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CLINICAL STUDY

Is IL-33 useful to detect early stage of renal failure?

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Abstract

IL-33 is a proinflammatory cytokine that is a member of IL-1 family. Previously the effect of IL-33 on kidney injury is showed in animal models. In this study, we searched if we can use IL-33 to show the early stage of kidney injury in diabetic patients. Three groups are identified: 26 patients in *Group 1: Healthy group*, that do not have any chronic diseases and not taking any medication; 42 patients in *Group 2: DM* (diabetes mellitus) group without any known kidney disease and with normal kidney functions; 32 patients in *Group 3: DM + MA* (microalbuminuria) group that are assumed to have nephropathy. IL-33 level of DM patient group is greater than healthy group; also IL-33 level of DM + MA patient group is greater than healthy group; but there is not any difference between DM and DM + MA group. The increase in IL-33 levels in diabetic nephropathy is not associated with kidney injury but the increase could be resulting because of diabetes. So IL-33 cannot be used in early recognition of diabetic nephropathy.

Keywords

Diabetes mellitus, diagnosis, IL-33, kidney, renal failure

History

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Introduction

Interleukin (IL-33) is a member of IL-1 family of cytokines; it binds to its plasma receptor.[1] It is mainly expressed by stromal cells like epithelial and endothelial cells.[2] It is known as a proinflammatory cytokine.[3] It is released from necrotic cells; it increases secretion of cytokines by binding the ST2R on immune cells that result in inflammation.[4] Akcay et al. showed that IL-33 promotes acute kidney injury through CD4 T cell-mediated production of CXCL1; additionally, they suggested that inhibiting IL-33 or CXCL1 may have therapeutic potential in acute kidney injury.[5]

Diabetes is the most common cause of end stage renal disease.[6] Hyperglycemia-induced hemodynamic and metabolic pathways are the mediators of kidney injury.[7] So, we investigated if the plasma IL-33 levels could be used to show the early indicator of the kidney injury in patients with diabetes mellitus.

Material and methods

This prospective study was performed with local ethical committee approval. Study was explained in detail to the patient and patients were included in the study after signed informed consent. There are three groups as follows: 26 patients in ***Group 1: Healthy group***, that do not have any chronic diseases and not taking any medication; 42 patients in ***Group 2: DM*** (diabetes mellitus) group without any known kidney disease and with normal kidney functions; 32 patients in ***Group 3: DM + MA*** (microalbuminuria) group that are assumed to have nephropathy because the persistent microalbuminuria in insulin-dependent diabetes mellitus (IDDM) is a predictive value of the future development of end-stage renal failure.[8] Also it is predictive of the end-stage renal disease in non-insulin-dependent diabetes mellitus (NIDDM).[8]

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IL-33 measurement

Peripheral blood was collected into a closed monovette system in the morning before breakfast. Samples immediately centrifuged at 1500*g* for 15 min. Then the samples were stored at $-70\,°C$ until measurement. IL-33 levels of the patients were measured by Enzyme-linked Immunosorbent Assay Kit. The kit is a sandwich enzyme immunoassay for the *in vitro* quantitative measurement of IL33 in human serum, plasma, and other biological fluids. IL-33 ***Test principle:*** The microtiter plate provided in this kit has been pre-coated with a monoclonal antibody specific to IL33. Standards or samples are then added to the appropriate microtiter plate wells with a biotin-conjugated polyclonal antibody preparation specific for IL33. Next, Avidin conjugated to Horseradish Peroxidase (HRP) is added to each microplate well and incubated. Then a TMB substrate solution is added to each well. Only those wells that contain IL33, biotin-conjugated antibody and enzyme-conjugated Avidin will exhibit a change in color. The enzyme–substrate reaction is terminated by the addition of a sulfuric acid solution and the color change is measured

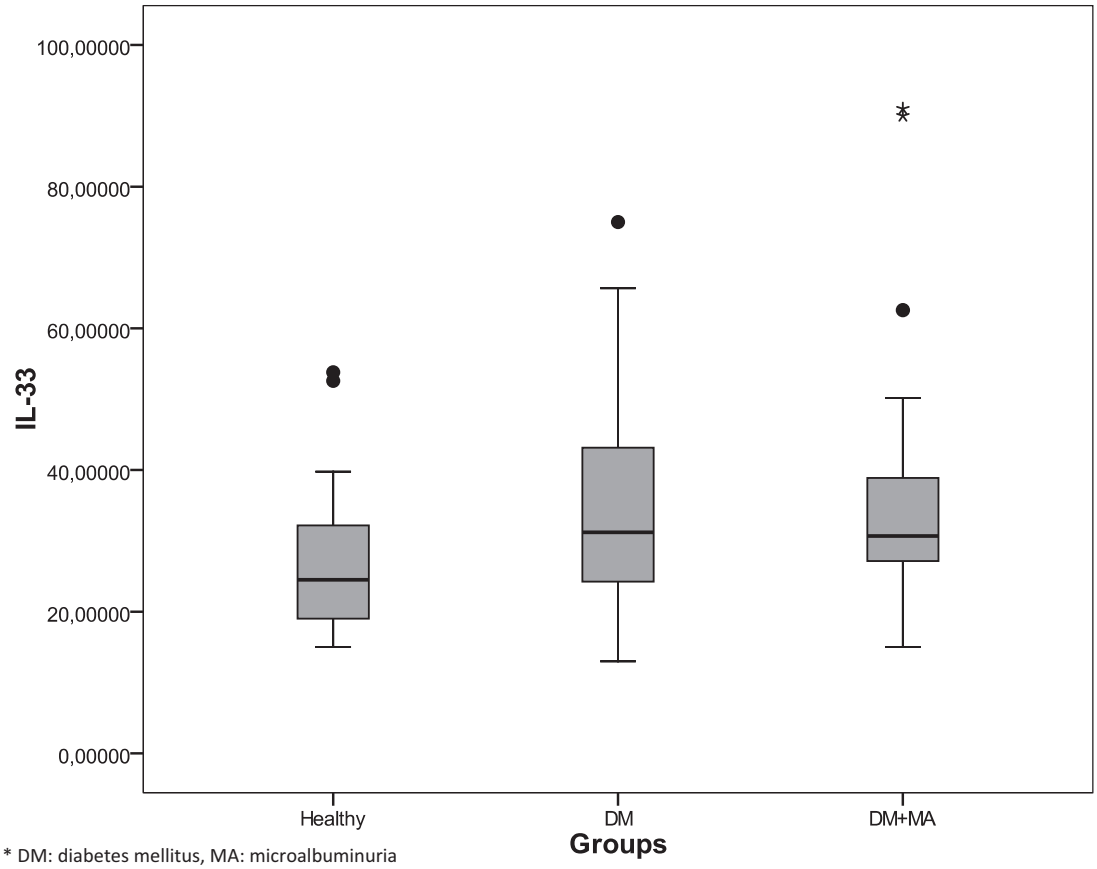

Figure 1. Box-blot graph of IL-33 levels of groups.

Table 1. Mean ± SD of IL-33 and comparisons of groups.

Mean ± SD			Comparison of groups		
Healthy	DM	DM + MA	Healthy versus DM	Healthy versus DM + MA	DM versus DM + MA
26.850 ± 10.260	33.597 ± 13.597	36.504 ± 17.091	$p = 0.029$ $t = 2.226$	$p = 0.014$ $t = 2.531$	$p = 0.411$ $t = 0.827$

Notes: SD: standard deviation, DM: diabetes mellitus, MA: microalbuminuria.

spectrophotometrically at a wavelength of 450 nm ± 10 nm. The concentration of IL33 in the samples is then determined by comparing the O.D. of the samples to the standard curve.

Statistical analysis

SPSS Statistics for Windows (Version 17.0., SPSS Inc., Chicago, IL) is used for statistical analysis. One-sample Kolmogorov–Smirnow test and histogram are used to determine if the IL-33 levels are normally distributed in each group. IL-33 levels of each group were normally distributed. So we used independent samples *t*-test in comparison of IL-33 levels of the groups. Spearmen's rho correlation was used to show the correlation between continuous variables. All calculations are done two-tailed, $p < 0.05$ is assumed as significant. Also box-blot graph of IL-33 levels of groups is shown in Figure 1.

Results

The study included 60 female patients (%60). Mean age was 55.3 ± 12.4. IL-33 level of DM patient group is greater than healthy group ($p = 0.029$, $t = 2.226$); also IL-33 level of DM + MA patient group is greater than healthy group ($p = 0.014$, $t = 2.531$); but there is not any difference between DM and DM + MA group ($p = 0.411$). Mean values of IL-33 and comparisons of all groups are shown in Table 1. Box-blot graph of IL-33 levels in groups is expressed in Figure 1. We see in this graph that DM and DM + MA groups have similar IL-33 levels.

IL-33 level of diabetic patients was higher than the healthy group ($p = 0.013$, $t = 2.525$). Among DM and DM + MA groups, microalbuminuria levels were not correlated with IL-33 levels ($p = 0.717$, $r = 0.043$).

Discussion

The principal etiologic factors causing type-2 DM and its complications like nephropathy are not clear yet.[9] To predict the potential renal complications in diabetic patients could lead to early management of the patients. Akcay et al. showed that the inhibition of IL-33 with sST2 provides functional and histological protection from acute kidney injury caused by cisplatin; so they indicated that IL-33 is a mediator of cisplatin-induced acute kidney injury.[5]

Akcay et al. showed that in diabetic patients with microalbuminuria, IL-33 levels were higher than healthy patient group.[5] In our study, we also found that IL-33 levels are higher in DM + MA ($p = 0.014$) and DM ($p = 0.029$) group than healthy group; but we also showed that IL-33 levels do not differ between DM and DM + MA group ($p = 0.411$). If we overview these findings, we can say the increase of IL-33 in diabetic patients could be a result of inflammation and microvascular complications of diabetes mellitus. So, we thought that IL-33 levels are higher because of diabetes mellitus independent from kidney injury because Miller et al. showed that soluble ST2 associates with diabetes mellitus.[10] Also Bao et al. reported that IL-33 levels do not differ between patients with chronic kidney disease and healthy individuals; in addition Il-33 levels are similar in three stages of kidney injury when they are divided into three groups according to their GFR.[11] In another study, the IL-33 levels did not differ between multiple myeloma patients with and without kidney failure.[12] These studies support our hypothesis that the increase of IL-33 could be resulted due to diabetes mellitus.

Finally, we can say the increase in IL-33 levels in diabetic nephropathy is not associated with kidney injury but the increase could be resulting because of diabetes. Further studies will clarify the value of IL-33 both in diabetes mellitus and early stage of kidney injury.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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