

Metabolic acidosis is associated with monocyte activation in diabetic kidney disease (DKD)

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BACKGROUND

- Systemic inflammation has been linked to adverse cardiovascular outcomes and it is thought to contribute to CKD progression in DKD.
- CD74 is a receptor for the cytokine MIF.
- MIF promotes kidney injury and CD74 expression is increased in renal biopsies from DKD patients and in atherosclerotic lesions.
- CxCl16 is a scavenger receptor and chemokine that has been associated to kidney and cardiovascular injury. However, the expression of CD74 and CxCl16 in circulating leukocytes from DKD patients has not been previously explored

METHODS

- We have assessed the cell surface expression of CD74 and CxCl16 in peripheral blood leucocytes from 88 DKD patients (Mean age 67 ± 13 years, 75 % males, eGFR 55 ± 22 ml/min/1.73 m², median urinary albumin/creatinine ratio 140 [30 - 480] mg/g) and 6 healthy controls (mean age 41 years).

RESULTS

- In peripheral blood leukocytes CD74 and CxCl16 were mainly expressed by monocytes. The distribution of monocyte subpopulations was similar in controls and DKD patients (**Figure 1**).
 - **Controls:** Median CxCl16 expression was 12, 28 and 33 fluorescence units (FU) in CD14⁺⁺/CD16⁻, CD14⁺⁺/CD16⁺, CD14⁺/CD16⁺⁺ monocytes, respectively. Median CD74 expression of 28, 32 and 8 FU in CD14⁺⁺/CD16⁻, CD14⁺⁺/CD16⁺, CD14⁺/CD16⁺⁺ monocytes
 - **DKD patients:** DKD monocytes presented a pattern of activation even in classic (CD14⁺⁺/CD16⁻) monocytes. Median CD74 expression was higher in monocyte subpopulations than in controls (44, 54, 21 FU vs 28, 32, 8 FU respectively) (**Figure 2**).
- ### Univariate analysis in DKD
- There was correlation between CD74 and CxCl16 expression in CD14⁺⁺/CD16⁻ ($r 0.55, p < 0.001$), CD14⁺⁺/CD16⁺ cells ($r 0.26, p 0.012$), CD14⁺/CD16⁺⁺ ($r 0.78, p < 0.001$).
 - Median CD74 fluorescence in CD14⁺⁺/CD16⁻ monocytes correlated directly with serum phosphorus ($r 0.23, p 0.02$), HbA1c% ($r=0.41, p 0.02$) and correlated inversely with eGFR ($r -0.27, p 0.05$) and CO₂ ($r -0.38, p 0.0003$) (**Figure 3**).
 - Median CD74 fluorescence correlated inversely with CO₂ in CD14⁺⁺/CD16⁺ monocytes ($r 0.79, p 0.002$) (**Figure 4**), CD14⁺/CD16⁺⁺ monocytes ($r 0.23, p 0.02$) (**Figure 5**), neutrophils ($r 0.28, p 0.0007$) (**Figure 6**), NK CD56⁺ ($r 0.25, p 0.01$) and NK CD56⁺⁺ ($r 0.24, p 0.024$).
 - Median CxCl16 fluorescence correlated inversely with CO₂ in CD14⁺⁺/CD16⁻ monocytes ($r -0.24, p 0.02$) and in neutrophils ($r 0.27, p 0.01$).
- ### Multivariate analysis in DKD
- The main factors independently associated with CD74 fluorescence in CD14⁺⁺/CD16⁻ were CO₂ ($p 0.04$) and HbA1c% ($p 0.0006$) (r^2 adjusted for the model 0.24).
 - CO₂ was associated with median CD74 expression in CD14⁺⁺/CD16⁺ monocytes (r^2 adjusted 0.12, $p 0.003$), CD14⁺/CD16⁺⁺ (r^2 adjusted 0.04, $p 0.001$), and neutrophils (r^2 adjusted 0.14, $p 0.03$).

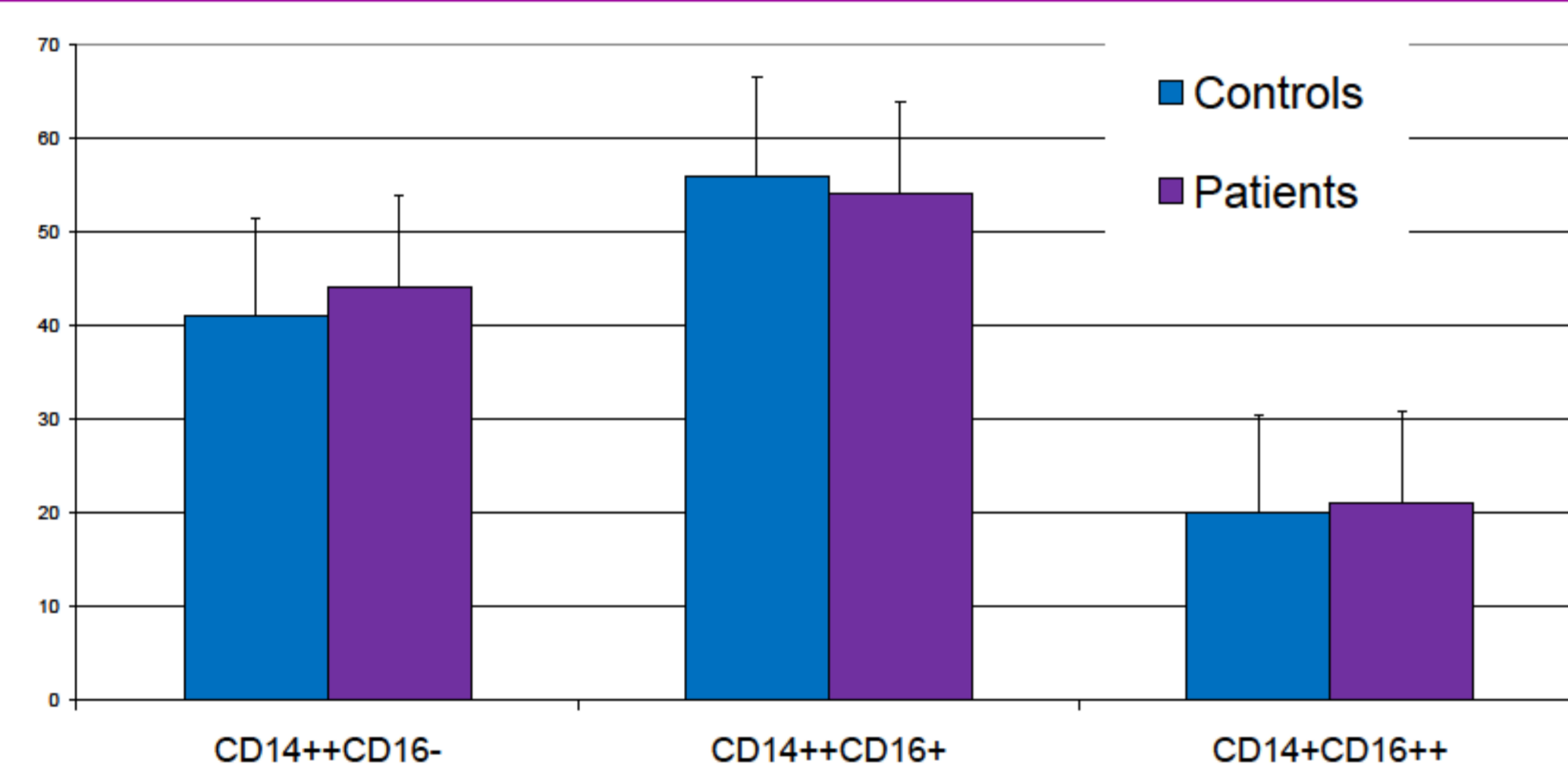


Figure 1: Monocyte subpopulations (% of monocytes) in DKD patients and healthy controls

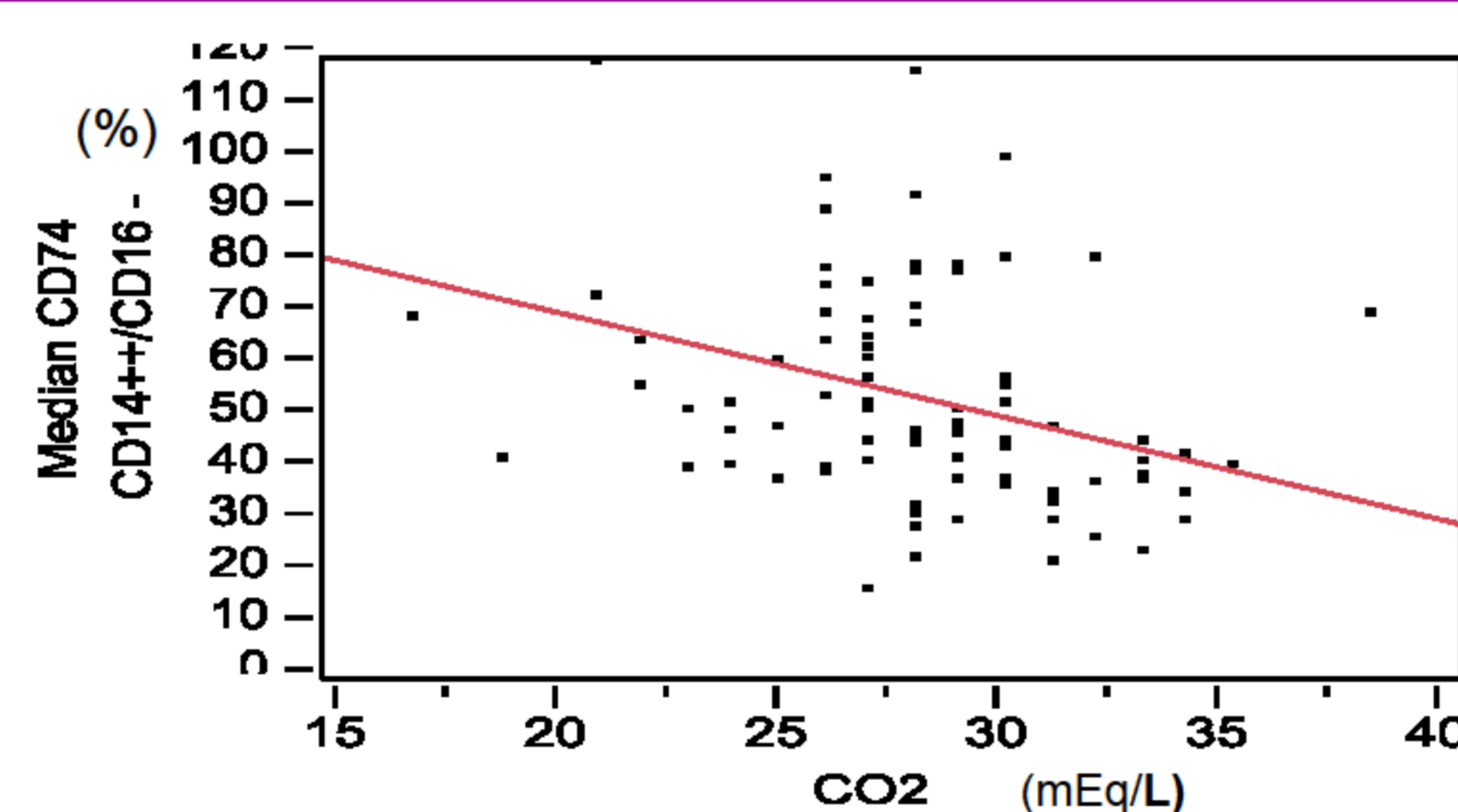


Figure 3: negative correlation between median CD 74 in CD14⁺⁺/CD16⁻ MN and CO₂

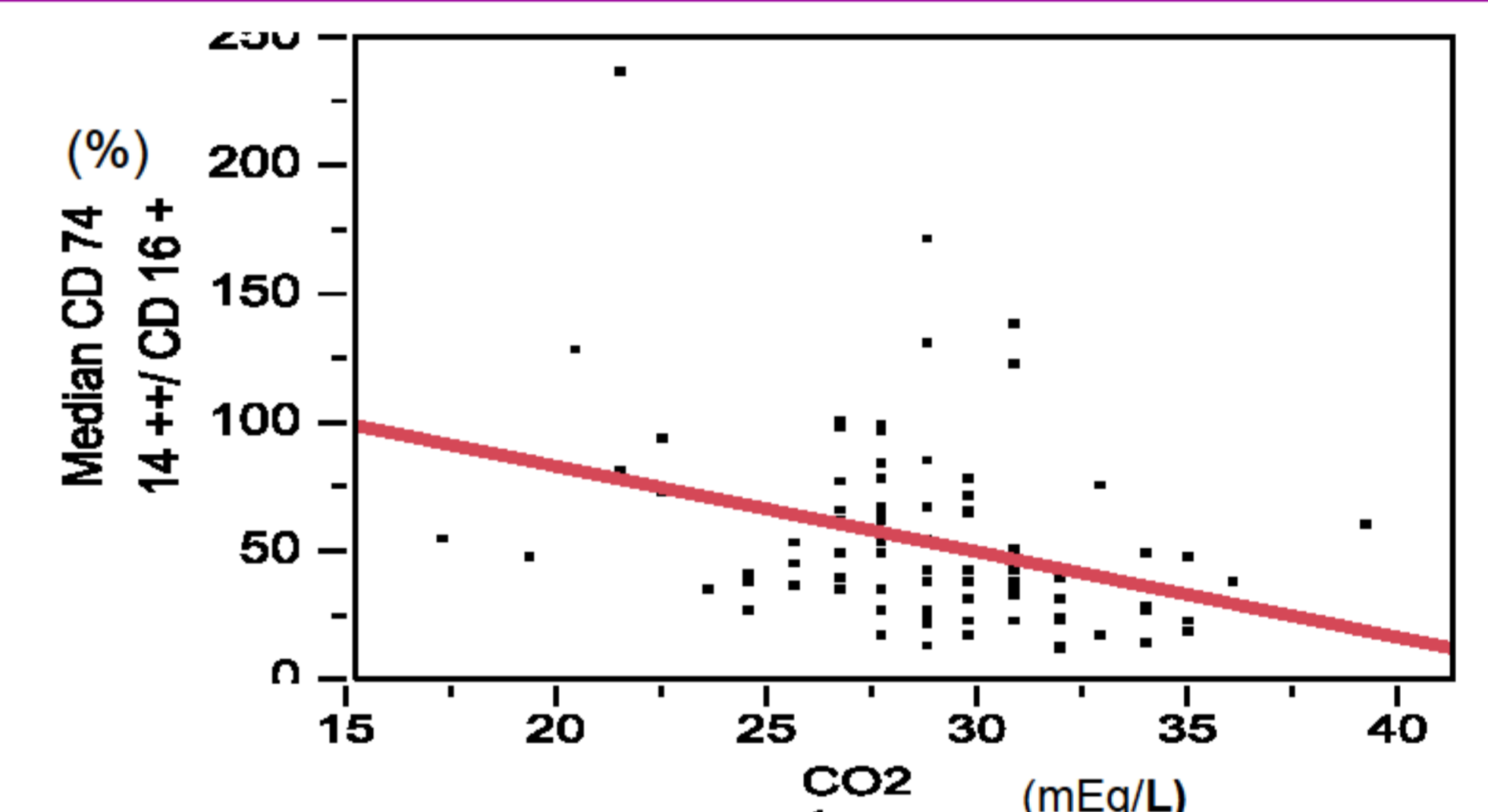


Figure 4: negative correlation between median CD 74 in CD14⁺⁺/CD16⁺ MN and CO₂

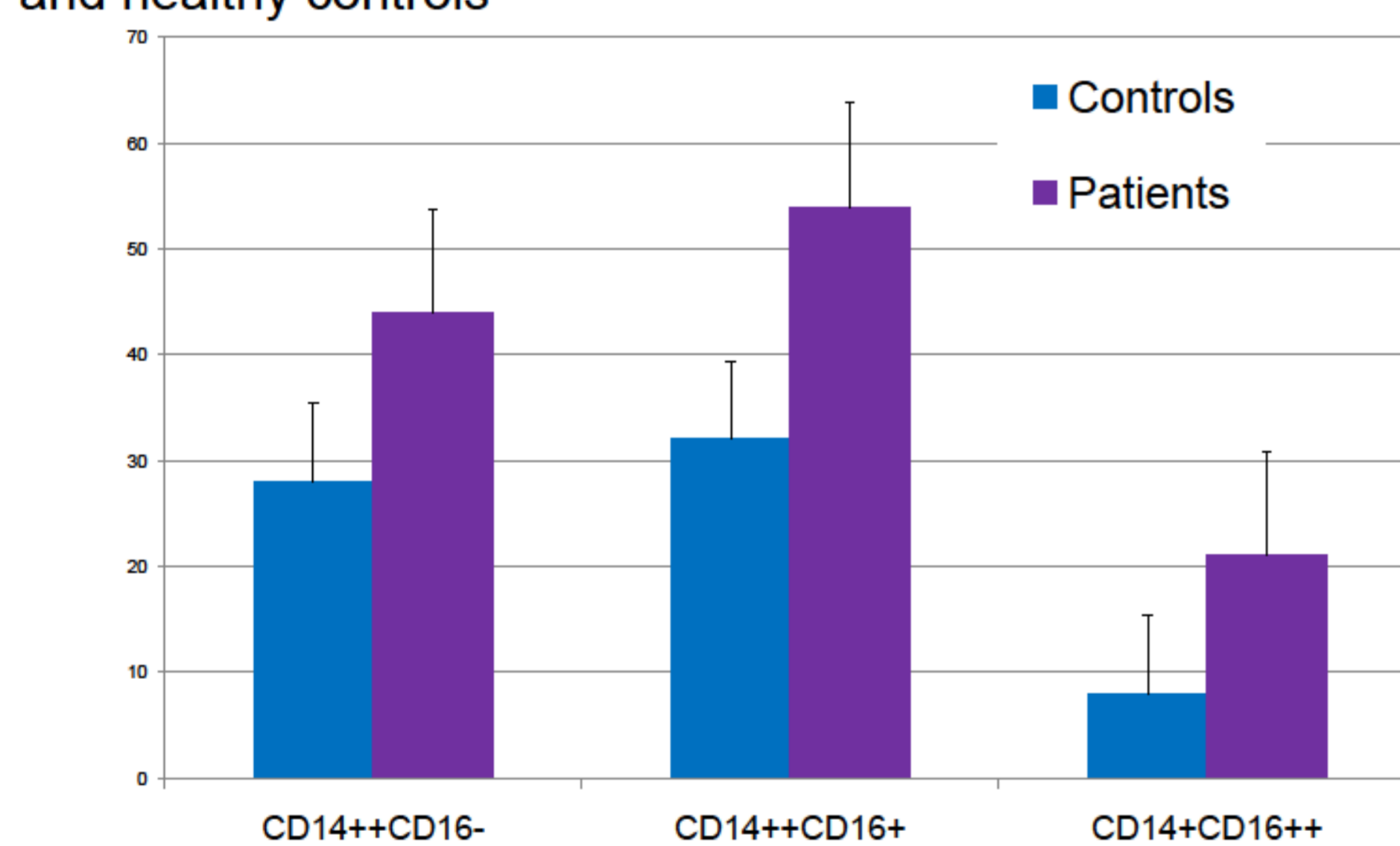


Figure 2: Median CD74 expression (FU) in monocytes from DKD patients and healthy controls

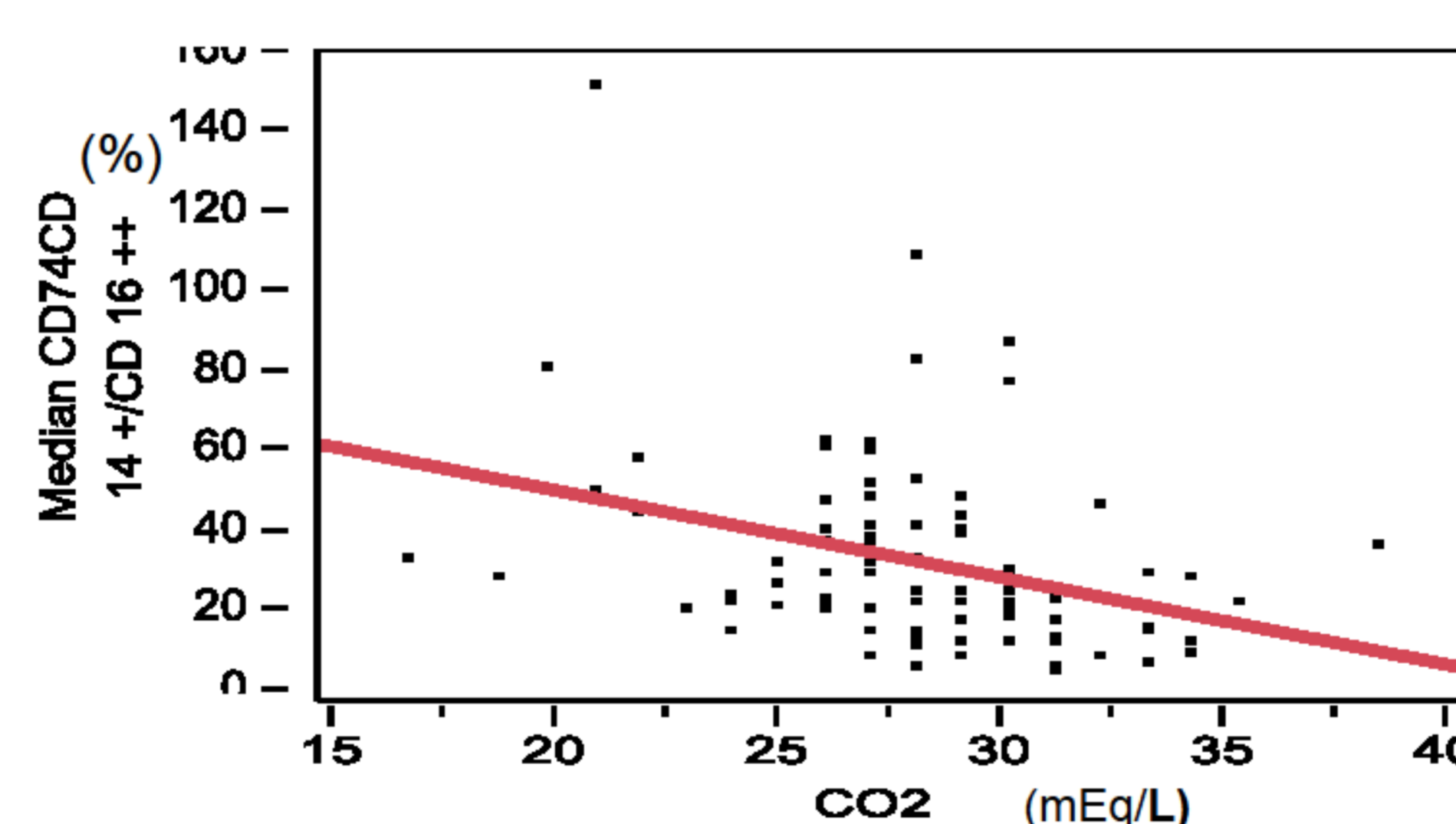


Figure 5: negative correlation between median CD 74 in CD14⁺/CD16⁺⁺ MN and CO₂

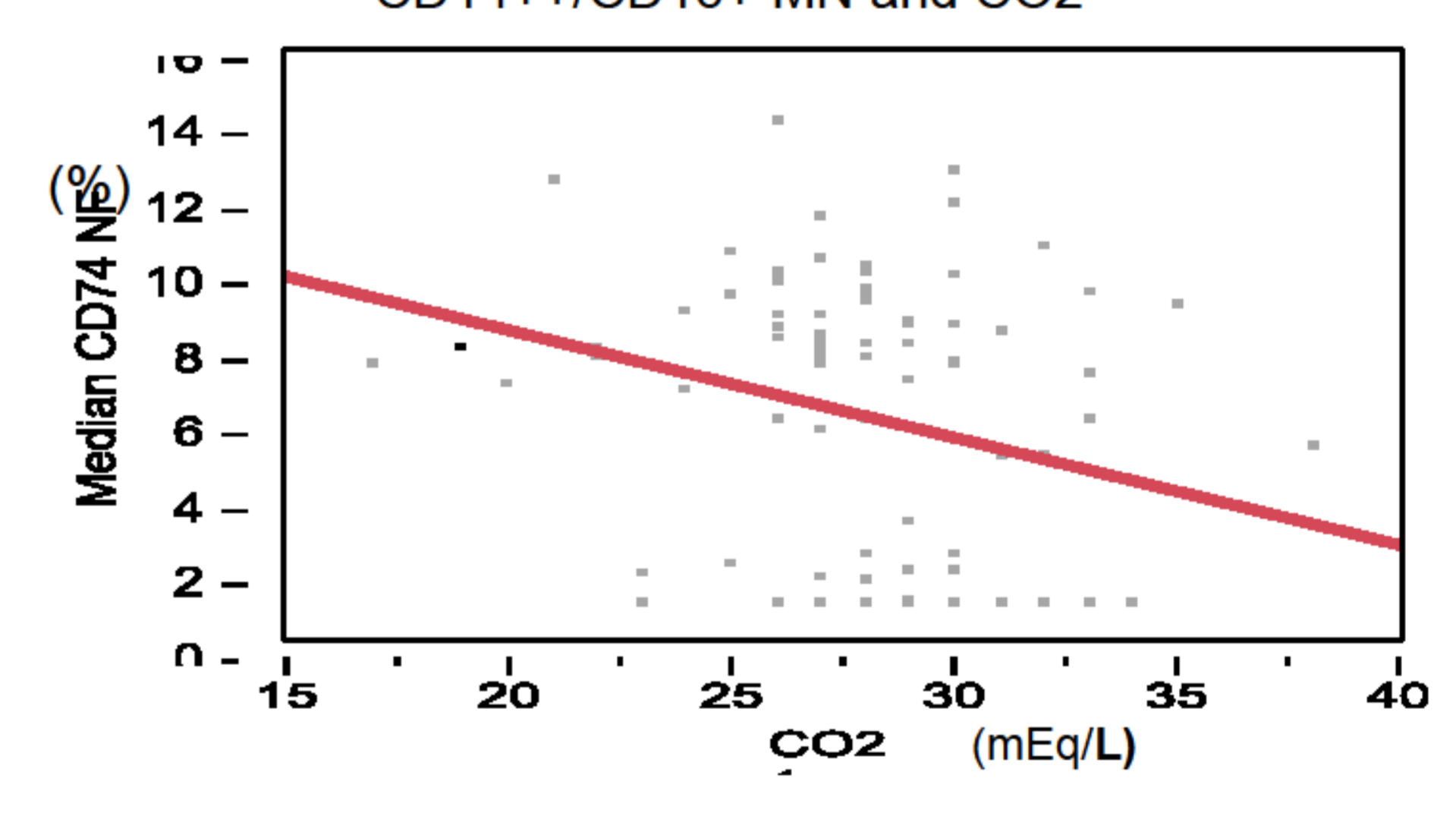


Figure 6: negative correlation between median CD 74 in NF and CO₂

CONCLUSIONS

CD74 expression in monocytes and in neutrophils was inversely correlated with CO₂ in a cross sectional analysis. This suggests that acidosis may be a driver of monocyte and neutrophil activation in DKD. The cohort is being followed in order to assess the relationship between these inflammatory markers and outcomes.

