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Serum and urinary levels of MIF, CD74, DDT and CXCR4 among patients with type 1 diabetes mellitus, type 2 diabetes and healthy individuals: Implications for further research

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ABSTRACT

Background: Macrophage migration inhibitory factor (MIF) is a highly conserved cytokine with pleiotropic properties, mainly pro-inflammatory. MIF seems to exert its pro-inflammatory features by binding to its transmembrane cellular receptor CD74. MIF also has CXCR4, which acts as a co-receptor in this inflammatory process. Apart from MIF, D-dopachrome tautomerase (DDT) or MIF2, which belongs to the MIF superfamily, also binds to receptor CD74. Therefore, these molecules, MIF, CD74, DDT and CXCR4 are suggested to work together orchestrating an inflammatory process. Diabetes mellitus is characterised by chronic low-grade inflammation. Therefore, the aim of the present study was to evaluate serum and urinary levels of the aforementioned molecules among patients with type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM) and among healthy controls.

Methods: We enrolled 13 patients with T1DM, 74 patients with T2DM and 25 healthy individuals as controls. Levels of CD74, CXCR4, DDT, and MIF were measured using ELISA Kits according to the manufacturer's instructions.

Results: We documented increased serum MIF levels together with higher urinary CD74 levels among patients with T1DM, when compared to patients with T2DM and healthy adults. In particular, patients with T1DM showed significantly increased levels of MIF compared to T2DM ($p = 0.011$) and healthy controls ($p = 0.0093$). CD74 in urine were significantly higher in patients with T1DM compared to those affected with T2DM ($p = 0.0302$) and healthy group ($p = 0.0099$). On the contrary, serum CD74 were similar among the three groups. No statistical differences were identified in CXCR4 levels both in serum and in urine of all groups. Patients with T2DM and overweight/obesity had increased urinary levels of CD74, when compared to lean patients with T2DM.

Conclusion: The increased serum MIF levels and urinary CD74 levels among patients with T1DM may be attributed to the autoimmune milieu, which characterises patients with T1DM, when compared to patients with T2DM. These two findings merit further attention as they could pave the way for further research regarding the potential beneficial effects of inhibitors of MIF among patients with T1DM, especially in the early stages of T1DM. Finally, the role of inhibitors of MIF could be further explored in the context of obesity among patients with T2DM.

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1. Introduction

Diabetes mellitus (DM) comprises a chronic metabolic disorder characterised mainly by increased serum glucose levels. It constitutes a major public health issue. According to the International Diabetes Federation (IDF), by 2030 643 million people are expected to have diabetes, while by 2050, 783 million people are projected to live with diabetes [1]. More than 90 % of patients with DM have type 2 DM (T2DM), which has been associated with insulin resistance. Besides, T2DM is related to the obesity pandemic, the sedentary lifestyle, urbanisation, the Western diet and the ageing process [1–3]. On the contrary, patients with type 1 DM (T1DM) constitute less than 10 % of people with DM and they are insulinopenic. T1DM is considered to be autoimmune in its origin and has been related to the presence of various autoantibodies, such as insulin autoantibodies (IAA), glutamic acid decarboxylase antibodies (GADA), tyrosine phosphatase like protein IA2 (IA-2A) and zinc transporter 8 antibody (ZnT8A) [4,5].

Macrophage migration inhibitory factor (MIF) is a proinflammatory cytokine with a molecular weight of 12.5 kDa [6]. MIF is a highly conserved cytokine with pleiotropic functions being also implicated in the pathogenesis of autoimmune disorders by binding to its receptor CD74. Apart from acting as a MHC class II chaperone, CD74 serves as a cell transmembrane receptor with high affinity for MIF and D-dopachrome tautomerase (DDT) or MIF2 [7–10]. In addition, MIF binds to CXCR4, which is a co-receptor for MIF, but does not appear to be specific solely for MIF [10–18].

As both T1DM and T2DM are metabolic disorders characterised by chronic low-grade inflammation, we hypothesised a potential association between MIF, CD74, DDT and CXCR4 in patients with T1DM and T2DM. Thus, the aim of the present study was to measure the serum and urinary levels of MIF, CD74, CXCR4 and DDT among patients with T1DM, T2DM and healthy individuals in order to assess whether there are any differences in their levels between these three distinct groups.

2. Materials and methods

For the purpose of the present study, between April 2019 and May 2022, we enrolled 13 patients with T1DM, 74 patients with T2DM and 25 healthy individuals as controls. Controls were consecutive healthy volunteers that agreed to participate in the study. The retrieved data were confidential, and the study followed the ethical considerations provided by the World Medical Association (52nd WMA General Assembly, Edinburgh, Scotland, October 2000). Moreover, the Institutional review board approved the design, procedures and aims of the study (GA 23/May 14, 2009). All participants were informed about the procedures of the study and agreed to participate providing written informed consent.

For the T2DM patients, the most frequently prescribed medication was Metformin, either alone or in combination with other drugs. Specifically, Metformin was used as monotherapy in 12 patients (20.3 %). The combination of Metformin with Sitagliptin was the most common, appearing in 12 cases (20.3 %). Metformin combined with other oral hypoglycemic agents, such as Vildagliptin, Empagliflozin, Alogliptin, and Dapagliflozin, was used in 13 patients (22 %). Additionally, Metformin was combined with insulin therapies (e.g., Insulin Glargine, Insulin Degludec, Insulin Lispro) in 8 patients (13.5 %). Insulin-based therapies, including various insulin formulations (e.g., Insulin Glargine, Insulin Lispro, Insulin Degludec, Insulin Aspart, Insulin Glulisine), were utilised in 13 patients (22 %), either alone or in combination with oral medications. GLP-1 receptor agonists (e.g., Dulaglutide and Liraglutide) were used in 6 patients (10.2 %), often in combination with Metformin or insulin. SGLT2 inhibitors (such as Empagliflozin) appeared in 3 cases (5 %), either as monotherapy or in combination with Metformin. Notably, 4 patients (6.8 %) were not on any active antidiabetic treatment.

2.1. Laboratory evaluation

Blood collection took place early in the morning. Serum and urine from participants were centrifuged for 20 min at 1000 g. Then, the supernatants were collected and stored in aliquots at −20 °C till the analyses. Protein levels (in pg/mL) of CD74, CXCR4, DDT, and MIF were measured using Human CD74 ELISA Kit (SEB369Hu, Cloud-Clone Corp., Houston, TX, USA), Human CXCR4 ELISA Kit (SEA940Hu, Cloud-Clone Corp., Houston, TX, USA), Human DDT ELISA Kit (SED777Hu, Cloud-Clone Corp., Houston, TX, USA), and Human MIF ELISA Kit (SEA698Hu, Cloud-Clone Corp., Houston, TX, USA) respectively, according to the manufacturer's instructions.

2.2. Transcriptomic analysis

We performed a comprehensive search of the GEO database to identify datasets generated from peripheral blood mononuclear cells (PBMCs) of Type 1 Diabetes and Type 2 Diabetes patients. For T2DM, we identified one microarray dataset, GSE9006, which included samples from 12 T2DM patients and 24 healthy controls. For T1DM, we retrieved three datasets: GSE9006, GSE72377, and GSE55100 [19,20]. The GSE9006 dataset contained data from 81 T1DM patients and 24 healthy controls [19]. The GSE72377 dataset provided mRNA gene expression profiles from unstimulated PBMCs of 15 T1DM patients and 20 healthy controls. The GSE55100 dataset included mRNA gene expression profiles from PBMCs of 12 T1DM patients and 10 healthy controls [20].

To identify differentially expressed genes in the pancreas of T2DM patients, we obtained the datasets GSE20966, GSE25724, and GSE38642, which collectively comprised data from 25 T2DM patients and 71 control islets [21–23]. For T1DM, we analysed the datasets GSE72492 and E-MEXP-1140, which included whole-genome mRNA data from a total of 24 T1DM patients and 13 controls [24,25].

Additionally, we selected the GSE1009 and GSE199838 datasets, which contained transcriptomic data from kidney tissues of patients with diabetic nephropathy and control cases [26,27].

Significant genes were identified using the R package LIMMA (Linear Models for Microarray Data), with a threshold of False Discovery Rate (FDR) < 0.05. For the meta-analysis, we utilised the Network Analyst web utility tool [28,29]. The normalisation of the datasets was performed using the variance stabilising normalisation algorithm, followed by quantile normalisation [30]. To adjust for batch effects in the meta-analysis, the ComBat procedure, embedded in the Network Analyst tool, was applied. The meta-analysis was then conducted using Fisher's P-value combination method.

2.3. Statistical analysis

Data are presented as Mean ± S.D. (Standard Deviation). Kolmogorov–Smirnov test was used to determine the distribution of the data. Based on the results from the normality test, the non-parametric Kruskal-Wallis test followed by Uncorrected Dunn's test was used to compare the differences among the groups. Spearman correlation coefficients (r) were used as measurements of correlation for continuous variables. To evaluate the effects of insulin and metformin on the levels of MIF, DDT, CXCR4, and CD74, we accounted for potential confounding factors, which included all drug treatments other than insulin and metformin. We corrected the ELISA data using the General Linear Model (GLM) to adjust for these confounding drug treatments and derived residuals that reflect the adjusted biomarker levels. Patients were categorised into four groups: those receiving Insulin only, those receiving Metformin only, those receiving Metformin + Insulin, and a fourth group representing all other treatments. The residuals were then compared across these four groups using the Kruskal-Wallis test. Differences were considered statistically significant with a p-value <0.05. Statistical analyses were performed using Graph-Pad Prism 7.0 software (La Jolla, CA, USA).

Table 1
Depicts the main demographic and clinical characteristics of study participants.

	Patients with T1DM (n = 13)	Patients with T2DM (n = 73)	Controls (n = 25)
Number of Patients	13	64	25
Gender (Male/Female in number)	9/4	44/20	8/17
Age (years, mean ± SD)	43.3 ± 12	60.2 ± 11.5	38.9 ± 11.4
Duration of DM (months, mean ± SD)	259.1 ± 183.1	109 ± 120.9	N/A
Diabetic Nephropathy (n, %)	2 (15.4 %)	15 (20.5 %)	N/A
Weight (Kg, mean ± SD)	79.4 ± 17.4	88.5 ± 18.1	66.7 ± 7.7
BMI (Kg/m^2, mean ± SD)	26.6 ± 5.2	31.2 ± 10.8	24.2 ± 5.2

3. Results

To evaluate whether DM disease is associated with altered levels of pro-inflammatory proteins, we measured the protein levels of CD74, CXCR4, DDT, and MIF in the serum and in the urine of patients with T1DM, T2DM, and healthy subjects (see Table 1). The results of these analyses showed significantly higher MIF levels in serum of patients with DM compared to healthy donors (Fig. 1A). In particular, patients with T1DM showed significantly increased levels of MIF compared to T2DM ($p = 0.011$) and healthy controls ($p = 0.0093$) (Table 2). However, in contrast to serum levels, urine MIF levels (Fig. 1B) were found to be significantly lower in T2DM patients compared to the healthy group ($p = 0.0233$). Furthermore, serum levels of DDT (Fig. 1C) were higher in patients with T1DM compared to healthy donors ($p = 0.038$). On the other hand, no statistical differences were observed in urine DDT levels among the three examined groups (Fig. 1D).

Levels of CD74 in urine (Fig. 2B) were found to be significantly higher in patients with T1DM compared to those affected with T2DM ($p = 0.0302$) and healthy group ($p = 0.0099$). On the contrary, serum CD74 levels were similar in the three groups (Fig. 2A). No statistical differences were identified in CXCR4 levels both in serum and in urine of all selected groups (Fig. 2C–D).

By doing a correlation analysis with BMI, we observed that in patients with T2DM, levels of CD74 in urine correlated positively with BMI (Fig. 3, Table 3). Furthermore, among patients with T2DM, CD74 levels in the blood were higher in females, when compared to males (Fig. 4). In addition, in patients with T2DM, we found an inverse relationship between urinary MIF levels and glycated haemoglobin (HbA1c) as well as erythrocyte sedimentation rate (ESR) ($p < 0.05$) (Fig. 5).

Our cohort of T2DM patients showed a predominant use of metformin-based therapies (63.5 %), either as monotherapy or in combination with other agents. There was also a notable use of insulin-based therapies (22 %) and combinations that included newer agents such as DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors. When comparing the four patient groups—Insulin only, Metformin only, Metformin + Insulin, and all other treatments—no significant differences were observed in the levels of MIF, DDT, CD74, and CXCR4. This suggests that none of the treatments had a distinct impact on these biomarker levels.

With regard to the transcriptomic datasets, none of the genes of interest (MIF, DDT, CD74 and CXCR4) were significantly modulated in PBMCs (peripheral blood mononuclear cells) of patients with type 2 (GSE9006) and type 1 diabetes (meta-analysis of the datasets GSE9006, GSE72377, GSE55100). No significant differences were also found in the pancreas (meta-analysis of the datasets GSE20966, GSE25724 and GSE38642 for T2DM; meta-analysis of GSE72492 and E-MEXP-1140 for T1DM). For the kidney, we analysed the GSE199838 and GSE1009 datasets for T2DM, and again the genes of interest were not modulated.

4. Discussion

In this study, we documented a higher level of serum MIF among patients with T1DM, when compared to patients with T2DM. Furthermore, serum concentrations of MIF were increased among patients with T1DM as well as T2DM, when compared to healthy individuals. As already mentioned, MIF is a pleiotropic cytokine considered to be involved in autoimmune and inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, sepsis and cancer. In particular, there are several lines of evidence suggesting involvement of MIF in the pathogenesis of T1DM [31–37]. Insulitis, which is the cornerstone of T1DM, has been suggested to be mediated-among other factors-via MIF. More specifically, MIF is implicated in autoantigen presentation, in the increased production of other inflammatory cytokines, such as interleukin-1β and Tumor Necrosis Factor (TNF)-a and in beta cell apoptosis in Langerhans islets [31–39]. MIF seems to be involved in the progression of T1DM as well. According to Korf et al. inhibition of MIF results in a delay in the onset of autoimmune diabetes [31]. Therefore, it would be useful to better identify the exact stage in the pathogenesis of T1DM, where inhibition of MIF would be beneficial. In this context, inhibition of MIF could lead to a delay in the onset of T1DM. However, due to the complexity of the pathways and the yet unknown stage that research should focus in order to impede onset of T1DM, results regarding MIF inhibition are yet inconclusive. Nevertheless, Korf et al. have

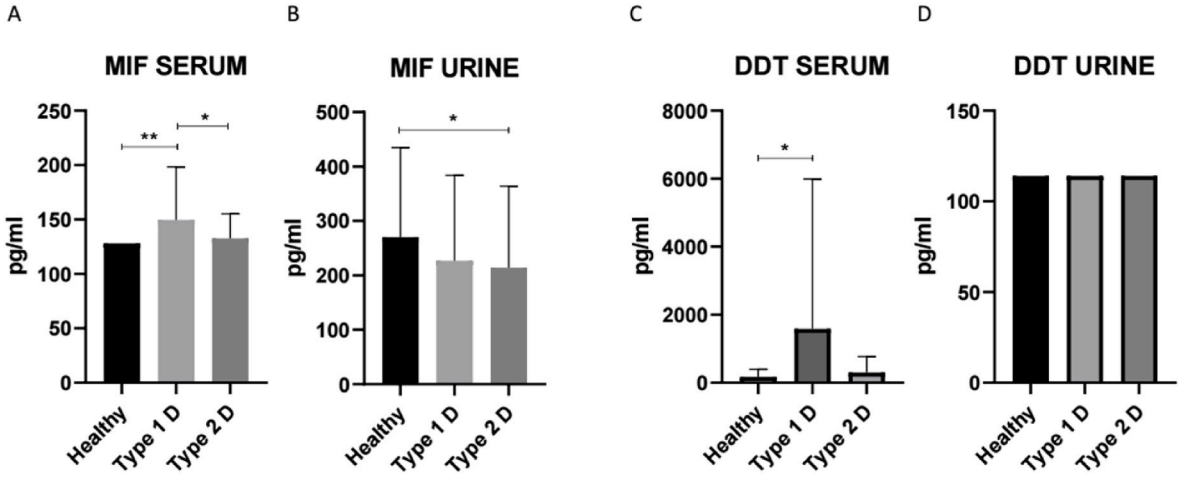

Fig. 1. Analysis of the MIF and DDT levels in the serum or urine from Healthy donors (Control), Type 1 Diabetes Mellitus (T1DM), and Type 2 Diabetes Mellitus (T2DM) patients. Data are presented as mean concentrations ± standard deviation. The statistical significance in the figures has been indicated by asterisks (*$P < 0.05$ and **$P < 0.01$).

Table 2
Statistical comparison analyses.

Uncorrected Dunn's test		
Serum MIF	Mean rank diff.	Individual P value
Control vs. T1DM	−11.62	0.0093
Control vs. T2DM	−1.6	0.6055
T1DM vs. T2DM	10.02	0.011
Urine MIF		
Control vs. T1DM	14.68	0.1148
Control vs. T2DM	15.08	0.0233
T1DM vs. T2DM	0.3944	0.9609
Serum DDT		
Control vs. T1DM	−17.74	0.038
Control vs. T2DM	−10.35	0.081
T1DM vs. T2DM	7.392	0.327
Urine DDT		
Control vs. T1DM	0	1
Control vs. T2DM	0	1
T1DM vs. T2DM	0	1
Serum CD74		
Control vs. T1DM	2.146	0.5312
Control vs. T2DM	−0.2003	0.9328
T1DM vs. T2DM	−2.346	0.4377
Urine CD74		
Control vs. T1DM	−11.46	0.0099
Control vs. T2DM	−3.079	0.3274
T1DM vs. T2DM	8.382	0.0302
Serum CXCR4		
Control vs. T1DM	−3.965	0.4699
Control vs. T2DM	−1.626	0.6691
T1DM vs. T2DM	2.338	0.629
Urine CXCR4		
Control vs. T1DM	−1.579	0.7983
Control vs. T2DM	−1.063	0.8116
T1DM vs. T2DM	0.5336	0.9212

demonstrated that blocking the MIF/CD74 pathway may be an effective way to delay the onset of T1DM, by interfering with macrophage cytokine secretion [31]. Notably, in our study, all patients with T1DM but one, had long lasting T1DM, i.e. of more than 12 months' duration. Even though the duration of diabetes mellitus among patients with T1DM was long enough, serum levels of MIF were still high in these patients.

In our study, apart from serum MIF levels, urinary levels of CD74 were elevated among patients with T1DM, when compared to patients with T2DM and healthy controls. Urinary levels of CD74 among patients with T1DM were statistically significantly increased, whereas no statistical significant relationship was noted regarding serum levels of CD74 among the three groups examined. This dissociation could be a random effect or could be attributed to a potential increased production of CD74 in the kidney of patients with T1DM. Notably, Valina-Rivas et al. have proposed that TNF-like weak inducer of apoptosis (TWEAK) upregulates CD74 and its ligands MIF and DDT in renal tubular cells [40]. TWEAK belongs to the TNF superfamily and is responsible for the activation of inflammatory cells in conjunction with the downregulation of the anti-inflammatory klotho factor, leading to acute or chronic kidney injury [41]. In our opinion, the aforementioned discrepancy requires further investigation in the near future.

Regarding DDT, we have documented a significant increase of its serum levels in patients with T1DM, when compared to healthy controls. Despite the fact that no statistically significant difference was noted between the three examined groups in terms of its urinary concentrations, we cannot overlook the elevated serum levels of DDT among patients with T1DM. As DDT or MIF2 belongs to the MIF superfamily and shares the same ligand with MIF, i.e. CD74 with substantial affinity, Merk et al. have proposed that MIF2 acts synergistically with MIF [42]. In this context, the elevated serum levels of DDT in patients with T1DM, when compared to healthy controls, could be attributed to the increased inflammatory process that is associated with T1DM.

T2DM and obesity are also characterised by chronic low-grade inflammation [43–52]. However, T2DM lacks the autoimmunity feature, which is indigenous to T1DM. T2DM and its complications are

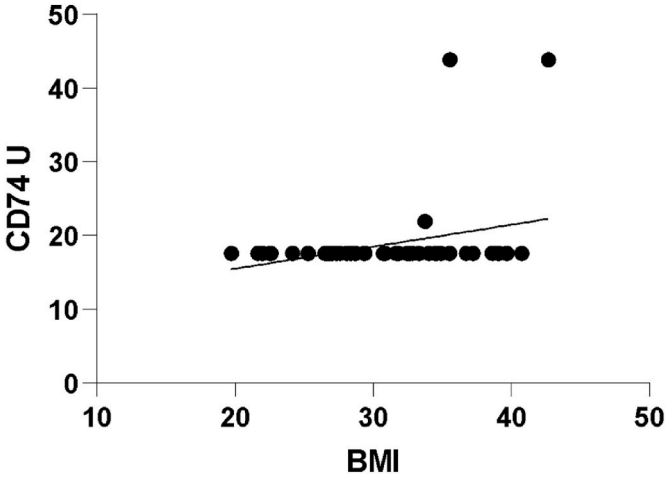

Fig. 3. Urinary levels of CD74 varied according to BMI among patients with T2DM. U denotes urinary.

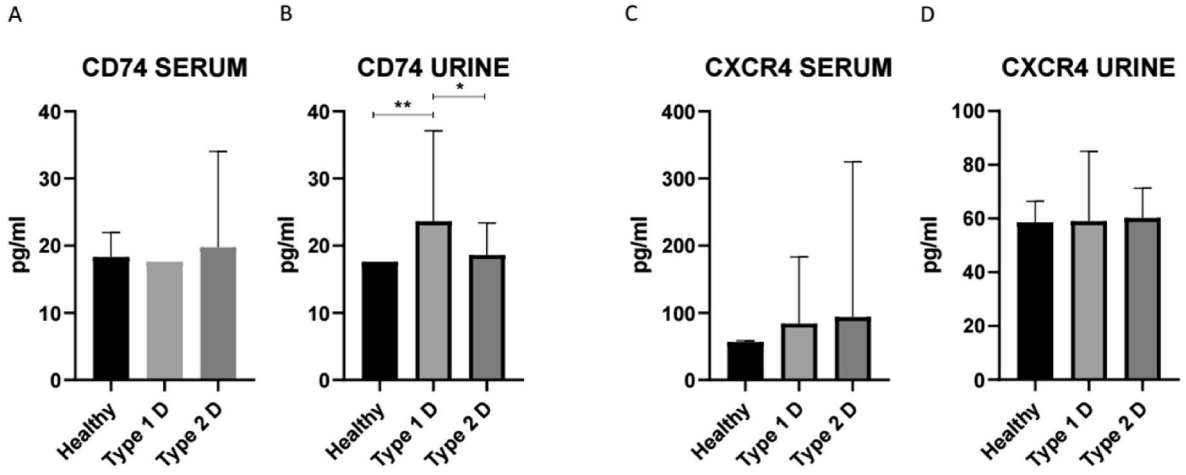

Fig. 2. Analysis of the CD74 and CXCR4 levels in the serum or urine from healthy donors (Control), Type 1 Diabetes Mellitus (T1DM), and Type 2 Diabetes Mellitus (T2DM) patients. Data are presented as mean concentrations ± standard deviation. The statistical significance in the figures has been indicated by asterisks (*P < 0.05 and **P < 0.01).

Table 3
Correlation analysis with BMI among patients with T2DM. U denotes urinary and S denotes serum.

T2DM	BMI vs. CD74 S	BMI vs. CD74 U	BMI vs. MIF S	BMI vs. MIF U	BMI vs. DDT S	BMI vs. DDT U	BMI vs. CXCR4 S	BMI vs. CXCR4 U
P (two-tailed)	0.347	0.040	0.894	0.937	0.428	NA	0.981	0.281

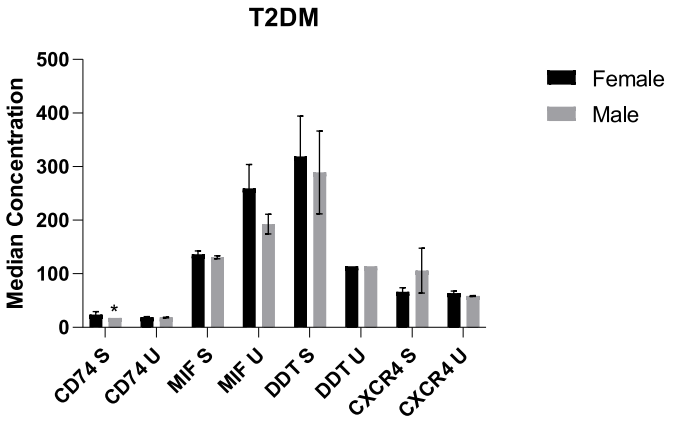

Fig. 4. This histogram depicts sex variations of the various serum and urinary levels of cytokines among patients with T2DM. U denotes urinary and S denotes serum.

strongly associated with chronic low-grade inflammation, especially due to obesity and the well-known adipogenic-related inflammatory milieu [53–60]. It is noteworthy that MIF has been documented to stimulate the release of inflammatory adipocytokines, such as resistin and interleukin-6 [61,62]. These inflammatory adipocytokines are deeply implicated in the development of insulin resistance, which is a characteristic component of T2DM and related comorbidities including obesity and associated disorders [63–75]. Nevertheless, T1DM in comparison to T2DM, apart and beyond the inflammatory process, exhibits an autoimmune profile, which accounts for the pathogenesis of T1DM and its complications [5,76,77]. Therefore, the highly elevated levels of serum MIF and urinary CD74, that we found among patients with T1DM, when compared with patients with T2DM, could be due to the inflammation together with the autoimmune milieu in T1DM. It is noteworthy that serum MIF and urinary CD74 levels were significantly decreased in healthy controls, when compared with patients with DM, either T1DM or T2DM. This finding points towards the inflammatory features of MIF and CD74. Indeed, as already mentioned above, MIF is a cytokine with pleiotropic inflammatory properties, which acts via its receptor CD74 on a plethora of cells and not solely on macrophages [78–82]. In addition, in this study we documented a statistically significant association between BMI and urinary levels of CD74 among patients with T2DM. More specifically, increased BMI was correlated to increased urinary levels of CD74 in patients with T2DM. This positive relationship could be attributed to the chronic low-grade inflammation, which is associated with overweight/obesity [78–82]. Only recently, it has been suggested that MIF downregulates the adipose tissue hormone sensitive lipase (HSL), thus contributing to the development of obesity [83]. This observation by Chen et al. may further shed light upon the pathogenetic mechanisms of obesity and could be useful in investigating inhibitors of MIF as potential agents for the prevention and treatment of obesity [83]. Therefore, the MIF/CD74 pathway merits further attention in terms of overweight/obesity, especially in the context of T2DM.

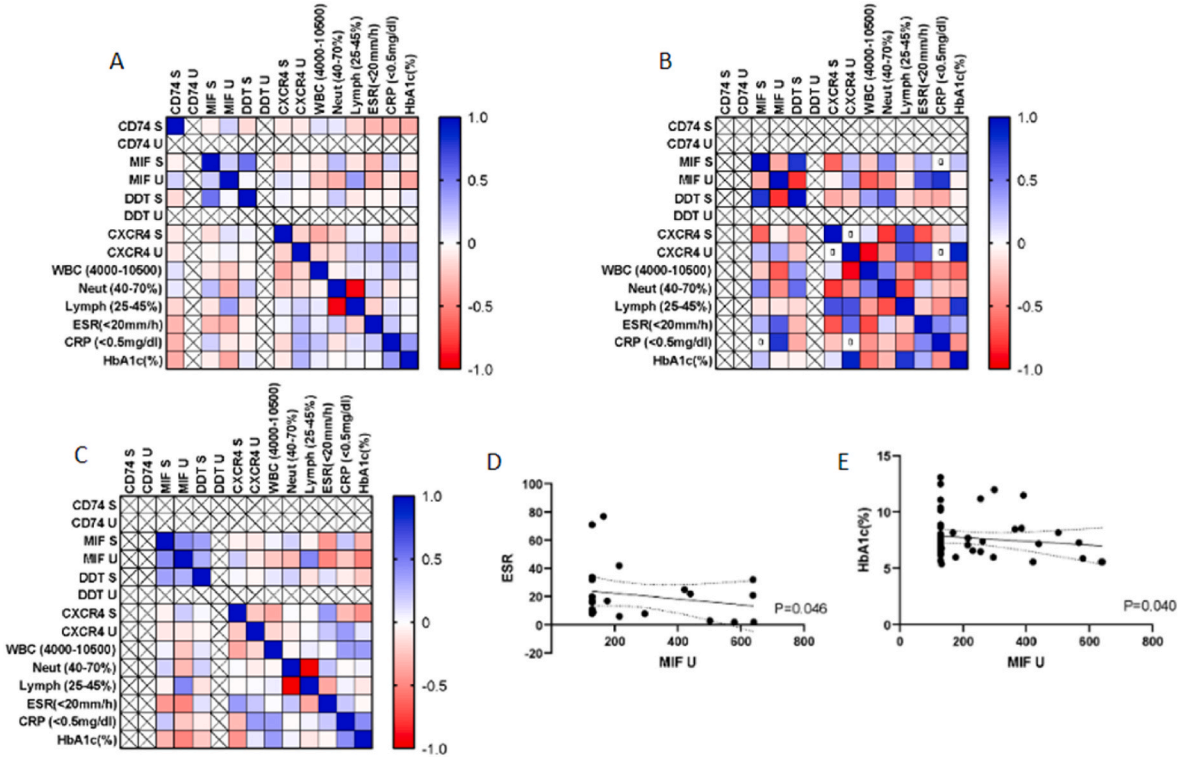

Fig. 5. Correlation analysis between MIF, DDT, CD74 and CXCR4 and blood biochemical-clinical data. A. Heatmap showing the Spearman's correlation analysis for all patients and healthy subjects. The heatmap is colour-coded based on Spearman's r; B. Heatmap showing the Spearman's correlation analysis for T1D patients. The heatmap is colour-coded based on Spearman's r; C. Heatmap showing the Spearman's correlation analysis for T2DM patients. The heatmap is colour-coded based on Spearman's r; D. Correlation between MIF U and ESR in T2D patients. E. Correlation between MIF U and HbA1c in T2DM patients.

This study has several limitations. First, the number of participants in this study was limited to 102 people, i.e. the sample size was rather small. However, the ratio of patients with T1DM to patients with T2DM was representative of the ratio in the general population. In addition, this study was performed among individuals from Athens in Greece. Therefore, we cannot draw any safe conclusions about people of other origin and not Caucasian.

5. Conclusion

In conclusion, we have documented a statistically significant increase in serum levels of MIF, DDT and urinary concentrations of CD74 among patients with DM, when compared to healthy controls. These differences were even more obvious among patients with T1DM, when compared to patients with T2DM. We have attributed these substantial differences in the autoimmune microenvironment apart from the inflammatory milieu in patients with T1DM, when compared to T2DM. Undoubtedly, MIF, DDT and CD74 are implicated in the pathogenesis of T1DM as well as of T2DM. Future studies could shed light on the potential role of inhibition of MIF in the delay of onset of T1DM. The inhibition of MIF should be further explored as a candidate for managing inflammation, atherosclerosis and overweight/obesity in patients with T2DM.

Declaration of interest statement

There is no conflict of interest regarding this manuscript.

Declaration of funding statement

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CRediT authorship contribution statement

Katia Mangano: Formal analysis, Conceptualization. **Aristidis Diamantopoulos:** Resources, Investigation, Data curation. **Natalia G. Vallianou:** Writing – original draft, Resources. **Theodora Stratigou:** Validation, Project administration. **Fotis Panagopoulos:** Validation, Data curation. **Dimitris Kounatidis:** Writing – original draft, Visualization. **Maria Dalamaga:** Writing – review & editing, Formal analysis. **Paolo Fagone:** Software, Methodology, Investigation. **Ferdinando Nicoletti:** Writing – review & editing, Supervision, Project administration, Conceptualization.

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