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Association of Vitamin D and Antioxidant Minerals with Interferon -λ1 (Interleukin-29) level in Type 2 Diabetic Patients

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Abstract

DBETES MELLITUS type 2 [T2DM] is associated with heightened inflammatory activity. The significance of inflammatory markers in the context of T2DM remains a subject of debate. Interferon-λ1 (IFN-λ1), also referred to as interleukin-29 [IL-29], represents a recent addition to the interferon family type III. Primarily secreted by macrophages and developing dendritic cells. IL- 29 has a crucial function in various immune reactions. Minerals and vitamins have important roles in antioxidation and anti-inflammation processes. The main aims of presented research were to assess vitamin D, antioxidant minerals (copper and zinc), and interleukin-29 in T2DM; also, to assess the diagnostic values and correlations of IL-29 with other parameters. A case-control study encompassed 30 type 2 diabetes patients (comprising 17 males and 13 females) who visited Al-Merjan Teaching Hospital in Babel, Iraq. Furthermore, a control group was established, consisting of 30 volunteers who were apparently in good health. Standard procedures and methodologies were employed to ascertain the levels of the parameters. There were significantly increases (P value < 0.05) in concentrations of IL- 29, fasting blood glucose, Hb A1c, triglyceride, total cholesterol, LDL-cholesterol and in T2DM patients. Meanwhile, there were significant decreases in zinc and vitamin D concentrations in patients in comparison with control. The most valuable receiver operator characteristic (ROC) was for FBG (0.987), Hb A1c (0.988) and IL–29 (1.0). Serum IL-29 level showed strong positive correlations with FBG and Hb A1c; on the other hand, it showed negative correlations with zinc and vitamin D (p- value < 0.05). The study found that there were increases in IL-29 levels and decreases in vitamin D, copper and zinc levels among T2DM patients. These changes are potentially the reason to develop diabetes and provide new biomarkers for detecting or assessing diabetes status.

Keywords: Interferon -λ1, interleukin- 29, Vitamin D, Type 2 Diabetes mellitus

Introduction

Globally, the incidence of Type 2 diabetes mellitus [T2DM] is surging at dangerous rate, currently affecting an estimated 463 million individuals, or over 9 % of the population, and listed as one of the top ten causes of mortality [1]. Consequently, there is a significant emphasis among public health experts and medical practitioners on strategies that delay its onset and slow its progression [2]. Inflammation significantly influences the emergence and advancement of T2DM, characterized by elevated inflammatory biomarker levels. IL-29, which enhances β-cell oxidative stress in the pancreatic islets. Reducing inflammation is an important outcome for the treatment of T2DM [3, 4].

Interleukin-29, also designated as interferon lambda 1(IFN-λ1), it is type III interferon family cytokine. IFN-λ1 represents a novel development and most exceptionally active cytokine member protein, that recently discovered [5, 6]. Interleukin-29 can able to up regulate levels of interleukins. IL-29 stimulates the production of other interleukins [IL-6, IL-10, IL-15, IL-23 and IL-27]; this suggests that IL-29 could be crucial in regulating the body's immune reactions. IL-29 role as immune regulatory in T2DM remains unclear [7].

Substantial researches have shown that vitamin D_3 enhance antioxidant capabilities by elevating glutathione levels [8-10]. Vitamin D_3 is vital for normal bone integrity, modulating of immune system, cell growth and differentiation, Neurological function and anti-inflammatory effects [11, 12]. Also, vitamin D_3 is essential in preserving metabolic balance in diabetic type 2 individuals. Incidence of complications in T2DM is related to deficiency of active vitamin D, such as: bone health issues, muscle weakness, increased risk of cardiovascular disease, impaired immune function and mental health disorders. However, additional researches are necessary to comprehensively grasp the effects of vitamin D3 in managing diabetes mellitus type 2 [13-15].

Copper (Cu) and zinc (Zn) are key constituents of the enzyme superoxide dismutase, which essential in mitigating oxidative stress by neutralizing free radicals, thereby being crucial in the pathophysiological development in individuals with diabetes [16]. A lack of vital minerals such as copper (Cu) and zinc (Zn) might lead to failure of antioxidant protection and contribute to an inability to regulate blood sugar levels [17]

Therefore, this study, would investigate IL- 29, vitamin D and minerals (Cu and Zn) in patients with T2DM to evaluate of diagnostic values of serum IL-29 and its correlations with other parameters.

Material and Methods

A case-control study was carried out, encompassing 30 individuals who were recently diagnosed with diabetic type 2. The participants were non-obese and over 45 years old, consisting of 13 males and 17 females.

The study was carried out at Merjan Teaching Hospital in Babel, Iraq. Additionally, a control group consisting of 30 apparently healthy volunteers were randomly selected.

The diagnosis of all patients was confirmed by specialist physicians based on clinical and laboratory investigations. Individuals with type 1 or type 2 diabetes who are receiving treatment, gestational diabetes, individuals with other chronic conditions were excluded from the study. Furthermore, individuals who were obese, smokers, or aged less than 45 years also excluded from the study.

Methods and kits were used to measure the concentrations of the following: lipid profile, HbA1c, AST, and ALT by Cobas C311autoanalyzer, Roche Diagnostics, Germany. Copper was measured by spectrophotometry technique. While, vitamin D was measured by Cobas E411 immunoassay autoanalyzer, Roche Diagnostics, Germany. The research received the green light from the Medical College's Ethics Committee at Kofa University, all subjects giving their informed consent agreements.

Statistical Analysis

The data presented as mean and standard deviations by utilizing SPSS software, version 25, from the USA. A P- value < 0.05 was indicated statistical significance.

Results

Table 1 encapsulates clinical and biochemical profiles of both cases and control subjects. Notably, diabetic patients exhibited elevated mean levels of serum fasting glucose, HbA1c, total cholesterol, triglycerides, zinc, vitamin D, and IL-29 in comparison with healthy group; (p- value < 0.05). However, and no significant differences with other parameters.

The study was evaluated the diagnostic performances of the parameters in patients with T2DM by using receiver operator characteristic curve analysis [ROC].

The results were shown in Table 2, and the ROC used to show the area under the curve, which is an indicator for test performance. In T2DM, the area under the curve were for: FBG (0.987), Hb A1c (0.988), TC (0.783), TG (0.670), LDL (0.697) and IL– 29 (1.0). They were useful as diagnostic tests because the AUCs were > 0.6 and statistically significant (P < 0.05). Whereas, other parameters were not, because the AUC was <0.6 and not statistically insignificant.

Spearman's correlation analysis between IL-29 and other parameters was performed, (Table 3). IL-29 levels revealed positive significant correlations (p-value < 0.05) for FBG, Hb A1c, TC, TG, and LDL; while, they showed negative significant correlations (p-value < 0.05) for zinc and vitamin D.

Discussion

Insulin resistance seems to be the central abnormality in T2DM, where pancreas fails to generate sufficient insulin or cells respond poorly to insulin. The origin of the impaired insulin action in

T2DM is still under investigation. The findings reveal elevated levels of acute-phase response markers in the blood; as well as, increased cytokine mediator's concertation in type 2 diabetes. However, the alteration of the cytokine secretion in T2DM is still under debate, on other hand vitamins and anti-oxidant were decreased [18]. The research posits that type 2 diabetes may be linked to inflammatory processes. Interleukin-29 has been identified, yet its function in the context of type 2 diabetes remains largely unexplored. Therefore, the current study may be the first study that evaluating serum IL-29 concentrations in diabetes type 2. The presented research was revealed that increased levels of IL- 29, and decrease vitamin D, copper and zinc, these changes might be risk to developing type 2 diabetes. Hence, among the inflammatory markers, IL- 29 might have a strong relationship with type 2 diabetes [19].

Interleukin-29 has been implicated in the enhancement of inflammation within adipose tissue, the attraction of macrophages, and the overall increase in systemic insulin resistance. When administered in vivo, IL-29 has been observed to escalate inflammatory responses, exacerbate insulin resistance, and intensify macrophage infiltration in adipose regions. Additionally, IL-29 had important role in the regulation process of glucose absorption by adipocytes. Experiments have demonstrated that treatment with IL-29 suppresses GLUT4 expression and diminishes the uptake of glucose stimulated by insulin [20].

According to ROC analysis, IL-29 was highly sensitive biomarker for type 2 diabetes, suggesting a potential role of IL-29 in diagnosis, assessment severity, pathogenesis and treatment of the disease. On the other hand, the serum IL-29 was negatively correlated with vitamin D_3, zinc, and copper.

Type 2 diabetes arises due to a combination of dysfunction pancreatic β cells and insulin resistance, both genetic and environmental factors seem to be involved in development disease [21]. Vitamin D_3 has effect on these pathways [22], because 1-α-hydroxylase and vitamin D receptor present in pancreatic β cells,; vitamin D is important for both synthesis and release of insulin [21, 23]. Low vitamin D may be cause decrease of insulin secretion [24], or changes in tissue response to insulin causes T2DM [25, 26]. Observational studies had shown, that vitamin D levels was negatively associated with diabetes risk [23].

The obtained results revealed that no real copper deficiency in diabetic type 2 patients. This finding is in agreement with (Durak 2010, Hussain 2009), [27, 28]. Unbound copper form is toxic and could cause redox imbalance. The increase in copper ion levels might be attributed to hyperglycaemia and accelerates the oxidative stress, which involved in the pathogenesis of diabetes or its complications [29].

This study was found low serum zinc concertation in diabetic group. A lot of studies tried to explain the alteration which occurs in mineral metabolism in diabetic patients [29]. Zinc has antioxidant properties, and It forms a crucial part of the vital antioxidant enzyme known as superoxide dismutase, which protect molecules from oxidation. Zinc has a crucial role in facilitating secretion, storage and proper function of insulin. Moreover, it is noteworthy that diabetes, akin to many other chronic conditions, leads to heightened excretion of essential minerals, including zinc. [28]. Thus, decrease levels of Zinc may emerge as a significant predisposing factor in the development of diabetes mellitus [30].

Conclusions

The current research unveiled, for the first time; elevation of IL-29 concentration can be novel diagnostic tool of T2DM, suggesting its potential implication in the pathogenesis and severity of the condition. So recommended to **u**se IL-29 as a predictor of T2DM development and severity status. Future researches may required to evaluate IL-29 as a therapeutic target in diabetes. While, moderate size of sample may impose limitations on the outcomes of the results.

Conflicts of interest

The authors declare that no conflicts related to this work**.**

Ethical considerations

The research received the green light from the Medical College's Ethics Committee at Kofa University, all subjects giving their informed consent agreements.

TABLE 1. Biochemical and clinical characteristics of participants groups

Variables		Patients (no.=30)	Control (no. =30)	P .Value
Age (years)		58.4±7.21	58.27±5.76	0.937
Gender	Males	13 (43.3%)	14 (46.66%)	0.795
	Females	17 (56.66%)	16 (53.33%)	
BMI (kg/m^2)		26.6±3.43	25.15±2.32	0.06
SBP (mm/Hg)		133.3±10.45	132.83±6.52	0.825
DBP (mm/Hg)		80.83±5.1	80.33±4.9	0.70
Fasting blood glucose (mg/dL)		178.56± 67.47	78.21± 13.1	<0.001
HbA1c (%)		8.93± 2.6	4.78± 0.52	<0.001
Total cholesterol (mg/dL)		182.33±39.46	149.97±21.38	<0.001
Triglyceride (mg/dL)		205.63± 76.61	163.9± 43.36	0.012
HDL-C (mg/dL)		42.26± 8.76	40.73± 9.3	0.515
LDL-C (mg/dL)		98.87±42.96	76.43±18.95	0.011
VLDL-C (mg/dL)		41.13± 15.32	32.78± 8.67	0.012
ALT (U/L)		19.53±3.77	18.6±6.04	0.476
AST (U/L)		25.73±8.39	23.8±4.9	0.281
Zinc (µg/dl)		38.31±15.39	77.37±10.5	<0.001
Cu (µg/dl)		63.93±10.6	62.5±6.7	0.534
Vitamin D (ng/ml)		33.08±18.69	72.12±43.13	<0.001
IL-29 (pg/mL)		1123± 124.18	147.67± 6.7	<0.001

TABLE 2. Receiver operating characteristic for diagnosis of Type 2DM

95% Confidence limits	P-Value	ROC area	Variables
Age (years)	0.389-0.687	0.615	0.538
BMI (kg/m^2)	0.469-0.756	0.133	0.613
FBG (mg/dL)	0.962-1.0	<0.001	0.987
HbA1c (%)	0.966-1.0	<0.001	0.988
Total cholesterol (mg/dL)	0.666-0.901	<0.001	0.783
Triglyceride (mg/dL)	0.526-0814	0.024	0.670
HDL-C (mg/dL)	0.436-0.731	0.268	0.583
LDL-C (mg/dL)	0.560-0.833	0.009	0.697
VLDL-C (mg/dL)	0.526-0.814	0.024	0.670
Cu (µg/dl)	0.354-0.653	0.959	0.504
Zinc (µg/dl)	0.0-0.058	<0.001	0.027
Vitamin D (ng/ml)	0.094-0.318	<0.001	0.206
IL-29 (pg/mL)	1.0-1.0	<0.001	1.00

TABLE 3. Serum IL-29 correlations with biochemical parameters

P-Value	r- Value	Variable
Age (years)	0.141	0.281
BMI (kg/m^2)	0.184	0.160
SBP (mm/Hg)	0.057	0.568
DBP (mm/Hg)	-0.216	0.097
FBG (mg∕dL)	0.723	000
HbA1c (%)	0.755	000
Total cholesterol(mg/dL)	0.433	000
Triglyceride (mg/dL)	0.326	0.011
HDL-C (mg/dL)	0.079	0.547
LDL-C (mg/dL)	0.306	0.017
VLDL-C (mg/dL)	0.326	0.011
ALT (U/l)	-0.151	0.250
AST(U/l)	0.091	0.488
Zinc (µg/dl)	- 0.649	<0.001
Cu (µg/dl)	-0.021	0.875
Vitamin D (ng/ml)	-0.444	<0.001

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دراسة ارتباط فيتامين د والمعادن المضادة للأكسدة بمستوى الإنترلوكين -29 لدى مرضى السكري من النوع الثاني

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المستخلص

الخلفية العلمية: يرتبط داء السكري من النوع 2 [T2DM] بزيادة النشاط الالتهابي. تظل أهمية العلامات الالتهابية في سياق T2DM موضوعًا للنقاش والجدل. Interferon-α1 (IFN-α1)+، والذي يشار إليه أيضًا باسم Interleukin-29 [IL-29، إضافة حديثة إلى عائلة Interferon من النوع III. بداية افرازه اولا عن طريق الخلايا البلعمية والخلايا الجذعية النامية. يلعب IL-29 وظيفة حاسمة في التفاعلات المناعية المختلفة. المعادن والفيتامينات لها أدوار مهمة كمضادات للأكسدة ومكافحة الالتهابات. كانت الأهداف الرئيسية للبحث المقدم هي تقييم فيتامين د، والمعادن المضادة للأكسدة (النحاس والزنك)، والإنترلوكين 29 في T2DM؛ أيضًا لتقييم القيم التشخيصية وارتباطات IL-29 مع المعلمات الأخرى.

طرق البحث: كانت دراسة حالات وشواهد او سيطرة. شملت 30 مريضا من مرضى السكري من النوع 2 (منهم 17 ذكرا و 13 أنثى) الذين زاروا مستشفى المرجان التعليمي في محافظة بابل، العراق. علاوة على ذلك، تم إنشاء مجموعة سيطرة او مراقبة مكونة من 30 متطوعًا يتمتعون بصحة جيدة بصورة واضحة. تم استخدام الإجراءات والمنهجيات وطرق العمل القياسية للتأكد من مستويات المعلمات البيوحياتية.

النتائج: كانت هناك زيادات معنوية (قيمة P <0.05) في تركيزات IL-29، وجلوكوز الدم الصائم، والسكر التراكمي Hb A1c، والدهون الثلاثية TG، والكوليسترول الكلي، والكوليسترول الضار LDL، وفي مرضى T2DM. وفي نفس الوقت، كان هناك انخفاض معنوي في تركيزات معدن الزنك وفيتامين د لدى المرضى مقارنة مع مجموعة السيطرة. كانت قيمة خصائص مشغل الاستقبال (ROC) هي FBG (0.987) و Hb A1c (0.988) و IL-29 (1.0). أظهر مستوى المصل IL-29 ارتباطات إيجابية قوية مع FBG و Hb A1c؛ من ناحية أخرى، أظهرت ارتباطات سلبية مع الزنك وفيتامين د (قيمة p <0.05).

الخلاصة: اوجدت الدراسة أن هناك زيادات نوعية في مستويات IL-29 وانخفاض في مستويات فيتامين د والنحاس والزنك بين مرضى T2DM. من المحتمل جدا أن هذه التغييرات هي سبب الإصابة بمرض السكري من النوع الثاني. وتوفر معدلات IL-29 مؤشرات حيوية جديدة للكشف عن وجود مرض السكري أو تقييم شدته.

الكلمات الدالة: إنترلوكين-29، فيتامين د، داء السكري من النوع الثاني.