiology of diabetes is not fully understood.

It can be speculated that the elevation of CXCL16 levels may be related to abnormalities in cholesterol metabolism in T2DM patients which is supported by the fact that the long duration of CXCL16 level elevation associated with high levels of ox-LDL was found in streptozotocin induced diabetes in mice (Gutwein et al., 2009). In the current study mean serum cholesterol levels were significantly higher in diabetic patients (202.50 ± 42.70 mg/dl) compared to the healthy controls (163.53 ± 2.30 mg/dl). Similarly, several recent clinical studies have revealed higher mean levels of total cholesterol in type 2 diabetes mellitus patients compared to control participants (Das & Bank, 2019; Sarfraz et al., 2016). Many factors are likely to be responsible for diabetic dyslipidaemias. Insulin exerts several effects on liver apoprotein production, regulation of lipoprotein lipase, cholesterol ester transfer proteins and also acts peripherally on adipose tissue as well as muscles. Secondary hyperlipidemia rather than diabetes itself may be the main etiology of atherosclerosis in type 2 diabetes mellitus patients (Reaven, 2005).

A variety of studies have highlighted the fact that chronic low-grade inflammation plays a crucial role in the development and progression of T2DM through a variety of immunologic mechanisms (Chen et al., 2018; Rehman & Akash, 2016). Results of the present study established a significant negative correlation between CXCL16 and active vitamin D in patients (r = – 0.837, P = 0.00001). A similar correlation was documented by a study carried out on diabetic kidney disease patients (Aljack et al., 2019). This indicates that vitamin D controls inflammation and is closely related to chronic diseases mainly T2DM. Consequently, deficiency of this essential vitamin acts as a risk factor that increases inflammatory markers and cytokines such as CXCL16.

5. Conclusion

The chemokine CXCL16 plays a fundamental role in inflammation and could partially contribute to the development and progression of T2DM. Serum CXCL16 could be used in monitoring the inflammatory status and glycemic control of patients together with active vitamin D, cholesterol and HbA1c and may help to predict future diabetic complications. Additional studies are necessary to interpret the exact mechanism and determine the extent to which these parameters could be used in glycemic control monitoring in diabetic patients.

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References
Abel, S., Hundhausen, C., Mentlein, R., Schulte, A., Berkhout, T. A., Broadway, N., Hartmann, D., Sedlacek, R., Dietrich, S., Muetze, B., Schuster, B., Kallen, K.-J., Saftig, P., Rose-John, S., & Ludwig, A. (2004). The transmembrane CXC-chemokine ligand 16 is induced by IFN-gamma and TNF-alpha and shed by the activity of the disintegrin-like metalloproteinase ADMAT10. The Journal of Immunology, 172(10), 6362–6372. https://doi.org/10.4049/jimmunol.172.10.6362

Almassi, V., Mentlein, R., Lucius, R., Synowitz, M., Held-Feindt, J., & Hattermann, K. (2017). The Chemokine Receptor CXC6 Evokes Reverse Signaling via the Transmembrane Chemokine CXCL16. International Journal of Molecular Sciences, 18(7), 1468. https://doi.org/10.3390/ijms18071468

Ajlak, H. A., Abdalla, M. K., Idris, O. F., & Ismail, A. M. (2019). Vitamin D deficiency increases risk of nephropathy and cardiovascular diseases in Type 2 diabetes mellitus patients. Journal of Research in Medical Sciences, 24(1), 47. https://doi.org/10.4103/jrms.JRMS_303_18

Alvarez, J. A., & Ashraf, A. (2010). Role of Vitamin D in insulin secretion and insulin sensitivity for glucose homeostasis. Article ID 531583. https://doi.org/10.1155/2010/531583

Bajaj, S., Singh, R. P., Dwivedi, N. C., Singh, K., Gupta, A., & Mathur, M. (2014). Vitamin D levels and microvascular complications in type 2 diabetes. Indian Journal of Endocrinology and Metabolism, 18(4), 537–541. https://doi.org/10.4103/2230-8210.137512

Berezowska, M., Cee, S., & Dawes, H. (2019). Effectiveness of Vitamin D supplementation in the management of multiple sclerosis: A systematic review. International Journal of Molecular Sciences, 20(6), 1301. https://doi.org/10.3390/ijms20061301

Chandrasekar, B., Bysani, S., & Mummidhi, S. (2004). CXCL16 Signals via G_i, phosphatidylinositol 3-Kinase, Akt, IKB kinase, and nuclear Factor-kB and induces cell-cell adhesion and aortic smooth muscle cell proliferation. Journal of Biological Chemistry, 279(5), 3188–3196. https://doi.org/10.1074/jbc.M311660200

Chen, I., & Heminger, L. (1984). Thyroid stimulating hormone. In L. A. Kaplan & A. J. Pesce (Eds.), Clinical Chemistry, 1st ed., (pp. 1160–1164). C.V. Mosby.

Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X., & Zhao, L. (2018). Inflammatory responses and inflammation-associated diseases in organs. Oncotarget, 9(6), 7204–7218. https://doi.org/10.18632/oncotarget.23208

Chiu, K. C., Chu, A., Go, V. L., & Saad, M. F. (2004). Hypovitaminosis D is associated with insulin resistance and beta cell dysfunction. The American Journal of Clinical Nutrition, 79(5), 820–828. https://doi.org/10.1093/ajcn/79.5.820

Das, H., & Bank, S. (2019). Prevalence of dyslipidemia among the diabetic patients in southern Bangladesh: A cross-sectional study. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, 13(1), 252–257. https://doi.org/10.1016/j.dsx.2018.09.006

Del Pinto, R., Ferri, C., & Cominelli, F. (2017). Vitamin D axis in inflammatory bowel diseases: Role, current uses and future perspectives. International Journal of Molecular Sciences, 18(11), 2360. https://doi.org/10.3390/ijms18112360

Elewa, U., Sanchez-Nino, M. D., Mahillo-Fernández, I., Martin-Cleary, C., Belen, S. A., Perez-Gomez, M. V., Fernandez-Fernandez, B., & Ortiz, A. (2016). Circulating CXCL16 in diabetic kidney disease. Kidney and Blood Pressure Research, 41, 663–671. https://doi.org/10.1159/000447935

Grant, R. W., & Kirkman, M. S. (2015). Trends in the evidence level for the American diabetes association (Standards of medical care in diabetes) from 2005 to 2014. Diabetes Care, 38(1), 6–8. https://doi.org/10.2337/dc14-2142

Gutwein, P., Abdel-Bakky, M. S., Dobrertstein, K., Schrame, A., Beckmann, J., Scheafer, L., Amann, K., Doller, A., Kämpfer-Kolb, N., Abdel-Aziz, A. A. H., Sayed, E. S. M. E., & Pfleischsifer, J. (2009). Cxcl16 and oxLDL are induced in the onset of diabetic nephropathy. Journal of Cellular and Molecular Medicine, 13(9B), 3809–3825. https://doi.org/10.1111/j.1582-4934.2009.00761.x

Hegazi, R., El-Gamal, M., & Abdel-Hady, H. O. (2015). Epidemiology of and risk factors for type 2 diabetes in Egypt. Annals of Global Health, 81(6), 814–820. https://doi.org/10.1016/j.agen.2015.12.011

Herder, C., Haastert, B., Müller-Scholze, S., Koenig, W., Thorand, B., Holle, R., Wichmann, H.-E., Scherbaum, W. A., Martin, S., & Kolb, H. (2005). Association of systemic chemokine concentrations with impaired glucose tolerance and type 2 diabetes: Results from the cooperative health research in the region of augsburg survey S4 (KORA S4). Diabetes, 54(supp 2), S11–S17. https://doi.org/10.2337/dia.suppl.2.511

Kahn, S. E., Cooper, M. E., & Del Prato, S. (2014). Pathophysiology and treatment of type 2 diabetes: Perspectives on the past, present, and future. Lancet, 383(9922), 1068–1083. https://doi.org/10.1016/S0140-6736(13)62154-6

Kheiri, B., Abdalla, A., Osman, M., Ahmed, S., Hassan, M., & Bachuwa, G. (2018). Vitamin D deficiency and risk of cardiovascular diseases: A narrative review. Clinical Hypertension, 24, 9. https://doi.org/10.1186/s40885-018-0094-4

Lekva, T., Michelsen, A. E., Aukrust, P., Roland, M. C., Henriksen, T., Bollerslev, J., & Ueland, T. (2017). CXC chemokine ligand 16 is increased in gestational diabetes mellitus and preeclampsia and associated with lipoproteins in gestational diabetes mellitus at 5 years follow-up. Diabetes and Vascular Disease Research, 14(6), 525–533. https://doi.org/10.1016/j.dvdr.2017.11.002

Lin, Y. C., Lee, H. H., Tseng, S. C., Lin, K. D., Tseng, L. P., Lee, J. F., Lee, Y. H., & Chen, B. H. (2019). Quantitation of serum 25(OH)D2 and 25(OH)D3 concentrations by liquid chromatography tandem mass spectrometry in patients with diabetes mellitus. Journal of Food and Drug Analysis, 27(2), 510–517. https://doi.org/10.1016/j.jfda.2018.12.004
Ma, K. L., Wu, Y., Zhang, Y., Wang, G. H., Hu, Z. B., & Ruan, X. Z. (2018). Activation of the CXCL16/CXCR6 pathway promotes lipid deposition in fatty livers of apolipoprotein E knockout mice and HepG2 cells. American Journal of Translational Research, 10(6), 1802–1816. http://www.ajtr.org/ajtr/files/0070658.pdf

Mackawy, A. M., & Badawi, M. E. (2014). Association of vitamin D and vitamin D receptor gene polymorphisms with chronic inflammation, insulin resistance and metabolic syndrome components in type 2 diabetic Egyptian patients. Meta Gene, 2, 540–556. https://doi.org/10.1016/j.mgene.2014.07.002

Mir, H., Kaur, G., Kapur, N., Bae, S., Lillard, J. W., Jr, & Singh, S. (2019). Higher CXCL16 exodomain is associated with aggressive ovarian cancer and promotes the disease by CXCR6 activation and MMP modulation. Scientific Reports, 9(1), Article number: 2527. https://doi.org/10.1038/s41598-019-38766-6

Nielsen, O. H., Hansen, T. I., & Gubatan, J. M. Managing vitamin D deficiency in inflammatory bowel disease. Frontline Gastroenterology(BMJ), 10(4), 394–400.

Nikooyeh, B., Neyestani, T. R., Farvid, M., Alavi-Majd, H., Houshiarrad, A., Kalayi, A., Shariatzadeh, N., Gharavi, A., Heravifar, S., Tayebinejad, N., Salekzamani, S., & Zahedirad, M. (2011). Daily consumption of vitamin D or vitamin D + calcium-fortified yogurt drink improved glycemcic control in patients with type 2 diabetes: Randomized clinical trial. The American Journal of Clinical Nutrition, 93(4), 764–771. https://doi.org/10.3945/ajcn.110.007336

Payne, J. F., Ray, R., Watson, D. G., Delille, C., Rimler, E., Cleveland, J., Lynn, M., Tangirica, V., & Srivastava, S. (2012). Vitamin D insufficiency in diabetic retinopathy. Endocrine Practice, 18, 185–193. https://doi.org/10.4158/EP111147.OR

Reaven, G. M. (2005). Insulin resistance, the insulin resistance syndrome, and cardiovascular disease. Panminerva medica, 47(4), 201–210. https://pubmed.ncbi.nlm.nih.gov/16489319/

Rehman, K., & Akash, M. S. (2016). Mechanisms of inflammatory responses and development of insulin resistance: How are they interlinked? Journal of Biomedical Science, 23, 87. https://doi.org/10.1186/s12929-016-0303-y

Roberts, W. L., Safar-Pour, S., De, B. K., Rohlfing, C. L., Weykamp, C. W., & Little, R. R. (2005). Effects of hemoglobin C and S traits on glycohemoglobin measurements by eleven methods. Clinical Chemistry, 51(4), 776–778. https://doi.org/10.1373/clinchem.2004.047142

Sarfraz, M., Sajid, S., & Ashraf, M. A. (2016, November). Prevalence and pattern of dyslipidemia in hyperglycemic patients and its associated factors among Pakistani population. Saudi Journal of Biological Sciences, 23(6), 761–766. https://doi.org/10.1016/j.sjbs.2016.03.001

Wang, Y., Zhu, J., & DeLuca, H. F. (2012). Where is the vitamin D receptor? Archives of Biochemistry and Biophysics, 523(1), 123–133. https://doi.org/10.1016/j.abb.2012.04.001

Xia, Y., Entman, M. L., & Wang, Y. (2013). Critical role of CXCL16 in hypertensive kidney injury and fibrosis. Hypertension, 62(6), 1129–1137. https://doi.org/10.1161/HYPERTENSIONAHA.113.01837

Xing, J., Liu, Y., & Chen, T. (2018). Correlations of chemokine CXCL16 and TNF-a with coronary atherosclerotic heart disease. Experimental and Therapeutic Medicine, 15(1), 773–776. https://doi.org/10.3892/etm.2017.5450

Yousefi Rad, E., Djalali, M., Koohdani, F., Saboor-Yaraghi, A. A., Esraghian, M. R., Javanbakht, M. H., Saboori, S., Zarei, M., & Hosseinzadeh-Attar, M. J. (2014). The Effects of Vitamin D Supplementation on Glucose Control and Insulin Resistance in Patients with Diabetes Type 2: A Randomized Clinical Trial Study. Iranian Journal of Public Health, 43(12), 1651–1656. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4490086/

Zerwekh, J. E. (2008). Blood biomarkers of vitamin D status. The American Journal of Clinical Nutrition, 87(4), 1087S–1091S. https://doi.org/10.1093/ajcn/87.4.1087S

Zhao, L., Wu, F., Jin, L., Lu, T., Yang, L., Fan, X., Shao, C., Li, X., & Lin, Z. (2014). Serum CXCL16 as a novel marker of renal injury in type 2 diabetes mellitus. PloS One, 9(1), e87786. https://doi.org/10.1371/journal.pone.0087786

Zhou, F., Wang, J., Wang, K., Zhu, X., Pang, R., Li, X., Zhu, G., & Pan, X. (2016). Serum CXCL16 as a novel biomarker of coronary artery disease in type 2 diabetes mellitus: A pilot study. Annals of Clinical and Laboratory Science, 46(2), 184–189. http://www.annclinlabsci.com/content/46/2/184.long

Zoppini, G., Galletti, A., Targher, G., Brangani, C., Pichiri, L., Negri, C., Stoico, V., Cacciatori, V., & Bonora, E. (2013). Glycated hemoglobin is inversely related to serum vitamin D levels in type 2 diabetic patients. PloS One, 8(12), e82733. https://doi.org/10.1371/journal.pone.0082733