Open Journal of Clinical & Medical Images

www.jclinmedimages.org

Research Article

Open Access, Volume 2

Serum levels of stromal cell derived factor-1/CXC chemokine receptor 4 and its clinical value in patients with type-2 diabetes mellitus accompanied by osteoarthritis

Jinwen Yu[1]; Weiyuan Li[1]; Rui Han[2]*; Weili Shi[2]; Yanlin Li[3]; Qi Wang[4]

[1]Department of Geriatrics, The Affiliated Hospital of Kunming University of Science and Technology & The First People's Hospital of Yunnan Province & Yunnan Province Clinical Research Center for Geriatrics, 650000, China.

[2]Department of Diabetes Mellitus, The First Affiliated Hospital, Kunming Medical University, 650032, China.

[3]Department of Sports Medicine, The First Affiliated Hospital, Kunming Medical University, 650032, China.

[4]Department of Vascular Surgery, The First Affiliated Hospital, Kunming Medical University, 650032, China.

***Corresponding Author: Rui Han**

Department of Diabetes Mellitus, The First Affiliated Hospital, Kunming Medical University, 650032, China.

Email: hanrui_201207@163.com

Received: Jun 17, 2022

Accepted: Jul 25, 2022

Published: Aug 01, 2022

Archived: www.jclinmedimages.org

Keywords: Osteoarthritis; Type 2 diabetes; SDF-1; CXCR4.

Abstract

Objective: To detect the clinical biochemical index and serum concentration changes of Stromal Cell Derived Factor-1 (SDF-1)/CXC chemokine receptor 4 (CXCR4) in patients with type 2 diabetes mellitus (T2DM) associated osteoarthritis (OA) and explore the correlation between these factors and the clinical morbidity of T2DM associated OA and its role in the disease.

Method: Patients treated in diabetes department, sports medicine department and orthopedics department of the first affiliated hospital of Kunming medical university from January 2019 to December 2020 were randomly selected. Two hundred cases with T2DM, 97cases with osteoarthritis, 83 cases with both diseases and 200 healthy controls (HC) from the examination center during the same period were recruited. The general clinical data and biochemical indicators of all patients were collected and ELISA was used to measure the serum concentration of SDF-1 and CXCR4. All data were analyzed with SPPS21.0 statistical package. The normal distribution data expressed as mean ± standard deviation (x ± SD), non-normal distributions as median (P25%, P75%). Variance analysis was used between groups, and LSD - t test for comparison between two groups. Logistic regression analysis and Pearson correlation analysis were used to analysis the correlation. P =0.05 was used as the significance test standard. P<0.05 represents statistically significant differences between groups.

Results: (1) Analysis of variance showed statistically significant differences of SDF - 1 and CXCR4 concentration among the four groups. After comparison among the four groups of SDF - 1, the order from high to low is: T2DM combined with OA group (7.84 ± 1.17 ng/mL), OA group (6.80 ± 1.21 ng/mL), T2DM group (5.24 ± 0.83 ng/mL), HC group (4.93 ± 0.66 ng/mL). Level of CXCR4 among four groups from high to low were T2DM combined with OA group (78.19 ± 3.67ng/mL), OA group (59.03 ± 8.38ng/mL), T2DM group (50.31 ± 8.56 ng/mL), HC group (48.08 ± 3.68 ng/mL) and P values < 0.05 (2) Pearson correlation

analysis showed that the serum concentration of SDF-1 were positively correlated to BMI, glycosylated Hemoglobin A1c(HbA1c), HOMA - IR (P<0.05), and negatively correlated with Ca^{2+} concentration (P < 0.05). (3) Logistic regression analysis results suggested SDF-1 level is a risk factor for diabetes associated with osteoarthritis.

Conclusion: High serum concentration of SDF-1 and CXCR4 were risk factors for T2DM associated osteoarthritis. They were positively correlated with BMI, HbA1c, HOMA – IR and negatively correlated with Ca^{2+} concentration. This axis may be involved in progression of osteoarthritis in diabetic patients and become future targets for the treatment of diabetes associated osteoarthritis.

Introduction

The changes of working environment, living habits and dietary structure have greatly increased the proportion of people eating high sugar and high fat food that causes the incidence of type-2 diabetes mellitus (T2DM) and its complications increased year by year. The previously neglected diabetic osteoarthritis has become the new field of study in recent years among many complications of diabetes. Evidence have demonstrated that OA is a metabolic disease, and diabetes may be an independent risk factor [1-4]. Unfortunately, due to the lack of effective diagnostic means and the preventive measures for the pathogenesis of the disease in early stage, lesions are often found after structural and functional changes, and therefore missing the best treatment timing. At the advanced stage of the disease, joint replacement surgery which is invasive, high risk, with high complications and high cost is the only option to delay its progression. Therefore, it is urgent to explore the pathogenesis of T2DM accompanied by OA for preventing it from risk factors at the early stage of the disease, and to reduce or prevent the structural degeneration of joint tissues by safer, more effective and economical means. In recent years, many studies have observed increasing expression of SDF-1/ CXCR4 axis in patients with T2DM and OA [5]. SDF-1 is a kind of endocrine chemoattractant protein, mainly derived from bone marrow stromal cells; as one of its receptors, CXCR4 is widely expressed on the surface of articular chondrocytes. The specific binding of the two can hasten chemotactic inflammatory cells, mediate immune inflammatory response, mobilize endothelial progenitor cells, increase neovascularization, damage the peripheral nerve function and regulate the expression and secretion of other cytokines, thus affecting the prognosis of diabetes and OA [6]. The inflammatory reaction, pathological angiogenesis and nerve fiber injury caused by the axis may become the bridge of diabetes and OA co-morbidity [7,8]. Treatment targeting at the axis is expected to be a breakthrough in blocking the degeneration of joints. Therefore, in this study, the general clinical data, concentration changes of related biochemical parameters and the concentration of SDF-1/ and CXCR4 in serum of patients with T2DM accompanied by OA was detected to explore the role of SDF-1/CXCR4 axis in the disease and the possibility of being a novel therapeutic target.

Objects and methods

Study objects

Two hundred cases of T2DM (DM group), 97 cases of OA (OA group), and 83 cases of T2DM&OA diagnosed and treated in the department of diabetes, the department of sports medicine and the department of orthopedics, the First Affiliated Hospital of Kunming Medical University, and 200 cases of healthy controls (HC group) from medical examination center in the same hospital were randomly selected according to the diagnostic criteria for diabetes issued by WHO in 1999 [9] and the diagnostic criteria for osteoarthritis issued by the Department of orthopedics of Chinese Medical Association in 2007 [10]. Exclusion criteria: ①Age <20 or >80 years old. ②Non Han population. ③Have blood relationship with those that enrolled in the group. ④History of nephritis, thyroid and parathyroid diseases or other autoimmune diseases. ⑤Taking vitamin D and sulfonylurea drugs recently .⑥People with other infectious diseases recently. ⑦Surgical treatment. ⑧Acute complications of diabetes or other severe complications. ⑨Type 1 diabetes. The study was approved by the local ethics committee, and informed consent was obtained from all the subjects.

Research methods

General clinical data collection: Subjects were selected strictly according to inclusion and exclusion criteria. Age, gander, history of diabetes and past history of each subject were recorded by questionnaire. Height (H) and body weight (W) were measured by height and weight measuring instruments. Body mass index (BMI) were calculated as W (kg) /H^2 (m). Blood pressure was measured using blood pressure cuff after subjects were rested for more than 10 min.

Blood samples collection: 3 mL of fasting blood of subjects were collected from cubital vein for detection of fasting blood glucose(FBG), fasting insulin (FINS), fasting C-peptid (FCP), Serum concentrations of Ca^{2+}, total cholesterol (TC), triglycerides (TG), glycosylated hemoglobin A1c (HbA1c), high density lipoprotein-cholesterol (HDLC) and low density lipoprotein-cholesterol (LDL-C); insulin resistance index (HOMA-IR)=FBG * FINS/22.5 was calculated; at the same time, 3-5 mL of fasting venous blood was collected by non anticoagulant tube. Serum was separated and stored at -80°C for later analysis.

Detection method: Serum concentrations of SDF-1 and CXCR4 were determined with ELISA kit purchased from Shang Hai mlbio Co, Ltd. and following the manufacturer's instructions strictly.

Statistical analysis

Relevant data was processed via SPSS 21.0 software. All measurement data were tested for normality; the normal distribution data were expressed as mean ± standard deviation (x ±

SD), biased measurement data were expressed as median (the first quartile, the third quartile) [M (P25, P75)]. All enumeration data were expressed as frequency and percentage. t-test was used to compare two groups, and homogeneity test of variance was performed among the groups. If homogeneous of variance, the LSD-t test was used for comparison. If heterogeneity of variance, the rank sum test was used. Correlation analysis was performed by Pearson correlation coefficient, logistic regression was used to analyze the related factors, the OR value and the 95% CI were calculated.

Results

1. Analysis of general data and biochemical indexes.

The differences in age and gender in the four groups were not statistically significant. There were statistically significant differences between the four groups in terms of HbA1c, HOMA-IR, BMI and Ca^{2+} concentrations, of which the glycosylated hemoglobin, HOMA-IR and BMI in T2DM & OA group were significantly higher than those in the other three groups, while the concentration of Ca^{2+} was lower than the other three groups. $P<0.05$, as shown in Table 1.

Table 1: Comparison of general information and biochemical parameters in the four groups [x±SD/M(P25, P75)].

Index	HC	T2DM	OA	T2DM and OA
Age (Year)	57.68 ± 8.92	57.76 ± 8.46	58.76 ± 7.56	59.04 ± 7.28
Gender (M/F)	108/92	105/95	47/50	43/40
BMI (Kg/m²)	21.64 ± 2.32	24.49 ± 2.93[a]	24.14 ± 2.02[a]	26.16 ± 2.72[a,b,c]
DBP (mmHg)	76.97 ± 9.53	84.77 ± 10.52[a]	80.46 ± 11.02[a]	87.96 ± 11.69[a,b,c]
SBP (mmHg)	125.27 ± 9.61	132.14 ± 13.46[a]	126.01 ± 10.064[b]	138.43 ± 14.72[a,b,c]
FPG (mmol/L)	5.25 (4.60, 6.08)	6.9 (6.0, 8.0)[a]	6.00 (4.75, 6.85)	8.30 (7.80, 9.30)[a,c]
HbA1c (%)	6.80 (5.80, 7.60)	8.20 (7.20, 9.08)[a]	6.30 (5.80, 6.95)[b]	8.30 (6.50, 9.40)[a,b,c]
TC (mmol/L)	3.99 ± 1.39	5.48 ± 1.71[a]	4.21 ± 1.18[b]	5.71 ± 1.62[a,c]
TG (mmol/L)	1.40 (1.00, 1.67)	1.55 (1.30, 1.92)[a]	1.50 (1.15,2.01)	1.78 (1.23, 2.09)[a]
LDL-C (mmol/L)	2.40 ± 0.91	2.78 ± 0.75[a]	2.50 ± 0.77[b]	2.78 ± 0.57[a,c]
HDL-C (mmol/L)	1.41 (1.17, 1.59)	0.99 (0.88, 1.15)[a]	1.05 (0.93, 1.20)[a]	1.07 (1.23, 0.94)[a,b]
Ca2+ (mmol/L)	2.30 (2.10,2.50)	2.00 (1.90, 2.20)[a]	2.00 (1.90, 2.10)[a]	1.90 (1.80, 2.10)[a,b,c]
C-peptide	1.64 ± 0.33	1.16 ± 0.45[a]	1.58 ± 0.26[b]	1.11 ± 0.31[a,c]
HOMA-IR	0.60 (0.50, 0.80)	1.00 (0.80, 1.40)[a]	0.90 (0.70, 1.30)	1.30 (0.90,1.70)[a,bc]

Note:[a] $P < 0.05$compare to HC group,[b] : $P< 0.05$ to T2DM group, [c]: $P < 0.05$compare to OA group

2. Serum SDF-1/CXCR4 concentrations are higher in patients with T2DM and/or OA

The concentration of the four groups from high to low were as follows: T2DM & OA group, OA group, T2DM group, HC group; the difference was statistically significant, as shown in Table 2 and Figure 1.

Table 2: Serum concentration of SDF-1/CXCR4 among four groups [x±s].

Index	HC	T2DM	OA	T2DM and OA
SDF-1 (ng/mL)	4.93 ± 0.66	5.24 ± 0.83[a]	6.80 ± 1.21[a,b]	7.84 ± 1.17[a,b,c]
CXCR4 (ng/Ml)	48.08 ± 3.68	50.31 ± 8.56[a]	59.03 ± 8.38[a,b]	78.19 ± 3.67[a,b,c]

Note:[a] $P < 0.05$compare to HC group,[b] : $P< 0.05$ to T2DM group, [c]: $P < 0.05$compare to OA group.

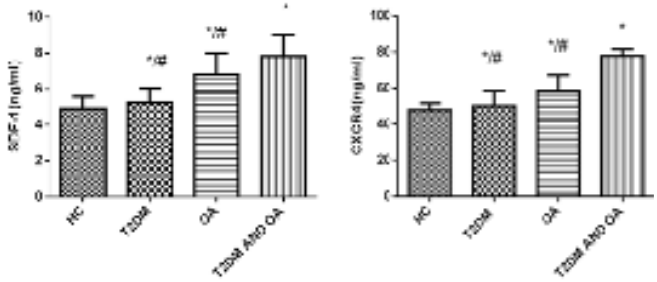

Figure 1: Comparison of serum *SDF-1and CXCR4* concentration among four groups *(ng /mL).*

Note:[a] $P < 0.05$compare to HC group,[b] : $P< 0.05$ to T2DM group, [c]: $P < 0.05$compare to OA group.

3. Relationship between serum SDF-1 concentration and clinical as well as biochemical parameters.

To explore the correlation between clinical characteristics and biochemical parameters and the expression of SDF-1/CXCR4 axis, the correlation analysis between SDF-1 concentration and HbA1c, age, TG, LDL-c, HDL-c, calcium ion, BMI, sex, TG, Ca^{2+} was analyzed by Pearson correlation analysis. Results showed that the concentration of SDF-1 was positively correlated with the concentration of BMI, HbA1c, HOMA-IR and CXCR4, and negatively correlated with the concentration of Ca^{2+}, the difference was statistically significant, as shown in table 3.

4. Related factors analysis of T2DM & OA

To explore the risk factors of T2DM & OA, binary Logistic regression analysis was performed With T2DM as the control group, with or without OA as the dependent variable, and Glycosylated hemoglobin, TG, LDL, fasting C peptide, sex, age, HDL, BMI, DBP, SBP, HOMA-IR as covariates. Glycosylated hemoglobin, BMI, HOMA-IR, SDF-1 and Ca^{2+} concentration entered into regression equation, the remaining variables did not enter the final equation. Logistic regression analysis indicated that BMI, HbA1c, HOMA-IR, SDF-1 might be the risk factors of OA, Ca^{2+} was a protective factor, and the $P<0.05$. The coefficient of the constant term was -28.982. Regression equation was: ln (P/1-P) =-28.982+0.447× (BMI) + 0.487× (HbA1c) + 2.581×(HOMA-IR) + 3.124× (SDF-1) -5.147 × (Ca^{2+})

Table 3: Pearson correlation analyses of between SDF-1 and each variables.

	age	BMI	gender	HbA1c	FINS	LDL	HDL	TG	Ca^{2+}	HOMA-IR	CXCR4
R	0.067	0.297	0.064	0.105	-0.060	0.064	-0.077	0.074	-0.424	0.267	0.627
P	0.109	0.000	0.126	0.011	0.147	0.121	0.062	0.073	0.000	0.000	0.000

Table 4: Two logistic regression analysis of risk factors of T2DM and OA.

	B	S.E.	Wald	sig	Exp(B)	95%C.I.	
						Upper limitation	lower limitation
HOMA-IR	2.581	0.765	11.399	0.001	13.214	2.953	59.131
HbA1c	0.487	0.227	4.592	0.032	1.627	1.042	2.540
Ca2+	-5.147	2.089	6.072	0.014	0.006	0.001	0.349
BMI	0.447	0.142	9.890	0.002	1.563	1.183	2.065
SDF-1	3.124	0.493	40.185	0.000	22.731	8.653	59.712

Discussion

In recent years, more and more diabetic osteoarthritis are presented to clinicians among lots of diabetic complications. A meta-analysis containing ten studies and fourteen ratios worldwide showed that Type 2 diabetes was significantly associated with the development or presence of OA (OR; 1·21, 95% CI: 1·02-1·41). In the subset of 7 studies that did control for weight or BMI there was an increased odds of OA associated with type 2 diabetes was (OR: 1·25, 95% CI: 1·05-1·46) from a smaller pool of patients (n=7156) [11]. The disease usually begins unnoticed with no or very mild early symptoms. With progression of the disease, pain aggravates and affected joints gradually lose their function. This disease seriously affects patients' daily activities and even leads to disability. It also results in a huge medical expense. However, the pathogenesis of this disease has not yet been defined, and targeted therapy is also left blank, therefore, to identify the risk factors and intervene in the early stage is the key to prevent the progression of the disease. Studies found that many cytokine pathways have been involved in the progression of T2DM & OA, of which the SDF-1/CXCR4 axis plays an important role in the pathogenesis of both as a result has become the focus of research. SDF-1 is a chemokine secreted by bone marrow stromal cell (MSC) [12]. CXCR4, as a receptor of SDF-1, is a G protein coupled receptor (GPCR) whose molecular structure is similar to that of CXC chemokine. After binding to each other, the second messenger is initiated, and the downstream protein kinase C, signal adaptor protein, nuclear factor -KB, extracellular regulated protein kinase and many other cell pathways will be activated [13], which plays an important physiological role in immune inflammation, pathological angiogenesis, chemotaxis etc. [14]. Therefore, the axis may become a target for early recognition and treatment.

The results in this research indicated that the concentration of SDF-1 was positively correlated with BMI, HbA1c and HOMA-IR, but negatively correlated with the concentration of Ca^{2+} (P<0.05), and had no correlation with gender, age, FPG, fasting C peptide, TC, TG, SBP, DBP, LDL-C, HDL-C. The results suggested that low levels of Ca^{2+}, blood glucose and weight control may increase the secretion of SDF-1. Diabetes is a low-grade systemic inflammatory state. Inhibition of insulin receptor signaling pathway is the main mechanism of insulin resistance induced by inflammation [15,16]. Compared to group HC, the serum levels of SDF-1 and CXCR4 in group T2DM and group T2DM & OA were higher (P<0.05), and HOMA-IR also increased. Logistic analysis indicated that SDF-1 concentration and HOMA-IR were risk factors of T2DM & OA, suggesting that the SDF-1/CXCR4 axis may also be involved in the development of insulin resistance in diabetic patients. A number of studies have put forward hypotheses on the mechanism that the axis leads to insulin resistance. As an efficient inflammatory chemokine, SDF-1 can up-regulate the release of TNF-α, activate NF-κB inhibitory factor kinase phosphorylation and then activate Nuclear factor κB(NF-κB). NF-κB is dissociated and degraded.After entering the nucleus and binding to the corresponding DNA, it activated inflammatory genes, which promote the increased expression of inflammatory factors such as TNF-α. As a result, the mitochondrial damage increased, oxidative stress and insulin resistance aggravated, which promote the occurrence of T2DM [17-19].

On the basis of insulin utilization disorder, elevated glucose concentration in the internal environment can alter cartilage matrix, activate chondrocytes and synovial cells, and produce pro-inflammatory cytokines and pro-inflammatory mediators, including SDF-1 [20]. The positive feedback of inflammatory factors further deteriorate the degree of arthritis lesion and form a vicious circle [21]. Many studies have confirmed that the expression of SDF-1 in the joints of OA patients is higher than that in healthy subjects [22,23]. The immune activated inflammatory cells aggregate into the cartilage space, cause joint inflammation, and reduce the quality of subchondral bone in these patients, which is the main cause of OA joint degeneration [24]. Insulin injection can reduce the incidence of OA by reducing oxidative index and inflammatory factors in diabetic patients [25]. Chondrocytes transported glucose by glucose transporter 1(GLUT1). The increase of glucose and reactive oxygen species leads to the decline of GLUT1 function, and the effect is more persistent in diabetic patients than in healthy subjects [26-28]. With long term use of insulin, patient's hemoglobin increased. Meanwhile the accumulation of advanced glycation end products, excessive oxidative stress, systemic inflammatory response and metabolic disorders of nutrients all affect the clinical manifestation, progress and prognosis of OA [29-31]. In this study, we found that the HbA1c in T2DM & OA group was higher than the other three groups, and was positively correlated with the concentration of SDF-1, but there was no significant difference in fasting blood glucose. It is possible that compared to the transient rise in blood glucose levels, long-term insufficient glycemic control is more likely to aggravate OA. Therefore, from the clinical point of view, the management of diabetic patients

is not only the immediate blood glucose control, but also should establish a long-term monitoring mechanism and focus on the long-term blood glucose level and stability.

Increased concentrations of SDF-1 and CXCR4 are more common in overweight and obese people and in people with metabolic syndrome [32]. Previous studies showed that the level of SDF-1 is closely related to insulin resistance caused by adipose tissue [33]. This research found that serum SDF-1 concentration was positively correlated with BMI, and both were risk factors of T2DM &OA. Increasing joint bearing caused by obesity; prolonged wear and tear results in local osteophyte formation in the joint; excessive activation of local proteolytic enzymes in the joint, as well as the release of inflammatory cytokines SDF-1 [34]. In addition, obesity itself is an inflammatory state that increases the incidence of OA. Many people with T2DM are overweight, so weight loss is important for avoiding the occurrence of OA. Statistical data also showed that the SDF-1/CXCR4 axis was negatively correlated with Ca^{2+} levels, which was not consistent with some research results. The results of Menichella suggested that SDF-1 pathway can increase the Ca^{2+} concentration, lead to intracellular calcium overload, damage of neuron cell, which is the cause of T2DM peripheral neuropathy, and the injection of antagonist AM3100 is an effective method for the treatment of diabetic peripheral neuropathy [35,36]. However, the opposite result was found in this research. The reason might be that only the serum Ca^{2+} level was measured in this study, while the physiological function of SDF-1/CXCR4 axis is to promote Ca^{2+} entering the cell. In addition, the average age of patients enrolled in the study was about 55 years old, that's when the problem of Ca^{2+} loss is quite common. Uneven Ca^{2+} distribution and intracellular calcium overload in chondrocytes both augment inflammation, but the concentration of calcium in the body is still at a lower level and cannot maintain the basic structure of cartilage . Therefore, appropriate supplementation of calcium may prevent the occurrence of OA. In this study, we found that from high to low, the difference of SDF-1 in four groups were: T2DM & OA group, OA group, T2DM group and HC group. In the logistic regression analysis of whether or not accompanied by OA, the SDF-1 concentration also entered the final regression equation. Obviously, the increase of SDF-1/CXCR4 expression is involved in the occurrence of OA. Correlation study with general information and biochemical indices indicated that the concentration of SDF-1 was positively correlated with the risk factors of T2DM & OA, and negatively correlated with protective factors, so these factors may play a bridge role. Osteoarthritis is a chronic progressive osteoarthrosis characterized by articular cartilage degeneration and peripheral bone hyperplasia [37,38]. The axis may also be involved in the degeneration of articular cartilage through other specific cell pathways. In vitro, chondrocytes were soaked with 250 ng/ml of SDF-1, and more than 50% of chondrocytes degeneration was found on the first day. Degeneration of collagen and proteoglycan dissolution were observed in almost all the articular cartilage blocks on the second day, proved that SDF-1 is a strong cartilage matrix degradation inducer and this effect can get obvious effect in a short time [39,40].

However, the mechanism of this degradation of chondrocytes remains unclear, and the current study is more focused on the matrix metalloproteinase kinase pathway. In vitro experiments showed that the binding of SDF-1 to CXCR4 could activate the downstream signaling pathway, start the promoter of Matrix metallopeptidases (MMP), up regulate the expression of MMP-3, MMP-9 and MMP-13 in chondrocytes in a dose-dependent manner, degrade proteoglycan, II, IV and XI collagen protein and glial, etc. resulting in the occurrence of cartilage destruction and arthritis [41,42]. Blocking SDF-1/CXCR4 signaling pathway with CXCR4 antibody can delay the release of serum MMPs in diabetic patients [43]. This study found an elevated levels of SDF-1/CXCR4 in patients with OA ($p<0.05$, and is a risk factor of whether suffering from OA. Therefore, the increase of SDF-1 concentration in diabetic patients may induce the release of MMPS, leading to matrix degradation. The mechanism of the treatment of T2DM & OA is to reduce the release of MMPs by lowering the concentration of SDF-1/CXCR4. Further investigation is needed to detect the concentration of MMPs in serum and synovial fluid to confirm the involvement of MMPs pathway in the mechanism of SDF-1 leading to T2DM & OA.

Conclusion

In summary, the mechanism of occurrence and development of T2DM & OA is caused by multiple factors. In this study, we found that glycosylated hemoglobin, HOMA-IR and BMI are risk factors for T2DM & OA, and Ca^{2+} may be a protective factor. Stable glucose control, weight loss and appropriate calcium supplementation can prevent the onset of OA in T2DM patients. As OA is a new complication of diabetes, there is still a lot of unknown field about its pathogenesis and treatment, and the SDF-1/CXCR4 axis is related to many aspects of body function and diseases. As the serum SDF-1/CXCR4 levels increase in T2DM & OA patients, this axis may be involved in the progression of T2DM & OA. Therefore, treatment targeting at this axis may interrupt the progression of the disease, and could be of great advantage for the disease control of T2DM & OA in the future. However, a large number of cell signaling pathways are involved in the SDF-1/CXCR4 axis, specific microenvironments and subsequent cytokines and target cell functions should be considered when in a biological setting. Therefore, more downstream factors need to be tested and validated to explore the pathogenic pathway at molecular level, and to provide more evidence for new treatment of the disease. SDF-1/CXCR4 axis antagonist therapy was not performed in this study to further confirm the effect of SDF-1/CXCR4 axis on T2DM & OA. In our future studies, the axis will be used as a therapeutic target, and the choice of targeted therapeutic drugs, administration route and dosage will be tested.

Declarations

Acknowledgments: The authors are funded by National Natural Science Foundation of China (Grant No: 81960157), Key joint project of Yunnan Science and Technology department and Kunming Medical University (Grant No: 2019FE001(-006)), Yunnan Provincial Health Planning Commission Project grants (Grant No: 2017NS041, 2018NS0123), Yunnan provincial young and middle-aged academic and technical leader reserve talent funding project (Grant No: 2017HB045), Yunnan Dong Birong Expert Workstation (Project No: 202105AF150032), "Clinical Medical Research Center of Aging Diseases of Yunnan Province" (Project No.: 202102AA310002). Associated Project of Yunnan Province Science & Technology Department and Kunming Medical University Basic Research for Application (2018FE001(-288)).

Disclosure statement: The authors have no conflicts of interest to declare.

References

1. Guss JD, Ziemian SN, Luna M, Sandoval TN, Holyoak DT, et al. The effects of metabolicsyndrome, obesity, and the gut microbiome on load-induced osteoarthritis [J]. Osteoarthritis Cartilage. 2019; 27: 129–39.

2. Courties A, Sellam J, Berenbaum F. Metabolic syndrome-associated osteoarthritis [J]. Curr Opin Rheumatol. 2017; 29: 214-222.

3. Alenazi AM, Alothman S, Alshehri MM, Rucker J, Waitman LR. et al. The prevalence of type 2 diabetes and associated risk factors with generalized osteoarthritis: a retrospective study using ICD codes for clinical data repository system. Clin Rheumatol. 2019; 38: 3539-3547.

4. Schett G, Kleyer A, Perricone C. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study [J]. Diabetes Care. 2013; 36: 403-9.

5. Aydin Ozgur B, Coskunpinar E, Bilgic Gazioglu S, Yilmaz A, Musteri Oltulu Y, Cakmakoglu B, et al. Effects of Complement Regulators and Chemokine Receptors in Type 2 Diabetes [J]. Immunol Invest. 2020.

6. Menichella DM, Abdelhak B, Ren D, Shum A, Frietag C, et al. CXCR4 chemokine receptor signaling mediates pain in diabetic neuropathy [J]. Mol Pain. 2014; 10: 42.

7. Nirupa D Jayaraj, Bula J Bhattacharyya, Abdelhak A Belmadani, et al. Reducing CXCR4-mediated nociceptor hyperexcitability reverses painful diabetic neuropathy [J]. J Clin Invest. 20181; 128: 2205-2225.

8. Luo X, Wang X, Xia Z, Chung SK, Cheung CW. CXCL12/CXCR4 axis: An emerging neuromodulator in pathological pain [J]. Rev Neurosci. 2016; 27: 83-92.

9. American Diabetes Association. Diagmosis and classification of diabetes mellitus [J]. Diabetes Care. 2014: 37: S81-S90.

10. Chinese Orthopaedic Association. Chinese guidelines for the diagnosis and treatment of Osteoarthritis [J].Chinese Journal of Clinicians. 2007; 36: 28-30.

11. Williams MF, London DA, Husni EM, Navaneethan S, Kashyap SR. Type 2 diabetes and osteoarthritis: a systematic review and meta-analysis [J]. J Diabetes Complications. 2016; 30: 944-50.

12. Hao-Xiang Tan, Zhi-Gang Xiao, Tao Huang, Zhi-Xue Fang, Yu Liu, et al. CXCR4/TGF-β1 mediated self-differentiation of human mesenchymal stem cells to carcinoma-associated fibroblasts and promoted colorectal carcinoma development [J]. Cancer Biol Ther. 2020; 21: 248-257.

13. Zaruba MM, Franz WM. Role of theSDF-1/CXCR4 axis in stem cell based therapies for ischemic cardiomyopathy [J].Expert Opin Biol Ther. 2010; 10: 321-335.

14. Kun Wang, Yanlin Li, Rui Han, Guofeng Cai, Chuan He, et al. T140 blocks the SDF-1/CXCR4 signaling pathway and prevents cartilage degeneration in an osteoarthritis disease model [J]. PLoS One. 2017; 12.

15. Donath MY, Shoelson SE. Type 2 diabetes as an inflammatory disease [J]. Nat Rev Immunol 2011; 11: 98–107.

16. Nicola Veronese, Cyrus Cooper, Jean-Yves Reginster, Marc Hochberg, Jaime Branco, et al. Type 2 diabetes mellitus and osteoarthritis [J]. Semin Arthritis Rheum. 2019; 49: 9–19.

17. Martin K, Salam MA, Akhter J, et al. Role of stromal-cell derived factor-1 in the development of autoimmune diseases in non-obese diabetic mice[J]. Immunology. 2002; 107: 222-232.

18. Hamada D, Maynard R, Schott E, Drinkwater CJ, Ketz JP, et al. Suppressive effects of insulin on tumor necrosis factor-dependent early osteoarthritic changes associated with obesity and type 2 diabetes mellitus [J]. Arthritis Rheumatol. 2016; 68: 1392–402.

19. Schett G, Kleyer A, Perricone C, Sahinbegovic E, Iagnocco A, et al. Diabetes is an independent predictor for severe osteoarthritis: results from a longitudinal cohort study [J]. Diabetes Care. 2013; 36: 403–9.

20. Karimabad MN, Hassanshahi G. Significance of CXCL12 in type 2 diabetes mellitus and its associated complications [J].Inflammation. 2015; 38: 710-7.

21. Stack J1, McCarthy G. Basic calcium phosphate crystals and osteoarthritis pathogenesis: novel pathways and potential targets[J]. Curr Opin Rheumatol. 2016; 28: 122-6.

22. Qin HJ, Xu T, Wu HT, Yao ZL, Hou YL, et al. SDF-1/CXCR4 axis coordinates crosstalk between subchondral bone and articular cartilage in osteoarthritis pathogenesis [J]. Bone. 2019; 125: 140-150.

23. Bragg R, Gilbert W, Elmansi AM, Isales CM, Hamrick MW, et al. Stromal cell-derived factor-1 as a potential therapeutic target for osteoarthritis and rheumatoid arthritis [J]. Ther Adv Chronic Dis. 2019; 10: 2040622319882531.

24. Nanki T. Treatment for rheumatoid arthritis by chemokine blockade [J]. Nihon Rinsho Meneki GakkaiKaishi. 2016; 39: 172–180.

25. El Karib AO, Al-Ani B, Al-Hashem F, Dallak M, Bin-Jaliah I, et al. Insulin and vanadium protect against osteoarthritis development secondary to diabetes mellitus in rats[J]. Arch Physiol Biochem. 2016; 29: 1-7.

26. Sellam J, Berenbaum F. Is osteoarthritis a metabolic disease [J]? Joint Bone Spine. 2013; 80: 568–73.

27. King KB, Rosenthal AK. The adverse effects of diabetes on osteoarthritis: update on clinicalevidence and molecular mechanisms [J]. Osteoarthritis Cartilage. 2015; 23: 841–50.

28. Rosa SC1, Gonçalves J, Judas F.Impaired glucose transporter-1 degradation and increased glucose transport and oxidative stress in response to high glucose in chondrocytes from osteoarthritic versus normal human cartilage [J]. Arthritis Res Ther. 2009; 11: 80-2.

29. Nielen JTH, Emans PJ, Dagnelie PC, Boonen A, Lalmohamed A, et al. Severity of Diabetes Mellitus and Total Hip or Knee Replacement A Population-Based Case–Control Study [J]. Medicine. 2016; 95: e3739.

30. Courties A, Sellam J. Osteoarthritis and type 2 diabetes mellitus: What are the links [J]? Diabetes Res.Clin Pract. 2016; 122: 198–206.

31. Mobasheri A. Glucose: an energy currency and structural precursor in articular cartilage and bone with emerging roles as an extracellular signaling molecule and metabolic regulator [J]. Front Endocrinol (Lausanne). 2012; 3: 153.

32. Kim D, Kim J, Yoon JH, et al. CXCL12 secreted from adipose tissue recruits macrophages and induces insulin resistance in mice [J]. Diabetologia. 2014; 57: 1456-1465.

33. Kintscher U, Hartge M, Hess K, et al. T-lymphocyte infiltration in visceral adipose tissue:a primary event inadipose tissue inflammation and the development of obesity mediated insulin resistance [J]. Arterioscler Thromb Vasc Biol. 2008; 28: 1304–1310.

34. He W, Wang M, Wang Y, Wang Q, Luo B. Plasma and Synovial Fluid CXCL12 Levels Are Correlated With Disease Severity in Patients

With Knee Osteoarthritis [J]. J Arthroplasty. 2016; 31: 373-7.

35. Menichella DM, Abdelhak B, Ren D, Shum A, Frietag C, Miller RJ. CXCR4 chemokine receptor signaling mediates pain in diabetic neuropathy [J]. Mol Pain.2014; 25: 42-43.

36. Estella Zuccolo, Christian Di Buduo, Francesco Lodola, Stefania Orecchioni, Giorgia Scarpellino, et al. Stromal Cell-Derived Factor-1α Promotes Endothelial Colony-Forming Cell Migration Through the Ca 2+-Dependent Activation of the Extracellular Signal-Regulated Kinase 1/2 and Phosphoinositide 3-Kinase/AKT Pathways [J]. Stem Cells Dev Actions. 2018; 27: 23-34.

37. Yoshimura N, Muraki S, Oka H. Association of knee osteoarthritis with the accumulation of metabolic risk factors such as overweight, hypertension, dyslipidemia, and impaired glucose tolerance in Japanese men and women: The ROAD study [J]. J Rheumatol. 2011; 38: 921–30.

38. Richard Barnett. Osteoarthritis. Lancet. 2018; 391: 1985.

39. Wei F, Moore DC, Wei L. Attenuation of osteoarthritis via blockade of the SDF-1/CXCR4 signaling pathway[J]. Arthritis Res Ther. 2012; 14: R177-178.

40. Qinac HJ, Xud T, Wuac HT, Yaoac ZL, Houac YL, et al. SDF-1/CXCR4 axis coordinates crosstalk between subchondral bone and articular cartilage in osteoarthritis pathogenesis [J]. BoneVolume. 2019; 125: 140-150.

41. Hemshekhar M, Thushara RM, Jnaneshwari S, Devaraja S, Kemparaju K, et al. Attenuation of adjuvant-induced arthritis by dietary sesamol via modulation of inflammatory mediators, extracellular matrix degrading enzymes and antioxidant status [J]. Eur J Nutr. 2013; 52: 1787–1799.

42. Chen Y, Lin S, Sun Y, Guo J, Lu Y, et al. Attenuation of subchondral bone abnormal changes in osteoarthritis by inhibition of SDF-1 signaling [J]. Osteoarthritis Cartilage Actions. 2017; 25: 986-994.

43. Mohle R, Bautz F, Rafii S, Moore MA. The chemokine receptor CXCR-4 is expressed on CD34+ hematopoietic progenitors and leukemic cells and mediates transendothelial migration induced by stromal cell-derived factor-1 [J]. Blood. 1998; 91: 4523-4530.