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Impact of Anti-Diabetic Treatments on Circulating Anti-Inflammatory Mediators (IL-10 and IL-13) in Type 2 Diabetes Patients

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Abstract

Background and Objectives: Type 2 diabetes mellitus (T2DM) is a chronic condition marked by persistent hyperglycemia and low-grade inflammation, involving cytokines like IL-10 and IL-13. While metformin is widely used to manage blood glucose levels, its effects on inflammatory markers, particularly IL-10 and IL-13, remain underexplored. This study aims to assess how metformin influences serum levels of these interleukins, evaluate its anti-inflammatory potential, and explore its role in managing T2DM complications. **Materials and Methods:** T2DM patients were divided into three groups: uncontrolled diabetes, metformin treatment, and insulin treatment, with a healthy control group for comparison. Serum IL-10 and IL-13 levels were measured using ELISA before and after treatment. The effects of metformin, insulin, and their combination on these cytokines were analyzed statistically. **Results:** IL-10 and IL-13 levels were significantly elevated in the uncontrolled T2DM group compared to healthy controls, reflecting the inflammatory state associated with hyperglycemia. Metformin treatment reduced IL-10 and IL-13 levels significantly ($p < 0.005$), indicating its anti-inflammatory effect. Insulin treatment also reduced these cytokines, but to a lesser degree. Combination therapy with metformin and insulin showed the most pronounced reduction in both interleukins, suggesting a synergistic anti-inflammatory effect. **Conclusion:** Metformin significantly modulates IL-10 and IL-13 in T2DM patients, demonstrating anti-inflammatory effects beyond glycemic control. Combination therapy with metformin and insulin provides a more robust anti-inflammatory response, highlighting its potential in managing T2DM and its complications.

Keywords: T2DM, metformin, IL-10, IL-13

1- Introduction

The global prevalence of diabetes is rising rapidly, with associated morbidity and mortality rates escalating due to numerous complications linked to this health condition. Clinically, diabetes manifests through various symptoms, including elevated blood glucose levels, impaired blood flow in peripheral vessels, damage to blood vessels, cardiac complications, retinal damage, and beta-cell dysfunction in the pancreas (1,2). Type 2 diabetes

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mellitus (T2DM) is a complex, chronic metabolic disorder characterized by persistent hyperglycemia and systemic low-grade inflammation. This inflammatory state is intricately associated with the dysregulation of key cytokines, including interleukin-10 (IL-10) and interleukin-13 (IL-13), which play pivotal roles in modulating immune responses. IL-10 is primarily recognized for its anti-inflammatory properties, while IL-13 contributes to tissue remodeling and inflammation resolution (3,4). The interplay of these cytokines in the pathophysiology of T2DM underscores the critical need to evaluate their modulation in therapeutic interventions (5).

Among the arsenal of treatments for T2DM, metformin remains the cornerstone due to its efficacy in lowering blood glucose levels and its multifaceted impact on metabolic pathways. However, its potential influence on inflammatory mediators such as IL-10 and IL-13 remains underexplored. Insulin therapy, another cornerstone of diabetes management, is similarly well-studied for its metabolic effects but less so for its immunomodulatory capabilities(6). The interaction between glycemic control and inflammation, particularly through the modulation of these cytokines, warrants a deeper investigation to understand their implications in reducing diabetes-associated complications(7).

This study aims to bridge this knowledge gap by evaluating the effects of anti-diabetic therapies, specifically metformin and insulin, on serum levels of IL-10 and IL-13 in patients with T2DM. By exploring these therapeutic interventions, the study seeks to elucidate their role in glycemic control and mitigating the inflammatory burden of T2DM, thereby contributing to improved management strategies for this pervasive condition(8).

2- Materials and Methods

2-1-Patient's sample collection

This study investigates patients diagnosed with diabetes mellitus, encompassing both treated and untreated individuals throughout their lifetime. Clinical blood samples were collected from four patient groups, including two categories undergoing antidiabetic therapy. A total of 100 participants, all middle-aged males, were enrolled from Al-Ramadi Teaching Hospital between January 2024 and May 2024. The participants were classified into five distinct groups based on specific clinical criteria: 25 patients receiving metformin only, 25 diabetic patients not on metformin, 20 patients on insulin therapy alone, 20 receiving a combination of insulin and metformin, and 10 non-diabetic individuals serving as a balanced control group.

Informed written consent was obtained from all participants before sample collection and analysis. The Ethical standard of Al-Ramadi Teaching Hospital / Anbar authorized the research.

2-2-Serum Preparation

Venous blood samples were obtained from participants following a 15-minute rest in a temperature-controlled environment (22-25°C). The samples were collected into sterile, anticoagulant-free tubes to facilitate clot formation. Essential patient information, including name, gender, age, and current medication, was accurately labeled on each tube based on the provided patient history records. The samples were left undisturbed for 20-30 minutes to allow complete clotting, followed by centrifugation to separate the serum. The resulting supernatant was carefully transferred into Eppendorf tubes and stored at temperatures ranging from -20°C to -80°C for subsequent analyses or experimental applications.

2-3-Laboratory assay for IL-10 and IL-13 hormones

During the initiation of laboratory analyses, comprehensive patient data encompassing age, personal medical history, and family medical background were systematically gathered through an

interviewer-administered questionnaire. Quantification of IL-10 and IL-13 levels was performed utilizing a commercially available enzyme-linked immunosorbent assay (ELISA) kit (DRG Diagnostics, Marburg, Germany).

3- Statistical analysis

Statistical analysis of the differences between mean values of control and treated groups was conducted using one-way analysis of variance (ANOVA) through GraphPad Prism® Version 5.0 software. Post-hoc comparisons were performed using Bonferroni's Multiple Comparison test and the unpaired T-test. A p-value of less than 0.05 was considered statistically significant.

4- RESULTS

4-1- Comparison of serum interleukin-10 level between nondiabetic (healthy) and diabetic (uncontrolled) groups:

To evaluate the baseline levels of interleukin-10 (IL-10) in healthy individuals, serum samples were collected from a control group. These were compared to samples from patients with uncontrolled type 2 diabetes mellitus (T2DM). The serum IL-10 levels in the healthy control group were notably low. In contrast, patients with uncontrolled T2DM exhibited significantly elevated IL-10 concentrations compared to healthy controls (mean ± SEM: 5.439 ± 0.863 vs. 27.972 ± 0.438, $p < 0.005$), as depicted in Figure 1. Subsequently, the effect of metformin treatment on serum IL-10 levels was examined. As anticipated, untreated T2DM patients demonstrated substantially higher serum IL-10 concentrations ($p < 0.005$). Further analyses were conducted to explore whether uncontrolled diabetes could amplify IL-10 levels. Serum assessments from both groups revealed significant suppression of IL-10 concentration following treatment.

4-2- Characterization of serum interleukin-10 level following treatment with Metformin in type 2 DM patients:

The serum interleukin-10 (IL-10) concentration in response to metformin therapy is illustrated in Figure 2. As expected, the healthy control (HC) group exhibited a normal baseline IL-10 level (mean ± SEM: 5.439 ± 0.863). In contrast, patients in the uncontrolled group demonstrated a significantly elevated IL-10 concentration, as previously detailed in Figure 1. Notably, individuals receiving metformin therapy displayed markedly lower IL-10 levels compared to the uncontrolled group. Metformin treatment was associated with a significant reduction in IL-10 concentration (Metformin group: mean ± SEM 13.963 ± 2.124 vs. uncontrolled group: 27.972 ± 0.438, $p < 0.005$), underscoring its regulatory impact on inflammatory cytokine expression.

4-3- Characterization of serum interleukin-10 level following treatment with Insulin in type 2 DM patients:

The impact of insulin therapy alone on serum interleukin-10 levels was evaluated. As illustrated in Figure 3, samples from the insulin-treated group were analyzed for this cytokine and compared with those from the uncontrolled group using the same experimental approach. Insulin administration resulted in a significant reduction in interleukin-10 levels compared to the uncontrolled group (Uncontrolled: mean ± SEM = 27.972 ± 1.115; Insulin: mean ± SEM = 20.158 ± 2.037). Notably, the kinetic increase of interleukin-10 was markedly suppressed in the uncontrolled group, demonstrating a statistically significant difference. This suppression was particularly evident when compared to the healthy group (Healthy: mean ± SEM = 5.439 ± 0.863).

4-4- Characterization of serum interleukin-10 level following treatment with metformin plus insulin (both) in type 2 DM patients:

The therapeutic potential of anti-diabetic drugs lies in their capacity to modulate interleukin-10 (IL-10) levels, aiming to reduce inflammation and improve clinical outcomes. Figures 2 and 3 reveal a reduction

in IL-10 levels following treatment, consistent with prior laboratory findings. To further assess this effect, the impact of metformin and insulin, both individually and in combination, was evaluated in diabetic patients. As shown in Figure 4, the mean ± SEM IL-10 levels were 13.963 ± 2.124 for metformin, 20.158 ± 2.037 for insulin, and 16.757 ± 3.060 for the combined treatment. Notably, co-administration of metformin and insulin significantly mitigated IL-10 elevation compared to either treatment of insulin alone, indicating a synergistic effect with enhanced regulatory potential.

4-5- Comparing serum interleukin-10 levels between uncontrolled and treatment with Metformin, Insulin, and both in type 2 DM patients:

Figure 5 illustrates the characterization of serum interleukin-10 (IL-10) levels among diabetic patients receiving different therapeutic regimens, including metformin, insulin, and their combination. As expected, the healthy control (HC) group exhibited a baseline IL-10 concentration within the normal range. In contrast, the uncontrolled diabetic group displayed a marked elevation in IL-10 levels. Treatment with metformin or insulin alone led to a notable reduction in IL-10 levels, with metformin showing a more pronounced effect compared to insulin monotherapy. Furthermore, the combination therapy of metformin and insulin exerted a synergistic impact, resulting in a more substantial decrease in IL-10 concentration than treatment with insulin alone. These findings underscore, for the first time, the modulatory role of metformin on serum IL-10 levels in diabetic patients.

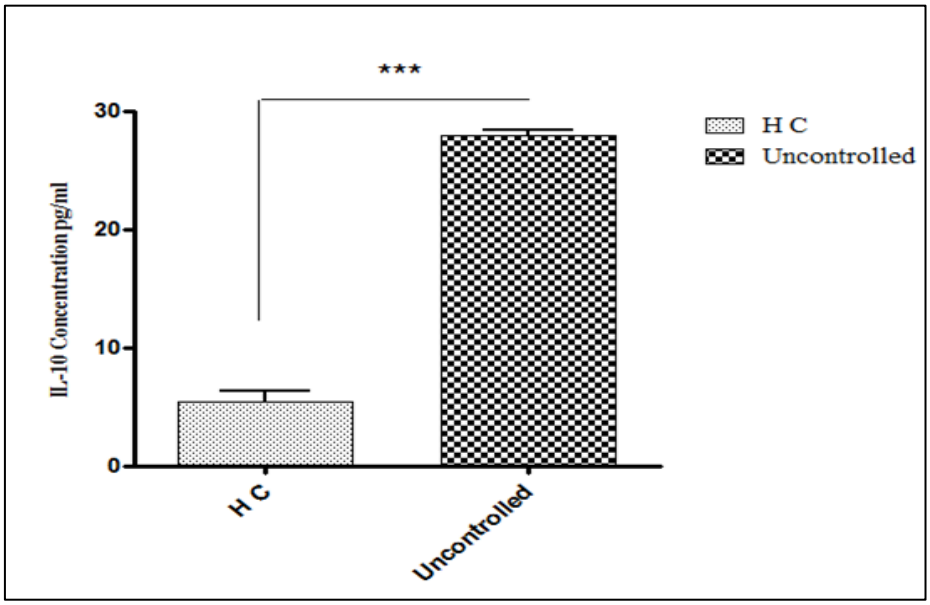

Figure 1. The effect of uncontrolled type 2 DM on serum interleukin-10 concentration in patients.

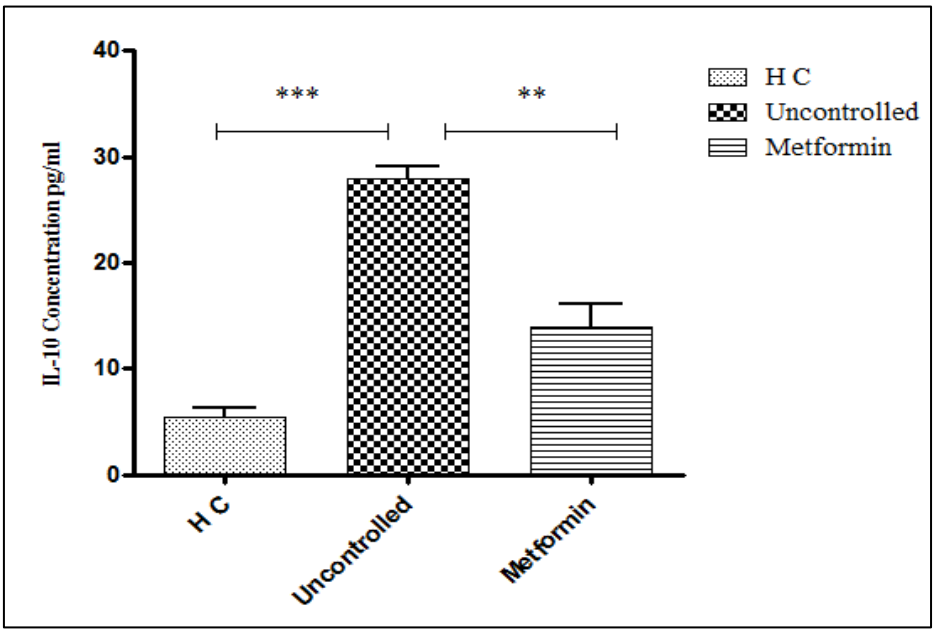

Figure 2. The effect of metformin on the serum interleukin-10 concentration in type 2 DM patients.

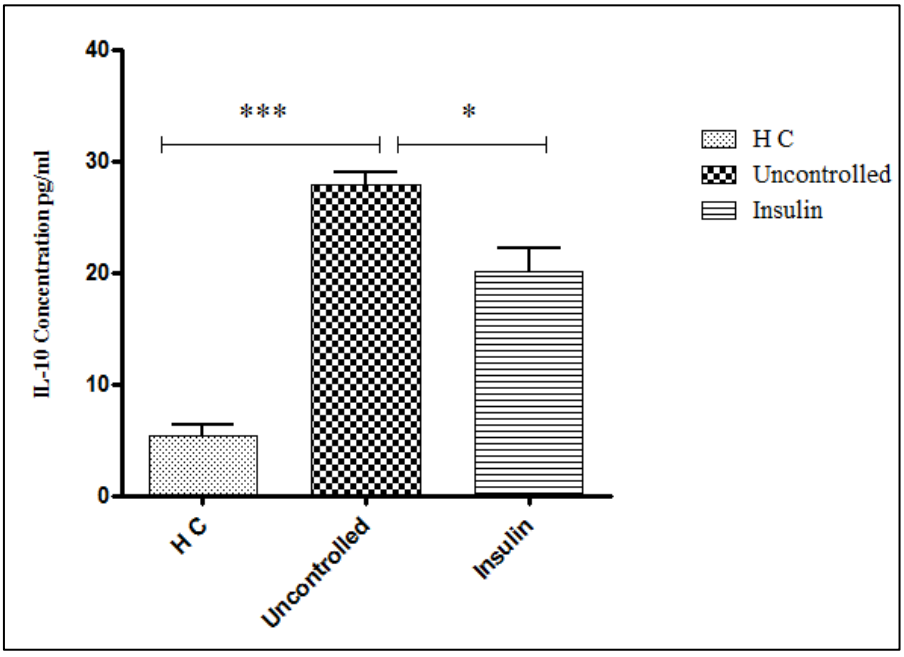

Figure 3. The effect of insulin on serum interleukin-10 concentration in type 2 DM patients.

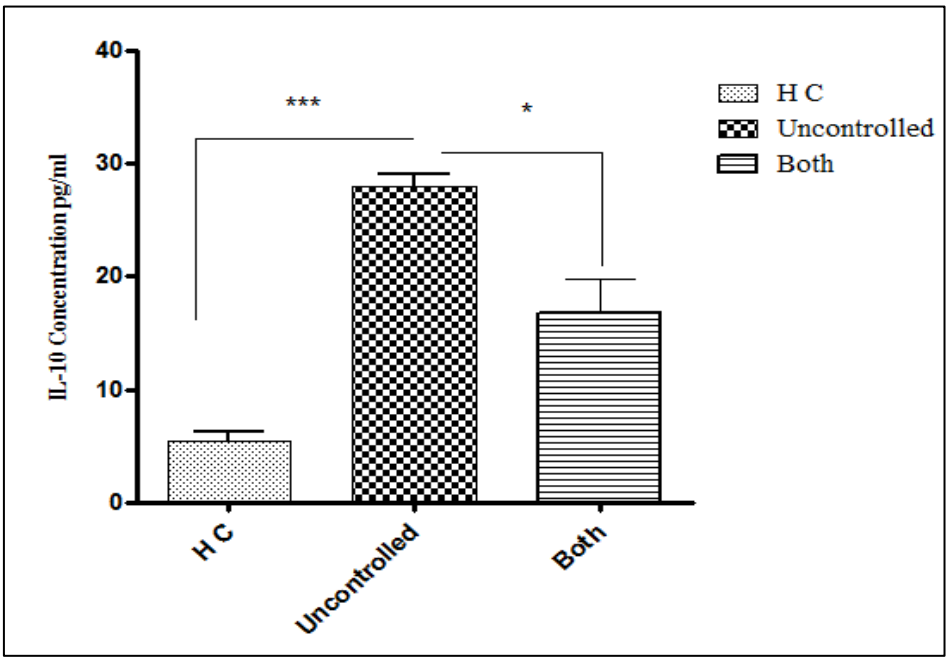

Figure 4. The effect of metformin plus insulin on serum interleukin-10 concentration in type 2 DM patients.

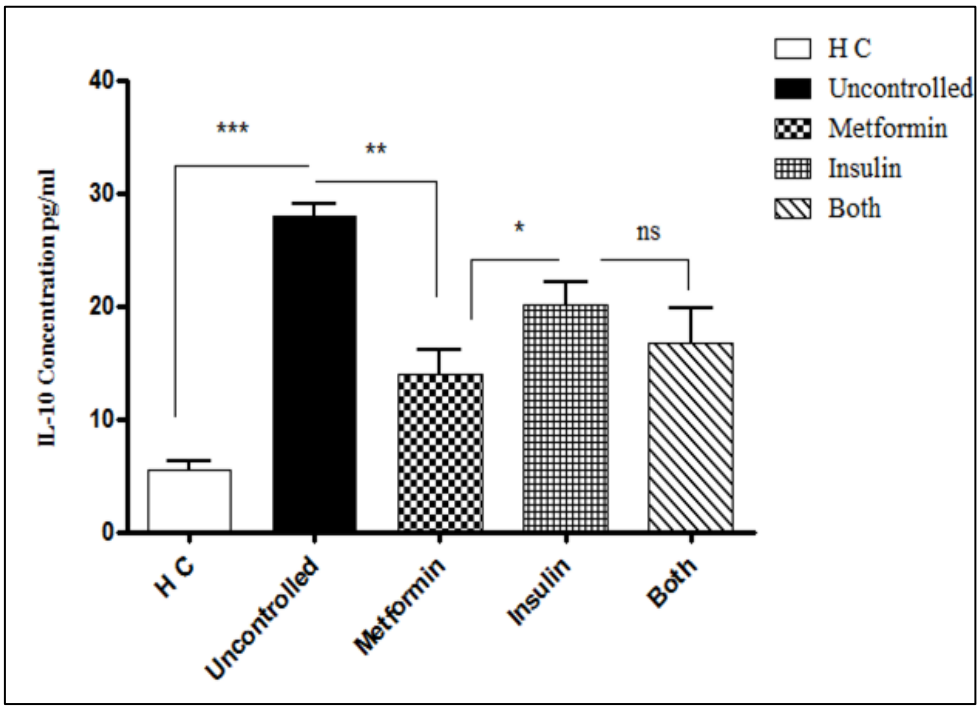

Figure 5. The effect of metformin, insulin, and both on serum interleukin-10 concentration in type 2 DM patients compared to uncontrolled patients.

3.6. Comparison of serum interleukin-13 level between nondiabetic (healthy) and diabetic (uncontrolled) groups:

To establish baseline levels of interleukin-13 (IL-13) in healthy individuals, serum samples from a control group were collected and compared to those from patients with uncontrolled type 2 diabetes mellitus (T2DM). Analysis revealed notably lower IL-13 concentrations in the healthy control group. In contrast, serum IL-13 levels were significantly elevated in patients with uncontrolled T2DM compared to the control group (mean ± SEM: 2.152 ± 0.753 vs. 48.408 ± 0.336, $p < 0.005$), as illustrated in Figure 6.

The therapeutic impact of metformin on IL-13 serum concentrations was subsequently examined. As anticipated, patients with untreated T2DM exhibited markedly higher IL-13 levels compared to their treated counterparts ($p < 0.005$). Furthermore, additional experiments were conducted to evaluate whether uncontrolled diabetes exacerbates IL-13 elevation. Comparative serum assessments confirmed that metformin treatment effectively reduced IL-13 concentrations in patients with T2DM.

3.7. Characterization of serum interleukin-13 level following treatment with Metformin in type 2 DM patients:

The characterization of serum levels in patients undergoing treatment, based on interleukin-13 concentration in response to metformin therapy, is presented in Figure 7. As expected, the healthy control group (HC) exhibited a significantly low normal value of interleukin-13 concentration (mean ± SEM: 2.152 ± 0.721). In contrast, the uncontrolled group demonstrated a marked and statistically significant increase in interleukin-13 levels, as shown in Figure 7. Patients receiving metformin therapy exhibited significantly lower interleukin-13 concentrations compared to the uncontrolled group. Metformin therapy notably reduced interleukin-13 levels (Metformin: mean ± SEM 20.260 ± 2.876 versus 48.408 ± 0.545, $p < 0.005$).

3.8. Characterization of serum interleukin-13 level following treatment with Insulin in type 2 DM patients:

The impact of insulin therapy on serum interleukin-13 levels was also assessed. As shown in Figure 8, samples from the insulin-treated group were evaluated for this cytokine and compared to the uncontrolled group using the same experimental methodology. Insulin treatment resulted in a significant reduction in interleukin-13 levels, with values notably lower than those observed in the uncontrolled group (Uncontrolled: mean ± SEM 48.408 ± 0.545; Insulin: mean ± SEM 28.371 ± 2.632). Additionally, the kinetic profile of interleukin-13 in the insulin-treated group showed a marked difference, with a substantial inhibition in the uncontrolled group. This difference was particularly evident when compared to the healthy group (Healthy: mean ± SEM 2.152 ± 0.721).

3.9. Characterization of serum interlukin-13 level following treatment with metformin plus insulin (both) in type 2 DM patients:

The expectation was that anti-diabetic drugs would effectively reduce and enhance the inhibition of interleukin-13 levels. However, as shown in Figures 7 and 8, a decrease in interleukin-13 was observed, consistent with previous laboratory findings. Following the treatment protocol, two agents were identified that could inhibit interleukin-13 in diabetic patients. Figure 9 illustrates the effects of metformin combined with insulin on interleukin-13 levels, revealing a similar response to metformin alone compared to insulin alone (Metformin: mean ± SEM 20.260 ± 2.876, insulin: mean ± SEM 28.371 ± 2.632, and both: mean ± SEM 25.417 ± 3.762). The combination treatment significantly reduced interleukin-13 levels across all tested samples when compared to the other groups. Notably, the response

was more pronounced with the combination of metformin and insulin than with insulin alone.

3.10. Comparing serum interleukin-13 levels between uncontrolled and treatment with Metformin, Insulin, and both in type 2 DM patients:

Figure 10 illustrates the serum characterization of patients in both uncontrolled and treated groups in response to metformin, insulin, and their combination. The data shows that the healthy control group (HC) exhibited a normal concentration of interleukin-13, as previously mentioned. In contrast, interleukin-13 levels were significantly elevated in the uncontrolled group. Treatment with metformin and insulin separately resulted in a significant reduction in interleukin-13 levels, with a more pronounced decrease observed in patients treated with metformin alone compared to those receiving insulin therapy. Furthermore, the combination of metformin and insulin produced a significantly greater reduction in interleukin-13 levels, highlighting the enhanced effect of metformin. These findings provide novel insight into the pharmacological impact of metformin on serum interleukin-13 levels in diabetic patients.

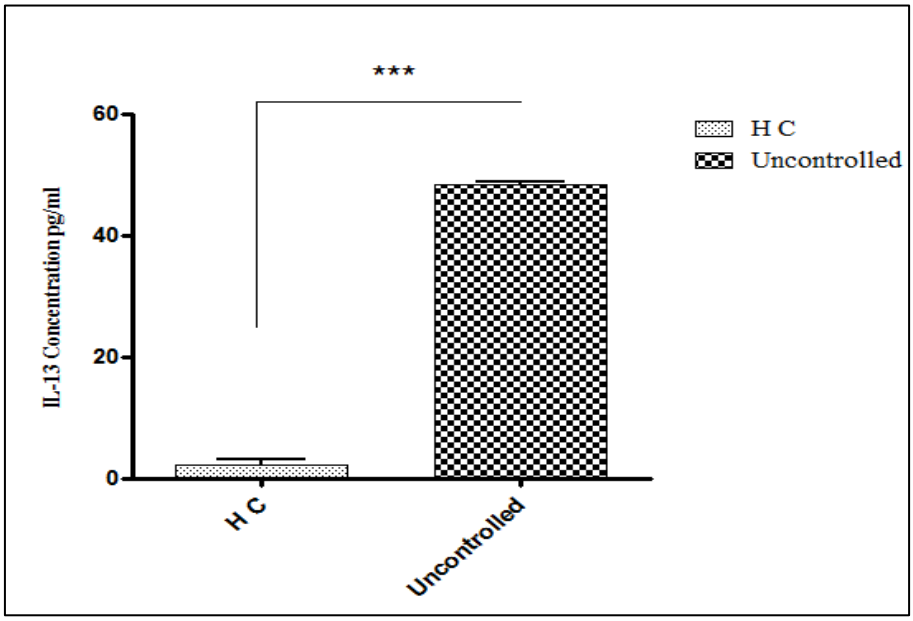

Figure 6. The effect of uncontrolled type 2 DM on serum interleukin-13 concentration in patients.

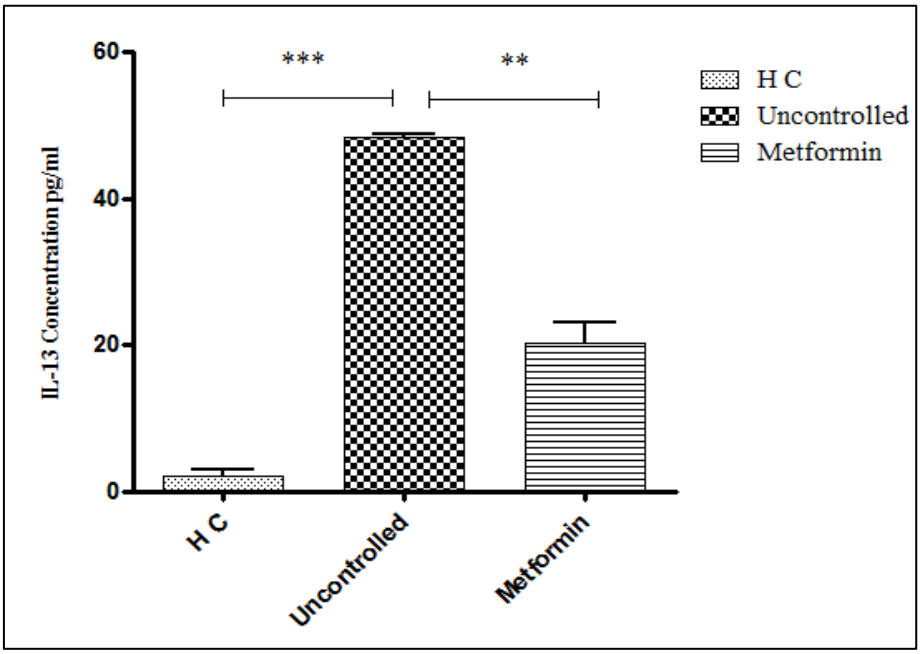

Figure 7. The effect of metformin on serum interleukin-13 concentration in type 2 DM patients.

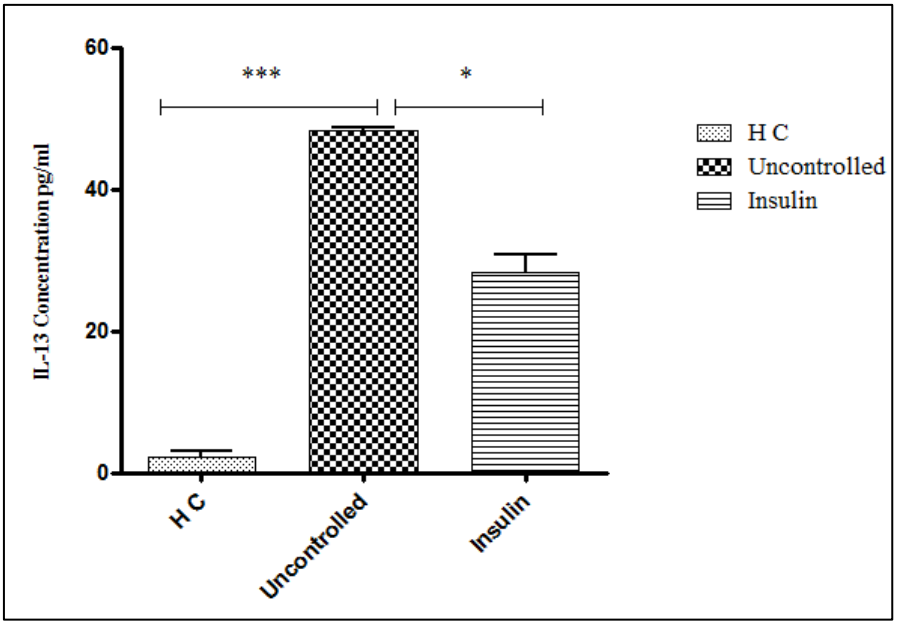

Figure 8: The effect of insulin on serum interlukin-13 concentration in type 2 DM patients.

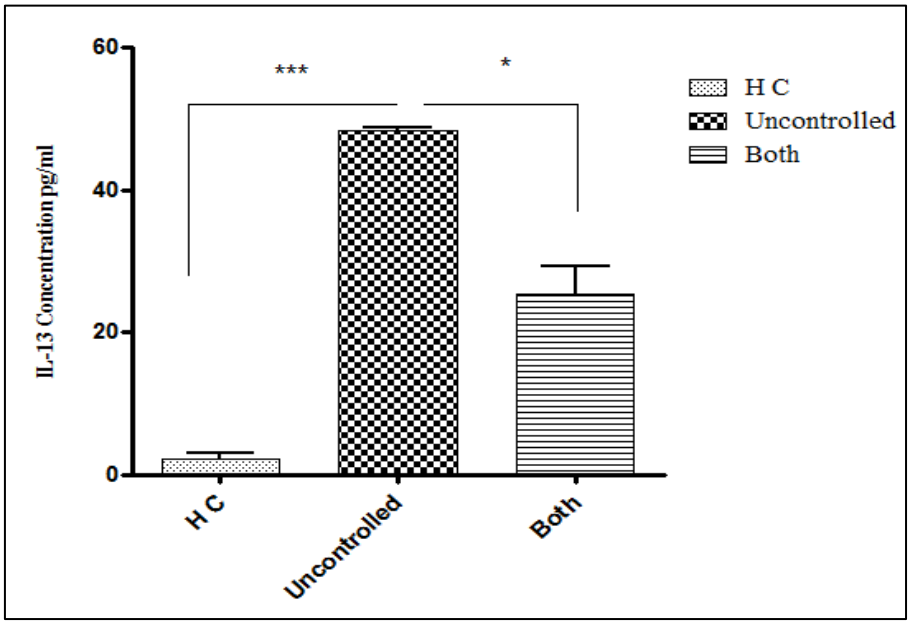

Figure 9. The effect of metformin plus insulin on serum interleukin-13 concentration in type 2 DM patients.

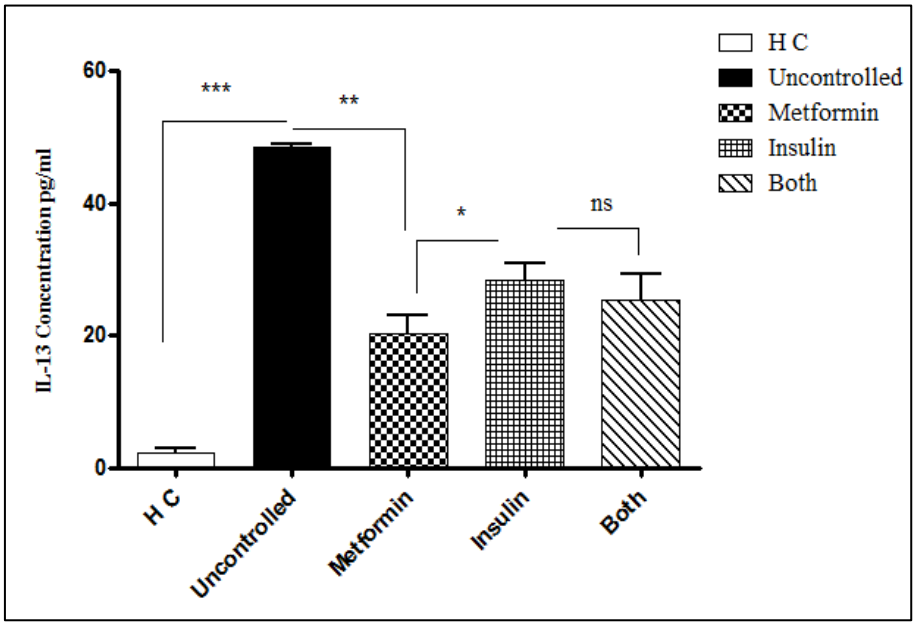

Figure 10. The effect of metformin, insulin, and both on serum interleukin-13 concentration in type 2 DM patients compared to uncontrolled patients.

5- Discussion

The findings suggest a notable discrepancy in serum interleukin-10 (IL-10) levels between healthy individuals and uncontrolled type 2 diabetes mellitus (T2DM) patients, highlighting the immunomodulatory changes associated with hyperglycemia. Previous studies have similarly reported elevated IL-10 levels in T2DM, indicating its potential role as an anti-inflammatory compensatory mechanism in response to chronic inflammation commonly observed in diabetic patients(9). The reported concentrations (mean ± SEM 5.439 ± 0.863 in controls vs 27.972 ± 0.438 in patients) align with prior research, such as studies by Singh (10), which showed elevated IL-10 levels as markers of metabolic stress. Furthermore, the observed reduction of IL-10 in treated patients corroborates findings that metformin and glycemic control can normalize inflammatory markers. However, contradictory reports in some studies, where IL-10 was reduced in diabetic states, warrant further exploration into the biphasic nature of this cytokine(11). These variations may stem from differences in sample size, patient demographics, or methodological approaches, necessitating larger cohort studies for conclusive evidence(12).

The presented findings highlight a significant modulation of serum interleukin-10 (IL-10) levels in type 2 diabetes mellitus (T2DM) patients undergoing metformin therapy, underscoring its potential anti-inflammatory effects. Healthy controls exhibited baseline IL-10 levels within normal ranges, as expected, which contrasted with significantly elevated levels in the uncontrolled diabetic group(13). Notably, metformin treatment led to a marked reduction in IL-10 concentrations compared to the uncontrolled group, as indicated by the substantial difference ($p < 0.005$). These results align with previous studies suggesting that metformin exerts immunomodulatory effects by reducing systemic inflammation markers(14). For example, prior research has shown that metformin attenuates pro-inflammatory cytokines and enhances anti-inflammatory mediators, supporting its role beyond glycaemic control. However, the observed variability in IL-10 levels necessitates further investigation to elucidate the precise mechanisms through which metformin modulates immune responses in T2DM patients, particularly regarding its dose-dependent and time-dependent effects(15).

The study investigates the impact of insulin therapy on serum interleukin-10 (IL-10) levels in type 2 diabetes mellitus (T2DM) patients. The results indicate a significant reduction in IL-10 levels in the insulin-treated group compared to the uncontrolled group (27.972 ± 1.115 vs. 20.158 ± 2.037, respectively)(16). This reduction contrasts with the highly inhibited IL-10 levels observed in the healthy group (5.439 ± 0.863), suggesting a regulatory effect of insulin on anti-inflammatory cytokines. Previous studies have reported elevated IL-10 levels in uncontrolled T2DM, potentially due to compensatory anti-inflammatory mechanisms. However, the current findings suggest that insulin therapy may attenuate these elevations, aligning with evidence indicating improved inflammatory profiles following glycaemic control. Further research is needed to elucidate the precise mechanisms of IL-10 modulation by insulin, particularly in the context of inflammation and immune regulation in T2DM. This study highlights the potential of insulin as a modulator of cytokine profiles, contributing to its therapeutic benefits(17).

The study investigates the effect of combined metformin and insulin treatment on serum interleukin-10 (IL-10) levels in patients with type 2 diabetes mellitus. Previous research highlights IL-10 as a key anti-inflammatory cytokine whose levels are often altered in diabetic conditions. While earlier findings suggested that metformin and insulin individually modulate IL-10, the present results indicate that their combination produces a more pronounced effect. Specifically, the combined therapy significantly reduced IL-10 levels (16.757 ±

3.060) compared to insulin alone (20.158 ± 2.037) and was comparable to metformin alone (13.963 ± 2.124)(18). This reduction may reflect an enhanced regulatory response by the combination therapy, potentially providing a synergistic anti-inflammatory benefit. Compared to previous studies, where insulin alone was reported to increase IL-10 levels, this study offers a nuanced perspective, highlighting the therapeutic potential of drug combinations in modulating immune responses in diabetic patients. Further studies should explore the clinical implications of these findings, including impacts on disease progression and inflammation(19).

The analysis of serum interleukin-10 (IL-10) levels in type 2 diabetes mellitus (T2DM) patients provides novel insights into the immunomodulatory effects of different therapeutic regimens. Our findings support prior research suggesting that IL-10 levels are elevated in the uncontrolled diabetic state, reflecting systemic inflammation. Treatment with metformin or insulin independently reduced IL-10 levels, consistent with their roles in mitigating hyperglycemia and its inflammatory consequences. Interestingly, metformin exhibited a more pronounced effect than insulin, corroborating earlier studies on its anti-inflammatory properties beyond glycaemic control(18). Furthermore, the combination of metformin and insulin significantly enhanced the reduction in IL-10 levels, a novel observation that highlights potential synergistic effects. These findings build upon previous studies by demonstrating the specific impact of metformin on IL-10 in diabetic patients and support its use in combination therapy for better inflammatory and metabolic outcomes(20).

The study provides compelling evidence that serum interleukin-13 (IL-13) levels differ significantly between healthy individuals and patients with uncontrolled type 2 diabetes mellitus (T2DM). IL-13 levels were markedly elevated in the diabetic group compared to healthy controls, suggesting a potential link between IL-13 and hyperglycemic conditions. This finding aligns with previous studies indicating that inflammatory cytokines, including IL-13, play a role in the pathophysiology of T2DM by contributing to chronic low-grade inflammation. Furthermore, the observed reduction in IL-13 levels among patients treated with metformin supports earlier research on its anti-inflammatory properties. Unlike prior studies that primarily focused on IL-6 or TNF-α, this investigation highlights IL-13 as a novel biomarker associated with diabetes(21). The results emphasize the potential of targeting IL-13 pathways for therapeutic interventions in diabetes management. Future studies should validate these findings in larger cohorts and explore the mechanistic underpinnings of IL-13's involvement in metabolic dysregulation(22).

The findings highlight a significant reduction in serum interleukin-13 (IL-13) levels in type 2 diabetes mellitus (T2DM) patients following insulin therapy, suggesting a modulatory role of insulin on this cytokine. The mean IL-13 concentration in the insulin-treated group (28.371 ± 2.632) was markedly lower compared to the uncontrolled group (48.408 ± 0.545), demonstrating the anti-inflammatory potential of insulin therapy. Furthermore, IL-13 levels in insulin-treated patients remained significantly elevated compared to healthy controls (2.152 ± 0.721), indicating incomplete normalization despite treatment. These results align with previous studies showing that insulin therapy can attenuate pro-inflammatory cytokines but may not fully restore cytokine balance(23). Notably, the pronounced inhibition of IL-13 kinetics in the uncontrolled group underscores the exacerbation of inflammatory responses in poorly managed T2DM. This study expands on existing literature by quantitatively evaluating IL-13, a less-explored cytokine in diabetes, and provides evidence for its partial regulation through insulin(24).

The study presents a significant observation regarding the serum interleukin-13 (IL-13) levels in

type 2 diabetes mellitus (T2DM) patients treated with a combination of metformin and insulin. As shown in Figure 9, the combined therapy resulted in a greater reduction in IL-13 levels compared to either agent alone. This finding aligns with previous studies indicating that metformin possesses anti-inflammatory properties, possibly through modulation of cytokine production. Insulin's independent role in reducing IL-13, albeit less effective than the combination, corroborates its metabolic regulatory effects. Notably, the observed reduction with metformin plus insulin supports the hypothesis that synergistic anti-inflammatory mechanisms may enhance therapeutic efficacy(25). Compared to earlier findings (Figures 7 and 8), which demonstrated variability in IL-13 inhibition, this combined approach underscores the potential for targeted cytokine modulation. These results warrant further investigation into the mechanistic pathways involved, aligning with prior research suggesting differential impacts of anti-diabetic agents on immune markers. The use of ELISA for precise cytokine quantification enhances the reliability of these findings, marking a step forward in understanding T2DM-associated inflammation(26).

The presented data offer critical insights into the differential effects of metformin, insulin, and their combination on serum interleukin-13 (IL-13) levels in type 2 diabetes mellitus (T2DM) patients. The significant elevation of IL-13 in the uncontrolled group aligns with previous findings linking chronic inflammation to poor glycaemic control in T2DM. Notably, metformin therapy resulted in a more pronounced reduction in IL-13 levels compared to insulin alone, consistent with its known anti-inflammatory properties(27). The combination of metformin and insulin exhibited the highest efficacy, suggesting a synergistic effect in modulating cytokine responses. This observation builds on prior studies, such as(28). This highlights metformin's impact on cytokine profiles and extends our understanding by emphasizing the role of IL-13 as a potential biomarker for therapeutic monitoring. Future research should explore the molecular pathways mediating these effects to optimize T2DM treatment strategies(29).

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Conflict of interest

The authors declare that they have no conflict of interest.

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