(effector) T cells in the absence of antigen-presenting cells. The expanded nTregs showed a transient loss of suppressive activity and suppression of the induction of Foxp3 mRNA in Tregs at the first 8-15 hours after T cell receptor activation [19]. One explanation for the infection-dependent induction of TLR2 might be related to the presence of Gram-positive *Streptococcus pyogenes* [20], therefore, the presence of streptococcal M protein which is known to bind with TLR-2 may be play an important role in loss of naturally occurring CD4+CD25+ nTreg cells their suppressive function.

According to our results, there was no correlation between disease severity and the low prevalence of CD4+CD25+ nTreg cells when compared with patient's clinical and physical parameters because the severity of disease may return to more than one factor that affect the disease activity, among them, number of acute rheumatic fever attacks, duration of disease, treatment, host susceptibility to suppressed autoimmunity, and the host susceptibility to the formation of fibrosis after tissue damage. Peripheral blood CD4+ T cells appeared in high numbers in CRHD patients when compared with controls. For several factors that make patients of HR^{WCM} group more exposed to group A streptococci infection and recurrent attacks of acute rheumatic fever, HR^{WCM} group displayed the highest percentage of CD4+ T cells (65.89%) than all groups under study which confirm the continuous inflammatory state even in the chronic stage of RHD. No significant difference was recorded in the mean percentage of CD4+ T cells among negative history, SA^{WCM}, HR^{WCM}, and also in SA^{UCM}, and HR^{UCM} groups when compared with others. The main cause of increasing the number of CD4+ T cells in some of patients with continuous medical therapy [SA^{UCM}-patient number 1: 51.06% , 2: 50% , 4: 52.38% and 5: 52%] and [HR^{UCM}-patient number 2: 57.5 %, 3: 54.54%, and 4: 50 %] may be referred to the bacterial resistance for penicillin. Long-term management is known to involve regular penicillin prophylaxis in high-risk patients, to prevent further episodes of rheumatic fever [21]. *Streptococcus pyogenes* has been shown to be resistant to penicillin, but because penicillin is inexpensive and available in most countries, it remains the drug of choice for treating group A streptococcal infections [22,23]. Also, other study found that streptococci are becoming increasingly resistant to penicillin and other β-lactams, owing to a decreased β-lactams affinity of their membrane-bound penicillin binding proteins [24] .Thus, more attacks of acute rheumatic fever due to penicillin resistant *Streptococcus pyogenes* A bacteria will affect the heart and lead to increase in the inflammatory response in which CD4+ T cells play the major role. Although CD4+ T cells displayed high numbers in some of patients with medical care, but this study found that other patients had lower values nearest to the normal range [SA^{UCM}-patient number 3: 43.33 %], and [HR^{UCM}-patient number 1: 44.82%], and this result may confirm the immunosuppressive role of naturally occurring CD4+CD25+ nTreg cells (which was found in high numbers in these medical care groups) against autoreactive CD4+ T cells.

In this regard, there was a significant correlation between CD4+CD25+ nTreg cells and CD4+ T cells expression in SA^{UCM}, SA^{WCM}, HR^{UCM} groups ($p< 0.05$), and highly significant correlation was recorded in the negative history and HR^{WCM} patients ($p< 0.01$). These results reveal the important role of CD4+CD25+ nTreg cells in autoreactive CD4+ T cells suppression leading to reverse the autoimmune reaction against the heart. At the same time these results strongly explain the role of CD4+ T cells in increasing the severity of